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(54) Title: USE OF CHK1 INHIBITORS TO CONTROL CELL PROLIFERATION

(57) Abstract: The present invention relates to improved methods for inhibiting aberrant cell proliferation involving the scheduling of administration of Chk1 activators (e.g., chemotherapeutic agents) and Chk1 inhibitors. At least one Chk1 activator is administered at a dose and for a time sufficient to induce substantial synchronization of cell cycle arrest in proliferating cells. Upon achieving substantial phase synchronization, at least one Chk1 inhibitor is administered to abrogate the cell cycle arrest and induce therapeutic cell death. The invention is useful with any Chk1 activator and any Chk1 inhibitor, and finds application in treating or preventing cancerous and non-cancerous aberrant cell proliferation.

USE OF CHK1 INHIBITORS TO CONTROL CELL PROLIFERATION

The present invention relates to methods for inhibiting aberrant cell proliferation involving the chemotherapeutic agents and Chk1 inhibitors.

BACKGROUND

An important goal in healthcare is to develop and make available safer and more effective drugs and drug combinations for the treatment of aberrantly proliferating cells, such as for treatment of cancer. Most anti-proliferation therapies (including chemotherapy and radiation) act by disrupting vital processes such as DNA metabolism, DNA synthesis, DNA transcription, and microtubule spindle function, or by perturbing chromosomal structural integrity by introducing DNA lesions. These processes affect both normal and aberrantly proliferating (e.g., tumor) cells, however. As the maintenance of DNA integrity is essential to cell viability in normal cells, anticancer drugs have the lowest therapeutic index (i.e., the highest proportion of damage to normal cells as well as tumor cells) of any drug class.

Recent work has focused on ways to increase the therapeutic index of cancer and other anti-cell proliferation therapeutics. In this regard, cellular mechanisms, known as cell cycle checkpoints, have received attention. Individual cells create an exact copy of their chromosomes and then segregate each copy into two cells by a process called mitosis. Cells have sensing mechanisms, called cell cycle checkpoints, to maintain the order of these steps and to insure that each step is executed with high fidelity. [Hartwell et al., *Science,* 246:629-634 (1989); Weinert et al., *Genes and Devlopment,* 8:652 (1994).]

When cells detect DNA damage induced by a chemotherapeutic agent or by radiation, cell cycle checkpoints arrest the cell cycle, allowing time for the cells to repair the DNA damage, often to a point sufficient to continue proliferation and prevent cell death. For instance, the chemotherapeutic gemcitabine, a nucleoside analog, is incorporated into synthesizing DNA causing improper synthesis and inducing cell cycle arrest. If the cells could not overcome this cell cycle arrest, the cells would die. Some cancers appear to have generated a mechanism of overcoming this cell cycle arrest, however. These resistant tumor cells simply accumulate in S phase while the chemotherapeutic agent is administered, and as soon as the drug is

removed, repair the DNA damage and progress through the remainder of the cell cycle (Shi et al., *Cancer Res.* 61:1065-1072. 2001). The inhibition of DNA damage checkpoints is therefore expected to sensitize aberrantly proliferating cells to DNA damaging agents. Such sensitization is in turn expected to increase the therapeutic index of such chemotherapeutic agents or radiation. Thus, Keegan et al., (PCT/US02/06452, the contents of which are incorporated herein by reference), have disclosed certain small molecule compounds that selectively inhibit Chk1 kinase and their use in inhibiting Chk1.

The cell cycle is structurally and functionally conserved in its basic process and mode of regulation across all eukaryotic species. The mitotic (somatic) cell cycle consists of four phases, the G1 (gap) phase, the S (synthesis) phase, the G2 (gap) phase, and the M (mitosis) phase. The G1, S, and G2 phases are collectively referred to as interphase of the cell cycle. During the G1 phase, biosynthetic activities of the cell progress at a high rate. The S phase begins when DNA synthesis starts and ends when the DNA content of the nucleus of the cell has been replicated and two identical sets of chromosomes are formed. The cell then enters the G2 phase which continues until mitosis starts. In mitosis, the chromosomes pair and separate and two new nuclei form, and cytokinesis occurs in which the cell itself splits into two daughter cells each receiving one nucleus containing one of the two sets of chromosomes. Cytokinesis terminates the M phase and marks the beginning of interphase of the next cell cycle. The sequence in which the events in the cell cycle proceed is tightly regulated such that the initiation of one cell cycle event is dependent on the completion of the prior cell cycle event. This allows fidelity in the duplication and segregation of genetic material from one generation of somatic cells to the next.

It has been reported that cell cycle checkpoints comprise at least three distinct classes of polypeptides which act sequentially in response to cell cycle signals or defects in chromosomal mechanisms (Carr, A.M., *Science*, 271:314-315 (1996). The first class is a family of proteins which detect or sense DNA damage or abnormalities in the cell cycle. These sensors include Atm and Atr. The second class of polypeptides amplify and transmit the signal detected by the detector and is exemplified by Rad53 [Alen et al. Genes Dev. 8:2416-2488 (1994)] and Chk1. A third class of polypeptides includes cell cycle effectors such as p53 that mediate a cellular response, for example, arrest of mitosis and apoptosis.

Much of the current understanding of the function of cell cycle checkpoints has been derived from the study of tumor-derived cell lines. In many cases, tumor cells have lost key cell cycle check-points (Hartwell et al., *Science* 266: 1821-28, 1994). It has been reported that a key step in the evolution of cells to a neoplastic state is the acquisition of mutations that inactivate cell cycle checkpoint pathways, such as those involving p53 (Weinberg, R.A. Cell 81:323-330, 1995; Levine, A. J. Cell 88: 3234-331, 1997). Loss of these cell cycle checkpoints results in the replication of tumor cells despite DNA damage.

Noncancerous tissue, which has intact cell cycle checkpoints, typically is insulated from temporary disruption of a single checkpoint pathway. Tumor cells, however, have defects in pathways controlling cell cycle progression such that the perturbation of additional checkpoints renders them particularly sensitive to DNA damaging agents. For example, tumor cells that contain mutant p53 are defective both in the G1 DNA damage checkpoint and in the ability to maintain the G2 DNA damage checkpoint (Bunz et al., *Science*, 282:1497-501, 1998). Checkpoint inhibitors that target initiation of the G2 checkpoint or the S phase checkpoint are expected to further cripple the ability of these tumor cells to repair DNA damage and, therefore, are candidates to enhance the therapeutic index of both radiation and systemic chemotherapy (Gesner, T., Abstract at SRI Conference: Protein Phosphorylation and Drug Discovery World Summit. March 2003.)

In the presence of DNA damage or any block to DNA replication, the checkpoint proteins Atm and Atr initiate a signal transduction pathway leading to cell cycle arrest. Atm has been shown to play a role in a DNA damage check-point in response to ionizing radiation (IR). Atr is stimulated by agents that cause double strand DNA breaks, single strand DNA breaks, and agents that block DNA from radiation.

Chk1 is a protein kinase that lies downstream from Atm and/or Atr in the DNA damage checkpoint signal transduction pathway. (Sanchez et al., *Science*, 277:1497-1501, 1997; U.S. Patent No. 6,218,109) In mammalian cells, Chk1 is phosphorylated in response to agents that cause DNA damage including ionizing radiation (IR), ultraviolet (UV) light, and hydroxyurea (Sanchez et al., supra; Lui et al., Genes Dev., 14:1448-1459, 2000). The phosphorylation and activation of Chk1 in mammalian cells is dependent on Atm (Chen et al., Oncogene, 18:249-256, 1999) and

Atr (Lui et al., supra). Furthermore, Chk1 has been shown to phosphorylate both wee1 (O'Connell et al., EMBO J., 16:545-554, 1997) and Pds1 (Sanchez et al., *Science*, 286:1166-1171, 1999) gene products known to be important in cell cycle control.

These studies demonstrate that mammalian Chk1 plays a role in the Atm-dependent DNA damage checkpoint leading to arrest at S phase. A role for Chk1 in the S phase mammalian cells has recently been elucidated (Feijoo et al., J. Cell Biol., 154:913-923, 2001; Zhao et al., PNAS USA, 99:14795-800, 2002; Xiao et al., J Biol Chem., 278(24):21767-21773, 2003; Sorensen et al., Cancer Cell, 3(3):247-58, 2003) highlighting the role of Chk1 in monitoring the integrity of DNA synthesis. Chk1 invokes an S-phase arrest by phosphorylating Cdc25A, which regulates cyclinA/cdk2 (Xiao et al., supra and Sorensen et al., supra). Chk1 also invokes a G2 arrest by phosphorylating and inactivating Cdc25C, the dual specificity phosphatase that normally dephosphorylates cyclin-B/cdc2 (also known as Cdk1) as cells progress into mitosis (Fernery et al., *Science*, 277: 1495-7, 1997; Sanchez et al., supra; Matsuoka et al., *Science*. 282:1893-1897, 1998; and Blasina et al., Curr. Biol., 9:1-10, 1999). In both cases, regulation of Cdk activity induces a cell cycle arrest to prevent cells from entering mitosis in the presence of DNA damage or unreplicated DNA.

Additional classes of cell cycle checkpoint inhibitors inhibit the cell cycle at either the G1 or G2/M phase. UCN-01, or 7-hydroxystaurosporine, a derivative of staurosporine, was originally isolated as a non-specific kinase inhibitor, and was found to have its primary effect on protein kinase C, but has recently been found to inhibit the activity of Chk1 and abrogate the G2 cell cycle checkpoint (Shi et al., supra). Thus, UCN-01 is a non-selective Chk1 inhibitor. As a result, UCN-01 is toxic to cells at high doses. At low doses, it non-specifically inhibits many cellular kinases and also inhibits the G1 checkpoint (Tenzer and Pruschy, Curr. Med. Chem. Anti-Cancer Agents, 3:35-46, 2003).

UCN-01 has been used in conjunction with chemotherapeutic therapies, such as irradiation, and with the anti-cancer agent camptothecin (Tenzer and Pruschy, supra), and gemcitabine (Shi et al., supra) with limited success. In addition, UCN-01 has also been used to potentiate the effects of temozolomide (TMZ) induced DNA mismatch repair (MMR) in glioblastoma cells (Hirose et al., Cancer Res., 61:5843-5849, 2001). In the clinic, UCN-01 is not as effective a

chemotherapeutic as once was hoped, perhaps due to a failure in treatment scheduling and a lack of identification of particular key molecular targets (Grant and Roberts, Drug Resistance Updates, 6:15-26, 2003). Thus, Mack et al. report cell cycle-dependent potentiation of cisplatin by UCN-01 in cultured non-small-cell lung carcinoma cell line, but do not identify with specificity the key cell cycle checkpoint(s) targeted by UCN-01. (Mack et al., Cancer Chemother Pharmacol., 51(4):337-348, 2003).

Several other strategies exist for sensitizing tumor cells to treatment with cell cycle affecting chemotherapeutics. For example, administration of 2-aminopurine abrogates multiple cell cycle checkpoint mechanisms, such as mimosine-induced G1 arrest or hydroxyurea-induced S phase arrest, allowing the cell to progress into and through mitosis (Andreassen et al., Proc Natl Acad Sci U S A., 86:2272-2276, 1992). Caffeine, a methylxanthine, has also been used to enhance cytotoxicity of DNA-damaging agents, such as cisplatin and ionizing radiation, by mediating progression through the G2 checkpoint and thereby inducing cell death. (Bracey et al., Clin Cancer Res., 3:1371-1381, 1997). However, the dose of caffeine used to accomplish the cell cycle abrogation exceeds clinically acceptable levels and is not a viable therapeutic option. Additionally, antisense nucleotides to Chk1 kinase have been used to increase sensitivity to the topoisomerase inhibitor BNP1350 (Yin et al., Biochem. Biophys. Res. Commun., 295:435-44, 2002), but demonstrate the problems typically associated with antisense treatment and gene therapy.

Thus, treatments that modulate the underlying molecular mechanisms of cell cycle progression and resistance to DNA damage were expected to potentiate tumor cell killing and enhance the therapeutic index of existing therapies. Inhibition of additional DNA damage checkpoints by Chk1 inhibitors was expected to potentiate such treatments by selectively sensitizing abnormally proliferating cells to DNA damaging agents. However, the degree of selective sensitization or potentiation obtained was not as effective as hoped in these methods.

Consequently, there is a need in the art to develop a therapeutic regimen that more specifically targets particular cell cycle checkpoints in aberrantly dividing cells, thus providing better, faster and safer therapies to patients with proliferative diseases. The present invention addresses this need.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 describes the effects of Chk1 inhibitor on HeLa cells. Figure 1A depicts the effects of ionizing radiation and Chk1 inhibitor on CyclinB/cdc2 kinase activity and induction of mitosis. Activity is shown as a percent relative to nocodazole (noc)-treated cells. Figure 1B depicts Chk1 inhibitor effects on HeLa cell cycle progression as shown by mitotic index experiments. Activity is based on CyclinB/cdc2 kinase activity.

Figure 2 describes the effects of Chk1 inhibitor on HT29 colon carcinoma cells. Figure 2A depicts the percent of cells in S phase after treatment with camptothecin and Chk1 inhibitor. Figure 2B depicts the effects of camptothecin and Chk1 inhibitor on HT29 cells as shown by mitotic index experiments. Figure 2C depicts the percent of HT29 cells in mitosis after treatment with either Ara-C, aphidicolin or fludarabine and Chk1 inhibitor.

Figure 3 is a Western blot showing the phosphorylation state of Chk1 after gemcitabine treatment of HT29 cells.

Figure 4 is a Western blot showing the phosphorylation state of serine 296 of Chk1 after treatment of HT29 cells with gemcitabine alone or gemcitabine plus Chk1 inhibitor.

SUMMARY OF THE INVENTION

The present invention provides a method for controlling aberrant cell proliferation. The method comprises contacting a cell population comprising aberrantly proliferating cells with at least one Chk1 activator in an amount and for a time sufficient to substantially synchronize cell cycle arrest among the aberrantly proliferating cells. Upon achieving substantial synchronization of cell cycle arrest in said population, the cell population is contacted with at least one Chk1 inhibitor in an amount and for a time sufficient to substantially abrogate the cell cycle arrest.

In one embodiment, the present invention provides a method for sensitizing a population of aberrantly proliferating cells to the effects of at least one Chk1 activator. In another embodiment, the present invention provides a method for

increasing the therapeutic index of at least one Chk1 activator in the treatment of at least one disease, condition, or disorder associated with, mediated by, or caused by aberrant cell proliferation.

The present invention also comprises articles of manufacture. Such articles comprise at least one Chk1 inhibitor, optionally together with a pharmaceutical carrier or diluent, and at least one label describing a method of use of the Chk1 inhibitor according to the invention. Such articles of manufacture may also optionally comprise at least one Chk1 activator.

The present invention also calls for use of a composition comprising at least one Chk1 inhibitor in the manufacture of a medicament for the inhibition or prevention of aberrant cell proliferation, or for the treatment or prophylaxis of a disease, condition, or disorder in a subject characterized or mediated by aberrant cell proliferation.

"Aberrant cell proliferation" means cell proliferation that deviates from the normal, proper, or expected course. For example, aberrant cell proliferation may include inappropriate proliferation of cells whose DNA or other cellular components have become damaged or defective. Aberrant cell proliferation may include cell proliferation whose characteristics are associated with a disease, condition, or disorder caused by, mediated by, or resulting in inappropriately high levels of cell division, inappropriately low levels of apoptosis, or both. Such diseases, conditions, or disorders may be characterized, for example, by single or multiple local abnormal proliferations of cells, groups of cells or tissue(s), whether cancerous or non-cancerous, benign or malignant, described more fully below.

"Controlling" aberrant cell proliferation encompasses inhibiting and preventing aberrant cell proliferation in either an *in vivo* or *ex vivo* contexts as described herein.

"Inhibiting aberrant cell proliferation" means to slow or stop the rate at which aberrantly proliferating cells proliferate. This may result either from a decreased rate of replication, an increased rate of cell death, or both. Cell death may occur by any mechanism, including apoptosis and mitotic catastrophe. Use of the present invention may result in partial or complete regression of aberrantly proliferating cells, i.e., the partial or complete disappearance of such cells from the

cell population. Thus, for example, when the population of aberrantly proliferating cells are tumor cells, the method of the invention may be used to slow the rate of tumor growth, decrease the size or number of tumors, or to induce partial or complete tumor regression.

"Preventing aberrant cell proliferation" means that the present invention may be used prophylactically to prevent or inhibit aberrant cell proliferation before it occurs, or to prevent or inhibit the recurrence thereof. Thus, in all embodiments, the invention may be used in vivo or ex vivo where no aberrant cell proliferation has been identified or where no aberrant cell proliferation is ongoing, but where aberrant cell proliferation is suspected or expected, respectively. Moreover, the invention may also be used in all its embodiments wherever aberrant cell proliferation has been previously treated to prevent or inhibit recurrence of the same. In these and related embodiments, the "cell population comprising aberrantly proliferating cells" may refer to any cell population where no aberrant cell proliferation has been identified or is ongoing, but where aberrant cell proliferation is suspected or expected, respectively, and/or any cell population previously treated for aberrant cell proliferation to prevent or inhibit recurrence of the same.

"Chk1 activator" means any agent, whether now known or after-discovered, whether naturally occurring or man-made, having an ability to activate Chk1 kinase sufficient to induce a cell cycle arrest. An agent may be identified as a Chk1 activator for purposes of this invention by methods known in the art. In one non-limiting method, the phosphorylation state of Chk1 is measured as an indication of Chk1 activation. For example, the phosphorylation of Chk1 serines 317 and 345 have been shown to correlate with Chk1 activation after treatment with agents known to activate Chk1, as described in Example 12 hereinbelow. Chk1 activators include those capable of arresting the cell cycle at a specific phase of the cell cycle, which phase may be referred to herein as the "target phase" for that activator. Target phases include any of the cell cycle phases except mitosis. Thus, in certain embodiments, the Chk1 activator will induce cell cycle arrest at the G1 phase. In certain other embodiments, the Chk1 activator will induce cell cycle arrest at the S phase. In certain other embodiments, the Chk1 activator will induce cell cycle arrest at the G2 phase.

Any chemotherapeutic agent, known or after-discovered, capable of functioning as a Chk1 activator may be used in the present invention. Any radiotherapeutic agent, known or after-discovered, capable of functioning as a Chk1 activator may be used in the present invention. The selection of a suitable Chk1 activator is within the level of skill of the ordinarily skilled artisan. Factors used in the selection will depend, for example, upon the condition being treated, the cell type of aberrantly proliferating cells targeted, whether such cells are to be exposed to the Chk1 activator *in vivo* or *ex vivo*, the recipient's health, and other factors which are known to those of ordinary skill in the art. Available Chk1 activators may be adapted for use in the control of any aberrantly proliferating cell type or the conditions listed herein. For example, when the method is used to treat non-cancerous aberrantly proliferating cells, lower levels will typically be used than when treating cancerous aberrantly proliferating cells. For example, levels of radiation, e.g., ultraviolet (UV) radiation, and/or low levels of suitable chemotherapeutic agents (e.g., methotrexate) may be used in the control of aberrantly proliferating cells according to the invention.

Examples of chemotherapeutic agents capable of serving as Chk1 activators include, but are not limited to

Alkylating agents, such as nitrogen mustards (e.g., mechlorethamine, cyclophosphamide, ifosfamide, melphalan, and chlorambucil); nitrosoureas (e.g., carmustine (BCNU), lomustine (CCNU), and semustine (methyl-CCNU)); ethylenimines and methyl-melamines (e.g., triethylenemelamine (TEM), triethylene thiophosphoramide (thiotepa), and hexamethylmelamine (HMM, altretamine)); alkyl sulfonates (e.g., buslfan); and triazines (e.g., dacabazine (DTIC));

Antimetabolites, such as folic acid analogs (e.g., methotrexate, trimetrexate, and pemetrexed (multi-targeted antifolate)); pyrimidine analogs (such as 5-fluorouracil (5-FU), fluorodeoxyuridine, gemcitabine, cytosine arabinoside (AraC, cytarabine), 5-azacytidine, and 2,2'-difluorodeoxycytidine); and purine analogs (e.g, 6-mercaptopurine, 6-thioguanine, azathioprine, 2'-deoxycoformycin (pentostatin), erythrohydroxynonyladenine (EHNA), fludarabine phosphate, 2-chlorodeoxyadenosine (cladribine, 2-CdA));

Type I topoisomerase inhibitors such as camptothecin (CPT), topotecan, and irinotecan;

Certain natural products, such as epipodophylotoxins (e.g., etoposide and teniposide); and vinca alkaloids (e.g., vinblastine, vincristine, and vinorelbine);

Anti-tumor antibiotics such as actinomycin D, doxorubicin, and bleomycin;

Certain radiosensitizers such as 5-bromodeozyuridine, 5-iododeoxyuridine, and bromodeoxycytidine;

Platinum coordination complexes such as cisplatin, carboplatin, and oxaliplatin;

Substituted ureas, such as hydroxyurea; and

Methylhydrazine derivatives such as N-methylhydrazine (MIH) and procarbazine.

Examples of radiotherapeutic Chk1 activators include, but are not limited to, ionizing radiation, such as x-ray radiation, ultraviolet light and mixtures thereof.

At least one Chk1 activator is used in the method of the invention. If more than one Chk1 activator is used, the Chk1 activators may be co-administered or administered at separate times as determined by those of ordinary skill in the art.

Chk1 activators may be used alone or in combination with other chemotherapeutic or radiotherapeutic agents that may or may not function as Chk1 activators. Radiotherapeutic agents may be used in conjunction with radiosensitizers and/or photosensitizers, as are known in the art. Any of the foregoing agents may be used in conjunction with other active and inactive agents, such as those capable of reducing side effects. Combination treatments are well known in the art or may readily be determined by those of ordinary skill in the art. Non-limiting examples of chemotherapeutic agents, radiotherapeutic agents and other active and ancillary agents are shown in Table 1.

TABLE 1

Alkylating agents
Nitrogen mustards
mechlorethamine
cyclophosphamide
ifosfamide
melphalan
chlorambucil

Nitrosoureas
carmustine (BCNU)
lomustine (CCNU)
semustine (methyl-CCNU)

Ethylenimine/Methyl-melamine
thriethylenemelamine (TEM)
triethylene thiophosphoramide (thiotepa)
hexamethylmelamine (HMM, altretamine)

Alkyl sulfonates
busulfan

Triazines
dacarbazine (DTIC)

Antimetabolites
Folic Acid analogs
methotrexate
Trimetrexate
Pemetrexed (Multi-targeted antifolate)

Pyrimidine analogs
5-fluorouracil
fluorodeoxyuridine
gemcitabine
cytosine arabinoside (AraC, cytarabine)
5-azacytidine
2,2′- difluorodeoxy-cytidine

Purine analogs
6-mercaptopurine
6-thioguanine
azathioprine
2'-deoxycoformycin (pentostatin)
erythrohydroxynonyl-adenine (EHNA)
fludarabine phosphate

Natural products
Antimitotic drugs

Taxanes
paclitaxel
Vinca alkaloids
vinblastine (VLB)
vincristine
vinorelbine
Taxotere® (docetaxel)
estramustine
estramustine phosphate

Epipodophylotoxins
etoposide
teniposide

Antibiotics
actimomycin D
daunomycin (rubido-mycin)
doxorubicin (adria-mycin)
mitoxantroneidarubicin
bleomycin
splicamycin (mithramycin)
mitomycinC
dactinomycin
aphidicolin

Enzymes
L-asparaginase
L-arginase

Radiosensitizers
metronidazole
misonidazole
desmethylmisonidazole
pimonidazole
etanidazole
nimorazole
RSU 1069
EO9
RB 6145
SR4233
nicotinamide
5-bromodeozyuridine
5-iododeoxyuridine
bromodeoxycytidine

2-chlorodeoxyadenosine
(cladribine, 2-CdA)

Type I Topoisomerase Inhibitors
camptothecin
topotecan
irinotecan

Biological response modifiers
G-CSF
GM-CSF

Differentiation Agents
retinoic acid derivatives

Hormones and antagonists
Adrenocorticosteroids/ antagonists
prednisone and equiv-alents
dexamethasone
ainoglutethimide

Progestins
hydroxyprogesterone caproate
medroxyprogesterone acetate
megestrol acetate

Estrogens
diethylstilbestrol
ethynyl estradiol/ equivalents

Antiestrogen
tamoxifen

Androgens
testosterone propionate
fluoxymesterone/equivalents

Antiandrogens
flutamide
gonadotropin-releasing
hormone analogs
leuprolide

Nonsteroidal antiandrogens
flutamide

Miscellaneous agents
Platinium coordination complexes
cisplatin
Carboplatin
oxaliplatin
Anthracenedione
mitoxantrone

Substituted urea
hydroxyurea

Methylhydrazine derivatives
N-methylhydrazine (MIH)
procarbazine

Adrenocortical suppressant
mitotane (*o,p'*- DDD)
ainoglutethimide

Cytokines
interferon (α, β, γ)
interleukin-2

Photosensitizers
hematoporphyrin derivatives
Photofrin®
benzoporphyrin derivatives
Npe6
tin etioporphyrin (SnET2)
pheoboride-a
bacteriochlorophyll-a
naphthalocyanines
phthalocyanines
zinc phthalocyanines

Radiation
X-ray
ultraviolet light
gamma radiation
visible light
infrared radiation
microwave radiation

"Chk1 inhibitor" means any agent, whether now known or after-discovered, whether naturally occurring or man-made, that is capable of at least partially abrogating cell cycle checkpoint activity of Chk1. Such agents include, but are not limited to, small molecule compounds, biologics, and antisense agents.

Abrogation of cell cycle checkpoint is achieved when the cellular checkpoint mechanism(s) is (are) overcome sufficiently to allow a cell to pass from the cell cycle phase in which it is halted by the Chk1 activator to the next phase in the cell cycle or to allow a cell to pass directly to cell death. Without wishing to be bound by theory, it is believed that abrogation of the cell cycle checkpoint permits cells to carry damage or imperfections, including damage induced by the Chk1 activator that might otherwise have been repaired, to subsequent cell cycle phases, thereby inducing or promoting cell death. Cell death may occur by any mechanism, including apoptosis and mitotic catastrophe. In one embodiment, the Chk1 activator and the Chk1 inhibitor each influence the same target phase, with the Chk1 activator arresting the cells in the target phase, and the Chk1 inhibitor abrogating that arrest. If more than one Chk1 inhibitor is used, the Chk1 inhibitors may be co-administered or administered at separate times as determined by the attending physician or laboratory technician. One way to assess Chk1 inhibitor activity is by assessing Chk1 activity, as described in Example 13 below.

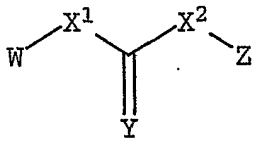
Chk1 inhibitors useful in the present invention include, but are not limited to, those described or claimed in the following publications, the entire disclosures of which are incorporated herein by reference:

Aryl- and heteroaryl-substituted urea compounds described in any one of the following co-owned, co-pending patent applications: U.S. Patent Application No. 10/087,715 (patent family member of International Patent Publication No.: WO 2002/070494), U.S. Provisional Patent Application Nos.: 60/583,080, 60/585,292, and 60/602,968; Diaryl urea compounds (described in US20040014765); US Patent Publication No. US2003/199511; US Patent Publication No. 2004/0014765; WO03/101444; Methylxanthines and related compounds (described in Fan et al., *Cancer Res.* 55:1649-54. 1995); Ureidothiphenes (described in International Patent Publication No. WO03/029241 and WO 03/028731); N-pyrrolopyridinyl carboxamides (described in International Patent Publication No.

WO03/028724); Antisense Chk1 oligonucleotides (described in International Patent Publication No. WO01/57206 and US Patent 6,211,164); Chk1 receptor antagonists (described in International Patent Publication No. WO00/16781); Heteroaromatic carboxamide derivatives (described in International Patent Publication No. WO03/037886); Aminothiophenes (described in International Patent Publication No. WO03/029242); (Indazolyl) benzimidazoles (described in International Patent Publication No. WO03/004488); Benzimidazole quinolinones (described in US Patent Publication No. 20040092535 and WO04/018419),Heterocyclic-hydroxyimino-fluorenes (described in International Patent Publication No. WO02/16326); Scytoneman skeleton containing derivatives (scytonemin) (described in U.S. Patent 6,495,586); Heteroarylbenzamides (described in International Patent Publication No. WO01/53274); Indazole compounds (described in International Patent Publication No. WO01/53268); Indolacarbazoles (described in Tenzer et al., supra); Chromane deriviatives (described in International Patent Publication No. WO02/070515); Paullones (described in Schultz, et al., J. Med. Chem., Vol:2909-2919. 1999); Indenopyrazoles (described in International Patent Publication No WO99/17769); Flavones (described in Sedlacek et al., Int J. Oncol. 9:1143-1168. 1996); Peptide derivatives of peptide loop of serine threonine kinases (described in International Patent Publication No. WO98/53050);Oxindoles (described in International Patent Publication No. WO03/051838); Diazepinoindolones (described in International Patent Publication No. WO 2004/063198); Pyrimidines (described in International Patent Publication No. WO 2004/048343); Urea compounds (described in International Patent Publication No. WO 2004/014876); and Pyrrolocarbazoles, benzofuroisoindoles, and azacyclopentafluorenes (described in International Patent Publication No. WO 2003/091255).

I. Diarylurea compounds as described in WO02070494, including:

i) A compound of formula:



wherein X1 is null,-O-, -S-, -CH2-, or - N (R1)- ;

X2 is -O-, -S-, or-N(R1)-; Y is O or S; or =Y represents two hydrogen atoms attached to a common carbon atom; W is selected from the group consisting of heteroaryl, aryl, heterocycloalkyl, cycloalkyl, and C13 alkyl substituted with a heteroaryl or aryl group;

Z is selected from the group consisting of hydro, aryl, and heteroaryl; wherein said aryl groups of W and Z are optionally substituted with one to four substituents represented by R2, said heteroaryl groups of W and Z are optionally substituted with one to four substituents represented by R5, and said heterocycloalkyl and cycloalkyl groups of W are optionally substituted with one to two substituents represented by R6 ;

R1 is selected from the group consisting of hydro, C1-6alkyl, C2-6alkenyl, C2-6alkynyl, and aryl;

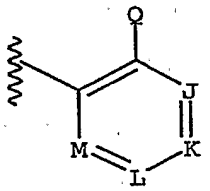
R2 is selected from the group consisting of halo, optionally substituted C1-6alkyl, C2-6alkenyl, OCF3, NO2, CN, NC, N(R3)2, OR3, CO2R3, C(O) N (R3)2, C (O)R3, N (R1) COR3, N (R1)C(O) OR3, N (R3) C (O) OR3, N(R3)C(O)C1-3alkyleneC(O)R3, N(R3)C(O)C1-3alkyleneC(O)OR3, N(R3)C(O)C1-3alkyleneOR3, N(R3)C(O)C1-3alkyleneNHC(O)-OR3, N(R3)C(O)C1-3alkyleneSO2NR3, C1-3alkyleneOR3, and SR3;

R3 is selected from the group consisting of hydro, C1-6alkyl, C2-6alkenyl, cycloalkyl, aryl, heteroaryl, SO2R4, C1-6alkyl substituted with one or more of halo, hydroxy, aryl, heteroaryl, heterocycloalkyl, N (R4) 2, and SO2R4, C1-3alkylenearyl, C1-3alkyleneheteroaryl, C1-3alkyleneC3-8heterocycloalkyl, C1-3alkyleneSO2aryl, optionally substituted Cl-3alkyleneN(R4)2, OCF3, C1-3alkyleneN(R4)3+, C3-8heterocycloalkyl, and CH(C1 3alkyleneN(R4)2)2, or two R3

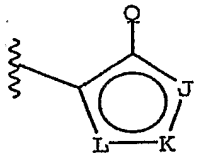
groups are taken together to form an optionally substituted 3-to 6-membered aliphatic ring;

R4 is selected from the group consisting of hydro, C1-6alkyl, cycloalkyl, aryl, heteroaryl, C1-3-alkylenearyl, and SO2C1-6alkyl, or two R4 groups are taken together to form an optionally substituted 3-to 6-membered ring;

R5 is selected from the group consisting of Cl-6alkyl, aryl, N(R3) 2, OR3, halo, N3, CN, C1-3alkylenearyl, C1-3alkyleneN(R3) 2, C(O)R3, and

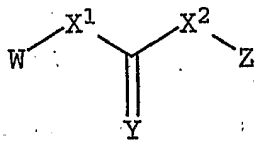


and



R6 is selected from the group consisting of halo and C1-6alkyl ; and pharmaceutically acceptable salts, prodrugs, or solvates thereof.

ii) A compound of formula:



wherein X1 is null,-O-,-S-,-CH2-, or - N (R1)- ;

X2 is -O-, -S-, or-N(R1)-; Y is O or S; or =Y represents two hydrogen atoms attached to a common carbon atom; W is selected from the group consisting of heteroaryl, aryl, heterocycloalkyl, cycloalkyl, and C13 alkyl substituted with a heteroaryl or aryl group;

Z is selected from the group consisting of hydro, aryl, and heteroaryl; wherein said aryl groups of W and Z are optionally substituted with one to four substituents represented by R2, said heteroaryl groups of W and Z are optionally substituted with one to four substituents represented by R5, and said heterocycloalkyl and cycloalkyl groups of W are optionally substituted with one to two substituents represented by R6 ;

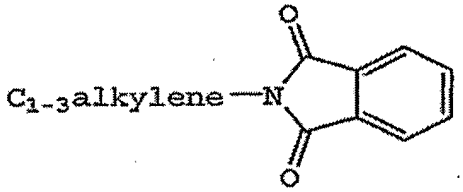
R1 is selected from the group consisting of hydro, C1-6alkyl, C2-6alkenyl, C2-6alkynyl, and aryl;

R2 is selected from the group consisting of halo, optionally substituted C1-6alkyl, C2-6alkenyl, OCF3, NO2, CN, NC, N(R3)2, OR3, CO2R3, C(0) N (R3)2, C (O)R3, N (R1) COR3, N (R1) C (O) OR3, N (R3) C (O) OR3, N (R3) C(0) C1-3alkyleneC(O)R3, N (R3) C (O) C1-3alkyleneC(O)OR3, N (R3) C (O)C1-3alkyleneOR3, N(R3)C(O)C1-3alkyleneNHC(O)-OR3, N(R3)C(O)C1-3alkyleneSO2NR3, C1-3alkyleneOR3, and SR3;

R3 is selected from the group consisting of hydro, C1-6alkyl, C2-6alkenyl, cycloalkyl, aryl, heteroaryl, SO2R4, C1-6alkyl substituted with one or more of halo, hydroxy, aryl, heteroaryl, heterocycloalkyl, N (R4) 2, and SO2R4, C1-3alkylenearyl, C1-3alkyleneheteroaryl, C1-3alkyleneC3-8heterocycloalkyl, C1-3alkyleneSO2aryl, optionally substituted Cl-3alkyleneN(R4)2, OCF3, C1-3alkyleneN(R4)3+, C3-8heterocycloalkyl, and CH(C1 3alkyleneN(R4)2)2, or two R3 groups are taken together to form an optionally substituted 3-to 6-membered aliphatic ring;

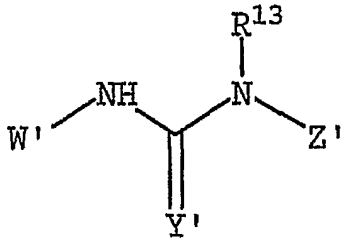
R4 is selected from the group consisting of hydro, C1-6alkyl, cycloalkyl, aryl, heteroaryl, C1-3-alkylenearyl, and SO2C1-6alkyl, or two R4 groups are taken together to form an optionally substituted 3-to 6-membered ring;

R5 is selected from the group consisting of Cl-6alkyl, aryl, N(R3) 2, OR3, halo, N3, CN, C1-3alkylenearyl, C1-3alkyleneN(R3) 2, C(O)R3, and



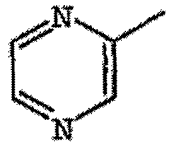
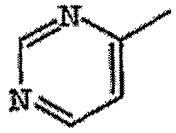
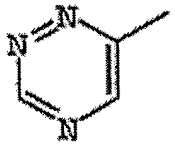
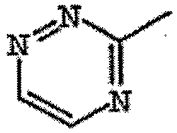
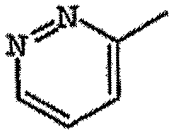
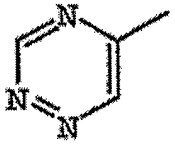
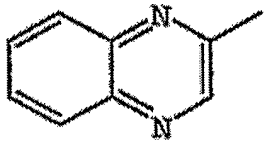
R6 is selected from the group consisting of halo and C1-6alkyl ; and pharmaceutically acceptable salts, prodrugs, or solvates thereof.

iii) A compound of formula:



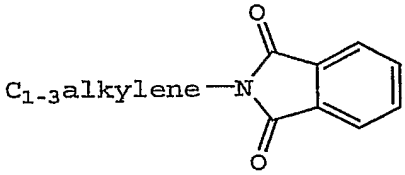
wherein Y' is O or S;

W' is selected from the group consisting of

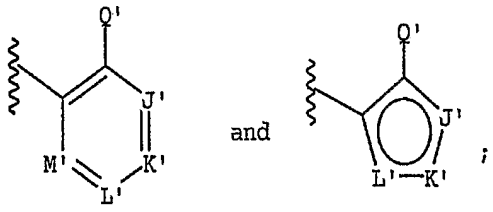
and

optionally substituted with from one to four substituents selected from the group consisting of Cl-6alkyl, aryl, N (R7)2, OR7, N3, CN, C(O) R7, C1-3alkylenearyl, C1-3alkyleneN (R12)2,



and halo;

Z' is selected from the group consisting of:



;

wherein:

Q' is selected from the group consisting of hydro, OR7, SR7, and N (R7) 2, with the proviso that Q' is hydro only when at least one of J', K', L', and M' is N, O, or S;

J' is selected from the group consisting of CR8, NR8, O, and S;

K' is selected from the group consisting of CR9, NR9, O, and S; L' is selected from the group consisting of CR10 , NR10, O, and S;

M' is selected from the group consisting of CR11, NR11,O, and S, with the proviso that Z is different from a pyridone;

wherein: R7, independently, is selected from the group consisting of hydro, C1-6alkyl, C2-6alkenyl, cycloalkyl, aryl, heteroaryl, SO2R12, C1-6alkyl substituted with one or more of halo, hydroxy, aryl, heteroaryl, heterocycloalkyl, N(R12)2, and SO2R12, C1-3alkylenearyl, C1-3alkyleneheteroaryl, C1-3alkyleneC3-8heterocycloalkyl, C1-3alkyleneSO2aryl, optionally substituted C1-3alkyleneN (R12)2, OCF3, C1-3alkyleneN (R12)3+, C3-8heterocycloalkyl, and CH (C1-3alkyleneN(R12)2)2, or two R7 groups are taken together to form an optionally substituted 3-to 6-membered aliphatic ring;

R8, R9, and R10 are each independently selected from the group consisting of null, hydro, halo, optionally substituted C1-6alkyl, C2-6alkenyl, OCF3, NO2, CN, NC, N (R7)2, OR, CO2R7, C(0) N(R7) 2, C(O)R7, N(R13)COR7, N(R13)C(O)OR7, N(R7)C(O)OR7, N(R7)C(O)C1-3alkyleneC(O)R7, N(R7)C(O)C1-3alkylene-C(O)OR7, N(R7)C(O) C1-3alkyleneOR7, N(R7)C(O)C1 3alkyleneNHC(O)OR7, N(R7)C(O)C1-3alkyleneSO2NR7, CF3, C1-3alkyleneN(R12)SO2aryl, C1-3alkyleneN(R12)SO2heteroaryl, C1-3alkyleneOC1-3alkylenearyl, C1-3alkyleneN(R12)C1-3alkylenearyl, C1-3alkyleneN(R12)C1-

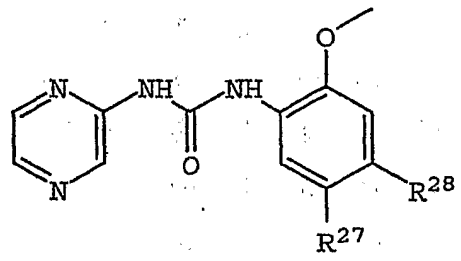
3alkyleneheteroaryl, C1-3alkyleneN(R12)C(O)R7, C1-3alkyleneN(R12)C(O) C1-3-alkyleneOR2, C1-3alkyleneN(R12)C(O) aryl, C1-3alkylene-N(R12)C(O)C1-3alkyleneN (R12)2, C1-3alkyleneN(R12)C(O)-heteroaryl, C1-3alkyleneOR7, and SR7, wherein R7 is as defined above;

Rll is selected from the group consisting of null, hydro, optionally substituted C1-6alkyl, and halo;

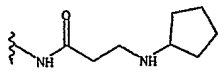
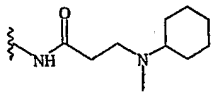
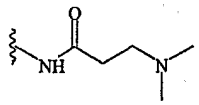
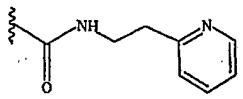
R12 is selected from the group consisting of hydro, C1-6alkyl, cycloalkyl, aryl, heteroaryl, C1-3alkylenearyl, and SO2C1-6alkyl, or two R12 groups are taken together to form an optionally substituted 3-to 6-membered ring; and

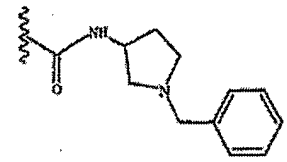
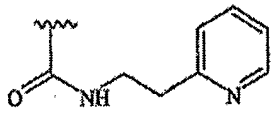
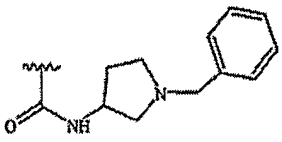
R13 is selected from the group consisting of hydro, C1-6alkylt C2-6alkenyl, C2-6alkynyl, and aryl; provided that when Q' is hydro or OCH3, at least one of R8, R9, and R10 is different from hydro, CH3, OCH3, and halo, and pharmaceutically acceptable salts, prodrugs, or solvates thereof.

iv) A compound of formula:

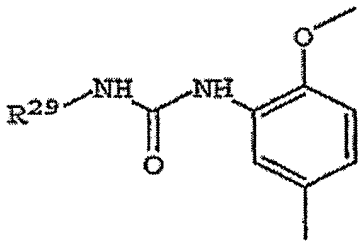


wherein R^{27} and R^{28} are

R^{27}	R^{28}
H	
H	
H	
CH_3	H
H	

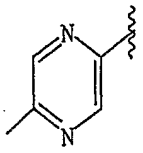
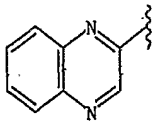
R^{27}	R^{28}
H	
	H
	H

or

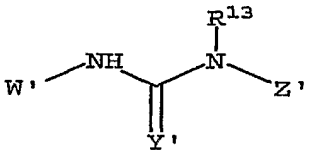


5

wherein R29 is

R^{29}



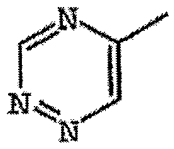
v) A compound of formula:

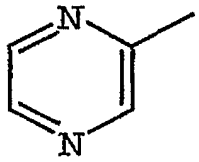


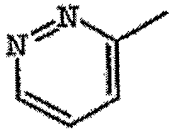
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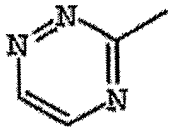
wherein Y' is O or S;

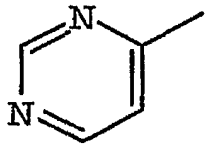
W' is selected from the group consisting of

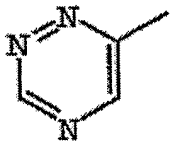


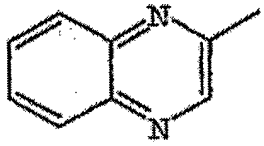








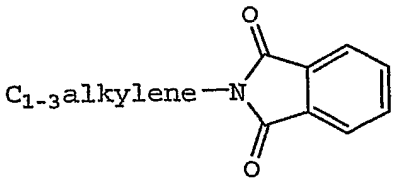




and

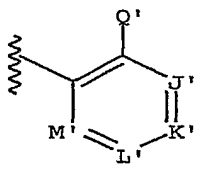
optionally substituted with from one to four substituents selected from the group consisting of

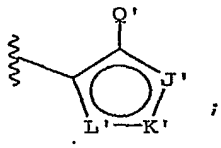
C1-6alkyl, aryl, N(R7)2, OR7, N3, CN, C(O)R7, C1-3alkylenearyl, C1-3alkyleneN(R12)2,



and halo;

Z' is selected from the group consisting of:



and


;

wherein:

Q' is selected from the group consisting of hydro, OR^7, SR^7, and $N(R^7)_2$,

with the proviso that Q' is hydro only when at least one of J', K', L', and M' is N, O, or S;

J' is selected from the group consisting of CR^8, NR^8, O, and S;

K' is selected from the group consisting of CR^9, NR^9, O, and S; L' is selected from the group consisting of CR^{10}, NR^{10}, O, and S;

M' is selected from the group consisting of CR^{11}, NR^{11}, O, and S, with the proviso that Z is different from a pyridone;

wherein: R^7, independently, is selected from the group consisting of hydro, C_{1-6}alkyl, C_{2-6}alkenyl, cycloalkyl, aryl, heteroaryl, SO_2R^{12}, C_{1-6}alkyl substituted with one or more of halo, hydroxy, aryl, heteroaryl, heterocycloalkyl, $N(R^{12})_2$, and SO_2R^{12}, C_{1-3}alkylenearyl, C_{1-3}alkyleneheteroaryl, C_{1-3}alkyleneC_{3-8}heterocycloalkyl, C_{1-3}alkyleneSO_2aryl, optionally substituted C_{1-3}alkylene$N(R^{12})_2$, OCF_3, C_{1-3}alkylene$N(R^{12})_3$+, C_{3-8}heterocycloalkyl, and $CH(C_{1-3}alkyleneN(R^{12})_2)_2$, or two R^7 groups are taken together to form an optionally substituted 3- to 6-membered aliphatic ring;

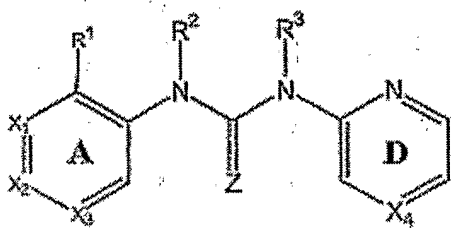
R^8, R^9, and R^{10} are each independently selected from the group consisting of null, hydro, halo, optionally substituted C_{1-6}alkyl, C_{2-6}alkenyl, OCF_3, NO_2, CN, NC, $N(R^7)_2$, OR^7, CO_2R^7, $C(O)N(R^7)_2$, $C(O)R^7$, $N(R^{13})$ COR^7, $N(R^{13})$ $C(O)OR^7$, $N(R^7)$ $C(O)OR^7$, $N(R^7)C(O)C_{1-3}alkyleneC(0)R^7$, $N(R^7)C(O)C_{1-3}$alkyleneC(O)OR^7, $N(R^7)C(O)C_{1-3}alkyleneOR^7$, $N(R^7)C(O)C_{1-3}alkyleneNHC(O)OR^7$, $N(R^7)C(O)C_{1-3}alkyleneSO_2NR^7$, $C_{1-3}alkyleneOR^7$, and SR^7, wherein R^7 is as defined above;

R^{11} is selected from the group consisting of null, hydro, optionally substituted C_{1-6}alkyl, and halo;

R^{12} is selected from the group consisting of hydro, C_{1-6}alkyl, cycloalkyl, aryl, heteroaryl, C_{1-3}alkylenearyl, and SO_2C_{1-6}alkyl, or two R^{12} groups are taken together to form an optionally substituted 3- to 6-membered ring; and R^{13} is selected from the group consisting of hydro, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, and aryl; provided that when Q' is hydro or OCH_3, at least one of R^8, R^9, and R^{10} is different from hydro, CH_3, OCH_3, and halo, and pharmaceutically acceptable salts, prodrugs, or solvates thereof.

II. Urea compounds described in US20040014765, including :

i) A compound of the formula:



III

or a pharmaceutically acceptable salt thereof, wherein:

X_1-X_3 are independently CH or N, that provided that X_1-X_3 are not all N;

X_4 is CH or N; Z is O, S,or N-CN ;

Ring A is optionally substituted at any substitutable carbon by R^4;

R^1 is -T-NH_2, -V-T-NH_2, -T-NHR^x, -V-T-NHR^x ;

T is a C_{1-6} straight or branched alkylidene chain that is optionally interrupted by -O-, -S-, -N(R^5)-, -S(O)-, -SO_2-, -C(O)-, -OC(O)-, -N(R^5)C(O)-, -C(O)N(R^5)-, -SO_2N(R^5)-, or-N(R^5)SO_2-,

wherein the alkylidene chain or a portion thereof is optionally part of a 3-6 membered ring system ;

V is -O-, -S-, -N(R^5)-, -S(O)-,-SO_2-,-C(O)-,-OC(O)-,-N(R^5)C(O)-, -C(O)N(R^5)-,-SO_2N(R^5)-, or-N(R^5) SO_2-;

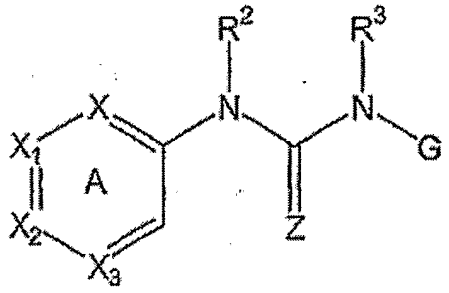
R^2 and R^3 are each independently selected from hydrogen, C_{1-6} alkyl optionally substitutedwith-N(R^8)$_2$,-C(=O)R,-CO_2R, or SO_2R, or R^2 and R^3 taken together with their intervening atoms form an optionally substituted 5-6 membered ring;

each R^4 is independently selected from halo,-OR,-SR,-CN,-NO_2, -N(R^5)$_2$, -N(R^5)C(O)R, -N(R^5)CO_2R, -N(R^5)C(O)N(R^5)$_2$, -C(O)N(R^5)$_2$,- C(O)R^5,-OC(O)N(R^5)$_2$, -CO_2R, -SO_2R, -S(O)R, -SO_2N(R^5)$_2$, -N(R^5)SO_2R, or an optionally substituted group selected from C_{1-8} aliphatic, aryl, aralkyl, heterocyclyl, heterocyclealkyl, heteroaryl, or heteroaralkyl, or two ortho R^4s, taken together with the ortho carbon atoms to which they are bonded, form an optionally substituted five or six membered phenyl, pyridyl or heterocyclyl fused to Ring A;

each R^5 is independently selected from hydrogen, C_{1-6} aliphatic, -CO_2R, -SO_2R, or-C(O)R, or two R^5 on the same nitrogen taken together with the nitrogen form a 5-8 membered heteroaryl or heterocycle ring having 1-4 heteroatoms selected from N, O, or S; each R^8 is independently a C_{1-3} alkyl or, taken together with the nitrogen atom to which they are bonded, a 5-7 membered nitrogen containing heterocycle;

Ring D is optionally substituted by C_{1-4} aliphatic or haloaliphatic, -OR^7, -SR^7, -C(O)R^7, -CO_2R^7, -SO_2R^7, -CN, -C(O)N(R^7)$_2$, -N(R^7)C(O)(C_{1-2} alkyl), or-N(R^7)$_2$ and is optionally fused to an optionally substituted phenyl or optionally substituted cyclohexyl ring; each R^7 is independently selected from hydrogen or an optionally substituted C_{1-3} aliphatic or-N (R^7)$_2$ is a nitrogen-containing heterocyclyl; each R is independently selected from hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, aryl, aralkyl, heteroaryl, or heteroaralkyl-butyl ; and R^x is C_{1}-C_{8} alkyl.

ii) A compound of the formula:



or a pharmaceutically acceptable salt thereof, wherein: X is CR^1 ;

X_1-X_3 are CH;

Z is O ;

Ring A is optionally substituted at any substitutable carbon by R^4 ;

R^1 is V-T-R^6 ;

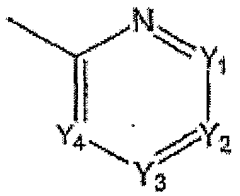
T is a C_{2-4} alkylidene chain;

V is -O-;

R^2 and R^3 are each hydrogen;

each R^4 is independently selected from halo,-OR,-SR,-CN,-NO_2, -$N(R^5)_2$, -$N(R^5)C(O)R$, -$N(R^5)CO_2R$, -$N(R^5)C(O)N(R^5)_2$, -$C(O)N(R^5)_2$,- $OC(O)N(R^5)_2$, -CO_2R, -SO_2R, -S(O)R, -$SO_2N(R^5)_2$, -$N(R^5)SO_2R$, or an optionally substituted group selected from C_{1-8} aliphatic, aryl, aralkyl, heterocyclyl, heterocyclealkyl, heteroaryl, or heteroaralkyl, or two ortho R^4s, taken together with the ortho carbon atoms to which they are bonded, form an optionally substituted five or six membered phenyl, pyridyl or heterocyclyl fused to Ring A;

each R^8 is independently a C_{1-3} alkyl or, taken together with the nitrogen atom to which they are bonded, a 5-7 membered nitrogen containing heterocycle;



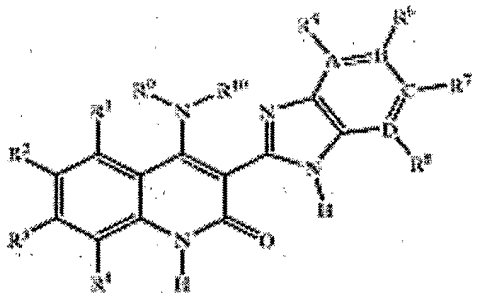
G is

Y_{1-4} are each independently selected from CH or nitrogen, provided that Ring B has no more than three nitrogen atoms and Y_1 and Y_2 are not both N, said

Ring B being optionally substituted by C_{1-4} aliphatic or haloaliphatic, OR^7, $-SR^7$, $-C(O)R^7$, $-CO_2R^7$, $-SO_2R^7$, -CN, $-C(O)N(R^7)_2$, $-N(R^7)C(O)(C_{1-2}$ alkyl), or-$N(R^7)_2$; each R^7 is independently selected from hydrogen or an optionally substituted C_{1-3} aliphatic or-N $(R^7)_2$ is a nitrogen-containing heterocyclyl; and each R is hydrogen.

III. Chk1 Inhibiting Compounds described in US20040092535, including"

i) A compound of formula:



and a tautomer, a pharmaceutically acceptable salt, a pharmaceutically acceptable salt of the tautomer, or mixtures thereof,

wherein: A, B, C, and D are independently selected from the group consisting carbon and nitrogen;

R^1 is selected from the group consisting of -H, -F, -Cl, -Br, -I, -CN, -NO_2, substituted and unsubstituted alkyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted alkenyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted alkynyl groups having from 1 to 8 carbon atoms, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted heterocyclylalkyl groups, -SH, substituted and unsubstituted -S-alkyl groups, substituted and unsubstituted $-S(-O)_2$-O-alkyl groups, substituted and unsubstituted -$S(-O)_2$-alkyl groups, substituted and unsubstituted -S(-O)-alkyl groups, $-S(-O)-NH_2$, substituted and unsubstituted -S(-O)-N(H)(alkyl) groups, substituted and unsubstituted $-S(-O)-N(alkyl)_2$ groups, -OH, substituted and unsubstituted alkoxy groups, substituted and unsubstituted aryloxy groups, substituted and unsubstituted arylalkoxy groups, substituted and unsubstituted heterocyclyloxy groups, substituted and unsubstituted heterocyclylalkoxy groups, $-NH_2$, substituted and unsubstituted -

N(H)(alkyl) groups, substituted and unsubstituted -N(alkyl)$_2$ groups, substituted and unsubstituted -N(H)(heterocyclyl) groups, substituted and unsubstituted -N(alkyl)(heterocyclyl) groups, substituted and unsubstituted -N(heterocyclyl)$_2$ groups, substituted and unsubstituted -N(H)(heterocyclylalkyl) groups, substituted and unsubstituted -N(alkyl)(heterocyclylalkyl) groups, substituted and unsubstituted -N(heterocyclylalkyl)$_2$ groups, substituted and unsubstituted -N(H)-C(-O)-alkyl groups, substituted and unsubstituted -N(H)-C(-O)-heterocyclyl groups, substituted and unsubstituted -N(H)-C(-O)-heterocyclylalkyl groups, substituted and unsubstituted -N(H)-S(-O)-alkyl groups, substituted and unsubstituted -C(-O)-alkyl groups, substituted and unsubstituted -C(-O)-heterocyclyl groups, substituted and unsubstituted -C(-O)-heterocyclylalkyl groups, -C(-O)-NH$_2$, substituted and unsubstituted -C(-O)-N(H)(alkyl) groups, substituted and unsubstituted -C(-O)-N(alkyl)$_2$ groups, substituted and unsubstituted -C(-O)-N(H)(aralkyl) groups, substituted and unsubstituted -C(-O)-N(H)(heterocyclyl) groups, -C(-O)-N(H)(heterocyclylalkyl) groups, -CO$_2$H, substituted and unsubstituted -C(-O)-O-alkyl groups, substituted and unsubstituted -C(-O)-O-heterocyclyl groups, and substituted and unsubstituted -C(-O)-O-heterocyclylalkyl groups;

R^2 and $R^3$are independently selected from the group consisting of-H, -F, -Cl, -Br, -I, -CN, -NO$_2$, substituted and unsubstituted alkyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted alkenyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted alkynyl groups having from 1 to 8 carbon atoms, substituted and unsubstituted aryl groups, substituted and unsubstituted aralkyl groups, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted heterocyclylalkyl groups, -SH, substituted and unsubstituted -S-alkyl groups, substituted and unsubstituted -S-aryl groups, substituted and unsubstituted -S-aralkyl groups, substituted and unsubstituted -S(-O)$_2$-O-alkyl groups, substituted and unsubstituted -S(-O)$_2$-alkyl groups, substituted and unsubstituted -S(-O)$_2$-heterocyclyl groups, substituted and unsubstituted -S(-O)-alkyl groups, substituted and unsubstituted -S(-O)-heterocyclyl groups, -S(-O)$_2$-NH$_2$, substituted and unsubstituted -S(-O)$_2$-N(H)(alkyl) groups, substituted and unsubstituted -S(-O)$_2$-N(alkyl)$_2$ groups, substituted and unsubstituted -S(-O)$_2$-N(H)(aryl) groups, substituted and unsubstituted -S(-O)$_2$-N(alkyl)(aryl) groups, substituted and unsubstituted -S(-O)$_2$-N(aryl)$_2$ groups, substituted and unsubstituted -S(-O)$_2$-N(H)(aralkyl) groups, substituted and

unsubstituted -S(-O)$_2$-N(alkyl)(aralkyl) groups, substituted and unsubstituted -S(-O)2-N(aralkyl)$_2$ groups, -OH, substituted and unsubstituted alkoxy groups, substituted and unsubstituted aryloxy groups, substituted and unsubstituted arylalkoxy groups, substituted and unsubstituted heterocyclyloxy groups, substituted and unsubstituted heterocyclylalkoxy groups, -NH_2, substituted and unsubstituted -N(H)(alkyl) groups, substituted and unsubstituted -N(alkyl)$_2$ groups, substituted and unsubstituted -N(H)(aryl) groups, substituted and unsubstituted -N(alkyl)(aryl) groups, substituted and unsubstituted -N(aryl)$_2$ groups, substituted and unsubstituted -N(H)(aralkyl) groups, substituted and unsubstituted -N(alkyl)(aralkyl) groups, substituted and unsubstituted -N(aralkyl)$_2$ groups, substituted and unsubstituted -N(H)(heterocyclyl) groups, substituted and unsubstituted -N(alkyl)(heterocyclyl) groups, substituted and unsubstituted -N(heterocyclyl)$_2$ groups, substituted and unsubstituted -N(H)(heterocyclylalkyl) groups, substituted and unsubstituted -N(alkyl)(heterocyclylalkyl) groups, substituted and unsubstituted -N(heterocyclylalkyl)$_2$ groups, substituted and unsubstituted -N(H)-S(-O)$_2$-alkyl groups, substituted and unsubstituted -N(H)-S(-O)$_2$-aryl groups, substituted and unsubstituted -N(H)-S(-O)$_2$-aralkyl groups, substituted and unsubstituted -N(H)-S(-O)$_2$-heterocyclyl groups, substituted and unsubstituted -N(H)-S(-O)$_2$-heterocyclylalkyl groups, substituted and unsubstituted -N(H)-C(-O)-alkyl groups, substituted and unsubstituted -N(H)-C(-O)-aryl groups, substituted and unsubstituted -N(H)-C(-O)-aralkyl groups, substituted and unsubstituted -N(H)-C(-O)-heterocyclyl groups, substituted and unsubstituted -N(H)-C(-O)-heterocyclylalkyl groups, substituted and unsubstituted -N(alkyl)-C(-O)-alkyl groups, substituted and unsubstituted -N(alkyl)-C(-O)-aryl groups, substituted and unsubstituted -N(alkyl)-C(-O)-aralkyl groups, substituted and unsubstituted -N(alkyl)-C(-O)-heterocyclyl groups, substituted and unsubstituted -N(alkyl)-C(-O)-heterocyclylalkyl groups, substituted and unsubstituted -N(alkyl)-S(-O)$_2$-alkyl groups, substituted and unsubstituted -N(alkyl)-S(-O)$_2$-aryl groups, substituted and unsubstituted -N(alkyl)-S(-O)$_2$-aralkyl groups, substituted and unsubstituted -N(alkyl)-S(-O)$_2$-heterocyclyl groups, substituted and unsubstituted -N(alkyl)-S(-O)$_2$-heterocyclylalkyl groups, -N(H)-C(-O)-NH_2, substituted and unsubstituted -N(H)-C(-O)-N(H)(alkyl) groups, substituted and unsubstituted -N(H)-C(-O)-N(alkyl)$_2$ groups, substituted and unsubstituted -N(H)-C(-O)-N(H)(aryl) groups, substituted and unsubstituted -N(H)-C(-O)-N(alkyl)(aryl) groups, substituted and unsubstituted -N(H)-C(-O)-N(aryl)$_2$

groups, substituted and unsubstituted -N(H)-C(-O)-N(H)(aralkyl) groups, substituted and unsubstituted -N(H)-C(-O)-N(alkyl)(aralkyl) groups, substituted and unsubstituted -N(H)-C(-O)-N(aralkyl)$_2$ groups, substituted and unsubstituted -N(H)-C(-O)-N(H)(heterocyclyl) groups, substituted and unsubstituted -N(H)-C(-O)-N(alkyl)(heterocyclyl) groups, substituted and unsubstituted -N(H)-C(-O)-N(heterocyclyl)$_2$ groups, substituted and unsubstituted -N(H)-C(-O)-N(H)(heterocyclylalkyl) groups, substituted and unsubstituted -N(H)-C(-O)-N(alkyl)(heterocyclylalkyl) groups, substituted and unsubstituted -N(H)-C(-O)-N(heterocyclylalkyl)$_2$ groups, substituted and unsubstituted -N(alkyl)-C(-O)-NH$_2$ groups, substituted and unsubstituted -N(alkyl)-C(-O)-N(H)(alkyl) groups, substituted and unsubstituted -N(alkyl)-C(-O)-N(alkyl)$_2$ groups, substituted and unsubstituted -N(alkyl)-C(-O)-N(H)(aryl) groups, substituted and unsubstituted -N(alkyl)-C(-O)-N(alkyl)(aryl) groups, substituted and unsubstituted -N(alkyl)-C(-O)-N(aryl)$_2$ groups, substituted and unsubstituted -N(alkyl)-C(-O)-N(H)(aralkyl) groups, substituted and unsubstituted -N(alkyl)-C(-O)-N(alkyl)(aralkyl) groups, substituted and unsubstituted -N(alkyl)-C(-O)-N(aralkyl)$_2$ groups, substituted and unsubstituted -N(alkyl)-C(-O)-N(H)(heterocyclyl) groups, substituted and unsubstituted -N(alkyl)-C(-O)-N(alkyl)(heterocyclyl) groups, substituted and unsubstituted -N(alkyl)-C(-O)-N(heterocyclyl)$_2$ groups, substituted and unsubstituted -N(alkyl)-C(-O)-N(H)(heterocyclylalkyl) groups, substituted and unsubstituted -N(alkyl)-C(-O)-N(alkyl)(heterocyclylalkyl) groups, substituted and unsubstituted -N(alkyl)-C(-O)-N(heterocyclylalkyl)$_2$ groups, substituted and unsubstituted -C(-O)-alkyl groups, substituted and unsubstituted -C(-O)-aryl groups, substituted and unsubstituted -C(-O)-aralkyl groups, substituted and unsubstituted -C(-O)-heterocyclyl groups, substituted and unsubstituted -C(-O)-heterocyclylalkyl groups, -C(-O)-NH$_2$, substituted and unsubstituted -C(-O)-N(H)(alkyl) groups, substituted and unsubstituted -C(-O)-N(alkyl)$_2$ groups, substituted and unsubstituted -C(-O)-N(H)(aryl) groups, substituted and unsubstituted -C(-O)-N(alkyl)(aryl) groups, substituted and unsubstituted -C(-O)-N(aryl)$_2$ groups, substituted and unsubstituted -C(-O)-N(H)(aralkyl) groups, substituted and unsubstituted -C(-O)-N(alkyl)(aralkyl) groups, substituted and unsubstituted -C(-O)-N(aralkyl)$_2$ groups, substituted and unsubstituted -C(-O)-N(H)(heterocyclyl) groups, substituted and unsubstituted -C(-O)-N(alkyl)(heterocyclyl) groups, substituted and unsubstituted -C(-O)-N(heterocyclyl)$_2$ groups, substituted and unsubstituted -C(-O)-

N(H)(heterocyclylalkyl) groups, substituted and unsubstituted -C(-O)-N(alkyl)(heterocyclylalkyl) groups, substituted and unsubstituted -C(-O)-N(heterocyclylalkyl)$_2$ groups, -CO_2H, substituted and unsubstituted -C(-O)-O-alkyl groups, substituted and unsubstituted -C(-O)-O-aryl groups, substituted and unsubstituted -C(-O)-O-heterocyclyl groups, and substituted and unsubstituted -C(-O)-O-heterocyclylalkyl groups;

R^4 is selected from the group consisting of -H, -F, -Cl, -Br, -I, -CN, -NO_2, substituted and unsubstituted alkyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted alkenyl groups having from 1 to 8 carbon atoms, substituted and unsubstituted alkynyl groups having from 1 to 8 carbon atoms, -SH, substituted and unsubstituted -S-alkyl groups, substituted and unsubstituted -S(-O)$_2$-O-alkyl groups, substituted and unsubstituted -S(-O)$_2$-alkyl groups, substituted and unsubstituted -S(-O)-alkyl groups, -S(-O)$_2$-NH_2, substituted and unsubstituted -S(-O)$_2$-N(H)(alkyl) groups, substituted and unsubstituted -S(-O)$_2$-N(alkyl)$_2$ groups, -OH, substituted and unsubstituted alkoxy groups, -NH_2, substituted and unsubstituted -N(H)(alkyl) groups, substituted and unsubstituted -N(alkyl)$_2$ groups, substituted and unsubstituted -N(H)-C(-O)-alkyl groups, substituted and unsubstituted -N(H)-S(-O)-alkyl groups, -C(-O)-NH2, substituted and unsubstituted -C(-O)-N(H)(alkyl) groups, substituted and unsubstituted -C(-O)-N(alkyl)$_2$ groups, and substituted and unsubstituted -C(-O)-O-alkyl groups;

R^5 and R^8 are independently selected from the group consisting of-H, -F, -Cl, -Br, -I, -CN, -NO_2, substituted and unsubstituted straight and branched chain alkyl groups having from 1 to 8 carbon atoms, substituted and unsubstituted alkenyl groups having from 1 to 8 carbon atoms, substituted and unsubstituted alkynyl groups having from 1 to 8 carbon atoms, substituted and unsubstituted heterocyclyl groups, -SH, substituted and unsubstituted -S-alkyl groups, substituted and unsubstituted -S(-O)$_2$-O-alkyl groups, substituted and unsubstituted -S(-O)$_2$-alkyl groups, substituted and unsubstituted -S(-O)-alkyl groups, -S(-O)$_2$-NH_2, substituted and unsubstituted -S(-O)$_2$-N(H)(alkyl) groups, substituted and unsubstituted -S(-O)$_2$-N(alkyl)$_2$ groups, -OH, substituted and unsubstituted alkoxy groups, -NH_2, substituted and unsubstituted -N(H)(alkyl) groups, substituted and unsubstituted -N(alkyl)$_2$ groups, substituted and unsubstituted -N(H)-C(-O)-alkyl groups, substituted and unsubstituted -N(H)-S(-O)-alkyl groups, -C(-O)-NH_2, substituted and unsubstituted -C(-O)-N(H)(alkyl) groups,

substituted and unsubstituted -C(-O)-N(alkyl)$_2$ groups, and substituted and unsubstituted -C(-O)-O-alkyl groups; or R^5 may be absent if A is nitrogen; or R^8 may be absent if D is nitrogen;

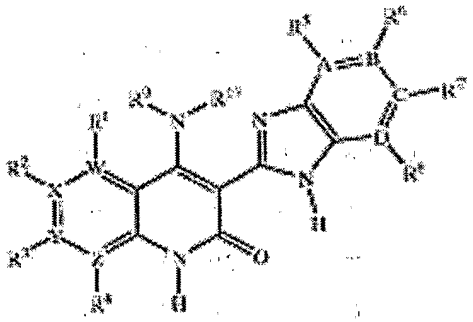
R^6 and R^7 are independently selected from the group consisting of-H, -F, -Cl, -Br, -I, -NO2, -CN, substituted and unsubstituted alkyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted alkenyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted alkynyl groups having from 1 to 8 carbon atoms, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted heterocyclylalkyl groups, -SH, substituted and unsubstituted -S-alkyl groups, substituted and unsubstituted -S(-O)$_2$-O-alkyl groups, substituted and unsubstituted -S(-O)$_2$-alkyl groups, substituted and unsubstituted -S(-O)$_2$-heterocyclyl groups, substituted and unsubstituted -S(-O)-alkyl groups, substituted and unsubstituted -S(-O)-heterocyclyl groups, -S(-O)$_2$-NH$_2$, substituted and unsubstituted -S(-O)$_2$-N(H)(alkyl) groups, substituted and unsubstituted -S(-O)$_2$-N(alkyl)$_2$ groups, substituted and unsubstituted -S(-O)$_2$-N(H)(heterocyclyl) groups, substituted and unsubstituted -S(-O)$_2$-N(alkyl)(heterocyclyl) groups, substituted and unsubstituted -S(-O)$_2$-N(heterocyclyl)$_2$ groups, substituted and unsubstituted -S(-O)$_2$-N(H)(heterocyclylalkyl) groups, substituted and unsubstituted -S(-O)$_2$-N(alkyl)(heterocyclylalkyl) groups, substituted and unsubstituted -S(-O)$_2$-N(heterocyclylalkyl)$_2$ groups, -OH, substituted and unsubstituted alkoxy groups, substituted and unsubstituted aryloxy groups, substituted and unsubstituted arylalkoxy groups, substituted and unsubstituted heterocyclyloxy groups, substituted and unsubstituted heterocyclylalkoxy groups, -NH$_2$, substituted and unsubstituted -N(H)(alkyl) groups, substituted and unsubstituted -N(alkyl)$_2$ groups, substituted and unsubstituted -N(H)(aryl) groups, substituted and unsubstituted -N(alkyl)(aryl) groups, substituted and unsubstituted -N(aryl)$_2$ groups, substituted and unsubstituted -N(H)(aralkyl) groups, substituted and unsubstituted -N(alkyl)(aralkyl) groups, substituted and unsubstituted -N(aralkyl)$_2$ groups, substituted and unsubstituted -N(H)(heterocyclyl) groups, substituted and unsubstituted -N(alkyl)(heterocyclyl) groups, substituted and unsubstituted -N(heterocyclyl)$_2$ groups, substituted and unsubstituted -N(H)(heterocyclylalkyl) groups, substituted and unsubstituted -N(alkyl)(heterocyclylalkyl) groups, substituted and unsubstituted -N(heterocyclylalkyl)$_2$ groups, substituted and unsubstituted -N(H)-S(-O)$_2$-alkyl

groups, substituted and unsubstituted -N(H)-S(-O)$_2$-heterocyclyl groups, substituted and unsubstituted -N(H)-S(-O)$_2$-heterocyclylalkyl groups, substituted and unsubstituted -N(H)-C(-O)-alkyl groups, substituted and unsubstituted -N(H)-C(-O)-heterocyclyl groups, substituted and unsubstituted -N(H)-C(-O)-heterocyclylalkyl groups, substituted and unsubstituted -N(alkyl)-C(-O)-alkyl groups, substituted and unsubstituted -N(alkyl)-C(-O)-heterocyclyl groups, substituted and unsubstituted -N(alkyl)-C(-O)-heterocyclylalkyl groups, substituted and unsubstituted -N(alkyl)-S(-O)$_2$-alkyl groups, substituted and unsubstituted -N(alkyl)-S(-O)$_2$-heterocyclyl groups, substituted and unsubstituted -N(alkyl)-S(-O)$_2$-heterocyclylalkyl groups, substituted and unsubstituted -C(-O)-alkyl groups, substituted and unsubstituted -C(-O)-heterocyclyl groups, substituted and unsubstituted -C(-O)-heterocyclylalkyl groups, -C(-O)-NH_2, substituted and unsubstituted -C(-O)-N(H)(alkyl) groups, substituted and unsubstituted -C(-O)-N(alkyl)$_2$ groups, substituted and unsubstituted -C(-O)-N(H)(aryl) groups, substituted and unsubstituted -C(-O)-N(alkyl)(aryl) groups, substituted and unsubstituted -C(-O)-N(aryl)$_2$ groups, substituted and unsubstituted -C(-O)-N(H)(aralkyl) groups, substituted and unsubstituted -C(-O)-N(alkyl)(aralkyl) groups, substituted and unsubstituted -C(-O)-N(aralkyl)$_2$ groups, substituted and unsubstituted -C(-O)-N(H)(heterocyclyl) groups, substituted and unsubstituted -C(-O)-N(alkyl)(heterocyclyl) groups, substituted and unsubstituted -C(-O)-N(heterocyclyl)$_2$ groups, substituted and unsubstituted -C(-O)-N(H)(heterocyclylalkyl) groups, substituted and unsubstituted -C(-O)-N(alkyl)(heterocyclylalkyl) groups, substituted and unsubstituted -C(-O)-N(heterocyclylalkyl)$_2$ groups, -CO_2H, substituted and unsubstituted -C(-O)-O-alkyl groups, substituted and unsubstituted -C(-O)-O-heterocyclyl groups, and substituted and unsubstituted -C(-O)-O-heterocyclylalkyl groups; or R^6 may be absent if B is nitrogen; or R^7 may be absent if C is nitrogen;

R^9 is selected from the group consisting of -H, substituted and unsubstituted alkyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted aryl groups, substituted and unsubstituted aralkyl groups, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted heterocyclylalkyl groups, substituted and unsubstituted heterocyclylaminoalkyl groups, substituted and unsubstituted alkoxy groups, and -NH_2, or R^9 and R^{10} join together to form one or more rings, each having 5, 6, or 7 ring members; and

R^{10} is -H, or R^9 and R^{10} join together to form one or more rings, each having 5, 6, or 7 ring members.

ii) A compound of formula:



and a tautomer, a pharmaceutically acceptable salt of the compound, a pharmaceutically acceptable salt of the tautomer, or mixtures thereof,

wherein: A, B, C, and D are independently selected from the group consisting of carbon and nitrogen;

W, X, Y, and Z are independently selected from the group consisting of carbon and nitrogen and at least one of W, X, Y, and Z is a nitrogen;

R^1 is selected from the group consisting of -H, -F, -Cl, -Br, -I, substituted and unsubstituted straight and branched chain alkyl groups having from 1 to 8 carbon atoms, substituted and unsubstituted alkenyl groups having from 1 to 8 carbon atoms, substituted and unsubstituted alkynyl groups having from 1 to 8 carbon atoms, -CN, $-NO_2$, -OH, -SH, substituted and unsubstituted alkoxy groups, substituted and unsubstituted -S-alkyl groups, substituted and unsubstituted $-S(-O)_2-O$-alkyl groups, substituted and unsubstituted $-S(-O)_2$-alkyl groups, substituted and unsubstituted -S(-O)-alkyl groups, $-S(-O)-NH_2$, substituted and unsubstituted -S(-O)-N(H)(alkyl) groups, substituted and unsubstituted $-S(-O)-N(alkyl)_2$ groups, $-C(-O)-NH_2$, substituted and unsubstituted -C(-O)-N(H)(alkyl) groups, substituted and unsubstituted $-C(-O)-N(alkyl)_2$ groups, substituted and unsubstituted -C(-O)-O-alkyl groups, $-NH_2$, substituted and unsubstituted -N(H)(alkyl) groups, substituted and unsubstituted $-N(alkyl)_2$ groups, substituted and unsubstituted -N(H)-C(-O)-alkyl

groups, and substituted and unsubstituted -N(H)-S(-O)-alkyl groups; or R^1 may be absent if W is nitrogen;

R^2 is selected from the group consisting of -H, -F, -Cl, -Br, -I, $-NO_2$, -CN, $-NH_2$, $-CO_2H$, -OH, substituted and unsubstituted straight and branched chain alkyl groups having from 1 to 8 carbon atoms, substituted and unsubstituted cycloalkenyl groups, substituted and unsubstituted cycloalkyl groups, substituted and unsubstituted alkoxy groups, substituted and unsubstituted -N(H)(alkyl) groups, substituted and unsubstituted $-N(alkyl)_2$ groups, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted aryl groups, substituted and unsubstituted alkenyl groups having from 1 to 8 carbon atoms, substituted and unsubstituted alkynyl groups having from 1 to 8 carbon atoms, -SH, substituted and unsubstituted -S-alkyl groups, substituted and unsubstituted $-S(-O)_2-O$-alkyl groups, substituted and unsubstituted $-S(-O)_2$-alkyl groups, substituted and unsubstituted $-S(-O)_2$-heterocyclyl groups, substituted and unsubstituted -S(-O)-alkyl groups, substituted and unsubstituted -S(-O)-heterocyclyl groups, $-S(-O)-NH_2$, substituted and unsubstituted -S(-O)-N(H)(alkyl) groups, substituted and unsubstituted -S(-O)-$N(alkyl)_2$ groups, $-C(-O)-NH_2$, substituted and unsubstituted -C(-O)-N(H)(alkyl) groups, substituted and unsubstituted $-C(-O)-N(alkyl)_2$ groups, substituted and unsubstituted -C(-O)-alkyl groups, substituted and unsubstituted -C(-O)-heterocyclyl groups, substituted and unsubstituted -C(-O)-O-alkyl groups, substituted and unsubstituted -N(H)-C(-O)-alkyl groups, substituted and unsubstituted -N(H)-C(-O)-heterocyclyl groups, substituted and unsubstituted -N(H)-S(-O)-alkyl groups, substituted and unsubstituted -N(H)-S(-O)-heterocyclyl groups, -N(alkyl)-C(-O)-alkyl groups, substituted and unsubstituted -N(alkyl)-C(-O)-heterocyclyl groups, substituted and unsubstituted -N(alkyl)-S(-O)-alkyl groups, substituted and unsubstituted -N(alkyl)-S(-O)-heterocyclyl groups, $-N(H)-C(-O)-NH_2$, substituted and unsubstituted -N(H)-C(-O)-N(H)(alkyl) groups, substituted and unsubstituted -N(H)-C(-O)-$N(alkyl)_2$ groups, $-N(alkyl)-C(-O)-NH_2$, substituted and unsubstituted -N(alkyl)-C(-O)-N(H)(alkyl) groups, and substituted and unsubstituted $-N(alkyl)-C(-O)-N(alkyl)_2$ groups; or R^2 and R^3 may join together to form a cyclic group when X and Y are both carbon; or R^2 may be absent if X is nitrogen;

R^3 is selected from the group consisting of -H, -F, -Cl, -Br, -I, -OH, substituted and unsubstituted straight and branched chain alkyl groups having from 1

to 8 carbon atoms, substituted and unsubstituted alkoxy groups, -CO_2H, -CN, substituted and unsubstituted -N(H)(alkyl) groups, substituted and unsubstituted -N(H)(cycloalkyl) groups, substituted and unsubstituted -$N(alkyl)_2$ groups, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted aryl groups, substituted and unsubstituted -C(-O)-heterocyclyl groups, substituted and unsubstituted -C(-O)-alkyl groups, substituted and unsubstituted -C(-O)-N(H)(alkyl) groups, substituted and unsubstituted -$C(-O)-N(alkyl)_2$ groups, -$C(-O)-NH_2$ groups, substituted and unsubstituted -C(-O)-N(H)(heterocyclyl) groups, substituted and unsubstituted -C(-O)-N(H)(aryl) groups, substituted and unsubstituted alkenyl groups having from 1 to 8 carbon atoms, substituted and unsubstituted alkynyl groups having from 1 to 8 carbon atoms, -NO_2, -SH, substituted and unsubstituted -S-alkyl groups, substituted and unsubstituted -$S(-O)_2$-O-alkyl groups, substituted and unsubstituted -$S(-O)_2$-alkyl groups, substituted and unsubstituted -$S(-O)_2$-heterocyclyl groups, substituted and unsubstituted -S(-O)-alkyl groups, substituted and unsubstituted -S(-O)-heterocyclyl groups, -$S(-O)-NH_2$, substituted and unsubstituted -S(-O)-N(H)(alkyl) groups, substituted and unsubstituted -$S(-O)-N(alkyl)_2$ groups, substituted and unsubstituted -C(-O)-O-alkyl groups, -NH_2, substituted and unsubstituted -N(H)-C(-O)-alkyl groups, substituted and unsubstituted -N(H)-C(-O)-heterocyclyl groups, substituted and unsubstituted -N(H)-S(-O)-alkyl groups, substituted and unsubstituted -N(H)-S(-O)-heterocyclyl groups, substituted and unsubstituted -N(alkyl)-C(-O)-alkyl groups, substituted and unsubstituted -N(alkyl)-C(-O)-heterocyclyl groups, substituted and unsubstituted -N(alkyl)-S(-O)-alkyl groups, substituted and unsubstituted -N(alkyl)-S(-O)-heterocyclyl groups, -N(H)-C(-O)-NH_2, substituted and unsubstituted -N(H)-C(-O)-N(H)(alkyl) groups, substituted and unsubstituted -N(H)-C(-O)-$N(alkyl)_2$ groups, -N(alkyl)-C(-O)-NH_2, substituted and unsubstituted -N(alkyl)-C(-O)-N(H)(alkyl) groups, and substituted and unsubstituted -N(alkyl)-C(-O)-$N(alkyl)_2$ groups; or R^2 and R^3 may join together to form a cyclic group when X and Y are both carbon; or R^3 may be absent if Y is nitrogen;

R^4 is selected from the group consisting of -H, -F, -Cl, -Br, -I, substituted and unsubstituted straight and branched chain alkyl groups having from 1 to 8 carbon atoms, substituted and unsubstituted alkenyl groups having from 1 to 8 carbon atoms, substituted and unsubstituted alkynyl groups having from 1 to 8 carbon atoms, -CN, -NO_2, -OH, -SH, substituted and unsubstituted alkoxy groups, substituted

and unsubstituted -S-alkyl groups, substituted and unsubstituted -S(-O)$_2$-O-alkyl groups, substituted and unsubstituted -S(-O)$_2$-alkyl groups, substituted and unsubstituted -S(-O)-alkyl groups, -S(-O)-NH$_2$, substituted and unsubstituted -S(-O)-N(H)(alkyl) groups, substituted and unsubstituted -S(-O)-N(alkyl)$_2$ groups, -C(-O)-NH$_2$, substituted and unsubstituted -C(-O)-N(H)(alkyl) groups, substituted and unsubstituted -C(-O)-N(alkyl)$_2$ groups, substituted and unsubstituted -C(-O)-O-alkyl groups, -NH$_2$, substituted and unsubstituted -N(H)(alkyl) groups, substituted and unsubstituted -N(alkyl)$_2$ groups, substituted and unsubstituted -N(H)-C(-O)-alkyl groups, and substituted and unsubstituted -N(H)-S(-O)-alkyl groups; or R^4 may be absent if Z is nitrogen

R^5 is selected from the group consisting of -H, -F, -Cl, -Br, -I, substituted and unsubstituted straight and branched chain alkyl groups having from 1 to 8 carbon atoms, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted alkenyl groups having from 1 to 8 carbon atoms, substituted and unsubstituted alkynyl groups having from 1 to 8 carbon atoms, -CN, -NO$_2$, -OH, -SH, substituted and unsubstituted alkoxy groups, substituted and unsubstituted -S-alkyl groups, substituted and unsubstituted -S(-O)$_2$-O-alkyl groups, substituted and unsubstituted -S(-O)$_2$-alkyl groups, substituted and unsubstituted -S(-O)-alkyl groups, -S(-O)-NH$_2$, substituted and unsubstituted -S(-O)-N(H)(alkyl) groups, substituted and unsubstituted -S(-O)-N(alkyl)$_2$ groups, -C(-O)-NH$_2$, substituted and unsubstituted -C(-O)-N(H)(alkyl) groups, substituted and unsubstituted -C(-O)-N(alkyl)$_2$ groups, substituted and unsubstituted -C(-O)-O-alkyl groups, -NH$_2$, substituted and unsubstituted -N(H)(alkyl) groups, substituted and unsubstituted -N(alkyl)$_2$ groups, substituted and unsubstituted -N(H)-C(-O)-alkyl groups, and substituted and unsubstituted -N(H)-S(-O)-alkyl groups; or R^5 may be absent if A is nitrogen;

R^6 is selected from the group consisting of -H, -Cl, -F, -Br, -OH, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted -N(H)(alkyl) groups, substituted and unsubstituted -N(H)(heterocyclyl) groups, substituted and unsubstituted -N(alkyl)(heterocyclyl) groups, substituted and unsubstituted alkoxy groups, substituted and unsubstituted alkyl groups having from 1 to 8 carbon atoms, substituted and unsubstituted alkenyl groups having from 1 to 8 carbon atoms, substituted and unsubstituted alkynyl groups having from 1 to 8 carbon atoms, -CN, -NO$_2$, -OH, -SH, substituted and unsubstituted -S-alkyl groups,

substituted and unsubstituted -S(-O)$_2$-O-alkyl groups, substituted and unsubstituted -S(-O)$_2$-alkyl groups, substituted and unsubstituted -S(-O)$_2$-heterocyclyl groups, substituted and unsubstituted -S(-O)-alkyl groups, substituted and unsubstituted -S(-O)-heterocyclyl groups, -S(-O)-NH$_2$, substituted and unsubstituted -S(-O)-N(H)(alkyl) groups, substituted and unsubstituted -S(-O)-N(alkyl)$_2$ groups, -C(-O)-NH$_2$, substituted and unsubstituted -C(-O)-N(H)(alkyl) groups, substituted and unsubstituted -C(-O)-N(alkyl)$_2$ groups, substituted and unsubstituted -C(-O)-alkyl groups, substituted and unsubstituted -C(-O)-heterocyclyl groups, substituted and unsubstituted -C(-O)-O-alkyl groups, -NH$_2$, substituted and unsubstituted -N(alkyl)$_2$ groups, substituted and unsubstituted -N(H)-C(-O)-alkyl groups, substituted and unsubstituted -N(H)-C(-O)-heterocyclyl groups, substituted and unsubstituted -N(alkyl)-C(-O)-alkyl groups, substituted and unsubstituted -N(alkyl)-C(-O)-heterocyclyl groups, substituted and unsubstituted -N(H)-S(-O)-alkyl groups, substituted and unsubstituted -N(H)-S(-O)-heterocyclyl groups, substituted and unsubstituted -N(alkyl)-S(-O)-alkyl groups, and substituted and unsubstituted -N(alkyl)-S(-O)-heterocyclyl groups; or R^6 may be absent if B is nitrogen;

R^7 is selected from the group consisting of -H, -Cl, -F, -Br, -OH, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted -N(H)(alkyl) groups, substituted and unsubstituted -N(H)(heterocyclyl) groups, substituted and unsubstituted -N(alkyl)(heterocyclyl) groups, substituted and unsubstituted alkoxy groups, substituted and unsubstituted alkyl groups having from 1 to 8 carbon atoms, substituted and unsubstituted alkenyl groups having from 1 to 8 carbon atoms, substituted and unsubstituted alkynyl groups having from 1 to 8 carbon atoms, -CN, -NO$_2$, -OH, -SH, substituted and unsubstituted -S-alkyl groups, substituted and unsubstituted -S(-O)$_2$-O-alkyl groups, substituted and unsubstituted -S(-O)$_2$-alkyl groups, substituted and unsubstituted -S(-O)$_2$-heterocyclyl groups, substituted and unsubstituted -S(-O)-alkyl groups, substituted and unsubstituted -S(-O)-heterocyclyl groups, -S(-O)-NH$_2$, substituted and unsubstituted -S(-O)-N(H)(alkyl) groups, substituted and unsubstituted -S(-O)-N(alkyl)$_2$ groups, -C(-O)-NH$_2$, substituted and unsubstituted -C(-O)-N(H)(alkyl) groups, substituted and unsubstituted -C(-O)-N(alkyl)$_2$ groups, substituted and unsubstituted -C(-O)-alkyl groups, substituted and unsubstituted -C(-O)-heterocyclyl groups, substituted and unsubstituted -C(-O)-O-alkyl groups, -NH$_2$, substituted and unsubstituted -N(alkyl)$_2$

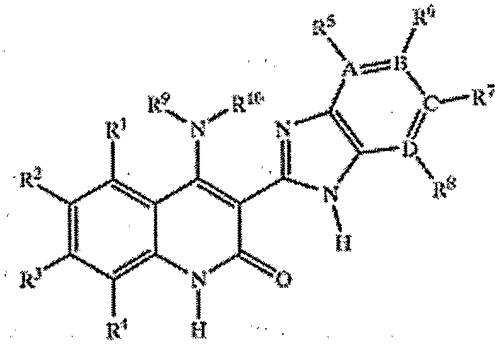
groups, substituted and unsubstituted -N(H)-C(-O)-alkyl groups, substituted and unsubstituted -N(H)-C(-O)-heterocyclyl groups, substituted and unsubstituted -N(alkyl)-C(-O)-alkyl groups, substituted and unsubstituted -N(alkyl)-C(-O)-heterocyclyl groups, substituted and unsubstituted -N(H)-S(-O)-alkyl groups, substituted and unsubstituted -N(H)-S(-O)-heterocyclyl groups, substituted and unsubstituted -N(alkyl)-S(-O)-alkyl groups, and substituted and unsubstituted -N(alkyl)-S(-O)-heterocyclyl groups; or R^7 may be absent if C is nitrogen;

R^8 is selected from the group consisting of -H, -F, -Cl, -Br, -I, substituted and unsubstituted straight and branched chain alkyl groups having from 1 to 8 carbon atoms, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted alkenyl groups having from 1 to 8 carbon atoms, substituted and unsubstituted alkynyl groups having from 1 to 8 carbon atoms, -CN, $-NO_2$, -OH, -SH, substituted and unsubstituted alkoxy groups, substituted and unsubstituted -S-alkyl groups, substituted and unsubstituted $-S(-O)_2-O$-alkyl groups, substituted and unsubstituted $-S(-O)_2$-alkyl groups, substituted and unsubstituted -S(-O)-alkyl groups, $-S(-O)-NH_2$, substituted and unsubstituted -S(-O)-N(H)(alkyl) groups, substituted and unsubstituted $-S(-O)-N(alkyl)_2$ groups; $-C(-O)-NH_2$, substituted and unsubstituted -C(-O)-N(H)(alkyl) groups, substituted and unsubstituted $-C(-O)-N(alkyl)_2$ groups, substituted and unsubstituted -C(-O)-O-alkyl groups, $-NH_2$, substituted and unsubstituted -N(H)(alkyl) groups, substituted and unsubstituted $-N(alkyl)_2$ groups, substituted and unsubstituted -N(H)-C(-O)-alkyl groups, and substituted and unsubstituted -N(H)-S(-O)-alkyl groups; or R^8 may be absent if D is nitrogen;

R^9 is selected from the group consisting of substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted aryl groups, substituted and unsubstituted alkoxy groups, $-NH_2$, substituted and unsubstituted cycloalkyl groups, and substituted and unsubstituted straight and branched chain alkyl groups having from 1 to 8 carbon atoms, or R^9 and R^{10} join together to form a ring having 5, 6, or 7 ring members; and

R^{10} is -H, or R^9 and R^{10} join together to form a ring having 5, 6, or 7 ring members.

iii) A compound of formula:



where, A, B, C, and D are independently selected from the group consisting of carbon and nitrogen;

R^1 is selected from the group consisting of -H, -F, -Cl, -Br, -I, -CN, -NO_2, substituted and unsubstituted alkyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted alkenyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted alkynyl groups having from 1 to 8 carbon atoms, substituted and unsubstituted heterocyclyl groups, -OH, substituted and unsubstituted alkoxy groups, substituted and unsubstituted aryloxy groups, substituted and unsubstituted arylalkoxy groups, substituted and unsubstituted heterocyclyloxy groups, substituted and unsubstituted heterocyclylalkoxy groups, -SH, substituted and unsubstituted -S-alkyl groups, -NH_2, substituted and unsubstituted -N(H)(alkyl) groups, substituted and unsubstituted -N(alkyl)$_2$ groups, substituted and unsubstituted -N(H)(heterocyclyl) groups, substituted and unsubstituted -N(alkyl)(heterocyclyl) groups, substituted and unsubstituted -N(heterocyclyl)$_2$ groups, substituted and unsubstituted -N(H)(heterocyclylalkyl) groups, substituted and unsubstituted -N(alkyl)(heterocyclylalkyl) groups, and substituted and unsubstituted -N(heterocyclylalkyl)$_2$ groups;

R^2 and R^3 are independently selected from the group consisting of -H, -F, -Cl, -Br, -I, -NO_2, -CN, substituted and unsubstituted alkyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted alkenyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted alkynyl groups having from 1 to 8 carbon atoms, substituted and unsubstituted aryl groups, substituted and unsubstituted aralkyl groups, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted heterocyclylalkyl groups, -SH, substituted and unsubstituted -S-alkyl groups, substituted and unsubstituted -S(-O)$_2$-O-alkyl groups, substituted and

unsubstituted -S(-O)$_2$-alkyl groups, substituted and unsubstituted -S(-O)$_2$-heterocyclyl groups, substituted and unsubstituted -S(-O)-alkyl groups, substituted and unsubstituted -S(-O)-heterocyclyl groups, -S(-O)$_2$-NH$_2$, substituted and unsubstituted -S(-O)$_2$-N(H)(alkyl) groups, substituted and unsubstituted -S(-O)$_2$-N(alkyl)$_2$ groups, substituted and unsubstituted -S(-O)$_2$-N(H)(aryl) groups, substituted and unsubstituted -S(-O)$_2$-N(alkyl)(aryl) groups, substituted and unsubstituted -S(-O)$_2$-N(aryl)$_2$ groups, substituted and unsubstituted -S(-O)$_2$-N(H)(aralkyl) groups, substituted and unsubstituted -S(-O)$_2$-N(alkyl)(aralkyl) groups, substituted and unsubstituted -S(-O)$_2$-N(aralkyl)$_2$ groups, -OH, substituted and unsubstituted alkoxy groups, substituted and unsubstituted aryloxy groups, substituted and unsubstituted arylalkoxy groups, substituted and unsubstituted heterocyclyloxy groups, substituted and unsubstituted heterocyclylalkoxy groups, -NH$_2$, substituted and unsubstituted -N(H)(alkyl) groups, substituted and unsubstituted -N(alkyl)$_2$ groups, substituted and unsubstituted -N(H)(aryl) groups, substituted and unsubstituted -N(alkyl)(aryl) groups, substituted and unsubstituted -N(aryl)$_2$ groups, substituted and unsubstituted -N(H)(aralkyl) groups, substituted and unsubstituted -N(alkyl)(aralkyl) groups, substituted and unsubstituted -N(aralkyl)$_2$ groups, substituted and unsubstituted -N(H)(heterocyclyl) groups, substituted and unsubstituted -N(alkyl)(heterocyclyl) groups, substituted and unsubstituted -N(heterocyclyl)$_2$ groups, substituted and unsubstituted -N(H)(heterocyclylalkyl) groups, substituted and unsubstituted -N(alkyl)(heterocyclylalkyl) groups, substituted and unsubstituted -N(heterocyclylalkyl)$_2$ groups, substituted and unsubstituted -N(H)-S(-O)$_2$-alkyl groups, substituted and unsubstituted -N(H)-S(-O)$_2$-aryl groups, substituted and unsubstituted -N(H)-S(-O)$_2$-aralkyl groups, substituted and unsubstituted -N(H)-S(-O)$_2$-heterocyclyl groups, substituted and unsubstituted -N(H)-S(-O)$_2$-heterocyclylalkyl groups, substituted and unsubstituted -N(H)-C(-O)-alkyl groups, substituted and unsubstituted -N(H)-C(-O)-aryl groups, substituted and unsubstituted -N(H)-C(-O)-aralkyl groups, substituted and unsubstituted -N(H)-C(-O)-heterocyclyl groups, substituted and unsubstituted -N(H)-C(-O)-heterocyclylalkyl groups, substituted and unsubstituted -N(alkyl)-C(-O)-alkyl groups, substituted and unsubstituted -N(alkyl)-C(-O)-aryl groups, substituted and unsubstituted -N(alkyl)-C(-O)-aralkyl groups, substituted and unsubstituted -N(alkyl)-C(-O)-heterocyclyl groups, substituted and unsubstituted -N(alkyl)-C(-O)-heterocyclylalkyl groups, substituted and unsubstituted -N(alkyl)-S(-O)-alkyl groups, substituted and

unsubstituted -N(alkyl)-S(-O)-aryl groups, substituted and unsubstituted -N(alkyl)-S(-O)-aralkyl groups, substituted and unsubstituted -N(alkyl)-S(-O)-heterocyclyl groups, substituted and unsubstituted -N(alkyl)-S(-O)-heterocyclylalkyl groups, -N(H)-C(-O)-NH_2, substituted and unsubstituted -N(H)-C(-O)-N(H)(alkyl) groups, substituted and unsubstituted -N(H)-C(-O)-N(alkyl)$_2$ groups, substituted and unsubstituted -N(H)-C(-O)-N(H)(aryl) groups, substituted and unsubstituted -N(H)-C(-O)-N(alkyl)(aryl) groups, substituted and unsubstituted -N(H)-C(-O)-N(aryl)$_2$ groups, substituted and unsubstituted -N(H)-C(-O)-N(H)(aralkyl) groups, substituted and unsubstituted -N(H)-C(-O)-N(alkyl)(aralkyl) groups, substituted and unsubstituted -N(H)-C(-O)-N(aralkyl)$_2$ groups, substituted and unsubstituted -N(H)-C(-O)-N(H)(heterocyclyl) groups, substituted and unsubstituted -N(H)-C(-O)-N(alkyl)(heterocyclyl) groups, substituted and unsubstituted -N(H)-C(-O)-N(heterocyclyl)$_2$ groups, substituted and unsubstituted -N(H)-C(-O)-N(H)(heterocyclylalkyl) groups, substituted and unsubstituted -N(H)-C(-O)-N(alkyl)(heterocyclylalkyl) groups, substituted and unsubstituted -N(H)-C(-O)-N(heterocyclylalkyl)$_2$ groups, substituted and unsubstituted -N(alkyl)-C(-O)-NH_2 groups, substituted and unsubstituted -N(alkyl)-C(-O)-N(H)(alkyl) groups substituted and unsubstituted -N(alkyl)-C(-O)-N(alkyl)$_2$ groups, substituted and unsubstituted -N(alkyl)-C(-O)-N(H)(aryl) groups, substituted and unsubstituted -N(alkyl)-C(-O)-N(alkyl)(aryl) groups, substituted and unsubstituted -N(alkyl)-C(-O)-N(aryl)$_2$ groups, substituted and unsubstituted -N(alkyl)-C(-O)-N(H)(aralkyl) groups, substituted and unsubstituted -N(alkyl)-C(-O)-N(alkyl)(aralkyl) groups, substituted and unsubstituted -N(alkyl)-C(-O)-N(aralkyl)$_2$ groups, substituted and unsubstituted -N(alkyl)-C(-O)-N(H)(heterocyclyl) groups, substituted and unsubstituted -N(alkyl)-C(-O)-N(alkyl)(heterocyclyl) groups, substituted and unsubstituted -N(alkyl)-C(-O)-N(heterocyclyl)$_2$ groups, substituted and unsubstituted -N(alkyl)-C(-O)-N(H)(heterocyclylalkyl) groups, substituted and unsubstituted -N(alkyl)-C(-O)-N(alkyl)(heterocyclylalkyl) groups, substituted and unsubstituted -N(alkyl)-C(-O)-N(heterocyclylalkyl)$_2$ groups, substituted and unsubstituted -C(-O)-alkyl groups, substituted and unsubstituted -C(-O)-aryl groups, substituted and unsubstituted -C(-O)-aralkyl groups, substituted and unsubstituted -C(-O)-heterocyclyl groups, substituted and unsubstituted -C(-O)-heterocyclylalkyl groups, -C(-O)-NH_2, substituted and unsubstituted -C(-O)-N(H)(alkyl) groups, substituted and unsubstituted -C(-O)-N(alkyl)$_2$ groups, substituted and unsubstituted -C(-O)-N(H)(aryl) groups, substituted and unsubstituted -C(-O)-N(alkyl)(aryl) groups,

substituted and unsubstituted -C(-O)-N(aryl)$_2$ groups, substituted and unsubstituted -C(-O)-N(H)(aralkyl) groups, substituted and unsubstituted -C(-O)-N(alkyl)(aralkyl) groups, substituted and unsubstituted -C(-O)-N(aralkyl)$_2$ groups, substituted and unsubstituted -C(-O)-N(H)(heterocyclyl) groups, substituted and unsubstituted -C(-O)-N(alkyl)(heterocyclyl) groups, substituted and unsubstituted -C(-O)-N(heterocyclyl)$_2$ groups, substituted and unsubstituted -C(-O)-N(H)(heterocyclylalkyl) groups, substituted and unsubstituted -C(-O)-N(alkyl)(heterocyclylalkyl) groups, substituted and unsubstituted -C(-O)-N(heterocyclylalkyl)$_2$ groups, -CO_2H, substituted and unsubstituted -C(-O)-O-alkyl groups, substituted and unsubstituted -C(-O)-O-aryl groups, substituted and unsubstituted -C(-O)-O-heterocyclyl groups, and substituted and unsubstituted -C(-O)-O-heterocyclylalkyl groups;

R^4 is selected from the group consisting of -H and substituted and unsubstituted alkyl groups having from 1 to 12 carbon atoms;

R^5 and R^8 are independently selected from the group consisting of -H, substituted and unsubstituted alkyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted alkenyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted heterocyclyl groups; or R^5 may be absent if A is nitrogen; or R^8 may be absent if D is nitrogen;

R^6 and R^7 are independently selected from the group consisting of -H, -F, -Cl, -Br, -I, -NO_2, -CN, substituted and unsubstituted alkyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted alkenyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted alkynyl groups having from 1 to 8 carbon atoms, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted heterocyclylalkyl groups, -SH, substituted and unsubstituted -S-alkyl groups, substituted and unsubstituted -S(-O)$_2$-O-alkyl groups, substituted and unsubstituted -S(-O)$_2$-alkyl groups, substituted and unsubstituted -S(-O)$_2$-heterocyclyl groups, substituted and unsubstituted -S(-O)-alkyl groups, substituted and unsubstituted -S(-O)-heterocyclyl groups, -S(-O)$_2$-NH_2, substituted and unsubstituted -S(-O)$_2$-N(H)(alkyl) groups, substituted and unsubstituted -S(-O)$_2$-N(alkyl)$_2$ groups, substituted and unsubstituted -S(-O)$_2$-N(H)(heterocyclyl) groups, substituted and unsubstituted -S(-O)$_2$-N(alkyl)(heterocyclyl) groups, substituted and unsubstituted -S(-O)$_2$-N(heterocyclyl)$_2$ groups, substituted and unsubstituted -S(-O)$_2$-

N(H)(heterocyclylalkyl) groups, substituted and unsubstituted -S(-O)$_2$-N(alkyl)(heterocyclylalkyl) groups, substituted and unsubstituted -S(-O)$_2$-N(heterocyclylalkyl)$_2$ groups, -OH, substituted and unsubstituted alkoxy groups, substituted and unsubstituted aryloxy groups, substituted and unsubstituted arylalkoxy groups, substituted and unsubstituted heterocyclyloxy groups, substituted and unsubstituted heterocyclylalkoxy groups, -NH_2, substituted and unsubstituted -N(H)(alkyl) groups, substituted and unsubstituted -N(alkyl)$_2$ groups, substituted and unsubstituted -N(H)(aryl) groups, substituted and unsubstituted -N(alkyl)(aryl) groups, substituted and unsubstituted -N(aryl)$_2$ groups, substituted and unsubstituted -N(H)(aralkyl) groups, substituted and unsubstituted -N(alkyl)(aralkyl) groups, substituted and unsubstituted -N(aralkyl)$_2$ groups, substituted and unsubstituted -N(H)(heterocyclyl) groups, substituted and unsubstituted -N(alkyl)(heterocyclyl) groups, substituted and unsubstituted -N(heterocyclyl)$_2$ groups, substituted and unsubstituted -N(H)(heterocyclylalkyl) groups, substituted and unsubstituted -N(alkyl)(heterocyclylalkyl) groups, substituted and unsubstituted -N(heterocyclylalkyl)$_2$ groups, substituted and unsubstituted -N(H)-S(-O)$_2$-alkyl groups, substituted and unsubstituted -N(H)-S(-O)$_2$-heterocyclyl groups, substituted and unsubstituted -N(H)-S(-O)$_2$-heterocyclylalkyl groups, substituted and unsubstituted -N(H)-C(-O)-alkyl groups, substituted and unsubstituted -N(H)-C(-O)-heterocyclyl groups, substituted and unsubstituted -N(H)-C(-O)-heterocyclylalkyl groups, substituted and unsubstituted -N(alkyl)-C(-O)-alkyl groups, substituted and unsubstituted -N(alkyl)-C(-O)-heterocyclyl groups, substituted and unsubstituted -N(alkyl)-C(-O)-heterocyclylalkyl groups, substituted and unsubstituted -N(alkyl)-S(-O)$_2$-alkyl groups, substituted and unsubstituted -N(alkyl)-S(-O)$_2$-heterocyclyl groups, substituted and unsubstituted -N(alkyl)-S(-O)$_2$-heterocyclylalkyl groups, substituted and unsubstituted -C(-O)-alkyl groups, substituted and unsubstituted -C(-O)-heterocyclyl groups, substituted and unsubstituted -C(-O)-heterocyclylalkyl groups, -C(-O)-NH_2, substituted and unsubstituted -C(-O)-N(H)(alkyl) groups, substituted and unsubstituted -C(-O)-N(alkyl)$_2$ groups, substituted and unsubstituted -C(-O)-N(H)(aryl) groups, substituted and unsubstituted -C(-O)-N(alkyl)(aryl) groups, substituted and unsubstituted -C(-O)-N(aryl)$_2$ groups, substituted and unsubstituted -C(-O)-N(H)(aralkyl) groups, substituted and unsubstituted -C(-O)-N(alkyl)(aralkyl) groups, substituted and unsubstituted -C(-O)-N(aralkyl)$_2$ groups, substituted and unsubstituted -C(-O)-N(H)(heterocyclyl) groups, substituted and unsubstituted -C(-

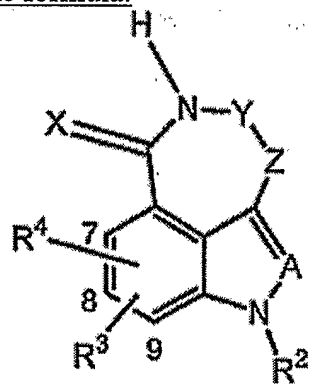
O)-N(alkyl)(heterocyclyl) groups, substituted and unsubstituted -C(-O)-N(heterocyclyl)$_2$ groups, substituted and unsubstituted -C(-O)-N(H)(heterocyclylalkyl) groups, substituted and unsubstituted -C(-O)-N(alkyl)(heterocyclylalkyl) groups, substituted and unsubstituted -C(-O)-N(heterocyclylalkyl)$_2$ groups, -CO_2H, substituted and unsubstituted -C(-O)-O-alkyl groups, substituted and unsubstituted -C(-O)-O-heterocyclyl groups, and substituted and unsubstituted -C(-O)-O-heterocyclylalkyl groups; or R^6 may be absent if B is nitrogen; or R^7 may be absent if C is nitrogen;

R^9 is selected from the group consisting of -H, substituted and unsubstituted alkyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted aryl groups, substituted and unsubstituted aralkyl groups, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted heterocyclylalkyl groups, substituted and unsubstituted heterocyclylaminoalkyl groups, substituted and unsubstituted alkoxy groups, and -NH_2, or R^9 and R^{10} join together to form one or more rings, each having 5, 6, or 7 ring members; and

R^{10} is -H, or R^9 and R^{10} join together to form one or more rings, each having 5, 6, or 7 ring members.

IV. Diazepinoindolone compounds described in International Patent Publication WO2004063198, including:.

i) A compound of the formula:



wherein: X is =O or =S; A is =CR^1-or =N-;

the group-Y-Z-has the formula -O-CH_2-or-N=CH-;

R^1 is:

(a)(C_1-C_8)alkyl;

(b) -C(=O)-R^5;

(c) -C(=O)-NR^6R^7; or

(d) R^{35}, or R^{36}, (C_2-C_8) alkenyl, or (C_2-C_8) alkynyl {wherein each of said(C_2-C_8)alkenyl or (C_2-C_8)alkynyl is unsubstituted or substituted with one to four substituents independently selected from the group consisting of F, CI, OH, -NH_2, R^{40}, and R^{42}};

R^2 is

(a) H, OH, or (C_1-C_8)alkyl;

(b) -C(=O)-R^8;

(c) -(C=S)-R^9 or -(C=S)-$NR^{10}R^{11}$; or

(d) R^{38} or R^{39};

R^3 is

(a)(C_1-C_8)alkyl;

(b) -C (=O)-R^{12};

(c) -C (=O)-$NR^{13}R^{14}$;

(d) -NR^{15}-C(=O)-R^{16};

(e) -NR^{17}-SO_2R^{18};

(f) -NR^{19}-SO_n-$NR^{20}R^{21}$ {wherein n is 1 or 2} ;

(g) -NR^{22}-(C=S)-R^{23} or -NR^{22}-(C=S)-$NR^{23}R^{24}$;

(h)R^{36}, (C_2-C_8)alkenyl, or (C_2-C_8)alkynyl {wherein each of said R^3 (C_2-C_8)alkenyl or (C_2-C_8)alkynyl is unsubstituted or substituted with one to four substituents independently selected from the group consisting of -(C=O)-O-(C_1-C_8)alkyl, -O-(C=O)-(C_1-C_8)alkyl, -(C=O)-(C_1-C_8)alkyl, R^{40}, R^{41}, and R^{42}};

(i) R^{37}, -NH_2, -NH((C_2-C_8)alkenyl), -NH((C_2-C_8)alkynyl), -N((C_1-C_8)alkyl)((C_2-C_8)alkenyl), or -N((C_1-C_8)alkyl)((C_2-C_8)alkynyl) {wherein each of said R^{26} (C_2-C_8)alkenyl or(C_2-C_8)alkynyl is unsubstituted or substituted with one to four substituents independently selected from the group consisting of R^{40}, R^{41}, and R^{42}}; or

(j)R^{38};

R^4 is selected from the group consisting of H, F, Br, Cl, and(C_1-C_8)alkyl;

R^5 is selected from the group consisting of H,(C_1-C_8)alkyl, (C_1-C_8)alkyl-O-, and R^{36};

Each R^6 and R^7 are independently selected from the group consisting of H, (C_1-C_8)alkyl, and R^{36} ;

R^8 is selected from the group consisting of (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl, -NH_2, R^{36}, and R^{37};

Each of R^9, R^{10} and R^{11} are independently selected from the group consisting of H, (C_1-C_8)alkyl, and R^{36};

R^{12} is selected from the group consisting of H, OH, (C_1-C_8)alkyl, (C_1-C_8)alkyl-O-, and R^{36};

R^{13} is H or(C_1-C_8)alkyl;

R^{14} is selected from the group consisting of H, (C_1-C_8)alkyl, -CH_2-(C=O)-O-(C_1-C_8)alkyl, and R^{36};

R^{15} is H or (C_1-C_8)alkyl;

R^{16} is selected from the group consisting of H, (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl, -NH_2, R^{36}, and R^{37}; wherein each of said R^{15} and R^{16} (C_2-C_8)alkenyl or (C_2-C_8)alkynyl is unsubstituted or substituted with one to four substituents independently selected from the group consisting of R^{40}, R^{41}, and R^{42};

R^{17} is selected from the group consisting of H, (C_1-C_8)alkyl, and R^{36};

R^{18} is(C_1-C_8)alkyl or R^{36};

R^{19}, R^{20}, and R^{21} are independently selected from the group consisting of H,(C_1-C_8)alkyl, and R^{36};

R^{22}, R^{23} and R^{24} are independently selected from the group consisting of H, (C_1-C_8)alkyl, and R^{36};

R^{25} is H or(C_1-C_8)alkyl;

R^{26} is selected from the group consisting of -C(=O)-O-C$(CH_3)_3$, (C_1-C_8)alkyl, (C_3-C_{10})cycloalkyl, (C_2-C_{10})heterocyclyl, (C_6-C_{10})aryl, and (C_1-C_{10})heteroaryl ; or R^{25} and R^{26} may optionally be taken together with the nitrogen to which they are attached to form a 5 to 8-membered heteroaryl or heterocyclyl ring;

R^{27} is selected from the group consisting of (C_1-C_8)alkyl, (C_3-C_{10})cycloalkyl, (C_2-C_{10}) heterocyclyl,(C_6-C_{10})aryl, and (C_1-C_{10}) heteroaryl ;

R^{28} is selected from the group consisting of (C_1-C_8)alkyl, (C_3-C_{10})cycloalkyl, (C_2-C_{10}) heterocyclyl, (C_6-C_{10})aryl, and (C_1-C_{10}) heteroaryl ;

R^{29} is H or (C_1-C_8)alkyl;

R^{30} is (C_1-C_8)alkyl, (C_3-C_{10})cycloalkyl, (C_2-C_{10})heterocyclyl, (C_6-C_{10})aryl, or (C_1-C_{10})heteroaryl; or R^{29} and R^{30} may optionally be taken together with the nitrogen to which they are attached to form a 5 to 8-membered heteroaryl or heterocyclyl ring;

R^{31} is H or (C_1-C_8)alkyl ;

R^{32} is independently selected from the group consisting of (C_1-C_8)alkyl, (C_3-C_{10})cycloalkyl, (C_2-C_{10})heterocyclyl, (C_6-C_{10})aryl, and (C_1-C_{10})heteroaryl ; or R^{31} and R^{32} may optionally be taken together with the nitrogen to which they are attached to form a 5 to 8-membered heteroaryl or heterocyclyl ring;

R^{33} is(C_1-C_8)alkyl, (C_3-C_{10})cycloalkyl, (C_2-C_{10})heterocyclyl, (C_6-C_{10})aryl, or (C_1-C_{10})heteroaryl;

R^{34} is (C_1-C_8)alkyl, (C_3-C_{10})cycloalkyl, (C_2-C_{10})heterocyclyl, (C_6-C_{10}), or (C_1-C_{10})heteroaryl ;

Each R^{35} is independently selected from the group consisting of H, F, Cl, Br, I, CN, OH, NO_2,-NH_2,-NH-C (=O)-O-C $(CH_3)_3$, and CF_3;

Each R^{36} is independently selected from the group consisting of (C_3-C_{10})cycloalkyl, (C_2-C_{10})heterocyclyl, (C_6-C_{10})aryl, and (C_1-C_{10})heteroaryl;

Each R^{37} is independently selected from the group consisting of:

(c) -$NR^{25}R^{26}$; and

(d) R^{27}-O-;

R^{38} is R^{28}-SO_n-; wherein n is 0,1, or 2 when -SO_n- is bonded to R^{28} via an R^{28} carbon atom, or wherein n is 1 or 2 when -SO_n- is bonded to R^{28} via an R^{28} ring nitrogen atom;

R^{39} is $R^{29}R^{30}N$-SO_n-; wherein n is 1 or 2; wherein each of said (C_1-C_8)alkyl, wherever it occurs in any of said R^1(a)-(d), R^2(a)-(d), R^3(a)-(j), R^4, R^{37}, R^{38}, or R^{39}, is unsubstituted or substituted with one to four substituents independently selected from the group consisting of (C_2-C_8)alkenyl, R^{40}, R^{41}, and R^{42}; wherein each of said (C_3-C_{10})cycloalkyl, (C_2-C_{10})heterocyclyl, (C_6-C_{10})aryl, or (C_1-C_{10})heteroaryl, wherever it occurs in said R^{36},R^{37}, R^{38}, or R^{39}, is independently unsubstituted or substituted with one to four substituents independently selected from R^{40};

R^{40} is selected from the group consisting of(C_1-C_8)alkyl, R^{41}, R^{42}, and R^{43};

Each R^{41} is independently selected from the group consisting of F, Cl, Br, I, CN, OH, NO_2, -NH_2, -NH-C (=O)-O-$C(CH_3)_3$, COOH, -C(=O)(C_1-C_8)alkyl, -C(=O)-O-(C_1-C_8)alkyl, -NH-SO_2-(C_1-C_8)alkyl, -NH-SO_2-(C_6-C_{10})aryl, and CF_3;

Each R^{42} is independently selected from the group consisting of (C_3-C_{10})cycloalkyl, (C_2-C_{10})heterocyclyl, (C_6-C_{10})aryl, and (C_1-C_{10})heteroaryl;

Each R^{43} is independently selected from the group consisting of:

(c) -$NR^{31}R^{32}$;

(d)R^{33}-O-; and

(c) R^{34}-SO_n-; wherein n is 0,1, or 2 when -SO_n- is bonded to R^{34} via an R^{34} carbon atom; or wherein n is 1 or 2 when -SO_n- is bonded to R^{34} via an R^{34} ring nitrogen atom;

wherein each of said (C_1-C_8)alkyl, wherever it occurs in any of R^{40} is independently unsubstituted or substituted with one to four substituents independently selected from the group consisting of R^{44} and R^{45};

wherein each of said (C_3-C_{10})cycloalkyl, (C_2-C_{10})heterocyclyl, (C_6-C_{10})aryl, or (C_1-C_{10})heteroaryl, wherever it occurs in any of said R^{42} or R^{43}, is independently unsubstituted or substituted with one to four substituents independently selected from the group consisting of R^{47} selected from the group consisting of (C_1-C_8)alkyl, R^{44}, and R^{45};

Each R^{44} is independently selected from the group consisting of F, Cl, Br, I, CN, OH, NO_2, $-NH_2$, $-CF_3$, $-C(=NH)-NH_2$, $-C(=NH)-NH-OH$, $-C(=NH)-NH-O-(C_1-C_8)$alkyl, $-(C=O)-O-(C_1-C_8)$alkyl, $-O-(C=O)-(C_1-C_8)$alkyl, $-(C=O)-(C_1-C_8)$alkyl, $-(C=O)-NH_2$, $-C(=O)-NH(C_1-C_8)$alkyl, $-(C=O)-N<[(C_1-C_8)alkyl]_2$, $-NH-(C=O)-(C_1-C_8)$alkyl, R^{37}, and R^{38};

Each R^{45} is independently selected from the group consisting of (C_3-C_{10})cycloalkyl, (C_2-C_{10})heterocyclyl, (C_6-C_{10})aryl, and(C_1-C_{10})heteroaryl;

wherein each of said(C_1-C_8)alkyl wherever it occurs in any of said R^{44} or R^{45} is independently unsubstituted or substituted with one to four substituents independently selected from the group consisting of R^{46} and R^{47};

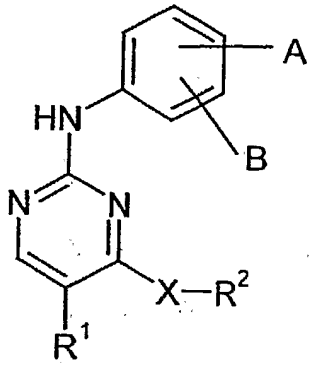
wherein each of said (C_3-C_{10})cycloalkyl, (C_2-C_{10})heterocyclyl, (C_6-C_{10})aryl, or (C_1-C_{10})heteroaryl, wherever it occurs in any of said R^{43} or R^{44} is independently unsubstituted or substituted with one to four substituents independently selected from the group consisting of (C_1-C_8)alkyl, R^{46} and R^{47};

Each R^{46} is independently selected from the group consisting of F, Cl, Br, I, CN, OH, NO_2, $-C(=NH)-NH_2$, $-C(=NH)-NH-OH$, $-C(=NH)-NH-O-(C_1-C_8)$alkyl, $-(C=O)-(C_1-C_8)$alkyl, $-O-(C=O)-(C_1-C_8)$alkyl, $-(C=O)-(C_1-C_8)$alkyl, $-(C=O)-NH_2$, $-(C=O)-NH(C_1-C_8)$alkyl, $-(C=O)-N<[(C_1-C_8)alkyl]_2$, $-NH-(C=O)-(C_1-C_8)$alkyl, $-C(=NH)-NH_2$, $-C(=NH)-NH-OH$, $-C(=NH)-NH-O-(C_1-C_8)$alkyl, $-(C=O)-O-(C_1-C_8)$alkyl, $-O-(C=O)-(C_1-C_8)$alkyl, $-(C=O)-(C_1-C_8)$alkyl, $-(C=O)-NH_2$, $-(C=O)-NH(C_1-C_8)$alkyl, $-(C=O)-N>[(C_1-C_8)alkyl]_2$, $-NH-(C=O)-(C_1-C^8)$alkyl, R^{37}, and R^{38}; and

Each R^{47} is independently selected from the group consisting of (C_3-C_{10})cycloalkyl; (C_2-C_{10}) heterocyclyl, (C_6-C_{10})aryl, and (C_1-C_{10})heteroaryl; or a pharmaceutical acceptable salt thereof;

V) Pyrimidine compounds described in International Patent Publication WO2004048343, including:.

i) A compound of formula:



(I)

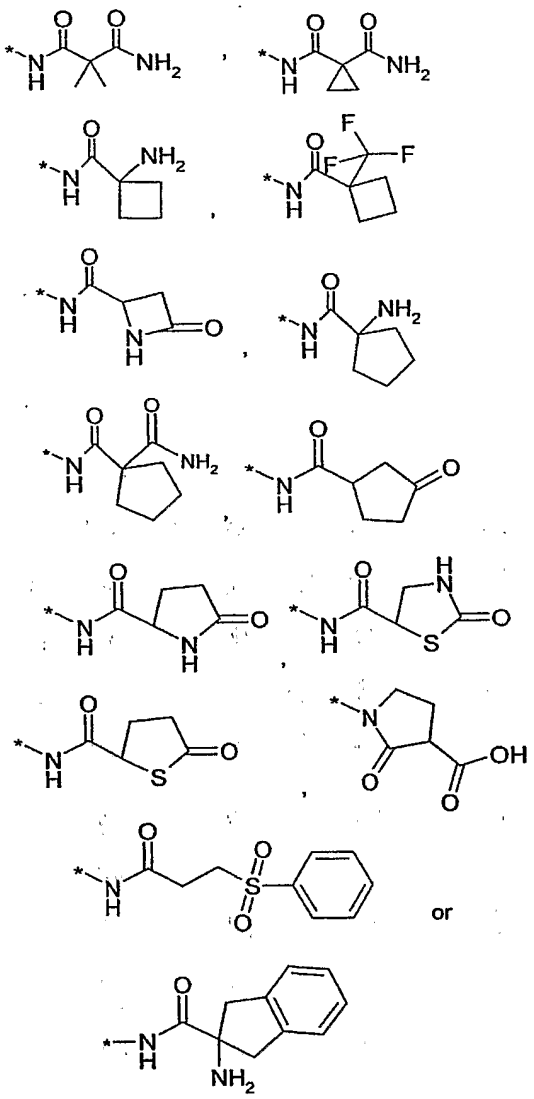
in which A or B in each case independently of one another represent cyano, halogen, hydrogen, hydroxy, aryl or the group $-NO_2$, $-NH_2$, $-NR^3R^4$, $-C_{1-6}$-alkyl-NR^3R^4, $-N(C_{1-6}$-hydroxyalkyl$)_2$, -NH-C(NH)-CH_3, -NH(CO)-R^5, -$NHCOOR^6$, -NR^7-(CO)-NR^8R^9, -NR^7-(CS)-NR^8R^9, -$COOR^5$, -CO-NR^8R^9, -CONH-C_{1-6}-alkyl-COOH, $-SO_2-CH_3$, 4- bromo-1-methyl-1 H-pyrazolo-3yl or represent C_{1-6}-alkyl

optionally substituted in one or more places, the same way or differently with halogen, hydroxy, cyano or with the group-$COOR^5$, -$CONR^8R^9$,-NH_2, -NH-SO_2-CH_3, -NR^8R^9, -NH-(CO)-R^5,-NR^7-(CO)-NR^8R^9, -SO_2-NHR^3, -O-(CO)-R^5 or -O-(CO)-C1-6-alkyl-R^5;

X represents an oxygen atom or the group -NH- or -NR^3R^4;

R^1 represents hydrogen, halogen, hydroxymethyl, C_{1-6}-alkyl, cyano or the group -COOH, -COO-iso-propyl, $-NO_2$, -NH-(CO)-$(CH_2)_2$-COOH or-NH-(CO)-$(CH_2)_2$-COO-C_{1-6}-alkyl, whereby the C_{1-6}-alkyl can optionally be substituted in one or more places, in the same way or differently with halogen;

R^2 represents hydrogen or the group-NH-(CO)-aryl or C_{1-6}-alkyl optionally substituted in one or more places, the same way or differently with cyano, hydroxy, aryl, heteroaryl, C_{3-6}-heterocycloalkyl ring, which can optionally be interrupted with one or more nitrogen atoms, or substituted with the group -NR^8R^9, -NH-(CO)-NR^8R^9, -NH-(CO)-S-C_{1-6}-alkyl, -NH-(CS)-NR^8R^9, -NH-(CO)O-CH_2-phenyl,-NH-(CO)H, -NH (CO)-R^5,-NH (CO)-OR^5, - (CO)-NH-NH_2, -(CO)-NH-CH_2-(CO)-NH_2, -(CO)-NH-C_{1-6}-alkyl-COOH,



whereby the aryl or the heteroaryl can optionally be substituted in one or more places, the same or differently with halogen, hydroxy, C_{1-6}-alkyl, $-NH_2$, -NH-(CO)-CH_2-NH_2, $-NO_2$, -(CO)-C(CH_2)-C_2H_5,- $COOR^6$,-$COOC(CH_3)_3$, or represents C_3-alkinyl;

R^3 or R^4 in each case independently of one another represent hydrogen or C_{1-6}-alkyl optionally substituted in one or more places, the same way or differently with hydroxy, phenyl or hydroxyphenyl, or

R^3 and R^4 together form a C_{3-6}-heterocycloalkylring containing at least one nitrogen atom and optionally can be interrupted by one or more oxygen and/or sulfur atoms and/or can be interrupted by one or more -(CO)- groups in the ring

and/or optionally can contain one or more possible double bonds in the ring, whereby the $C_{3\,6}$-heterocycloalkylring can optionally be substituted with C_{1-6}-alkyl, C_{1-6}-alkyl-COOH or C_{1-6}-alkyl-NH_2;

R^5 represents hydrogen, C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{2-6}-alkenyl, C_{3-6}-cycloalkylring, aryl, heteroaryl, the group- (CO)-NH_2 or C_{3-6} heterocycloalkylring that can optionally be interrupted with one or more nitrogen and/or oxygen and/or sulfur atoms and/or can be interrupted by one or more -(CO)- groups in the ring and/or optionally can contain one or more possible double bonds in the ring and C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{3-6}- cycloalkylring, C3-6 heterocycloalkylring defined above, aryl or heteroaryl can optionally be substituted in one or ore places, the same way or differently with halogen, hydroxy, C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{3-6}- cycloalkylring, C_{3-6} heterocycloalkylring defined above, aryl, heteroaryl or with the group NR^8R^9, -NO_2, -NR-(CO)-R^5, -NH(CO)-C_{1-6}-alkyl-NH-(CO)-C_{1-6}-alkyl, -NR^7-(CO)-NR^8R^9, -CO-CH_3, -COOH-, CO-NR^8R^9, -SO_2-aryl, -SH, -S-C_{1-6}-alkyl, -SO_2-NR^8R^9, whereby aryl itself can optionally be substituted in one or more places, the same way or differently with halogen, hydroxy, C_{1-6}-alkyl of C_{1-6}-alkoxy;

R^6 represents C_{1-6}-alkyl, C_{2-6}-alkenyl or phenyl, whereby C_{1-6}-alkyl may optionally be substituted with C_{3-6}-heterocycloalkylring that can optionally be interrupted with one or more nitrogen and/or oxygen and/or sulfur atoms and/or can be interrupted by one or more- (CO)- groups in the ring and/or optionally can contain one or more possible double bonds in the ring;

R^7 represents hydrogen or C_{1-6}-alkyl;

R^8 or R^9 in each case independently of one another represent hydrogen, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{3-6}-cycloalkyl, aryl or heteroaryl or the group R^{10},

whereby C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{3-6}-cycloalkyl, aryl or heteroaryl can optionally be substituted in one or more places, the same way or differently with halogen, heteroaryl, hydroxy, -C_{1-6}-alkoxy, hydroxy-$C_{1\,6}$-alkoxy or the group -COOH, -NO_2, -NR^8R^9, -N(C_{1-6}- alkyl)$_2$ or with a C_{3-6}-heterocycloalkylring can optionally be interrupted with one or more nitrogen and/or oxygen and/or sulfur atoms and/or can be interrupted by one or more- (CO)- groups in the ring and/or optionally can contain one or more possible double bonds in the ring, or

R^8 and R^9 together form a C_{3-6}-heterocycloalkylring containing at least one nitrogen atom and optionally can be interrupted by one or more oxygen and/or sulfur atoms and/or can be interrupted by one or more- (CO)- groups in the ring and/or optionally can contain one or more possible double bonds in the ring, whereby the C_{3-6}- heterocycloalkylring can optionally be substituted in one or more places, the same way or differently with hydroxy or the group $-NR^8R^9$, -NH (CO)-R^5, hydroxy-C_{1-6}-alkyl or-COOH; and

R^{10} represents $-SO_2$-aryl, -SO2-heteroaryl or -SO2-NH2 or -SO2-C1-6-alkyl,

whereby the aryl can be substituted with $-C_{1-6}$-alkyl, with the following provisos: whereby when X represents-NR^3R^4 then R^2 does not represent a substituent,

whereby when A and B represent hydrogen, X represents-NH-and R^2 represents C_{1-6}-alkyl, then R^1 represents-NH-(CO)-CH (NH_2)-$(CH_2)_2$-COOH or-NH-(CO)-CH(NH_2)-$(CH_2)_2$-$COOC_2H_5$;

whereby when A represents -(CO)-OC_2H_5 or hydroxy, B represents hydrogen, X represents oxygen, R^1 represents halogen, then R^2 represents C3-alkinyl;

whereby when A represents- (CO)-OC_2H_5 or hydroxy, B represents hydrogen, X represents -NH-, R^1 represents $-NO_2$, then R^2 represents C_3-alkinyl;

whereby when A represents- (CO)-OCH_3, then X represents oxygen, R^1 represents halogen, R^2 represents C_3-alkinyl and B represents $-NH_2$, $-NHC_2H_4OH$, $-N(C_2H_4OH)_2$, -NH-(CO)-CH_2-O(CO)CH_3,

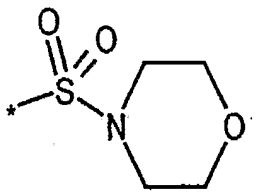
whereby when A represents (CO)-OCH_3, then X represents –NH-, R^1 represents halogen, R^2 represents $-C_2H_4$-imidazolyl and B represents $-NH_2$;

whereby when A represents $-NHSO_2CH_3$, then X represents –NH-, R^1 represents halogen, R^2 represents $-C_2H_4$-imidazolyl;

whereby when R1 represents –COO-iso-propyl, then X represents –NH, R^2 represents C_3-alkinyl and A or B independently of one another represent the group $-NO_2$ or –NH-(CO)-CF_3;

whereby when R^1 represents halogen, X represents –NH, B represents hydrogen, and R^2 represents C_{1-6}-alkyl substituted with $–NH_2$, then A represents –NH-(CO)-C_6-cycloalkyl-NH_2;

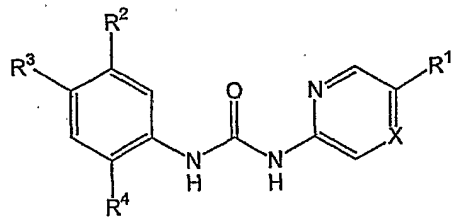
whereby when R^1 represents halogen, X represents –NH, B represents $–S-CH_3$ and R^2 represents imidazolyl, then A represents the group



as well as all related isotopes, diastereomers, enantiomers, solvates, polymorphs or pharmaceutical acceptable salts thereof.

VI. Diaryl urea compounds as described in International Patent Publication WO2004014876, including.

i) A compound of formula:



(I),

or a therapeutically acceptable salt thereof, wherein

X is -N- or -CH-;

R^1 is selected from the group consisting of hydrogen, alkoxy, alkyl, amino, carboxy, cyano, halo, hydroxy, and hydroxyalkyl;

R^2 is selected from the group consisting of alkoxy, alkyl, alkylcarbonyl, amino, cyano, halo, and nitro;

R^3 is selected from the group consisting of hydrogen, alkoxy, alkyl, amino, aminoalkyl, aminocarbonyl, arylalkyl, cyano,nitro,-CO_2R^5,-COR^5,and-SR^5;

R^4 is selected from the group consisting of -$(CHR^6)_mOR^7$, and -$(CH_2)_nNR^8R^9$;

R^5 is selected from the group consisting of hydrogen, alkenyl, alkyl, aryl, arylalkyl, cycloalkyl, and (cycloalkyl) alkyl;

R^6 is selected from the group consisting of hydrogen, alkyl, aryl, and heteroaryl;

R^7 is selected from the group consisting of hydrogen, alkenyl, alkoxyalkoxyalkyl, alkoxyalkyl, alkoxycarbonylalkyl, alkylsulfanylalkyl, alkynyl, aminoalkyl, arylalkyl, arylcarbonylalkyl, aryloxyalkyl, arylsulfanylalkyl, cycloalkenyl, (cycloalkenyl) alkyl, cycloalkyl, (cycloalkyl) alkyl, heteroarylalkoxyalkyl, heteroarylalkyl, (heterocyclyl) alkoxyalkyl, (heterocyclyl) alkyl, and hydroxyalkyl;

R^8 and R^9 are independently selected from the group consisting of hydrogen, alkenyl, alkoxyalkyl, alkyl, alkylsulfanylalkyl, alkynyl, aminoalkyl,

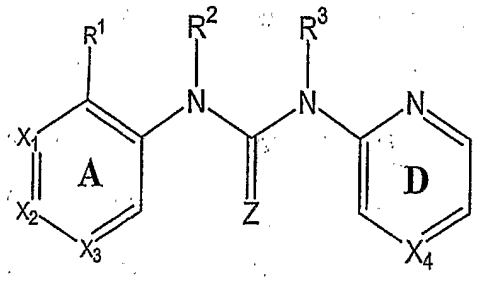
arylalkyl, cycloalkenyl, (cycloalkenyl) alkyl, cycloalkyl, (cycloalkyl) alkyl, heteroarylalkyl, (heterocyclyl) alkyl, and hydroxyalkyl;

m is 0-6; provided that when R^7 is hydrogen m is other than 0; and

n is 0-6; provided that when R^8 and R^9 are both hydrogen, n is other than 0.

VII. Diaryl urea compounds as described in International Patent Publication WO2003101444, including:

i) A compound of formula:



or a pharmaceutically acceptable salt thereof, wherein:
X_1-X_3 are independently CH or N, that provided that X_1-X_3 are not all N;
X_4 is CH or N ;Z is O, S, or N-CN ; Ring A is optionally substituted at any substitutable carbon by R^4 ;

R^1 is -T-NH_2, -V-T-NH_2, -T-NHR^x, -V-T-NHR^x ; T is a C_{1-6} straight or branched alkylidene chain that is optionally interrupted by -O-, -S-, -N (R^5)-, -S(O)-,-SO_2-,-C(O)-,-OC (O)-, -N(R^5)C(O)-,-C(O)N(R^5)-,-SO_2N(R^5)-, or-N (R^5)SO_2-, wherein the alkylidene chain or a portion thereof is optionally part of a 3-6 membered ring system ; V is -O-, -S-, -N($R^{5)}$-,-S(O)-,-SO_2-,-C(O)-,-OC(O)-,-N(R^5)C(O)-, -C(O)N(R^5)-,-SO_2N(R^5)-, or-N(R^5)SO_2-;

R^2 and R^3 are each independently selected from hydrogen, C_{1-6} alkyl optionally substituted with-N(R^8)$_2$,-C(=O)R,-CO_2R, or SO_2R, or R_2 and R_3 taken together with their intervening atoms form an optionally substituted an optionally substituted 5-6 membered ring;

each R^4 is independently selected from halo,-OR,-SR,-CN,-NO_2, -$N(R^5)_2$, -$N(R^5)C(O)R$,-$N(R^5)C0_2R$,-$N(R^5)$ $C(O)N(R^5)_2$, -$C(O)N(R^5)_2$,- $C(O)R^5$,-$OC(O)N(R^5)_2$,-CO_2R,-SO_2R,-S(O)R, -$SO_2N(R^5)_2$, -$N(R^5)SO_2R$, or an optionally substituted group selected from C_{1-8} aliphatic, aryl, aralkyl, heterocyclyl, heterocyclealkyl, heteroaryl, or heteroaralkyl, or two *ortho* R^4s, taken together with the *ortho* carbon atoms to which they are bonded, form an optionally substituted five or six membered phenyl, pyridyl or heterocyclyl fused to Ring A;

each R^5 is independently selected from hydrogen, C_{1-6} aliphatic, -CO_2R, -SO_2R, or-C(O)R, or two R^5 on the same nitrogen taken together with the nitrogen form a 5-8 membered heteroaryl or heterocycle ring having 1-4 heteroatoms selected from N, O, or S;

each R^8 is independently a C_{1-3} alkyl or, taken together with the nitrogen atom to which they are bonded, a 5-7 membered nitrogen containing heterocycle;

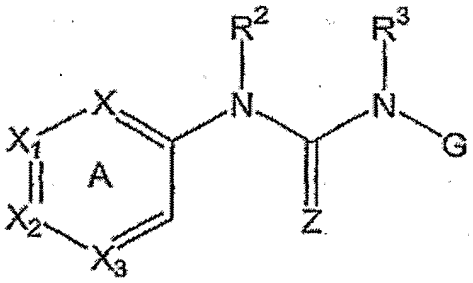
Ring D is optionally substituted by C_{1-4} aliphatic or haloaliphatic, -OR^7, -SR^7, -$C(O)R^7$, -CO_2R^7, -SO_2R^7, -CN, -$C(O)N(R^7)_2$,-N $(R^7)C(O)(C_{1-2}$ alkyl), or-$N(R^7)_2$ and is optionally fused to an optionally substituted phenyl or optionally substituted cyclohexyl ring;

each R^7 is independently selected from hydrogen or an optionally substituted C_{1-3} aliphatic or-$N(R^7)_2$ is a nitrogen-containing heterocyclyl;

each R is independently selected from hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, aryl, aralkyl, heteroaryl, or heteroaralkyl-butyl ; and

R^x is C1-C8 alkyl.

ii) A compound of formula:



or a pharmaceutically acceptable salt thereof, wherein: X is CR^1 ; X_1-X_3 are CH; Z is O ; Ring A is optionally substituted at any substitutable carbon by R^4;

R^1 is V-T-R^6 ; T is aC_{2-4} alkylidene chain; V is -O-;

R^2 and R^3 are each hydrogen;

each R^4 is independently selected from halo,-OR,-SR,-CN,-NO_2, -$N(R^5)_2$, -$N(R^5)C(O)R$, -$N(R^5)C0_2R$,-$N(R^5)C(O)N(R^5)_2$,-$C(O)N(R^5)_2$,- $OC(O)N(R^5)_2$,-CO_2R,-SO_2R,-S(O)R,-$SO_2N(R^5)_2$,-$N(R^5)SO_2R$,

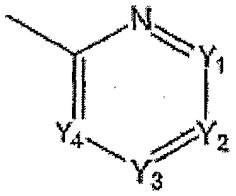
or an optionally substituted group selected from C_{1-8} aliphatic, aryl, aralkyl, heterocyclyl, heterocyclealkyl, heteroaryl, or heteroaralkyl, or two *ortho* R^4s, taken together with the *ortho* carbon atoms to which they are bonded, form an optionally substituted five or six membered phenyl, pyridyl or heterocyclyl fused to Ring A;

each R^5 is independently selected from hydrogen, C_{1-6} aliphatic, CO_2R, -SO_2R, or –C(O)R, or two R^5s on the same nitrogen taken together with the nitrogen form a 5-8 membered heteroaryl or heterocycle ring having 1-4 heteroatoms selected from N, O, or S;

R^6 – NH_2;

Each R^8 is indepently a $C_{1.3}$ alkyl or, taken together with the nitrogen atom to which they are bounded, a 5-7 membered nitrogen containing heterocycle;

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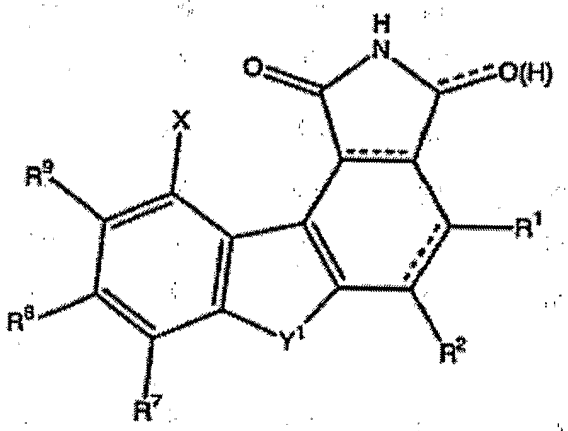


Y_{1-4} are each independently selected from CH or nitrogen, provided that Ring B has no more than three nitrogen atoms and Y_1 and Y_2 are not both N, said Ring B being optionally substituted by C_{1-4} aliphatic or haloaliphatic, $-OR^7$, $-SR^7$, $-C(O)R^7$, $-CO_2R^7$, $-SO_2R^7$, -CN, $-C(O)N(R^7)_2$, $-N(R^7)C(O)(C_{1-2}$ alykl), or $-N(R^7)_2$;

each R^7 is independently selected from hydrogen or an optionally substituted C_{1-3} aliphatic or $-N(R^7)_2$ is a nitrogen-containing heterocyclyl; and each R is hydrogen;

VIII. Pyrrolocarbazole compounds as described in International Patent Publication WO2003091255, including:

i) A compound of formula



wherein each dashed line represents an optional bond;

R^1 is hydrogen, halogen, alkyl, NR^5R^6 or an aryl or heteroaryl ring optionally substituted with up to five substituents selected from

halogen, alkyl, haloalkyl, hydroxyl, nitro, cyano, $C(O)R^3$, OR^3, $S(O)mR^3$, NR^3R^4, $OC(O)R^3$, $NR^3(CO)OR^4$, $CH_2NR^3R^4$, CH^20R^3, $COOR^3$, $CONR^3R^4$, NR^3COR^4, $SO_2NR^3R^4$, $CONHS0_2R^3$, $NR^3S(O)_mR^4$, $NHCONR^3R^4$, NR^3CONHR^4; or a cycloalkyl or cycloalkenyl ring optionally substituted with up to five substituents

selected from, halogen, alkyl, haloalkyl, hydroxyl, nitro, cyano, $C(O)R^3$, OR^3, $S(O)_mR^3$, NR^3R^4, $OC(O)R^3$, $NR^3(CO)OR^4$, $CH_2NR^3R^4$, CH_2OR^3 $COOR^3$, $CONR^3R^4$, NR^3COR^4, $SO_2NR^3R^4$, $CONHSO_2R^3$, $NR^3S(O)_mR^4$, $NHCONR^3R^4$, NR^3CONHR^4; or a heterocyclic ring optionally substituted with up to five substituents selected from,

halogen, alkyl, haloalkyl, hydroxyl, nitro, cyano, $C(O)R^3$, OR^3, $S(O)_mR^3$, NR^3R^4, $OC(O)R^3$, $NR^3(CO)OR^4$, $CH_2NR^3R^4$, CH_20R^3, $COOR^3$, $CONR^3R^4$, NR^3COR^4, $S0_2NR^3R^4$, $CONHSO_2R^3$, $NR^3S(O)_mR^4$ $NHCONR^3R^4$, NR^3CONHR^4;

m is 0-2; X is hydrogen or halogen;

Y^1 is O, S (O) m, or NR^{10};

R^9 is hydrogen, hydroxyl, halogen, $NR^3C(O)R^4$, $NHCONR^3R^4$, $(C=NR^3)$ NHR^4, $NH(C=NR^3)NHR^4$, $NH(C=NH)NR^3R^4$, $NH(C=O)OR^3$, NR^5R^6, $(CR^5R^6)_r$- Z;

r is 0-6;

R^2, R^7, R^8 and R^{10} are in each instance independently selected from $((CR^5 R^6)_nT)a(CR^{11}R^{12})_b)$-Z wherein the sum n, a and b is in each instance less than 10;

T may be absent, or, when present, is in each instance independently selected from O, $CONR^3$, $CONHSO_2$, $S(O)_m$, NR^3, NR^3-O, O-$S(O)_m$, $S(O)_m$-O, NR^3-$S(O)_2$, or $S(O)_2$-NR^3;

n is in each instance independently 0-6; a is in each instance independently 0-6; b is in each instance independently 0-6;

Z is selected from hydrogen, halogen, alkyl, haloalkyl, cycloalkyl, cycloalkenyl, heterocyclyl, aryl, heteroaryl, cyano, nitro, hydroxy, $C(O)R^3$, $CONHS0_2R^3$, OR^3, $S(O)_mR^3$, OSO_2R^3, NR^3R^4, CO_2R^3, $CONR^3R^4$, NR^3COR^4, $SO_2NR^3R^4$, $OPO(OR^3)(OR^4)$, $CH=CR^3R^4$, CCR^3, $(C=NR^3)NHR^4$, $NH(C=NR^3)NHR^4$, $NH(C=NH)$ NR^3R^4,

wherein the alkyl, cycloalkyl, cycloalkenyl, heterocyclyl, aryl or heteroaryl group may be substituted with up to four groups independently selected from halogen, alkyl, hydroxyl, nitro, cyano, OR^3, $S(O)_mR^3$, NR^3R^4, $OC(O)R^3$, $NR^3(CO)OR^4$, $C(O)R^3$, $COOR^3$, $CONR^3R^4$, NR^3COR^4, $SO_2NR^3R^4$, $CONHSO_2R^3$, $NR^3S(O)_mR^4$, $CH_2NR^3R^4$, CH_2OR^3, $NHCONR^3R^4$, NR^3CONHR^4;

R^5, R^6, R^{11} and R^{12} are in each instance independently selected from hydrogen, hydroxyl, alkyl, haloalkyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclyl, halogen, cyano, nitro, $CH_2NR^3R^4$, CH_2OR^3, $C(O)R^3$, OR^3, $S(O)_mR^3$, NR^3R^4, $COOR^3$, $CONR^3R^4$, $SO_2NR^3R^4$, $NHCONR^3R^4$, NR^3CONHR^4;

wherein the alkyl, haloalkyl, cycloalkyl, cycloalkenyl, heterocyclyl, aryl or heteroaryl group may be substituted with up to four groups independently selected from halogen, alkyl, hydroxyl, nitro, cyano, OR^3, $S(O)_mR^3$, NR^3R^4, $OC(O)R^3$, $NR^3(CO)OR^4$, $C(O)R^3$, $COOR^3$, $CONR^3R^4$, NR^3COR^4, $SO_2NR^3R^4$, $CONHSO_2R^3$, $NR^3S(O)_mR^4$, $NHCONR^3R^4$, NR^3CONHR^4;

R^5, R^6, R^{11} and R^{12} together with the carbon atom to which they are attached may form a carbonyl group; or together with the carbon or heteratom to which they are attached may form a cycloalkyl or heterocyclyl group,

said carbonyl, cycloalkyl or heterocycloyl group may be substituted with up to four groups independently selected from halogen, hydroxyl, nitro, cyano, alkyl, haloalkyl, alkyl, nitro, cyano. OR^3, $S(O)_mR^3$, NR^3R^4, $OC(O)R^3$, $NR^3(CO)OR^4$, $C(O)R^3$, $COOR^3$, $CONR^3R^4$, NR^3COR^4, NR^3COR^4, $SO_2NR^3R^4$, $CONHSO_2R^3$, $NR^3S(O)_mR^4$, $NHCONR^3R^4$, NR^3CONHR^4;

R^3, R^4 are independently selected from hydrogen, alkyl, haloalkyl or a substituted or unsubstituted carbocyclic group

selected from cycloalkyl, cycloalkenyl, heterocyclyl, aryl, and heteroaryl, wherein the said alkyl, or a substituted group may be substituted with up to 4 groups selected from halogen, hydroxyl, nitro, cyano, alkyl, haloalkyl, alkyloxy, carboxy, COOH, $CONH_2$, $NHCOCH_3$, $N(CH_3)_2$, $NHCH_3$, thiomethyl, thioethyl, $SOCH_3$, SO_2CH_3;

R^3 and R^4 together with the carbon atom or heteroatom to which they are attached may form a cycloalkyl or heterocyclyl group substituted with up to four groups independently selected from halogen, hydroxyl, nitro, cyano, alkyl, haloalkyl, alkyloxy, formyl, carboxy,acetyl, CH_2NH_2, CH_2OH, COOH, $CONH_2$, $NHCOCH_3$, $N(CH_3)_2$, thiomethyl, thioethyl, $SOCH_3$, SO_2CH_3, alkoxycarbonyl, alkylcarbonyl, alkynylamino, aminoalkyl, aminoalkylcarbonyl, amino, mono-or dialkylamino, or

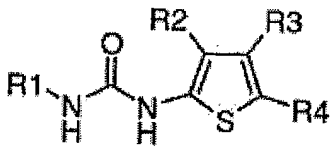
R^3 and R^4 together with the nitrogen to which they are attached may form a heterocyclic ring containing 3-8 members, up to four of which members are optionally carbonyl groups or heteroatoms independently selected from,

oxygen, sulfur, S(O), $S(O)_2$, and nitrogen, wherein the carbocyclic group is unsubstituted or substituted with up to four groups independently selected from halogen, hydroxy, hydroxyalkyl, alkyl, haloalkyl, alkoxy, alkoxycarbonyl,

alkylcarbonyl, alkynylamino, aminoalkyl,aminoalkylcarbonyl, amino, mono-or dialkylamino.

IX. Ureidothiophenes as described in International Patent Publication WO2003/029241, including:

i) A compound of formula:



wherein:

R1 is selected from the group consisting of H, C_{1-2} alkyl, XH, XCH_3, C_{1-2} alkyl-XH, C_{1-2} alkyl-XCH_3, $C(O)NH_2$, $C(O)NHCH_3$, and $C(O)$-C_{1-2} alkyl ;X is selected from the group consisting of O, S, and NH;

R2 is selected from the group consisting of $C(O)R^5$, CO_2R^5, $C(O)NHR^5$, $C(O)NHC(=NH)R^5$, $C(O)NHC(=NH)NR^5R^6$, $C(O)NHC(O)R^5$, $C(O)NHC(O)NR^5R^6$, SO_2R^5, $S(O)R^5$, SO_3R^5, and $PO_3R^5R^6$;

R^5 and R^6 are, independently, selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{1-10} alkanoyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{0-6} alkylaryl, C_{0-6} alkylheterocyclyl, and C_{0-6} alkylheteroaryl, or R^5 and R^6 taken together with the nitrogen to which they are attached, may optionally form a ring having 3 to 7 carbon atoms, optionally containing 1, 2, or 3 heteroatoms selected from nitrogen, sulfur, oxygen, or nitrogen, substituted with hydrogen, C_{1-6} alkyl or $(CH_2)_{0-3}$aryl, such that any of the foregoing may be optionally substituted by one or more of group A and on any position;

R3 is H or halogen;

R4 is aryl or heteroaryl optionally substituted by one or more of group A and on any position ;

A is selected from the group consisting of C_{1-10} alkyl, C_{1-10} alkanoyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{0-6} alkylaryl, C_{0-6} alkylheterocyclyl, C_{0-6} alkylheteroaryl, $C(=NH)R^7$, COR^7, $CONR^7R^8$, $CON(O)R^7R^8$, $CONR^7R^8R^9Y$,

CO_2R^7, $C(O)SR^7$, $C(S)R^7$, cyano, trifluoromethyl, NR^7R^8, $N(O)R^7R^8$, $NR^7R^8R^9Y$, NR^7COR^7, $NR^7CONR^7R^8$, $NR^7CON(O)R^7R^8$, $NR^7CONR^7R^8R^9Y$, $NR^7CO_2R^7$, $NR^7C(O)SR^7$, $NR^7SO_2R^7$, $NR^7SO2NR^7R^8$, nitro, OR^7, OCF_3, aryloxy, heteroaryloxy, SR^7, $S(O)R^7$, $S(O)_2R^7$, SCF_3, $S(O)CF_3$, $S(O)_2CF_3$, $SO_2NR^7R^8$, SO_3R^7, $PO_3R^7R^8$, and halo,

wherein C_{1-10} alkyl, C_{1-10} alkanoyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{0-6} alkylaryl, C_{0-6} alkylheterocyclyl, C_{0-6} alkylheteroaryl, $(CH_2)_{0-6}$ heteroaryl, aryloxy, and heteroaryloxy may be optionally substituted by one or more of group D and on any position;

Y is an organic or inorganic anion;

D is selected from the group consisting of C_{1-10} alkyl, C_{1-10} alkanoyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{0-6} alkylaryl, C_{0-6} alkylheterocyclyl, C_{0-6} alkylheteroaryl, $C(=NH)R^7$, COR^7, $CONR^7R^8$, $CON(O)R^7R^8$, $CONR^7R^8R^9Y$, CO_2R^7, $C(O)SR^7$, $C(S)R^7$, cyano, trifluoromethyl, NR^7R^8, $N(O)R^7R^8$, $NR^7R^8R^9Y$, NR^7COR^7, $NR^7CONR^7R^8$, $NR^7CON(O)R^7R^8$, $NR^7CONR^7R^8R^9Y$, $NR^7CO_2R^7$, $NR^7C(O)SR^7$, $NR^7SO_2R^7$, $NR^7SO2NR^7R^8$, nitro, OR^7, OCF_3, aryloxy, heteroaryloxy, SR^7, $S(O)R^7$, $S(O)_2R^7$, SCF_3, $S(O)CF_3$, $S(O)_2CF_3$, $SO_2NR^7R^8$, SO_3R^7, $PO_3R^7R^8$, and halo,

wherein C_{1-10} alkyl, C_{1-10} alkanoyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{0-6} alkylaryl, C_{0-6} alkylheterocyclyl, C_{0-6} alkylheteroaryl, $(CH_2)_{0-6}$ heteroaryl, aryloxy, and heteroaryloxy may be optionally substituted by one or more of group E and on any position;

R^7, R^8, and R^9 are independently selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{1-10} alkanoyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{0-6} alkylaryl, C_{0-6} alkylheterocyclyl, and C_{0-6} alkylheteroaryl,

or R^7 and R^8 taken together with the nitrogen to which they are attached may optionally form a ring having 3 to 7 carbon atoms optionally containing 1, 2, or 3 heteroatoms selected from nitrogen, sulfur, oxygen, or nitrogen, substituted with hydrogen, C_{1-6} alkyl or $(CH_2)_{0-3}$ aryl, wherein any of the foregoing may be substituted by one or more of group E and on any position;

E is selected from the group consisting of C_{1-10} alkyl, C_{1-10} alkanoyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{0-6} alkylaryl, C_{0-6} alkylheterocyclyl, C_{0-}

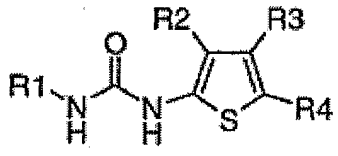
$_6$ alkylheteroaryl, $C(=NH)R^{10}$, COR^{10}, $CONR^{10}R^{11}$, $CON(O)R^{10}R^{11}$, $CONR^{10}R^{11}R^{12}Y$, CO_2R^{10}, $C(O)SR^{10}$, $C(S)R^{10}$, cyano, trifluoromethyl, $NR^{10}R^{11}$, $N(O)R^{10}R^{11}$, $NR^{10}R^{11}R^{12}Y$, $NR^{10}COR^{10}$, $NR^{10}CONR^{10}R^{11}$, $NR^{10}CON(O)R^{10}R^{11}$, $NR^{10}CONR^{10}R^{11}R^{12}Y$, $NR^{10}CO_2R^{10}$, $NR^{10}C(O)SR^{10}$, $NR^{10}SO_2R^{10}$, $NR^{10}SO_2NR^{10}R^{11}$, nitro, OR^{10}, OCF_3, aryloxy, heteroaryloxy, SR^{10}, $S(O)R^{10}$, $S(O)_2R^{10}$, SCF_3, $S(O)CF_3$, $S(O)_2CF_3$, $SO_2NR^{10}R^{11}$, SO_3R^{10}, $PO_3R^{10}R^{11}$, and halo,

wherein C_{1-10} alkyl, C_{1-10} alkanoyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{0-6} alkylaryl, C_{0-6} alkylheterocyclyl, C_{0-6} alkylheteroaryl may be substituted by one or more of $C(=NH)R^{10}$, COR^{10}, $CONR^{10}R^{11}$, $CON(O)R^{10}R^{11}$, $CONR^{10}R^{11}R^{12}Y$, CO_2R^{10}, $C(O)SR^{10}$, $C(S)R^{10}$, cyano, trifluoromethyl, $NR^{10}R^{11}$, $N(O)R^{10}R^{11}$, $NR^{10}R^{11}R^{12}Y$, $NR^{10}COR^{10}$, $NR^{10}CONR^{10}R^{11}$, $NR^{10}CON(O)R^{10}R^{11}$, $NR^{10}CONR^{10}R^{11}R^{12}Y$, $NR^{10}CO_2R^{10}$, $NR^{10}C(O)SR^{10}$, $NR^{10}SO_2R^{10}$, $NR^{10}SO_2NR^{10}R^{11}$, nitro, OR^{10}, OCF_3, aryloxy, heteroaryloxy, SR^{10}, $S(O)R^{10}$, $S(O)_2R^{10}$, SCF_3, $S(O)CF_3$, $S(O)_2CF_3$, $SO_2NR^{10}R^{11}$, SO_3R^{10}, $PO_3R^{10}R^{11}$, or halo, and on any position;

R^{10}, R^{11}, and R^{12} are independently, selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{1-10} alkanoyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{0-6} alkylaryl, C_{0-6} alkylheterocyclyl, and C_{0-6} alkylheteroaryl, or R^{10} and R^{11} taken together with the nitrogen to which they are attached complete a ring having 3 to 7 carbon atoms optionally containing 1, 2, or 3 heteroatoms selected from nitrogen, sulfur, oxygen, or nitrogen, substituted with hydrogen, C_{1-6} alkyl or $(CH_2)_{0-3}$ aryl ;

or a pharmaceutically acceptable inorganic or organic salt, esters, or other prodrug.

ii) A compound of formula:



wherein:

R1 is selected from the group consisting of H, C_{1-2} alkyl, XH, XCH_3, $C_{1\,2}$ alkyl-XH, C_{1-2} alkyl-XCH_3, $C(O)NH_2$, $C(O)NHCH_3$, and $C(O)$-C_{1-2} alkyl,

provided that when R1 is H, R2 is not $CONH_2$, or provided that when R1 is C_{1-2} alkyl, R2 is not $CONH_2$; with the preferred substitution being H or CH_3 ; X is selected from the group consisting of O, S, and NH;

R2 is selected from the group consisting of $C(O)R^5$, CO_2R^5, $C(O)NHR^5$, $C(O)NHC(=NH)R^5$, $C(O)NHC(=NH)NR^5R^6$, $C(O)NHC(O)R^5$, $C(O)NHC(O)NR^5R^6$, SO_2R^5, $S(O)R^5$, $S0_3R^5$, and $PO_3R^5R^6$;

R^5 and R^6 are, independently, selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{1-10} alkanoyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{0-6} alkylaryl, C_{0-6} alkylheterocyclyl, and C_{0-6} alkylheteroaryl, or R^5 and R^6 taken together with the nitrogen to which they are attached may optionally form a ring having 3 to 7 carbon atoms, optionally containing 1, 2, or 3 heteroatoms selected from nitrogen, sulfur, oxygen, or nitrogen, substituted with hydrogen, C_{1-6} alkyl or $(CH_2)_{0-3}$aryl, such that any of the foregoing may be optionally substituted by one or more of group A and on any position;

R3 is H or halogen; with the preferred substitution being H;

R4 is aryl or heteroaryl optionally substituted by one or more of group A and on any position, provided that when R2 is CO_2R^5 or $CONH_2$, R4 is not phenyl, or provided that when R1 is H, R4 is not 4-pyridyl;

A is selected from the group consisting of C_{1-10} alkyl, C_{1-10} alkanoyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{0-6} alkylaryl, C_{0-6} alkylheterocyclyl, C_{0-6} alkylheteroaryl, $C(=NH)R^7$, COR^7, $CONR^7R^8$, $CON(O)R^7R^8$, $CONR^7R^8R^9Y$, CO_2R^7, $C(O)SR^7$, $C(S)R^7$, cyano, trifluoromethyl, NR^7R^8, $N(O)R^7R^8$, $NR^7R^8R^9Y$, NR^7COR^7, $NR^7CONR^7R^8$, $NR^7CON(O)R^7R^8$, $NR^7CONR^7R^8R^9Y$, $NR^7CO_2R^7$, $NR^7C(O)SR^7$, $NR^7SO_2R^7$, $NR^7SO2NR^7R^8$, nitro, OR^7, OCF_3, aryloxy, heteroaryloxy, SR^7, $S(O)R^7$, $S(O)_2R^7$, SCF_3, $S(O)CF_3$, $S(O)_2CF_3$, $SO_2NR^7R^8$, SO_3R^7, $PO_3R^7R^8$, and halo, wherein C_{1-10} alkyl, C_{1-10} alkanoyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{0-6} alkylaryl, C_{0-6} alkylheterocyclyl, C_{0-6} alkylheteroaryl, $(CH_2)_{0-6}$heteroaryl, aryloxy, and heteroaryloxy may be optionally substituted by one or more of group D and on any position;

Y is an organic or inorganic anion;

D is selected from the group consisting of C_{1-10} alkyl, C_{1-10} alkanoyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{0-6} alkylaryl, C_{0-6} alkylheterocyclyl, C_{0-}

$_6$ alkylheteroaryl, C(=NH)R^7, COR^7, CONR^{7}R^8, CON(O)R^{7}R^8, CONR^{7}R^{8}R^{9}Y, CO_2R^7, C(O)SR^7, C(S)R^7, cyano, trifluoromethyl, NR^{7}R^8, N(O)R^{7}R^8, NR^{7}R^{8}R^{9}Y, NR^{7}COR^7, NR^{7}CONR^{7}R^8, NR^{7}CON(O)R^{7}R^8, NR^{7}CONR^{7}R^{8}R^{9}Y, NR^{7}CO$_2$R^7, NR^{7}C(O)SR^7, NR^{7}SO$_2$R^7, NR^{7}SO2NR^{7}R^8, nitro, OR^7, OCF_3, aryloxy, heteroaryloxy, SR^7, S(O)R^7, S(O)$_2$R^7, SCF_3, S(O)CF_3, S(O)$_2CF_3$, SO$_2$NR^{7}R^8, SO$_3$R^7, PO$_3$R^{7}R^8, and halo,

wherein C_{1-10} alkyl, C_{1-10} alkanoyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{0-6} alkylaryl, C_{0-6} alkylheterocyclyl, C_{0-6} alkylheteroaryl, $(CH_2)_{0-6}$ heteroaryl, aryloxy, and heteroaryloxy may be optionally substituted by one or more of group E and on any position;

R^7, R^8, and R^9 are independently selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{1-10} alkanoyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{0-6} alkylaryl, C_{0-6} alkylheterocyclyl, and C_{0-6} alkylheteroaryl,

or R^7 and R^8 taken together with the nitrogen to which they are attached may optionally form a ring having 3 to 7 carbon atoms optionally containing 1, 2, or 3 heteroatoms selected from nitrogen, sulfur, oxygen, or nitrogen, substituted with hydrogen, C_{1-6} alkyl or $(CH_2)_{0-3}$ aryl, wherein any of the foregoing may be substituted by one or more of group E and on any position;

E is selected from the group consisting of C_{1-10} alkyl, C_{1-10} alkanoyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{0-6} alkylaryl, C_{0-6} alkylheterocyclyl, C_{0-6} alkylheteroaryl, C(=NH)R^{10}, COR^{10}, CONR^{10}R^{11}, CON(O)R^{10}R^{11}, CONR^{10}R^{11}R^{12}Y, CO_2R^{10}, C(O)SR^{10}, C(S)R^{10}, cyano, trifluoromethyl, NR^{10}R^{11}, N(O)R^{10}R^{11}, NR^{10}R^{11}R^{12}Y, NR^{10}COR^{10}, NR^{10}CONR^{10}R^{11}, NR^{10}CON(O)R^{10}R^{11}, NR^{10}CONR^{10}R^{11}R^{12}Y, NR^{10}CO$_2$R^{10}, NR^{10}C(O)SR^{10}, NR^{10}SO$_2$R^{10}, NR^{10}SO$_2$NR^{10}R^{11}, nitro, OR^{10}, OCF_3, aryloxy, heteroaryloxy, SR^{10}, S(O)R^{10}, S(O)$_2$R^{10}, SCF_3, S(O)CF_3, S(O)$_2CF_3$, S(O)$_2$NR^{10}R^{11}, SO$_3$R^{10}, PO$_3$R^{10}R^{11}, and halo,

wherein C_{1-10} alkyl, C_{1-10} alkanoyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{0-6} alkylaryl, C_{0-6} alkylheterocyclyl, C_{0-6} alkylheteroaryl may be substituted by one or more of C(=NH)R^{10}, COR^{10}, CONR^{10}R^{11}, CON(O)R^{10}R^{11}, CONR^{10}R^{11}R^{12}Y, CO_2R^{10}, C(O)SR^{10}, C(S)R^{10}, cyano, trifluoromethyl, NR^{10}R^{11}, N(O)R^{10}R^{11}, NR^{10}R^{11}R^{12}Y, NR^{10}COR^{10}, NR^{10}CONR^{10}R^{11}, NR^{10}CON(O)R^{10}R^{11}, NR^{10}CONR^{10}R^{11}R^{12}Y, NR^{10}CO$_2$R^{10}, NR^{10}C(O)SR^{10}, NR^{10}SO$_2$R^{10}, NR^{10}SO$_2$NR^{10}R^{11},

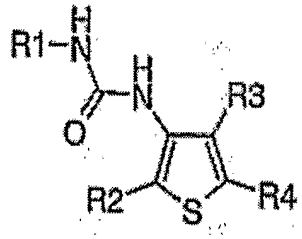
nitro, OR^{10}, OCF_3, aryloxy, heteroaryloxy, SR^{10}, $S(O)R^{10}$, $S(0)_2R^{10}$, SCF_3, $S(O)CF_3$, $S(0)_2CF_3$, $SO_2NR^{10}R^{11}$, SO_3R^{10}, $PO_3R^{10}R^{11}$, or halo, and on any position;

R^{10}, R^{11}, and R^{12} are independently, selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{1-10} alkanoyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{0-6} alkylaryl, C_{0-6} alkylheterocyclyl, and C_{0-6} alkylheteroaryl, or R^{10} and R^{11} taken together with the nitrogen to which they are attached complete a ring having 3 to 7 carbon atoms optionally containing 1, 2, or 3 heteroatoms selected from nitrogen, sulfur, oxygen, or nitrogen, substituted with hydrogen, C_{1-6} alkyl or $(CH_2)_{0-3}$aryl ;

or a pharmaceutically acceptable inorganic or organic salt, esters, or other prodrug of said compound.

X. Ureidothiophene compounds as described in Interational Patent Publication WO2003028731, including:

i) A compound of formula:



wherein: R1 is selected from the group consisting of H, C_{1-2} alkyl, XH, XCH_3, C_{1-2} alkyl-XH, C_{1-2} alkyl-XCH_3, $C(O)NH_2$, $C(O)NHCH_3$, and $C(O)$-C_{1-2} alkyl; X is selected from the group consisting of O, S, and NH;

R2 is selected from the group consisting of $C(O)R^5$, CO_2R^5, $C(O)NHR^5$, C(O)NHC (=NH)R^5, C(O)NHC (=NH)NR^5R^6, $C(O)NHC(O)R^5$, $C(O)NHC(O)NR^5R^6$, SO_2R^5, $S(O)R^5$, SO_3R^5, and $PO_3R^5R^6$; R^5 and R^6 are, independently, selected from the group consisting of hydrogen,C_{1-10} alkyl, C_{1-10} alkanoyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{0-6} alkylaryl, C_{0-6} alkylheterocyclyl, and C_{0-6} alkylheteroaryl,

or R^5 and R^6, taken together with the nitrogen to which they are attached, may optionally form a ring having 3 to 7 carbon atoms optionally containing 1,2, or 3 heteroatoms selected from nitrogen, sulfur, oxygen, or nitrogen, substituted with hydrogen,C_{1-6} alkyl or $(CH_2)_{0-3}$aryl,

wherein any of the foregoing may be optionally substituted by one or more of group A and on any position;

R3 is H or halogen;

R4 is aryl or heteroaryl optionally substituted by one or more of group A and on any position;

A is selected from the group consisting of C_{1-10} alkyl, C_{1-10} alkanoyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{0-6} alkylaryl, C_{0-6} alkylheterocyclyl, C_{0-6} alkylheteroaryl, C (=NH)R^7, COR^7, CONR^{7}R^8, CON(O)R^{7}R^8,CONR^{7}R^{8}R^{9}Y, CO_2R^7, C(O)SR^7, C(S)R^7, cyano, trifluoromethyl, NR^{7}R^8, N(O)R^{7}R^8, NR^{7}R^{8}R^{9}Y, NR^{7}COR^7, NR^{7}CONR^{7}R^8, NR^{7}CON(O)R^{7}R^8, NR^{7}CONR^{7}R^{8}R^{9}Y, NR^{7}CO$_2$R^7, NR^{7}C(O)SR^7, NR^{7}SO$_2$R^7, NR^{7}SO2NR^{7}R^8, nitro, OR^7,OCF_3, aryloxy, heteroaryloxy, SR^7, S(O)R^7, S(O)$_2$R^7,SCF_3, S(O)CF_3, S(O)$_2CF_3$, SO$_2$NR^{7}R^8, S0$_3$R^7, P0$_3$R^{7}R^8, and halo,

wherein C_{1-10} alkyl, C_{1-10} alkanoyl,C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{0-6} alkylaryl, C_{0-6} alkylheterocyclyl, C_{0-6} alkylheteroaryl, $(CH_2)_{0-6}$heteroaryl, aryloxy, and heteroaryloxy may be optionally substituted by one or more of group D and on any position;

Y is an organic or inorganic anion ;

D is selected from the group consisting of C_{1-10} alkyl, C_{1-10} alkanoyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{0-6} alkylaryl, C_{0-6} alkylheterocyclyl, C_{0-6} alkylheteroaryl, C(=NH)R^7, COR^7, CONR^{7}R^8, CON(O)R^{7}R^8, CONR^{7}R^{8}R^{9}Y, CO_2R^7, C(O)SR^7, C(S)R^7, cyano, trifluoromethyl, NR^{7}R^8, N(O)R^{7}R^8, NR^{7}R^{8}R^{9}Y, NR^{7}COR^7, NR^{7}CONR^{7}R^8, NR^{7}CON(O)R^{7}R^8, NR^{7}CONR^{7}R^{8}R^{9}Y, NR^{7}CO$_2$R^7, NR^{7}C(O)SR^7, NR^{7}SO$_2$R^7, NR^{7}SO$_2$NR^{7}R^8, nitro, OR^7, OCF_3, aryloxy, heteroaryloxy,SR^7, S(O)R^7, S(O)$_2$R^7, SCF_3, S(O)CF_3,S(O)$_2CF_3$, S(O)$_2$NR^{7}R^8, SO$_3$R^7, PO$_3$R^{7}R^8, and halo,

wherein C_{1-10} alkyl, C_{1-10} alkanoyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{0-6} alkylaryl, C_{0-6} alkylheterocyclyl, C_{0-6} alkylheteroaryl, $(CH_2)_{0-6}$heteroaryl, aryloxy, and heteroaryloxy may be optionally substituted by one or more of group E and on any position;

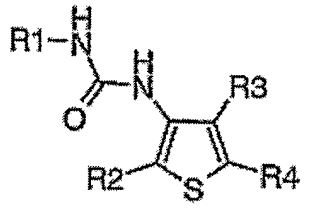
R^7, R^8, and R^9 are, independently, selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{1-10} alkanoyl, C_{2-10} alkenyl, c_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{0-6} alkylaryl, C_{0-6} alkylheterocyclyl, and C_{0-6} alkylheteroaryl, or R^7 and R^8, taken together with the nitrogen to which they are attached, may optionally form a ring having 3 to 7 carbon atoms, optionally containing 1,2, or 3 heteroatoms selected from nitrogen, sulfur, oxygen, or nitrogen, substituted with hydrogen, C_{1-6} alkyl or $(CH_2)_{0-3}$aryl, wherein any of the foregoing may be optionally substituted by one or more of group E and on any position;

E is selected from the group consisting of C_{1-10} alkyl, C_{1-10} alkanoyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{0-6} alkylaryl, C_{0-6} alkylheterocyclyl, C_{0-6} alkylheteroaryl, C (=NH) R^{10}, COR^{10} $CONR^{10}R^{11}$, $CON(O)R^{10}R^{11}$, $CONR^{10}R^{11}R^{12}Y$, CO_2R^{10}, $C(O)SR^{10}$, $C(S)R^{10}$, cyano, trifluoromethyl, $NR^{10}R^{11}$, $N(O)R^{10}R^{11}$, $NR^{10}R^{11}R^{12}Y$, $NR^{10}COR^{10}$, $NR^{10}CONR^{10}R^{11}$, $NR^{10}CON(O)R^{10}R^{11}$, $NR^{10}CONR^{10}R^{11}R^{12}Y$, $NR^{10}CO_2R^{10}$, $NR^{10}C(O)SR^{10}$, $NR^{10}SO_2R^{10}$, $NR^{10}SO_2NR^{10}R^{11}$, nitro, OR^{10}, OCF_3, aryloxy, heteroaryloxy, SR^{10}, $S(O)R^{10}$, $S(O)_2R^{10}$, SCF_3, $S(O)CF_3$, $S(O)_2CF_3$, $SO_2NR^{10}R^{11}$, SO_3R^{10}, $PO_3R^{10}R^{11}$, and halo,

wherein C_{1-10} alkyl, C_{1-10} alkanoyl, C_{2-10}, alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{0-6} alkylaryl, C_{0-6} alkylheterocyclyl,C_{0-6} alkylheteroaryl may be optionally substituted by one or more of C (=NH)R^{10} , COR^{10}, $CONR^{10}R^{11}$, $CON(O)R^{10}R^{11}$, $CONR^{10}R^{11}R^{12}Y$, CO_2R^{10}, $C(O)SR^{10}$, $C(S)R^{10}$, cyano, trifluoromethyl, $NR^{10}R^{11}$, $N(O)R^{10}R^{11}$, $NR^{10}R^{11}R^{12}Y$, $NR^{10}COR^{10}$, $NR^{10}CONR^{10}R^{11}$, $NR^{10}CON(O)R^{10}R^{11}$, $NR^{10}CONR^{10}R^{11}R^{12}Y$, $NR^{10}CO_2R^{10}$, $NR^{10}C(O)SR^{10}$, $NR^{10}SO_2R^{10}$, $NR^{10}SO_2NR^{10}R^{11}$, nitro, OR^{10}, OCF_3, aryloxy, heteroaryloxy, SR^{10} , $S(O)R^{10}$, $S(O)_2R^{10}$, SCF_3, $S(O)CF_3$, $S(O)_2CF_3$, $SO_2NR^{10}R^{11}$, SO_3R^{10}, $PO_3R^{10}R^{11}$, or halo, and on any position;

R^{10}, R^{11}, and R^{12} are, independently, selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{1-10} alkanoyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{0-6} alkylaryl, C_{0-6} alkylheterocyclyl, and C_{0-6} alkylheteroaryl, or R^{10} and R^{11}, taken together with the nitrogen to which they are attached, forms a ring having 3 to 7 carbon atoms optionally containing 1, 2, or 3 heteroatoms selected from nitrogen, sulfur, oxygen, or nitrogen, substituted with hydrogen, C_{1-6} alkyl or$(CH_2)_{0-3}$aryl; or a pharmaceutically acceptable inorganic or organic salt, esters, or other prodrug of said compound.

ii) A compound of formula:



wherein:

R1 is selected from the group consisting of H_2 C_{1-2} alkyl, XH, XCH_3,C_{1-2} alkyl-XH, C_{1-2} alkyl-XCH_3, $C(O)NH_2$, $C(O)NHCH_3$, and $C(O)$-C_{1-2} alkyl, provided that when R1 is H, R2 is not $CONH_2$, or provided that when R1 is C_{1-2} alkyl, R2 is not $CONH_2$; with the preferred substitution being H or CH_3 ; X is selected from the group consisting of O, S, and NH;

R2 is selected from the group consisting of $C(O)R^5$, CO_2R^5, $C(O)NHR^5$, C(O) $NHC(=NH)R^5$, $C(O)NHC(=NH)NR^5R^6$, $C(O)NHC(O)R^5$, $C(O)NHC(O)NR^5R^6$, SO_2R^5, $S(O)R^5$, SO_3R^5, and $PO_3R^5R^6$; R^5 and R^6 are, independently, selected from the group consisting of

hydrogen, C_{1-10} alkyl, C_{1-10} alkanoyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{0-6} alkylaryl, C_{0-6} alkylheterocyclyl, and C_{0-6} alkylheteroaryl, or R^5 and R^6, taken together with the nitrogen to which they are attached, may optionally form a ring having 3 to 7 carbon atoms optionally containing 1,2, or 3 heteroatoms selected from nitrogen, sulfur, oxygen, or nitrogen, substituted with hydrogen, C_{1-6} alkyl or $(CH_2)_{0-3}$aryl, wherein any of the foregoing may be optionally substituted by one or more of group A and on any position;

R3 is H or halogen; with the preferred substitution being H;

R4 is aryl or heteroaryl optionally substituted by one or more of group A and on any position, provided that when R1 is CH_3 and R2 is CO_2R^5, R4 is not phenyl, or provided that when R1 is H, R4 is not 4-pyridyl;

A is selected from the group consisting of C_{1-10} alkyl, C_{1-10} alkanoyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{0-6} alkylaryl, C_{0-6} alkylheterocyclyl, C_{0-6} alkylheteroaryl,C $(=NH)R^7$, COR^7, $CONR^7R^8$, $CON(O)R^7R^8$, $CONR^7R^8R^9Y$, CO_2R^7, $C(O)SR^7$, $C(S)R^7$, cyano, trifluoromethyl, NR^7R^8, $N(O)R^7R^8$, $NR^7R^8R^9Y$,

NR^7COR^7, $NR^7CONR^7R^8$, $NR^7CON(O)R^7R^8$, $NR^7CONR^7R^8R^9Y$, $NR^7CO_2R^7$, $NR^7C(O)SR^7$, $NR^7SO_2R^7$, $NR^7SO2NR^7R^8$, nitro,OR^7, OCF_3, aryloxy, heteroaryloxy,SR^7, $S(O)R^7$, $S(O)_2R^7$, SCF_3, $S(O)CF_3$, $S(O)_2CF_3$, $SO_2NR^7R^8$, SO_3R^7, $PO_3R^7R^8$, and halo,

wherein C_{1-10} alkyl, C_{1-10} alkanoyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{0-6} alkylaryl, C_{0-6} alkylheterocyclyl, C_{0-6} alkylheteroaryl, $(CH_2)_{0-6}$heteroaryl, aryloxy, and heteroaryloxy may be optionally substituted by one or more of group D and on any position;

Y is an organic or inorganic anion;

D is selected from the group consisting of C_{1-10} alkyl, C_{1-10} alkanoyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{0-6} alkylaryl, C_{0-6} alkylheterocyclyl, C_{0-6} alkylheteroaryl, C (=NH)R^7, COR^7, $CONR^7R^8$, $CON(O)R^7R^8$, $CONR^7R^8R^9Y$, CO_2R^7, $C(O)SR^7$, $C(S)R^7$, cyano, trifluoromethyl, NR^7R^8, $N(O)R^7R^8$, $NR^7R^8R^9Y$, NR^7COR^7, $NR^7CONR^7R^8$, $NR^7CON(O)R^7R^8$, $NR^7CONR^7R^8R^9Y$, $NR^7CO_2R^7$, $NR^7C(O)SR^7$, $NR^7SO_2R^7$, $NR^7SO_2NR^7R^8$, nitro, OR^7, OCF_3, aryloxy, heteroaryloxy, SR^7, $S(O)R^7$, $S(O)_2R^7$, SCF_3, $S(O)CF_3$, $S(O)_2CF_3$, $SO_2NR^7R^8$, SO_3R^7, $PO_3R^7R^8$, and halo,

wherein C_{1-10} alkyl, C_{1-10}alkanoyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{0-6} alkylaryl, C_{0-6} alkylheterocyclyl, C_{0-6} alkylheteroaryl, $(CH_2)_{0-6}$heteroaryl, aryloxy, and heteroaryloxy may be optionally substituted by one or more of group E and on any position;

R^7, R^8, and R^9 are, independently, selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{1-10} alkanoyl, C_{2-10} alkenyl,C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{0-6} alkylaryl, C_{0-6} alkylheterocyclyl, and C_{0-6} alkylheteroaryl,

or R^7 and R^8, taken together with the nitrogen to which they are attached, may optionally form a ring having 3 to 7 carbon atoms, optionally containing 1, 2, or 3 heteroatoms selected from nitrogen, sulfur, oxygen, or nitrogen, substituted with hydrogen, C_{1-6} alkyl or $(CH_2)_{0-3}$aryl, wherein any of the foregoing may be optionally substituted by one or more of group E and on any position;

E is selected from the group consisting of C_{1-10} alkyl, C_{1-10} alkanoyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{0-6} alkylaryl, C_{0-6} alkylheterocyclyl, C_{0-6} alkylheteroaryl, C(=NH)R^{10}, COR^{10}, $CONR^{10}R^{11}$, $CON(O)R^{10}R^{11}$,

$CONR^{10}R^{11}R^{12}Y$, CO_2R^{10}, $C(O)SR^{10}$, $C(S)R^{10}$, cyano, trifluoromethyl, $NR^{10}R^{11}$, $N(O)R^{10}R^{11}$, $NR^{10}R^{11}R^{12}Y$, $NR^{10}COR^{10}$, $NR^{10}CONR^{10}R^{11}$, $NR^{10}CON(O)R^{10}R^{11}$, $NR^{10}CONR^{10}R^{11}R^{12}Y$, $NR^{10}CO_2R^{10}$, NR^{10} $C(O)SR^{10}$, NR^{10} SO_2R^{10}, $NR^{10}SO_2NR^{10}$ R^{11}, nitro, OR^{10}, OCF_3, aryloxy, heteroaryloxy, SR^{10}, $S(O)R^{10}$, $S(O)_2R^{10}$, SCF_3, $S(O)CF_3$, $S(O)_2CF_3$, $SO_2NR^{10}R^{11}$, SO_3R^{10}, $PO_3R^{10}R^{11}$, and halo, wherein C_{1-10} alkyl, C_{1-10} alkanoyl, C_{2-10} alkenyl, C_{2-10} alkynyl,C_{3-10} cycloalkyl, C_{0-6} alkylaryl, C_{0-6} alkylheterocyclyl, C_{0-6} alkylheteroaryl may be optionally substituted by one or more of

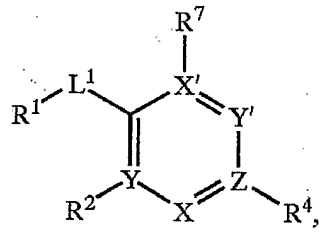
$C(=NH)R^{10}$, COR^{10}, $CONR^{10}R^{11}$, $CON(O)R^{10}R^{11}$, $CONR^{10}R^{11}R^{12}Y$, CO_2R^{10}, $C(O)SR^{10}$, $C(S)R^{10}$, cyano, trifluoromethyl, $NR^{10}R^{11}$, $N(O)R^{10}R^{11}$, $NR^{10}R^{11}R^{12}Y$, $NR^{10}COR^{10}$, $NR^{10}CONR^{10}R^{11}$, $NR^{10}CON(O)R^{10}R^{11}$, $NR^{10}CONR^{10}R^{11}R^{12}Y$, $NR^{10}CO_2R^{10}$, $NR^{10}C(O)SR^{10}$, $NR^{10}SO_2R^{10}$, $NR^{10}SO_2NR^{10}R11$, nitro, OR^{10}, OCF_3, aryloxy, heteroaryloxy, SR^{10} , $S(O)R^{10}$, $S(O)_2R^{10}$, SCF_3, $S(O)CF_3$, $S(O)_2CF_3$, $SO_2NR^{10}R^{11}$, SO_3R^{10}, $PO_3R^{10}R^{11}$, or halo, and on any position;

R^{10}, R^{11}, and R^{12} are, independently, selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{1-10} alkanoyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{0-6} alkylaryl, C_{0-6} alkylheterocyclyl, and C_{0-6} alkylheteroaryl;

or R^{10} and R^{11}, taken together with the nitrogen to which they are attached, forms a ring having 3 to 7 carbon atoms optionally containing 1,2, or 3 heteroatoms selected from nitrogen, sulfur, oxygen, or nitrogen, substituted with hydrogen, C_{1-6} alkyl or $(CH_2)_{0-3}$aryl; or a pharmaceutically acceptable inorganic or organic salt, esters, or other prodrug of said compound.

XI. Heterocyclic compounds as described in US Patent Publication 2003199511, including:

i) A compound of formula:



or a therapeutically acceptable salt thereof, wherein

X is selected from the group consisting of $C(R^8)$ and N; wherein R^8 is selected from the group consisting of hydrogen, alkyl, amino , carboxy, cyano, halo, hydroxy, and amido;

X' is selected from the group consisting of C and N;

Y is selected from the group consisting of C and N;

Y' is selected from the group consisting of $C(R^9)$ and N; wherein R^9 is selected from the group consisting of hydrogen and $-L^2-L^3-(R^3)(R^6)$;

Z is selected from the group consisting of C and N; provided that 0, 1, or 2 of X, X', Y, Y', and Z are N;

L^1 is selected from the group consisting of a bond, -0-, $-NR^5$, alkenyl, alkynyl, -C(O)-, -S-, -S(O)-, $-S(O)_2-$, $-S(O)_2N(R)^5-$, $-N(R^5)S(O)_2-$, $-C(R^{12})_2-$, $-C(R^{12})_2N(R^5)-$, $-N(R^5)C(O)-$, and $-C(O)N(R^5)-$; wherein each group is drawn with its left end attached to R^1 and its right end attached to the aromatic ring;

L^2 is selected from the group consisting of a bond, -O-, $-C(R^{12})_2-$, -S-, $-N(R^5)-$, $-N(R^5)C(O)-$, and $-C(O)N(R^5)-$;

L^3 is selected from the group consisting of a bond, alkylidene and alkylene, wherein the alkylidene and the alkylene are optionally substituted with one or two substituents independently selected from the group consisting of alkoxy, amino, cyano, and hydroxy;

R^1 is selected from the group consisting of aryl, heteroaryl, and heterocycle;

R^2 and R^4 are independently absent or selected from the group consisting of hydrogen, alkenyl, alkyl, alkynyl, amino, aryl, arylalkynyl, cyano, cyanoalkenyl, halo, heteroaryl, heterocycle, hydroxyalkyl, and nitro; or

R^2 and L^1, together with the carbon atoms to which they are attached, form a ring selected from the group consisting of aryl, heteroaryl, and heterocycle; or

R^4 and L^2, together with the carbon atoms to which they are attached, form a ring selected from the group consisting of aryl, heteroaryl, and heterocycle;

provided that when L^3 is alkylidene, R^4 and L^2, together with the carbon atoms to which they are attached, form a ring slected from the group consisting of aryl, heteroaryl, and heterocycle;

R^3 is absent or selected from the group consisting of hydrogen, aryl, arylalkoxy, arylalkylamino, arylalkylthio, aryloxy, arylthio, cycloalkyl, heteroaryl, heteroarylalkoxy, heteroaryloxy, and heterocycle;

R^6 is selected from the group consisting of hydrogen, aryl, arylalkoxy, arylalkylamino, arylalkylthio, aryloxy, arylthio, cycloalkyl, heteroaryl, heteroarylalkoxy, heteroaryloxy, and heterocycle; provided that when L^1 and L^2 are bonds, at least one of R^3 and R^6 is other than hydrogen;

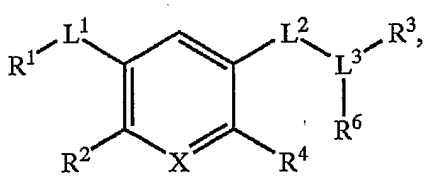
R^5 is selected from the group consisting of hydrogen, alkyl, alkylcarbonyl, alkylsulfonyl, arylcarbonyl, arylsulfonyl, and heteroarylsulfonyl;

R^7 is absent or selected from the group consisting of hydrogen, alkyl, cyanoalkenyl, and $-L^2$-L3(R^3)(R^6); or

R^7 and L^1, together with the carbon atoms to which they are attached, form a ring selected from the group consisting of aryl, heteroaryl, and heterocycle; and

Each R^{12} is selected from the group consiting of hydrogen, alkenyl, alkyl, alkynyl, amino, aryl, cyano, halo, heteroaryl, heterocycle, and nitro.

ii) A compound of formula:



or a therapeutically acceptable salt thereof, wherein

L^1 is selected from the group consisting of a bond, -O-, -N(R^5)-, alkenyl, alkynyl, -N(R^5)C(O)-, and –C(O)N(R^5)-;

L^2 is selected from the group consisting of a bond, -O-, -N(R^5)-, -N(R^5)C(O)-, and –C(O)N(R^5)-;

L^3 is selected from the group consisting of a bond, alkylidene, and alkylene, wherein the alkylidene and the alkylene are optionally substituted with one or two substituents independently selected from the group consisting of amino, cyano, and hydroxy;

R^1 is selected from the group consisting of aryl, heteroaryl, and heterocycle;

R^2 and R^4 are independently selected from the group consiting of hydrogen, alkenyl, alkynyl, arylalkynyl, amino, cyano, cyanoalkenyl, halo, hydroxyalkyl, and heteroaryl; wherein the heteroaryl is selected from the group consisting of furyl, pyrazinyl, thiazolyl, and thienyl; or

R^2 and L^1 , together with the carbon atoms to which they are attached, form a ring selected from the group consisting of dihydropyrrolyl, pyrazolyl, and phenyl; or

R^4 and L^2, together with the carbon atoms to which they are attached, form a ring selected from the group consisting of dihydropyrrolyl, phenyl, pyridinyl, and pyrrolyl; wherein the ring can be optionally substituted with oxo;

provided that when L^3 is alkylidene, R^4 and L^2, together with the carbon atoms to which they are attached, form a ring selected from the group consisting of dihydropyrrolyl, phenyl, pyridinyl, and pyrrolyl; wherein the ring can be optionally substituted with oxo;

R^3 is absent or selected from the group consisting of hydrogen, aryl, arylalkoxy, arylalkylthio, aryloxy, arylthio, cycloalkyl, heteroaryl, heteroarylalkoxy, heteroaryloxy, and heterocycle;

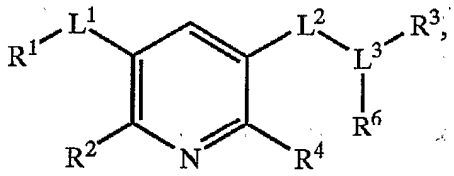
R^6 are independently selected from the group consisting of hydrogen, aryl, arylalkoxy, arylalkylthio, aryloxy, arylthio, cycloalkyl, heteroaryl, and heteroarylalkoxy, heteroaryloxy, and heterocycle; provided that when L^1 and L^2 are bonds, at least one of R^3 and R^6 is other than hydrogen;

R^5 is selected from the group consisting of hydrogen, alkyl, alkylcarbonyl, alkylsulfonyl, arylcarbonyl, arylsulfonyl, and heteroarylsulfonyl; and

X is selected from the group consisting of $C(R^8)$ and N;

wherein R^8 is selected from the group consisting of hydrogen, amino, carboxy, cyano, and halo.

iii) A compound of formula:



or a therapeutically acceptable salt thereof, wherein

L^1 is selected from the group consisting of a bond, ---O---, ---$N(R^5)$---, alkenyl, alkynyl, and ---$N(R^5)C(O)$---;

L^2 is selected from the group consisting of a bond, ---O---, ---$N(R^5)$---, ---$N(R^5)C(O)$---, and ---$C(O)N(R^5)$---;

L^3 is alkylene, wherein the alkylene is substituted with one or two substituents independently selected from the group consisting of amino and hydroxy;

R^1 is selected from the group consisting of aryl, heteroaryl, and heterocycle;

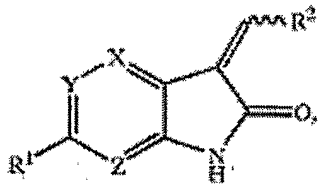
R^2 and R^4 are independently selected from the group consisting of hydrogen and halo;

R^3 and R^6 are independently selected from the group consisting of hydrogen, aryl, arylalkoxy, and heteroaryl; provided that when L^1 and L^2 are bonds, at least one of R^3 and R^6 is other than hydrogen; and

R^5 is selected from the group consisting of hydrogen and alkyl.

XII. Heterocyclic compounds as described in U.S. Patent Publication US2003162785, including:

i) A compound of formula:



or a therapeutically acceptable salt thereof,

wherein X is selected from the group consisting of -N- and -CR^x-;

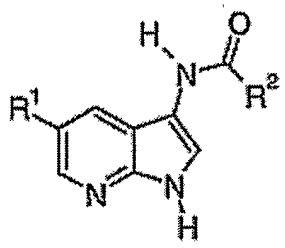
Y is selected from the group consisting of -N- and -CR^y-;

Z is selected from the group consisting of -N- and -CR^z-; with the proviso that at least one of Y and Z is other than -N-; one of R^x, R^y, R^z, and R^1 is selected from the group consisting of aryl and heterocycle and the others are hydrogen; and

R^2 is selected from the group consisting of heterocycle and aryl; with the proviso that when R^2 is heterocycle the heterocycle is other than imidazolyl.

XIII. N-pyrrolopyridinyl compounds as described in International Patent Publication WO03028724, including:

i) A compound of formula:



wherein:

R^1 is aryl or heteroaryl,

wherein aryl or heteroaryl may optionally be substituted by one or more of group A and on any position with the exception that R^1 is not 3,4-dichlorophenyl,

A is selected from the group consisting of C_{1-10} alkyl, C_{1-10} alkanoyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{0-6} alkylaryl, C_{0-6} alkylheterocyclyl,C_{0-6} alkylheteroaryl, $C(=NH)R^3$, COR^3, $CONR^3R^4$, $CON(O)R^3R^4$, CO_2R^3, $C(O)SR^3$, $C(S)R^3$, cyano, trifluoromethyl, NR^3R^4, $N(O)R^3R^4$, NR^3COR^4, $NR^3CONR^4R^5$, $NR^3CON(O)R^4R^5$, $NR^3CO_2R^3$, $NR^3C(O)SR^3$, $NR^3SO_2R^3$, nitro, OR^3, OCF_3, aryloxy, heteroaryloxy, SR^3, $S(O)R^3$, $S(O)_2R^3$, SCF_3, $S(O)CF_3$, $S(O)_2CF_3$, $SO_2NR^3R^4$, SO_3R^3, $PO_3R^3R^4$, and halo,

wherein C_{1-10} alkyl, C_{1-10} alkanoyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{0-5} alkylaryl, C_{0-5} alkylheterocyclyl,C_{0-5},)-, alkylheteroaryl, $(CH_2)_{05}$ heteroaryl, aryloxy, and heteroaryloxy may be optionally substituted by one or more of group B and on any position;

B is selected from the group consisting of C_{1-10} alkyl, C_{1-10} alkanoyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{0-5} alkylaryl, C_{0-5} alkylheterocyclyl, C_{0-6} alkylheteroaryl, $C(=NH)R^3$, COR^3, $CONR^3R^4$, $CON(O)R^3R^4$, CO_2R^3, $C(O)SR^3$, $C(S)R^3$, cyano, trifluoromethyl, NR^3R^4, $N(O)R^3R^4$, NR^3COR^4, $NR^3CONR^4R^5$, $NR^3CON(O)R^4R^5$, $NR^3CO_2R^3$, $NR^3C(O)SR^3$, $NR^3SO_2R^3$, nitro,OR^3, OCF_3, aryloxy, heteroaryloxy, SR^3, $S(O)R^3$, $S(O)_2R^3$, SCF_3, $S(O)CF_3$, $S(O)_2CF_3$, $SO_2NR^3R^4$, SO_3R^3, $PO_3R^3R^4$, and halo,

wherein C_{1-10} alkyl, C_{1-10} alkanoyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{0-6} alkylaryl, C_{0-6} alkylheterocyclyl, C_{0-6} alkylheteroaryl, $(CH_2)_{0-6}$heteroaryl, aryloxy, and heteroaryloxy may be optionally substituted by one or more of group C and on any position;

R^3, R^4, and R^5 are independently selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{1-10} alkanoyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{0-6} alkylaryl, C_{0-6} alkylheterocyclyl, and C_{0-6} alkylheteroaryl;

or R^3 and R^4 taken together with the nitrogen to which they are attached form a ring having 3 to 7 carbon atoms optionally containing 1, 2, or 3 heteroatoms selected from nitrogen, sulfur, oxygen, or nitrogen, substituted with

hydrogen, C_{1-6} alkyl or $(CH_2)_{0-3}$aryl, wherein any of the foregoing may be optionally substituted by one or more of group C and on any position;

C is selected from the group consisting of C_{1-10} alkyl, C_{1-10} alkanoyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{0-6} alkylaryl, C_{0-6} alkylheterocyclyl,C_{0-6} alkylheteroaryl, $C(=NH)R^6$, COR^6, $CONR^6R^7$, $CON(O)R^6R^7$, CO_2R^6, $C(O)SR^6$, $C(S)R^6$, cyano, trifluoromethyl, NR^6R^7, $N(O)R^6R^7$, NR^6COR^6, $NR^6CONR^7R^8$, $NR^6CON(O)R^7R^8$, $NR^6CO_2R^6$, $NR^6C(O)SR^6$, $NR^6SO_2R^6$, nitro, OR^6, OCF_3, aryloxy, heteroaryloxy, SR^6, $S(O)R^6$, $S(0)_2R^6$, SCF_3, $SOCF_3$, $S(O)_2CF_3$, $SO_2NR^6R^7$, SO_3R^6, $P0_3R^6R^7$, and halo, wherein C_{1-8} alkyl, C_{1-8} alkanoyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{3-8} cycloalkyl, C_{0-6} alkylaryl, C_{0-6} alkylheterocyclyl, C_{0-6} alkylheteroaryl may be optionally substituted by one or more of

$C(=NH)R^6$, COR^6, $CONR^6R^7$, $CON(O)R^6R^7$, CO_2R^6, $C(O)SR^6$, $C(S)R^6$, cyano, trifluoromethyl, NR^6R^7, $N(O)R^6R^7$, NR^6COR^6, $NR^6CONR^7R^8$, $NR^6CON(O)R^7R^8$, $NR^6CONR^6R^7R^8Y$, $NR^6CO_2R^6$, $NR^6C(O)SR^6$, $NR^6SO_2R^6$, nitro,OR^6, aryloxy, heteroaryloxy, SR^6, $S(O)R^6$, $S(O)_2R^6$, $SO_2NR^6R^7$, SO_3R^6, $PO_3R^6R^7$, or halo, and on any position;

R^6, R^7, and R^8 are independently selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{1-10} alkanoyl, C_{2-10} alkenyl, C_{2-10} alknyl, C_{3-10} cycloalkyl, C_{0-6} alkylaryl, C_{0-6} alkylheterocyclyl, and C_{0-6} alkylheteroaryl;

or R^7 and R^8 taken together with the nitrogen to which they are attached form a ring having 3 to 7 carbon atoms optionally containing 1, 2, or 3 heteroatoms selected from nitrogen, sulfur, oxygen, or nitrogen, substituted with hydrogen, C_{1-6} alkyl or$(CH_2)_{0-3}$aryl;

R^2 is selected from the group consisting of C_{1-8} alkyl, C_{2-8} alkenyl, C_{3-6} cycloalkyl, OR^9, $NR^{10}R^{11}$, phenyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazolinyl, thiazinyl, pyrrolyl, furyl, thienyl, pyrazolyl, imidazolyl, triazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl and thiadiazolyl,

wherein alkyl and alkenyl and cycloalkyl may optionally be substituted with one of more of group D and at any position and wherein phenyl may be optionally subtituted at positions 3-, 4-, and 5- with one to three of group E and

wherein pyridyl, pyridazinyl, pyrimidinyl, pyrazolinyl, thiazinyl, pyrrolyl, furyl, thienyl, pyrazolyl, imidazolyl, triazolyl, oxazolyl, isoxazolyl,

thiazolyl, isothiazolyl and thiadiazolyl may optionally be substituted by one or more of group F and at any position,

with the preferred substitution being *n*-propyl or pyridyl or pyrazolinyl, with the more preferred substitution being 3-pyridyl

R^9 is hydrogen or C_{1-6} alkyl, wherein any of the foregoing groups are optionally substituted with one or more of group D and at any position, with the exception that R^9 is not *tert*-butyl ;

R^{10} is selected from the group consisting of hydrogen, methyl and ethyl; R^{11} is selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-8} alkenyl and C_{3-6} cycloalkyl,

wherein any of the foregoing groups are optionally substituted with one or more of group D and at any position;

R^{10} and R^{11} taken together with the nitrogen to which they are attached may form a ring having 3 to 7 carbon atoms optionally containing 1,2, or 3 heteroatoms selected from nitrogen, sulfur, oxygen, or nitrogen, substituted with hydrogen or C_{1-6} alkyl ;

D is selected from the group consisting of C_{1-6} alkyl, C_{2-8} alkenyl, C_{3-6} cycloalkyl, OR^{12}, $OC(O)NR^{12}R^{13}$, $NR^{14}SO_2R^{12}R^{13}$, $NR^{14}C(O)OR^{12}$, $NR^{14}C(O)NR^{12}R^{13}$, halo, cyano, trifluoromethyl, SR^{12}, $S(O)R^{12}$, $S0_2R^{12}$, $S0_3R^{12}$, $S0_2NR^{12}R^{13}$, $C(O)SR^{12}$, $CONR^{12}R^{13}$ and $P0_3R^{12}$;

R^{12}, R^{13}, R^{14} are independently selected from the group consisting of hydrogen, C_{1-3} alkyl, C_{2-3} alkanoyl, C_{2-3} alkenyl, C_{2-3} alkynyl, and C_{3-5} cycloalkyl; or R^{12} and R^{13} taken together with the nitrogen to which they are attached form a ring having 3 to 7 carbon atoms optionally containing 1,2, or 3 heteroatoms selected from nitrogen, sulfur, oxygen, or nitrogen, substituted with hydrogen or C_{1-3} alkyl;

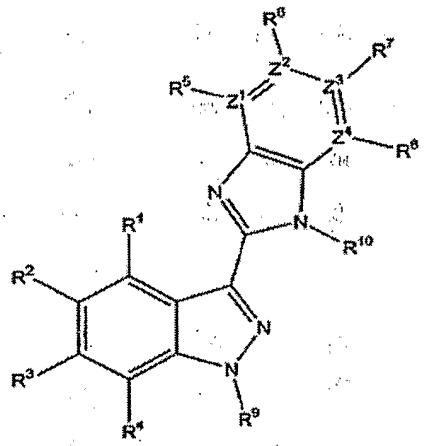
E is selected from the group consisting of C_{1-4} alkyl, o R^{I5} and $NR^{15}R^{16}$, with the exception that R^2 is not 3, 4-dimethoxyphenyl or 3-methoxyphenyl,

F is selected from the group consisting of C_{1-6} alkyl, $C_{2\,8}$ alkenyl, C_{3-6} cycloalkyl, OR^{12}, $OC(O)NR^{12}R^{13}$, $NR^{12}R^{13}$, $NR^{14}SO_2R^{12}R^{13}$, $NR^{14}C(O)OR^{12}$, $NR^{14}C(O)NR^{12}R^{13}$, halo, cyano, trifluoromethyl, SR^{12}, $S(O)R^{12}$, SO_2R^{12}, SO_3R^{12}, $SO_2NR^{12}R^{13}$, $C(O)SR^{12}$, $CONR^{12}R^{13}$ and PO_3R^{12};

R^{15} and R^{16} are independently selected from the group consisting of hydrogen, C_{1-3} alkyl, C_{2-3} alkanoyl, C_{2-3} alkenyl, C_{2-3} alkynyl, and C_{3-5} cycloalkyl; or R^{15} and R^{16} taken together with the nitrogen to which they are attached form a ring having 3 to 7 carbon atoms optionally containing 1,2, or 3 heteroatoms selected from nitrogen, sulfur, oxygen, or nitrogen, substituted with hydrogen or C_{1-3} alkyl.

IX. Indazolyl compounds as described in international Patent Publication WO03004488, including:

i) a compound having the structure below, a tautomer of the compound, a pharmaceutically acceptable salt of the compound, or a pharmaceutically acceptable salt of the tautomer:



wherein

Z^1, Z^2, Z^3, andZ^4 are independently selected from C or N;

R^1 is selected from the group consisting of-H, -F,-Cl, and-Br; R^2 is selected from the group consistingof -H, -F, -Cl, -Br, -C≡N, -NO_2, -CO_2H, substituted and unsubstituted amino groups, substituted and unsubstituted alkyl groups, substituted and unsubstituted-C (=O)O-alkyl groups, substituted and unsubstituted-C(=O)O-aryl groups, substituted and unsubstituted -C (=O)O-heteroaryl groups, substituted and unsubstituted-C(=O)N(H)-alkyl groups, substituted and unsubstituted-C(=O)N(H)-aryl groups, substituted and unsubstituted-C(=O)N(H)-heterocyclyl groups, substituted and unsubstituted - N (H)C(=O)-alkyl groups, substituted and unsubstituted-N(H)C(=O)-aryl groups, substituted and unsubstituted-N(H)C(=O)-heterocyclyl groups, substituted and unsubstituted -N(H)C(=O)N(H)-alkyl groups,

substituted and unsubstituted -N(H)C(=O)N(H)-aryl groups, substituted and unsubstituted -N(H)-heterocyclyl groups, substituted and unsubstituted alkoxy groups, substituted and unsubstituted arylalkoxy groups, and substituted and unsubstituted heterocyclylalkoxy groups;

R^3 is selected from the group consisting of-H,-F,-Cl,-Br, and substituted and unsubstituted alkoxy groups; R^4 is-H ; R^5 is selected from the group consisting of-H, -F,-Cl, substituted and unsubstituted alkyl groups, substituted and unsubstituted alkoxy groups, substituted and unsubstituted amino groups, substituted and unsubstituted alkylamino groups, substituted and unsubstituted dialkylamino groups, and substituted and unsubstituted heterocyclyl groups, orR^5 is absent if Z^1 is N;

R^6 is selected from the group consisting of-H, -F, -Cl, -Br, -CF_3, -$C0_2H$, substituted and unsubstituted alkyl groups, substituted and unsubstituted alkoxy groups including substituted and unsubstituted heterocyclylalkoxy groups, substituted and unsubstituted arylalkoxy groups, and substituted and unsubstituted alkoxyalkoxy groups; substituted and unsubstituted heterocyclyl groups including substituted and unsubstituted heterocyclylheterocyclyl groups, substituted and unsubstituted arylheterocyclyl groups, and substituted and unsubstituted cycloalkylheterocyclyl groups; substituted and unsubstituted heterocyclyloxy groups, substituted and unsubstituted aryloxy groups, substituted and unsubstituted amino groups including substituted and unsubstituted dialkylamino groups, substituted and unsubstituted (alkyl)(heterocyclyl) amino groups, substituted and unsubstituted heterocyclylalkylamino groups, substituted and unsubstituted arylalkylamino groups, and substituted and unsubstituted heterocyclylamino groups; substituted and unsubstituted-C(=O)N(H)-alkyl groups, substituted and unsubstituted -C(=O)N(H)-aryl groups, and substituted and unsubstituted -C(=O)N(H)-heterocyclyl groups; or R^6 is absent if Z^2 is N;

R^7 is selected from the group consisting of -H, -F, -Cl, -Br, -CF_3, -CO_2H, substituted and unsubstituted alkyl groups, substituted and unsubstituted alkoxy groups including substituted and unsubstituted heterocyclylalkoxy groups, substituted and unsubstituted arylalkoxy groups, and substituted and unsubstituted alkoxyalkoxy groups; substituted and unsubstituted heterocyclyl groups including substituted and unsubstituted heterocyclylheterocyclyl groups, substituted and

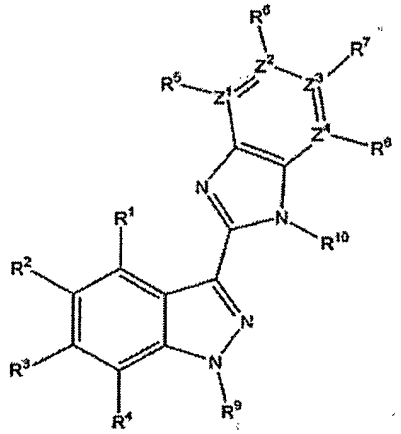
unsubstituted arylheterocyclyl groups, and substituted and unsubstituted cycloalkylheterocyclyl groups; substituted and unsubstituted heterocyclyloxy groups, substituted and unsubstituted aryloxy groups, substituted and unsubstituted amino groups including substituted and unsubstituted dialkylamino groups, substituted and unsubstituted (alkyl)(heterocyclyl) amino groups, and substituted and unsubstituted heterocyclylalkylamino groups, substituted and unsubstituted arylalkylamino groups, substituted and unsubstituted heterocyclylamino groups; substituted and unsubstituted -C(=O)N(H)-alkyl groups, substituted and unsubstituted -C(=O)N(H)-aryl groups, and substituted and unsubstituted -C(=O)N(H)-heterocyclyl groups; or R^7 is absent if Z^3 is N;

R^8 is selected from the group consisting of -H, -F, -Cl, substituted and unsubstituted alkyl groups, substituted and unsubstituted alkoxy groups, substituted and unsubstituted amino groups, substituted and unsubstituted alkylamino groups, substituted and unsubstituted dialkylamino groups, and substituted and unsubstituted heterocyclyl groups, orR^8 is absent if Z^4 is N;

R^9 is -H ; and

R^{10} is-H, and further wherein at least one of R^1, R^2, R^3, R^5, R^6, R^7 or R^8 is not- H.

ii) A compound having the structure below, a tautomer of the compound, a pharmaceutically acceptable salt of the compound, or a pharmaceutically acceptable salt of the tautomer:



wherein

Z^1, Z^2, Z^3, and Z^4 are independently selected from C or N;

R^1 is selectedfrom -H, -F, -Cl, -Br, $-NO_2$, -C≡N, -C(=O)-O-alkyl groups, -OH, substituted and unsubstituted arylalkoxy groups, substituted and unsubstituted heterocyclyloxy groups, substituted and unsubstituted alkoxyalkyl groups, substituted and unsubstituted arylalkoxyalkyl groups, substituted and unsubstituted aryloxy groups, substituted and unsubstituted -N(H)C(=O)-aryl groups, substituted and unsubstituted -N (H)-C(=O)-alkyl groups, substituted and unsubstituted -N(H)-SO_2-alkyl groups, substituted and unsubstituted-N(H)-SO_2-aryl groups, -N (H)-SO_2-CF_3 groups, substituted and unsubstituted -N(H)-SO_2-heterocyclyl groups, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted alkyl groups, substituted and unsubstituted alkoxy groups, substituted and unsubstituted amino groups, substituted and unsubstituted -C(=O)-N(H)-alkyl groups, substituted and unsubstituted -C(=O)-N (H)-alkyl-heterocyclyl groups, substituted and unsubstituted (alkyl)(alkyl) aminoalkyl groups, substituted and unsubstituted (alkyl)(aryl) aminoalkyl groups, substituted and unsubstituted (alkyl) (heterocyclyl) aminoalkyl groups, substituted and unsubstituted (alkyl)(arylalkyl) aminoalkyl groups, substituted and unsubstituted (alkyl)(heterocyclylalkyl) aminoalkyl groups, substituted and unsubstituted -alkyl-N(alkyl)-C(=O)-alkyl groups, substituted and unsubstituted -alkyl-N (alkyl)-C(=O)-aryl groups, substituted and unsubstituted -alkyl-N(alkyl)-C(=O)-heterocyclyl groups, substituted and unsubstituted -alkyl-N(alkyl)-C (=O)-alkyl-aryl groups, substituted and unsubstituted -alkyl-N(alkyl)-C(=O)-alkyl-heterocyclyl groups, substituted and unsubstituted alkylaminoalkyl groups, substituted and unsubstituted arylaminoalkyl groups, substituted and unsubstituted heterocyclylaminoalkyl groups, substituted and unsubstituted arylalkylaminoalkyl groups, substituted and unsubstitutedheterocyclylalkylaminoalkyl groups, substituted and unsubstituted -alkyl-N(H)-C(=O)-alkyl groups, substituted and unsubstituted -alkyl-N(H)-C(=O)-aryl groups, substituted and unsubstituted -alkyl-N (H)-C(=O)-heterocyclyl groups, substituted and unsubstituted -alkyl-N(H)-C(=O)-alkyl-aryl groups, and substituted and unsubstituted -alkyl-N(H)-C(=O)-alkyl-heterocyclyl groups;

R^2 is selectedfrom-H, -F, -Cl, -Br, -C≡N, $-NO_2$,$-CO_2H$, -OH, substituted and unsubstituted guanidinyl groups, substituted and unsubstituted amino groups, substituted and unsubstituted alkyl groups, substituted and unsubstituted -

C(=O)O-alkyl groups, substituted and unsubstituted -C(=O)O-aryl groups, substituted and unsubstituted -C(=O)O-heteroaryl groups, substituted and unsubstituted -C(=O)N(H)-alkyl groups, substituted and unsubstituted -C(=O)-N(H)-alkyl-heterocyclyl groups, substituted and unsubstituted -C(=O)N(H)-aryl groups, substituted and unsubstituted -C(=O)N(H)-heterocyclyl groups, substituted and unsubstituted-N(H)C(=O)-alkyl groups, substituted and unsubstituted -N(H)C(=O)-aryl groups, substituted and unsubstituted -N(H)C(=O)-heterocyclyl groups, substituted and unsubstituted - N (H) C (=O) N (H) -alkyl groups, substituted and unsubstituted - N(H)C(=O)N(H)-aryl groups, substituted and unsubstituted - N(H)C(=O)N(H) -heterocyclyl groups, substituted and unsubstituted -N(H)- (SO_2)-alkyl groups, substituted and unsubstituted -N(H)-(SO_2)-aryl groups, -N (H)-(SO_2)-CF_3 groups, substituted and unsubstituted -N(H)-(SO_2)-heterocyclyl groups, substituted and unsubstituted -N(H)-heterocyclyl groups, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted alkoxy groups, substituted and unsubstituted arylalkoxy groups, substituted and unsubstituted aryloxy groups, substituted and unsubstituted akoxyalkyl groups, substituted and unsubstituted arylalkoxyalkyl groups, substituted and unsubstituted heterocyclyloxy, substituted and unsubstituted heterocyclylalkoxy groups, substituted and unsubstituted (alkyl)(alkyl) aminoalkyl groups, substituted and unsubstituted (alkyl)(aryl) aminoalkyl groups, substituted and unsubstituted (alkyl)(heterocyclyl) aminoalkyl groups substituted and unsubstituted (alkyl)(arylalkyl) aminoalkyl groups, substituted and unsubstituted (alkyl)(heterocyclylalkyl) aminoalkyl groups, substituted and unsubstituted -alkyl-N(alkyl)-C(=O)-alkyl groups, substituted and unsubstituted -alkyl-N(alkyl)-C(=O)-aryl groups, substituted and unsubstituted -alkyl-N (alkyl)-C(=O)-heterocyclyl groups, substituted and unsubstituted -alkyl-N (alkyl)-C (=O)-alkyl-aryl groups, substituted and unsubstituted -alkyl-N(alkyl)-C(=O)-alkyl-heterocyclyl groups, substituted and unsubstituted alkylaminoalkyl groups, substituted and unsubstituted arylaminoalkyl groups, substituted and unsubstituted heterocyclylaminoalkyl groups substituted and unsubstitutedarylalkylaminoalkyl groups, substituted and unsubstituted heterocyclylalkylaminoalkyl groups, substituted and unsubstituted -alkyl-N(H)-C(=O)-alkyl groups, substituted and unsubstituted -alkyl-N(H)-C(=O)-aryl groups, substituted and unsubstituted -alkyl-N(H)-C(=O)-heterocyclyl groups, substituted and unsubstituted - alkyl-N(H)-C(=0)-alkyl-aryl groups, and substituted and unsubstituted - alkyl-N(H)-C(=O)-alkyl-heterocyclyl groups; or R^2 and R^3 are a

group of formula -OCH_2O- such that R^2 and R^3 define a fused 5-membered ring that includes 2 oxygen atoms;

R^3 is selectedfrom -H, -F, -Cl, -Br, -CF_3, -C≡N, substituted and unsubstituted alkyl groups, substituted and unsubstituted amino groups, substituted and unsubstituted alkoxy groups, substituted and unsubstituted -C(=O)-O-alkyl groups, substituted and unsubstituted arylalkoxy groups, substituted and unsubstituted saturated heterocyclyloxy groups, substituted and unsubstituted alkoxyalkyl groups, substituted and unsubstituted arylalkoxyalkyl groups, substituted and unsubstituted saturated heterocycyl groups, substituted and unsubstituted- N(H)-C(=O)-alkyl groups, substituted and unsubstituted -N(H)-C(=O)-aryl groups, substituted and unsubstituted-N(H)-(SO_2)-alkyl groups substituted and unsubstituted -N(H)-(SO_2)-aryl groups, -N(H)-(SO_2)-CF_3 groups, substituted and unsubstituted -N(H)- (SO_2)-heterocyclyl groups, substituted and unsubstituted -N(H)C(=O)N(H)-alkyl groups, substituted and unsubstituted - N (H)C(=O)N(H) -aryl groups, substituted and unsubstituted (alkyl) (alkyl) aminoalkyl groups, substituted and unsubstituted (alkyl)(aryl) aminoalkyl groups, substituted and unsubstituted (alkyl) (heterocyclyl) aminoalkyl groups substituted and unsubstituted (alkyl) (arylalkyl) aminoalkyl groups, substituted and unsubstituted (alkyl) (heterocyclylalkyl) aminoalkyl groups, substituted and unsubstituted -alkyl-N (alkyl)-C(=O)-alkyl groups, substituted and unsubstituted-alkyl-N(alkyl)-C(=O)-aryl groups, substituted and unsubstituted alkyl-N(alkyl)-C(=O)-heterocyclyl groups, substituted and unsubstituted -alkyl-N (alkyl)-C (=O)-alkyl-aryl groups, and substituted and unsubstituted -alkyl-N (alkyl)-C (=O)-alkyl-heterocyclyl groups;

R^4 is -H, -F, -Br, -Cl, -NO_2, -C≡N, -C(=O)-O-alkyl groups, -OH, substituted and unsubstituted arylalkoxy groups, substituted and unsubstituted heterocyclyloxy groups, substituted and unsubstituted alkoxyalkyl groups, substituted and unsubstituted arylalkoxyalkyl groups, substituted and unsubstituted aryloxy groups, substituted and unsubstituted -N(H)-C (=O)-aryl groups, substituted and unsubstituted -N(H)-C (=O)-alkyl groups, substituted and unsubstituted- N(H)-SO_2-alkyl groups, substituted and unsubstituted-N(H)-SO_2-aryl groups,-N (H)-SO_2-CF_3 groups, substituted and unsubstituted-N(H)-SO_2-heterocyclyl groups, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted amino groups, substituted and unsubstituted alkyl groups, substituted and unsubstituted alkoxy

groups, substituted and unsubstituted-C (=O)-N(H)-alkyl groups, substituted and unsubstituted-C(=O)-N(H)-alkyl-heterocyclyl groups, substituted and unsubstituted (alkyl) (alkyl) aminoalkyl groups, substituted and unsubstituted (alkyl) (aryl) aminoalkyl groups, substituted and unsubstituted (alkyl) (heterocyclyl) aminoalkyl groups, substituted and unsubstituted (alkyl)(arylalkyl) aminoalkyl groups, substituted and unsubstituted (alkyl)(heterocyclylalkyl) aminoalkyl groups, substituted and unsubstituted -alkyl-N (alkyl)-C(=O)-alkyl groups, substituted and unsubstituted -alkyl-N (alkyl)-C(=O)-aryl groups, substituted and unsubstituted-alkyl-N(alkyl)-C(=O)-heterocyclyl groups, substituted and unsubstituted - alkyl-N(alkyl)-C(=O)-alkyl-aryl groups, substituted and unsubstituted -alkyl-N (alkyl)-C (=O)-alkyl-heterocyclyl groups, substituted and unsubstituted alkylaminoalkyl groups, substituted and unsubstituted arylaminoalkyl groups, substituted and unsubstituted heterocyclylaminoalkyl groups substituted and unsubstitutedarylalkylaminoalkyl groups, substituted and unsubstituted heterocyclylalkylaminoalkyl groups, substituted and unsubstituted -alkyl-N(H)-C(=O)-alkyl groups, substituted and unsubstituted -alkyl-N(H)-C(=O)-aryl groups, substituted and unsubstituted - alkyl-N(H)-C(=O)-heterocyclyl groups, substituted and unsubstituted - alkyl-N(H)-C(=O)-alkyl-aryl groups, and substituted and unsubstituted -alkyl-N(H)-C(=O)-alkyl-heterocyclyl groups;

R^5 is selected from -H, -F, -Cl, substituted and unsubstituted alkyl groups, substituted and unsubstituted alkoxy groups, substituted and unsubstituted amino groups, substituted and unsubstituted alkylamino groups, substituted and unsubstituted dialkylamino groups, and substituted and unsubstituted heterocyclyl groups, or R^5 is absent if Z^1 is N;

R^6 is selected from -H, -F, -Cl, -Br, $-CF_3$, $-CO_2H$, substituted and unsubstituted alkyl groups, substituted and unsubstituted alkoxy groups including substituted and unsubstituted heterocyclylalkoxy groups, substituted and unsubstituted arylalkoxy groups, and substituted and unsubstituted alkoxyalkoxy groups; substituted and unsubstituted heterocyclyl groups including substituted and unsubstituted heterocyclylheterocyclyl groups, substituted and unsubstituted arylheterocyclyl groups, substituted and unsubstituted alkylheterocyclyl groups, and substituted and unsubstituted cycloalkylheterocyclyl groups; substituted and unsubstituted heterocyclyloxy groups, substituted and unsubstituted aryloxy groups, substituted and

unsubstituted amino groups including substituted and unsubstituted dialkylamino groups, substituted and unsubstituted (alkyl)(heterocyclyl) amino groups, substituted and unsubstituted heterocyclylalkylamino groups, substituted and unsubstituted arylalkylamino groups, and substituted and unsubstituted heterocyclylamino groups; substituted and unsubstituted -C(=O)N(H)-alkyl groups, substituted and unsubstituted -C(=O)N(H)-aryl groups, substituted and unsubstituted -C(=O)N(H)-heterocyclyl groups, substituted and unsubstituted -C (=O) N (alkyl) (heterocyclyl) groups, and substituted and unsubstituted -C(=O)-heterocyclyl groups; or R^6 is absent if Z^2 is N;

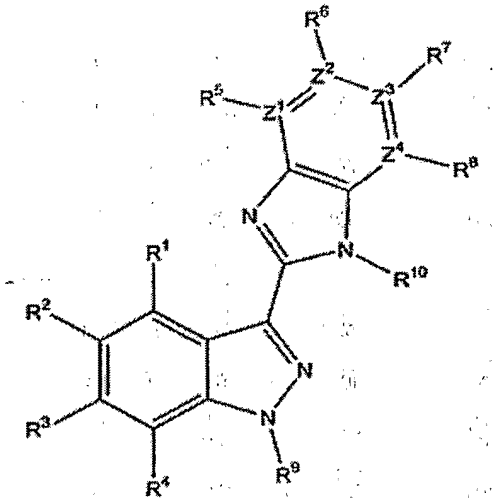
R^7 is selected from -H, -F, -Cl, -Br, $-CF_3$,$-CO_2H$, substituted and unsubstituted alkyl groups, substituted and unsubstituted alkoxy groups including substituted and unsubstituted heterocyclylalkoxy groups, substituted and unsubstituted arylalkoxy groups, and substituted and unsubstituted alkoxyalkoxy groups; substituted and unsubstituted heterocyclyl groups including substituted and unsubstituted heterocyclylheterocyclyl groups, substituted and unsubstituted arylheterocyclyl groups, substituted and unsubstituted alkylheterocyclyl groups, and substituted and unsubstituted cycloalkylheterocyclyl groups; substituted and unsubstituted heterocyclyloxy groups, substituted and unsubstituted aryloxy groups, substituted and unsubstituted amino groups including substituted and unsubstituted dialkylamino groups, substituted and unsubstituted (alkyl)(heterocyclyl) amino groups, substituted and unsubstituted heterocyclylalkylamino groups, substituted and unsubstituted arylalkylamino groups, and substituted and unsubstituted heterocyclylamino groups; substituted and unsubstituted -C(=O)N(H)-alkyl groups, substituted and unsubstituted -C(=O)N(H) -aryl groups, substituted and unsubstituted -C(=O)N(H)-heterocyclyl groups, substituted and unsubstituted -C(=O)N(alkyl)(heterocyclyl) groups, and substituted and unsubstituted -C(=O)-heterocyclyl groups; or R^7 is absent if Z^3 is N;

R^8 is selected from -H, -F, -Cl, substituted and unsubstituted alkyl groups, substituted and unsubstituted alkoxy groups, substituted and unsubstituted amino groups, substituted and unsubstituted alkylamino groups, substituted and unsubstituted dialkylamino groups, and substituted and unsubstituted heterocyclyl groups, or R^8 is absent if Z^4 is N;

R^9 is-H ; and

R^{10} is selected from the group consisting of -H, and substituted and unsubstituted alkyl groups, and further wherein at least one of R^1, R^2, R^3, R^4, R^5, R^6, R^7 or R^8 is not-H.

iii) A compound having the structure below, a tautomer of the compound, a pharmaceutically acceptable salt of the compound, or a pharmaceutically acceptable salt of the tautomer:



wherein

Z^1, Z^2, Z^3, and Z^4 are independently selected from C or N;

R^1 is selectedfrom -H, -F, -Cl, -Br, $-NO_2$, -C≡N, -C(=O)-O-alkyl groups, -OH, substituted and unsubstituted arylalkoxy groups, substituted and unsubstituted heterocyclyloxy groups, substituted and unsubstituted alkoxyalkyl groups, substituted and unsubstituted arylalkoxyalkyl groups, substituted and unsubstituted aryloxy groups, substituted and unsubstituted -N(H)-C(=O)-aryl groups, substituted and unsubstituted -N(H)-C(=O)-alkyl groups, substituted and unsubstituted -N(H)-SO_2-alkyl groups, substituted and unsubstituted -N(H)-SO_2-aryl groups, -N (H)-SO_2-CF_3 groups, substituted and unsubstituted -N (H)-SO_2-heterocyclyl groups, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted alkyl groups, substituted and unsubstituted alkoxy groups, substituted and unsubstituted amino groups, substituted and unsubstituted -C(=O)-N(H)-alkyl groups, substituted and unsubstituted -C(=O)-N(H)-alkyl-heterocyclyl groups, substituted and unsubstituted (alkyl)(alkyl) aminoalkyl groups, substituted

and unsubstituted (alkyl)(aryl) aminoalkyl groups, substituted and unsubstituted (alkyl) (heterocyclyl) aminoalkyl groups substituted and unsubstituted (alkyl)(arylalkyl) aminoalkyl groups, substituted and unsubstituted (alkyl)(heterocyclylalkyl) aminoalkyl groups, substituted and unsubstituted -alkyl-N(alkyl)-C(=O)-alkyl groups, substituted and unsubstituted -alkyl-N (alkyl)-C(=O)-aryl groups, substituted and unsubstituted -alkyl-N (alkyl)-C(=0)-heterocyclyl groups, substituted and unsubstituted -alkyl-N(alkyl)-C(=O)-alkyl-aryl groups, substituted and unsubstituted -alkyl-N(alkyl)-C(=O)-alkyl-heterocyclyl groups, substituted and unsubstituted alkylaminoalkyl groups, substituted and unsubstituted arylaminoalkyl groups, substituted and unsubstituted heterocyclylaminoalkyl groups substituted and unsubstitutedarylalkylaminoalkyl groups, substituted and unsubstitutedheterocyclylalkylaminoalkyl groups, substituted and unsubstituted -alkyl-N(H)-C(=O)-alkyl groups, substituted and unsubstituted -alkyl-N(H)-C(=O)-aryl groups, substituted and unsubstituted -alkyl-N(H)-C(=O)-heterocyclyl groups, substituted and unsubstituted -alkyl-N(H)-C(=O)-alkyl-aryl groups, and substituted and unsubstituted- alkyl-N(H)-C(=O)-alkyl-heterocyclyl groups;

R^2 is selected from -H, -F, -Cl, -Br, -C≡N, $-NO_2$, $-CO_2H$, -OH, substituted and unsubstituted guanidinyl groups, substituted and unsubstituted amino groups, substituted and unsubstituted alkyl groups, substituted and unsubstituted -C(=O)O-alkyl groups, substituted and unsubstituted -C(=O)O-aryl groups, substituted and unsubstituted -C (=O) O-heteroaryl groups, substituted and unsubstituted -C(=O)N(H) -alkyl groups, substituted and unsubstituted -C(=O)-N(H)-alkyl-heterocyclyl groups, substituted and unsubstituted- C(=O)N(H)-aryl groups, substituted and unsubstituted -C(=O)N(H)-heterocyclyl groups, substituted and unsubstituted -N(H)C(=O)-alkyl groups, substituted and unsubstituted -N(H)C(=O)-aryl groups, substituted and unsubstituted -N(H)C(=O)-heterocyclyl groups, substituted and unsubstituted -N(H)C(=O)N(H)-alkyl groups, substituted and unsubstituted -N(H)C(=O)N(H)-aryl groups, substituted and unsubstituted -N(H)C(=O)N(H)-heterocyclyl groups, substituted and unsubstituted -N(H)-(SO_2)-alkyl groups, substituted and unsubstituted -N(H)-(SO_2)-aryl groups, -N(H)-(SO_2)-CF_3 groups, substituted and unsubstituted -N(H)-(SO_2)-heterocyclyl groups, substituted and unsubstituted-N(H)-heterocyclyl groups, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted alkoxy groups, substituted and

unsubstituted arylalkoxy groups, substituted and unsubstituted aryloxy groups, substituted and unsubstituted alkoxyalkyl groups, substituted and unsubstituted arylalkoxyalkyl groups, substituted and unsubstituted heterocyclyloxy, substituted and unsubstituted heterocyclylalkoxy groups, substituted and unsubstituted (alkyl)(alkyl) aminoalkyl groups, substituted and unsubstituted (alkyl) (aryl) aminoalkyl groups, substituted and unsubstituted (alkyl) (heterocyclyl) aminoalkyl groups substituted and unsubstituted (alkyl) (arylalkyl) aminoalkyl groups, substituted and unsubstituted (alkyl) (heterocyclylalkyl) aminoalkyl groups, substituted and unsubstituted -alkyl-N(alkyl)-C(=O)-alkyl groups, substituted and unsubstituted -alkyl-N(alkyl)-C(=O)-aryl groups, substituted and unsubstituted - alkyl-N(alkyl)-C(=O)-heterocyclyl groups, substituted and unsubstituted -alkyl-N (alkyl)-C(=O)-alkyl-aryl groups, substituted and unsubstituted -alkyl-N (alkyl)-C(=O)-alkyl-heterocyclyl groups, substituted and unsubstituted alkylaminoalkyl groups, substituted and unsubstituted arylaminoalkyl groups, substituted and unsubstituted heterocyclylaminoalkyl groups substituted and unsubstitutedarylalkylaminoalkyl groups, substituted and unsubstituted heterocyclylalkylaminoalkyl groups, substituted and unsubstituted -alkyl-N(H)-C(=O)-alkyl groups, substituted and unsubstituted -alkyl-N(H)-C(=O)-aryl groups, substituted and unsubstituted - alkyl-N (H)-C(=O)-heterocyclyl groups, substituted and unsubstituted -alkyl-N (H)-C (=O)-alkyl-aryl groups, and substituted and unsubstituted -alkyl-N (H)-C(=O)-alkyl-heterocyclyl groups; or R^2 and R^3 are a group of formula - OCH_2O-such that R^2 and R^3 define a fused 5-membered ring that includes 2 oxygen atoms;

R^3 is selected from -H, -F, -Cl, -Br, $-CF_3$, -C≡N, $-NO_2$, $-CO_2H$, substituted and unsubstituted amino groups, substituted and unsubstituted alkyl groups, substituted and unsubstituted alkoxy groups, substituted and unsubstituted -C(=O)-O-alkyl groups, substituted and unsubstituted arylalkoxy groups, substituted and unsubstituted heterocyclyloxy groups, substituted and unsubstituted alkoxyalkyl groups, substituted and unsubstituted arylalkoxyalkyl groups, substituted and unsubstituted aryloxy group, substituted and unsubstituted heterocycyl groups, substituted and unsubstituted -N (H)-C(=O)-alkyl groups, substituted and unsubstituted -N(H)-C(=O)-aryl groups, substituted and unsubstituted -N(H)-(SO_2)-alkyl groups substituted and unsubstituted -N(H)-(SO_2)-aryl groups, -N (H)-(SO_2)-CF_3 groups, substituted and unsubstituted-N(H)-(SO_2)-heterocyclyl groups,

substituted and unsubstituted -N(H)C(=O)N(H)-alkyl groups, substituted and unsubstituted -N(H)C(=O)N(H)-aryl groups, substituted and unsubstituted -C(=O)-N(H)-alkyl groups, substituted and unsubstituted -C(=O)-N(H)-alkyl-heterocyclyl groups, substituted and unsubstituted (alkyl) (alkyl) aminoalkyl groups, substituted and unsubstituted (alkyl) (aryl) aminoalkyl groups, substituted and unsubstituted (alkyl) (heterocyclyl) aminoalkyl groups substituted and unsubstituted (alkyl) (arylalkyl) aminoalkyl groups, substituted and unsubstituted (alkyl) (heterocyclylalkyl) aminoalkyl groups, substituted and unsubstituted -alkyl-N(alkyl)-C (=O)-alkyl groups, substituted and unsubstituted -alkyl-N (alkyl)-C(=O)-aryl groups, substituted and unsubstituted -alkyl-N (alkyl)-C(=O)-heterocyclyl groups, substituted and unsubstituted -alkyl-N (alkyl)-C(=O)-alkyl-aryl groups, substituted and unsubstituted -alkyl-N (alkyl)-C(=O)-alkyl-heterocyclyl groups, substituted and unsubstituted alkylaminoalkyl groups, substituted and unsubstitutedarylaminoalkyl groups, substituted and unsubstituted heterocyclylaminoalkyl groups substituted and unsubstituted arylalkylaminoalkyl groups, substituted and unsubstituted heterocyclylalkylaminoalkyl groups, substituted and unsubstituted - alkyl-N(H)-C(=O)-alkyl groups, substituted and unsubstituted-alkyl-N(H)-C(=O)-aryl groups, substituted and unsubstituted - alkyl-N (H)-C(=O)-heterocyclyl groups, substituted and unsubstituted - alkyl-N(H)-C(=O)-alkyl-aryl groups, and substituted and unsubstituted - alkyl-N (H)-C(=O)-alkyl-heterocyclyl groups;

R^4 is selectedfrom -H, -F, -Br, -Cl, $-NO_2$, -C≡N, -C(=O)-O-alkyl groups, -OH, substituted and unsubstituted arylalkoxy groups, substituted and unsubstituted heterocyclyloxy groups, substituted and unsubstituted alkoxyalkyl groups, substituted and unsubstituted arylalkoxyalkyl groups, substituted and unsubstituted aryloxy groups, substituted and unsubstituted -N(H)-C(=O)-aryl groups, substituted and unsubstituted -N(H)-C(=O)-alkyl groups, substituted and unsubstituted -N (H)-SO_2-alkyl groups, substituted and unsubstituted-N(H)-SO_2-aryl groups, -N(H)-SO_2-CF_3 groups, substituted and unsubstituted -N(H)-SO_2-heterocyclyl groups, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted amino groups, substituted and unsubstituted alkyl groups, substituted and unsubstituted alkoxy groups, substituted and unsubstituted -C(=O)-N(H)-alkyl groups, substituted and unsubstituted -C(=O)-N(H)-alkyl-heterocyclyl groups, substituted and unsubstituted (alkyl)(alkyl) aminoalkyl groups, substituted and

unsubstituted (alkyl) (aryl) aminoalkyl groups, substituted and unsubstituted (alkyl) (heterocyclyl) aminoalkyl groups substituted and unsubstituted (alkyl) (arylalkyl) aminoalkyl groups, substituted and unsubstituted (alkyl) (heterocyclylalkyl) aminoalkyl groups, substituted and unsubstituted -alkyl-N (alkyl)-C(=O)-alkyl groups, substituted and unsubstituted -alkyl-N(alkyl)-C(=O)-aryl groups, substituted and unsubstituted -alkyl-N(alkyl)-C(=O)-heterocyclyl groups, substituted and unsubstituted -alkyl-N(alkyl)-C(=O)-alkyl-aryl groups, substituted and unsubstituted -alkyl-N(alkyl)-C(=O)-alkyl-heterocyclyl groups, substituted and unsubstituted alkylaminoalkyl groups, substituted and unsubstituted arylaminoalkyl groups, substituted and unsubstituted heterocyclylaminoalkyl groups substituted and unsubstituted arylalkylaminoalkyl groups, substituted and unsubstituted heterocyclylalkylaminoalkyl groups, substituted and unsubstituted - alkyl-N(H)-C(=O)-alkyl groups, substituted and unsubstituted -alkyl-N(H)-C(=O)-aryl groups, substituted and unsubstituted - alkyl-N(H)-C(=O)-heterocyclyl groups, substituted and unsubstituted - alkyl-N(H)-C(=O)-alkyl-aryl groups, and substituted and unsubstituted -alkyl-N(H)-C(=O)-alkyl-heterocyclyl groups;

R^5 is selected from -H, -F, -Cl, substituted and unsubstituted alkyl groups, substituted and unsubstituted alkoxy groups, substituted and unsubstituted amino groups, substituted and unsubstituted alkylamino groups, substituted and unsubstituted dialkylamino groups, and substituted and unsubstituted heterocyclyl groups, or R^5 is absent if Z^1 is N;

R^6 is selected from -H, -F, -Cl, -Br, $-CF_3$, $-CO_2H$, substituted and unsubstituted alkyl groups, substituted and unsubstituted alkoxy groups including substituted and unsubstituted heterocyclylalkoxy groups, substituted and unsubstituted arylalkoxy groups, and substituted and unsubstituted alkoxyalkoxy groups; substituted and unsubstituted heterocyclyl groups including substituted and unsubstituted heterocyclylheterocyclyl groups, substituted and unsubstituted arylheterocyclyl groups, substituted and unsubstituted alkylheterocyclyl groups, and substituted and unsubstituted cycloalkylheterocyclyl groups; substituted and unsubstituted heterocyclyloxy groups, substituted and unsubstituted aryloxy groups, substituted and unsubstituted amino groups including substituted and unsubstituted dialkylamino groups, substituted and unsubstituted (alkyl) (heterocyclyl) amino groups, substituted and unsubstituted heterocyclylalkylamino groups, substituted and unsubstituted

arylalkylamino groups, and substituted and unsubstituted heterocyclylamino groups; substituted and unsubstituted -C(=O)N(H)-alkyl groups, substituted and unsubstituted -C(=O)N(H)-aryl groups, substituted and unsubstituted -C(=O)N(H)-heterocyclyl groups, substituted and unsubstituted -C(=O)N(alkyl) (heterocyclyl) groups, and substituted and unsubstituted -C(=O)-heterocyclyl groups; or R^6 is absent if Z^2 is N;

R^7 is selected from -H, -F, -Cl, -Br, $-CF_3$, $-CO_2H$, substituted and unsubstituted alkyl groups, substituted and unsubstituted alkoxy groups including substituted and unsubstituted heterocyclylalkoxy groups, substituted and unsubstituted arylalkoxy groups, and substituted and unsubstituted alkoxyalkoxy groups; substituted and unsubstituted heterocyclyl groups including substituted and unsubstituted heterocyclylheterocyclyl groups, substituted and unsubstituted arylheterocyclyl groups, substituted and unsubstituted alkylheterocyclyl groups, and substituted and unsubstituted cycloalkylheterocyclyl groups; substituted and unsubstituted heterocyclyloxy groups, substituted and unsubstituted aryloxy groups, substituted and unsubstituted amino groups including substituted and unsubstituted dialkylamino groups, substituted and unsubstituted (alkyl) (heterocyclyl) amino groups, substituted and unsubstituted heterocyclylalkylamino groups, substituted and unsubstituted arylalkylamino groups, and substituted and unsubstituted heterocyclylamino groups; substituted and unsubstituted -C(=O)N(H) -alkyl groups, substituted and unsubstituted -C(=O)N(H)-aryl groups, substituted and unsubstituted -C(=O)N(H)-heterocyclyl groups, substituted and unsubstituted -C(=O)N(alkyl)(heterocyclyl) groups, and substituted and unsubstituted -C(=O)-heterocyclyl groups; orR7 is absent if Z^3 is N;

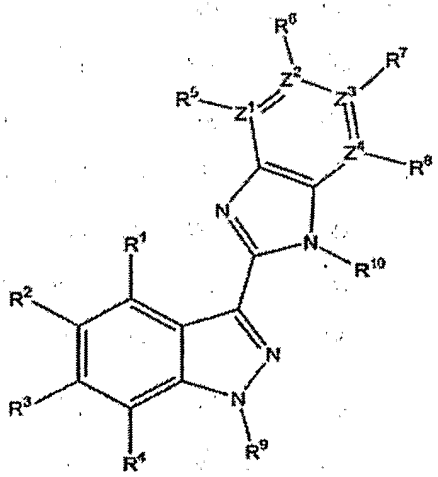
R^8 is selected from -H, -F, -Cl, substituted and unsubstituted alkyl groups, substituted and unsubstituted alkoxy groups, substituted and unsubstituted amino groups, substituted and unsubstituted alkylamino groups, substituted and unsubstituted dialkylamino groups, and substituted and unsubstituted heterocyclyl groups, orR^8 is absent if Z^4 is N;

R^9 is -H ; and

R^{10} is selected from the group consisting of -H, and substituted and unsubstituted alkyl groups, and further wherein at least one of Z^2 orZ^3 is C and at least one of R^6 or R^7 is selected from the group consistingof -Br, $-CO_2H$, substituted and unsubstituted heterocyclylalkoxy groups, substituted and unsubstituted arylalkoxy

groups, substituted and unsubstituted alkoxyalkoxy groups, substituted and unsubstituted heterocyclylheterocyclyl groups, substituted and unsubstituted arylheterocyclyl groups, substituted and unsubstituted cycloalkylheterocyclyl groups, substituted and unsubstituted heterocyclyloxy groups, substituted and unsubstituted aryloxy groups, substituted and unsubstituted (alkyl) (heterocyclyl) amino groups, substituted and unsubstituted heterocyclylalkylamino groups, substituted and unsubstituted arylalkylamino groups, substituted and unsubstituted heterocyclylamino groups, substituted and unsubstituted -C(=O)N(H)-aryl groups, substituted and unsubstituted -C (=O)N(H)-heterocyclyl groups, substituted and unsubstituted -C(=O)N(alkyl) (heterocyclyl) groups, and substituted and unsubstituted -C(=O)-heterocyclyl groups.

iv) A compound having the structure below, a tautomer of the compound, a pharmaceutically acceptable salt of the compound, or a pharmaceutically acceptable salt of the tautomer:



wherein

Z^1, Z^2, Z^3, and Z^4 are independently selected from C or N;

R^1 is selectedfrom -H, -F, -Cl, -Br, -NO_2, -C≡N, -C(=O)-O-alkyl groups, -OH, substituted and unsubstituted arylalkoxy groups, substituted and unsubstituted heterocyclyloxy groups, substituted and unsubstituted alkoxyalkyl groups, substituted and unsubstituted arylalkoxyalkyl groups, substituted and unsubstituted aryloxy groups, substituted and unsubstituted -N(H)-C(=O)-aryl groups,

substituted and unsubstituted -N(H)-C(=O)-alkyl groups, substituted and unsubstituted -N(H)-SO_2-alkyl groups, substituted and unsubstituted -N(H)-SO_2-aryl groups, -N (H)-SO_2-CF_3 groups, substituted and unsubstituted -N(H)-SO_2-heterocyclyl groups, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted alkyl groups, substituted and unsubstituted alkoxy groups, substituted and unsubstituted amino groups, substituted and unsubstituted -C(=O)-N (H)-alkyl groups, substituted and unsubstituted -C(=O)-N(H)-alkyl-heterocyclyl groups, substituted and unsubstituted (alkyl)(alkyl) aminoalkyl groups, substituted and unsubstituted (alkyl)(aryl) aminoalkyl groups, substituted and unsubstituted (alkyl)(heterocyclyl) aminoalkyl groups, substituted and unsubstituted (alkyl)(arylalkyl) aminoalkyl groups, substituted and unsubstituted (alkyl)(heterocyclylalkyl) aminoalkyl groups, substituted and unsubstituted - alkyl-N(alkyl)-C(=O)-alkyl groups, substituted and unsubstituted - alkyl-N (alkyl)-C(=O)-aryl groups, substituted and unsubstituted -alkyl-N (alkyl)-C (=O)-heterocyclyl groups, substituted and unsubstituted -alkyl-N(alkyl)-C(=O)-alkyl-aryl groups, substituted and unsubstituted -alkyl-N (alkyl)-C(=O)-alkyl-heterocyclyl groups, substituted and unsubstituted alkylaminoalkyl groups, substituted and unsubstituted arylaminoalkyl groups, substituted and unsubstituted heterocyclylaminoalkyl groups, substituted and unsubstituted arylalkylaminoalkyl groups, substituted and unsubstituted heterocyclylalkylaminoalkyl groups, substituted and unsubstituted - alkyl-N(H)-C(=O)-alkyl groups, substituted and unsubstituted -alkyl-N(H) -C (=O)-aryl groups, substituted and unsubstituted -alkyl-N (H)-C(=O)-heterocyclyl groups, substituted and unsubstituted -alkyl-N (H)-C(=O)-alkyl-aryl groups, and substituted and unsubstituted -alkyl-N (H)-C(=O)-alkyl-heterocyclyl groups;

R^2 is selected from -H, -F, -Cl, -Br, -C≡N, -NO_2, -CO_2H,-OH, substituted and unsubstituted guanidinyl groups, substituted and unsubstituted amino groups, substituted and unsubstituted alkyl groups, substituted and unsubstituted -C(=O)O-alkyl groups, substituted and unsubstituted -C(=O)O-aryl groups, substituted and unsubstituted -C(=O)O-heteroaryl groups, substituted and unsubstituted -C(=O)N(H) -alkyl groups, substituted and unsubstituted -C(=O)-N(H)-alkyl-heterocyclyl groups, substituted and unsubstituted -C(=O)N(H)-aryl groups, substituted and unsubstituted -C(=O)N(H)-heterocyclyl groups, substituted and unsubstituted-N (H)C(=O)-alkyl groups, substituted and unsubstituted -N(H)C(=O)-

aryl groups, substituted and unsubstituted - N(H)C(=O)-heterocyclyl groups, substituted and unsubstituted -N(H)C(=O)N(H) -alkyl groups, substituted and unsubstituted -N(H)C(=O)N(H)-aryl groups, substituted and unsubstituted - N(H)C(=O)N(H) -heterocyclyl groups, substituted and unsubstituted -N(H)- (SO_2)- alkyl groups, substituted and unsubstituted-N(H)-(SO_2)-aryl groups, -N(H)-(SO_2)-CF_3 groups, substituted and unsubstituted-N(H)- (SO_2)-heterocyclyl groups, substituted and unsubstituted-N(H) -heterocyclyl groups, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted alkoxy groups, substituted and unsubstituted arylalkoxy groups, substituted and unsubstituted aryloxy groups, substituted and unsubstituted akoxyalkyl groups, substituted and unsubstitutedarylalkoxyalkyl groups, substituted and unsubstituted heterocyclyloxy, substituted and unsubstituted heterocyclylalkoxy groups, substituted and unsubstituted (alkyl)(alkyl) aminoalkyl groups, substituted and unsubstituted(alkyl)(aryl) aminoalkyl groups, substituted and unsubstituted (alkyl)(heterocyclyl) aminoalkyl groups substituted and unsubstituted (alkyl)(arylalkyl) aminoalkyl groups, substituted and unsubstituted (alkyl)(heterocyclylalkyl) aminoalkyl groups, substituted and unsubstituted -alkyl-N(alkyl) -C(=O)-alkyl groups, substituted and unsubstituted - alkyl-N(alkyl)-C(=O)-aryl groups, substituted and unsubstituted -alkyl-N(alkyl)- C(=O)-heterocyclyl groups, substituted and unsubstituted -alkyl-N(alkyl)-C (=O)- alkyl-aryl groups, substituted and unsubstituted -alkyl-N(alkyl)-C(=O)-alkyl- heterocyclyl groups, substituted and unsubstituted alkylaminoalkyl groups, substituted and unsubstituted arylaminoalkyl groups, substituted and unsubstituted heterocyclylaminoalkyl groups, substituted and unsubstituted arylalkylaminoalkyl groups, substituted and unsubstituted heterocyclylalkylaminoalkyl groups, substituted and unsubstituted -alkyl-N(H)-C(=O)-alkyl groups, substituted and unsubstituted - alkyl-N(H)-C(=O)-aryl groups, substituted and unsubstituted -alkyl-N(H)-C(=O)- heterocyclyl groups, substituted and unsubstituted - alkyl-N(H)-C(=O)-alkyl-aryl groups, and substituted and unsubstituted -alkyl-N(H)-C(=O)-alkyl-heterocyclyl groups; or R^2 and R^3 are a group of formula -OCH_2O-such that R^2 and R^3 define a fused 5-membered ring that includes 2 oxygen atoms;

R^3 is selected from -F, -Cl, -Br, -CF_3, -C≡N, substituted and unsubstituted alkyl groups, substituted and unsubstituted alkoxy groups, substituted and unsubstituted arylalkoxy groups, substituted and unsubstituted saturated

heterocyclyloxy groups, substituted and unsubstituted alkoxyalkyl groups, substituted and unsubstitutedarylalkoxyalkyl groups, substituted and unsubstituted saturated heterocycyl groups, substituted and unsubstituted -N(H)-C(=O)-alkyl groups, substituted and unsubstituted -N(H)-C(=O)-aryl groups, substituted and unsubstituted -N(H)-(SO_2)-alkyl groups substituted and unsubstituted -N(H)-(SO_2)-aryl groups, -N(H)-(SO_2)-CF_3 groups, substituted and unsubstituted -N(H)-(SO_2)-heterocyclyl groups, substituted and unsubstituted -N(H)C(=O)N(H)-alkyl groups, and substituted and unsubstituted - N(H)C(=O)N(H)-aryl ;

R^4 is -H, -F, -Br, -Cl, -NO_2, -C≡N, -C(=O)-O-alkyl groups, -OH, substituted and unsubstituted arylalkoxy groups, substituted and unsubstituted heterocyclyloxy groups, substituted and unsubstituted alkoxyalkyl groups, substituted and unsubstituted arylalkoxyalkyl groups, substituted and unsubstituted aryloxy groups, substituted and unsubstituted -N(H)-C(=O)-aryl groups, substituted and unsubstituted -N(H)-C(=O)-alkyl groups, substituted and unsubstituted -N(H)-SO_2-alkyl groups, substituted and unsubstituted -N(H)-SO_2-aryl groups, -N (H)-SO_2-CF_3 groups, substituted and unsubstituted -N(H)-SO_2-heterocyclyl groups, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted amino groups, substituted and unsubstituted alkyl groups, substituted and unsubstituted alkoxy groups, substituted and unsubstituted -C(=O)-N(H)-alkyl groups, substituted and unsubstituted -C(=O)-N(H)-alkyl-heterocyclyl groups, substituted and unsubstituted (alkyl)(alkyl) aminoalkyl groups, substituted and unsubstituted(alkyl)(aryl) aminoalkyl groups, substituted and unsubstituted (alkyl) (heterocyclyl) aminoalkyl groups, substituted and unsubstituted (alkyl)(arylalkyl) aminoalkyl groups, substituted and unsubstituted (alkyl)(heterocyclylalkyl) aminoalkyl groups, substituted and unsubstituted -alkyl-N(alkyl)-C(=O)-alkyl groups, substituted and unsubstituted -alkyl-N (alkyl) -C(=O)-aryl groups, substituted and unsubstituted -alkyl-N(alkyl)-C(=O)-heterocyclyl groups, substituted and unsubstituted -alkyl-N (alkyl)-C(=O)-alkyl-aryl groups, substituted and unsubstituted -alkyl-N(alkyl)-C(=O)-alkyl-heterocyclyl groups, substituted and unsubstituted alkylaminoalkyl groups, substituted and unsubstituted arylaminoalkyl groups, substituted and unsubstituted heterocyclylaminoalkyl groups, substituted and unsubstituted arylalkylaminoalkyl groups, substituted and unsubstituted heterocyclylalkylaminoalkyl groups, substituted and unsubstituted- alkyl-N(H)-C(=O)-alkyl groups, substituted and unsubstituted -

alkyl-N(H)-C(=O)-aryl groups, substituted and unsubstituted -alkyl-N(H)-C(=O)-heterocyclyl groups, substituted and unsubstituted -alkyl-N(H)-C(=O)-alkyl-aryl groups, and substituted and unsubstituted -alkyl-N(H)-C(=O)-alkyl-heterocyclyl groups;

R^5 is selected from -H, -F, -Cl, substituted and unsubstituted alkyl groups, substituted and unsubstituted alkoxy groups, substituted and unsubstituted amino groups, substituted and unsubstituted alkylamino groups, substituted and unsubstituted dialkylamino groups, and substituted and unsubstituted heterocyclyl groups, or R^5 is absent if Z^1 is N;

R^6 is selected from -H, -F, -Cl, -Br, $-CF_3$, $-CO_2H$, substituted and unsubstituted alkyl groups, substituted and unsubstituted alkoxy groups including substituted and unsubstituted heterocyclylalkoxy groups, substituted and unsubstituted arylalkoxy groups, and substituted and unsubstituted alkoxyalkoxy groups; substituted and unsubstituted heterocyclyl groups including substituted and unsubstituted heterocyclylheterocyclyl groups, substituted and unsubstituted arylheterocyclyl groups, substituted and unsubstituted alkylheterocyclyl groups, and substituted and unsubstituted cycloalkylheterocyclyl groups; substituted and unsubstituted heterocyclyloxy groups, substituted and unsubstituted aryloxy groups, substituted and unsubstituted amino groups including substituted and unsubstituted dialkylamino groups, substituted and unsubstituted (alkyl)(heterocyclyl) amino groups, substituted and unsubstituted heterocyclylalkylamino groups, substituted and unsubstituted arylalkylamino groups, and substituted and unsubstituted heterocyclylamino groups; substituted and unsubstituted -C(=O)N(H)-alkyl groups, substituted and unsubstituted -C(=O)N(H)-aryl groups, substituted and unsubstituted -C(=O)N(H)-heterocyclyl groups, substituted and unsubstituted -C(=O)N(alkyl)(heterocyclyl) groups, and substituted and unsubstituted -C(=O)-heterocyclyl groups; or R^6 is absent if Z^2 is N;

R^7 is selected from -H, -F, -Cl, -Br, $-CF_3$, $-CO_2H$, substituted and unsubstituted alkyl groups, substituted and unsubstituted alkoxy groups including substituted and unsubstituted heterocyclylalkoxy groups, substituted and unsubstituted arylalkoxy groups, and substituted and unsubstituted alkoxyalkoxy groups; substituted and unsubstituted heterocyclyl groups including substituted and unsubstituted heterocyclylheterocyclyl groups, substituted and unsubstituted arylheterocyclyl groups, substituted and unsubstituted alkylheterocyclyl groups, and substituted and

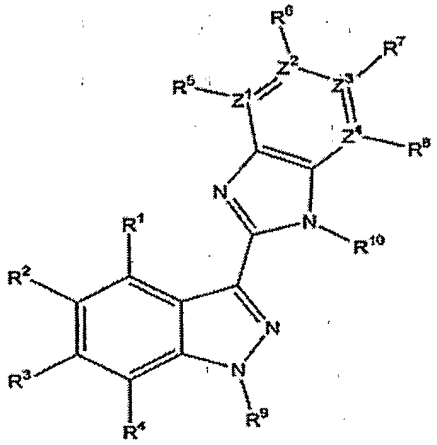
unsubstituted cycloalkylheterocyclyl groups; substituted and unsubstituted heterocyclyloxy groups, substituted and unsubstituted aryloxy groups, substituted and unsubstituted amino groups including substituted and unsubstituted dialkylamino groups, substituted and unsubstituted (alkyl)(heterocyclyl) amino groups, substituted and unsubstituted heterocyclylalkylamino groups, substituted and unsubstituted arylalkylamino groups, and substituted and unsubstituted heterocyclylamino groups; substituted and unsubstituted -C(=O)N(H)-alkyl groups, substituted and unsubstituted -C(=O)N(H) -aryl groups, substituted and unsubstituted -C(=O)N(H)-heterocyclyl groups, substituted and unsubstituted -C(=O)N(alkyl)(heterocyclyl) groups, and substituted and unsubstituted -C(=O)-heterocyclyl groups; or R^7 is absent if Z^3 is N;

R^8 is selected from -H, -F, -Cl, substituted and unsubstituted alkyl groups, substituted and unsubstituted alkoxy groups, substituted and unsubstituted amino groups, substituted and unsubstituted alkylamino groups, substituted and unsubstituted dialkylamino groups, and substituted and unsubstituted heterocyclyl groups, or R^8 is absent if Z^4 is N;

R^9 is -H ; and

R^{10} is selected from the group consisting of -H, and substituted and unsubstituted alkyl groups.

v) A compound having the structure below, a tautomer of the compound, a pharmaceutically acceptable salt of the compound, or a pharmaceutically acceptable salt of the tautomer:



wherein

Z^1, Z^2, Z^3, and Z^4 are independently selected from C or N;

R^1 is selected from -H, -F, -Cl, -Br, $-NO_2$, -C≡N, -C(=O)-O-alkyl groups, -OH, substituted and unsubstituted arylalkoxy groups, substituted and unsubstituted heterocyclyloxy groups, substituted and unsubstituted alkoxyalkyl groups, substituted and unsubstitutedarylalkoxyalkyl groups, substituted and unsubstituted aryloxy groups, substituted and unsubstituted -N(H)-C(=O)-aryl groups, substituted and unsubstituted -N(H)-C(=O)-alkyl groups, substituted and unsubstituted-N(H)-SO_2-alkyl groups, substituted and unsubstituted -N(H)-SO_2-aryl groups, -N(H) -SO_2-CF_3 groups, substituted and unsubstituted -N(H)-SO_2-heterocyclyl groups, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted alkyl groups, substituted and unsubstituted alkoxy groups, substituted and unsubstituted amino groups, substituted and unsubstituted - C(=O)-N(H)-alkyl groups, substituted and unsubstituted -C(=O)-N(H)-alkyl-heterocyclyl groups, substituted and unsubstituted (alkyl)(alkyl) aminoalkyl groups, substituted and unsubstituted (alkyl)(aryl) aminoalkyl groups, substituted and unsubstituted (alkyl) (heterocyclyl) aminoalkyl groups substituted and unsubstituted (alkyl)(arylalkyl) aminoalkyl groups, substituted and unsubstituted (alkyl)(heterocyclylalkyl) aminoalkyl groups, substituted and unsubstituted -alkyl-N(alkyl)-C(=O)-alkyl groups, substituted and unsubstituted -alkyl-N(alkyl)-C(=O)-aryl groups, substituted and unsubstituted -alkyl-N(alkyl)-C(=O)-heterocyclyl groups, substituted and unsubstituted -alkyl-N(alkyl)-C(=O)-alkyl-aryl groups, substituted and unsubstituted -alkyl-N (alkyl)-C(=O)-alkyl-heterocyclyl groups, substituted and unsubstituted alkylaminoalkyl groups, substituted and unsubstituted arylaminoalkyl groups, substituted and unsubstituted heterocyclylaminoalkyl groups substituted and unsubstituted arylalkylaminoalkyl groups, substituted and unsubstituted heterocyclylalkylaminoalkyl groups, substituted and unsubstituted -alkyl-N(H)-C(=O)-alkyl groups, substituted and unsubstituted - alkyl-N(H)-C(=O)-aryl groups, substituted and unsubstituted -alkyl-N(H)-C(=O)-heterocyclyl groups, substituted and unsubstituted -alkyl-N (H) -C (=O)-alkyl-aryl groups, and substituted and unsubstituted- alkyl-N(H)-C(=O)-alkyl-heterocyclyl groups;

R^2 is selected from -F, -Cl, -Br, -C≡N, $-NO_2$, $-CO_2H$, -OH, substituted and unsubstituted guanidinyl groups, substituted and unsubstituted -C (=O) O-alkyl groups, substituted and unsubstituted -C(=O)O-aryl groups, substituted and

unsubstituted -C(=O) O-heteroaryl groups, substituted and unsubstituted -C(=O)N(H)-alkyl groups, substituted and unsubstituted -C (=O)N(H) -aryl groups, substituted and unsubstituted -C(=O)N(H)-heterocyclyl groups, substituted and unsubstituted -N(H)C(=O)-alkyl groups, substituted and unsubstituted - N(H)C(=O)-aryl groups, substituted and unsubstituted -N(H)C(=O)-heterocyclyl groups, substituted and unsubstituted -N(H)C(=O)N(H)-alkyl groups, substituted and unsubstituted -N(H)C(=O)N(H) -aryl groups, substituted and unsubstituted -N(H)C(=O)N(H) -heterocyclyl groups, substituted and unsubstituted -N(H)-(SO_2)-alkyl groups, substituted and unsubstituted-N(H)-(SO_2)-aryl groups, -N(H)-(SO_2)-CF_3 groups, substituted and unsubstituted-N(H)-(SO_2)-heterocyclyl groups, substituted and unsubstituted alkoxy groups, substituted and unsubstituted arylalkoxy groups, substituted and unsubstituted aryloxy groups, substituted and unsubstituted heterocyclyloxy, and substituted and unsubstituted heterocyclylalkoxy groups; or R^2 and R^3 are a group of formula -OCH_2O- such that R^2 and R^3 define a fused 5-membered ring that includes 2 oxygen atoms;

R^3 is selected from -H, -F, -Cl, -Br, -CF_3, -C≡N, -NO_2, -CO_2H, substituted and unsubstituted amino groups, substituted and unsubstituted alkyl groups, substituted and unsubstituted alkoxy groups, substituted and unsubstituted -C(=O)-O-alkyl groups, substituted and unsubstituted arylalkoxy groups, substituted and unsubstituted heterocyclyloxy groups, substituted and unsubstituted alkoxyalkyl groups, substituted and unsubstituted arylalkoxyalkyl groups, substituted and unsubstituted aryloxy group, substituted and unsubstituted heterocycyl groups, substituted and unsubstituted -N(H)-C(=O)-alkyl groups, substituted and unsubstituted -N(H)-C(=O)-aryl groups, substituted and unsubstituted -N(H)-(SO_2)-alkyl groups substituted and unsubstituted -N(H)-(SO_2)-aryl groups, -N(H)-(SO_2)-CF_3 groups, substituted and unsubstituted -N (H)-(SO_2)-heterocyclyl groups, substituted and unsubstituted -N(H)C(=O)N(H)-alkyl groups, substituted and unsubstituted -N(H)C(=O)N(H) -aryl groups, substituted and unsubstituted -C(=O)-N(H)-alkyl groups, substituted and unsubstituted -C(=O)-N(H)-alkyl-heterocyclyl groups, substituted and unsubstituted (alkyl)(alkyl) aminoalkyl groups, substituted and unsubstituted (alkyl)(aryl) aminoalkyl groups, substituted and unsubstituted (alkyl)(heterocyclyl) aminoalkyl groups substituted and unsubstituted (alkyl)(arylalkyl) aminoalkyl groups, substituted and unsubstituted

(alkyl)(heterocyclylalkyl) aminoalkyl groups, substituted and unsubstituted -alkyl-N(alkyl)-C(=O)-alkyl groups, substituted and unsubstituted -alkyl-N(alkyl)-C(=O)-aryl groups, substituted and unsubstituted -alkyl-N(alkyl)-C(=O)-heterocyclyl groups, substituted and unsubstituted -alkyl-N(alkyl)-C(=O)-alkyl-aryl groups, substituted and unsubstituted -alkyl-N(alkyl)-C(=O)-alkyl-heterocyclyl groups, substituted and unsubstituted alkylaminoalkyl groups, substituted and unsubstituted arylaminoalkyl groups, substituted and unsubstituted heterocyclylaminoalkyl groups, substituted and unsubstituted arylalkylaminoalkyl groups, substituted and unsubstituted heterocyclylalkylaminoalkyl groups, substituted and unsubstituted -alkyl-N(H)-C(=O)-alkyl groups, substituted and unsubstituted -alkyl-N(H)-C(=O)-aryl groups, substituted and unsubstituted -alkyl-N(H)-C(=O)-heterocyclyl groups, substituted and unsubstituted -alkyl-N(H)-C(=O)-alkyl-aryl groups, and substituted and unsubstituted - alkyl-N(H)-C(=O)-alkyl-heterocyclyl groups;

R^4 is -H, -F, -Br, -Cl, $-NO_2$, -C≡N, -C(=O)-O-alkyl groups, -OH, substituted and unsubstituted arylalkoxy groups, substituted and unsubstituted heterocyclyloxy groups, substituted and unsubstituted alkoxyalkyl groups, substituted and unsubstituted arylalkoxyalkyl groups, substituted and unsubstituted aryloxy groups, substituted and unsubstituted -N (H)-C(=O)-aryl groups, substituted and unsubstituted -N (H)-C (=O)-alkyl groups, substituted and unsubstituted -N(H)-(SO_2)-alkyl groups, substituted and unsubstituted -N(H)-(SO_2)-aryl groups, -N(H)-(SO_2)-CF_3 groups, substituted and unsubstituted -N (H)-(SO_2)-heterocyclyl groups, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted amino groups, substituted and unsubstituted alkyl groups, substituted and unsubstituted alkoxy groups, substituted and unsubstituted -C(=O)-N(H)-alkyl groups, substituted and unsubstituted -C(=O)-N(H)-alkyl-heterocyclyl groups, substituted and unsubstituted (alkyl)(alkyl) aminoalkyl groups, substituted and unsubstituted (alkyl)(aryl) aminoalkyl groups, substituted and unsubstituted (alkyl) (heterocyclyl) aminoalkyl groups substituted and unsubstituted (alkyl) (arylalkyl) aminoalkyl groups, substituted and unsubstituted (alkyl) (heterocyclylalkyl) aminoalkyl groups, substituted and unsubstituted -alkyl-N(alkyl)-C(=O)-alkyl groups, substituted and unsubstituted -alkyl-N(alkyl)-C(=O)-aryl groups, substituted and unsubstituted -alkyl-N(alkyl)-C(=O)-heterocyclyl groups, substituted and unsubstituted -alkyl-N(alkyl)-C(=O)-alkyl-aryl groups, substituted and unsubstituted -alkyl-N(alkyl)-C(=O)-alkyl-

heterocyclyl groups, substituted and unsubstituted alkylaminoalkyl groups, substituted and unsubstituted arylaminoalkyl groups, substituted and unsubstituted heterocyclylaminoalkyl groups, substituted and unsubstituted arylalkylaminoalkyl groups, substituted and unsubstituted heterocyclylalkylaminoalkyl groups, substituted and unsubstituted -alkyl-N(H)-C(=O)-alkyl groups, substituted and unsubstituted -alkyl-N(H)-C(=O)-aryl groups, substituted and unsubstituted -alkyl-N(H)-C(=O)-heterocyclyl groups, substituted and unsubstituted -alkyl-N(H)-C(=O)-alkyl-aryl groups, and substituted and unsubstituted -alkyl-N(H)-C(=O)-alkyl-heterocyclyl groups;

R^5 is selected from -H, -F, -Cl, substituted and unsubstituted alkyl groups, substituted and unsubstituted alkoxy groups, substituted and unsubstituted amino groups, substituted and unsubstituted alkylamino groups, substituted and unsubstituted dialkylamino groups, and substituted and unsubstituted heterocyclyl groups, or R^5 is absent if Z^1 is N;

R^6 is selected from -H, -F, -Cl, -Br, $-CF_3$, $-CO_2H$, substituted and unsubstituted alkyl groups, substituted and unsubstituted alkoxy groups including substituted and unsubstituted heterocyclylalkoxy groups, substituted and unsubstituted arylalkoxy groups, and substituted and unsubstituted alkoxyalkoxy groups; substituted and unsubstituted heterocyclyl groups including substituted and unsubstituted heterocyclylheterocyclyl groups, substituted and unsubstituted arylheterocyclyl groups, substituted and unsubstituted alkylheterocyclyl groups, and substituted and unsubstituted cycloalkylheterocyclyl groups; substituted and unsubstituted heterocyclyloxy groups, substituted and unsubstituted aryloxy groups, substituted and unsubstituted amino groups including substituted and unsubstituted dialkylamino groups, substituted and unsubstituted (alkyl)(heterocyclyl) amino groups, substituted and unsubstituted heterocyclylalkylamino groups, substituted and unsubstituted arylalkylamino groups, and substituted and unsubstituted heterocyclylamino groups; substituted and unsubstituted -C(=O)N(H)-alkyl groups, substituted and unsubstituted -C(=O)N(H) -aryl groups, substituted and unsubstituted -C(=O)N(H)-heterocyclyl groups, substituted and unsubstituted -C(=O)N(alkyl)(heterocyclyl) groups, and substituted and unsubstituted -C(=O)-heterocyclyl groups; or R^6 is absent if Z^2 is N;

R^7 is selected from -H, -F, -Cl, -Br, $-CF_3$, $-CO_2H$, substituted and unsubstituted alkyl groups, substituted and unsubstituted alkoxy groups including

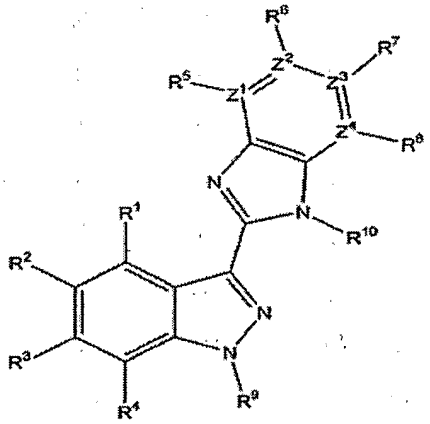
substituted and unsubstituted heterocyclylalkoxy groups, substituted and unsubstituted arylalkoxy groups, and substituted and unsubstituted alkoxyalkoxy groups; substituted and unsubstituted heterocyclyl groups including substituted and unsubstituted heterocyclylheterocyclyl groups, substituted and unsubstituted arylheterocyclyl groups, substituted and unsubstituted alkylheterocyclyl groups, and substituted and unsubstituted cycloalkylheterocyclyl groups; substituted and unsubstituted heterocyclyloxy groups, substituted and unsubstituted aryloxy groups; substituted and unsubstituted amino groups including substituted and unsubstituted dialkylamino groups, substituted and unsubstituted (alkyl)(heterocyclyl) amino groups, substituted and unsubstituted heterocyclylalkylamino groups, substituted and unsubstituted arylalkylamino groups, and substituted and unsubstituted heterocyclylamino groups; substituted and unsubstituted -C(=O)N(H)-alkyl groups, substituted and unsubstituted -C(=O)N(H)-aryl groups, substituted and unsubstituted -C(=O)N(H)-heterocyclyl groups, substituted and unsubstituted -C(=O)N(alkyl)(heterocyclyl) groups, and substituted and unsubstituted -C(=O)-heterocyclyl groups; or R^7 is absent if Z^3 is N;

R^8 is selected from -H, -F, -Cl, substituted and unsubstituted alkyl groups, substituted and unsubstituted alkoxy groups, substituted and unsubstituted amino groups, substituted and unsubstituted alkylamino groups, substituted and unsubstituted dialkylamino groups, and substituted and unsubstituted heterocyclyl groups, or R^8 is absent if Z^4 is N;

R^9 is -H ; and

R^{10} is selected from the group consisting of -H, and substituted and unsubstituted alkyl groups.

vi) A compound having the structure below, a tautomer of the compound, a pharmaceutically acceptable salt of the compound, or a pharmaceutically acceptable salt of the tautomer:



wherein

Z^1, Z^2, Z^3, and Z^4 are independently selected from C or N;

R^1 is selectedfrom -H, -F, -Cl, -Br, $-NO_2$, -C≡N, -C(=O)-O-alkyl groups, -OH, substituted and unsubstituted arylalkoxy groups, substituted and unsubstituted heterocyclyloxy groups, substituted and unsubstituted alkoxyalkyl groups, substituted and unsubstituted arylalkoxyalkyl groups, substituted and unsubstituted aryloxy groups, substituted and unsubstituted -N (H)-C(=O)-aryl groups, substituted and unsubstituted -N (H)-C(=O)-alkyl groups, substituted and unsubstituted $-N(H)-(SO_2)$-alkyl groups, substituted and unsubstituted $-N(H)-(SO_2)$-aryl groups, $-N(H)-(SO_2)-CF_3$ groups, substituted and unsubstituted $-N(H)-(SO_2)$-heterocyclyl groups, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted alkyl groups, substituted and unsubstituted alkoxy groups, substituted and unsubstituted amino groups, substituted and unsubstituted -C(=O)-N(H)-alkyl groups, substituted and unsubstituted -C(=O)-N(H)-alkyl-heterocyclyl groups, substituted and unsubstituted (alkyl)(alkyl) aminoalkyl groups, substituted and unsubstituted (alkyl)(aryl) aminoalkyl groups, substituted and unsubstituted (alkyl) (heterocyclyl) aminoalkyl groups substituted and unsubstituted (alkyl)(arylalkyl) aminoalkyl groups, substituted and unsubstituted (alkyl)(heterocyclylalkyl) aminoalkyl groups, substituted and unsubstituted -alkyl-N(alkyl)-C(=O)-alkyl groups, substituted and unsubstituted -alkyl-N (alkyl)-C(=O)-aryl groups, substituted and unsubstituted -alkyl-N(alkyl)-C(=O)-heterocyclyl groups, substituted and unsubstituted -alkyl-N(alkyl)-C(=O)-alkyl-aryl groups, substituted and unsubstituted -alkyl-N(alkyl)-C(=O)-alkyl-heterocyclyl groups, substituted and unsubstituted alkylaminoalkyl groups, substituted and unsubstituted arylaminoalkyl groups, substituted and unsubstituted heterocyclylaminoalkyl groups substituted and

unsubstituted arylalkylaminoalkyl groups, substituted and unsubstituted heterocyclylalkylaminoalkyl groups, substituted and unsubstituted -alkyl-N(H)-C(=O)-alkyl groups, substituted and unsubstituted -alkyl-N(H)-C(=0)-aryl groups, substituted and unsubstituted -alkyl-N(H)-C(=O)-heterocyclyl groups, substituted and unsubstituted - alkyl-N(H)-C(=0)-alkyl-aryl groups, and substituted and unsubstituted - alkyl-N(H)-C(=O)-alkyl-heterocyclyl groups;

R^2 is selected from -H, -F, -Cl, -Br, -C≡N, $-NO_2$, $-CO_2H$,-OH, substituted and unsubstituted guanidinyl groups, substituted and unsubstituted amino groups, substituted and unsubstituted alkyl groups, substituted and unsubstituted -C(=O)O-alkyl groups, substituted and unsubstituted -C(=O)O-aryl groups, substituted and unsubstituted -C(=O)O-heteroaryl groups, substituted and unsubstituted -C(=O)N(H)-alkyl groups, substituted and unsubstituted -C(=O)-N (H)-alkyl-heterocyclyl groups, substituted and unsubstituted -C(=O)N(H) -aryl groups, substituted and unsubstituted -C(=O)N(H)-heterocyclyl groups, substituted and unsubstituted -N(H)C(=O)-alkyl groups, substituted and unsubstituted -N (H) C (=O)-aryl groups, substituted and unsubstituted - N(H)C(=O)-heterocyclyl groups, substituted and unsubstituted -N(H)C(=O)N(H)-alkyl groups, substituted and unsubstituted -N(H)C(=O)N(H) -aryl groups, substituted and unsubstituted - N(H)C(=O)N(H)-heterocyclyl groups, substituted and unsubstituted -N(H)-(SO_2)-alkyl groups, substituted and unsubstituted -N(H)-(SO_2)-aryl groups, -N(H)-(SO_2)-CF_3 groups, substituted and unsubstituted -N(H)-(SO_2)-heterocyclyl groups groups, substituted and unsubstituted-N(H)-heterocyclyl groups, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted alkoxy groups, substituted and unsubstituted arylalkoxy groups, substituted and unsubstituted aryloxy groups, substituted and unsubstituted akoxyalkyl groups, substituted and unsubstituted arylalkoxyalkyl groups, substituted and unsubstituted heterocyclyloxy, substituted and unsubstituted heterocyclylalkoxy groups, substituted and unsubstituted (alkyl)(alkyl) aminoalkyl groups, substituted and unsubstituted (alkyl)(aryl) aminoalkyl groups, substituted and unsubstituted (alkyl)(heterocyclyl) aminoalkyl groups substituted and unsubstituted (alkyl)(arylalkyl) aminoalkyl groups, substituted and unsubstituted (alkyl)(heterocyclylalkyl) aminoalkyl groups, substituted and unsubstituted -alkyl-N(alkyl)-C(=O)-alkyl groups, substituted and unsubstituted -alkyl-N (alkyl)-C(=O)-aryl groups, substituted and unsubstituted -alkyl-N(alkyl)-C(=O)-heterocyclyl groups,

substituted and unsubstituted -alkyl-N(alkyl)-C(=O)-alkyl-aryl groups, substituted and unsubstituted -alkyl-N(alkyl)-C(=O)-alkyl-heterocyclyl groups, substituted and unsubstituted alkylaminoalkyl groups, substituted and unsubstituted arylaminoalkyl groups, substituted and unsubstitutedheterocyclylaminoalkyl groups substituted and unsubstituted arylalkylaminoalkyl groups, substituted and unsubstitutedheterocyclylalkylaminoalkyl groups, substituted and unsubstituted -alkyl-N(H)-C(=O)-alkyl groups, substituted and unsubstituted - alkyl-N(H)-C(=O)-aryl groups, substituted and unsubstituted -alkyl-N(H)-C(=O)-heterocyclyl groups, substituted and unsubstituted -alkyl-N(H)-C(=O)-alkyl-aryl groups, and substituted and unsubstituted -alkyl-N(H)-C(=O)-alkyl-heterocyclyl groups; or R^2 and R^3 are a group of formula -OCH_20-such that R^2 and R^3 define a fused 5-membered ring that includes 2 oxygen atoms;

R^3 is selected from -H, -F, -Cl, -Br, -CF_3, -C≡N, -NO_2, -CO_2H, substituted and unsubstituted amino groups, substituted and unsubstituted alkyl groups, substituted and unsubstituted alkoxy groups, substituted and unsubstituted -C(=O)-O-alkyl groups, substituted and unsubstituted arylalkoxy groups, substituted and unsubstituted heterocyclyloxy groups, substituted and unsubstituted alkoxyalkyl groups, substituted and unsubstituted arylalkoxyalkyl groups, substituted and unsubstituted aryloxy group, substituted and unsubstituted heterocycyl groups, substituted and unsubstituted -N(H)-C(=O)-alkyl groups, substituted and unsubstituted-N (H)-C(=O)-aryl groups, substituted and unsubstituted -N(H)-(SO_2)-alkyl groups, substituted and unsubstituted -N(H)-(SO_2)-aryl groups, -N(H)-(SO_2)-CF_3 groups, substituted and unsubstituted -N(H)-(SO_2)-heterocyclyl groups, substituted and unsubstituted -N(H)C(=O)N(H)-alkyl groups, substituted and unsubstituted -N(H)C(=O)N(H)-aryl groups, substituted and unsubstituted -C(=O)-N(H)-alkyl groups, substituted and unsubstituted -C(=O)-N(H)-alkylheterocyclyl groups, substituted and unsubstituted (alkyl)(alkyl) aminoalkyl groups, substituted and unsubstituted (alkyl)(aryl) aminoalkyl groups, substituted and unsubstituted (alkyl)(heterocyclyl) aminoalkyl groups substituted and unsubstituted (alkyl)(arylalkyl) aminoalkyl groups, substituted and unsubstituted (alkyl)(heterocyclylalkyl) aminoalkyl groups, substituted and unsubstituted -alkyl-N(alkyl)-C(=O)-alkyl groups, substituted and unsubstituted -alkyl-N(alkyl)-C(=O)-aryl groups, substituted and unsubstituted -alkyl-N(alkyl)-C(=O)-heterocyclyl groups,

substituted and unsubstituted -alkyl-N(alkyl)-C(=O)-alkyl-aryl groups, substituted and unsubstituted-alkyl-N (alkyl)-C(=O)-alkyl-heterocyclyl groups, substituted and unsubstituted alkylaminoalkyl groups, substituted and unsubstitutedarylaminoalkyl groups, substituted and unsubstituted heterocyclylaminoalkyl groups, substituted and unsubstituted arylalkylaminoalkyl groups, substituted and unsubstituted heterocyclylalkylaminoalkyl groups, substituted and unsubstituted - alkyl-N(H)-C(=O)-alkyl groups, substituted and unsubstituted -alkyl-N(H)-C(=O)-aryl groups, substituted and unsubstituted -alkyl-N(H)-C(=O)-heterocyclyl groups, substituted and unsubstituted -alkyl-N(H)-C(=O)-alkyl-aryl groups, and substituted and unsubstituted- alkyl-N (H)-C(=O)-alkyl-heterocyclyl groups;

R^4 is -H, -F, -Br, -Cl, $-NO_2$, -C≡N, -C(=O)-O-alkyl groups, -OH, substituted and unsubstituted arylalkoxy groups, substituted and unsubstituted heterocyclyloxy groups, substituted and unsubstituted alkoxyalkyl groups, substituted and unsubstituted arylalkoxyalkyl groups, substituted and unsubstituted aryloxy groups, substituted and unsubstituted -N(H)-C(=O)-aryl groups, substituted and unsubstituted -N(H)-C(=O)-alkyl groups, substituted and unsubstituted -N(H)-(SO_2)-alkyl groups, substituted and unsubstituted -N(H)-(SO_2)-aryl groups, -N(H)-(SO_2)-CF_3 groups, substituted and unsubstituted -N(H)-(SO_2)-heterocyclyl groups, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted amino groups, substituted and unsubstituted alkyl groups, substituted and unsubstituted alkoxy groups, substituted and unsubstituted -C(=O)-N(H)-alkyl groups, substituted and unsubstituted -C(=O)-N(H)-alkyl-heterocyclyl groups, substituted and unsubstituted (alkyl)(alkyl) aminoalkyl groups, substituted and unsubstituted (alkyl)(aryl) aminoalkyl groups, substituted and unsubstituted (alkyl)(heterocyclyl) aminoalkyl groups substituted and unsubstituted (alkyl)(arylalkyl) aminoalkyl groups, substituted and unsubstituted (alkyl)(heterocyclylalkyl) aminoalkyl groups, substituted and unsubstituted -alkyl-N(alkyl)-C(=O)-alkyl groups, substituted and unsubstituted -alkyl-N(alkyl)-C(=O)-aryl groups, substituted and unsubstituted -alkyl-N(alkyl)-C(=O)-heterocyclyl groups, substituted and unsubstituted -alkyl-N(alkyl)-C(=O)-alkyl-aryl groups, substituted and unsubstituted -alkyl-N (alkyl)-C(=O)-alkyl-heterocyclyl groups, substituted and unsubstituted alkylaminoalkyl groups, substituted and unsubstitutedarylaminoalkyl groups, substituted and unsubstituted heterocyclylaminoalkyl groups substituted and unsubstituted arylalkylaminoalkyl

groups, substituted and unsubstituted heterocyclylalkylaminoalkyl groups, substituted and unsubstituted -alkyl-N(H)-C(=O)-alkyl groups, substituted and unsubstituted -alkyl-N(H)-C(=O)-aryl groups, substituted and unsubstituted -alkyl-N(H)-C(=O)-heterocyclyl groups, substituted and unsubstituted -alkyl-N(H)-C(=O)-alkyl-aryl groups, and substituted and unsubstituted -alkyl-N(H)-C(=O)-alkyl-heterocyclyl groups;

R^5 is selected from -H, -F, -Cl, substituted and unsubstituted alkyl groups, substituted and unsubstituted alkoxy groups, substituted and unsubstituted amino groups, substituted and unsubstituted alkylamino groups, substituted and unsubstituted dialkylamino groups, and substituted and unsubstituted heterocyclyl groups, or R^5 is absent if Z^1 is N;

R^6 is selected from -H, -F, -Cl, -Br, $-CF_3$, $-CO_2H$, substituted and unsubstituted alkyl groups, substituted and unsubstituted alkoxy groups including substituted and unsubstituted heterocyclylalkoxy groups, substituted and unsubstituted arylalkoxy groups, and substituted and unsubstituted alkoxyalkoxy groups; substituted and unsubstituted heterocyclyl groups including substituted and unsubstituted heterocyclylheterocyclyl groups, substituted and unsubstituted arylheterocyclyl groups, substituted and unsubstituted alkylheterocyclyl groups, and substituted and unsubstituted cycloalkylheterocyclyl groups; substituted and unsubstituted heterocyclyloxy groups, substituted and unsubstituted aryloxy groups, substituted and unsubstituted amino groups including substituted and unsubstituted dialkylamino groups, substituted and unsubstituted (alkyl)(heterocyclyl) amino groups, substituted and unsubstituted heterocyclylalkylamino groups, substituted and unsubstituted arylalkylamino groups, and substituted and unsubstituted heterocyclylamino groups; substituted and unsubstituted -C(=O)N(H)-alkyl groups, substituted and unsubstituted -C (=O)N(H)-aryl groups, substituted and unsubstituted -C(=O)N(H) -heterocyclyl groups, substituted and unsubstituted -C(=O)N(alkyl)(heterocyclyl) groups, and substituted and unsubstituted -C(=O)-heterocyclyl groups; orR^6 is absent if Z^2 is N;

R^7 is selected from -H, -F, -Cl, -Br, $-CF_3$, $-CO_2H$, substituted and unsubstituted alkyl groups, substituted and unsubstituted alkoxy groups including substituted and unsubstituted heterocyclylalkoxy groups, substituted and unsubstituted arylalkoxy groups, and substituted and unsubstituted alkoxyalkoxy groups; substituted and unsubstituted heterocyclyl groups including substituted and unsubstituted

heterocyclylheterocyclyl groups, substituted and unsubstituted arylheterocyclyl groups, substituted and unsubstituted alkylheterocyclyl groups, and substituted and unsubstituted cycloalkylheterocyclyl groups; substituted and unsubstituted heterocyclyloxy groups, substituted and unsubstituted aryloxy groups, substituted and unsubstituted amino groups including substituted and unsubstituted dialkylamino groups, substituted and unsubstituted (alkyl)(heterocyclyl) amino groups, substituted and unsubstituted heterocyclylalkylamino groups, substituted and unsubstituted arylalkylamino groups, and substituted and unsubstituted heterocyclylamino groups; substituted and unsubstituted -C(=O)N(H)-alkyl groups, substituted and unsubstituted -C(=O)N(H)-aryl groups, substituted and unsubstituted -C(=O)N(H)-heterocyclyl groups, substituted and unsubstituted -C(=O)N(alkyl)(heterocyclyl) groups, and substituted and unsubstituted -C(=O)-heterocyclyl groups; or R^7 is absent if Z^3 is N;

R^8 is selected from -H, -F, -Cl, substituted and unsubstituted alkyl groups, substituted and unsubstituted alkoxy groups, substituted and unsubstituted amino groups, substituted and unsubstituted alkylamino groups, substituted and unsubstituted dialkylamino groups, and substituted and unsubstituted heterocyclyl groups, or R^8 is absent if Z^4 is N;

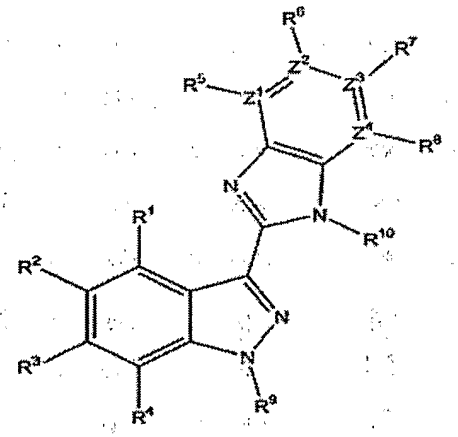
R^9 is -H; and

R^{10} is selected from the group consisting of-H, and substituted and unsubstituted alkyl groups, and further wherein at least one of Z^2 or Z^3 is C and at least one of R^6 or R^7 is selected from the group consisting of substituted and unsubstituted piperidinyl substituted heterocyclyl groups, substituted and unsubstituted heterocyclyl substituted piperidinyl groups, substituted and unsubstituted hydroxymethyl substituted piperidinyl groups, dimethylaminoalkyl substituted pyrrolidinyl groups, substituted and unsubstituted 3-alkyl substituted piperazinyl groups, substituted and unsubstituted 3,5-dialkyl substituted piperazinyl groups, substituted and unsubstituted N-hydroxyalkyl substituted piperazinyl groups, substituted and unsubstituted 1,4-diazacycloheptyl groups, substituted and unsubstituted 1-aza-4-oxacycloheptane groups, substituted and unsubstituted N-ethylpiperazinyl groups, substituted and unsubstituted N-isopropylpiperazinyl groups, substituted and unsubstituted N-sec-butylpiperazinyl groups, substituted and unsubstituted N-2-pyridyl substituted piperazinyl groups, substituted and unsubstituted N-3-pyridyl substituted piperazinyl groups, substituted and

unsubstituted N-4-pyridyl substituted piperazinyl groups, substituted and unsubstituted N(H)-CH_2-pyridyl groups, substituted and unsubstituted imidazolyl groups, substituted and unsubstituted 3-alkyl substituted morpholinyl groups, substituted and unsubstituted 3,5-dialkyl substituted morpholinyl groups, dialkylamino substituted pyrrolidinyl groups, pyrrolidinyl groups substituted with both dialkylamino and alkyl groups, substituted and unsubstituted 4-hydroxy substituted piperidinyl groups, substituted and unsubstituted 4-aryl substituted piperidinyl groups, substituted and unsubstituted 4-hydroxy-4-phenyl substituted piperidinyl groups, substituted and unsubstituted cyclohexylpiperazinyl groups, substituted and unsubstituted cyclopentylpiperazinyl groups, substituted and unsubstituted N-alkyl substituted diazabicycloalkane groups, substituted and unsubstituted -$N(CH_3)$(N-alkyl(4-piperidinyl)) groups, substituted and unsubstituted piperazinyl groups further substituted with a -C(=O)-alkyl group bonded to one of the N atoms of the piperazinyl group, substituted and unsubstituted - $N(H)CH_2CH_2CH_2$-imidazolyl groups, substituted and unsubstituted -$N(H)CH_2CH_2CH_2$-pyrrolidinyl groups, substituted and unsubstituted -$N(H)CH_2CH_2CH_2$-morpholinyl groups, substituted and unsubstituted -$N(H)CH_2CH_2CH_2$-piperazinyl groups, substituted and unsubstituted -$N(H)CH_2CH_2CH_2$-piperidinyl groups, substituted and unsubstituted - $N(H)CH_2CH_2CH_2$-pyridyl groups, substituted and unsubstituted - $N(H)CH_2CH_2$-imidazolyl groups, substituted and unsubstituted - $N(H)CH_2CH_2$-pyrrolidinyl groups, substituted and unsubstituted -$N(H)CH_2CH_2$-morpholinyl groups, substituted and unsubstituted -$N(H)CH_2CH_2$-piperazinyl groups, substituted and unsubstituted - $N(H)CH_2CH_2$-piperidinyl groups, substituted and unsubstituted - $N(H)CH_2CH_2$-pyridyl groups, substituted and unsubstituted cyclobutylpiperazinyl groups, substituted and unsubstituted -OCH_2-pyrrolidinyl groups, substituted andunsubstituted -OCH_2CH_2-pyrrolidinyl groups, substituted and unsubstituted -$OCH_2CH_2CH_2$-pyrrolidinyl groups, substituted and unsubstituted piperazinyl groups further substituted with a -$CH_2C(=O)$-O-alkyl group bonded to one of the N atoms of the piperazinyl group, substituted and unsubstituted piperazinyl groups further substituted with a-C(=O)-O-alkyl group bonded to one of the N atoms of the piperazinyl group, substituted and unsubstituted hydroxypyrrolidinyl groups, substituted and unsubstituted hydroxypiperidinyl groups, substituted and unsubstituted -OCH_2-pyridyl groups, substituted and unsubstituted piperidinylamino groups, substituted and unsubstituted pyridyloxy groups with a -C(=O)-N(H)(alkyl) group bonded to a carbon

atom of the pyridine ring of the pyridyloxy group, and substituted and unsubstituted pyridyloxy groups with a-C(=O)-N(alkyl)$_2$ group bonded to a carbon atom of the pyridine ring of the pyridyloxy group.

vii) A compound having the structure below, a tautomer of the compound, a pharmaceutically acceptable salt of the compound, or a pharmaceutically acceptable salt of the tautomer:



wherein

Z^1, Z^2, Z^3, and Z^4 are independently selected from C or N;

R^1 is selected from -H, -F, -Cl, -Br, -NO_2, -C≡N, -C(=O)-O-alkyl groups, -OH, substituted and unsubstituted arylalkoxy groups, substituted and unsubstituted heterocyclyloxy groups, substituted and unsubstituted alkoxyalkyl groups, substituted and unsubstituted arylalkoxyalkyl groups, substituted and unsubstituted aryloxy groups, substituted and unsubstituted -N(H)-C(=O)-aryl groups, substituted and unsubstituted -N(H)-C(=O)-alkyl groups, substituted and unsubstituted -N(H)-(SO_2)-alkyl groups, substituted and unsubstituted -N(H)-(SO_2)-aryl groups, -N(H)-(SO_2)-CF_3 groups, substituted and unsubstituted -N(H)-(SO_2)-heterocyclyl groups, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted alkyl groups, substituted and unsubstituted alkoxy groups, substituted and unsubstituted amino groups, substituted and unsubstituted -C(=O)-N(H)-alkyl groups, substituted and unsubstituted -C(=O)-N(H)-alkyl-heterocyclyl groups, substituted and unsubstituted (alkyl)(alkyl) aminoalkyl groups, substituted and unsubstituted(alkyl)(aryl) aminoalkyl groups, substituted and unsubstituted (alkyl)(heterocyclyl) aminoalkyl groups substituted and unsubstituted

(alkyl)(arylalkyl) aminoalkyl groups, substituted and unsubstituted (alkyl)(heterocyclylalkyl) aminoalkyl groups, substituted and unsubstituted -alkyl-N(alkyl)-C(=O)-alkyl groups, substituted and unsubstituted -alkyl-N(alkyl)-C(=O)-aryl groups, substituted and unsubstituted -alkyl-N(alkyl)-C(=O)-heterocyclyl groups, substituted and unsubstituted -alkyl-N(alkyl)-C(=O)-alkyl-aryl groups, substituted and unsubstituted -alkyl-N(alkyl)-C(=O)-alkyl-heterocyclyl groups, substituted and unsubstituted alkylaminoalkyl groups, substituted and unsubstituted arylaminoalkyl groups, substituted and unsubstituted heterocyclylaminoalkyl groups, substituted and unsubstituted arylalkylaminoalkyl groups, substituted and unsubstituted heterocyclylalkylaminoalkyl groups, substituted and unsubstituted -alkyl-N(H)-C(=O)-alkyl groups, substituted and unsubstituted -alkyl-N(H)-C(=O)-aryl groups, substituted and unsubstituted -alkyl-N(H)-C(=O)-heterocyclyl groups, substituted and unsubstituted -alkyl-N(H)-C(=O)-alkyl-aryl groups, and substituted and unsubstituted -alkyl-N(H)-C(=O)-alkyl-heterocyclyl groups;

R^2 is selected from -H, -F, -Cl, -Br, -C≡N, -NO_2, -CO_2H,-OH, substituted and unsubstituted guanidinyl groups, substituted and unsubstituted amino groups, substituted and unsubstituted alkyl groups, substituted and unsubstituted -C(=O)O-alkyl groups, substituted and unsubstituted -C(=O)O-aryl groups, substituted and unsubstituted -C(=O)O-heteroaryl groups, substituted and unsubstituted -C(=O)N(H) -alkyl groups, substituted and unsubstituted -C(=O)-N(H)-alkyl-heterocyclyl groups, substituted and unsubstituted -C(=O)N(H)-aryl groups, substituted and unsubstituted -C(=O)N(H)-heterocyclyl groups, substituted and unsubstituted -N (H)C(=O)-alkyl groups, substituted and unsubstituted -N(H)C(=O)-aryl groups, substituted and unsubstituted - N(H)C(=O)-heterocyclyl groups, substituted and unsubstituted -N(H)C(=O)N(H)-alkyl groups, substituted and unsubstituted -N(H)C(=O)N(H)-aryl groups, substituted and unsubstituted –N(H)C(=O)N(H)-heterocyclyl groups, substituted and unsubstituted -N(H)-(SO_2)-alkyl groups, substituted and unsubstituted -N(H)-(SO_2)-aryl groups, -N(H)-(SO_2)-CF_3 groups, substituted and unsubstituted -N(H)-(SO_2)-heterocyclyl groups, substituted and unsubstituted -N(H)-heterocyclyl groups, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted alkoxy groups, substituted and unsubstituted arylalkoxy groups, substituted and unsubstituted aryloxy groups, substituted and unsubstituted akoxyalkyl groups, substituted and unsubstituted

arylalkoxyalkyl groups, substituted and unsubstituted heterocyclyloxy, substituted and unsubstituted heterocyclylalkoxy groups, substituted and unsubstituted (alkyl)(alkyl) aminoalkyl groups, substituted and unsubstituted (alkyl)(aryl) aminoalkyl groups, substituted and unsubstituted (alkyl)(heterocyclyl) aminoalkyl groups substituted and unsubstituted (alkyl)(arylalkyl) aminoalkyl groups, substituted and unsubstituted (alkyl)(heterocyclylalkyl) aminoalkyl groups, substituted and unsubstituted -alkyl-N(alkyl)-C(=O)-alkyl groups, substituted and unsubstituted -alkyl-N(alkyl)-C(=O)-aryl groups, substituted and unsubstituted -alkyl-N(alkyl)-C(=O)-heterocyclyl groups, substituted and unsubstituted -alkyl-N(alkyl)-C(=O)-alkyl-aryl groups, substituted and unsubstituted -alkyl-N(alkyl)-C(=O)-alkyl-heterocyclyl groups, substituted and unsubstituted alkylaminoalkyl groups, substituted and unsubstituted arylaminoalkyl groups, substituted and unsubstituted heterocyclylaminoalkyl groups, substituted and unsubstituted arylalkylaminoalkyl groups, substituted and unsubstituted heterocyclylalkylaminoalkyl groups, substituted and unsubstituted -alkyl-N(H)-C(=O)-alkyl groups, substituted and unsubstituted -alkyl-N(H)-C(=O)-aryl groups, substituted and unsubstituted -alkyl-N(H)-C(=O)-heterocyclyl groups, substituted and unsubstituted -alkyl-N(H)-C(=O)-alkyl-aryl groups, and substituted and unsubstituted -alkyl-N(H)-C(=O)-alkyl-heterocyclyl groups; or R^2 andR^3 are a group of formula -OCH_2O-such that R^2 and R^3 define a fused 5-membered ring that includes 2 oxygen atoms;

R^3 is selected from -H, -F, -Cl, -Br, $-CF_3$, -C≡N, $-NO_2$, $-CO_2H$, substituted and unsubstituted amino groups, substituted and unsubstituted alkyl groups, substituted and unsubstituted alkoxy groups, substituted and unsubstituted -C(=O)-O-alkyl groups, substituted and unsubstituted arylalkoxy groups, substituted and unsubstituted heterocyclyloxy groups, substituted and unsubstituted alkoxyalkyl groups, substituted and unsubstituted arylalkoxyalkyl groups, substituted and unsubstituted aryloxy group, substituted and unsubstituted heterocycyl groups, substituted and unsubstituted -N(H)-C(=O)-alkyl groups, substituted and unsubstituted -N(H)-C(=O)-aryl groups, substituted and unsubstituted -N(H)-(SO_2)-alkyl groups, substituted and unsubstituted -N(H)-(SO_2)-aryl groups, -N(H)-(SO_2)-CF_3 groups, substituted and unsubstituted -N(H)-(SO_2)-heterocyclyl groups, substituted and unsubstituted -N(H)C(=O)N(H)-alkyl groups, substituted and unsubstituted -N(H)C(=O)N(H)-aryl groups, substituted and unsubstituted -C(=O)-

N(H) -alkyl groups, substituted and unsubstituted -C(=O)-N(H)-alkyl-heterocyclyl groups, substituted and unsubstituted (alkyl)(alkyl) aminoalkyl groups, substituted and unsubstituted (alkyl)(aryl) aminoalkyl groups, substituted and unsubstituted (alkyl) (heterocyclyl) aminoalkyl groups, substituted and unsubstituted (alkyl)(arylalkyl) aminoalkyl groups, substituted and unsubstituted (alkyl)(heterocyclylalkyl) aminoalkyl groups, substituted and unsubstituted -alkyl-N(alkyl)-C(=O)-alkyl groups, substituted and unsubstituted - alkyl-N(alkyl)-C(=O)-aryl groups, substituted and unsubstituted -alkyl-N (alkyl)-C (=O)-heterocyclyl groups, substituted and unsubstituted -alkyl-N(alkyl)-C(=O)-alkyl-aryl groups, substituted and unsubstituted -alkyl-N(alkyl)-C(=O)-alkyl-heterocyclyl groups, substituted and unsubstituted alkylaminoalkyl groups, substituted and unsubstituted arylaminoalkyl groups, substituted and unsubstituted heterocyclylaminoalkyl groups, substituted and unsubstituted arylalkylaminoalkyl groups, substituted and unsubstituted heterocyclylalkylaminoalkyl groups, substituted and unsubstituted -alkyl-N(H)-C(=O)-alkyl groups, substituted and unsubstituted -alkyl-N(H)-C(=O)-aryl groups, substituted and unsubstituted -alkyl-N(H)-C(=O)-heterocyclyl groups, substituted and unsubstituted - alkyl-N(H)-C(=O)-alkyl-aryl groups, and substituted and unsubstituted -alkyl-N(H)-C(=O)-alkyl-heterocyclyl groups;

R^4 is -H, -F, -Br, -Cl, $-NO_2$, -C≡N, -C(=O)-O-alkyl groups, -OH, substituted and unsubstituted arylalkoxy groups, substituted and unsubstituted heterocyclyloxy groups, substituted and unsubstituted alkoxyalkyl groups, substituted and unsubstituted arylalkoxyalkyl groups, substituted and unsubstituted aryloxy groups, substituted and unsubstituted -N(H)-C(=O)-aryl groups, substituted and unsubstituted -N(H)-C(=O)-alkyl groups, substituted and unsubstituted -N(H)-(SO_2)-alkyl groups, substituted and unsubstituted -N(H)-(SO_2)-aryl groups, -N(H)-(SO_2)-CF_3 groups, substituted and unsubstituted -N(H)-(SO_2)-heterocyclyl groups, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted amino groups, substituted and unsubstituted alkyl groups, substituted and unsubstituted alkoxy groups, substituted and unsubstituted -C(=O)-N(H)-alkyl groups, substituted and unsubstituted -C(=O)-N(H)-alkyl-heterocyclyl groups, substituted and unsubstituted (alkyl)(alkyl) aminoalkyl groups, substituted and unsubstituted (alkyl)(aryl) aminoalkyl groups, substituted and unsubstituted (alkyl)(heterocyclyl) aminoalkyl groups substituted and unsubstituted (alkyl) (arylalkyl) aminoalkyl

groups, substituted and unsubstituted (alkyl)(heterocyclylalkyl) aminoalkyl groups, substituted and unsubstituted -alkyl-N(alkyl)-C(=O)-alkyl groups, substituted and unsubstituted -alkyl-N(alkyl)-C(=O)-aryl groups, substituted and unsubstituted -alkyl-N(alkyl)-C(=O)-heterocyclyl groups, substituted and unsubstituted -alkyl-N(alkyl)-C(=O)-alkyl-aryl groups, substituted and unsubstituted -alkyl-N(alkyl)-C(=O)-alkyl-heterocyclyl groups, substituted and unsubstituted alkylaminoalkyl groups, substituted and unsubstituted arylaminoalkyl groups, substituted and unsubstituted heterocyclylaminoalkyl groups substituted and unsubstituted arylalkylaminoalkyl groups, substituted and unsubstituted heterocyclylalkylaminoalkyl groups, substituted and unsubstituted -alkyl-N(H)-C(=O)-alkyl groups, substituted and unsubstituted-alkyl-N(H)-C(=O)-aryl groups, substituted and unsubstituted -alkyl-N(H)-C(=O)-heterocyclyl groups, substituted and unsubstituted -alkyl-N(H)-C(=O)-alkyl-aryl groups, and substituted and unsubstituted -alkyl-N(H)-C(=O)-alkyl-heterocyclyl groups;

R^5 is selected from -H, -F, -Cl, substituted and unsubstituted alkyl groups, substituted and unsubstituted alkoxy groups, substituted and unsubstituted amino groups, substituted and unsubstituted alkylamino groups, substituted and unsubstituted dialkylamino groups, and substituted and unsubstituted heterocyclyl groups, or R^5 is absent if Z^1 is N;

R^6 is selected from -H, -F, -Cl, -Br, $-CF_3$, $-CO_2H$, substituted and unsubstituted alkyl groups, substituted and unsubstituted alkoxy groups including substituted and unsubstituted heterocyclylalkoxy groups, substituted and unsubstituted arylalkoxy groups, and substituted and unsubstituted alkoxyalkoxy groups; substituted and unsubstituted heterocyclyl groups including substituted and unsubstituted heterocyclylheterocyclyl groups, substituted and unsubstituted arylheterocyclyl groups, substituted and unsubstituted alkylheterocyclyl groups, and substituted and unsubstituted cycloalkylheterocyclyl groups; substituted and unsubstituted heterocyclyloxy groups, substituted and unsubstituted aryloxy groups, substituted and unsubstituted amino groups including substituted and unsubstituted dialkylamino groups, substituted and unsubstituted (alkyl)(heterocyclyl) amino groups, substituted and unsubstituted heterocyclylalkylamino groups, substituted and unsubstituted arylalkylamino groups, and substituted and unsubstituted heterocyclylamino groups; substituted and unsubstituted -C(=O)N(H)-alkyl groups, substituted and unsubstituted

-C(=O)N(H)-aryl groups, substituted and unsubstituted -C(=O)N(H)-heterocyclyl groups, substituted and unsubstituted -C(=O)N(alkyl) (heterocyclyl) groups, and substituted and unsubstituted -C(=O)-heterocyclyl groups; or R^6 is absent if Z^2 is N;

R^7 is selected from -H, -F, -Cl, -Br, $-CF_3$, $-CO_2H$, substituted and unsubstituted alkyl groups, substituted and unsubstituted alkoxy groups including substituted and unsubstituted heterocyclylalkoxy groups, substituted and unsubstituted arylalkoxy groups, and substituted and unsubstituted alkoxyalkoxy groups; substituted and unsubstituted heterocyclyl groups including substituted and unsubstituted heterocyclylheterocyclyl groups, substituted and unsubstituted arylheterocyclyl groups, substituted and unsubstituted alkylheterocyclyl groups, and substituted and unsubstituted cycloalkylheterocyclyl groups; substituted and unsubstituted heterocyclyloxy groups, substituted and unsubstituted aryloxy groups, substituted and unsubstituted amino groups including substituted and unsubstituted dialkylamino groups, substituted and unsubstituted (alkyl)(heterocyclyl) amino groups, substituted and unsubstituted heterocyclylalkylamino groups, substituted and unsubstituted arylalkylamino groups, and substituted and unsubstituted heterocyclylamino groups; substituted and unsubstituted -C (=O) N (H)-alkyl groups, substituted and unsubstituted -C(=O)N(H)-aryl groups, substituted and unsubstituted -C(=O)N(H)-heterocyclyl groups, substituted and unsubstituted -C(=O)N(alkyl)(heterocyclyl) groups, and substituted and unsubstituted -C(=O)-heterocyclyl groups; or R^7 is absent if Z^3 is N;

R^8 is selected from -H, -F, -Cl, substituted and unsubstituted alkyl groups, substituted and unsubstituted alkoxy groups, substituted and unsubstituted amino groups, substituted and unsubstituted alkylamino groups, substituted and unsubstituted dialkylamino groups, and substituted and unsubstituted heterocyclyl groups, or R^8 is absent if Z^3 is N;

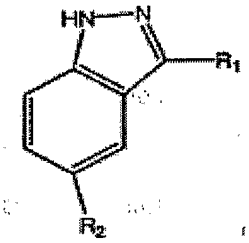
R^9 is -H ; and

R^{10} is selected from the group consisting of -H, and substituted and unsubstituted alkyl groups, and further wherein at least one of the following is true: (i) R^1 is selected from the group consisting of unsubstituted $-NH_2$ groups, and substituted and unsubstituted pyrrolidinylalkylamino groups; (ii) R^2 is selected from the group consisting of substituted and unsubstituted thiazolylalkylamino groups, substituted

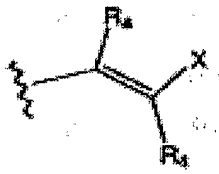
and unsubstituted pyrrolidinylalkylamino groups, and substituted and unsubstituted aminoalkylamino groups; or (iii) R^3 is selected from the group consisting of substituted and unsubstituted thiazolylalkylamino groups, substituted and unsubstituted benzimidazolylalkylamino groups, substituted and unsubstituted imidazolylalkylamino groups, substituted and unsubstituted furanylalkylamino groups, and substituted and unsubstituted arylalkylamino groups.

XV. Indazole compounds as described inInternational Patent Publication WO01053268, including:

i) A compound of formula:

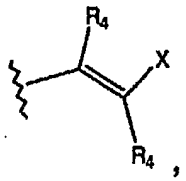


wherein R_1, is hydrogen or a substituted or unsubstituted alkyl, aryl, heteroaryl, carbocycle, or heterocycle group, or



wherein R_4 is H or lower alkyl, and X is a substituted or unsubstituted alkyl, aryl, heteroaryl, carbocycle, or heterocycle group ; and

R_2 is a substituted or unsubstituted alkyl, aryl, heteroaryl, carbocycle, or heterocycle group, or

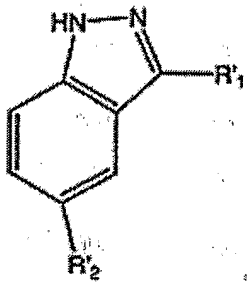


wherein

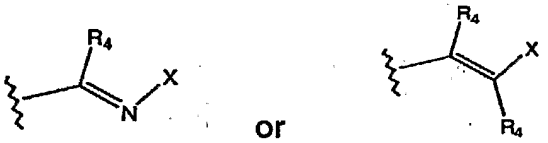
R_4 is H or lower alkyl, and X is a substituted or unsubstituted aryl, heteroaryl, carbocycle, or heterocycle group ; or a pharmaceutically acceptable salt of

the compound; or a prodrug or pharmaceutical active metabolite of the compound, or a pharmaceutically acceptable salt of a prodrug or metabolite thereof.

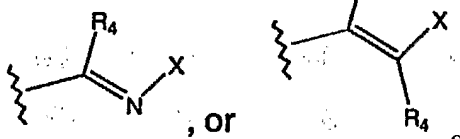
ii) A compound of formula:



wherein R'_1, is a substituted or unsubstituted alkyl, aryl, heteroaryl, carbocycle, or heterocycle group or



wherein each R_4 is individually H or lower alkyl, and X is a substituted or unsubstituted alkyl, aryl, heteroaryl, carbocycle, or heterocycle group ; and R'_2 is a substituted or unsubstituted amino, nitro, alkenyl, alkyl, aryl, heteroaryl, carbocycle, heterocycle



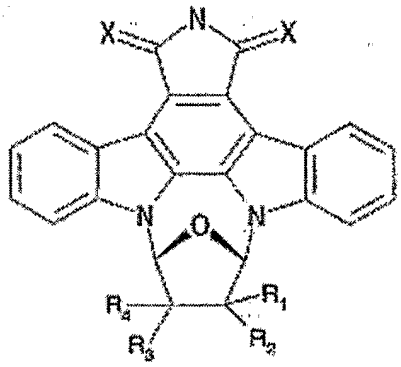
group

wherein the R_4 groups are independently H or lower alkyl, and X is selected from a substituted or unsubstituted alkyl, aryl, heteroaryl, carbocycle, or heterocycle group ;

or a pharmaceutically acceptable salt of the compound; or a prodrug or pharmaceutically active metabolite of the compound, or a pharmaceutically acceptable salt of the prodrug or metabolite thereof.

XVI. Chk1 receptor antagonists as described in International Patent Publication WO00/016781, including:

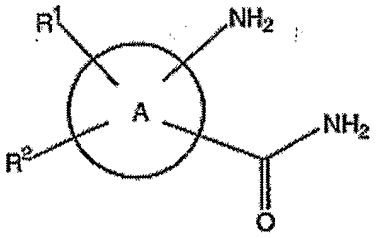
i) A compound of formula:



wherein X represents N, S or OH and R^1, R^2, R^3, and R^4 independently represent C_{1-6} alkyl, OH, or SH or H.

XVII. Heteroaromatic carboxamide compounds as described in International Patent Publication WO03/037886, including:

i) A compound of formula:



wherein A is a 5-membered heteroaromatic ring containing one or two heteroatoms independently selected from oxygen, nitrogen, or sulfur;

R^1 is selected from the group consisting of: hydrogen, halogen, cyano, nitro,-$N(R^3)_2$,-$CON(R^3)_2$,-$COOR^3$, -NR^3COR^3, $S(O)mR^3$,-$S0_2N$ $(R^3)_2$,-$NR^3SO_2R^3$, alkyl, trifluoromethyl, trifluoromethoxy, alkenyl, alkynyl, alkoxy, alkanoyl, substituted or unsubstituted aryl, and a substituted or unsubstituted 5-to 7- membered heteroaromatic ring containing one to three heteroatoms independently selected from oxygen, nitrogen, or sulfur, wherein said substituent (s) are independently selected from the group consisting of : halogen, cyano, nitro,-$N(R^4)_2$, -$CON(R^4)_2$, -$COOR^4$, -NR^4COR^4, $S(O)mR^4$-SO_2N $(R^4)_2$, -$NR^4SO_2R^4$, alkyl,

trifluoromethyl, trifluoromethoxy, alkenyl, alkynyl, alkoxy, alkanoyl, aminoalkyl, and aryl;

R^2 is selected from the group consisting of: substituted or unsubstituted aryl, and a 5-to 7-membered substituted or unsubstituted heteroaromatic ring containing one to three heteroatoms independently selected from oxygen, nitrogen, or sulfur,

wherein said substituent(s) are independently selected from the group consisting of: halogen, cyano, nitro,-N $(R^4)_2$, -CON(R4)$_2$, -COOR4, -NR4COR4, $S(O)_mR4$, -SO2N (R4) $_2$, $-NR^4SO_2R^4$, alkyl, trifluoromethyl, trifluoromethoxy, alkenyl, alkynyl, alkoxy, alkanoyl, aminoalkyl, and aryl;

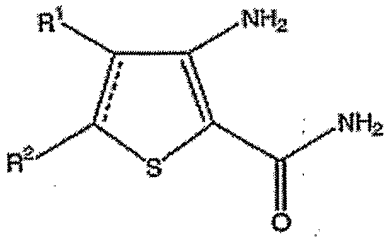
R^1 and R^2 can optionally be taken together form a 5 or 6 membered saturated or unsaturated ring optionally substituted with one or more substituent selected from the group consisting of: halogen, cyano, nitro,-$N(R^3)_2$, -$CON(R^3)_2$, -$COOR^3$, -NR^3COR^3, $S(O)_mR^3$, -$SO_2N(R^3)_2$,-$NR^3SO_2R^3$, alkyl, trifluoromethyl, trifluoromethoxy, alkenyl, alkynyl, alkoxy, alkanoyl, substituted or unsubstituted aryl, and a substituted or unsubstituted 5-to 7-membered heteroaromatic ring containing one to three heteroatoms independently selected from

oxygen, nitrogen, or sulfur, wherein said substituent(s) are independently selected from the group consisting of: halogen, cyano, nitro,-$N(R^4)_2$, -$CON(R^4)_2$, -$COOR^4$, -NR^4COR^4, $S(O)_mR^4$, -SO_2N $(R^4)_2$,- $NR^4SO_2R^4$, alkyl, trifluoromethyl, trifluoromethoxy, alkenyl, alkynyl, alkoxy, alkanoyl, aminoalkyl, and aryl;

R^3 is selected from the group consisting of : hydrogen or alkyl;

R^4 is selected from the group consisting of: hydrogen or alkyl; m is an integer 0, 1, or 2; and isomers, tautomers, carriers, prodrugs, pharmaceutically acceptable salts thereof.

ii) A compound of formula:



wherein,

R^1 is selected from the group consisting of: hydrogen, halogen, cyano, nitro,-$N(R^3)_2$,-$CON(R^3)_2$, -$COOR^3$, -NR^3COR^3, $S(O)_mR^3$, -$SO_2N(R^3)_2$, -$NR^3SO_2R^3$, alkyl, trifluoromethyl, trifluoromethoxy, alkenyl, alkynyl, alkoxy, alkanoyl, substituted or unsubstituted aryl, and a substituted or unsubstituted 5-to 7- membered heteroaromatic ring containing one to three heteroatoms independently selected from oxygen, nitrogen, or sulfur, wherein said substituent(s) are independently selected from the group consisting of : halogen, cyano,nitro,-$N(R^4)_2$, -$CON(R^4)_2$, -$COOR^4$, -NR^4COR^4, $S(O)_mR^4$, -$SO_2N(R^4)_2$, -$NR^4SO_2R^4$, alkyl, trifluoromethyl, trifluoromethoxy, alkenyl, alkynyl, alkoxy, alkanoyl, aminoalkyl, and aryl;

R^2 is selected from the group consisting of: substituted or unsubstituted aryl, and a 5-to 7-membered substituted or unsubstituted heteroaromatic ring containing one to three heteroatoms independently selected from oxygen, nitrogen, or sulfur, wherein said substituent(s) are independently selected from the group consistingof : halogen, cyano, nitro, -$N(R^4)_2$, -$CON(R^4)_2$, -$COOR^4$, -NR^4COR^4, $S(O)_mR^4$, -$SO_2N(R^4)_2$, -$NR^4SO_2R^4$, alkyl, trifluoromethyl, trifluoromethoxy, alkenyl, alkynyl, alkoxy, alkanoyl, aminoalkyl, and aryl;

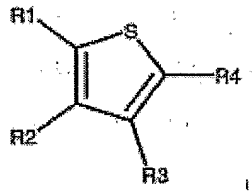
R^1 and R^2 can optionally be taken together form a 5 or 6 membered saturated or unsaturated ring optionally substituted with one or more substituent selected from the group consisting of: halogen, cyano, nitro, -N $(R^3)_2$,-$CON(R^3)_2$, -$COOR^3$,-from the group consisting of: halogen, cyano, nitro, -$N(R^4)_2$,- $CON(R^4)_2$, -$COOR^4$, -NR^4COR^4, $S(O)_mR^4$,-$SO_2N(R^4)_2$, -$NR^4SO_2R^4$, alkyl, trifluoromethyl, trifluoromethoxy, alkenyl, alkynyl, alkoxy, alkanoyl, aminoalkyl, and aryl.

R^3 is selected from the group consisting of : hydrogen or alkyl;

R^4 is selected from the group consisting of: hydrogen or alkyl; m is an integer 0, 1, or 2; and isomers, tautomers, carriers, prodrugs, pharmaceutically acceptable salts thereof.

XVIII. Aminothiophene compounds as described in International Patent Publication WO03/029242, including:

i) A compound of formula:



wherein,

R_1 is $CONH_2$, or SO_2NH_2, ;R_2 is NR_5R_6 ;

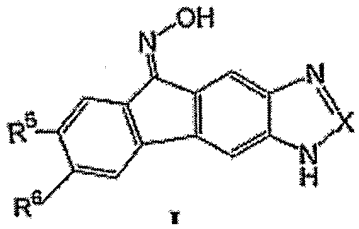
R_3 is H, or halogen; R_4 is aryl, or heteroaryl; R5 is H, or alkyl ; provided that when R_1 is $CONH_2$, R_6 is selected from the group consisting of H, CO-alkyl, SO_2-alkyl, $CONH_2$, CONH-alkyl, CONH-aryl, CONH-heteroaryl, $CSNH_2$, CSNH-alkyl, CSNH-aryl, CSNH-heteroaryl, SO_2NH_2, SO_2NH-alkyl, SO_2NH-aryl, and SO_2NH-heteroaryl ;

When R_1, is SO_2NH_2, R_6 is CONH; and when R_1 is CONH, R_2 is not $NHCONH_2$;

and pharmaceutically acceptable salts, hydrates and solvated thereof.

XIX. Heterocyclic-hydroxyimino-fluorene compounds as described in Iternational Patent Publication WO0216326, including:

i) A compound of formula:

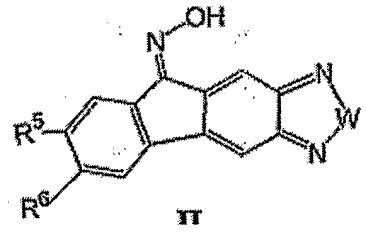


I

wherein: R^5 and R^6 are each independently hydrogen, halo, or a substituted or unsubstituted C_1-C_8 alkyl, C_1-C_8 alkoxy, aryl, heteroaryl, acyl, thioalkyl, sulfonyl, or sulfoxyl; and X is C-Y or N,

where Y is hydrogen, halo, NH_2, NO_2, or a substituted or unsubstituted alkyl, cycloalkyl, heterocycloalkyl, alkoxy, alkenyl, aryl, heteroaryl, aryloxy, alkylamino, dialkylamino, thioalkyl, acyl, sulfonyl, sulfoxide, or thioaryl; or a pharmaceutically acceptable prodrug of said compound, pharmaceutically active metabolite of said compound, or pharmaceutically acceptable salt of said compound or metabolite.

ii) A compound of formula:



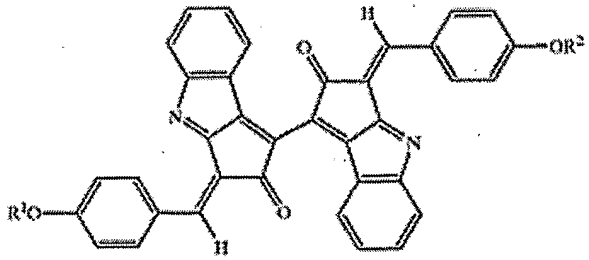
II

wherein: R^5 and R^6 are each independently hydrogen, halo, or a substituted or unsubstituted C_1-C_8 alkyl, C_1-C_8 alkoxy, aryl, heteroaryl, acyl, thioalkyl, sulfonyl, or sulfoxyl ; and

W is O or S ; or a pharmaceutically acceptable prodrug of said compound, pharmaceutically active metabolite of said compound, or pharmaceutically acceptable salt of said compound or metabolite.

XX. Scytoneman skeleton containing compounds as described in U.S. Patent No. 6,495,586, including:

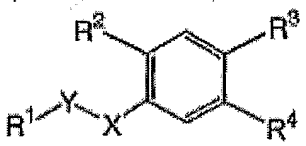
i) A compound of formula:



wherein R^1 and R^2 are independently H, an alkyl group having up to 5 carbon atoms, or -CO-(CH_2)n-CH3 where n=O to 16.

XXI. Heteroarylbenzamide compounds as described in International Patent Publication WO0153274, including:

i) A compound of formula:



wherein : R^1 is a moiety represented by the formula



where

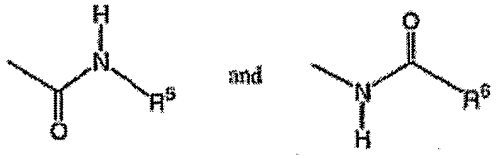
Z is selected from the group consisting of CH and NH, and Q is a moiety such that R^1 is a substituted or unsubstituted monocyclic or bicyclic heteroaryl which has at least two carbon atoms in the heteroaryl ring system ;

X is selected from the group consisting of CH_2, O, S, and NH ;

Y is selected from the group consisting of CH_2, O, and S, provided that at least one of X and Y is CH_2, or X and Y together with the bond there-between form a cyclopropyl ;

R^2 and R^3 are independently selected from the group consisting of hydrogen, methyl, halogen, trifluoromethyl, and cyano ; and

R^4 is selected from the group consisting of



where R^5 is selected from the group consisting of substituted and unsubstituted aryl, heteroaryl, cycloalkyl, heterocycloalkyl, O-R^7, NR^8R^9, C_1-C_8 alkyl, and monocyclic heterocycloalkyl,

R^6 is selected from the group consisting of substituted and unsubstituted aryl, heteroaryl,cycloalkyl, heterocycloalkyl, alkenyl, O-R^7, C(O)R^7, NR^8R^9, C_2-C_8 alkyl, and monocyclic heterocycloalkyl,

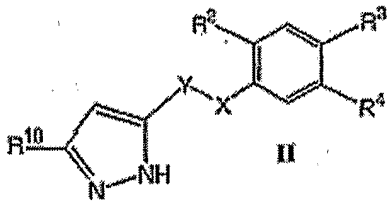
where R^7 is selected from the group consisting of substituted and unsubstituted alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl,

R^8 is selected from the group consisting of hydrogen, and substituted and unsubstituted alkyl, and

R^9 is selected from the group consisting of substituted and unsubstituted alkyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl ;

or a pharmaceutically acceptable prodrug, pharmaceutically active metabolite, or pharmaceutically acceptable salt thereof.

ii) A compound of formula:



II

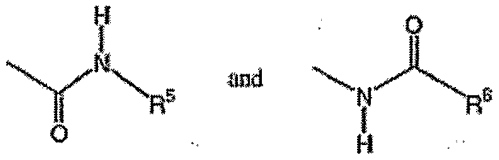
wherein :

X is selected from the group consisting of CH_2, O, and S;

Y is selected from the group consisting of CH_2 and S, provided that at least one of X and Y is CH_2 ;

R^2 and R^3 are independently selected from the group consisting of hydrogen, methyl, fluorine, and chlorine ;

R^4 is selected from the group consisting of



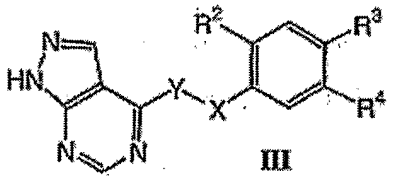
where R^5 and R^6 are each independently selected from the group consisting of substituted and unsubstituted aryl and heteroaryl; and

R^{10} is selected from the group consisting of substituted and unsubstituted alkenyl, aryl, heteroaryl, and HNR^9,

where R^9 is selected from the group consisting of substituted and unsubstituted alkyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl ;

or a pharmaceutically acceptable prodrug, pharmaceutically active metabolite, or pharmaceutically acceptable salt thereof.

iii) A compound of formula:



III

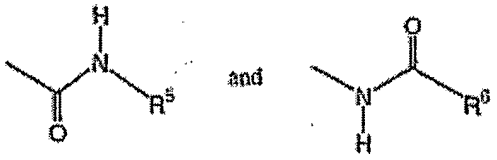
wherein :

X is selected from the group consisting of CH_2, O, S, and NH ;

Y is selected from the group consisting of CH_2, O, and S, provided that at least one of X and Y is CH_2, or X and Y together with the bond there-between form a cyclopropyl ;

R^2 and R^3 are independently selected from the group consisting of hydrogen, methyl, halogen, trifluoromethyl, and cyano; and

R^4 is selected from the group consisting of



where R^5 is selected from the group consisting of substituted and unsubstituted aryl, heteroaryl, cycloalkyl, heterocycloalkyl, O-R^7, NR^8R^9, C_1-C_8 alkyl, and monocyclic heterocycloalkyl,

R^6 is selected from the group consisting of substituted and unsubstituted aryl, heteroaryl, cycloalkyl, heterocycloalkyl, alkenyl, O-R^7, C(O)R^7, NR^8R^9, C_2-C_8 alkyl, and monocyclic heterocycloalkyl,

where R^7 is selected from the group consisting of substituted and unsubstituted alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl,

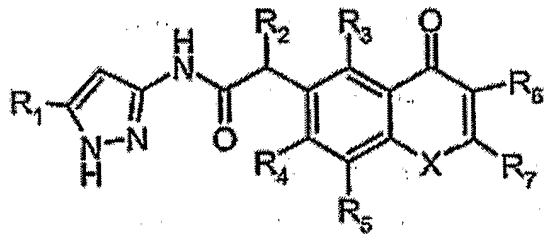
R^8 is selected from the group consisting of hydrogen and substituted and unsubstituted alkyl, and

R^9 is selected from the group consisting of substituted and unsubstituted alkyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl ;

or a pharmaceutically acceptable prodrug, pharmaceutically active metabolite, or pharmaceutically acceptable salt thereof.

XXII. Chromane compounds as described in International Patent Publication WO02070515, including:

i) A compound of formula:



wherein

R_1 is a C_3-C_6 cycloalkyl group optionally substituted by a straight or branched C_1-C_6 alkyl or by aryl C_1-C_6 alkyl group;

R_2 is a hydrogen atom or a straight or branched C_1-C_6 alkyl or C_2-C_4 alkenyl group, each of which being optionally substituted by hydroxy, C_1-C_6 alkoxy, amino or C_1-C_6 alkylamino;

R_3, R_4 and R_5 are, each independently, hydrogen, halogen, hydroxy, amino or straight or branched C_1-C_6 alkyl, C_1–C_6 alkoxy or C_1-C_6 alkylamino ;

R_6 and R_7 are, each independently, hydrogen, hydroxy, amino, aminocarbonyl, ureido, guanidyl, pyrrolidinyl optionally substituted by oxo groups, straight or branched C_1-C6 alkyl optionally substituted by hydroxy or amino groups, straight or branched C_1-C_6 alkoxy, aryl or arylcarbonyl

optionally substituted by halogen, hydroxy, amino, straight or branchedCl-C6 alkyl or C_1-C_6 alkoxy groups, or a group selected from alkylcarbonyl, alkylamino, alkylaminocarbonyl or arylalkyloxy wherein alkyl stands for straight or branched C_1-C_6 alkyl;

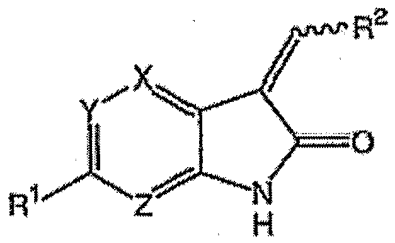
X is an oxygen or sulfur atom or represents a group -N(R_8)-

wherein R_8 is hydrogen or a straight or branched C_1-C_6 alkyl or C_2-C_4 alkenyl group, each of which being optionally substituted by hydroxy, amino, C_1-C_6 alkoxy or C_1-C_6 alkylamino;

or a pharmaceutically acceptable salt thereof; provided that the compound is other than N-(5-cyclopropyl-lH-pyrazol-3- yl)-2- [2- (4-methoxyphenyl)-4-oxo-4H-chromen-6-yl] acetamide;

XXIII. Oxindole compounds as described in International Patent Publication WO03051838, including:

i) A compound of formula:



or a therapeutically acceptable salt thereof, wherein

X is selected from the group consistingof-N-and-CR^X-;

Y is selected from the group consisting of-N-and-CR^Y- ;

Z is selected from the group consisting of-N- and -CR^Z-;

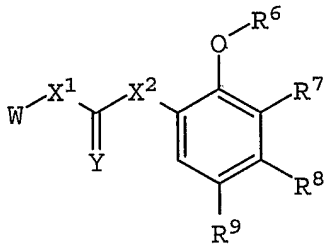
with the proviso that at least one of Y and Z is other than-N- ;

one of R^X, R^Y, R^Z, and R^1 is selected from the group consisting of aryl and heterocycle and the others are hydrogen; and

R^2 is selected from the group consisting of heterocycle and aryl ; with the proviso that when R^2 is heterocycle the heterocycle is other than imidazolyl.

XXIV. Diarylurea compounds are described in U.S. Provisional Patent Application 60/583,080, including:

i) A compound of formula:



wherein X^1 is null, -O-, -S-, $-CH_2-$, or $-N(R^1)-$;

X^2 is -O-, -S-, or $-N(R^1)-$;

Y is O or S; or =Y represents two hydrogen atoms attached to a common carbon atom;

W is selected from the group consisting of heteroaryl, aryl, heterocycloalkyl, cycloalkyl, and C_{1-6}alkyl substituted with a heteroaryl or aryl group, wherein said aryl group W is optionally substituted with one to four substituents represented by R^2, said heteroaryl group W is optionally substituted with one to four substituents represented by R^5, and said heterocycloalkyl and cycloalkyl groups W are optionally substituted with one or two C_{1-6}alkyl substituents;

R^1 is selected from the group consisting of hydro, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, and aryl;

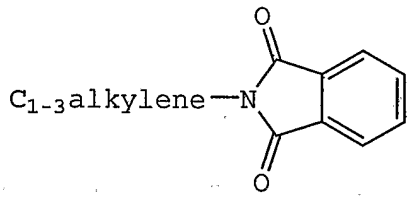
R^2 is selected from the group consisting of heteroaryl, halo, optionally substituted C_{1-6}alkyl, C_{2-6}alkenyl, OCF_3, NO_2, CN, NC, $N(R^3)_2$, OR^3, CO_2R^3, C(O)-

$N(R^3)_2$, $C(O)R^3$, $N(R^1)COR^3$, $N(R^1)C(O)OR^3$, $N(R^1)C(O)C_{1-6}alkyleneC(O)R^3$, $N(R^1)C(O)C_{1-6}alkyleneC(O)OR^3$, $N(R^1)C(O)C_{1-6}alkyleneOR^3$, $N(R^1)C(O)$-$C_{1-6}alkyleneNHC(O)OR^3$, $N(R^1)C(O)C_{1-6}alkyleneSO_2NR^3$, $C_{1-6}alkyleneOR^3$, and SR^3;

R^3 is selected from the group consisting of hydro, C_{1-6}alkyl, C_{2-6}alkenyl, cycloalkyl, aryl, heteroaryl, SO_2R^4, halo, C_{1-6}alkyl substituted with one or more of halo, hydroxy, aryl, heteroaryl, heterocycloalkyl, $N(R^4)_2$, and SO_2R^4, $C_{1-6}alkylenearyl$, $C_{1-6}alkyleneheteroaryl$, $C_{1-6}alkyleneC_{3-8}heterocycloalkyl$, $C_{1-6}alkyl$-$eneSO_2aryl$, optionally substituted $C_{1-6}alkyleneN(R^4)_2$, OCF_3, $C_{1-6}alkyleneN(R^4)_3^+$, C_{3-8}heterocycloalkyl, and $CH(C_{1-6}alkyleneN(R^4)_2)_2$, or two R^3 groups are taken together to form an optionally substituted 3- to 8-membered aliphatic ring;

R^4 is selected from the group consisting of null, hydro, C_{1-6}alkyl, cycloalkyl, aryl, heteroaryl, $C_{1-6}alkylenearyl$, and SO_2C_{1-6}alkyl, or two R^4 groups are taken together to form an optionally substituted 3- to 8-membered ring;

R^5 is selected from the group consisting of C_{1-6}alkyl, C_{2-6}alkynyl, aryl, heteroaryl, heterocycloalkyl, $N(R^3)_2$, $N(R^1)C(O)R^3$, $N(R^1)CO_2R^3$, OR^3, halo, N_3, CN, $C_{1-6}alkylenearyl$, $C_{1-6}alkyleneN(R^3)_2$, $C(O)R^3$, $C(O)OR^3$, $C(O)N(R^3)_2$, CF_3, and



;

R^6 is selected from the group consisting of hydro, C_{1-6}alkyl, C_{2-6}alkenyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, SO_2R^4, C_{1-6}alkyl substituted with one or more of halo, hydroxy, aryl, heteroaryl, heterocycloalkyl, $N(R^4)_2$, and SO_2R^4, $C_{1-6}alkylenearyl$, $C_{1-6}alkyleneheteroaryl$, $C_{1-6}alkylene$-C_{3-8}heterocycloalkyl, $C_{1-6}alkyleneSO_2aryl$, optionally substituted $C_{1-6}alkyleneN(R^4)_2$, OCF_3, $C_{1-6}alkyleneN(R^4)_3^+$, C_{3-8}heterocycloalkyl, and $CH(C_{1-6}alkyleneN(R^4)_2)_2$;

R^7 and R^8, independently, are selected from the group consisting of hydro, OR^3, C_{1-6}alkyl, halo, $N(R^3)_2$, $C(O)N(R^3)_2$, $C_{1-3}alkylenearyl$, CN, NO_2, $C(O)OR^{11}$, $C(O)R^{11}$, and SR^{11};

R^9 is $-C\equiv C-R^{10}$ or $-CF_3$, or an R^8 and an R^9 group are taken together with the carbons to which they are attached to form a 5- or 6-membered carbocyclic aliphatic or aromatic ring system optionally containing one to three heteroatoms selected from the group consisting of O, NR^4, and S;

R^{10} is selected from the group consisting of hydro, C_{1-6}alkyl, aryl, C_{1-6}alkylenearyl, heteroaryl, and C_{1-6}alkyleneheteroaryl;

R^{11} is selected from the group consisting of hydro, C_{1-6}alkyl, C_{2-6}alkenyl, aryl, C_{1-3}alkylenearyl, C_{3-8}cycloalkyl, and C_{1-3}alkyleneC_{3-8}cycloalkyl;

n is 1 or 2;

or a pharmaceutically acceptable salt, or prodrug, or solvate thereof.

A compound selected from

1-[5-ethynyl-2-(1-methyl-piperidin-3-ylmethoxy)-phenyl]-3-(5-methyl-pyrazin-2-yl)-urea;

1-[2-(2-dimethylamino-ethoxy)-5-ethynyl-phenyl]-3-(5-methyl-pyrazin-2-yl)-urea;

1-[5-ethynyl-2-(pyridin-3-ylmethoxy)-phenyl]-3-(5-methyl-pyrazin-2-yl)-urea;

1-[3-(1-methyl-piperidin-3-ylmethoxy)-5,6,7,8-tetrahydro-naphthalen-2-yl]-3-(5-methyl-pyrazin-2-yl)-urea;

1-[3-(1-methyl-piperidin-2-ylmethoxy)-5,6,7,8-tetrahydro-naphthalen-2-yl]-3-(5-methyl-pyrazin-2-yl)-urea;

(S)-1-(5-methyl-pyrazin-2-yl)-3-[2-(piperidin-3-ylmethoxy)-5-trifluoromethyl-phenyl]-urea;

(R)-1-(5-methyl-pyrazin-2-yl)-3-[2-(piperidin-3-ylmethoxy)-5-trifluoromethyl-phenyl]-urea;

1-[2-(1-methyl-piperidin-4-yloxy)-5-trifluoromethyl-phenyl]-3-(5-methyl-pyrazin-2-yl)-urea;

1-(5-methyl-pyrazin-2-yl)-3-[2-(piperidin-3-ylmethoxy)-5-trifluoromethyl-phenyl]-urea;

1-[2-(1-methyl-piperidin-3-ylmethoxy)-5-trifluoromethyl-phenyl]-3-(5-methyl-pyrazin-2-yl)-urea;

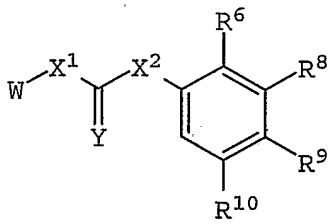
1-(5-methyl-pyrazin-2-yl)-3-[7-(pyridin-3-ylmethoxy)-2,3-dihydro-benzo[1,4]dioxin-6-yl]-urea;

1-[7-(2-dimethylamino-ethoxy)-2,3-dihydro-benzo[1,4]dioxin-6-yl]-3-(5-methyl-pyrazin-2-yl)-urea; and

1-[3-(2-dimethylamino-ethoxy)-5,6,7,8-tetrahydro-naphthalen-2-yl]-3-(5-methyl-pyrazin-2-yl)-urea.

XXV. Diarylurea compounds as described in U.S. Provisional Patent Application 60/585,292, including:

i) A compound of formula



wherein X^1 is null, -O-, -S-, $-CH_2-$, or $-N(R^1)-$;

X^2 is -O-, -S-, or $-N(R^1)-$;

Y is O or S; or =Y represents two hydrogen atoms attached to a common carbon atom;

W is selected from the group consisting of heteroaryl, aryl, heterocycloalkyl, cycloalkyl, and C_{1-6}alkyl substituted with a heteroaryl or aryl group, wherein said aryl group W is optionally substituted with one to four substituents represented by R^2, said heteroaryl group W is optionally substituted with one to four substituents represented by R^5, and said heterocycloalkyl and cycloalkyl groups W are optionally substituted with one or two C_{1-6}alkyl substituents;

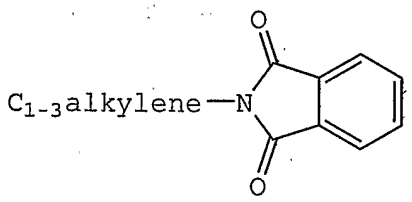
R^1 is selected from the group consisting of hydro, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, and aryl;

R^2 is selected from the group consisting of heteroaryl, halo, optionally substituted C_{1-6}alkyl, C_{2-6}alkenyl, OCF_3, NO_2, CN, NC, $N(R^3)_2$, OR^3, CO_2R^3, $C(O)N(R^3)_2$, $C(O)R^3$, $N(R^1)COR^3$, $N(R^1)C(O)OR^3$, $N(R^1)C(O)C_{1-6}$alkyleneC(O)R^3, $N(R^1)C(O)C_{1-6}$alkyleneC(O)OR^3, $N(R^1)C(O)C_{1-6}$alkyleneOR^3, $N(R^1)C(O)C_{1-6}$alkyleneNHC(O)OR^3, $N(R^1)C(O)C_{1-6}$alkyleneSO$_2$NR^3, C_{1-6}alkyleneOR^3, and SR^3;

R^3 is selected from the group consisting of hydro, halo, C_{1-6}alkyl, C_{2-6}alkenyl, cycloalkyl, aryl, heteroaryl, CO_2R^4, SO_2R^4, C_{1-6}alkyl substituted with one or more of halo, hydroxy, aryl, heteroaryl, heterocycloalkyl, $N(R^4)_2$, and SO_2R^4, C_{1-6}alkylenearyl, C_{1-6}alkyleneheteroaryl, C_{1-6}alkyleneC_{3-8}heterocycloalkyl, C_{1-6}alkyleneSO_2aryl, optionally substituted C_{1-6}alkylene$N(R^4)_2$, OCF_3, C_{1-6}alkylene$N(R^4)_3^+$, C_{3-8}heterocycloalkyl, and $CH(C_{1-6}$alkylene$N(R^4)_2)_2$, or two R^3 groups are taken together to form an optionally substituted 3- to 6-membered aliphatic ring;

R^4 is selected from the group consisting of hydro, C_{1-6}alkyl, cycloalkyl, aryl, heteroaryl, C_{1-6}alkylenearyl, and SO_2C_{1-6}alkyl, or two R^4 groups are taken together to form an optionally substituted 3- to 6-membered ring;

R^5 is selected from the group consisting of C_{1-6}alkyl, aryl, heteroaryl, heterocycloalkyl, $N(R^3)_2$, OR^3, halo, N_3, CN, C_{1-6}alkylenearyl, C_{1-6}alkylene$N(R^3)_2$, $C(O)R^3$, $C(O)OR^3$, $C(O)N(R^3)_2$, $N(R^1)C(O)R^3$, $N(R^1)C(O)OR^3$, CF_3, and



;

R^6 is -C≡C-R^7 or heteroaryl;

R^7 is selected from the group consisting of hydro, C_{1-6}alkyl, aryl, C_{1-6}alkylenearyl, heteroaryl, C_{1-6}alkyleneheteroaryl, and alkoxy;

R^8, R^9, and R^{10}, independently, are selected from the group consisting of halo, optionally substituted C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, OCF_3, CF_3, NO_2, CN, NC, $N(R^3)_2$, OR^3, CO_2R^3, $C(O)N(R^3)_2$, $C(O)R^3$, $N(R^1)COR^3$, $N(R^1)C(O)OR^3$, $N(R^8)C(O)OR^3$, $N(R^1)C(O)C_{1-3}$alkylene$C(O)R^3$, $N(R^1)C(O)C_{1-3}$alkylene$C(O)OR^3$, $N(R^1)C(O)C_{1-3}$alkyleneOR^3, $N(R^1)C(O)C_{1-3}$alkylene$NHC(O)OR^3$, $N(R^1)C(O)$-C_{1-3}alkyleneSO_2NR^3, C_{1-3}alkyleneOR^3, and SR^3;

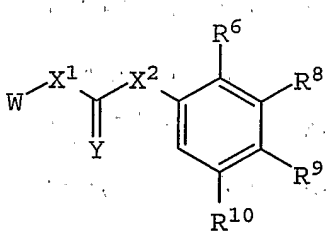
and a pharmaceutically acceptable salts, or prodrug, or solvate thereof.

A compound selected from: 1-(5-methyl-pyrazin-2-yl)-3-(5-methyl-2-pyridin-3-ylethynyl-phenyl)-urea, 1-(5-methyl-pyrazin-2-yl)-3-(5-methyl-2-pyridin-3-

yl-phenyl)-urea, 1-(5-methyl-pyrazin-2-yl)-3-(5-methyl-2-pyridin-4-yl-phenyl)-urea, 1-(5-methyl-pyrazine-2-yl)-3-(2-oxazol-5-yl-phenyl)-urea, 1-(5-methyl-pyrazin-2-yl)-3-(5-methyl-2-thiazol-2-yl-phenyl) urea, 1-[2-(4-dimethylaminomethyl-thiazol-2-yl)-5-methyl-phenyl]-3-(5-methyl-pyrazin-2-yl)-urea, and mixtures thereof.

XXVI. Diarylurea compounds are described in U.S. Provisional Patent Application 60/602,968, including:

i) A compound of formula:



wherein X^1 is null, -O-, -S-, $-CH_2-$, or $-N(R^1)-$;

X^2 is -O-, -S-, or $-N(R^1)-$;

Y is O or S; or =Y represents two hydrogen atoms attached to a common carbon atom;

W is selected from the group consisting of heteroaryl, aryl, heterocycloalkyl, cycloalkyl, and C_{1-6}alkyl substituted with a heteroaryl or aryl group, wherein (a) said aryl or heteroaryl group of group W is substituted with at least one of CF_3 and heteroaryl, (b) said aryl group of group W is optionally substituted with one to three substituents represented by R^2, and (c) said heteroaryl group of group W is optionally substituted with one to three substituents represented by R^5;

R^1 is selected from the group consisting of hydro, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, and aryl;

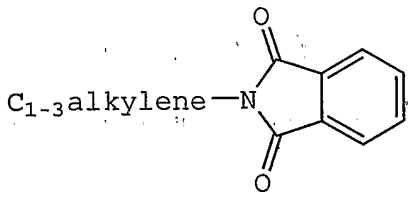
R^2 is selected from the group consisting of heteroaryl, halo, optionally substituted C_{1-6}alkyl, C_{2-6}alkenyl, OCF_3, NO_2, CN, NC, $N(R^3)_2$, OR^3, CO_2R^3, $C(O)N(R^3)_2$, $C(O)R^3$, $N(R^1)COR^3$, $N(R^1)C(O)OR^3$, $N(R^1)C(O)C_{1-6}$alkyleneC(O)R^3, $N(R^1)C(O)C_{1-6}$alkyleneC(O)OR^3, $N(R^1)C(O)C_{1-6}$alkyleneOR^3,

$N(R^1)C(O)C_{1-6}alkyleneNHC(O)OR^3$, $N(R^1)C(O)C_{1-6}alkyleneSO_2NR^3$, $C_{1-6}alkyleneOR^3$, and SR^3;

R^3 is selected from the group consisting of hydro, halo, C_{1-6}alkyl, C_{2-6}alkenyl, cycloalkyl, aryl, heteroaryl, CO_2R^4, SO_2R^4, C_{1-6}alkyl substituted with one or more of halo, hydroxy, aryl, heteroaryl, heterocycloalkyl, $N(R^4)_2$, and SO_2R^4, C_{1-6}alkylenearyl, C_{1-6}alkyleneheteroaryl, C_{1-6}alkyleneC_{3-8}heterocycloalkyl, C_{1-6}alkyleneSO$_2$aryl, optionally substituted C_{1-6}alkylene$N(R^4)_2$, OCF_3, C_{1-6}alkylene$N(R^4)_3^+$, C_{3-8}heterocycloalkyl, and $CH(C_{1-6}alkyleneN(R^4)_2)_2$, or two R^3 groups are taken together to form an optionally substituted 3- to 6-membered aliphatic ring;

R^4 is selected from the group consisting of hydro, C_{1-6}alkyl, cycloalkyl, aryl, heteroaryl, C_{1-6}alkylenearyl, and SO_2C_{1-6}alkyl, or two R^4 groups are taken together to form an optionally substituted 3- to 6-membered ring;

R^5 is selected from the group consisting of C_{1-6}alkyl, aryl, heteroaryl, heterocycloalkyl, $N(R^3)_2$, OR^3, halo, N_3, CN, C_{1-6}alkylenearyl, $C_{1-6}alkyleneN(R^3)_2$, $C(O)R^3$, $C(O)OR^3$, $C(O)N(R^3)_2$, $N(R^1)C(O)R^3$, $N(R^1)C(O)OR^3$, CF_3, and



;

R^6 is selected from the group consisting of OR^{11}, -C≡C-R^7, and heteroaryl;

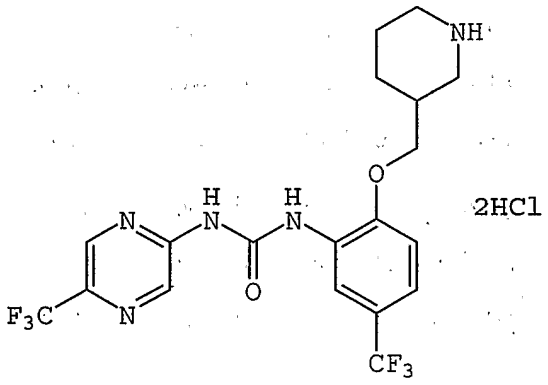
R^7 is selected from the group consisting of hydro, C_{1-6}alkyl, aryl, C_{1-6}alkylenearyl, heteroaryl, C_{1-6}alkyleneheteroaryl, and alkoxy;

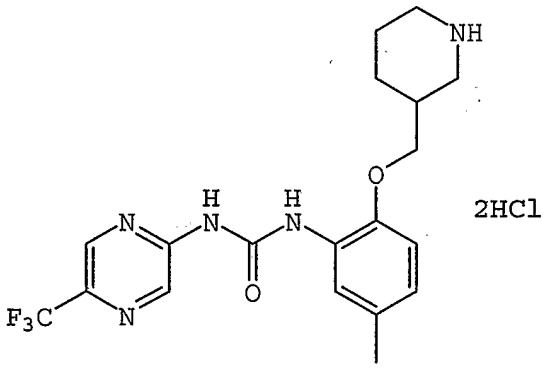
R^8, R^9, and R^{10}, independently, are selected from the group consisting of hydro, halo, optionally substituted C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, OCF_3, CF_3, NO_2, CN, NC, $N(R^3)_2$, OR^3, CO_2R^3, $C(O)N(R^3)_2$, $C(O)R^3$, $N(R^1)COR^3$, $N(R^1)C(O)OR^3$, $N(R^8)C(O)OR^3$, $N(R^1)C(O)C_{1-6}alkyleneC(O)R^3$, $N(R^1)C(O)C_{1-6}alkyleneC(O)OR^3$, $N(R^1)C(O)C_{1-3}alkyleneOR^3$, $N(R^1)C(O)C_{1-6}alkyleneNHC(O)OR^3$, $N(R^1)C(O)C_{1-6}alkyleneSO_2NR^3$, $C_{1-6}alkyleneOR^3$, and SR^3;

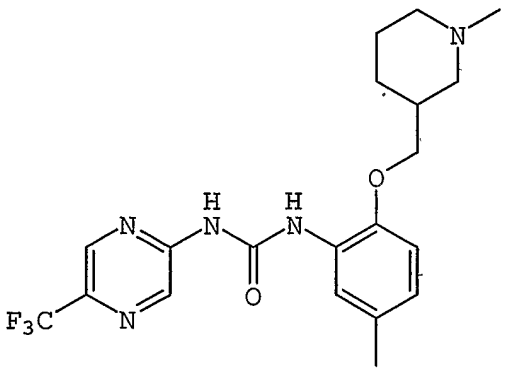
R^{11} is selected from the group consisting of hydro, C_{1-6}alkyl, C_{2-6}alkenyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, SO_2R^4, C_{1-6}alkyl substituted with one or more of halo, hydroxy, aryl, heteroaryl, $N(R^4)_2$, and SO_2R^4, C_{1-6}alkylenearyl, C_{1-6}alkyleneheteroaryl, C_{1-6}alkyleneC_{3-8}heterocycloalkyl, C_{1-6}alkyleneSO_2aryl, optionally substituted C_{1-6}alkylene$N(R^4)_2$, OCF_3, C_{1-6}alkylene-$N(R^4)_3^+$, C_{3-8}heterocycloalkyl, and $CH(C_{1-6}$alkylene$N(R^4)_2)_2$;

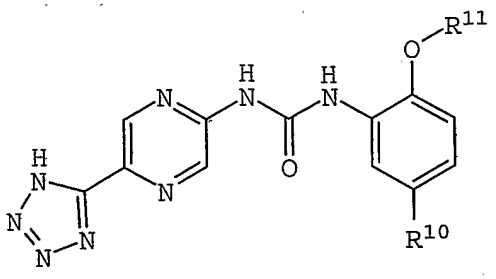
and a pharmaceutically acceptable salt, or prodrug, or solvate thereof.

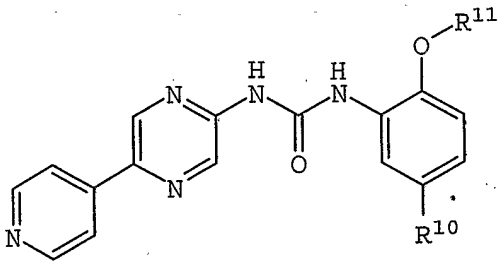
A compound selected from:

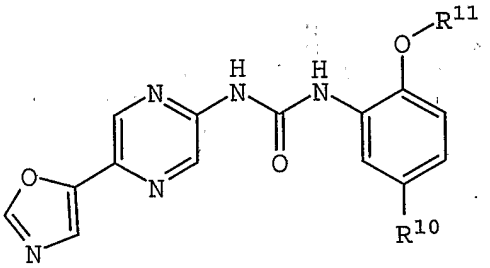


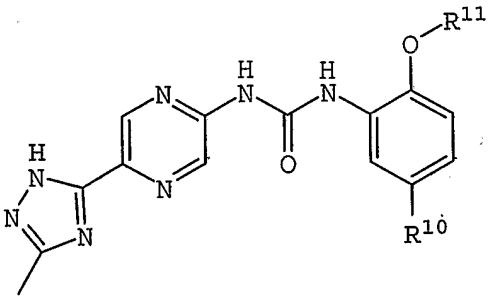


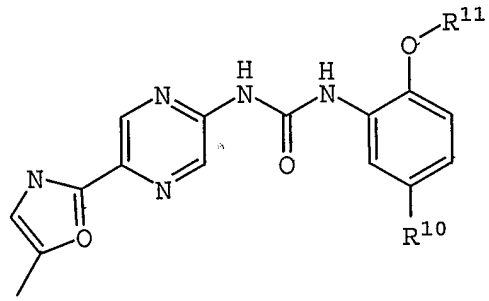












It is possible to compare the selectivity or specificity of a Chk1 inhibitor for Chk1 as against other kinases of interest by way of biochemical (acellular) tests to establish IC50 (defined below) for Chk1, as described elsewhere herein. Thus, selective Chk1 inhibitors may have a lower IC50 for Chk1 inhibition than for inhibition of other kinases of interest.

In certain embodiments, Chk1 inhibitors will not function as a chemotherapy agent when administered alone. A Chk1 inhibitor, in contrast, may act as a chemotherapy agent by virtue of its ability to inhibit additional protein kinases or enzymes that are required for cell growth. This may result in additional cellular effects that lead to side effects and/or a reduced therapeutic index.

In certain embodiments, Chk1 inhibitors useful according to the invention possess at least 20-fold selectivity in inhibiting Chk1 over the following protein kinases: protein kinase A, protein kinase C, cdc2 and pp60v-src. In other embodiments, Chk1 inhibitors as set out above exhibit at least 75-fold selectivity in inhibiting Chk1 over the following protein kinases: protein kinase A, protein kinase C, cdc2 and pp60v-src. In still other embodiments, Chk1 inhibitors set out above preferably demonstrate at least 75-fold selectivity against protein kinase A, protein kinase C, cdc2, pp60v-src and protein kinase B/Akt-1, p38MapK, ERK1, p70S6K, cdc2, cdk2, chk2 and the abl tyrosine kinase. "Fold selectivity" is a ratio of the IC50 of the Chk1 inhibitor for the comparison kinase divided by the IC50 of the Chk1 inhibitor for Chk1.

Active agents (e.g., Chk1 activator and/or Chk1 inhibitor) are employed in amounts effective to achieve their intended purpose. As used herein, a "therapeutically effective amount" or means an amount effective to inhibit development of, or to alleviate the existing symptoms of, the condition of the subject being treated. "Dose-effective to inhibit" means an amount effective to inhibit or prevent the proliferation of a population of aberrantly proliferating cells, *in vivo* or *ex vivo*. Toxicity and therapeutic efficacy of such compounds can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., for determining the LD50 (the dose lethal to 50% of the population) and the ED50 (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index, which is expressed as the ratio of

LD50 to ED50. Compounds that exhibit high therapeutic indices (i.e., a toxic dose that is substantially higher than the effective dose) are preferred.

Inhibition of the checkpoint kinase typically is measured using a dose-response assay in which a sensitive assay system is contacted with a compound of interest over a range of concentrations, including concentrations at which no or minimal effect is observed, through higher concentrations at which partial effect is observed, to saturating concentrations at which a maximum effect is observed. Theoretically, such assays of the dose-response effect of inhibitor compounds can be described as a sigmoidal curve expressing a degree of inhibition as a function of concentration. The curve also theoretically passes through a point at which the concentration is sufficient to reduce activity of the checkpoint enzyme to a level that is 50% that of the difference between minimal and maximal enzyme activity in the assay. This concentration is defined as the Inhibitory Concentration (50%) or IC50 value. Determination of IC50 values preferably is made using conventional biochemical (acellular) assay techniques or cell-based assay techniques such as that illustrated herein.

Comparisons of the efficacy of inhibitors often are provided with reference to comparative IC50 values, wherein a higher IC50 indicates that the test compound is less potent, and a lower IC50 indicates that the compound is more potent, than a reference compound. Chk1 inhibitor compounds demonstrating IC50 values of less than about 1000 nM, or less than about 250 nM, or less than about 100 nM, or less than about 50 nM, or less than about 20 nM, or less than about 1 nM, when measured using the dose-response assay, may be employed according to the invention.

The data obtained in such dose-response assays can be used as a factor in formulating a dosage range for use in humans. The dosage of such compounds preferably lies within a range of circulating concentrations that include the ED50 with little or no toxicity. The dosage can vary within this range depending upon the dosage form, and the route of administration utilized.

The exact formulation, route of administration, and dosage is chosen by the individual physician in view of the patient's condition. Dosage amount and interval can be adjusted individually to provide plasma levels of the active compound

that are sufficient to maintain desired therapeutic effects. In general, however, doses employed for adult human treatment typically are in the range of 0.001 mg/kg to about 1000 mg/kg per day, in a range of about 0.1 mg/kg to about 500 mg/kg per dose.

The present invention may be applied to cell populations *in vivo* or *ex vivo*. "*In vivo*" means within a living subject, as within an animal or human. In this context, the invention may be used therapeutically in a subject to slow or stop the proliferation of aberrantly replicating cells. The invention may also be used as a prophylactic to prevent the occurrence or recurrence of aberrant cell proliferation or the manifestation of symptoms associated therewith. Other *in vivo* uses for which the invention may be therapeutic or preventative are described herein, or will be apparent to those skilled in the art.

"*Ex vivo*" means outside a living subject. Examples of *ex vivo* cell populations include *in vitro* cell cultures and biological samples such as fluid or tissue samples from humans or animals. Such samples may be obtained by methods well known in the art. Exemplary biological fluid samples include blood, cerebrospinal fluid, urine, saliva. Exemplary tissue samples include tumors and biopsies thereof. In this context, the invention may be used for a variety of purposes, including therapeutic and experimental. For example, the invention may be used *ex vivo* to determine the optimal schedule and/or dosing of administration of a Chk1 activator and Chk1 inhibitor for a given indication, cell type, patient, and other parameter. Information gleaned from such use may be used for experimental purposes or in the clinic to set protocol for *in vivo* treatment. Other *ex vivo* uses for which the invention may be suited are described below or will become apparent to those skilled in the art.

Chk1 activators useful in the invention increase the percentage of cells in their target phase of the somatic cell cycle (defined below). By way of background, cells in the somatic cell cycle typically cycle asynchronously. They are a dynamic population comprising cells in various phases of the cell cycle. The percentage of cells at any given phase in the cell cycle depends upon various factors, including, for example, cell type, environment, and cycle rate. Chk1 activators shift these proportions, increasing the percentage of cells in the target phase for the activator. This shift in percentage may be referred to herein as "synchronization," "arrest," or "piling up" in the target phase.

As indicated above, the "target phase" of a cell cycle means the phase at which a Chk1 activator will cause a percentage of cells to increase. Different Chk1 activators may have different target phases. For example, ionizing radiation has been shown to increase the percentage of certain cells at the G2 phase. Thus, the G2 phase may be referred to herein as the target phase for ionizing radiation for at least some cell types. The chemotherapeutic agents taxol and nocodazole have been shown to each increase the percentage of cells at the M phase. Thus, the M phase may be referred to as the target phase for taxol or nocodazole. Gemcitabine and low levels of camptothecin will each increase the percentage of cells at the S phase. Thus, the S phase may be referred to as the target phase for each of these chemotherapeutic agents. Any Chk1 activator having any target phase may be used in the present invention.

The proportion of cells in different phases of the cell cycle can be measured by those skilled in the art using any one of a variety of techniques. For example, a fluorescent DNA-binding dye, propidium iodide, can be used to distinguish cells in different cell cycle phases. Since cells in G2 have twice as much DNA as cells in G1, and S phase cells show an intermediate amount of DNA, the technique allows one to identify cells in different phases based on the DNA content of a cell. This method can be carried out on cell lines and tumor specimens (Cerra et al., *Methods in Cell Biology, 33*:1-12, 1990) Furthermore, cells in S phase can be labeled with the nucleotide analog, bromo-deoxyuridine (BrdU) and then fixed and stained with an fluorescent-tagged antibody to BrdU. Both of these methods employ fluorescence cytometry or fluorescence activity cell sorting (FACS) to quantify the proportion of cells staining with these fluorescent markers.

An additional method for identification of cells in different phases of the cell cycle includes staining the cells with antibodies to markers that are either specific or selective for cell cycle phases. An antibody to the phosphorylated serine 10 residue of histone H3 is highly selective for mitotic cells. An antibody to phosphorylated serine 795 of the retinoblastoma protein, Rb, is selective for S phase cells (Connell-Crowley et al., *Mol. Biol. Cell, 8*:287-301, 1997). Staining of cells with these antibodies can be used to quantify the proportion of cells in these cell cycle phases by immuno-histochemistry or western blot analysis.

Another method for identification of cells in different phases of the cell cycle includes radioisotope labeling. For example, the ability of gemcitabine to arrest tumor cells in S phase may be assessed in multiple tumor types. Gandhi *et al* (*J. Clin. Ocol., 20*:665-73, 2002) discloses a method for assessing S phase arrest in acute myelogenous leukemia patients after treatment with gemcitabine. Patients received gemcitabine at a constant dose of 10/mg/m^2/min for various durations of time and tumor cells isolated from blood of patients 24 hours after the start of therapy to determine the number of cells in S phase arrest. Cells may be plated in triplicate (2 x 10^6) in RPMI-1640/10% Fetal bovine serum and 1 μCi of [^{3}H]thymidine. Cells may then be allowed to incubate for 30 minutes, after which time thymidine incorporation may be measured. A decrease in radioisotope uptake after treatment with Chk1 activator indicates whether the cells are arrested in S phase, and the duration of the S phase arrest.

The first of the foregoing techniques was used to illustrate the influence of camptothecin, a well known chemotherapeutic agent that, in low doses, activates Chk1 at the S-phase, as shown in Table 2.

TABLE 2

HT29 Cells:	G1 (%)	S (%)	G2/M* (%)
In the absence of Chk1 activator (asynchronous)	34.2	45.7	14.5
After low-level camptothecin treatment	6.75	80.86	7

*Combined total in G2+M phase.

Two cell samples, each containing the same human carcinoma cell line (HT29) were prepared. Using propidium iodide (PI) to monitor DNA content, the percentage of cells the G1, S, and G2/M phases of the cell cycle were measured before and after contact with low levels of camptothecin. (Because PI staining indicates total DNA content, this technique does not distinguish between cells in G2 vs. M phase. Accordingly, data reported in the G2/M column of Table 1 shows the total percentage of cells of the population in G2+M-phases.) The first sample was measured to establish the percentage of cells present in each phase asynchronous cell cycling, i.e., in the absence of Chk1 activator. Specifically, in the absence of Chk1 activator, 34.2% of the cells in the sample were in the G1 phase; 45.7% of the cells were in S phase; and 14.5% of the cells were in G2/M phase. The second sample was

contacted with low levels of camptothecin (20 nM for 24 hours). At low levels, the target phase of camptothecin is S phase. As Table 1 shows, camptochecin increased the percentage of cells in S phase from 45.7% to more than 80%, and decreased the percentage of cells in the other phases.

In the present invention, Chk1 activator is contacted with the cell population in an amount and for a time sufficient to substantially synchronize cell cycle arrest at the target phase for the Chk1 activator used, prior to contacting the population with Chk1 inhibitor. Preferably, the cell population undergoes optimal synchronization prior to contact with Chk1 inhibitor. For optimal synchronization, a maximum percentage of cells in the population to are allowed to "pile up" or arrest in the target phase for the activator used, with a minimum percentage having progressed into mitosis. However, those skilled in the art will appreciate that lesser degrees of cell cycle synchronization prior to contact with the Chk1 inhibitor will provide some benefit. Thus, "substantial synchronization" includes any degree of synchronization of cell cycle arrest, including optimal, that results in a cytotoxic effect greater than that seen without use of Chk1 inhibitor, or greater than that seen with co-administration of Chk1 activator and inhibitor, or greater than that seen when the cells are contacted with Chk1 inhibitor prior to Chk1 activator. The degree of cell cycle arrest corresponding to or exceeding these references qualifies as "substantial synchronization" and is considered within the scope of this invention.

Treatment with a Chk1 inhibitor according to the invention may follow at least about a 10% increase in the number of aberrantly proliferating cells in the target phase of the Chk1 activator used; optionally at least about 20%, at least about 50%, at least about 100%; at least about 150%; at least about 200%; at least about 250%; at least about 300%; at least about 350%; at least about 400% increase, at least about 450%, or at least about 500%, as compared to the number of aberrantly proliferating cells present in such phase in the absence of a Chk1 activator. These ranges are merely exemplary, however, and are dependent upon cell type, the particular Chk1 activator used, and other factors readily discernable to those skilled in the art. For example, the skilled artisan will appreciate that the maximum percent increase for any particular cell sample population of aberrantly proliferating cells will be limited by various factors, including percentage of cells present in the target phase of the population prior to Chk1 activator contact.

As indicated above, upon achieving substantial synchronization of cell cycle arrest in the cell population, the present invention calls for contacting the cell population with a Chk1 inhibitor in an amount and for a time sufficient to substantially abrogate the cell cycle arrest. The term "substantially abrogate" is used to indicate that complete abrogation of all arrested cells may not be necessary for efficacy. Those skilled in the art will appreciate that a sufficient degree of cell cycle checkpoint abrogation may be achieved to disrupt cell cycle checkpoint mechanisms and allow cells to pass to a subsequent phase in the cell cycle with unrepaired DNA damage sufficient to cause cell death or otherwise slow or stop aberrant cell proliferation.

Those skilled in the art will appreciate how to convert information concerning cell cycle synchronization and abrogation to practical use in the clinic or laboratory. For example, for any given cell line, Chk1 activator, and Chk1 inhibitor, the dose and time to achieve substantial cell cycle synchronization and substantial abrogation, respectively, may be measured *ex vivo*. *Ex vivo* measurements may then be applied to the clinic as a practical surrogate for direct measurement of the percentage of cells in various phases of the cell cycle.

In determining such measurements, those skilled in the art will appreciate that the duration of Chk1 activator contact with the cell population may, as indicated above, be influenced by the cell type exhibiting unwanted cell proliferation. Like most cells, aberrantly proliferating cells do not cycle at a universal rate. Some types proliferate faster than others, *i.e.*, have a faster doubling time. Thus, for example, treatment of a tumor cell type with a fast doubling time (e.g., pancreatic cancer or melanoma) may require shorter treatment with Chk1 activator to substantially synchronize cell cycle arrest, while treatment of a tumor with a slower doubling time (e.g., some colon, breast or prostate tumors) would require longer contact with Chk1 activator, all other things being equal, to induce substantially synchronous cell cycle arrest.

Times effective to allow substantial cell cycle synchronization by the Chk1 activator may vary from a few minutes up to 96 hours or more. In some embodiments, it may be preferable or desirable to administer Chk1 activator for up to several weeks or more, as determined by the attending physician or technician. Thus, Chk1 activator may contact the cell population for up to about 30 minutes, up to about

1 hour, up to about 2 hours, up to about 3 hours, up to about 4 hours, up to about 6 hours, up to about 12 hours, up to about 18 hours, up to about 24 hours, up to about 48 hours, up to about 72 hours or up to about 96 hours or more. Those skilled in the art will appreciate that the ranges of time expressed herein are merely exemplary; ranges and sub-ranges within those expressed are also within the scope of the invention.

Contact of the cell population with the Chk1 activator may occur in single doses or over a plurality of doses, according to methods well known in the art for the particular Chk1 activator or activators used. For example, the Chk1 activator may be given at a frequency of: 4 doses delivered as one dose per day at 4-day intervals (q4d x 4); 4 doses delivered as one dose per day at 3-day intervals (q3d x 4); 1 dose delivered per day at 5-day intervals (qd x 5); one dose per week for 3 weeks (qwk3); 5 daily doses, with two days rest, and another 5 daily doses (5/2/5); or, any dose regimen determined to be appropriate for circumstance. Some time may optionally be allowed to lapse between the last dose of Chk1 activator to achieve substantial synchronization of cell cycle arrest prior to contact with the first dose of Chk1 inhibitor as necessary. Similar regimens may be used when Chk1 activator is chemotherapeutic or radiotherapeutic. Additional radiotherapeutic doses are well known to those of ordinary skill in the art.

Contact of the cell population with the Chk1 inhibitor may likewise occur at any dose and time sufficient to achieve substantial abrogation of the cell cycle checkpoint. Typically, though not necessarily, such times include up to about 72 to about 96 hours, depending upon various factors such as those discussed above. In some embodiments, it may be desirable or necessary to administer Chk1 inhibitor over a period of up to about several weeks or more, as determined by the attending physician or technician. Thus, Chk1 inhibitor may typically be administered for up to about 1 hour, up to about 2 hours, up to about 3 hours, up to about 4 hours, up to about 6 hours, up to about 12 hours, up to about 18 hours, up to about 24 hours, up to about 48 hours, or up to about 72 hours. Those skilled in the art will appreciate that the ranges of time expressed herein are merely exemplary; ranges and sub-ranges within those expressed are also within the scope of the invention.

The Chk1 inhibitor may be administered over a plurality of doses. For example, the Chk1 inhibitor may be given at a frequency of: 4 doses delivered as one

dose per day at 4-day intervals (q4d x 4); 4 doses delivered as one dose per day at 3-day intervals (q3d x 4); 1 dose delivered per day at 5-day intervals (qd x 5); one dose per week for 3 weeks (qwk3); 5 daily doses, with two days rest, and another 5 daily doses (5/2/5); or, any dose regimen pre-determined to be appropriate for the circumstance.

Use of the invention is indicated in treatment of any condition involving aberrant cell proliferation, including cancerous and non-cancerous cell proliferation. In one aspect, treatment may be of any condition responsive to agents that activate cell cycle arrest or are responsive to inhibitors of cell cycle checkpoint proteins.

Cancers include tumors or neoplasms derived from growths of tissue cells wherein multiplication of cells is uncontrolled and progressive. Some such neoplasms are benign, but others are termed "malignant," and can lead to death of the organism. Malignant neoplasms are distinguished from benign growths in that, in addition to exhibiting aggressive cellular proliferation, the malignant neoplasms can invade surrounding tissues and metastasize. Moreover, malignant neoplasms are characterized by showing a greater loss of differentiation (greater "dedifferentiation") and organization relative to one another and surrounding tissues. (This property is called "anaplasia")

Cancers treatable by the present invention include solid tumors such as carcinomas and sarcomas. Carcinomas derive from epithelial cells which infiltrate (i.e., invade) surrounding tissues and give rise to metastases. Adenocarcinomas are carcinomas derived from glandular tissue, or from tissues that form recognizable glandular structures. Sarcomas are tumors whose cells are embedded in a fibrillar or homogeneous substance, like embryonic connective tissue. The invention also enables treatment of cancers of the myeloid or lymphoid systems, including leukemias, lymphomas, and other cancers that typically are not present as a tumor mass, but are distributed in the vascular or lymphoreticular systems.

Further contemplated are cancers including, but not limited to, myxoid and round cell carcinomas, human soft tissue sarcomas including Ewing's sarcoma, cancer metastases including lymphatic metastases, squamous cell carcinomas particularly of the head and neck, esophageal squamous cell carcinomas, oral

carcinomas, blood cell malignancies, including multiple myelomas, leukemias, including acute lymphocytic leukemias, acute nonlymphocytic leukemias, chronic lymphocytic leukemias, chronic myelocytic leukemias, and hairy cell leukemias, effusion lymphomas (body cavity based lymphomas), thymic lymphoma lung cancers (including small cell carcinomas of the lungs, cutaneous T cell lymphomas, Hodgkin's lymphomas, non-Hodgkin's lymphomas, cancers of the adrenal cortex, ACTH-producing tumors, non-small cell lung cancers, breast cancers, including small cell carcinomas and ductal carcinomas), gastro-intestinal cancers (including stomach cancers, colon cancers, colorectal cancers, and polyps associated with colorectal neoplasias), pancreatic cancers, liver cancers, urological cancers (including bladder cancers, such as primary superficial bladder tumors, invasive transitional cell carcinomas of the bladder, and muscle-invasive bladder cancers), prostate cancers, malignancies of the female genital tract (including ovarian carcinomas, primary peritoneal epithelial neoplasms, cervical carcinomas, uterine endometrial cancers, vaginal cancers, cancers of the vulva, uterine cancers and solid tumors in the ovarian follicle), malignancies of the male genital tract (including testicular cancers and penile cancers), kidney cancers (including renal cell carcinomas), brain cancers (including intrinsic brain tumors, neuroblastomas, astrocytomas, gliomas, and metastatic tumor cell invasions in the central nervous system), bone cancers (including osteomas and osteosarcomas), skin cancers (including malignant melanomas, tumor progressions of human skin keratinocytes, basal cell carcinomas, and squamous cell cancers), thyroid cancers, retinoblastomas, peritoneal effusions, malignant pleural effusions, mesotheliomas, Wilms's tumors, gall bladder cancers, trophoblastic neo-plasms, hemangiopericytomas, and Kaposi's sarcomas.

As non-limiting examples, the method according to the invention may be adapted to the following uses of Chk1 activators (alone or in combination with other active agents):

Gemcitabine for the treatment of proliferative disorders including pancreatic cancer (e.g., locally advanced (nonresectable state II or stage III) or metastatic (stage IV) adenocarcinoma of the pancreas); gemcitabine for the first-line treatment and for patients previously treated with a 5-FU-contianing regimine; gemcitabine in combination with platinum coordination complexes (e.g., cisplatin) for

the treatment non-small cell lung cancer (e.g., inoperable, locally advanced (stage IIIA or IIIIB) or metastatic (stage IV) non-small cell lung cancer);

Pemetrexed for the treatment of proliferative disorders including non-small lung cell carcinomas, solid tumors, malignant mesothelioma, urothelium, cervical cancer, recurrent endometrial cancer, peritoneal cancer, pleural mesothelioma, gall bladder cancer, breast cancer, and colorectal cancer;

Topotecan for the treatment of proliferative disorders including meningeal cancers, cervical cancer, ovarian cancer, epithelial cancer, esophageal cancer, fallopian tube cancer, primary peritoneal cancer, small cell lung cell cancer, prostate cancer, neuroblastomas, gliomas, solid tumors, acute myeloid leukemia, chromic myelogenous leukemia, advanced meylodysplastic syndromes, and rhabdomyosarcoma;

Irinotecan for the treatment of proliferative disorders including colorectal cancer, glioblastoma multiforme, solid tumors, breast cancer, penile cancer, liver cancer, metastatic gastric carcinoma, gastroesophageal junction adenocarcinoma, small bowel adenocarcinoma, rhabdomyosarcoma, urothelium cancer, stomach cancer, bladder cancer, kidney cancer, small cell lung cancer, pancreatic cancer, head and neck cancer, glioma, sarcoma, metastatic carcinoma of the colon or rectum;

Chlorambucil for the treatment of proliferative disorders including chronic lymphocytic leukemia, Hodgkin's lymphoma; non-Hodgkin's lymphoma, follicular lymphoma, chronic lymphocytic cancer;

Platinum coordination complexes, e.g., cisplatin, for the treatment of proliferative disorders including testicular cancer, ovarian cancer, bladder cancer, head and neck cancer, esophageal cancer, small cell and non-small cell lung cancer, non-Hodgkin's lymphoma, trophoblastic neoplasms; adrenal cortical cancer, anal cancer, bile duct cancer, bladder cancer, bone cancer, cervical cancer, endometrial cancer, gall bladder cancer, gastrointestinal carcinoid tumors, laryngeal cancer, hypopharyngeal cancer, liver cancer, lung cancer, small cell lung cancer, malignant mesothelioma, nasal cavity cancer, paranasal cancer, nasopharyngeal cancer, neuroblastoma, oral cavity cancer, oropharyngeal cancer, osteosarcoma, ovarian cancer, germ cell tumors of the ovary, pancreatic cancer, penile cancer,

retinoblastoma, salivary gland cancer sarcoma, melanoma, stomach cancer, testicular cancer, thymus cancer, uterine sarcoma, vulvar cancer;

Carboplatin for the treatment of proliferative disorders including ovarian cancer, germ cell tumors, head and neck cancer, small cell and non-small cell lung cancer, bladder cancer, relapsed and refractory acute leukemia, endometrial cancer;

Camptothecin for the treatment of proliferative disorders including stomach cancer, gastroesophageal junction cancer, soft tissue sarcoma, malignant glioma;

Etoposide for the treatment of proliferative disorders including small cell and other lung cancers, gastric cancer, germ cell tumors, adrenal cortical cancer, bone cancer, gastrointestinal carcinoid tumors, gestational trophoblastic disease, Hodgkin's disease, acute lumphocytic cancer, childhood leukemia, small cell lung cancer, lung carcinoid tumor, neuroblastoma, osteosarcoma, ovarian cancer, germ cell tumors of the ovary, prostate cancer, retinoblastoma, stomach cancer, testicular cancer, Wilm's Tumor;

Ara-C for the treatment of proliferative disorders including acute myeloid leukemia, high-risk meylodysplastic syndrome, CML, lymphoma, solid tumor, chronic lymphocytic leukemia, acute lymphocytic leukemia, acute non-lymphocytic leukemia, chronic myelocytic leukemia, precursor T-lymphoblastic lymphoma/leukemia, Burkitt lumphoma;

Aphidocolin for *ex vivo* studies of proliferative disorders including breast cancer and acute myeloid leukemia;

Fludarabine for the treatment of proliferative disorders including chronic lymphocytic leukemia, follicular lymphoma, metastatic melanoma, renal cell carcinoma, acute myeloid leukemia, acute lymphoblastic leukemia, non-Hodkin's lymphoma, breast cancer, hairy cell leukemia, multiple myeloma, cervical cancer, vaginal cancer, leukemia, childhood leukemia, chronic granulomatous disease, mastocytosis, kidney cancer, urinary tract cancer, skin tumors, bladder cancer, basal cell carcinoma, adrenal carcinoma, esophageal and gastric cancer, hepatocellular cancer, ovarian cancer, B-cell leukemia, chronic lymphcytic leukemia, follicular lymphoma; and

Methotrexate for the treatment of proliferative disorders including gestational choriocarcinoma, chorioadenoma, destruens and hydatidiform moles, acute lymphocytic leukemia, meningeal leukemia, breast cancer, epidermoid cancers of the head and neck, advanced mycosis fungoides (cutaneous T-cell lymphoma), lung cancer (especially squamous cell and small cell types), non-Hodgkin's lymphomas; bladder cancer, bone cancer, breast cancer, esophageal cancer, gestational trophoblastic disease, laryngeal and hypopharyngeal cancer, acute lymphocytic leukemia, acute myeloid leukemia, small cell lung cancer, Burkitt's lymphoma, precursor T-lymphoblastic mesothelioma, nasal cavity and paranasal cancer, nasopharyngeal cancer, oral cavity and oropharyngeal cancer, osteosarcoma, penile cancer, salivary gland cancer, and stomach cancer.

The invention may also be used to treat conditions involving non-cancerous aberrantly proliferating cells. Such conditions include, but are not limited to, atherosclerosis, restenosis, vasculitis, nephritis, retinopathy, renal disease, proliferative skin disorders, psoriasis, keloid scarring, actinic keratosis, Stevens-Johnson Syndrome, rheumatoid arthritis (RA), systemic-onset juvenile chronic arthritis (JCA), osteoporosis, systemic lupus (SLE) erythmatosus, hyperproliferative diseases of the eye including epithelial down growth; proliferative vitreoretinopathy (PVR); diabetic retropathy, hemangio-proliferative diseases, ichthyosis, or papillomas.

Non-cancerous conditions treatable by the present invention may also include a variety of inflammation and inflammatory diseases, conditions, or disorders. Examples of such indications include, but are not limited to, rheumatoid arthritis, psoriasis, vitiligo, Wegener's granulomatosis, and SLE. Treatment of arthritis, Wegener's granulomatosis, and SLE often involves the use of immunosuppressive therapies, such as ionizing radiation, methotrexate, and cyclophosphamide. Psoriasis and vitiligo commonly are treated with ultraviolet radiation (UV) in combination with a psoralen. Such treatments typically induce, either directly or indirectly, DNA damage. Inhibition of Chk1 activity within the offending immune cells renders the cells more sensitive to control by these standard treatments. In general, Chk1 inhibitors useful in the invention may optionally be used to potentiate control of inflammatory disease cells when administered in combination with immunosuppressive drugs.

Animal models of some of the foregoing cancerous and non-cancerous conditions treatable by the present invention include for example: athymic nude mice injected with viable cancer cells from the HL60 cell line (human non-small cell lung cancer), athymic nude mice injected with Panc-01 human tumor cells (human pancreatic cancer), athymic nude mice injected with A375 human tumor cells (human melanoma), athymic nude mice injected with SKMES lung cancer cells (human lung cancer), athymic nude mice injected with SKOV-3.ip. ovarian carcinoma cells (human ovarian cancer), athymic nude mice injected with MDA-MB-361 breast cancer cells (human breast cancer), rats injected with 137-62 cells (breast cancer), and c56BL/Ka mice (cpdm/cpdm) (human psoriasis) (Gijbels et al., Exp. Dermatol., 9:351-358 (2000).

Chk1 inhibitors of the invention are contemplated for use in a composition comprising Chk1 inhibitors in a pharmaceutically acceptable diluent or carrier. In one aspect, the pharmaceutical composition comprises Chk1 inhibitors as set out above.

Formulations of the present invention can be administered in a standard manner for the treatment of the indicated diseases, such as orally, parenterally, transmucosally (e.g., sublingually or buccally), topically, transdermally, rectally, via inhalation (e.g., nasal or deep lung inhalation). Parenteral administration includes, but is not limited to intravenous, intra-arterial, intraperitoneal, subcutaneous, intramuscular, intrathecal and intra-articular. Parenteral administration also can be accomplished using a high pressure technique, like POWDERJECT™.

For oral administration, or for buccal administration, the composition can be in the form of tablets or lozenges formulated in conventional manner. For example, tablets and capsules for oral administration can contain conventional excipients such as binding agents (for example, syrup, acacia, gelatin, sorbitol, tragacanth, mucilage of starch, or polyvinylpyrrolidone), fillers (for example, lactose, sugar, microcrystalline cellulose, maize-starch, calcium phosphate, or sorbitol), lubricants (for example, magnesium stearate, stearic acid, talc, polyethylene glycol or silica), disintegrants (for example, potato starch or sodium starch glycolate), or wetting agents (for example, sodium lauryl sulfate). The tablets can be coated according to methods well known in the art.

Alternatively, the compounds of the present invention can be incorporated into oral liquid preparations such as aqueous or oily suspensions, solutions, emulsions, syrups, or elixirs, for example. Moreover, formulations containing these compounds can be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations can contain conventional additives, for example suspending agents, such as sorbitol syrup, methyl cellulose, glucose/sugar syrup, gelatin, hydroxyethylcellulose, hydroxypropylmethylcellulose, carboxymethylcellulose, aluminum stearate gel, and hydrogenated edible fats; emulsifying agents, such as lecithin, sorbitan monooleate, or acacia; nonaqueous vehicles (which can include edible oils), such as almond oil, fractionated coconut oil, oily esters, propylene glycol, and ethyl alcohol; and preservatives, such as methyl or propyl p-hydroxybenzoate and sorbic acid.

Such preparations also can be formulated as suppositories, e.g., containing conventional suppository bases, such as cocoa butter or other glycerides. Compositions for inhalation typically can be provided in the form of a solution, suspension, or emulsion that can be administered as a dry powder or in the form of an aerosol using a conventional propellant, such as dichlorodifluoromethane or trichlorofluoromethane. Typical topical and transdermal formulations comprise conventional aqueous or nonaqueous vehicles, such as eye drops, creams, ointments, lotions, and pastes, or are in the form of a medicated plaster, patch, or membrane.

Additionally, compositions of the present invention can be formulated for parenteral administration by injection or continuous infusion. Formulations for injection can be in the form of suspensions, solutions, or emulsions in oily or aqueous vehicles, and can contain formulation agents, such as suspending, stabilizing, and/or dispersing agents. Alternatively, the active ingredient can be in powder form for constitution with a suitable vehicle (e.g., sterile, pyrogen-free water) before use.

A composition in accordance with the present invention also can be formulated as a depot preparation. Such long acting formulations can be administered by implantation (for example, subcutaneously or intramuscularly) or by intramuscular injection. Accordingly, the compounds of the invention can be formulated with suitable polymeric or hydrophobic materials (e.g., an emulsion in an acceptable oil), ion exchange resins, or as sparingly soluble derivatives (e.g., a sparingly soluble salt).

The compounds useful according to the invention may be conjugated or linked to auxiliary moieties that promote any property of the compounds that may be beneficial in methods of therapeutic use. Such conjugates can enhance delivery of the compounds to a particular anatomical site or region of interest (e.g., a tumor), enable sustained therapeutic concentrations of the compounds in target cells, alter pharmacokinetic and pharmacodynamic properties of the compounds, and/or improve the therapeutic index or safety profile of the com-pounds. Suitable auxiliary moieties include, for example, amino acids, oligopeptides, or polypeptides, e.g., antibodies such as monoclonal anti-bodies and other engineered antibodies; and natural or synthetic ligands to receptors in target cells or tissues. Other suitable auxiliaries include fatty acid or lipid moieties, to promote biodistribution or uptake of the compound by target cells (see, e.g., Bradley et al., Clin. Cancer Res. (2001) 7:3229.

It is further contemplated that the method of the invention comprises administration of at least one agent to reduce side effects resulting from treatment of the subject. In one aspect, the side-effect reducing agent comprises at least one growth factor. In a related aspect, the side-effect reducing agent comprises at least one cytokine, at least one lymphokine, or at least one hematopoetic factor. Growth factors, cytokines, and hematopoetic factors useful in the methods of the invention include, but are not limited to, M-CSF, GM-CSF, TNF, IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-14, IL-15, IL-16, IL-17, IL-18, IFN, TNF, G-CSF, Meg-CSF, GM-CSF, thrombopoietin, stem cell factor, erythropoietin, angiopoietins, including Ang-1, Ang-2, Ang-4, Ang-Y, and/or the human angiopoietin-like polypeptide, vascular endothelial growth factor (VEGF), angiogenin, bone morphogenic protein-1 (BMP-1), BMP-2, BMP-3, BMP-4, BMP-5, BMP-6, BMP-7, BMP-8, BMP-9, BMP-10, BMP-11, BMP-12, BMP-13, BMP-14, BMP-15, BMP receptor IA, BMP receptor IB, brain derived neurotrophic factor, ciliary neutrophic factor, ciliary neutrophic factor receptor cytokine-induced neutrophil chemotactic factor 1, cytokine-induced neutrophil chemotactic factor 2, cytokine-induced neutrophil chemotactic factor 2, endothelial cell growth factor, endothelin 1, epidermal growth factor, epithelial-derived neutrophil attractant, fibroblast growth factor (FGF) 4, FGF 5, FGF 6, FGF 7, FGF 8, FGF 8b, FGF 8c, FGF 9, FGF 10, FGF acidic, FGF basic, glial cell line-derived neutrophic factor receptor 1, glial cell line-derived neutrophic factor receptor 2, growth related protein,

growth related protein, growth related protein, growth related protein, heparin binding epidermal growth factor, hepatocyte growth factor, hepatocyte growth factor receptor, insulin-like growth factor I, insulin-like growth factor receptor, insulin-like growth factor II, insulin-like growth factor binding protein, keratinocyte growth factor, leukemia inhibitory factor, leukemia inhibitory factor receptor, nerve growth factor nerve growth factor receptor, neurotrophin-3, neurotrophin-4, placenta growth factor, placenta growth factor 2, platelet-derived endothelial cell growth factor, platelet derived growth factor, platelet derived growth factor A chain, platelet derived growth factor AA, platelet derived growth factor AB, platelet derived growth factor B chain, platelet derived growth factor BB, platelet derived growth factor receptor, platelet derived growth factor receptor, pre-B cell growth stimulating factor, stem cell factor, stem cell factor receptor, transforming growth factor (TGF), TGF, TGF 1, TGF 1.2, TGF 2, TGF 3, TGF 5, latent TGF 1, TGF, binding protein I, TGF binding protein II, TGF binding protein III, tumor necrosis factor receptor type I, tumor necrosis factor receptor type II, urokinase-type plasminogen activator receptor, vascular endothelial growth factor, and chimeric proteins and biologically or immunologically active fragments thereof.

EXAMPLES

The following examples illustrate various non-limiting embodiments of the invention and/or provide support therefore. Example 1 compares the present invention to co-administration of Chk1 activator and Chk1 inhibitor in an art-recognized in vitro model. Example 2 provides a similar comparison using a mitotic index assay. Example 3 compares the present invention to co-administration of Chk1 activator and Chk1 inhibitor in an animal tumor model. Example 4 describes a sensitive assay that may be used to measure Chk1 inhibitor activity in animal models. Example 5 demonstrates that selective Chk1 inhibitors are capable of abrogating DNA damage-induced G2 and S phase checkpoints. Example 6 demonstrates that Chk1 inhibitor is taken up by tumor cells in the presence of Chk1 activator in an art recognized xenograft tumor model. Example 7 describes the use of the previously exemplified assay to determine the effect of Chk1 inhibitors on cell cycle arrest. This assay is again used in Example 8 to provide an example of the determination of the optimal dose and time of Chk1 activator required to achieve selective cell cycle synchronization. Example 9 describes an assessment of the optimal contact time of a

population of aberrantly proliferating cells with a Chk1 inhibitor to achieve substantial abrogation of cell cycle arrest. Example 10 describes an assessment of a dose response relationship between Chk1 inhibitor and abrogation of cell cycle arrest. Example 11 describes an assessment of optimal dose of Chk1 inhibitor for use in an embodiment of the invention. Example 12 describes an assay that may be used to determine whether an agent is a Chk1 activator. Example 13 describes an assay that may be used to monitor Chk1 activity in response to a Chk1 inhibitor.

EXAMPLE 1

Contacting Aberrantly Proliferating Cells With Chk1 Inhibitor After Substantial Cell Cycle Synchronization By Chk1 Activator Showed Better Anti-Proliferative Activity Than Co-Administration In A Non-Small Cell Lung Cancer Cancer Animal Model

A method of the invention provided an improved antiproliferative effect over co-administration in an art-recognized in vitro tumor model. In the experiment, gemcitabine was used as the Chk1 activator and a diaryl urea compound according to Keegan et al., PCT/US02/06452, was used as the selective Chk1 inhibitor. (The same Chk1 inhibitor was used in the examples 2-11.) The target phase of gemcitabine is the S phase of the cell cycle. A non-small cell lung tumor xenograft tumor model, H460, was the art-recognized in vitro tumor model.

Nude mice were engrafted with H460 tumor cells and allowed to grow to an average of 75 mm3. Tumor-bearing mice were then treated with vehicle, gemcitabine or gemcitabine plus 400 mg/kg selective Chk1 inhibitor. The gemcitabine was administered at a dose of 160 mg/kg q3d x3 either simultaneously with the Chk1 inhibitor (co-administration) or, according to the invention, 18 hours prior to the Chk1 inhibitor to allow for S phase synchronization.

Tumors were measured every 2-3 days. On day 10, the median tumor volume for the vehicle group was 10 times the starting volume, while the gemcitabine alone group was four times the starting volume. The tumor volume for the gemcitabine plus Chk1 inhibitor co-administration group was also four times the starting volume. The tumor volume for the gemcitabine followed by Chk1 inhibitor group was only 1.1 times the starting volume. This experiment demonstrates that pretreatment with gemcitabine in an amount and for a time sufficient to substantially

synchronize the tumor cells prior to checkpoint release by the Chk1 inhibitor leads to greater anti-tumor activity than co-administration of the two agents together.

EXAMPLE 2

Contacting Aberrantly Proliferating Cells With Chk1 Inhibitor After Substantial Cell Cycle Synchronization By Chk1 Activator Reduced Required Exposure Time To Chk1 Inhibitors In A Mitotic Index Assay

Chk1 inhibitors were tested in a cell-based proliferation assay for the ability to sensitize tumor cells to ionizing radiation or chemotherapy agents. Chk1 inhibitors were tested in combination with 5-FU, gemicitabine, ionizing radiation, camptothecin, etoposide, hydroxyurea, cisplatin, fludarabine, Ara-C and aphidicolin. For each experiment, a serial dilution of each compound in combination with a ten-point dilution of each chemotherapy agent was included, in order to determine the concentration of chemotherapeutic required to inhibit the growth of 90% (GI90) of the cells in the presence and absence of the Chk1 inhibitor. This ratio of GI90 in the absence of Chk1 inhibitor to that in the presence of Chk1 inhibitor is called the "fold sensitization." Fold sensitization was plotted as a function of Chk1 inhibitor concentration and the amount of drug required to yield two-fold sensitization was calculated. The fold sensitization of Chk1 inhibitors to these chemotherapy agents is shown below (Table 3). This concentration is referred to as the "ECTFS" or, the Effective Concentration of Inhibitor required for yielding Two-Fold Sensitization. Another parameter analyzed was the fold sensitization achieved at the LD50 (the dose of compound alone that inhibits growth of 50% of cells) for the compound. These two values allow direct ranking of both the potency and toxicity of Chk1 inhibitors with respect to one another.

TABLE 3

CHK1 INHIBITORS SENSITIZE TUMOR CELLS TO CHEMOTHERAPY AGENTS.

Chemotherapy Agent	Fold Sensitization to Agent by Chk1 Inhibitor
Gemcitabine	12
5-FU	12
Ara-C	9
Camptothecin	5
Cisplatin	3
Etoposide	3

The sensitization assay described above was used to assess the ability of the Chk1 inhibitors to promote cell death after contact with a selective Chk1 inhibitor according to an embodiment of the invention. This in vitro assay is believed to correlate to anti-tumor activity of the Chk1 inhibitors in vivo. The sensitization studies indicated that, in the samples tested, if gemcitabine and the Chk1 inhibitor were dosed simultaneously, the exposure time required for a Chk1 inhibitor to yield maximal sensitization (14 fold sensitization) was approximately 24 hours. However, if cells were treated first with gemcitabine for approximately 2 hours and the cells allowed approximately 24 hours to arrest in S phase before treating with the Chk1 inhibitor, as little as 4-6 hours of inhibitor exposure led to maximum sensitization (over 12-fold sensitization). In contrast, simultaneous treatment of gemcitabine and the Chk1 inhibitor for 6 hours resulted in no sensitization in the samples tested. These data suggest that allowing aberrantly proliferating cells to substantially synchronize cell cycle arrest before administering Chk1 inhibitor reduces the required time of exposure to Chk1 inhibitors to result in tumor cell death in combination with a Chk1 activating agent.

EXAMPLE 3

Contacting Aberrantly Proliferating Cells With Chk1 Inhibitor After Substantial Cell Cycle Synchronization By Chk1 Activator Showed Better Anti-Proliferative Activity Than Co-Administration In A Colon Cancer Animal Model

Nude mice were engrafted with HT29 colon carcinoma cells and tumors were grown to 200 mm^3 for 10 days. The HT-29 tumor-bearing mice were

treated with vehicle, 600 mg/kg Chk1 inhibitor (p.o.), 160 mg/kg gemcitabine (i.p.) or the co-administration of gemcitabine and Chk1 inhibitor. Alternatively, mice were pretreated according to the invention with gemcitabine for 24 hours, dosed with Chk1 inhibitor on day 2, and allowed to rest on day 3. The treatment regimen was repeated four times. This dosing strategy combined the MTD dosing for gemcitabine (160 mg/kg q3d x 4, i.e. 4 doses delivered as one dose per day at 3-day intervals) with a gemcitabine pretreatment strategy.

Tumors were measured every 2-3 days until they reached 1200 mg and then the animals were sacrificed. Median tumor growth delay, survival benefit and tumor regressions were measured. The median time for tumors to grow from 200 mm3 to 800 mm3 was 14.5 days longer in the animals treated with gemcitabine then Chk1 inhibitor compared to animals treated with gemcitabine alone. The survival benefit was 15 days greater in mice treated with the combination therapy over gemcitabine alone.

In summary, substantial synchronization of the tumor cells in S-phase by gemcitabine followed by checkpoint release via the Chk1 inhibitor resulted in a significant improvement in the anti-tumor activity. Whereas co-administration resulted in a 4 day growth delay as described in Example 6, pretreatment with gemcitabine according to the invention resulted in a 14.5 day tumor growth delay.

EXAMPLE 4

A Sensitive Assay to Measure Chk1 Inhibitor Activity in Animal Models

The following sensitive assay was developed to measure Chk1 inhibitor activity in rodent tumor models. In particular, the assay may be used, inter alia, to measure the ability of Chk1 inhibitors to block Chk1 function in the tumor model, and to allow for assessment of conditions that facilitate Chk1 inhibitors' access to the molecular target.

The ability of selective Chk1 inhibitors to abrogate a chemotherapy-induced checkpoint was measured using a quantitative immunofluourescent assay that measures mitotic index by monitoring histone H3 phosphorylation on serine 10 (H3-P), a mitosis-specific event (Ajiro et al., J Biol Chem. 271:13197-201. 1996; Goto et al., J Biol Chem.;274:25543-9, 1999). The assay protocol was as follows. Tumors from rodents treated or untreated with Chk1 activator (in the present study,

chemotherapy agent) and/or Chk1 inhibitor, were excised and paraffin embedded. The tumors are cut into 6 micron thick slices and mounted on glass slides. The paraffin was removed from the slides by 3 minute successive treatments with xylene, 100% ethanol, 95% ethanol, 70% ethanol and deionized water. The slides are then heated to 95°C in 10mM sodium citrate for 10 minutes followed by a 20 minute cooling step. The slides are blocked for 30 minutes with Block buffer (20% normal human serum and 2% bovine serum albumin in phosphate buffered saline containing 0.05% Triton X-100 (PBST)). The anti-phospho histone H3 antibody (Upstate Biotech, Cat. #06-570) is diluted 1:200 in the Block buffer and incubated with the slides for one hour. The slides are washed 3 times 5 minutes in PBST. The secondary antibody, donkey anti-rabbit rhodamine (Jackson, cat #711-295-152) was added for 30 minutes. The slides were then washed twice in PBST and 75μM of 0.1μM/ml DAPI (Sigma) in PBS is added and allowed to stain for 30 minutes. The slides were then washed two more times in PBST and mounted with Vectashield (Vector, cat # H-1400). Slides were viewed using fluorescence microscopy. The percentage of cells stained with H3-P antibody relative to total (DAPI stained) cells were quantified using Metamorph software (Universal Imaging Corporation, Version 4.6).

EXAMPLE 5

Selective Chk1 Inhibitors Abrogate DNA Damage-Induced G2 and S Phase Checkpoints

Previous studies have demonstrated that selective Chk1 inhibitors substantially abrogate the DNA damage-induced G2/M and S phase checkpoints. In the former, DNA damage was induced by ionizing radiation (IR), whose target phase is the G2 phase. In the latter, DNA damage was induced by chemotherapeutic agents whose target phase is the S phase. See published U.S. patent application 2003/0069284 and references cited therein.

Briefly, the Chk1 inhibitor abrogation of IR-induced G2 DNA damage checkpoint was assayed by mitotic index experiments. Approximately $1x10^6$ HeLa cells were irradiated with 800 rads and incubated for 7 hours at 37° C. Because these cells are functionally p53 negative, they arrest exclusively in G2. Nocodazole was then added to a concentration of 0.5 μg/mL and incubated for 15 hours at 37° C. (The addition of nocodazole was designed to trap any cells that progressed through

the G2 arrest in mitosis thus preventing them from further progressing into G1 and allowing for quantification of M phase cells.) A selective Chk1 inhibitor was added for 8 hours, and the cells harvested by centrifugation, washed once with PBS, then resuspended in 2.5 mL 75 mM KCl and centrifuged again. The cells then were fixed in 3 mL of freshly prepared cold, acetic acid: methanol (1:3) and incubated on ice for 20 minutes. Cells were pelleted, the fix solution was aspirated and the cells were resuspended in 0.5 mL of PBS. Mitotic spreads were prepared by pipeting 100 µL of the fixed cells onto a glass microscope slide and flooding the sample with 1 ml of fix solution. Slides were then air dried, stained with Wrights stain (Sigma, St. Louis, MO) for 1 minute, followed by one wash in water and one wash in 50% methanol. The presence of condensed chromosomes and lack of nuclear envelope identified mitotic cells. The selective Chk1 inhibitors (diarylurea compounds according to US 2003/0069284) tested resulted in an increase in the number of mitotic cells in the presence of irradiation, thereby demonstrating abrogation of the IR-induced G2 arrest (Figure 1A). This checkpoint abrogation results in an enhancement in the activity of CyclinB/cdc2, which is required for progression of cells into mitosis. Cells treated with IR followed by Chk1 inhibitor thus progress into mitosis with damaged DNA. These experiments confirm the hypothesis that Chk1 is involved in the IR-induced G2

EXAMPLE 5A

Chk1 Inhibitors Abrogate the DNA Damage-Induced G2 Checkpoint

As figure 1 illustrates, Chk1 inhibitors abrogate the DNA damage-induced G2 checkpoint in HeLa cells. Figure 1A illustrates that IR and Chk1 inhibitor treated cells show increased CyclinB/cdc2 kinase activity. Activity is shown as a percent relative to nocodazole (noc)-treated cells. Figure 1B illustrates mitotic index experiments demonstrating that Chk1 inhibitors allow HeLa cells to progress through the irradiation (IR)-induced G2 checkpoint. These data show a dose-dependent effect of the Chk1 inhibitor arrest and that selective inhibitors of Chk1 allow cells to continue cycling in the presence of DNA damage.

EXAMPLE 5B

Chk1 Inhibitors Abrogate the DNA Damage-Induced S-Phase Checkpoint

As illustrated in Figure 2, selective Chk1 inhibitors abrogate the S phase checkpoint induced by Chk1 activators whose target phase is the S-phase:

camptothecin (CPT) (Figure 2A and 2B), Ara-C, gemcitibine, fludarabine and aphidicolin in HT29 colon carcinoma cells (Figure 2C). The S phase abrogation was induced by these agents in a dose-dependent manner and resulted in entry into mitosis despite DNA damage, resulting in cell death. (Microscopic analysis of mitotic cells treated with Chk1 inhibitor suggested that the chromosomes were improperly aligned on the mitotic spindles. Without wishing to be bound by theory, one hypothesis suggests that premature entry into mitosis results in defects in attachment of microtubules to kinetocores, inducing a spindle checkpoint and metaphase arrest, ultimately leading to death caused by mitotic catastrophe.)

Thus, HT29 colon carcinoma cells were treated with 20 nM CPT in the presence and absence of a Chk1 inhibitor. A. Cells were pulse-labeled with BrdU and % BrdU–staining cells quantified. B. HT29 cells were treated with CPT in the presence and absence of a Chk1 inhibitor. Cells were also treated with nocodazole (noc) to trap cells in mitosis. Cells that progressed out of S phase into mitosis were measured by CyclinB/cdc2 kinase activity. C. HT29 cells were treated with 20mM Ara-C, 20 mM fludaribine or 10 mg/mL aphidicolin, each with a Chk1 inhibitor. Mitotic cells were defined as percent cells that stained positive with histone H3 antibodies. The data shows that selective Chk1 inhibitors abrogate the S phase checkpoint induced by Chk1 activators whose target phase is the S phase.

EXAMPLE 6

Chk1 Inhibitor Is Taken Up by Tumor Cells in the Presence of Chk1 Activator in a Xenograft Tumor Model.

In a xenograft tumor model, nude mice were engrafted with HT29 colon carcinoma tumors on the flank and allowed to grow to 200 mm^3. Mice were then treated with either vehicle, 300 mg/kg Chk1 inhibitor, 20 mg/kg gemcitabine or co-administered with 300 mg/kg Chk1 inhibitor and 20 mg/kg gemcitabine two times, three days apart on Days 1 and 4. Treatment of tumor-bearing mice by co-administration of Chk1 inhibitor and gemcitabine resulted in a four-day growth delay in tumors compared to gemcitabine alone.

To assess the diffusion of Chk1 inhibitors into tumor tissue, plasma and tissue levels of Chk1 inhibitor were measured. Using an Alzet pump, 500 mg/kg Chk1 inhibitor was administered to HT29 tumor-bearing mice in a continuous delivery system over a 24 hour period. Plasma samples were taken and then tumors,

kidney, liver, spleen and lung were harvested. Time points were collected at 1, 2, 4, 8 and 24 hours. Tissues were extracted and levels of Chk1 inhibitor were quantified. This experiment demonstrated that the Chk1 inhibitor showed penetration into normal and tumor tissue and reached a level of approximately 15 μM in tumor tissue and peaked in spleen tissue at 8 hours at approximately 20 μM. Thus, Chk1 inhibitors were readily taken up by the proliferating cells and deemed useful, in conjunction with Chk1 activating chemotherapeutic agents, as therapies for the treatment of proliferative diseases.

EXAMPLE 7

Use of H3-P Assay to Determine the Effect of Chk1 Inhibitors on Cell Cycle Arrest

The effect of selective Chk1 inhibitors on Chk1 activator induced cell cycle arrest may be assessed using the assay described above. In this example, gemcitabine was used in mice bearing HT29 tumors.

Mice bearing HT29 tumors were treated with vehicle, 100 mg/kg gemcitabine for 48 hours, or 100 mg/kg gemcitabine for 48 hours followed by the addition of Chk1 inhibitor for 24 hours. Tumors were removed, embedded in paraffin and HT29 tumor slices were stained with antibody against H3-P. Mice pretreated with gemicitabine for 48 hours followed by a 24-hour Chk1 inhibitor treatment demonstrated abrogation of the S phase checkpoint, showing approximately 14% mitotic cells, compared to approximately 4% in gemcitabine-treated mice. This experiment demonstrated that the Chk1 inhibitor allows S phase arrested tumor cells to progress out of the gemcitabine-induced cell cycle arrest and into mitosis.

Using this assay, the scheduling and timing of gemcitabine and Chk1 inhibitors may be optimized. The assay also allows, inter alia, for the measurement of biologically efficacious doses of Chk1 inhibitors and optimization of the Chk1 activator dose and/or pretreatment time.

EXAMPLE 8

Use of H3-P Assay to Determine Optimal Dose and Time to Achieve Cell Cycle Synchronization by Chk1 Activator

In a non-limiting embodiment, the H3-P assay discussed above may be used to determine an optimal degree of cell cycle arrest by Chk1 activator. In the

present example, the Chk1 activator was gemcitabine, whose target phase is S phase. The animal model was HT29 tumor-bearing mice.

HT29 tumor-bearing mice were treated with 100 mg/kg gemcitabine intraperitoneally (i.p.) and mice were harvested at 1 hr, 2 hr, 4 hr, 6 hr, 12 hr, 24 hr, 48 hr and 72 hr. Tumors from these animals were resected, paraffin embedded and stained with an antibody to H3-P followed by a counter-stained with DAPI. The percentage of mitotic cells (positive to H3-P) was quantified at each time point. The data indicated that most cells arrested in S phase between 12 and 24 hr after gemcitabine administration, with a mitotic index of approximately 1.5, compared to an index of approximately 3 at the 1-6 hr time points.

To confirm that low H3-P staining corresponds to S phase arrest, tumors were also stained with an S phase marker, phosphorylated Rb-Pser795. Tumor slices taken in the experiment above were stained with the Rb-Pser795 antibody (Cell Signaling Cat# 9301S) and the number of positive staining cells quantified. The results demonstrated that there were more Rb-P staining cells at 24, 48 and 72 hours than at earlier timepoints. Taken together, these data indicate that the optimal S phase arrest induced by gemcitabine in HT29 tumors occurred in the particular sample tested at 24-48 hours post-gemcitabine treatment.

The kinetics of S phase arrest in response to gemcitabine varies in tumors depending on their doubling time. The human non-small cell lung carcinoma, H460, and the rat breast cancer 137-62 tumors, which have faster doubling times than HT29 tumors (4.5 and 2 days respectively, compared to 10 days or HT29) show reduced H3-P staining at earlier times than HT29 tumors. In an experiment similar to that described above for HT29 cells, H460 and 137-62 were treated with gemcitabine and tumors were harvested at various timepoints. In both tumor types, the lowest H3-P staining is at 12 hours (compared to 48 hr in HT29 cells) and the cells exited S phase arrest at 24 hours in 137-62 cells and 48 hours in H460 cells.

These results suggest that faster growing tumors cycle around into S phase and arrest more rapidly than slower growing tumors. Furthermore, the faster the doubling time of the tumor, the faster they enter back into the cell cycle after gemcitabine arrest. Thus, the optimal gemcitabine pretreatment time may vary depending on the doubling time of the tumor. The fairly broad range of observed

pretreatment times that resulted in an S phase arrest suggests that it will be practical to translate this regime to the clinic or laboratory.

EXAMPLE 9

An Assessment Of Optimal Contact Time With Chk1 Inhibitor Following Substantial Cell Cycle Synchronization

This example illustrates an assessment of the effects of Chk1 inhibitors on kinetics of the abrogation of the cell cycle arrest following substantial synchronization by Chk1 activator. In the present non-limiting example, a cell population comprising human colon carcinoma cell line HT29 was treated with 20 μM gemcitabine for two hours, the gemcitabine washed out, and cells allowed to substantially synchronize at S phase. After 18 hours, the cells were then treated with Chk1 inhibitor and time points taken from 30 minutes to 24 hours. Results showed that progression through the S phase checkpoint started at 2 hours and peaked at 8 hours, with approximately 80% of cells in mitosis. Levels of cells entering into mitosis dropped off by 24 hours, presumably because the cells began to die. These data suggest that the optimal time of exposure of HT29 cells to Chk1 inhibitor after gemcitabine-induced S phase arrest in the samples tested was 6-8 hours. It was observed that some cell lines that are sensitized to Chk1 inhibitors and gemcitabine (such as the 137-62 breast cell carcinoma) enter into mitosis after S phase arrest with this chemotherapy treatment. However, based on the cell sensitization data gathered, it is believed likely that in these cells the Chk1 inhibitors allow abrogation of the cell cycle checkpoint, but rather than progress into mitosis, they progress out of S phase and then die via apoptosis.

EXAMPLE 10

An Assessment Of Dose Response Of Chk1 Inhibitor Abrogation Following Substantial Cell Cycle Synchronization

To determine whether checkpoint abrogation by selective Chk1 inhibitor was dose-dependent, HT29 tumor-bearing mice were pretreated with gemcitabine and 32 hours later dosed with increasing doses of selective Chk1 inhibitor. After 18 hours, tumors were harvested and stained for H3-P as described above. Results indicated that entry into mitosis after checkpoint abrogation is dose dependent, with about 5% of cells in mitosis at 100 mg/kg of Chk1 inhibitor, increasing to approximately 11% at 400 mg/kg. The response is saturated at 400

mg/kg. These data confirm a dose-dependent response to Chk1 inhibitor up to a saturation point.

EXAMPLE 11

Dose Response of Tumors Treated With Chk1 Inhibitors and Gemcitabine

To determine an efficacious dose of Chk1 inhibitor following gemcitabine treatment and whether the dose-dependent checkpoint abrogation correlated with anti-tumor activity, a dose response experiment was performed.

Nude mice were engrafted with HT29 tumor cells and tumors allowed to develop for 10 days. The tumors at the start were approximately 100 mm3. Animals were treated with gemcitabine at the MTD (160 mg/kg) followed by Chk1 inhibitor at 50 mg/kg, 200 mg/kg or 400 mg/kg administered as in Example 1. Gemcitabine pretreatment time was 32 hours in this experiment, as the cell-based assay indicated this timepoint was optimal for this type of tumor. Analysis of tumor volume in each treatment regimen indicated that treatment of HT29 tumor bearing mice with the described therapy slowed tumor growth greater than gemcitabine alone, with either 200 mg/kg or 400 mg/kg Chk1 inhibitor plus gemcitabine again showing dose-dependent effects of the Chk1 inhibitor.

EXAMPLE 12

An Assay to Determine Whether An Agent is a Chk1 Activator

To determine whether an agent is a Chk1 activator, the phosphorylation state of Chk1 can be measured using phospho-specific antibodies to specific phosphorylation sites on Chk1. Serines 317 and 345 have been shown to be phosphorylated after treatment of cells with ionizing radiation, ultraviolet radiation, hydroxyurea, N-methyl-N'-nitro-N-nitrosoguanidine (MNNG), temozolamide and gemcitabine. Liu, Q., et al., (2000) *Genes Dev.* 14, 1448–1459; Zhao, H., et al., (2001) *Mol. Cell Biol.* 21, 4129–4139; Lopez-Girona, A., et al., (2001) *Proc. Natl. Acad. Sci. U. S. A.* 98, 11289–11294; Guo, Z., et al., (2000) *Genes Dev.* 14, 2745–2756; Gatei, M., et al., (2003) *J. Biol. Chem.* 278, 14806–14811; Ng CP, et al., *J Biol Chem.* 2004 Mar 5;279(10):8808-19; Wang Y, et al., *Natl Acad Sci* U S A. 2003 Dec 23;100(26):15387-92; Stojic L, et al., *Genes Dev.* 2004 Jun 1;18(11):1331-44. These serine sites are phosphorylated by upstream checkpoint kinases, Atm and Atr. Liu,

Q., et al., S.J. (2000) *Genes Dev.* 14, 1448–1459; Zhao, H., et al. (2001) *Mol. Cell Biol.* **21,** 4129–4139).

The phosphorylation of these sites in response to a candidate Chk1 activator can be monitored by Western blot or immunohistochemistry of tumor cells. For example, the following procedure was used to demonstrate that gemcitabine results in Chk1 activation at serine 345 and 317. HT29 cells were treated with 20 μM gemcitabine for two hours. The gemcitabine was washed out of the cell growth media and cells were incubated for 22 additional hours. Protein lysates were prepared and separated by an SDS-polyacrylamide gel electrophoresis. Proteins were transferred to PVDF membranes and probed with antisera (Cell Signalling) specific for either phosphorylated serine 317 or 345 (Cell Signalling). Figure 3 shows, by Western blot, that gemcitabine treatment of HT29 colon carcinoma cells results in the phosphorylation of both serines 317 and 345.

EXAMPLE 13

An Assay to Monitor Chk1 Activity in Response To a Chk1 Inhibitor

Applicants have found that phosphorylation of Chk1 at serine 296 is stimulated by treatment of tumor cells with gemcitabine, and that phosphorylation at this site is inhibited by Chk1 inhibitors. Phosphorylation at this site is not inhibited by Wortmannin, which inhibits Atm and Atr. Therefore the phosphorylation of serine 296 is distinct from phosphorylation at serines 317 and 345 described in Example 12. In addition, Applicants have found that this site is phosphorylated in purified Chk1 preparations, suggesting that the purified enzyme is able to phosphorylate itself or other Chk1 molecules at serine 296. Taken together, these data suggest that phosphorylation at serine 296 is performed by Chk1 itself. Therefore, this approach may be used to monitor Chk1 activity in tumors in response to Chk1 activators. Further, this approach may be used to measure inhibition of Chk1 activation by Chk1 inhibitors.

Thus, HT 29 cells were treated with 20 μM gemcitabine for two hours. The gemcitabine was washed out of the cell growth media and cells were incubated for 22 additional hours. Protein lysates were prepared and separated by an SDS-polyacrylamide gel electrophoresis. Proteins were transferred to polyvinylidene fluoride (PVDF) membranes and probed with antisera (Cell Signalling) specific for

phosphorlyated serine 296 (Cell Signalling). Figure 4 shows, by Western blot, that gemcitabine treatment of HT29 colon carcinoma cells results in the phosphorylation of serine 296. Further, HT29 cells treated with selective Chk1 inhibitors for 15 minutes show no serine 296 phosphorylation. These data suggest that serine 296 phosphorylation is performed by the Chk1 kinase.

The present invention is not to be limited in scope by the exemplified embodiments, which are intended as illustrations of single aspects of the invention, and compositions and methods which are functionally equivalent are within the scope of the invention. Indeed, numerous modifications and variations in the practice of the invention are expected to occur to those skilled in the art upon consideration of the present preferred embodiments. Consequently, the only limitations that should be placed upon the scope of the invention are those that appear in the appended claims. All references cited within the body of the instant specification are hereby incorporated by reference in their entirety.

We claim:

1. A method for controlling aberrant cell proliferation comprising

a) contacting a cell population comprising aberrantly proliferating cells with at least one Chk1 activator in am amount sufficient to substantially synchronize cell cycle arrest among said aberrantly proliferating cells at a target phase, and

b) upon achieving said substantial synchronization of cell cycle arrest among said aberrantly proliferating cells, contacting said cell population with a selective Chk1 inhibitor in an amount sufficient to substantially abrogate said cell cycle arrest.

2. The method of claim 1, wherein said Chk1 inhibitor is a specific Chk1 inhibitor.

3. The method of claim 1, wherein said cell population is contacted with a Chk1 activator for from about 30 minutes to about 96 hours, and subsequently contacted with a selective Chk1 inhibitor for from up to about 1 hour to up to about 72 hours.

4. The method of claim 3, wherein said cell population is contacted with a Chk1 activator for from about 30 minutes to about 48 hours.

5. The method of claim 1, wherein said Ck1 activator induces substantial synchronization of cell cycle arrest cells at the target phase G1.

6. The method of claim 1, wherein said Chk1 activator induces substantial synchronization of cell cycle arrest at the target phase S.

7. The method of claim 1, wherein said Chk1 activator induces substantial synchronization of cell cycle arrest at the target phase G2.

8. The method of claim 1, wherein said cell population is *ex vivo*.

9. The method of claim 1, wherein said cell population is *in vivo*.

10. The method of claim 9, wherein said cell population is in a human.

11. The method of claim 1, wherein said Chk1 activator comprises a chemotherapeutic agent.

12. The method of claim 1, wherein said Chk1 activator is an alkylating agent.

13. The method of claim 12, wherein said alkylating agent is a nitrogen mustard.

14. The method of claim 13, wherein said nitrogen mustard is mechlorethamine, cyclophosphamide, ifosfamide, melphalan, or chlorambucil.

15. The method of claim 1, wherein said Chk1 activator is a nitrosourea.

16. The method of claim 15, wherein said nitrosourea is carmustine (BCNU), lomustine (CCNU), or semustine (methyl-CCNU).

17. The method of claim 1, wherein said Chk1 activator is an ethylenimine or a methyl-melamine.

18. The method of claim 17, wherein said ethylenimine or said methylmelanine is triethylenemelamine (TEM), triethylene thiophosphoramide (thiotepa), or hexamethylmelamine (HMM, altretamine).

19. The method of claim 1, wherein said Chk1 activator is an alkyl sulfonate.

20. The method of claim 19, wherein said alkyl sulfonate is busulfan.

21. The method of claim 1, wherein said Chk1 activator is a triazine.

22. The method of claim 21, wherein said triazine is dacarbazine (DTIC).

23. The method of claim 1, wherein said Chk1 activator is an antimetabolite.

24. The method of claim 23, wherein said antimetabolite is a folic acid analog.

25. The method of claim 24, wherein said folic acid analog is methotrexate, trimetrexate, or pemetrexed (multi-targeted antifolate).

26. The method of claim 23, wherein said antimetabolite is a pyrimidine analog.

27. The method of claim 26, wherein said pyrimidine analog is 5-fluorouracil (5-FU), fluorodeoxyuridine, gemcitabine, cytosine arabinoside (AraC, cytarabine), 5-azacytidine, or 2,2'-difluorodeoxycytidine.

28. The method of claim 23, wherein said antimetabolite is a purine analog.

29. The method of claim 28, wherein said purine analog is 6-mercaptopurine, 6-thioguanine, azathioprine, 2'-deoxycoformycin (pentostatin), erythrohydroxynonyladenine (EHNA), a fludarabine salt, or 2-chlorodeoxyadenosine (cladribine, 2-CdA).

30. The method of claim 23, wherein said antimetabolite is a type I topoisomerase inhibitor.

31. The method of claim 30, wherein said type I topoisomerase inhibitor is camptothecin (CPT), topotecan, or irinotecan.

32. The method of claim 1, wherein said Chk1 activator is derived from a natural product.

33. The method of claim 32, wherein said natural product is a epipodophylotoxin.

34. The method of claim 33, wherein said epipodophylotoxin is etoposide or teniposide.

35. The method of claim 32, wherein said natural product is a vinca alkaloid.

36. The method of claim 35, wherein said vinca alkaloid is vinblastine, vincristine, or vinorelbine.

37. The method of claim 1, wherein said Chk1 activator is an antibiotic.

38. The method of claim 37, wherein said antibiotic is actinomycin D, doxorubicin, or bleomycin.

39. The method of claim 1, wherein said Chk1 activator is a radiosensitizer.

40. The method of claim 39, wherein said radiosensitizer is 5-bromodeozyuridine, 5-iododeoxyuridine, or bromodeoxycytidine.

41. The method of claim 1, wherein said Chk1 activator is a platinum coordination complex.

42. The method of claim 41, wherein said platinum coordination complex is a cisplatin, carboplatin, or oxaliplatin.

43. The method of claim 1, wherein said Chk1 activator is hydroxyurea.

44. The method of claim 1, wherein said Chk1 activator is a methylhydrazine derivative.

45. The method of claim 44, wherein said methylhydrazine derivative is N-methylhydrazine (MIH) or procarbazine.

46. The method of claim 1, wherein said Chk1 activator comprises radiation.

47. The method of claim 46, wherein said radiation is x-ray radiation or ultraviolet radiation.

48. The method of claim 47, wherein said radiation is administered in conjunction with a radiosensitizer and/or a photosensitizer.

49. The method of claim 1, further comprising the administration of at least one chemotherapeutic agent or at least one radiotherapeutic agent that does not activate Chk1.

50. The method of claim 1, further comprising the administration of at least one side effect reducing agent.

51. The method of claim 1, wherein said cell population is contacted with a Chk1 inhibitor after a time sufficient to allow said Chk1 activator to induce a maximum degree of synchronization in said cell population of cell cycle arrest and a minimum number of cells in mitosis.

52. The method of claim 1, wherein the substantially synchronized cell cycle arrest achieved by contacting said cell population with said Chk1 activator comprises at least about a 50% increase in the number of aberrantly proliferating cells in the target phase of said Chk1 activator in comparison to the number of aberrantly proliferating cells in the target phase prior to contact with said Chk1 activator.

53. The method of claim 52, wherein said increase is at least about 100%.

54. The method of claim 53, wherein said increase is at least about 200%.

55. The method of claim 54, wherein said increase is at least about 300%.

56. The method of claim 55, wherein said increase is at least about 400%.

57. The method of claim 1, wherein said cell population is contacted with said Chk1 activator for at least one doubling period typical of aberrantly proliferating cells in said cell population.

58. The method of claim 1, wherein said cell population is contacted with said Chk1 activator for at least two doubling periods typical of aberrantly proliferating cells in said cell population.

59. The method of claim 1, further comprising determining the presence or absence of substantial synchronization of cell cycle arrest in a biological sample.

60. The method of claim 59 wherein the biological sample is a fluid sample or a tissue sample.

61. The method of claim 1, wherein said Chk1 inhibitor is administered over a plurality of doses.

62. The method of claim 25, wherein said doses comprise a frequency of (q4d x 4), (q3d x 4), (qd x 5), (qwk3), or (5/2/5).

63. The method of claim 1, wherein said aberrantly proliferating cells are cancerous.

64. The method of claim 63, wherein said cancerous cells comprise cells from myxoid and round cell carcinomas, locally advanced tumors, metastatic cancer, Ewing's sarcoma, cancer metastases, lymphatic metastases, squamous cell carcinomas, esophageal squamous cell carcinomas, oral carcinomas, multiple myelomas, acute lymphocytic leukemias, acute non-lymphocytic leukemias, chronic lymphocytic leukemias, chronic myelocytic leukemias, hairy cell leukemias, effusion lymphomas (body cavity based lymphomas), thymic lymphoma lung cancers, small cell carcinomas of the lung, cutaneous T cell lymphomas, Hodgkin's lymphomas, non-Hodgkin's lymphomas, cancers of the adrenal cortex, ACTH-producing tumors, non-small cell lung cancers, breast cancers, small cell carcinomas, ductal carcinomas, stomach cancers, colon cancers, colorectal cancers, polyps associated with colorectal neoplasias, pancreatic cancers, liver cancers, bladder cancers, primary superficial bladder tumors, invasive transitional cell carcinomas of the bladder, muscle-invasive bladder cancers, prostate cancers, ovarian carcinomas, primary peritoneal epithelial neoplasms, cervical carcinomas, uterine endometrial cancers, vaginal cancers, cancers of the vulva, uterine cancers and solid tumors in the ovarian follicle, testicular cancers, penile cancers, renal cell carcinomas, intrinsic brain tumors, neuroblastomas, astrocytic brain tumors, gliomas, metastatic tumor cell invasions in the central nervous system, osteomas and osteosarcomas, malignant melanomas, tumor progressions of human skin keratinocytes, squamous cell cancers, thyroid cancers, retinoblastomas, neuroblastomas, peritoneal effusions, malignant pleural effusions, mesotheliomas, Wilms's tumors, gall bladder cancers, trophoblastic neoplasms, hemangiopericytomas, Kaposi's sarcomas or other cancers treatable with chemotherapy agents or inhibitors of cell cycle checkpoint proteins.

65. The method of claim 1, wherein said aberrantly proliferating cells are non-cancerous.

66. The method of claim 63, wherein said non-cancerous cells comprise cells originating from atherosclerosis, restenosis, vasculitis, nephritis, retinopathy, renal disease, proliferative skin disorders, psoriasis, keloid scarring, actinic keratosis, Stevens-Johnson Syndrome, rheumatoid arthritis, systemic-onset juvenile chronic

arthritis, osteoporosis, systemic lupus erythematosus, hyperproliferative diseases of the eye including epithelial down growth, proliferative vitreoretinopathy (PVR), hemangio-proliferative diseases, ichthyosis, or papillomas.

67. Use of a composition comprising at least one Chk1 inhibitor in the manufacture of a medicament for the inhibition of aberrant cell proliferation.

68. An article of manufacture comprising a Chk1 inhibitor and a label indicating a method according to claim 1.

FIGURE 1

Figure 1A

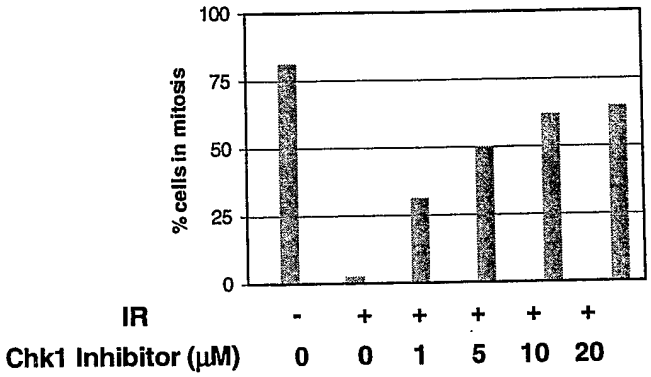


Figure 1B

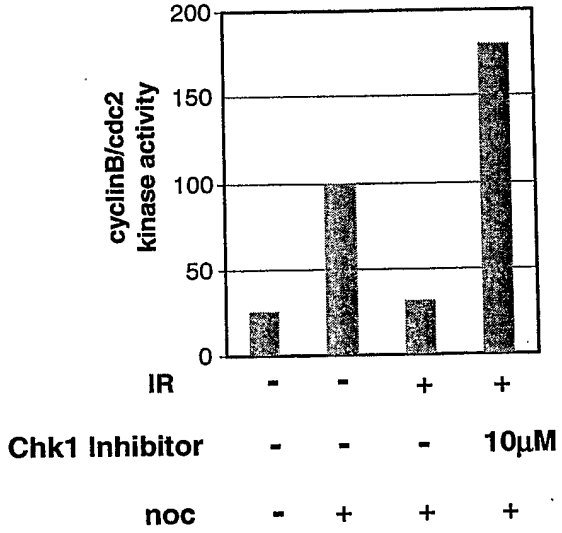


FIGURE 2

Figure 2A

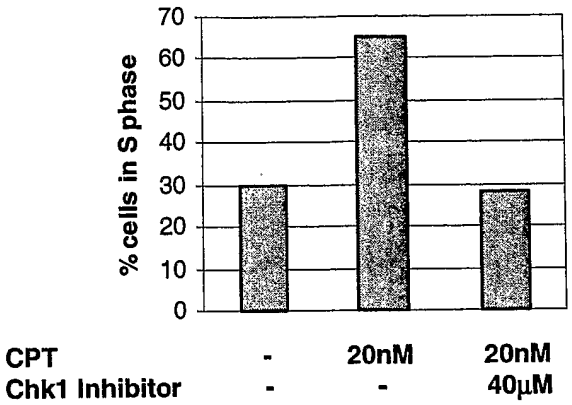


Figure 2B

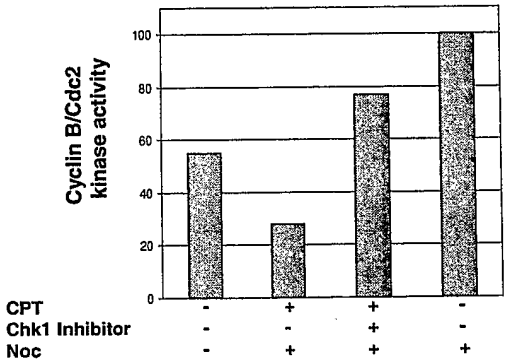


Figure 2C

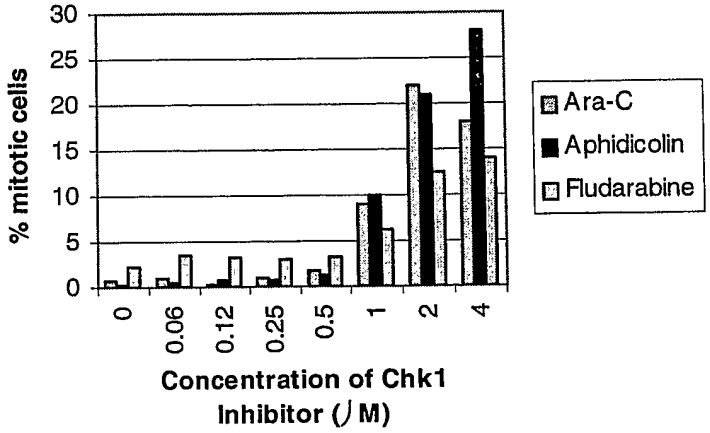


FIGURE 3

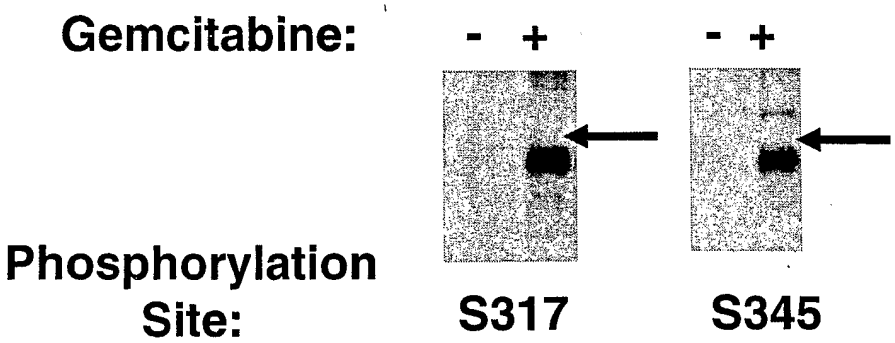
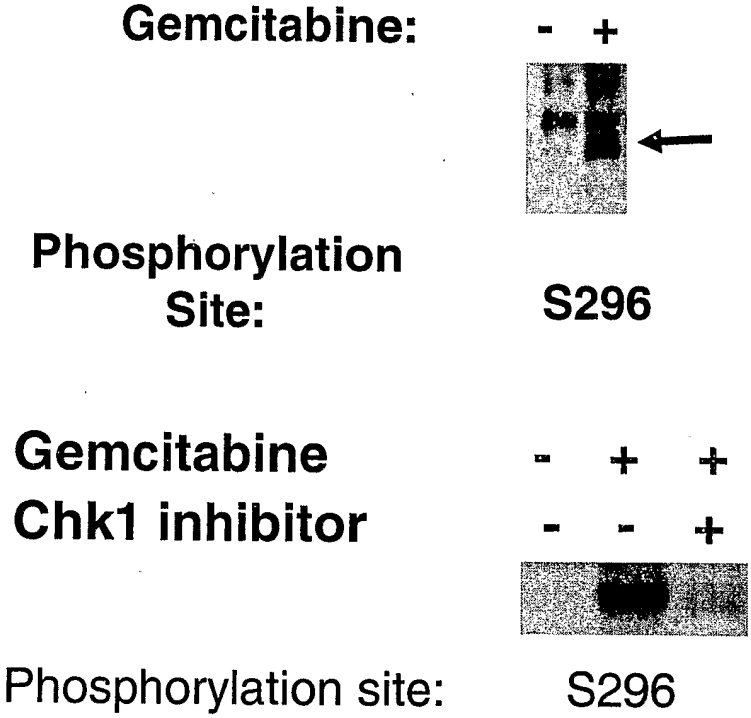


FIGURE 4


Gemcitabine:
- +
Phosphorylation Site:
S296
Gemcitabine
Chk1 inhibitor
- + +
- - +
Phosphorylation site:
S296

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US2004/030806

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/4745 A61K31/513 A61K31/7048 A61K31/7068 A61K33/24
A61P35/00 A61P43/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, CHEM ABS Data, MEDLINE, EMBASE, BIOSIS, CANCERLIT

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 03/029241 A (PARRISH CYNTHIA A ; SMITHKLINE BEECHAM CORP (US); HOLT DENNIS A (US);) 10 April 2003 (2003-04-10) cited in the application abstract claims 1-11	1-68
A	WO 02/070494 A (ICOS CORP) 12 September 2002 (2002-09-12) cited in the application abstract claims 1-30	1-68

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

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"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

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"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.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 December 2004	21/01/2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Taylor, G.M.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US2004/030806

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A	GRAVES, PR ET AL.: "The Chk1 Protein Kinase and the Cdc25C Regulatory Pathways Are Targets of the Anticancer Agent UCN-01" JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 275, no. 8, 25 February 2000 (2000-02-25), pages 5600-5605, XP002309541 the whole document	1-68
P,A	KESICKI, EA ET AL.: "Discovery of pyrazinyl ureas as inhibitors of the cell-cycle checkpoint kinase CHK1" ABSTRACTS OF PAPERS, 228TH ACS NATIONAL MEETING, PHILADELPHIA, PA, USA, no. 225, 22 August 2004 (2004-08-22), - 26 August 2004 (2004-08-26) XP009040780 abstract	1-68
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INTERNATIONAL SEARCH REPORT

International Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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Information on patent family members

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		AU	7548500 A	24-04-2001
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		WO	0121771 A2	29-03-2001
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