The present invention relates to Bcl-2 inhibitors and their use in the treatment of cell proliferative diseases such as cancer.
Bcl-2 INHIBITORS

RELATED APPLICATION

This application claims the benefit of U.S. Provisional Application No. 60/971,053, filed on September 10, 2007. The entire teachings of the above application are incorporated herein by reference.

BACKGROUND OF THE INVENTION

Programmed cell-death or apoptosis is a regulated process that involves an orchestrated series of biochemical events leading to characteristic cell morphology and eventually cell death, and is necessary in an organism's development and during the life cycle. For example, the differentiation of digits in a developing embryo requires cells between the digits to initiate apoptosis so that they can separate. Deregulated apoptotic processes have been implicated in an extensive variety of diseases. Excessive apoptosis causes hypotrophy, such as in ischemic damage, whereas an insufficient amount results in uncontrolled cell proliferation, such as in cancer.

Bcl-2 proteins

Bcl-2 is the prototype of a family of mammalian genes and the proteins they produce (Chao, D.T., Korsmeyer, S.J., Annu Rev Immunol 16, 1998, 395-419; Cory, S., Adams, J.M. Nat Rev Cancer 2(9), 2002, 647-656), which govern mitochondrial outer membrane permeabilisation, and which can be either anti-apoptotic (including Bcl-2 proper, Bcl-xL, and Bcl-w) or pro-apoptotic (Bax, BAD, Bak and Bok among others). More than 20 genes in the Bcl-2 family are known to date. Bcl-2 derives its name from B-cell lymphoma 2, as it is the second member of a group of genes described to be translocated in follicular lymphomas from chromosome 14 to 18 (Pegoraro, L., et al, Proc Natl Acad Sci USA 81, 1984, 7166-7170).

The Bcl-2 family has a general structure that consists of a hydrophobic helix surrounded by amphipathic helices. Many members of the family have transmembrane domains. Bcl-2 and its closely related Bcl-X(L) counterpart are one of several pro-survival proteins which can share up to four highly conserved domains known as BH1, BH2, BH3 and BH4. These domains form the basis of a

The BH domains are known to be crucial for function, as deletion of these domains affects apoptosis rates. In anti-apoptotic Bcl-2 proteins, such as Bcl-2 and Bcl-xL, all four BH domains are conserved.

The site of action for the Bcl-2 family is mostly on the outer mitochondrial membrane. Within the mitochondria are pro-apoptotic factors (e.g., cytochrome C) that if released, activate caspases which are key proteins in the apoptotic cascade. Depending on their function, once activated, Bcl-2 proteins either promote the release of these factors, or keep them sequestered in the mitochondria. The exact mechanisms surrounding Bcl-2 regulated mitochondrial outer membrane permeabilization have yet to be elucidated, but it is believed that the multidomain, pro-apoptotic Bcl-2 proteins can activate it directly, a process that is inhibited by the binding of anti-apoptotic Bcl-2 proteins.

There are a number of theories concerning how Bcl-2 family genes and their resulting proteins exert their pro- or anti-apoptotic effects. An important one states that this is achieved by activation or inactivation of an inner mitochondrial permeability transition pore, which is involved in the regulation of matrix Ca2+, pH, and voltage. It is also thought that some Bcl-2 family proteins can induce (pro-apoptotic members) or inhibit (anti-apoptotic members) the release of cytochrome C into the cytosol, which, once there, activates caspase-9 and caspase-3, leading to apoptosis (Zamzami, N. et al., Oncogene 16, 1998, 2265-2282.) Overexpression of Bcl-2 is known to block cytochrome C release.

**Bcl-2’s role in disease**

Cancer is one of the world's leading causes of death and occurs when the homeostatic balance between cell growth and death is disturbed. Extensive evidence indicates a strong correlation between neoplastic progression and deregulation of apoptotic pathways. Overexpression of Bcl-2 family proteins is associated with tumor progression, poor prognosis and resistance to chemotherapy (Stauffer, S.R., Curr Top Med Chem 7(10), 2007, 961-965), hence the development of therapies which inhibit Bcl-2 proteins may prove to be beneficial in cancer and other proliferative disorders.
The Bcl-2 gene has been implicated in a number of cancers, including melanoma, breast, prostate, and lung cancer, supporting its role for decreased apoptosis in the pathogenesis of cancer. A particularly interesting example has been observed in follicular B-cell lymphoma, where a chromosomal translocation occurs between chromosomes 14 and 18 which places the Bcl-2 gene next to the immunoglobulin heavy chain locus (Jaeger, U. et al., Leuk Lymphoma 14, 1994, 197-202). The resulting fusion gene is deregulated, leading to the transcription of excessively high levels of anti-apoptotic Bcl-2 protein and decreasing these cells' rate of apoptosis (Vaux D. L. et al., Nature 335, 1988, 440-442).

**Targeted Bcl-2 therapies**

Specifically, antagonism of the protein-protein interactions of Bcl-2 family proteins (including Bcl-2 and Bcl-xL) are considered extremely important points for drug intervention in cancer. Abbott has recently described a novel inhibitor of Bcl-2 and Bcl-xL, known as ABT-737 (Oltersdorf, T., et al. Nature 435, 2005, 677-681). ABT-737 is one of several BH3 mimetic small molecule inhibitors targeting Bcl-2 and Bcl-2-related proteins such as Bcl-xL and McI-I. It has been shown to cause complete regression in small-cell lung carcinoma tumor xenografts in mice and may prove to be clinically useful as a new anticancer agent capable of overcoming apoptosis resistance. It is currently at the preclinical stage.

![ABT-737](image_url)

An antisense oligonucleotide drug, Genasense (G3139), has also been developed to target Bcl-2 after it was shown that the proliferation of human lymphomas with t(14;18) translocation could be inhibited by antisense RNA targeted to the start coding region of Bcl-2 mRNA (Dias, N., Stein, CA, Eur J Pharm Biopharm 54, 2002, 263-269). Genasense's clinical development program
indicates that its manufacturer has evidence for its potential therapeutic utility in a range of tumor types, as has been studied in patients with non-small cell and small cell lung cancer, non-Hodgkin's lymphoma, myeloid and lymphocytic leukemia, multiple myeloma, melanoma, colorectal, prostate, skin, breast, renal, pancreatic, liver and gastric cancer.

Enormous efforts are still directed to the development of selective anti-cancer drugs as well as to new and more efficacious combinations of known anti-cancer drugs.

SUMMARY OF THE INVENTION

The present invention relates to Bcl-2 inhibitors that have enhanced and unexpected properties as inhibitors of Bcl-2 and their use in the treatment of Bcl-2 related diseases and disorders such as cancer.

Accordingly, the present invention provides a compound having a general formula I:

or its geometric isomers, enantiomers, diastereomers, racemates, pharmaceutically acceptable salts, prodrugs and solvates thereof, wherein

Ar is aryl, substituted aryl, heteroaryl, substituted heteroaryl;

R_{23} is selected from hydrogen, acyl, aliphatic and substituted aliphatic;

W is N or CH;

W_i is absent, N or CH;

R_{26} is hydrogen, alkyl, aryl, alkylcarbonyl, or arylcarbonyl;

R_{27} is aryl, substituted aryl, heteroaryl, or substituted heteroaryl; and

R_{28} is hydrogen, oxo, aryl, substituted aryl, heteroaryl, or substituted heteroaryl.
DETAILED DESCRIPTION OF THE INVENTION

In a first embodiment of the compounds of the present invention are compounds represented by formula (I) as illustrated above, or its geometric isomers, enantiomers, diastereomers, racemates, pharmaceutically acceptable salts, prodrugs and solvates thereof.

In one embodiment of the compounds of the present invention are compounds represented by formula (II) as illustrated below, or its geometric isomers, enantiomers, diastereomers, racemates, pharmaceutically acceptable salts, prodrugs and solvates thereof:

wherein Xi-X4 are independently N or CR25, where R25 is independently selected from hydrogen, hydroxy, amino, halogen, substituted or unsubstituted alkoxy, substituted or unsubstituted alkylamino, substituted or unsubstituted dialkylamino, CF3, CN, NO2, N3, sulfonyl, acyl, aliphatic, and substituted aliphatic; R22 is selected from hydrogen, acyl, aliphatic and substituted aliphatic; n is 1-5; B1 is absent, N(Rs), CO, C1-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, cycloalkyl, heterocyclic or aryl; B2 is absent, O, S, SO, SO2, N(R8) or CO; B3 is absent, O, S, SO, SO2, N(R8), CO, C1-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, cycloalkyl, heterocyclic, aryl, or heteroaryl; B4 is absent, O, S, SO, SO2, N(R8), CO, C1-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, cycloalkyl, heterocyclic, aryl, or heteroaryl; B5 is absent, O, S, SO, SO2, N(R8), CO, C1-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, cycloalkyl, heterocyclic, aryl, or heteroaryl; B6 is absent, C1-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocyclic, aryl, substituted aryl, heteroaryl or substituted heteroaryl; each R8 is independently hydrogen, acyl,
aliphatic or substituted aliphatic; Ar, Z, W, W₁, R₂₆-R₂₈ and R₂₃ are as previously defined.

In one embodiment of the compounds of the present invention are compounds represented by formula (III) as illustrated below, or its geometric isomers, enantiomers, diastereomers, racemates, pharmaceutically acceptable salts, prodrugs and solvates thereof:

10 wherein X₁-X₉ are independently N or CR₂₅, where R₂₃ is independently selected from hydrogen, hydroxy, amino, halogen, substituted or unsubstituted alkoxy, substituted or unsubstituted alkylamino, substituted or unsubstituted dialkylamino, CF₃, CN, NO₂, N₃, sulfonyl, acyl, aliphatic, and substituted aliphatic; R₂₂ is selected from hydrogen, acyl, aliphatic and substituted aliphatic; n is 1-5; R₂₀ and R₂₁ are each independently selected from hydrogen, acyl, aliphatic and substituted aliphatic; alternatively, R₂₀ and R₂₁ can be taken together with the atom they are attached to form a heterocyclic or substituted heterocyclic;

Z, W, W₁, R₂₆-R₂₈ and R₂₃ are as previously defined.

In one embodiment of the compounds of the present invention are compounds represented by formula (IV) as illustrated below, or its geometric isomers, enantiomers, diastereomers, racemates, pharmaceutically acceptable salts, prodrugs and solvates thereof:
wherein \( X_1 \)-\( X_4 \) are independently \( N \) or \( CR_{25} \), where \( R_{25} \) is independently selected from hydrogen, hydroxy, amino, halogen, substituted or unsubstituted alkoxy, substituted or unsubstituted alkylamino, substituted or unsubstituted dialkylamino, \( CF_3, \) CN, \( NO_2, \) \( N_3, \) sulfonyl, acyl, aliphatic, and substituted aliphatic; \( R_{22} \) is selected from hydrogen, acyl, aliphatic and substituted aliphatic; \( n \) is 1-5; \( R_{20} \) and \( R_{21} \) are each independently selected from hydrogen, acyl, aliphatic and substituted aliphatic; alternatively, \( R_{20} \) and \( R_{21} \) can be taken together with the atom they are attached to form a heterocyclic or substituted heterocyclic; \( W, W_1, R_{26}-R_{28} \) and \( R_{23} \) are as previously defined.

Representative compounds according to the invention are those selected from the Table A below or its geometric isomers, enantiomers, diastereomers, racemates, pharmaceutically acceptable salts, prodrugs and solvates thereof:

<table>
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<tr>
<th>Compound #</th>
<th>Structure</th>
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The invention further provides methods for the prevention or treatment of diseases or conditions involving aberrant proliferation, differentiation or survival of cells. In one embodiment, the invention further provides for the use of one or more compounds of the invention in the manufacture of a medicament for halting or decreasing diseases involving aberrant proliferation, differentiation, or survival of cells. In preferred embodiments, the disease is cancer. In one embodiment, the invention relates to a method of treating cancer in a subject in need of treatment comprising administering to said subject a therapeutically effective amount of a compound of the invention.

The term "cancer" refers to any cancer caused by the proliferation of malignant neoplastic cells, such as tumors, neoplasms, carcinomas, sarcomas, leukemias, lymphomas and the like. For example, cancers include, but are not limited to, mesothelioma, leukemias and lymphomas such as cutaneous T-cell lymphomas (CTCL), noncutaneous peripheral T-cell lymphomas, lymphomas
associated with human T-cell lymphotrophic virus (HTLV) such as adult T-cell leukemia/lymphoma (ATLL), B-cell lymphoma, acute nonlymphocytic leukemias, chronic lymphocytic leukemia, chronic myelogenous leukemia, acute myelogenous leukemia, lymphomas, and multiple myeloma, non-Hodgkin lymphoma, acute lymphatic leukemia (ALL), chronic lymphatic leukemia (CLL), Hodgkin’s lymphoma, Burkitt lymphoma, adult T-cell leukemia lymphoma, acute-myeloid leukemia (AML), chronic myeloid leukemia (CML), or hepatocellular carcinoma. Further examples include myelodisplastic syndrome, childhood solid tumors such as brain tumors, neuroblastoma, retinoblastoma, Wilms’ tumor, bone tumors, and soft-tissue sarcomas, common solid tumors of adults such as head and neck cancers (e.g., oral, laryngeal, nasopharyngeal and esophageal), genitourinary cancers (e.g., prostate, bladder, renal, uterine, ovarian, testicular), lung cancer (e.g., small-cell and non small cell), breast cancer, pancreatic cancer, melanoma and other skin cancers, stomach cancer, brain tumors, tumors related to Gorlin’s syndrome (e.g., medulloblastoma, meningioma, etc.), and liver cancer. Additional exemplary forms of cancer which may be treated by the subject compounds include, but are not limited to, cancer of skeletal or smooth muscle, stomach cancer, cancer of the small intestine, rectum carcinoma, cancer of the salivary gland, endometrial cancer, adrenal cancer, anal cancer, rectal cancer, parathyroid cancer, and pituitary cancer.

Additional cancers that the compounds described herein may be useful in preventing, treating and studying are, for example, colon carcinoma, familiary adenomatous polyposis carcinoma and hereditary non-polyposis colorectal cancer, or melanoma. Further, cancers include, but are not limited to, labial carcinoma, larynx carcinoma, hypopharynx carcinoma, tongue carcinoma, salivary gland carcinoma, gastric carcinoma, adenocarcinoma, thyroid cancer (medullary and papillary thyroid carcinoma), renal carcinoma, kidney parenchyma carcinoma, cervix carcinoma, uterine corpus carcinoma, endometrium carcinoma, chorion carcinoma, testis carcinoma, urinary carcinoma, melanoma, brain tumors such as glioblastoma, astrocytoma, meningioma, medulloblastoma and peripheral neuroectodermal tumors, gall bladder carcinoma, bronchial carcinoma, multiple myeloma, basalioma, teratoma, retinoblastoma, choroidea melanoma, seminoma, rhabdomyosarcoma, craniopharyngeoma, osteosarcoma, chondrosarcoma, myosarcoma, liposarcoma, fibrosarcoma, Ewing sarcoma, and plasmocytoma. In one aspect of the invention, the present invention provides for the use of one or more
compounds of the invention in the manufacture of a medicament for the treatment of cancer.

In one embodiment, the present invention includes the use of one or more compounds of the invention in the manufacture of a medicament that prevents further aberrant proliferation, differentiation, or survival of cells. For example, compounds of the invention may be useful in preventing tumors from increasing in size or from reaching a metastatic state. The subject compounds may be administered to halt the progression or advancement of cancer or to induce tumor apoptosis or to inhibit tumor angiogenesis. In addition, the instant invention includes use of the subject compounds to prevent a recurrence of cancer.

This invention further embraces the treatment or prevention of cell proliferative disorders such as hyperplasias, dysplasias and pre-cancerous lesions. Dysplasia is the earliest form of pre-cancerous lesion recognizable in a biopsy by a pathologist. The subject compounds may be administered for the purpose of preventing said hyperplasias, dysplasias or pre-cancerous lesions from continuing to expand or from becoming cancerous. Examples of pre-cancerous lesions may occur in skin, esophageal tissue, breast and cervical intra-epithelial tissue.

"Combination therapy" includes the administration of the subject compounds in further combination with other biologically active ingredients (such as, but not limited to, a second and different antineoplastic agent) and non-drug therapies (such as, but not limited to, surgery or radiation treatment). For instance, the compounds of the invention can be used in combination with other pharmacologically active compounds, preferably compounds that are able to enhance the effect of the compounds of the invention. The compounds of the invention can be administered simultaneously (as a single preparation or separate preparation) or sequentially to the other drug therapy. In general, a combination therapy envisions administration of two or more drugs during a single cycle or course of therapy.

In one aspect of the invention, the subject compounds may be administered in combination with one or more separate agents that modulate protein kinases involved in various disease states. Examples of such kinases may include, but are not limited to: serine/threonine specific kinases, receptor tyrosine specific kinases and non-receptor tyrosine specific kinases. Serine/threonine kinases include mitogen activated protein kinases (MAPK), meiosis specific kinase (MEK), RAF and aurora kinase. Examples of receptor kinase families include epidermal growth
factor receptor (EGFR) (e.g. HER2/neu, HER3, HER4, ErbB, ErbB2, ErbB3, ErbB4, Xmrk, DER, Let23); fibroblast growth factor (FGF) receptor (e.g. FGF-R1,GFF-R2/BEK/CEK3, FGF-R3/CEK2, FGF-R4/TKF, KGF-R); hepatocyte growth/scatter receptor factor receptor (HGF-R) (e.g. MET, RON, SEA, SEX); insulin receptor (e.g. IGFI-R); Eph (e.g. CEK5, CEK8, EBK, ECK, EHK-I, EHK-2, ELK, EPB, ERK, HEG, MDK2, MDK5, SEK); AxI (e.g. Mer/Nyk, Rse); RET; and platelet-derived growth factor receptor (PDGFR) (e.g. PDGFα-R, PDGFβ-R, CSF-R/FMS, SCF-R/C-KIT, VEGF-R/FLT, NEK/FLK1, FLT3/FLK2/STK-1). Non-receptor tyrosine kinase families include, but are not limited to, BCR-ABL (e.g. p43abl, ARG); BTK (e.g. ITK/EMT, TEC); CSK, FAK, FPS, JAK, SRC, BMX, FER, CDK and SYK.

In another aspect of the invention, the subject compounds may be administered in combination with one or more separate agents that modulate non-kinase biological targets or processes. Such targets include histone deacetylases (HDAC), DNA methyltransferase (DNMT), heat shock proteins (e.g. Bcl-2), and proteasomes.

In a preferred embodiment, subject compounds may be combined with antineoplastic agents (e.g. small molecules, monoclonal antibodies, antisense RNA, and fusion proteins) that inhibit one or more biological targets such as Zolinza, Tarceva, Iressa, Tykerb, Gleevec, Sprycel, Nexavar, Sorafinib, CNF2024, RG108, BMS387032, Affinitak, Avastin, Herceptin, Erbitux, AG24322, PD325901, ZD6474, PD184322, Obatodax, ABT737 and AEE788. Such combinations may enhance therapeutic efficacy over efficacy achieved by any of the agents alone and may prevent or delay the appearance of resistant mutational variants.

In certain preferred embodiments, the compounds of the invention are administered in combination with a chemotherapeutic agent. Chemotherapeutic agents encompass a wide range of therapeutic treatments in the field of oncology. These agents are administered at various stages of the disease for the purposes of shrinking tumors, destroying remaining cancer cells left over after surgery, inducing remission, maintaining remission and/or alleviating symptoms relating to the cancer or its treatment. Examples of such agents include, but are not limited to, alkylating agents such as mustard gas derivatives (Mechloretamine, cyclophosphamide, chlorambucil, melphalan, ifosfamide), ethylenimines (thiotepa, hexamethylmelamine), Alkylsulfonates (Busulfan), Hydrazines and Triazines...
(Altretamine, Procarbazine, Dacarbazine and Temozolomide), Nitrosoureas (Carmustine, Lomustine and Streptozocin), Ifosfamide and metal salts (Carboplatin, Cisplatin, and Oxaliplatin); plant alkaloids such as Podophyllotoxins (Etoposide and Teniposide), Taxanes (Paclitaxel and Docetaxel), Vinca alkaloids (Vincristine, Vinblastine, Vindesine and Vinorelbine), and Camptothecan analogs (Irinotecan and Topotecan); anti-tumor antibiotics such as Chromomycins (Dactinomycin and Plicamycin), Anthracyclines (Doxorubicin, Daunorubicin, Epirubicin, Mitoxantrone, Valrubicin and Idarubicin), and miscellaneous antibiotics such as Mitomycin, Actinomycin and Bleomycin; anti-metabolites such as folic acid antagonists (Methotrexate, Pemetrexed, Raltitrexed, Aminopterin), pyrimidine antagonists (5-Fluorouracil, Floxuridine, Cytarabine, Capecitabine, and Gemcitabine), purine antagonists (6-Mercaptopurine and 6-Thioguanine) and adenosine deaminase inhibitors (Cladribine, Fludarabine, Mercaptopurine, Clofarabine, Thioguanine, Nelarabine and Pentostatin); topoisomerase inhibitors such as topoisomerase I inhibitors (Irinotecan, topotecan) and topoisomerase II inhibitors (Amsacrine, etoposide, etoposide phosphate, teniposide); monoclonal antibodies (Alemtuzumab, Gemtuzumab ozogamicin, Rituximab, Trastuzumab, Ibritumomab Tioxtetan, Cetuximab, Panitumumab, Tositumomab, Bevacizumab); and miscellaneous anti-neoplastics such as ribonucleotide reductase inhibitors (Hydroxyurea);
adrenocortical steroid inhibitor (Mitotane); enzymes (Asparaginase and Pegaspargase); anti-microtubule agents (Estramustine); and retinoids (Bexarotene, Isotretinoin, Tretinoin (ATRA).

In certain preferred embodiments, the compounds of the invention are administered in combination with a chemoprotective agent. Chemoprotective agents act to protect the body or minimize the side effects of chemotherapy. Examples of such agents include, but are not limited to, amfostine, mesna, and dextrazoxane.

In one aspect of the invention, the subject compounds are administered in combination with radiation therapy. Radiation is commonly delivered internally (implantation of radioactive material near cancer site) or externally from a machine that employs photon (x-ray or gamma-ray) or particle radiation. Where the combination therapy further comprises radiation treatment, the radiation treatment may be conducted at any suitable time so long as a beneficial effect from the co-action of the combination of the therapeutic agents and radiation treatment is achieved. For example, in appropriate cases, the beneficial effect is still achieved
when the radiation treatment is temporally removed from the administration of the therapeutic agents, perhaps by days or even weeks.

It will be appreciated that compounds of the invention can be used in combination with an immunotherapeutic agent. One form of immunotherapy is the generation of an active systemic tumor-specific immune response of host origin by administering a vaccine composition at a site distant from the tumor. Various types of vaccines have been proposed, including isolated tumor-antigen vaccines and anti-idiotypic vaccines. Another approach is to use tumor cells from the subject to be treated, or a derivative of such cells (reviewed by Schirrmacher et al. (1995) J. Cancer Res. Clin. Oncol. 121:487). In U.S. Pat. No. 5,484,596, Hanna Jr. et al. claims a method for treating a resectable carcinoma to prevent recurrence or metastases, comprising surgically removing the tumor, dispersing the cells with collagenase, irradiating the cells, and vaccinating the patient with at least three consecutive doses of about $10^7$ cells.

It will be appreciated that the compounds of the invention may advantageously be used in conjunction with one or more adjunctive therapeutic agents. Examples of suitable agents for adjunctive therapy include a 5HTi agonist, such as a triptan (e.g. sumatriptan or naratriptan); an adenosine A1 agonist; an EP ligand; an NMDA modulator, such as a glycine antagonist; a sodium channel blocker (e.g. lamotrigine); a substance P antagonist (e.g. an NKi antagonist); a cannabinoid; acetaminophen or phenacetin; a 5-lipoxygenase inhibitor; a leukotriene receptor antagonist; a DMARD (e.g. methotrexate); gabapentin and related compounds; a tricyclic antidepressant (e.g. amitriptylline); a neurone stabilizing antiepileptic drug; a mono-aminergic uptake inhibitor (e.g. venlafaxine); a matrix metalloproteinase inhibitor; a nitric oxide synthase (NOS) inhibitor, such as an iNOS or an nNOS inhibitor; an inhibitor of the release, or action, of tumour necrosis factor α; an antibody therapy, such as a monoclonal antibody therapy; an antiviral agent, such as a nucleoside inhibitor (e.g. lamivudine) or an immune system modulator (e.g. interferon); an opioid analgesic; a local anaesthetic; a stimulant, including caffeine; an H₂- antagonist (e.g. ranitidine); a proton pump inhibitor (e.g. omeprazole); an antacid (e.g. aluminium or magnesium hydroxide; an antiflatulent (e.g. simethicone); a decongestant (e.g. phenylephrine, phenylpropanolamine, pseudoephedrine, oxymetazoline, epinephrine, naphazoline, xylometazoline, propylhexedrine, or levo-desoxyephedrine); an antitussive (e.g. codeine,
hydrocodone, carmiphen, carbetapentane, or dextromethorphan); a diuretic; or a sedating or non-sedating antihistamine.

In one embodiment, compounds of the invention can be used to induce or inhibit apoptosis, a physiological cell death process critical for normal development and homeostasis. Alterations of apoptotic pathways contribute to the pathogenesis of a variety of human diseases. Compounds of the invention, as modulators of apoptosis, will be useful in the treatment of a variety of human diseases with aberrations in apoptosis including cancer (particularly, but not limited to, follicular lymphomas, carcinomas with p53 mutations, hormone dependent tumors of the breast, prostate and ovary, and precancerous lesions such as familial adenomatous polyposis), viral infections (including, but not limited to, herpes virus, poxvirus, Epstein-Barr virus, Sindbis virus and adenovirus), autoimmune diseases (including, but not limited to, systemic lupus, erythematosus, immune mediated glomerulonephritis, rheumatoid arthritis, psoriasis, inflammatory bowel diseases, and autoimmune diabetes mellitus), neurodegenerative disorders (including, but not limited to, Alzheimer's disease, AIDS-related dementia, Parkinson's disease, amyotrophic lateral sclerosis, retinitis pigmentosa, spinal muscular atrophy and cerebellar degeneration), AIDS, myelodysplastic syndromes, aplastic anemia, ischemic injury associated myocardial infarctions, stroke and reperfusion injury, arrhythmia, atherosclerosis, toxin-induced or alcohol induced liver diseases, hematological diseases (including, but not limited to, chronic anemia and aplastic anemia), degenerative diseases of the musculoskeletal system (including, but not limited to, osteoporosis and arthritis), aspirin-sensitive rhinosinusitis, cystic fibrosis, multiple sclerosis, kidney diseases, and cancer pain.

In one aspect, the invention provides the use of compounds of the invention for the treatment and/or prevention of immune response or immune-mediated responses and diseases, such as the prevention or treatment of rejection following transplantation of synthetic or organic grafting materials, cells, organs or tissue to replace all or part of the function of tissues, such as heart, kidney, liver, bone marrow, skin, cornea, vessels, lung, pancreas, intestine, limb, muscle, nerve tissue, duodenum, small-bowel, pancreatic-islet-cell, including xeno-transplants, etc.; to treat or prevent graft-versus-host disease, autoimmune diseases, such as rheumatoid arthritis, systemic lupus erythematosus, thyroiditis, Hashimoto's thyroiditis, multiple sclerosis, myasthenia gravis, type I diabetes uveitis, juvenile-onset or recent-onset
diabetes mellitus, uveitis, Graves disease, psoriasis, atopic dermatitis, Crohn's
disease, ulcerative colitis, vasculitis, auto-antibody mediated diseases, aplastic
anemia, Evan's syndrome, autoimmune hemolytic anemia, and the like; and further
to treat infectious diseases causing aberrant immune response and/or activation, such
as traumatic or pathogen induced immune disregulation, including for example, that
which are caused by hepatitis B and C infections, HIV, staphylococcus aureus
infection, viral encephalitis, sepsis, parasitic diseases wherein damage is induced by
an inflammatory response (e.g., leprosy); and to prevent or treat circulatory diseases,
such as arteriosclerosis, atherosclerosis, vasculitis, polyarteritis nodosa and
myocarditis. In addition, the present invention may be used to prevent-suppress an
immune response associated with a gene therapy treatment, such as the introduction
of foreign genes into autologous cells and expression of the encoded product. Thus
in one embodiment, the invention relates to a method of treating an immune
response disease or disorder or an immune-mediated response or disorder in a
subject in need of treatment comprising administering to said subject a
therapeutically effective amount of a compound of the invention.

In one aspect, the invention provides the use of compounds of the invention
in the treatment of a variety of neurodegenerative diseases, a non-exhaustive list of
which includes: I. Disorders characterized by progressive dementia in the absence of
other prominent neurologic signs, such as Alzheimer's disease; Senile dementia of
the Alzheimer type; and Pick's disease (lobar atrophy); II. Syndromes combining
progressive dementia with other prominent neurologic abnormalities such as A)
syndromes appearing mainly in adults (e.g., Huntington's disease, Multiple system
atrophy combining dementia with ataxia and/or manifestations of Parkinson's
disease, Progressive supranuclear palsy (Steel-Richardson-Olszewski), diffuse Lewy
body disease, and corticodentatonigral degeneration); and B) syndromes appearing
mainly in children or young adults (e.g., Hallervorden-Spatz disease and progressive
familial myoclonic epilepsy); III. Syndromes of gradually developing abnormalities
of posture and movement such as paralysis agitans (Parkinson's disease),
striatonigral degeneration, progressive supranuclear palsy, torsion dystonia (torsion
spasm; dystonia musculorum deformans), spasmodic torticollis and other dyskinesia,
familial tremor, and Gilles de la Tourette syndrome; IV. Syndromes of progressive
ataxia such as cerebellar degenerations (e.g., cerebellar cortical degeneration and
olivopontocerebellar atrophy (OPCA)); and spinocerebellar degeneration
(Friedreich's ataxia and related disorders); V. Syndrome of central autonomic nervous system failure (Shy-Drager syndrome); VI. Syndromes of muscular weakness and wasting without sensory changes (motorneuron disease such as amyotrophic lateral sclerosis, spinal muscular atrophy (e.g., infantile spinal muscular atrophy (Werdnig-Hoffman), juvenile spinal muscular atrophy (Wohlfart-Kugelberg-Welander) and other forms of familial spinal muscular atrophy)), primary lateral sclerosis, and hereditary spastic paraplegia; VII. Syndromes combining muscular weakness and wasting with sensory changes (progressive neural muscular atrophy; chronic familial polyneuropathies) such as peroneal muscular atrophy (Charcot-Marie-Tooth), hypertrophic interstitial polyneuropathy (Dejerine-Sottas), and miscellaneous forms of chronic progressive neuropathy; VIII. Syndromes of progressive visual loss such as pigmentary degeneration of the retina (retinitis pigmentosa), and hereditary optic atrophy (Leber's disease). Furthermore, compounds of the invention can be implicated in chromatin remodeling.

The invention encompasses pharmaceutical compositions comprising pharmaceutically acceptable salts of the compounds of the invention as described above. The invention also encompasses pharmaceutical compositions comprising hydrates of the compounds of the invention. The term "hydrate" includes but is not limited to hemihydrate, monohydrate, dihydrate, trihydrate and the like. The invention further encompasses pharmaceutical compositions comprising any solid or liquid physical form of the compound of the invention. For example, the compounds can be in a crystalline form, in amorphous form, and have any particle size. The particles may be micronized, or may be agglomerated, particulate granules, powders, oils, oily suspensions or any other form of solid or liquid physical form.

The compounds of the invention, and derivatives, fragments, analogs, homologs, pharmaceutically acceptable salts or hydrate thereof can be incorporated into pharmaceutical compositions suitable for administration, together with a pharmaceutically acceptable carrier or excipient. Such compositions typically comprise a therapeutically effective amount of any of the compounds above, and a pharmaceutically acceptable carrier. Preferably, the effective amount when treating cancer is an amount effective to selectively induce terminal differentiation of suitable neoplastic cells and less than an amount which causes toxicity in a patient.
Compounds of the invention may be administered by any suitable means, including, without limitation, parenteral, intravenous, intramuscular, subcutaneous, implantation, oral, sublingual, buccal, nasal, pulmonary, transdermal, topical, vaginal, rectal, and transmucosal administrations or the like. Topical administration can also involve the use of transdermal administration such as transdermal patches or iontophoresis devices. Pharmaceutical preparations include a solid, semisolid or liquid preparation (tablet, pellet, troche, capsule, suppository, cream, ointment, aerosol, powder, liquid, emulsion, suspension, syrup, injection etc.) containing a compound of the invention as an active ingredient, which is suitable for selected mode of administration. In one embodiment, the pharmaceutical compositions are administered orally, and are thus formulated in a form suitable for oral administration, i.e., as a solid or a liquid preparation. Suitable solid oral formulations include tablets, capsules, pills, granules, pellets, sachets and effervescent, powders, and the like. Suitable liquid oral formulations include solutions, suspensions, dispersions, emulsions, oils and the like. In one embodiment of the present invention, the composition is formulated in a capsule. In accordance with this embodiment, the compositions of the present invention comprise in addition to the active compound and the inert carrier or diluent, a hard gelatin capsule.

Any inert excipient that is commonly used as a carrier or diluent may be used in the formulations of the present invention, such as for example, a gum, a starch, a sugar, a cellulosic material, an acrylate, or mixtures thereof. A preferred diluent is microcrystalline cellulose. The compositions may further comprise a disintegrating agent (e.g., croscarmellose sodium) and a lubricant (e.g., magnesium stearate), and may additionally comprise one or more additives selected from a binder, a buffer, a protease inhibitor, a surfactant, a solubilizing agent, a plasticizer, an emulsifier, a stabilizing agent, a viscosity increasing agent, a sweetener, a film forming agent, or any combination thereof. Furthermore, the compositions of the present invention may be in the form of controlled release or immediate release formulations.

For liquid formulations, pharmaceutically acceptable carriers may be aqueous or non-aqueous solutions, suspensions, emulsions or oils. Examples of non-aqueous solvents are propylene glycol, polyethylene glycol, and injectable organic esters such as ethyl oleate. Aqueous carriers include water, alcoholic/aqueous solutions, emulsions or suspensions, including saline and buffered
media. Examples of oils are those of petroleum, animal, vegetable, or synthetic origin, for example, peanut oil, soybean oil, mineral oil, olive oil, sunflower oil, and fish-liver oil. Solutions or suspensions can also include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid (EDTA); buffers such as acetates, citrates or phosphates, and agents for the adjustment of tonicity such as sodium chloride or dextrose. The pH can be adjusted with acids or bases, such as hydrochloric acid or sodium hydroxide.

In addition, the compositions may further comprise binders (e.g., acacia, cornstarch, gelatin, carboxmer, ethyl cellulose, guar gum, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, povidone), disintegrating agents (e.g., cornstarch, potato starch, alginic acid, silicon dioxide, croscarmellose sodium, crospovidone, guar gum, sodium starch glycolate, Primogel), buffers (e.g., tris-HCL, acetate, phosphate) of various pH and ionic strength, additives such as albumin or gelatin to prevent absorption to surfaces, detergents (e.g., Tween 20, Tween 80, Pluronic F68, bile acid salts), protease inhibitors, surfactants (e.g., sodium lauryl sulfate), permeation enhancers, solubilizing agents (e.g., glycerol, polyethylene glycerol, cyclodextrins), a glidant (e.g., colloidal silicon dioxide), anti-oxidants (e.g., ascorbic acid, sodium metabisulfite, butylated hydroxyanisole), stabilizers (e.g., hydroxypropyl cellulose, hydroxypropylmethyl cellulose), viscosity increasing agents (e.g., carboxmer, colloidal silicon dioxide, ethyl cellulose, guar gum), sweeteners (e.g., sucrose, aspartame, citric acid), flavoring agents (e.g., peppermint, methyl salicylate, or orange flavoring), preservatives (e.g., Thimerosal, benzyl alcohol, parabens), lubricants (e.g., stearic acid, magnesium stearate, polyethylene glycol, sodium lauryl sulfate), flow-aids (e.g., colloidal silicon dioxide), plasticizers (e.g., diethyl phthalate, triethyl citrate), emulsifiers (e.g., carboxmer, hydroxypropyl cellulose, sodium lauryl sulfate), polymer coatings (e.g., poloxamers or poloxamines), coating and film forming agents (e.g., ethyl cellulose, acrylates, polymethacrylates) and/or adjuvants.

In one embodiment, the active compounds are prepared with carriers that will protect the compound against rapid elimination from the body, such as a controlled release formulation, including implants and microencapsulated delivery.
systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Methods for preparation of such formulations will be apparent to those skilled in the art. The materials can also be obtained commercially from Alza Corporation and Nova Pharmaceuticals, Inc. Liposomal suspensions (including liposomes targeted to infected cells with monoclonal antibodies to viral antigens) can also be used as pharmaceutically acceptable carriers. These can be prepared according to methods known to those skilled in the art, for example, as described in U.S. Pat No. 4,522,811.

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

The pharmaceutical compositions can be included in a container, pack, or dispenser together with instructions for administration.

Daily administration may be repeated continuously for a period of several days to several years. Oral treatment may continue for between one week and the life of the patient. Preferably the administration may take place for five consecutive days after which time the patient can be evaluated to determine if further administration is required. The administration can be continuous or intermittent, e.g., treatment for a number of consecutive days followed by a rest period. The compounds of the present invention may be administered intravenously on the first day of treatment, with oral administration on the second day and all consecutive days thereafter.

The preparation of pharmaceutical compositions that contain an active component is well understood in the art, for example, by mixing, granulating, or tablet-forming processes. The active therapeutic ingredient is often mixed with excipients that are pharmaceutically acceptable and compatible with the active
ingredient. For oral administration, the active agents are mixed with additives customary for this purpose, such as vehicles, stabilizers, or inert diluents, and converted by customary methods into suitable forms for administration, such as tablets, coated tablets, hard or soft gelatin capsules, aqueous, alcoholic or oily solutions and the like as detailed above.

The amount of the compound administered to the patient is less than an amount that would cause toxicity in the patient. In certain embodiments, the amount of the compound that is administered to the patient is less than the amount that causes a concentration of the compound in the patient's plasma to equal or exceed the toxic level of the compound. Preferably, the concentration of the compound in the patient's plasma is maintained at about 10 nM. In one embodiment, the concentration of the compound in the patient's plasma is maintained at about 25 nM. In one embodiment, the concentration of the compound in the patient's plasma is maintained at about 50 nM. In one embodiment, the concentration of the compound in the patient's plasma is maintained at about 100 nM. In one embodiment, the concentration of the compound in the patient's plasma is maintained at about 500 nM. In one embodiment, the concentration of the compound in the patient's plasma is maintained at about 1000 nM. In one embodiment, the concentration of the compound in the patient's plasma is maintained at about 2500 nM. In one embodiment, the concentration of the compound in the patient's plasma is maintained at about 5000 nM. The optimal amount of the compound that should be administered to the patient in the practice of the present invention will depend on the particular compound used and the type of cancer being treated.

DEFINITIONS

Listed below are definitions of various terms used to describe this invention. These definitions apply to the terms as they are used throughout this specification and claims, unless otherwise limited in specific instances, either individually or as part of a larger group.

An "aliphatic group" or "aliphatic" is non-aromatic moiety that may be saturated (e.g. single bond) or contain one or more units of unsaturation, (e.g., double and/or triple bonds). An aliphatic group may be straight chained, branched or cyclic, contain carbon, hydrogen or, optionally, one or more heteroatoms and may be substituted or unsubstituted. An aliphatic group preferably contains between
about 1 and about 24 atoms, more preferably between about 4 to about 24 atoms, more preferably between about 4-12 atoms, more typically between about 4 and about 8 atoms.

The term "acyl" refers to hydrogen, alkyl, partially saturated or fully saturated cycloalkyl, partially saturated or fully saturated heterocycle, aryl, and heteroaryl substituted carbonyl groups. For example, acyl includes groups such as (C<sub>1</sub>-C<sub>6</sub>)alkanoyl (e.g., formyl, acetyl, propionyl, butyryl, valeryl, caproyl, t-buty lacetyl, etc.), (C<sub>3</sub>-C<sub>6</sub>)cycloalkylcarbonyl (e.g., cyclopropylcarbonyl, cyclobutylcarbonyl, cyclopentylcarbonyl, cyclohexylcarbonyl, etc.), heterocyclic carbonyl (e.g., pyrrolidinylcarbonyl, pyrrolid-2-one-5-carbonyl, piperidinylcarbonyl, piperazinylcarbonyl, tetrahydrofuranylcarbonyl, etc.), aroyl (e.g., benzoyl) and heteroaroyl (e.g., thiophenyl-2-carbonyl, thiophenyl-3-carbonyl, furanyl-2-carbonyl, furanyl-3-carbonyl, 1H-pyrrolyl-2-carbonyl, 1H-pyrrolyl-3-carbonyl, benzo[b]thiophenyl-2-carbonyl, etc.). In addition, the alkyl, cycloalkyl, heterocycle, aryl and heteroaryl portion of the acyl group may be any one of the groups described in the respective definitions. When indicated as being "optionally substituted", the acyl group may be unsubstituted or optionally substituted with one or more substituents (typically, one to three substituents) independently selected from the group of substituents listed below in the definition for "substituted" or the alkyl, cycloalkyl, heterocycle, aryl and heteroaryl portion of the acyl group may be substituted as described above in the preferred and more preferred list of substituents, respectively.

The term "alkyl" embraces linear or branched radicals having one to about twenty carbon atoms or, preferably, one to about twelve carbon atoms. More preferred alkyl radicals are "lower alkyl" radicals having one to about ten carbon atoms. Most preferred are lower alkyl radicals having one to about eight carbon atoms. Examples of such radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, iso-amyl, hexyl and the like.

The term "alkenyl" embraces linear or branched radicals having at least one carbon-carbon double bond of two to about twenty carbon atoms or, preferably, two to about twelve carbon atoms. More preferred alkenyl radicals are "lower alkenyl" radicals having two to about ten carbon atoms and more preferably about two to about eight carbon atoms. Examples of alkenyl radicals include ethenyl, allyl, propenyl, butenyl and 4-methylbutenyl. The terms "alkenyl", and "lower alkenyl",...
embrace radicals having "cis" and "trans" orientations, or alternatively, "E" and "Z" orientations.

The term "alkynyl" embraces linear or branched radicals having at least one carbon-carbon triple bond of two to about twenty carbon atoms or, preferably, two to about twelve carbon atoms. More preferred alkynyl radicals are "lower alkynyl" radicals having two to about ten carbon atoms and more preferably about two to about eight carbon atoms. Examples of alkynyl radicals include propargyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl and 1-pentynyl.

The term "cycloalkyl" embraces saturated carbocyclic radicals having three to about twelve carbon atoms. The term "cycloalkyl" embraces saturated carbocyclic radicals having three to about twelve carbon atoms. More preferred cycloalkyl radicals are "lower cycloalkyl" radicals having three to about eight carbon atoms. Examples of such radicals include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

The term "cycloalkenyl" embraces partially unsaturated carbocyclic radicals having three to twelve carbon atoms. Cycloalkenyl radicals that are partially unsaturated carbocyclic radicals that contain two double bonds (that may or may not be conjugated) can be called "cycloalkylidenyl". More preferred cycloalkenyl radicals are "lower cycloalkenyl" radicals having four to about eight carbon atoms. Examples of such radicals include cyclobutenyl, cyclopentenyl and cyclohexenyl.

The term "alkoxy" embraces linear or branched oxy-containing radicals each having alkyl portions of one to about twenty carbon atoms or, preferably, one to about twelve carbon atoms. More preferred alkoxy radicals are "lower alkoxy" radicals having one to about ten carbon atoms and more preferably having one to about eight carbon atoms. Examples of such radicals include methoxy, ethoxy, propoxy, butoxy and tert-butoxy.

The term "alkoxyalkyl" embraces alkyl radicals having one or more alkoxy radicals attached to the alkyl radical, that is, to form monoalkoxyalkyl and dialkoxyalkyl radicals.

The term "aryl", alone or in combination, means a carbocyclic aromatic system containing one, two or three rings wherein such rings may be attached together in a pendent manner or may be fused. The term "aryl" embraces aromatic radicals such as phenyl, naphthyl, tetrahydronaphthyl, indane and biphenyl.
The term "carbonyl", whether used alone or with other terms, such as "alkoxycarbonyl", denotes (C=O).

The term "carbanoyl", whether used alone or with other terms, such as "arylcarbanoylyalkyl", denotes C(O)NH.

The terms "heterocyclyl", "heterocycle" "heterocyclic" or "heterocyclo" embrace saturated, partially unsaturated and unsaturated heteroatom-containing ring-shaped radicals, which can also be called "heterocyclyl", "heterocycloalkenyl" and "heteroaryl" correspondingly, where the heteroatoms may be selected from nitrogen, sulfur and oxygen. Examples of saturated heterocyclyl radicals include saturated 3 to 6-membered heteromonocyclic group containing 1 to 4 nitrogen atoms (e.g., pyrrolidinyl, imidazolidinyl, piperidino, piperazinyl, etc.); saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms (e.g. morpholinyl, etc.); saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms (e.g., thiazolidinyl, etc.). Examples of partially unsaturated heterocyclyl radicals include dihydrothiophene, dihydrofuran, dihydrofuran and dihydrothiazole. Heterocyclyl radicals may include a pentavalent nitrogen, such as in tetrazolium and pyridinium radicals. The term "heterocycle" also embraces radicals where heterocyclyl radicals are fused with aryl or cycloalkyl radicals. Examples of such fused bicyclic radicals include benzofuran, benzothiophene, and the like.

The term "heteroaryl" embraces unsaturated heterocyclyl radicals. Examples of heteroaryl radicals include unsaturated 3 to 6 membered heteromonocyclic group containing 1 to 4 nitrogen atoms, for example, pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, triazolyl, 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, etc.) tetrazolyl (e.g. 1H-tetrazolyl, 2H-tetrazolyl, etc.), etc.; unsaturated condensed heterocyclyl group containing 1 to 5 nitrogen atoms, for example, indolyl, isoindolyl, indoliziny, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl, tetrazolopyridazinyl (e.g., tetrazolo[1,5-b]pyridazinyl, etc.), etc.; unsaturated 3 to 6-membered heteromonocyclic group containing an oxygen atom, for example, pyranyl, furyl, etc.; unsaturated 3 to 6-membered heteromonocyclic group containing a sulfur atom, for example, thieryl, etc.; unsaturated 3- to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, for example, oxazolyl, isoxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-
oxadiazolyl, etc.) etc.; unsaturated condensed heterocyclyl group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms (e.g. benzoaxazolyl, benzoxadiazolyl, etc.); unsaturated 3 to 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms, for example, thiazolyl, thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, etc.), etc.; unsaturated condensed heterocyclyl group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms (e.g., benzothiazolyl, benzothiadiazolyl, etc.) and the like.

The term "heterocycloalkyl" embraces heterocyclo-substituted alkyl radicals. More preferred heterocycloalkyl radicals are "lower heterocycloalkyl" radicals having one to six carbon atoms in the heterocyclo radicals.

The term "alkylthio" embraces radicals containing a linear or branched alkyl radical, of one to about ten carbon atoms attached to a divalent sulfur atom. Preferred alkylthio radicals have alkyl radicals of one to about twenty carbon atoms or, preferably, one to about twelve carbon atoms. More preferred alkylthio radicals have alkyl radicals are "lower alkylthio" radicals having one to about ten carbon atoms. Most preferred are alkylthio radicals having lower alkyl radicals of one to about eight carbon atoms. Examples of such lower alkylthio radicals are methylthio, ethylthio, propylthio, butylthio and hexythio.

The terms "aralkyl" or "arylalkyl" embrace aryl-substituted alkyl radicals such as benzyl, diphenylmethyl, triphenylmethyl, phenylethyl, and diphenylethyl.

The term "aryloxy" embraces aryl radicals attached through an oxygen atom to other radicals.

The terms "aralkoxy" or "arylalkoxy" embrace aralkyl radicals attached through an oxygen atom to other radicals.

The term "aminoalkyl" embraces alkyl radicals substituted with amino radicals. Preferred aminoalkyl radicals have alkyl radicals having about one to about twenty carbon atoms or, preferably, one to about twelve carbon atoms. More preferred aminoalkyl radicals are "lower aminoalkyl" that have alkyl radicals having one to about ten carbon atoms. Most preferred are aminoalkyl radicals having lower alkyl radicals having one to eight carbon atoms. Examples of such radicals include aminomethyl, aminopropyl, and the like.

The term "alkylamino" denotes amino groups which are substituted with one or two alkyl radicals. Preferred alkylamino radicals have alkyl radicals having about one to about twenty carbon atoms or, preferably, one to about twelve carbon atoms.
More preferred alkylamino radicals are "lower alkylamino" that have alkyl radicals having one to about ten carbon atoms. Most preferred are alkylamino radicals having lower alkyl radicals having one to about eight carbon atoms. Suitable lower alkylamino may be monosubstituted N-alkylamino or disubstituted N,N-alkylamino, such as N-methylamino, N-ethylamino, N,N-dimethylamino, N,N-diethylamino or the like.

The term "linker" means an organic moiety that connects two parts of a compound. Linkers typically comprise a direct bond or an atom such as oxygen or sulfur, a unit such as NR₈, C(O), C(O)NH, SO, SO₂, SO₂NH or a chain of atoms, such as substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, arylalkyl, arylalkenyl, arylalkynyl, heteroarylalkyl, heteroarylalkenyl, heterocyclylalkyl, heterocyclylalkenyl, heterocyclylalkynyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkylarylalkyl, alkylarylalkenyl, alkylarylalkynyl, alkenylarylalkyl, alkenylarylalkenyl, alkenylarylalkynyl, alkylheterocyclylalkyl, alkylheterocyclylalkenyl, alkylheterocyclylalkynyl, alkenylheterocyclylalkyl, alkenylheterocyclylalkenyl, alkenylheterocyclylalkynyl, alkynylheterocyclylalkyl, alkynylheterocyclylalkenyl, alkynylheterocyclylalkynyl, alkylheteroarylalkyl, alkylheteroarylalkenyl, alkylheteroarylalkynyl, arylheteroarylalkyl, arylheteroarylalkenyl, arylheteroarylalkynyl, alkylaryl, arylalkyl, arylalkenyl, arylalkynyl, arylheteroaryl, arylheterocyclyl, arylheteroarylalkyl, arylheteroarylalkenyl, arylheteroarylalkynyl, alkylaryl, arylalkyl, arylalkenyl, arylalkynyl, where one or more methylenes can be interrupted or terminated by O, S, S(O), SO₂, N(R₈), C(O), substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclic; where R₈ is hydrogen, acyl, aliphatic or substituted aliphatic. In one embodiment, the linker B is between 1-24 atoms, preferably 4-24 atoms, preferably 4-18 atoms, more preferably 4-12 atoms, and most preferably about 4-10 atoms.

The term "substituted" refers to the replacement of one or more hydrogen radicals in a given structure with the radical of a specified substituent including, but not limited to: halo, alkyl, alkenyl, aryl, heterocyclyl, thiol, alkylthio, arylthio, alkylthioalkyl, arylthioalkyl, alkylsulfonyl, alkylsulfonylethyl, arylsulfonylethyl, alkoxy, aryloxy, aralkoxy, aminocarbonyl, alkylaminocarbonyl,
arylaminocarbonyl, alkoxy carbonyl, arlyloxycarbonyl, halo alkyl, amino, trifluoromethyl, cyano, nitro, alkyl amino, aryl amino, alky lamino alkyl, aryl am ino alkyl, amino alkyl am ino, hydroxy, alkoxy alkyl, carboxy alkyl, alkoxy carbonyl alkyl, aminocarbonyl alkyl, acyl, aralkoxy carbonyl, carboxylic acid, sulfonic acid, sulfonyl, phosphonic acid, aryl, heteroaryl, heterocyclic, and aliphatic.

It is understood that the substituent may be further substituted.

For simplicity, chemical moieties are defined and referred to throughout can be univalent chemical moieties (e.g., alkyl, aryl, etc.) or multivalent moieties under the appropriate structural circumstances clear to those skilled in the art. For example, an "alkyl" moiety can be referred to a monovalent radical (e.g. CH3-CH2-), or in other instances, a bivalent linking moiety can be "alkyl," in which case those skilled in the art will understand the alkyl to be a divalent radical (e.g., -CH2-CH2-), which is equivalent to the term "alkylene." Similarly, in circumstances in which divalent moieties are required and are stated as being "alkoxy", "alkylamino", "aryloxy", "alkythio", "aryl", "heterocyclic", "alkyl", "alkenyl", "alkynyl", "aliphatic", or "cycloalkyl", those skilled in the art will understand that the terms alkoxy", "alkylamino", "aryloxy", "alkythio", "aryl", "heteroaryl", "heterocyclic", "alkyl", "alkenyl", "alkynyl", "aliphatic", or "cycloalkyl" refer to the corresponding divalent moiety.

The terms "halogen" or "halo" as used herein, refers to an atom selected from fluorine, chlorine, bromine and iodine.

As used herein, the term "aberrant proliferation" refers to abnormal cell growth.

The phrase "adjunctive therapy" encompasses treatment of a subject with agents that reduce or avoid side effects associated with the combination therapy of the present invention, including, but not limited to, those agents, for example, that reduce the toxic effect of anticancer drugs, e.g., bone resorption inhibitors, cardioprotective agents; prevent or reduce the incidence of nausea and vomiting associated with chemotherapy, radiotherapy or operation; or reduce the incidence of infection associated with the administration of myelosuppressive anticancer drugs.

The term "angiogenesis," as used herein, refers to the formation of blood vessels. Specifically, angiogenesis is a multi-step process in which endothelial cells focally degrade and invade through their own basement membrane, migrate through interstitial stroma toward an angiogenic stimulus, proliferate proximal to the
migrating tip, organize into blood vessels, and reattach to newly synthesized
basement membrane (see Folkman et al., Adv. Cancer Res., Vol. 43, pp. 175-203
(1985)). Anti-angiogenic agents interfere with this process. Examples of agents that
interfere with several of these steps include thrombospordin-1, angiostatin,
endostatin, interferon alpha, and compounds such as matrix metalloproteinase
(MMP) inhibitors that block the actions of enzymes that clear and create paths for
newly forming blood vessels to follow; compounds, such as .alpha.v.beta.3
inhibitors, that interfere with molecules that blood vessel cells use to bridge between
a parent blood vessel and a tumor; agents, such as specific COX-2 inhibitors, that
prevent the growth of cells that form new blood vessels; and protein-based
compounds that simultaneously interfere with several of these targets.

The term "apoptosis" as used herein refers to programmed cell death as
signaled by the nuclei in normally functioning human and animal cells when age or
state of cell health and condition dictates. An "apoptosis inducing agent" triggers
the process of programmed cell death.

The term "cancer" as used herein denotes a class of diseases or disorders
characterized by uncontrolled division of cells and the ability of these cells to invade
other tissues, either by direct growth into adjacent tissue through invasion or by
implantation into distant sites by metastasis.

The term "compound" is defined herein to include pharmaceutically
acceptable salts, solvates, hydrates, polymorphs, enantiomers, diastereoisomers,
racemates and the like of the compounds having a formula as set forth herein.

The term "devices" refers to any appliance, usually mechanical or electrical,
designed to perform a particular function.

As used herein, the term "dysplasia" refers to abnormal cell growth, and
typically refers to the earliest form of pre-cancerous lesion recognizable in a biopsy
by a pathologist.

The term "hyperplasia," as used herein, refers to excessive cell division or
growth.

The phrase an "immunotherapeutic agent" refers to agents used to transfer
the immunity of an immune donor, e.g., another person or an animal, to a host by
inoculation. The term embraces the use of serum or gamma globulin containing
performed antibodies produced by another individual or an animal; nonspecific
systemic stimulation; adjuvants; active specific immunotherapy; and adoptive
immunotherapy. Adoptive immunotherapy refers to the treatment of a disease by
therapy or agents that include host inoculation of sensitized lymphocytes, transfer
factor, immune RNA, or antibodies in serum or gamma globulin.

The term "inhibition," in the context of neoplasia, tumor growth or tumor
cell growth, may be assessed by delayed appearance of primary or secondary
tumors, slowed development of primary or secondary tumors, decreased occurrence
of primary or secondary tumors, slowed or decreased severity of secondary effects
of disease, arrested tumor growth and regression of tumors, among others. In the
extreme, complete inhibition, is referred to herein as prevention or
chemoprevention.

The term "metastasis," as used herein, refers to the migration of cancer cells
from the original tumor site through the blood and lymph vessels to produce cancers
in other tissues. Metastasis also is the term used for a secondary cancer growing at a
distant site.

The term "neoplasm," as used herein, refers to an abnormal mass of tissue
that results from excessive cell division. Neoplasms may be benign (not cancerous),
or malignant (cancerous) and may also be called a tumor. The term "neoplasia" is
the pathological process that results in tumor formation.

As used herein, the term "pre-cancerous" refers to a condition that is not
malignant, but is likely to become malignant if left untreated.

The term "proliferation" refers to cells undergoing mitosis.

The phrase a "radio therapeutic agent" refers to the use of electromagnetic or
particulate radiation in the treatment of neoplasia.

The term "recurrence" as used herein refers to the return of cancer after a
period of remission. This may be due to incomplete removal of cells from the initial
cancer and may occur locally (the same site of initial cancer), regionally (in vicinity
of initial cancer, possibly in the lymph nodes or tissue), and/or distally as a result of
metastasis.

The term "treatment" refers to any process, action, application, therapy, or
the like, wherein a mammal, including a human being, is subject to medical aid with
the object of improving the mammal's condition, directly or indirectly.

The term "vaccine" includes agents that induce the patient's immune system
to mount an immune response against the tumor by attacking cells that express
tumor associated antigens (Teas).
As used herein, the term "effective amount of the subject compounds," with respect to the subject method of treatment, refers to an amount of the subject compound which, when delivered as part of desired dose regimen, brings about, e.g. a change in the rate of cell proliferation and/or state of differentiation and/or rate of survival of a cell to clinically acceptable standards. This amount may further relieve to some extent one or more of the symptoms of a neoplasia disorder, including, but is not limited to: 1) reduction in the number of cancer cells; 2) reduction in tumor size; 3) inhibition (i.e., slowing to some extent, preferably stopping) of cancer cell infiltration into peripheral organs; 4) inhibition (i.e., slowing to some extent, preferably stopping) of tumor metastasis; 5) inhibition, to some extent, of tumor growth; 6) relieving or reducing to some extent one or more of the symptoms associated with the disorder; and/or 7) relieving or reducing the side effects associated with the administration of anticancer agents.

As used herein, the term "pharmaceutically acceptable salt" refers to those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, S. M. Berge, et al. describes pharmaceutically acceptable salts in detail in J. Pharmaceutical Sciences, 66: 1-19 (1977). The salts can be prepared in situ during the final isolation and purification of the compounds of the invention, or separately by reacting the free base function with a suitable organic acid or inorganic acid. Examples of pharmaceutically acceptable nontoxic acid addition salts include, but are not limited to, salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, maleic acid, tartaric acid, citric acid, succinic acid lactobionic acid or malonic acid or by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include, but are not limited to, adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanecarboxylic acid, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate,
methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p-toluene sulfonate, undecanoate, valerate salts, and the like. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, alkyl having from 1 to 6 carbon atoms, sulfonate and aryl sulfonate.

As used herein, the term "pharmaceutically acceptable ester" refers to esters which hydrolyze \textit{in vivo} and include those that break down readily in the human body to leave the parent compound or a salt thereof. Suitable ester groups include, for example, those derived from pharmaceutically acceptable aliphatic carboxylic acids, particularly alkanoic, alkenoic, cycloalkanoic and alkanedioic acids, in which each alkyl or alkenyl moiety advantageously has not more than 6 carbon atoms. Examples of particular esters include, but are not limited to, formates, acetates, propionates, butyrates, acrylates and ethylsuccinates.

The term "pharmaceutically acceptable prodrugs" as used herein refers to those prodrugs of the compounds of the present invention which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals with undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio, and effective for their intended use, as well as the zwitterionic forms, where possible, of the compounds of the present invention. "Prodrug", as used herein means a compound which is convertible \textit{in vivo} by metabolic means (e.g. by hydrolysis) to a compound of the invention. Various forms of prodrugs are known in the art, for example, as discussed in Bundgaard, (ed.), Design of Prodrugs, Elsevier (1985); Widder, et al. (ed.), Methods in Enzymology, vol. 4, Academic Press (1985); Krosggaard-Larsen, et al., (ed). "Design and Application of Prodrugs, Textbook of Drug Design and Development", Chapter 5, 113-191 (1991); Bundgaard, \textit{et al.}, Journal of Drug Deliver Reviews, 8:1-38(1992); Bundgaard, J. of Pharmaceutical Sciences, 77:285 et seq. (1988); Higuchi and Stella (eds.) Prodrugs as Novel Drug Delivery Systems, American Chemical Society (1975); and Bernard Testa & Joachim Mayer,

As used herein, "pharmaceutically acceptable carrier" is intended to include any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like, compatible with pharmaceutical administration, such as sterile pyrogen-free water. Suitable carriers are described in the most recent edition of Remington's Pharmaceutical Sciences, a standard reference text in the field, which is incorporated herein by reference. Preferred examples of such carriers or diluents include, but are not limited to, water, saline, finger's solutions, dextrose solution, and 5% human serum albumin.

Liposomes and non-aqueous vehicles such as fixed oils may also be used. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active compound, use thereof in the compositions is contemplated. Supplementary active compounds can also be incorporated into the compositions.

As used herein, the term "pre-cancerous" refers to a condition that is not malignant, but is likely to become malignant if left untreated.

The term "subject" as used herein refers to an animal. Preferably the animal is a mammal. More preferably the mammal is a human. A subject also refers to, for example, dogs, cats, horses, cows, pigs, guinea pigs, fish, birds and the like.

The compounds of this invention may be modified by appending appropriate functionalities to enhance selective biological properties. Such modifications are known in the art and may include those which increase biological penetration into a given biological system (e.g., blood, lymphatic system, central nervous system), increase oral availability, increase solubility to allow administration by injection, alter metabolism and alter rate of excretion.

The synthesized compounds can be separated from a reaction mixture and further purified by a method such as column chromatography, high pressure liquid chromatography, or recrystallization. As can be appreciated by the skilled artisan, further methods of synthesizing the compounds of the formulae herein will be evident to those of ordinary skill in the art. Additionally, the various synthetic steps may be performed in an alternate sequence or order to give the desired compounds. Synthetic chemistry transformations and protecting group methodologies (protection and deprotection) useful in synthesizing the compounds described herein are known

The compounds described herein contain one or more asymmetric centers and thus give rise to enantiomers, diastereomers, and other stereoisomeric forms that may be defined, in terms of absolute stereochemistry, as (R)- or (S)-, or as (D)- or (L)- for amino acids. The present invention is meant to include all such possible isomers, as well as their racemic and optically pure forms. Optical isomers may be prepared from their respective optically active precursors by the procedures described above, or by resolving the racemic mixtures. The resolution can be carried out in the presence of a resolving agent, by chromatography or by repeated crystallization or by some combination of these techniques which are known to those skilled in the art. Further details regarding resolutions can be found in Jacques, et al, Enantiomers, Racemates, and Resolutions (John Wiley & Sons, 1981). When the compounds described herein contain olefinic double bonds, other unsaturation, or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both E and Z geometric isomers and/or cis- and trans- isomers. Likewise, all tautomeric forms are also intended to be included. The configuration of any carbon-carbon double bond appearing herein is selected for convenience only and is not intended to designate a particular configuration unless the text so states; thus a carbon-carbon double bond or carbon-heteroatom double bond depicted arbitrarily herein as trans may be cis, trans, or a mixture of the two in any proportion.

Pharmaceutical Compositions

The pharmaceutical compositions of the present invention comprise a therapeutically effective amount of a compound of the present invention formulated together with one or more pharmaceutically acceptable carriers or excipients.

As used herein, the term "pharmaceutically acceptable carrier or excipient" means a non-toxic, inert solid, semi-solid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type. Some examples of materials which can serve as pharmaceutically acceptable carriers are sugars such as lactose, glucose...
and sucrose; cyclodextrins such as alpha- (α), beta- (β) and gamma- (γ) cyclodextrins; starches such as corn starch and potato starch; cellulose and its derivatives such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients such as cocoa butter and suppository waxes; oils such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; glycols such as propylene glycol; esters such as ethyl oleate and ethyl laurate; agar; buffering agents such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol, and phosphate buffer solutions, as well as other non-toxic compatible lubricants such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, releasing agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the composition, according to the judgment of the formulator.

The pharmaceutical compositions of this invention may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir, preferably by oral administration or administration by injection. The pharmaceutical compositions of this invention may contain any conventional non-toxic pharmaceutically-acceptable carriers, adjuvants or vehicles. In some cases, the pH of the formulation may be adjusted with pharmaceutically acceptable acids, bases or buffers to enhance the stability of the formulated compound or its delivery form. The term parenteral as used herein includes subcutaneous, intracutaneous, intravenous, intramuscular, intraarticular, intraarterial, intrasynovial, intrasternal, intrathecal, intralesional and intracranial injection or infusion techniques.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert
diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions, may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution, suspension or emulsion in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butane diol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, U.S.P. and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables.

The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium prior to use.

In order to prolong the effect of a drug, it is often desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution, which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle. Injectable depot forms are made by forming microencapsule matrices of the drug in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of drug to polymer and the nature of the particular polymer employed, the rate of drug release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the drug in liposomes or microemulsions that are compatible with body tissues.

Compositions for rectal or vaginal administration are preferably suppositories which can be prepared by mixing the compounds of this invention with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at ambient temperature but liquid at
body temperature and therefore melt in the rectum or vaginal cavity and release the active compound.

Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or: a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidinone, sucrose, and acacia, c) humectants such as glycerol, d) disintegrating agents such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, e) solution retarding agents such as paraffin, f) absorption accelerators such as quaternary ammonium compounds, g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite clay, and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents.

Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes.

Dosage forms for topical or transdermal administration of a compound of this invention include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants or patches. The active component is admixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives or buffers as may be required. Ophthalmic formulation, ear drops, eye ointments, powders and solutions are also contemplated as being within the scope of this invention.
The ointments, pastes, creams and gels may contain, in addition to an active compound of this invention, excipients such as animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures thereof.

Powders and sprays can contain, in addition to the compounds of this invention, excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and polyamide powder, or mixtures of these substances. Sprays can additionally contain customary propellants such as chlorofluorohydrocarbons.

Transdermal patches have the added advantage of providing controlled delivery of a compound to the body. Such dosage forms can be made by dissolving or dispensing the compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate can be controlled by either providing a rate controlling membrane or by dispersing the compound in a polymer matrix or gel.

For pulmonary delivery, a therapeutic composition of the invention is formulated and administered to the patient in solid or liquid particulate form by direct administration e.g., inhalation into the respiratory system. Solid or liquid particulate forms of the active compound prepared for practicing the present invention include particles of respirable size: that is, particles of a size sufficiently small to pass through the mouth and larynx upon inhalation and into the bronchi and alveoli of the lungs. Delivery of aerosolized therapeutics, particularly aerosolized antibiotics, is known in the art (see, for example U.S. Pat. No. 5,767,068 to VanDevanter et al., U.S. Pat. No. 5,508,269 to Smith et al., and WO 98/43650 by Montgomery, all of which are incorporated herein by reference). A discussion of pulmonary delivery of antibiotics is also found in U.S. Pat. No. 6,014,969, incorporated herein by reference.

By a "therapeutically effective amount" of a compound of the invention is meant an amount of the compound which confers a therapeutic effect on the treated subject, at a reasonable benefit/risk ratio applicable to any medical treatment.

The therapeutic effect may be objective (i.e., measurable by some test or marker) or subjective (i.e., subject gives an indication of or feels an effect). An effective amount of the compound described above may range from about 0.1 mg/Kg to about 500 mg/Kg, preferably from about 1 to about 50 mg/Kg. Effective doses will also vary depending on route of administration, as well as the possibility
of co-usage with other agents. It will be understood, however, that the total daily usage of the compounds and compositions of the present invention will be decided by the attending physician within the scope of sound medical judgment. The specific therapeutically effective dose level for any particular patient will depend upon a variety of factors including the disorder being treated and the severity of the disorder; the activity of the specific compound employed; the specific composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or contemporaneously with the specific compound employed; and like factors well known in the medical arts.

The total daily dose of the compounds of this invention administered to a human or other animal in single or in divided doses can be in amounts, for example, from 0.01 to 50 mg/kg body weight or more usually from 0.1 to 25 mg/kg body weight. Single dose compositions may contain such amounts or submultiples thereof to make up the daily dose. In general, treatment regimens according to the present invention comprise administration to a patient in need of such treatment from about 10 mg to about 1000 mg of the compound(s) of this invention per day in single or multiple doses.

The compounds of the formulae described herein can, for example, be administered by injection, intravenously, intraarterially, subdermally, intraperitoneally, intramuscularly, or subcutaneously; or orally, buccally, nasally, transmucosally, topically, in an ophthalmic preparation, or by inhalation, with a dosage ranging from about 0.1 to about 500 mg/kg of body weight, alternatively dosages between 1 mg and 1000 mg/dose, every 4 to 120 hours, or according to the requirements of the particular drug. The methods herein contemplate administration of an effective amount of compound or compound composition to achieve the desired or stated effect. Typically, the pharmaceutical compositions of this invention will be administered from about 1 to about 6 times per day or alternatively, as a continuous infusion. Such administration can be used as a chronic or acute therapy. The amount of active ingredient that may be combined with pharmaceutically excipients or carriers to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. A typical preparation will contain from about 5% to about 95% active compound (w/w).
Alternatively, such preparations may contain from about 20% to about 80% active compound.

Lower or higher doses than those recited above may be required. Specific dosage and treatment regimens for any particular patient will depend upon a variety of factors, including the activity of the specific compound employed, the age, body weight, general health status, sex, diet, time of administration, rate of excretion, drug combination, the severity and course of the disease, condition or symptoms, the patient's disposition to the disease, condition or symptoms, and the judgment of the treating physician.

Upon improvement of a patient's condition, a maintenance dose of a compound, composition or combination of this invention may be administered, if necessary. Subsequently, the dosage or frequency of administration, or both, may be reduced, as a function of the symptoms, to a level at which the improved condition is retained when the symptoms have been alleviated to the desired level. Patients may, however, require intermittent treatment on a long-term basis upon any recurrence of disease symptoms.

**Synthetic Methods**

The compounds of formulae I and II, or a pharmaceutically-acceptable salt thereof, may be prepared by any process known to be applicable to the preparation of chemically-related compounds. Suitable processes for making certain intermediates include, for example, those illustrated in PCT publication numbers WO 2005049593, WO 2005049594, US Publication nos. 2006/0258657 and 2006/0128706, which are herein incorporated by reference. Necessary starting materials may be obtained by standard procedures of organic chemistry. The preparation of such starting materials is described within the accompanying non-limiting Examples. Alternatively necessary starting materials are obtainable by analogous procedures to those illustrated which are within the ordinary skill of a chemist.

The compounds and processes of the present invention will be better understood in connection with the following representative synthetic schemes that illustrate the methods by which the compounds of the invention may be prepared, which are intended as an illustration only and not limiting of the scope of the invention.
Scheme 1

1: R=H
2: R=F

5: R=Me
6: R=COMe
4: R=COPh
7: R=H
Scheme 5

Scheme 6
EXAMPLES

The compounds and processes of the present invention will be better understood in connection with the following examples, which are intended as an illustration only and not limiting of the scope of the invention. Various changes and modifications to the disclosed embodiments will be apparent to those skilled in the art and such changes and modifications including, without limitation, those relating to the chemical structures, substituents, derivatives, formulations and/or methods of the invention may be made without departing from the spirit of the invention and the scope of the appended claims.

EXAMPLE 1: Preparation of (R)-4-(4-benzhydrylpiperazin-1-yl)-N-(4-(4-(dimethylamino)-1-(phenylthio)butan-2-ylamino)-3-nitrophenylsulfonyle)benzamide (Compound 1)

Step 1a: Ethyl 4-(piperazin-1-yl) benzoate (Compound 0101)

A mixture of piperazine (12.8 g, 0.15 mol), ethyl-4-fluorobenzoate (8.4 g, 0.05 mol), and K$_2$CO$_3$ (13.8 g, 0.1 mol) in DMSO (20 mL) was stirred at 120°C for 6 hours. The mixture was then diluted with ethyl acetate (200 ml), washed with water (200 ml×5). The combined extracts was dried and evaporated to obtain the title compound 0101 (10.3 g, 92%) as a white solid: LC-MS: 235 [M+I]$^+$; $^1$H NMR
(DMSO- $d_6$): $\delta$ 7.75 (d, 1H, $J = 9$ Hz), 6.93 (d, 1H, $J = 9$ Hz), 4.22 (q, 2H, $J = 6$ Hz), 3.20 (s, 1H), 2.80 (s, 1H), 2.30 (s, 1H), 1.28 (t, 3H, $J = 6$ Hz).

**Step 1b:** Ethyl 4-(4-benzhydrylpiperazin-1-yl)benzoate (Compound 0102)

A mixture of 0101 (0.345 g, 1.47 mmol), chlorodiphenylmethane (0.298 g, 1.47 mmol), and $K_2CO_3$ (0.20 g, 1.47 mmol) in CH$_3$CN (3 mL) was refluxed overnight. The mixture was then extracted with ethyl acetate (20 mL $\times$ 3). The combined organic layer was washed with water (20 mL $\times$ 2), dried and evaporated to obtain the title compound 0102 (0.372 g, 63%) as a pale yellow solid. The crude product was used for next step reaction without further purification: LC-MS: 401 [$M+1$]$^+$. 

**Step 1c:** 4-(4-Benzhydrylpiperazin-1-yl)benzoic acid (Compound 0104)

A mixture of compd. 0102 (0.372 g, 0.93 mmol), lithium hydroxide monohydrate (0.16 g, 3.7 mmol), dioxane (10 mL) and water (4 mL) was stirred overnight. The mixture was then acidified to pH = 6 with acetic acid, and filtered to obtain the title compound 0104 (0.306 g, 88%) as a white solid. LC-MS: 373 [$M+1$]$^+$. 1H NMR (DMSO- $d_6$) $\delta$ 7.70 (d, 2H, $J = 9$ Hz), 7.44 (d, 4H, $J = 9$ Hz), 7.30 (m, 4H), 7.12 (m, 2H), 6.84 (d, 2H, $J = 9$ Hz), 4.31 (s, 1H), 3.25 (brs, 4H), 2.42 (brs, 4H).

**Step 1d:** (R)-Benzy1 4-(dimethylamino)-4-oxo-1-(phenylthio)butan-2-ylcarbamate (Compound 0123)

(R)-Benzy1 5-oxo-tetrahydrofuran-3-ylcarbamate (24 g, 0.1 mol) was added to the solution ofMe$_2$NH (45 g, 1 mol) in CH$_2$Cl$_2$ (500 ml). The mixture was stirred overnight. The solid was collected by filtration. Toluene (500 mL) was added to dissolve the solid, followed by (PhS)$_2$ (32.7 g, 0.15 mol) and Bu$_3$P (40 g, 0.2 mol). The mixture was heated to 80°C and stirred for 18 h. The solvent was removed in vacuo. The residue was subjected to flash column chromatography on silica gel eluting with 50% EtOAc/petroleum ether to provide 0123 (13.4 g, 35.3%). LC-MS: 373 [$M+1$]$^+$. 1H NMR (CDCl$_3$): $\delta$ 2.46 (m, 1H), 2.82 (s, 3H), 2.84 (s, 3H), 2.88 (m, 1H), 3.20 (m, 1H), 3.33 (m, 1H), 4.13 (m, 1H), 5.07 (s, 2H), 6.30 (d, $J = 9.0$ Hz, 1H), 7.15 (m, 1H), 7.32 (m, 9H).

**Step 1e:** (R)-3-Amino-N,N-dimethyl-4-(phenylthio)butanamide (Compound 0124)

To a solution of 0123 (664 mg, 1.8 mmol) in 12 ml of HOAc was added HBr (432 mg, 40% water solution) at room temperature. The mixture was heated to 80°C and stirred for 2 hours. The mixture was adjusted to pH > 12 with KOH, extracted with EtOAc. The extracts were washed with water and dried. The solvents were
removed in vacuo to give 0124 (305 mg, 71.8%). The product was used in next step reaction without further purification.

**Step 1f**: (R)-N,N-Dimethyl-3-(2-nitro-4-sulfamoylphenylamino)-4-(phenylthio)butanamide (Compound 0125)

A solution of 0124 (424 mg, 1.8 mmol), 4-Fluoro-3-nitrobenzenesulfonamide (396 mg, 1.8 mmol), and DIPEA (232 mg, 1.8 mmol) in DMF (10 mL) was stirred for 4 hours. The mixture was poured into water and extracted with EtOAc (50 mL). The extracts were washed with water, dried (Na₂SO₄), concentrated. The residue was subjected to flash column chromatography on silica gel eluting with 5% MeOH/CH₂Cl₂ to provide 0125 (680 mg, 87.2%). LC-MS: 439 [M+1]+. 1H NMR (DMSO-d₆): δ 2.77 (s, 3H), 2.89 (s, 3H), 3.00 (m, 1H), 3.40 (d, J = 6.5 Hz, 2H), 4.40 (b, 1H), 7.06 (d, J = 10.0 Hz, 1H), 7.19 (m, 1H), 7.25 (m, 2H), 7.32 (m, 4H), 7.72 (m, 1H), 8.38 (d, J = 2.3 Hz, 1H), 8.75 (d, J = 10.0 Hz, 1H).

**Step 1g**: (R)-4-(4-(Dimethylamino)-1-(phenylthio)butan-2-ylamino)-3-nitrobenzenesulfonamide (Compound 0126)

A mixture of compound 0125 (6.7 g, 15 mmol) and 1M BH3 in THF (30 ml) was stirred for 16 hours. To the resulting mixture were added MeOH (8 mL) and concentrated HCl (3 ml) and the mixture was stirred at 80°C for 3 hours. The mixture was cooled to room temperature, adjusted to pH10 with 4M Na₂CO₃. To the mixture ethyl acetate (300 mL) was added. The separated organic layer was washed with water (70 mL), dried (MgSO4), filtered and concentrated. The residue was subjected to flash column chromatography on silica gel eluting with 20% MeOH/CH₂Cl₂ to provide 0126 (3.0 g, 46.3%). LC-MS: 425 [M+1]+. 1H NMR (CDCl₃): δ 1.86 (m, 1H), 2.04 (m, 1H), 2.21 (s, 6H), 2.30 (m, 1H), 2.50 (m, 1H), 3.13 (d, J = 5.7 Hz, 2H), 4.00 (m, 1H), 5.22 (br, 2H), 6.74 (d, J = 9.3 Hz, 1H), 7.23 (m, 3H), 7.34 (m, 2H), 7.72 (d, J = 9.3 Hz, 1H), 8.63 (s, 1H), 8.97 (d, J = 8.1 Hz, 1H).

**Step 1h**: (R)-4-(4-Benzhydrylpiperazin-1-yl)-N-(4-(4-(dimethylamino)-1-(phenylthio)butan-2-ylamino)-3-nitrophenylsulfonyl)benzamide (compound 1)

A mixture of compound 0104 (88 mg, 0.236 mmol), compound 0126 (100 mg, 0.236 mmol), EDCI (56 mg, 0.295 mmol), and DMAP (14 mg, 0.118 mmol) in dry dichloromethane (3 mL) was stirred at r.t. overnight. The solvent was removed to get the crude product. It was purified with column chromatography (silica gel, elution: 1:10 = methanol / dichloromethane) to obtain the title compound 1 (35 mg,
20%) as a yellow solid: LC-MS: 780 [M+1]⁺; ¹H NMR (DMSO-d₆) δ 8.43 (d, 1H, \( J = 1.8 \) Hz), 8.34 (d, 1H, \( J = 9 \) Hz), 7.75 (m, 1H), 7.70 (d, 2H, \( J = 9 \) Hz), 7.44 (d, 2H, \( J = 9 \) Hz), 7.24 (m, 12H), 6.82 (d, 1H, \( J = 9 \) Hz), 6.76 (d, 2H, \( J = 9 \) Hz), 4.30 (s, 1H), 4.02 (brs, 1H), 3.19 (m, 4H), 2.42 (brs, 6H), 2.24 (s, 6H), 1.85 (m, 2H).

**EXAMPLE 2:** Preparation (R)-4-(4-(bis(4-fluorophenyl)methyl)piperazin-1-yl)-N-(4-(4- (dimethylamino)-1-(phenylthio)butan-2-ylamino)-3-nitrophenylsulfon) benzamide (Compound 2)

**Step 2a:** Ethyl 4-(4-(bis(4-fluorophenyl)methyl)piperazin-1-yl)benzoate (Compound 0103)

A mixture of 0101 (0.39 g, 1.68 mmol), chlorobis-(4-fluorophenyl)methane (0.40 g, 1.68 mmol), \( K_2CO_3 \) (0.46 g, 3.36 mmol) in \( CH_3CN \) (10 mL) was refluxed overnight. The mixture was then extracted with ethyl acetate (20 mL×3). The combined organic layer was washed with water (20 mL×2), dried and evaporated to obtain the title compound 0103 (0.58 g, 79%) as a pale yellow solid. The crude product was used in next step reaction without further purification. LC-MS: 437 [M+1]⁺.

**Step 2b:** 4-(4-(Bis(4-fluorophenyl)methyl)piperazin-1-yl)benzoic acid (Compound 0105)

A mixture of 0103 (0.58 g, 1.33 mmol), lithium hydroxide monohydrate (0.28 g, 6.7 mmol) in dioxane (15 mL) and water (6 mL) was stirred overnight. The mixture was then acidified to pH 6 with acetic acid, and filtered to give the title compound 0105 (0.43 g, 80%) as a white solid. LC-MS: 409 [M+1]⁺. ¹H NMR (DMSO-d₆): δ 7.70 (d, 2H, \( J = 9 \) Hz), 7.44 (d, 4H, \( J = 9 \) Hz), 7.30 (m, 4H), 7.12 (m, 2H), 6.84 (d, 2H, \( J = 9 \) Hz), 4.31 (s, 1H), 3.25 (brs, 4H), 2.42 (brs, 4H).

**Step 2c:** (R)-4-(4-(Bis(4-fluorophenyl)methyl)piperazin-1-yl)-N-(4-(4- (dimethylamino)-1-(phenylthio)butan-2-ylamino)-3-nitrophenylsulfon) benzamide (Compound 2)

A mixture of compd. 0105 (96 mg, 0.236 mmol), 0126 (100 mg, 0.236 mmol), EDCI (56 mg, 0.295 mmol), and DMAP(14 mg, 0.118 mmol) in dry dichloromethane (3 mL) was stirred at r.t. overnight. The solvent was removed to get the crude product. It was purified with column chromatography on silica gel eluting with methanol / dichloromethane=1/10 to obtain the title compound 2 (38 mg, 20%) as a yellow solid: LC-MS: 816 [M+1]⁺. ¹H NMR (DMSO-d₆): δ 8.42 (d,
1H, J = 2.4 Hz), 8.34 (d, 1H, J = 8.1 Hz), 7.75 (m, 1H), 7.70 (d, 2H, J = 9 Hz), 7.45 (m, 4H), 7.30 (m, 2H), 7.23 (m, 2H), 7.12 (m, 5H), 6.84 (d, 1H, J = 9 Hz), 6.76 (d, 2H, J = 9 Hz), 4.39 (s, 1H), 4.05 (brs, 1H), 3.16 (m, 4H), 2.39 (brs, 6H), 2.33 (s, 6H), 1.90 (m, 2H).

EXAMPLE 3: Preparation of (R)-2-bromo-N-(1-(4-(4-(dimethylamino)-1-(phenylthio)butan-2-ylamino)-3-nitrophenylsulfonylcarbamoyl)phenyl)piperidin-4-yl)benzamide (Compound 3)

**Step 3a:** Tert-butyl 4-(2-bromobenzamido)piperidine-1-carboxylate (Compound 0106)

A mixture of tert-butyl 4-aminopiperidine-1-carboxylate (0.30 g, 1.5 mmol), 2-bromobenzoic acid (0.30 g, 1.5 mmol), HOBt (0.3 g, 2.25 mmol) and EDCI (0.44 g, 2.25 mmol) in CH₂Cl₂ (5 mL) was stirred at room temperature for 10 hours. The solvent was then removed and the residue was purified by column chromatography on silica gel eluting with petroleum ether/ethyl acetate=1/5 to obtain the title compound 0106 (0.37 g, 65%) as a white solid. LC-MS: 405 [M+23]+. ¹H NMR (CDCl₃): δ 4.51 (m, 2H), 7.37 (m, 2H), 5.87 (ds, 1H), 4.09 (m, 3H), 2.95 (m, 2H), 2.07 (m, 2H), 1.58 (m, 2H), 1.46 (s, 9H).

**Step 3b:** 2-Bromo-N-(piperidin-4-yl)benzamide (Compound 0107)

A solution of 0106 (0.66 g, 1.72 mmol), TFA (3 mL) in CH₂Cl₂ (5 mL) was stirred for 2 hours. To the solution water was added and adjusted pH to 6-7. The mixture was extracted with ethyl acetate (20 mL×3). The combined organic layer was washed with water (20 mL×2), dried and evaporated to obtain the title compound 0107 (0.28 g, 57%) as a pale yellow solid. LC-MS: 284 [M+1]+. ¹H NMR (DMSO-d₆): δ 8.38 (m, 1H), 7.63 (m, 1H), 7.37 (m, 3H), 3.80 (ds, 1H), 2.99 (m, 2H), 2.58 (m, 2H), 1.79 (m, 2H), 1.40 (m, 2H).

**Step 3c:** Ethyl 4-(4-(2-bromobenzamido)piperidin-1-yl)benzoate (Compound 0108)

A mixture of 0107 (0.18 g, 0.64 mmol), ethyl 4-fluorobenzoate (0.11 g, 0.64 mmol) and K₂CO₃ (0.18 g, 1.3 mmol) in DMSO (8 mL) was stirred at 120°C for 6 hours. The mixture was poured into water, then was stirred for half hour, filtrated, obtained title compound 0108 (0.25 g, 92%) as a white solid. LC-MS: 431 [M+1]+.

**Step 3d:** 4-(4-(2-Bromobenzamido)piperidin-1-yl)benzoic acid (Compound 0109)

A mixture of 0108 (0.90 g, 2.1 mmol), LiOH·H₂O (0.35 g, 8.4 mmol) in dioxane (18 mL) and water (7.5 mL) was stirred at 80°C for 8 hours, adjusted pH to
7.0, extracted with ethyl acetate (25 mL>>3). The combined organic layer was washed with water (20 mL>>2), dried and evaporated to obtain the title compound 0109 (0.63 g, 74%) as a white solid. LC-MS: 404 [M+1]+.

**Step 3e:** (R)-2-Bromo-N-(1-(4-(4-(dimethylamino)-1-(phenylthio)butan-2-ylamino)-3-nitrophenylsulfonylcarbamoyl)(phenyl)piperidin-4-yl)benzamide

A mixture of 0109 (75 mg, 0.177 mmol), 0126 (79 mg, 0.177 mmol), EDCI (42 mg, 0.221 mmol), and DMAP(11 mg, 0.088 mmol) in dry dichloromethane (3 mL) was stirred at r.t. overnight. The solvent was removed to get the crude product. It was purified with column chromatography on silica gel (elution: 1:10 = methanol / dichloromethane) to obtain the title compound 3 (52 mg, 38%) as a yellow solid. LC-MS: 811 [M+1]+. 1H NMR (DMSO-d6): δ 8.27 (M, 1H), 8.17 (M, 1H), 7.71 (m, 2H), 7.62 (M, 3H), 7.40 (M, 7H), 7.22 (m, 3H), 4.06 (m, 1H), 3.92 (m, 1H), 3.78 (m, 2H), 3.08 (s, 3H), 2.93 (m, 4H), 2.85 (s, 1H), 2.63 (s, 3H), 2.01 (m, 2H), 1.90 (m, 2H).

**EXAMPLE 4: Preparation of N-benzyl-N-(1-(4-(4-(dimethylamino)-1-(phenylthio)butan-2-ylamino)-3-nitrophenylsulfonylcarbamoyl)(phenyl)piperidin-4-yl)benzamide (Compound 4)**

**Step 4a:** Ethyl 4-(4-(1,3-dioxolyl)piperidin-1-yl)benzoate (Compound 0110)

A mixture of 4-piperidone ethylene acetal (93.65 mg, 0.654 mmol), ethyl-4-fluoro-benzoate (100 mg, 0.595 mmol), and K2CO3 (123 mg, 0.893 mmol) in DMSO (10mL) was stirred at 120°C for 6 hours. The mixture was poured into water, stirred for 30 minutes, and filtered. The solid was collected and dried to obtain the title compound 0110 (170 mg, 89%) as a white solid. LC-MS: 292 [M+1]+.

**Step 4b:** Ethyl 4-(4-oxopiperidin-1-yl)benzoate (Compound 0111)

A solution of compound 0110 (200mg, 0.687 mmol), 10% H2SO4 solution (5 mL) in THF (5 mL) was stirred at 25°C for 48 hours. The reaction mixture was neutralized with NaHCO3, concentrated to remove THF, extracted with ethyl acetate (20 mL>>3). The organic layer was combined, washed by brine, dried (Na2SO4), filtered and concentrated under reduced pressure to obtain compound 0111 as a light yellow solid (150 mg, 88%): LC-MS: 248 [M+1]+.
Step 4c: Ethyl 4-(4-(benzylamino)piperidin-1-yl)benzoate  (Compound 0112)

A mixture of compound 0111 (150mg, 0.607mmol), NaBH₃ (32.6 mg, 0.849mmol), AcOH (36.4 mg, 0.607 mmol), phenylmethanamine (65 mg, 0.607mmol) in 1, 2-dichloroethane was stirred at room temperature for 6 hours. To the mixture was then added saturated NaHCO₃ solution, extracted with ethyl acetate. The organic layer was washed with brine, dried (Na₂SO₄), filtered and concentrated. The residue was purified by column chromatography on silica gel (elution: 1:1 = ethyl acetate: petroleum ether) to obtain compound 0112 as a white solid (159 mg, 41%) LC-MS: 821 [M]+. 

\[ \delta 1.65 (m, 4H) 2.14 (m, 8H) 2.10 (m, 9H) \]

Step 4d: Ethyl 4-(4-(N-benzylbenzamido)piperidin-1-yl)benzoate  (Compound 0115)

The compound 0112 (150 mg, 0.443 mmol) was dissolved in dichloromethane (3 mL) and to the solution triethylamine (0.3 mL) was added. The mixture was stirred and cooled to 0°C, then benzoyl chloride (93 mg, 0.664 mmol) was added and stirred for 3 hours. Water (2 ml) was added and stirred for 5 minutes followed by addition of saturated NaCO₃ solution. The mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried (MgSO₄), filtered and concentrated, purified by column chromatography to obtain compound 0115 as a white solid (156 mg, 80%). LC-MS: 443 [M+H]+.

Step 4e: 4-(4-(N-benzylbenzamido)piperidin-1-yl)benzoic acid  (Compound 0118)

A mixture of 0115 (140mg, 0.316 mmol) and lithium hydroxide hydrate (53 mg, 1.27mmol) in 1,4-dioxane (10ml) and water (10ml) was stirred at 95°C for 16 hours, neutralized with hydrochloric acid. The solid was filtered, washed with water, and dried to obtain compound 0118 (93 mg, 72%) as a light white solid: LC-MS: 415 [M+H]+. ¹H NMR (DMSO-d₆): δ 1.70 (s, 4H), 3.31 (s, 2H), 3.85 (m, 3H), 4.46 (s, 2H), 6.85 (d, 2H) 7.28 (m, 10 H), 7.67 (d, 2H), 12.21(s, 1H).

Step 4f: N-Benzyl-N-((1-(4-(4-(4-(dimethylamino)-1-(phenylthio)butan-2-ylamino)-3-nitrophenylsulfonylcarbamoyl)phenyl)piperidin-4-yl)benzamide  (compound 4)

A mixture of compound 0118 (100 mg,0.24 mmol), compound 0126 (96 mg, 0.228 mmol), EDCI (54.7 mg, 0.286 mmol) DMAP (12 mg, 0.114 mmol) and dichloromethane was stirred at room temperature for 24 hours, concentrated, purified by column chromatography (silica gel, elution: 1:15 = Methanol : Dichloromethane) to obtain compound 1 as a yellow solid (80 mg, 41%): LCMS: 821[M]+. ¹H NMR (500 MHz, DMSO-d₆): δ 1.65 (m, 4H) 2.14 (m, 8H) 2.10 (m, 9H)
3.61 (s, 2H), 3.85 (m, 2H), 4.81 (m, 1H), 6.75 (b, 2H) 6.85 (b, 1H) 7.15 (m, 4H) 7.28 (m, 5 H), 7.35 (m, 3 H), 7.71 (m, 2H), 7.75 (b, 1H), 8.35 (b, 2H), 8.45 (s, 2H).

Example 5: 4-(4-(benzyl(methyl)amino)piperidin-1-yl)- N-(4-(4-
(dimethylamino)-1- (phenylthio)butan-2-ylamino)-3-
nitrophenylsulfonyl)benzamide (Compound 5)

Step 5a: Ethyl 4-(4-(benzyl(methyl)amino)piperidin-1-yl)benzoate (Compound 0113)

A mixture of 1112 (169 mg, 0.5 mmol), HCHO (40.54 mg, 0.5 mmol), Na(AcO)₃BH (148 mg, 0.7 mmol), in 1, 2-dichloroethane was stirred at room temperature for 6 hours. To the mixture was then added a saturated NaHCO₃, extracted with ethyl acetate. The organic layer was washed with brine, dried (Na₂SO₄), filtered, and concentrated. The residue was purified by column chromatography on silica gel (elution: 1:1 = ethyl acetate: petroleum ether) to obtain compound 0113 (150 mg, 70%) as a white solid. LC-MS 352 [M+I].

Step 5b: 4-(4-(Benzyl(methyl)amino)piperidin-1-yl)benzoic acid (Compound 0116)

The title compound 0116 was prepared as a white solid (100 mg, 72%) from compound 0113 (150 mg, 0.428 mmol) using a procedure similar to that described for compound 0119: LC-MS 325 [M+I]⁺. ¹H NMR (DMSO-d₆): δ 1.70 (m, 4H), 2.14 (m, 3H), 2.22 (m, 1H) 2.66 (m, 4H), 2.72 (m, 5H), 2.98 (m, 3H), 3.12 (s, 1H), 3.51 (s, 1H), 3.95 (m, 3H), 4.5 (m, 2H), 6.85 (d, 2H) 7.28 (m, 5 H), 7.67 (d, 2H), 12.21 (s, 1H).

Step 5c: 4-(4-(Benzyl(methyl)amino)piperidin- 1-yl)-N-(4-(4-(dimethylamino)- 1-(phenylthio)butan-2-ylamino)-3-nitrophenylsulfonyl)benzamide (Compound 5)

The title compound 5 was prepared as a white solid (100 mg, 72%) from compound 0116 (150 mg, 0.428 mmol) using a procedure similar to that described for compound 4: LCMS: 731 [M+I]⁺. ¹H NMR (DMSO-d₆): δ 1.87 (m, 3H), 2.14 (m, 3H) 2.22 (m, 1H) 2.66 (m, 4H), 2.72 (m, 5H), 2.98 (m, 3H), 3.12 (s, 1H), 6.17 (b, 1H) 7.21 (br, 8H) 7.28 (m, 5 H), 7.42 (m, 3 H), 7.76 (br, 5H), 8.27 (b, 1H), 8.51 (s, 1H), 10.72 (br, 1H), 11.01 (br, 1H).

Example 6: Preparation of 4-(4-(N-benzylacetamido)piperidin-1-yl)-N-(4-(4-
(dimethylamino)-1-(phenylthio)butan-2-ylamino)-3-
nitrophenylsulfonyl)benzamide (Compound 6)
Step 6a: Ethyl 4-(4-(N-benzylacetamido)piperidin-1-yl)benzoate (Compound 0 1 1 4)

The title compound 0 1 1 4 was prepared as a white solid (134 mg, 80%) from compound 0 1 1 2 (150 mg, 0.443 mmol) using a procedure similar to that described for compound 1 1 5: LC-MS 381 [M+1].

Step 6b: 4-(4-(N-benzylacetamido)piperidin-1-yl)benzoic acid (Compound 0 1 1 7)

The title compound 0 1 1 7 was prepared as a white solid (100 mg, 90%) from compound 0 1 1 4 (120 mg, 0.315 mmol) using a procedure similar to that described for compound 1 1 5: LC-MS 353 [M+1].

Step 6c: 4-(4-(N-benzylacetamido)piperidin-1-yl)-N-(4-(4-(dimethylamino)-1-(phenylthio)butan-2-ylamino)-3-nitrophenylsulfonyl)benzamide (Compound 6)

The title compound 6 was prepared as a white solid (71 mg, 22%) from compound 0 1 1 7 (150 mg, 0.428 mmol) using a procedure similar to that described for compound 1 1 5: LC-MS: 759 [M+1].

1H NMR (500 MHz DMSO-6):
δ 1.65 (m, 4H) 1.95 (m, 5H) 2.10 (m, 9H) 2.3 (s, 2H), 3.71 (m, 2H), 3.81 (m, 1H), 4.05 (m, 1H), 5.01 (s, 1H), 6.75 (br, 2H) 6.85 (br, 1H) 7.15 (m, 2H) 7.20 (m, 5 H), 7.35 (m, 3 H), 7.71 (m, 2H), 7.75 (b, 1H), 8.35 (b, 1H), 8.45 (s, 1H).

Example 7: Preparation of 4-(4-(benzylamino)piperidin-1-yl)-N-(4-(4-(dimethylamino)-1-(phenylthio)butan-2-ylamino)-3-nitrophenylsulfonyl)benzamide (Compound 7)

Step 7a: 4-(4-(Benzylamino)piperidin-1-yl)benzoic acid (Compound 0 1 1 9)

The title compound 0 1 1 9 was prepared as a white solid (70 mg, 64%) from compound 0 1 1 2 (120 mg, 0.315 mmol) using a procedure similar to that described for compound 1 1 5: LC-MS: 717 [M+1].

1H NMR (500 MHz DMSO-d6): δ 1.51 (s, 2H), 1.95 (m, 5H) 2.10 (m, 9H) 2.3 (s, 2H), 3.71 (m, 2H), 3.81 (m, 1H), 4.05 (m, 1H), 5.01 (s, 1H), 6.75 (br, 2H) 6.85 (br, 1H) 7.15 (m, 2H) 7.20 (m, 5 H), 7.35 (m, 3 H), 7.71 (m, 2H), 7.75 (b, 1H), 8.35 (b, 1H), 8.45 (s, 1H).

Step 7b: 4-(4-(Benzylamino)piperidin-1-yl)-N-(4-(4-(dimethylamino)-1-(phenylthio)butan-2-ylamino)-3-nitrophenylsulfonyl)benzamide

(Compound 7)

The title compound 7 was prepared as a white solid (34 mg, 21%) from compound 0 1 1 9 (70 mg, 0.225 mmol) using a procedure similar to that described for compound 4: LC-MS: 717 [M+1]+. 1H NMR (DMSO-d6): δ 1.45 (m, 3H) 1.84 (br,
Example 8: Preparation of (S)-4-(4-((4'-chlorobiphenyl-2-yl)methylamino)piperidin-1-yl)-N-(4-(dimethylamino)-1-(phenylthio)butan-2-ylamino)-3-nitrophenylsulfonyl)benzamide (Compound 8)

**Step 8a:** Ethyl 4-(4-(2-bromobenzylamino)piperidin-1-yl)benzoate (Compound 0120)

To the solution of ethyl 4-piperidin-1-yl-benzoate (2.47 g, 10 mmol) in dichloroethane (40 mL) was added 2-bromobenzamine (2.05 g, 11 mmol), NaBH(OAc)$_3$ (2.97 g, 14 mmol). The resulting mixture was stirred at room temperature for 16 h. The reaction mixture was concentrated, dissolved in ethyl acetate, washed with water, dried and evaporated to give the product (2.24 g, 54% yield) as a white solid. LC-MS: 417 [(M+1)$^+$].

**Step 8b:** Ethyl 4-(4-((4'-chlorobiphenyl-2-yl)methylamino)piperidin-1-yl)benzoate (Compound 0121)

A mixture of 0120 (1.67 g, 4.0 mmol), 4-chlorophenylboric acid (936 mg, 6.0 mmol), palladium acetate (90 mg, 0.4 mmol), PPh$_3$ (210 mg, 0.8 mmol), and Cs$_2$CO$_3$ (3.26 g, 10 mmol) in dioxane (12 mL) was heated to 90°C under nitrogen for 16 h. The resulting mixture was concentrated and the residue was purified by column chromatography to afford the product as a solid (1.2 g, 67% yield): $^1$H NMR (DMSO-de): δ 7.73 (d, J = 9.3 Hz, 1H), 7.53-7.55 (m, 1H), 7.46 (s, 4H), 7.29-7.34 (m, 2H), 7.17-7.20 (m, 2H), 6.90 (d, J = 9.3 Hz, 1H), 4.21 (q, J = 6.9 Hz, 2H), 3.70-3.74 (m, 2H), 3.60 (s, 2H), 2.83 (m, 2H), 2.48-2.49 (m, 1H), 1.90 (s, 1H), 1.70-1.71 (m, 2H), 1.21-1.28 (m, 5H). LC-MS: 449 [(M+1)$^+$].

**Step 8c:** 4-(4-((4'-Chlorobiphenyl-2-yl)methylamino)piperidin-1-yl)benzoic acid (Compound 0122)

Compound 0121 (294 mg, 0.636 mmol) was dissolved in a mixed solution of 1,4-dioxane (8 ml) and water (4 ml). Lithium hydroxide monohydrate (133.5 mg, 3.182 mmol) was added to the mixture. The resulting mixture was stirred at 90°C for 16 hours. The solvent was removed and 10 ml of water was added. It was adjusted to pH 7 using concentrated HCl. The precipitate was filtered to give the crude product 0122 (219 mg, 79%) which was directly used in next step without further purification. LC-MS: 434 [(M+1)$^+$].
**Step 8d:** (S)-4-[(4’-Chlorobiphenyl-2-yl)methylamino]piperidin-1-yl)-N-(4-(4-(dimethylamino)-1-(phenylthio)butan-2-ylamino)-3-nitrophenylsulfonyl)benzamide (Compound 8)

A solution of 0122 (198 mg, 0.47 mmol), 0126 (200 mg, 0.47 mmol), DMAP (57.34 mg, 0.47 mmol), and EDCI (112.6 mg, 0.59 mmol) in CH₂Cl₂ (5 ml) was stirred at 25°C for 16 hours. The solvent was removed and the residue was purified by prep. HPLC to afford the product, compound 8 as a solid (40 mg, 10%). LC-MS: 827 [M+H]⁺. ¹H-NMR (DMSO-d₆): δ 8.43 (s, 1H), 8.29 (d, J = 9.0 Hz, 1H), 7.70 (m, 5H), 7.52 (m, 7H), 7.22 (m, 6H), 6.89 (d, J = 6.0 Hz, 1H), 6.81 (d, J = 8.4 Hz, 2H), 4.00 (m, 3H), 3.79 (d, J = 12.0 Hz, 2H), 2.96 (m, 3H), 2.69 (m, 2H), 2.57 (m, 6H), 2.06 (s, 6H), 1.84 (m, 2H), 1.43 (m, 2H).

**EXAMPLE 9: Preparation of (S)-4-[(4’-Chlorobiphenyl-2-yl)methyl](methyl)amino)piperidin-1-yl)-N-(4-(4-(dimethylamino)-1-(phenylthio)butan-2-ylamino)-3-nitrophenylsulfonyl)benzamide (Compound 9)**

**Step 9a:** Ethyl 4-4-((4’-Chlorobiphenyl-2-yl)methyl)(methyl)amino)piperidin-1-yl)benzoate (compound 0127)

A mixture of compound 0121 (0.312 g, 0.696 mmol), HCHO (123 mg, 0.696 mmol), and NaBH(OAc)₃ (206 mg, 0.97 mmol) was stirred at room temperature overnight. The reaction mixture was concentrated, dissolved in ethyl acetate, washed with water. The organic layer was dried and concentrated under vacuo to give the product as a white solid (210 mg, 65% yield): ¹H NMR (DMSO-d₆): δ 7.13 (d, J = 8.1 Hz, 1H), 7.29-7.51 (m, 7H), 7.17 (d, J = 7.5 Hz, 1H), 6.91 (d, J = 9.0 Hz, 2H), 4.21 (q, J = 6.6 Hz, 2H), 3.87 (d, J = 13.2 Hz, 2H), 3.46 (s, 2H), 2.72 (t, J = 13.7 Hz, 2H), 1.97 (s, 3H), 1.58-1.62 (m, 2H), 1.36-1.42 (m, 2H), 1.25 (t, J = 6.6 Hz, 3H). LC-MS: 463 (M+).

**Step 9b:** 4-4-((4’-Chlorobiphenyl-2-yl)methyl)(methyl)amino)piperidin-1-yl)benzoic acid (Compound 0128)

Compound 0127 (200 mg, 0.433mmol) was dissolved in a mixed solution of 1.4-dioxane (8 ml) and water (4 ml). Then lithium hydroxide monohydrate (91 mg, 2.165 mmol) was added to the mixture at room temperature. The resulting mixture was heated to 90°C in an oil bath for 16 hours. The solvent was removed and 8 ml of water was added. It was adjusted to pH 7 using concentrated HCl. The precipitate
was filtered to give the crude product 0128 (142 mg, 75% yield) which was directly used in next step reaction without further purification. LC-MS: 435 [M+1]+.

**Step 9c:** (S)-4-((4’-Chlorobiphenyl-2-yl)methyl)(methylamino)- piperidin-1-yl)-N-(4- (4-(dimethylamino)- 1-(phenylthio)butan-2-ylamino)-3-nitrophenylsulfonyl)benzamide (Compound 9)

A mixture of 0128 (130 mg, 0.3 mmol), 0126 (127 mg, 0.3 mmol), DMAP (36.6 mg, 0.3 mmol), and EDCI (71.6 mg, 0.375 mmol) in CH₂Cl₂ (3 ml) was stirred at 25°C for 16 hours. The solvent was removed and the residue was purified by prep. HPLC to afford the product, compound 9 (35 mg, 14%). ¹H-NMR (DMSO-d₆): δ 8.64 (s, 1H), 8.50 (d, J = 7.5 Hz, 1H), 7.81 (m, 3H), 7.63 (d, J = 7.5 Hz, 1H), 7.34 (m, 3H), 7.18 (m, 4H), 6.70 (m, 2H), 5.29 (s, 1H), 4.03 (s, 1H), 3.77 (d, J = 12.9 Hz, 2H), 3.62 (s, 2H), 3.11 (s, 2H), 2.88 (m, 2H), 2.72 (m, 2H), 2.61 (s, 6H), 2.14 (s, 3H), 1.68 (m, 2H), 1.56 (m, 2H). LC-MS: 827 [M+1]+.

**EXAMPLE 10: Preparation of (S)-4’-chlo-ro-7V-(1-(4-(4-(dimethylamino)-1-(phenylthio)butan-2-ylamino)-3-nitrophenylsulfonylcarbamoyl) phenyl)piperidin-4-yl)biphenyl-2-carboxamide (Compound 10)**

**Step 10a:** Ethyl 4-(4’-(4’-chlorobiphenyl-2-ylcarboxamido)piperidin-1-yl)benzoate (Compound 0129)

A mixture of 0108 (862 mg, 2.0 mmol), 4-chlorophenylboric acid (468 mg, 3.0 mmol), palladium acetate (45 mg, 0.2 mmol), PPh₃ (52 mg, 0.2 mmol), and Cs₂CO₃ (1.63 g, 5 mmol) in dioxane (6 mL) was stirred at 90°C under nitrogen for 16h. The resulting mixture was concentrated to give a residue which was purified by column chromatography to afford the product 0129 as a solid (300 mg, 33% yield).

LC-MS: 463 (M+).

**Step 10b:** 4-(4’-(4’-Chlorobiphenyl-2-ylcarboxamido)piperidin-1-yl)- benzoic acid (Compound 0130)

To a solution of 0129 (231 mg, 0.5mmol) in a mixed solvent of 1, 4-dioxane (5 ml) and water (2.5 ml) was added lithium hydroxide monohydrate (126 mg, 3.0 mmol) at room temperature. The resulting mixture was stirred at 90°C in an oil bath for 16 hours. The solvent was removed and 10 ml of water was added. It was adjusted to pH 7 using concentrated HCl. The precipitate was filtered to give the crude product 0130 (170 mg, 73%) which was directly used in next step reaction without further purification. LC-MS: 435 [M+1]+.
Step 10c: (S)-4'-Chloro-N-(1-(4-(4-(dimethylamino)-1-(phenylthio)-butan-2-ylamino)-3-nitrophenylsulfonylcarbamoyl)phenyl)piperidin-4-yl)biphenyl-2-carboxamide (Compound 10)

A solution of 0130 (103 mg, 0.236 mmol), 0126 (100 mg, 0.236 mmol), DMAP (28.8 mg, 0.236 mmol), and EDCI (56 mg, 0.295 mmol) in CH₂Cl₂ (3 ml) was stirred at 25°C for 16 hours. The solvent was removed and the residue was purified by prep. HPLC to afford the product, compound 10 (35 mg, 14%). ³H-NMR (DMSO-d₆): δ 8.46 (s, 1H), 8.19 (d, J = 7.8, 2H), 7.82 (dd, J₁ = 1.8 Hz, J₂ = 8.7 Hz, 1H), 7.71 (d, J = 9.3 Hz, 2H), 7.40 (m, 8H), 7.23 (m, 5H), 6.94 (d, J = 8.7 Hz, 1H), 6.81 (d, J = 9.3 Hz, 2H), 4.07 (s, 1H), 3.79 (s, 1H), 3.81 (d, J = 12.0 Hz, 2H), 3.01 (m, 2H), 2.83 (t, 2H), 2.65 (s, 6H), 2.08 (m, 2H), 1.70 (m, 2H), 1.339 (m, 4H); LC-MS: 841 [M+l]+.

Biological Assays:

As stated hereinbefore the derivatives defined in the present invention possess anti-proliferation activity. These properties may be assessed, for example, using one or more of the procedures set out below:

Bcl-2 and Bcl-xL Competition Binding (Fluorescence Polarization) Assay

Background:

Bcl-2 and Bcl-xL proteins are antiapoptotic proteins whose biological function can be inhibited by proapoptotic proteins such as Bak, Bad and Bax through protein interaction. The interaction between antiapoptotic and proapoptotic proteins are mediated primarily by Bcl-2 homology (BH) 3 domain of Bak, Bad, Bax that bind to the hydrophobic groove of Bcl-2 and Bcl-xL. The demonstration of BH3 peptide alone induce apoptosis encourage the possibility of design or identify a chemical compound that mimics the function of BH3 peptide by blocking Bcl-2 or Bcl-xLs' interaction with their downstream binding partners. These chemical compounds are expected to bind to the hydrophobic groove of Bcl-xL or Bcl-2 proteins with high affinity. A labeled BH3 peptide can be used for competition binding and to monitor the interaction between compounds and Bcl-2 and Bcl-xL proteins.

Assay A:

A 26-mer fluorescein labeled BH3 peptide (NLWAAQRYGRELRRMSDKFVD) was purchase from CalBiochem (197216). The interaction between Bcl-xL or Bcl-2
and peptide forms the basis for the fluorescence polarization assay. A free and fast-tumbling fluorescein labeled BH3 peptide emits random light with respect to the plane of polarization plane of excited light, resulting in a lower polarization degree (mP) value. When the peptide is bound to Bcl-xl or Bcl-2, the complex tumble slower and the emitted light is polarized, resulting in a higher mP value. This binding assay was performed in 96-well plate and with each assay contained 1 and 100nM of labeled peptide and purified Bcl-xL (R&D System, 894-BX-050) or Bcl-2 protein (R&D System, 827-BC-050) respectively. The assay buffer contained 120mM sodium phosphate (pH 7.55), 0.01% BSA and 0.1% sodium azide. Compounds were diluted in DMSO and added to the final assay with concentration range from 20uM to 2nM. mP value was determined by BioTek Synergy II with background subtraction after 3 hours of incubation at room temperature.

The following TABLE B lists compounds representative of the invention and their activity in the Bcl-2 assay under the conditions of Assay A. In this assay, the following grading was used: I ≥ 10 µM, 10 µM > II > 1 µM, 1 µM > III > 0.1 µM, and IV ≤ 0.1 µM for IC_{50}.

<table>
<thead>
<tr>
<th>Compound No.</th>
<th>Bcl-2 Assay A</th>
</tr>
</thead>
<tbody>
<tr>
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<td>7</td>
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</tr>
<tr>
<td>8</td>
<td>II</td>
</tr>
</tbody>
</table>

Assay B:

A 26-mer fluorescein labeled BH3 peptide (NLWAAQRYGRELRRMSDKFVD) was purchased from CalBiochem (197216). The interaction between Bcl-xL or Bcl-2 and peptide forms the basis for the fluorescence polarization assay. A free and fast-tumbling fluorescein labeled BH3 peptide emits random light with respect to the plane of polarization plane of excited light, resulting in a lower polarization degree (mP) value. When the peptide is bound to Bcl-xl or Bcl-2, the complex tumble slower and the emitted light is polarized, resulting in a higher mP value. This binding assay was performed in 96-well plate and with each assay contained 15 and
30 nM of labeled peptide and purified Bcl-xL (R&D System, 894-BX-050) or Bcl-2 protein (R&D System, 827-BC-050) respectively. The assay buffer contained 20mM Hepes (pH 7.0), 50mM KCl, 5mM MgCl2, 20mM Na2MoO4, 0.1mg/ml Bovine Gamma Globulin and 0.01% NP40. Compounds were diluted in DMSO and added to the final assay with concentration range from 20µM to 2nM. mP value was determined by BioTek Synergy II with background subtraction after 3 hours of incubation at room temperature.

The following TABLE C lists compounds representative of the invention and their activity in the Bcl-2 assay under the conditions of Assay B. In this assay, the following grading was used: I ≥ 10 µM, 10 µM > II > 1 µM, 1 µM > III > 0.1 µM, and IV ≤ 0.1 µM for IC₅₀.

<table>
<thead>
<tr>
<th>Compound No.</th>
<th>Bcl-2 Assay B</th>
</tr>
</thead>
<tbody>
<tr>
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</tr>
<tr>
<td>10</td>
<td>IV</td>
</tr>
</tbody>
</table>

The patent and scientific literature referred to herein establishes the knowledge that is available to those with skill in the art. All United States patents and published or unpublished United States patent applications cited herein are incorporated by reference. All published foreign patents and patent applications cited herein are hereby incorporated by reference. All other published references, documents, manuscripts and scientific literature cited herein are hereby incorporated by reference.

While this invention has been particularly shown and described with references to preferred embodiments thereof, it will be understood by those skilled in the art that various changes in form and details may be made therein without departing from the scope of the invention encompassed by the appended claims.
CLAIMS

What is claimed is:

1. A compound represented by formula I:

![Chemical Structure Image](I)

or its geometric isomers, enantiomers, diastereomers, racemates, pharmaceutically acceptable salts, prodrugs and solvates thereof, wherein:

- \( \text{Ar} \) is aryl, substituted aryl, heteroaryl, or substituted heteroaryl;
- \( R_{23} \) is hydrogen, acyl, aliphatic or substituted aliphatic;
- \( W \) is \( N \) or \( \text{CH} \);
- \( W \) is absent, \( N \) or \( \text{CH} \);
- \( R_{26} \) is hydrogen, alkyl, aryl, alkylcarbonyl, or arylcarbonyl;
- \( R_{27} \) is aryl, substituted aryl, heteroaryl, or substituted heteroaryl;
- \( R_{28} \) is hydrogen, oxo, aryl, substituted aryl, heteroaryl, or substituted heteroaryl.

2. A compound according to Claim 1 represented by formula (II):

![Chemical Structure Image](II)
or its geometric isomers, enantiomers, diastereomers, racemates, pharmaceutically acceptable salts, prodrugs and solvates thereof, wherein X₁-X₉ are independently N or CR₂₅, where R₂₅ is independently selected from hydrogen, hydroxy, amino, halogen, substituted or unsubstituted alkoxy, substituted or unsubstituted alkylamino, substituted or unsubstituted dialkylamino, CF₃, CN, NO₂, N₃, sulfonyl, acyl, aliphatic, and substituted aliphatic; R₂₂ is hydrogen, acyl, aliphatic or substituted aliphatic; n is 1-5; B₁ is absent, N(R₈), CO, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, cycloalkyl, heterocyclic or aryl; B₂ is absent, O, S, SO, SO₂, N(R₉) or CO; B₃ is absent, O, S, SO, SO₂, N(R₉), CO, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, cycloalkyl, heterocyclic or aryl; B₄ is absent, O, S, SO, SO₂, N(R₈), CO, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, cycloalkyl, heterocyclic or aryl, or heteroaryl; B₅ is absent, O, S, SO, SO₂, N(R₈), CO, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, cycloalkyl, heterocyclic, aryl, or heteroaryl; B₆ is absent, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocyclic, aryl, substituted aryl, heteroaryl or substituted heteroaryl; R₈ is independently hydrogen, acyl, aliphatic or substituted aliphatic; Ar, Z, W₁, W₂, W₂₆ and R₂₃ are as previously defined in Claim 1.

3. A compound according to Claim 1 represented by formula (III):

or its geometric isomers, enantiomers, diastereomers, racemates, pharmaceutically acceptable salts, prodrugs and solvates thereof, wherein X₁-X₉ are independently N or CR₂₅, where R₂₅ is independently selected from hydrogen, hydroxy, amino, halogen, substituted or unsubstituted alkoxy, substituted or unsubstituted alkylamino, substituted or unsubstituted dialkylamino, CF₃, CN, NO₂, N₃, sulfonyl,
acyl, aliphatic, and substituted aliphatic; \( R_{22} \) is selected from hydrogen, acyl, aliphatic and substituted aliphatic; \( n \) is 1-5; \( R_{20} \) and \( R_{21} \) are each independently selected from hydrogen, acyl, aliphatic and substituted aliphatic; alternatively, \( R_{20} \) and \( R_{21} \) can be taken together with the atom they are attached to form a heterocyclic or substituted heterocyclic; \( Z, W, W_1, R_{26}-R_{28} \) and \( R_{23} \) are as previously defined in Claim 1.

4. A compound according to Claim 1 represented by formula (IV):

or its geometric isomers, enantiomers, diastereomers, racemates, pharmaceutically acceptable salts, prodrugs and solvates thereof, wherein \( X_1-X_4 \) are independently \( N \) or \( CR_{25} \), where \( R_{25} \) is independently selected from hydrogen, hydroxy, amino, halogen, substituted or unsubstituted alkoxy, substituted or unsubstituted alkylamino, substituted or unsubstituted dialkylamino, \( CF_3 \), \( CN \), \( NO2 \), \( N_3 \), sulfonyl, acyl, aliphatic, and substituted aliphatic; \( R_{22} \) is hydrogen, acyl, aliphatic or substituted aliphatic; \( n \) is 1-5; \( R_{20} \) and \( R_{21} \) are each independently selected from hydrogen, acyl, aliphatic and substituted aliphatic; alternatively, \( R_{20} \) and \( R_{21} \) can be taken together with the atom they are attached to form a heterocyclic or substituted heterocyclic; \( W, W_1, R_{26}-R_{28} \) and \( R_{23} \) are as previously defined in Claim 1.

5. A compound according to Claim 1 selected from the compounds delineated in Table A or its geometric isomers, enantiomers, diastereomers, racemates, pharmaceutically acceptable salts, prodrugs and solvates thereof:
<table>
<thead>
<tr>
<th>Compound #</th>
<th>Structure</th>
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<tbody>
<tr>
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</tr>
<tr>
<td>5</td>
<td><img src="image5.png" alt="Structure 5" /></td>
</tr>
</tbody>
</table>
6. A pharmaceutical composition comprising as an active ingredient a compound of Claim 1 and a pharmaceutical acceptable carrier.

7. A method of treating cell proliferative disorder in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of the pharmaceutical composition of Claim 6.

INTERNATIONAL SEARCH REPORT

A CLASSIFICATION OF SUBJECT MATTER
IPC(8)- A01N 57/00; A01N 41/06, A61K 31/66 (2008.04)
USPC - 514/117, 601

B FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
USPC- 514/117, 601

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC- 514/315 (see keywords below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
WEST DB=PGB, USPTO, USOC, EPAB, JPAB, Google scholar/patents Bcl 2 inhibitors ABT-737 cancer

C DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No</th>
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<td>Y</td>
<td>US 2003/0008924 A1 (WANG et al.) 09 January 2003 (09 01 2003) para [0013H0014], [0016], [0019]-[0020], [0212], [0217]</td>
<td>6-9</td>
</tr>
</tbody>
</table>

☐ Further documents are listed in the continuation of Box C ☐

* Special categories of cited documents
  "A" document defining the general state of the art which is not considered to be of particular relevance
  "E" earlier application or patent but published on or after the international filing date
  "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
  "O" document referring to an oral disclosure, use, exhibition or other means
  "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

Date of the actual completion of the international search: 13 November 2008 (13 11 2008)
Date of mailing of the international search report: 21 NOV 2008

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Facsimile No 571-273-3201

Authorized officer: Lee W Young
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PCT OSP 571-272-7774

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