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Triazole compounds that modulate HSP90 activity

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(54) Title: TRIAZOLE COMPOUNDS THAT MODULATE HSP90 ACTIVITY

(57) Abstract: The present invention relates to substituted triazole compounds and compositions comprising substituted triazole compounds. The invention further relates to methods of inhibiting the activity of Hsp90 in a subject in need thereof and methods for preventing or treating hyperproliferative disorders, such as cancer, in a subject in need thereof comprising administering to the subject a substituted triazole compound of the invention, or a composition comprising such a compound.

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TRIAZOLE COMPOUNDS THAT MODULATE HSP90 ACTIVITY

RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application No. 60/709,310, filed August 18, 2005, and U.S. Provisional Application
5 No. 60/724,105, filed October 6, 2005, the entire teachings of which are incorporated herein by reference.

BACKGROUND OF THE INVENTION

Although tremendous advances have been made in elucidating the genomic abnormalities that cause malignant cancer cells, currently available chemotherapy
10 remains unsatisfactory, and the prognosis for the majority of patients diagnosed with cancer remains dismal. Most chemotherapeutic agents act on a specific molecular target thought to be involved in the development of the malignant phenotype. However, a complex network of signaling pathways regulate cell proliferation, and the majority of malignant cancers are facilitated by multiple genetic abnormalities in
15 these pathways. Therefore, it is unlikely that a therapeutic agent that acts on one molecular target will be fully effective in curing a patient who has cancer.

Heat shock proteins (HSPs) are a class of chaperone proteins that are up-regulated in response to elevated temperature and other environmental stresses, such as ultraviolet light, nutrient deprivation, and oxygen deprivation. HSPs act as
20 chaperones to other cellular proteins (called client proteins) and facilitate their proper folding and repair, and aid in the refolding of misfolded client proteins. There are several known families of HSPs, each having its own set of client proteins. The Hsp90 family is one of the most abundant HSP families, accounting for about 1-2% of proteins in a cell that is not under stress and increasing to about 4-6% in a cell
25 under stress. Inhibition of Hsp90 results in degradation of its client proteins via the ubiquitin proteasome pathway. Unlike other chaperone proteins, the client proteins of Hsp90 are mostly protein kinases or transcription factors involved in signal transduction, and a number of its client proteins have been shown to be involved in

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the progression of cancer. Examples of Hsp90 client proteins that have been implicated in the progression of cancer are described below.

Her-2 is a transmembrane tyrosine kinase cell surface growth factor receptor that is expressed in normal epithelial cells. Her2 has an extracellular domain that
5 interacts with extracellular growth factors and an internal tyrosine kinase portion that transmits the external growth signal to the nucleus of the cell. Her2 is overexpressed in a significant proportion of malignancies, such as breast cancer, ovarian cancer, prostate cancer, and gastric cancers, and is typically associated with a poor prognosis.

10 Akt kinase is a serine/threonine kinase which is a downstream effector molecule of phosphoinositide 3-kinase and is involved in protecting the cell from apoptosis. Akt kinase is thought to be involved in the progression of cancer because it stimulates cell proliferation and suppresses apoptosis.

Cdk4/cyclin D complexes are involved in phosphorylation of retinoblastoma
15 protein which is an essential step in progression of a cell through the G1 phase of the cell cycle. Disruption of Hsp90 activity has been shown to decrease the half life of newly synthesized Cdk4.

Raf-1 is a MAP 3-kinase (MAP3K) which when activated can phosphorylate and activate the serine/threonine specific protein kinases ERK1 and ERK2.
20 Activated ERKs play an important role in the control of gene expression involved in the cell division cycle, apoptosis, cell differentiation and cell migration.

The transforming protein of Rous sarcoma virus, v-src, is a prototype of an oncogene family that induces cellular transformation (i.e., tumorigenesis) by non-regulated kinase activity. Hsp90 has been shown to complex with v-src and inhibit
25 its degradation.

Hsp90 is required to maintain steroid hormone receptors in a conformation capable of binding hormone with high affinity. Inhibition of the action of Hsp90 therefore is expected to be useful in treating hormone-associated malignancies such as breast cancer.

30 p53 is a tumor suppressor protein that causes cell cycle arrest and apoptosis. Mutation of the p53 gene is found in about half of all human cancers making it one of the most common genetic alterations found in cancerous cells. In addition, p53

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mutation is associated with a poor prognosis. Wild-type p53 has been shown to interact with Hsp90, but mutated p53 forms a more stable association than wild-type p53 as a result of its misfolded conformations. A stronger interaction with Hsp90 protects the mutated protein from normal proteolytic degradation and prolongs its half-life. In a cell that is heterozygous for mutated and wild-type p53, inhibition of the stabilizing effect of Hsp90 causes mutant p53 to be degraded and restores the normal transcriptional activity of wild-type p53.

Hif-1 α is a hypoxia-inducible transcription factor that is up-regulated under low oxygen conditions. Under normal oxygen conditions Hif-1 α associates with Von Hippel-Lindau (VHL) tumor suppressor protein and is degraded. Low oxygen conditions inhibit this association and allows Hif-1 α to accumulate and complex with Hif-1 β to form an active transcription complex that associates with hypoxia-response elements to activate the transcription of vascular endothelial growth factor (VEGF). Increased Hif-1 α is associated with increased metastasis and a poor prognosis.

There are two classes of PKs: protein tyrosine kinases (PTKs), which catalyze the phosphorylation of tyrosine kinase residues, and the serine-threonine kinases (STKs), which catalyze the phosphorylation of serine or threonine residues. Growth factor receptors with PTK activity are known as receptor tyrosine kinases. Receptor tyrosine kinases are a family of tightly regulated enzymes, and the aberrant activation of various members of the family is one of the hallmarks of cancer. The receptor tyrosine kinase family can be divided into subgroups that have similar structural organization and sequence similarity within the kinase domain.

Epidermal Growth Factor Receptor (EGFR) is a member of the type 1 subgroup of receptor tyrosine kinase family of growth factor receptors, which play critical roles in cellular growth, differentiation, and survival. Activation of these receptors typically occurs via specific ligand binding which results in hetero- or homodimerization between receptor family members, with subsequent autophosphorylation of the tyrosine kinase domain. Specific ligands which bind to EGFR include epidermal growth factor (EGF), transforming growth factor α (TGF α), amphiregulin and some viral growth factors. Activation of EGFR triggers a cascade of intracellular signaling pathways involved in both cellular proliferation

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(the ras/raf/MAP kinase pathway) and survival (the PI3 kinase/Akt pathway). Members of this family, including EGFR and HER2, have been directly implicated in cellular transformation.

A number of human malignancies are associated with aberrant or
5 overexpression of EGFR and/or overexpression of its specific ligands (Gullick, *Br. Med. Bull.* (1991), 47:87-98; Modjtahedi and Dean, *Int. J. Oncol.* (1994), 4:277-96; Salomon, *et al.*, *Crit. Rev. Oncol. Hematol.* (1995); 19:183-232, the entire teachings of each of these references are incorporated herein by reference). Aberrant or overexpression of EGFR has been associated with an adverse prognosis in a number
10 of human cancers, including head and neck, breast, colon, prostate, lung (e.g., NSCLC, adenocarcinoma and squamous lung cancer), ovaries, gastrointestinal cancers (gastric, colon, pancreatic), renal cell cancer, bladder cancer, glioma, gynecological carcinomas, and prostate cancer. In some instances, overexpression of tumor EGFR has been correlated with both chemoresistance and a poor prognosis
15 (Lei, *et al.*, *Anticancer Res.* (1999), 19:221-8; Veale, *et al.*, *Br. J. Cancer* (1993); 68:162-5, the entire teachings of each of these references are incorporated herein by reference).

Gefitinib, a chemotherapeutic agent that inhibits the activity of EGFR, has been found to be highly efficacious in a subset of lung cancer patients that have
20 mutations in the tyrosine kinase domain of EGFR. In the presence of EGF, these mutants displayed two to three times higher activity than wild type EGFR. In addition, wild type EGFR was internalized by the cells and down-regulated after 15 minutes, where as mutant EGFR was internalized more slowly and continued to be activated for up to three hours (Lynch, *et al.*, *The New England Journal of Medicine*
25 (2006), 350:2129-2139, the entire teachings of which are incorporated herein by reference).

Gliomas are another type of cancer that is characterized by amplification and/or mutation of the EGFR gene. One of the most common mutations in the EGFR gene is a deletion of exons 2-7 which results in a truncated form of EGFR in
30 which amino acids 6-273 of the extracellular domain are replaced with a single glycine residue. This mutation is called EGFRvIII and is expressed in about half of all glioblastomas. EGFRvIII is unable to bind EGF and TGF α and has constitutive,

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- ligand-independent tyrosine kinase activity. Hsp90 co-purifies with EGFRvIII indicating that Hsp90 complexes with EGFRvIII. Moreover, Hsp90 inhibitor geldanamycin, a benzoquinone ansamycin antibiotic, was able to decrease the expression of EGFRvIII indicating that interaction with Hsp90 is essential to
- 5 maintain high expression levels of EGFRvIII (Lavioire, et al., *Journal of Biological Chemistry* (2003), 278(7):5292-5299, the entire teachings of which are incorporated herein by reference). These results demonstrate that inhibiting the activity of Hsp90 is an effective strategy for treating cancers that are associated with inappropriate EGFR activity.
- 10 The members of the type III group of receptor tyrosine kinases include platelet-derived growth factor (PDGF) receptors (PDGF receptors alpha and beta), colony-stimulating factor (CSF-1) receptor (CSF-1R, c-Fms), Fms-like tyrosine kinase (FLT3), and stem cell factor receptor (c-kit). FLT3 is primarily expressed on immature hematopoietic progenitors and regulates their proliferation and survival.
- 15 Hematologic cancers, also known as hematologic or hematopoietic malignancies, are cancers of the blood or bone marrow; including leukemia and lymphoma. Acute myelogenous leukemia (AML) is a clonal hematopoietic stem cell leukemia that represents about 90% of all acute leukemias in adults with an incidence of 3.9 per 100,000 (See e.g., Lowenberg et al., *N. Eng. J. Med.* 341: 1051-
- 20 62 (1999) and Lopesde Menezes, et al, *Clin. Cancer Res.* (2005), 11(14):5281-5291, the entire teachings of both references are incorporated by reference). While chemotherapy can result in complete remissions, the long term disease-free survival rate for AML is about 14% with about 7,400 deaths from AML each year in the United States. Approximately 70 % of AML blasts express wild type FLT3 and
- 25 about 25 % to about 35 % express FLT3 kinase receptor mutations which result in constitutively active FLT3. Two types of activating mutations have been identified in AML patients: internal tandem duplications (ITDs) and point mutation in the activating loop of the kinase domain. FLT3-ITD mutations in AML patients is indicative of a poor prognosis for survival, and in patients who are in remission,
- 30 FLT3-ITD mutations are the most significant factor adversely affecting relapse rate with 64% of patients having the mutation relapsing within 5 years (see *Current Pharmaceutical Design* (2005), 11:3449-3457, the entire teachings of which are

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incorporated herein by reference). The prognostic significance of FLT3 mutations in clinical studies suggests that FLT3 plays a driving role in AML and may be necessary for the development and maintenance of the disease.

Mixed Lineage Leukemia (MLL) involve translocations of chromosome 11
 5 band q23 (11q23) and occur in approximately 80% of infant hematological malignancies and 10 % of adult acute leukemias. Although certain 11q23 translocation have been shown to be essential to immortalization of hematopoietic progenitors in vitro, a secondary genotoxic event is required to develop leukemia. There is a strong concordance between FLT3 and MLL fusion gene expression, and
 10 the most consistently overexpressed gene in MLL is FLT3. Moreover, it has been shown that activated FLT3 together with MLL fusion gene expression induces acute leukemia with a short latency period (see Ono, *et al.*, *J. of Clinical Investigation* (2005), 115:919-929, the entire teachings of which are incorporated by reference). Therefore, it is believed that FLT3 signally is involved in the development and
 15 maintenance of MLL (see Armstrong, *et al.*, *Cancer Cell* (2003), 3:173-183, the entire teachings of which are incorporated herein by reference).

The FLT3-ITD mutation is also present in about 3% of cases of adult myelodysplastic syndrome and some cases of acute lymphocytic leukemia (ALL) (*Current Pharmaceutical Design* (2005), 11:3449-3457).

20 FLT3 has been shown to be a client protein of Hsp90, and 17AAG, a benzoquinone ansamycin antibiotic that inhibits Hsp90 activity, has been shown to disrupts the association of Flt3 with Hsp90. The growth of leukemia cell that express either wild type FLT3 or FLT3-ITD mutations was found to be inhibited by treatment with 17^AAAG (Yao, *et al.*, *Clinical Cancer Research* (2003), 9:4483-
 25 4493, the entire teachings of which are incorporated herein by reference).

c-Kit is a membrane type III receptor protein tyrosine kinase which binds Stem Cell Factor (SCF) to its extracellular domain. c-Kit has tyrosine kinase activity and is required for normal hematopoiesis. However, mutations in c-kit can result in
 30 ligand-independent tyrosine kinase activity, autophosphorylation, and uncontrolled cell proliferation. Aberrant expression and/or activation of c-Kit has been implicated in a variety of pathologic states. For example, evidence for a contribution of c-Kit to neoplastic pathology includes its association with leukemias and mast

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cell tumors, small cell lung cancer, testicular cancer, and some cancers of the gastrointestinal tract and central nervous system. In addition, c-Kit has been implicated in playing a role in carcinogenesis of the female genital tract sarcomas of neuroectodermal origin, and Schwann cell neoplasia associated with neurofibromatosis. (Yang *et al.*, *J Clin Invest.* (2003), 112:1851-1861; Viskochil, *J Clin Invest.* (2003), 112:1791-1793, the entire teachings of each of these reference are incorporated herein by reference). c-Kit has been shown to be a client protein of Hsp90, and Hsp90 inhibitor 17AAG, a benzoquinone ansamycin, has been shown to induce apoptosis in Kasumi-1 cells, an acute myeloid leukemia cell line that harbors a mutation in c-kit.

c-Met is a receptor tyrosine kinase that is encoded by the Met protooncogene and transduces the biological effects of hepatocyte growth factor (HGF), which is also referred to as scatter factor (SF). Jiang *et al.*, *Crit. Rev. Oncol. Hemtol.* 29: 209-248 (1999), the entire teachings of which are incorporated herein by reference. c-Met and HGF are expressed in numerous tissues, although their expression is normally confined predominantly to cells of epithelial and mesenchymal origin, respectively. c-Met and HGF are required for normal mammalian development and have been shown to be important in cell migration, cell proliferation and survival, morphogenic differentiation, and organization of 3-dimensional tubular structures (e.g., renal tubular cells, gland formation, etc.). The c-Met receptor has been shown to be expressed in a number of human cancers. c-Met and its ligand, HGF, have also been shown to be co-expressed at elevated levels in a variety of human cancers (particularly sarcomas). However, because the receptor and ligand are usually expressed by different cell types, c-Met signaling is most commonly regulated by tumor-stroma (tumor-host) interactions. Furthermore, c-Met gene amplification, mutation, and rearrangement have been observed in a subset of human cancers. Families with germline mutations that activate c-Met kinase are prone to multiple kidney tumors as well as tumors in other tissues. Numerous studies have correlated the expression of c-Met and/or HGF/SF with the state of disease progression of different types of cancer (including lung, colon, breast, prostate, liver, pancreas, brain, kidney, ovarian, stomach, skin, and bone cancers). Furthermore, the overexpression of c-Met or HGF have been shown to correlate with poor prognosis

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and disease outcome in a number of major human cancers including lung, liver, gastric, and breast.

BCR-ABL is an oncoprotein with tyrosine kinase activity and has been associated with chronic myelogenous leukemia (CML), with a subset of patients with acute lymphocytic leukemia (ALL) and with a subset of patients with acute myelogenous leukemia (AML). In fact, the BCR-ABL oncogene has been found in at least 90-95% of patients with CML, 20% of adults with ALL, 5% of children with ALL, and in about 2% of adults with AML. The BCR-ABL oncoprotein is generated by the translocation of gene sequences from the c-ABL protein tyrosine kinase on chromosome 9 into the BCR sequences on chromosome 22, producing the Philadelphia chromosome. The BCR-ABL gene has been shown to produce at least three alternative chimeric proteins, p230 Bcr-Abl, p210 Bcr-Abl, and p190 Bcr-Abl which have unregulated tyrosine kinase activity. The p210 Bcr-Abl fusion protein is most often associated with CML, while the p190 Bcr-Abl fusion protein is most often associated with ALL. Bcr-Abl has also been associated with a variety of additional hematological malignancies including granulocytic hyperplasia, myelomonocytic leukemia, lymphomas and erythroid leukemia.

Studies have shown that lowering the expression or activity of Bcr-Abl is effective in treating Bcr-Abl-positive leukemias. For example, agents such as As_2O_3 which lower Bcr-Abl expression have been shown to be highly effective against Bcr-Abl leukemias. In addition, inhibition of Bcr-Abl tyrosine kinase activity by Imatinib (also known as STI571 and Gleevec) induces differentiation and apoptosis and causes eradication of Bcr-Abl positive leukemia cells both *in vivo* and *in vitro*. In patients with CML in the chronic phase, as well as in a blast crisis, treatment with Imatinib typically will induce remission. However, in many cases, particularly in those patients who were in a blast crisis before remission, the remission is not durable because the Bcr-Abl fusion protein develops mutations that cause it to be resistance to Imatinib. (See Nimmanapalli, *et al.*, *Cancer Research* (2001), 61:1799-1804; and Gorre, *et al.*, *Blood* (2002), 100:3041-3044, the entire teachings of each of these references are incorporated herein by reference).

Bcr-Abl fusion proteins exist as complexes with Hsp90 and are rapidly degraded when the action of Hsp90 is inhibited. It has been shown that

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geldanamycin, a benzoquinone ansamycin antibiotic that disrupts the association of Bcr-Abl with Hsp90, results in proteasomal degradation of Bcr-Abl and induces apoptosis in Bcr-Abl leukemia cells.

Hsp90 has been shown by mutational analysis to be necessary for the survival of normal eukaryotic cells. However, Hsp90 is over expressed in many tumor types indicating that it may play a significant role in the survival of cancer cells and that cancer cells may be more sensitive to inhibition of Hsp90 than normal cells. For example, cancer cells typically have a large number of mutated and overexpressed oncoproteins that are dependent on Hsp90 for folding. In addition, because the environment of a tumor is typically hostile due to hypoxia, nutrient deprivation, acidosis, etc., tumor cells may be especially dependent on Hsp90 for survival. Moreover, inhibition of Hsp90 causes simultaneous inhibition of a number of oncoproteins, as well as hormone receptors and transcription factors making it an attractive target for an anti-cancer agent. In fact, benzoquinone ansamycins, a family of natural products that inhibit Hsp90, has shown evidence of therapeutic activity in clinical trials.

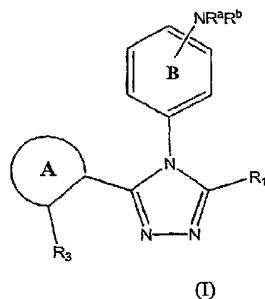
Although promising, benzoquinone ansamycins, and their derivatives, suffer from a number of limitations. For example, they have low oral bioavailability, and their limited solubility makes them difficult to formula. In addition, they are metabolized by polymorphic cytochrome P450 CYP3A4 and are a substrate for P-glycoprotein export pump involved in the development of multidrug resistance. Therefore, a need exist for new therapeutics that improve the prognosis of cancer patients and that reduces or overcomes the limitations of currently used anti-cancer agents.

SUMMARY OF THE INVENTION

The present invention provides compounds which inhibit the activity of Hsp90 and are useful in the treatment of proliferative disorders, such as cancer.

In one embodiment, the present invention provides compounds represented by structural formula (I):

- 10 -



or a tautomer, pharmaceutically acceptable salt, solvate, clathrate or a
5 prodrug thereof.

In formula (I), Ring A is an aryl or a heteroaryl, wherein the aryl or the
heteroaryl are optionally further substituted with one or more substituents in addition
to R₃;

R₁ is -OH, -SH, -NR₇H, -OR₂₆, -SR₂₆, -NHR₂₆, -O(CH₂)_mOH,
10 -O(CH₂)_mSH, -O(CH₂)_mNR₇H, -S(CH₂)_mOH, -S(CH₂)_mSH, -S(CH₂)_mNR₇H,
-OC(O)NR₁₀R₁₁, -SC(O)NR₁₀R₁₁, -NR₇C(O)NR₁₀R₁₁, -OC(O)R₇, -SC(O)R₇,
-NR₇C(O)R₇, -OC(O)OR₇, -SC(O)OR₇, -NR₇C(O)OR₇, -OCH₂C(O)R₇,
-SCH₂C(O)R₇, -NR₇CH₂C(O)R₇, -OCH₂C(O)OR₇, -SCH₂C(O)OR₇,
-NR₇CH₂C(O)OR₇, -OCH₂C(O)NR₁₀R₁₁, -SCH₂C(O)NR₁₀R₁₁,
15 -NR₇CH₂C(O)NR₁₀R₁₁, -OS(O)_pR₇, -SS(O)_pR₇, -S(O)_pOR₇, -NR₇S(O)_pR₇,
-OS(O)_pNR₁₀R₁₁, -SS(O)_pNR₁₀R₁₁, -NR₇S(O)_pNR₁₀R₁₁, -OS(O)_pOR₇, -SS(O)_pOR₇,
-NR₇S(O)_pOR₇, -OC(S)R₇, -SC(S)R₇, -NR₇C(S)R₇, -OC(S)OR₇, -SC(S)OR₇,
-NR₇C(S)OR₇, -OC(S)NR₁₀R₁₁, -SC(S)NR₁₀R₁₁, -NR₇C(S)NR₁₀R₁₁, -OC(NR₈)R₇,
-SC(NR₈)R₇, -NR₇C(NR₈)R₇, -OC(NR₈)OR₇, -SC(NR₈)OR₇, -NR₇C(NR₈)OR₇,
20 -OC(NR₈)NR₁₀R₁₁, -SC(NR₈)NR₁₀R₁₁, or -NR₇C(NR₈)NR₁₀R₁₁, -OP(O)(OR₇)₂ or
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R₃ is -OH, -SH, -NR₇H, -NHR₂₆, -O(CH₂)_mOH, -O(CH₂)_mSH,
-O(CH₂)_mNR₇H, -S(CH₂)_mOH, -S(CH₂)_mSH, -S(CH₂)_mNR₇H, -OC(O)NR₁₀R₁₁,
-SC(O)NR₁₀R₁₁, -NR₇C(O)NR₁₀R₁₁, -OC(O)R₇, -SC(O)R₇, -NR₇C(O)R₇,
25 -OC(O)OR₇, -SC(O)OR₇, -NR₇C(O)OR₇, -OCH₂C(O)R₇, -SCH₂C(O)R₇,

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- $-\text{NR}_7\text{CH}_2\text{C}(\text{O})\text{R}_7$, $-\text{OCH}_2\text{C}(\text{O})\text{OR}_7$, $-\text{SCH}_2\text{C}(\text{O})\text{OR}_7$, $-\text{NR}_7\text{CH}_2\text{C}(\text{O})\text{OR}_7$,
 $-\text{OCH}_2\text{C}(\text{O})\text{NR}_{10}\text{R}_{11}$, $-\text{SCH}_2\text{C}(\text{O})\text{NR}_{10}\text{R}_{11}$, $-\text{NR}_7\text{CH}_2\text{C}(\text{O})\text{NR}_{10}\text{R}_{11}$, $-\text{OS}(\text{O})_p\text{R}_7$,
 $-\text{SS}(\text{O})_p\text{R}_7$, $-\text{S}(\text{O})_p\text{OR}_7$, $-\text{NR}_7\text{S}(\text{O})_p\text{R}_7$, $-\text{OS}(\text{O})_p\text{NR}_{10}\text{R}_{11}$, $-\text{SS}(\text{O})_p\text{NR}_{10}\text{R}_{11}$,
 $-\text{NR}_7\text{S}(\text{O})_p\text{NR}_{10}\text{R}_{11}$, $-\text{OS}(\text{O})_p\text{OR}_7$, $-\text{SS}(\text{O})_p\text{OR}_7$, $-\text{NR}_7\text{S}(\text{O})_p\text{OR}_7$, $-\text{OC}(\text{S})\text{R}_7$,
5 $-\text{SC}(\text{S})\text{R}_7$, $-\text{NR}_7\text{C}(\text{S})\text{R}_7$, $-\text{OC}(\text{S})\text{OR}_7$, $-\text{SC}(\text{S})\text{OR}_7$, $-\text{NR}_7\text{C}(\text{S})\text{OR}_7$, $-\text{OC}(\text{S})\text{NR}_{10}\text{R}_{11}$,
 $-\text{SC}(\text{S})\text{NR}_{10}\text{R}_{11}$, $-\text{NR}_7\text{C}(\text{S})\text{NR}_{10}\text{R}_{11}$, $-\text{OC}(\text{NR}_8)\text{R}_7$, $-\text{SC}(\text{NR}_8)\text{R}_7$, $-\text{NR}_7\text{C}(\text{NR}_8)\text{R}_7$,
 $-\text{OC}(\text{NR}_8)\text{OR}_7$, $-\text{SC}(\text{NR}_8)\text{OR}_7$, $-\text{NR}_7\text{C}(\text{NR}_8)\text{OR}_7$, $-\text{OC}(\text{NR}_8)\text{NR}_{10}\text{R}_{11}$,
 $-\text{SC}(\text{NR}_8)\text{NR}_{10}\text{R}_{11}$, $-\text{NR}_7\text{C}(\text{NR}_8)\text{NR}_{10}\text{R}_{11}$, $-\text{C}(\text{O})\text{OH}$, $-\text{C}(\text{O})\text{NHR}_8$, $-\text{C}(\text{O})\text{SH}$,
 $-\text{S}(\text{O})\text{OH}$, $-\text{S}(\text{O})_2\text{OH}$, $-\text{S}(\text{O})\text{NHR}_8$, $-\text{S}(\text{O})_2\text{NHR}_8$, $-\text{OP}(\text{O})(\text{OR}_7)_2$, or $-\text{SP}(\text{O})(\text{OR}_7)_2$.
10 In another embodiment, $-\text{OR}_{26}$ and $-\text{SR}_{26}$, are additional values for R_3 ;
ring B is further optionally substituted with one or more substituents in
addition to $-\text{NR}^a\text{R}^b$;
 R^a and R^b , for each occurrence, is independently -H, an optionally substituted
alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an
15 optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an
optionally substituted heterocyclyl, an optionally substituted aryl or heteroaryl, an
optionally substituted aralkyl; or R^a and R^b , taken together with the nitrogen to
which they are attached, form an optionally substituted heteroaryl or heterocyclyl;
 R_7 and R_8 , for each occurrence, is independently, -H, an optionally
20 substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl,
an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an
optionally substituted heterocyclyl, an optionally substituted aryl, an optionally
substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted
heteraralkyl;
25 R_{10} and R_{11} , for each occurrence, is independently -H, an optionally
substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl,
an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an
optionally substituted heterocyclyl, an optionally substituted aryl, an optionally
substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted
30 heteraralkyl; or R_{10} and R_{11} , taken together with the nitrogen to which they are
attached, form an optionally substituted heterocyclyl or an optionally substituted
heteroaryl;

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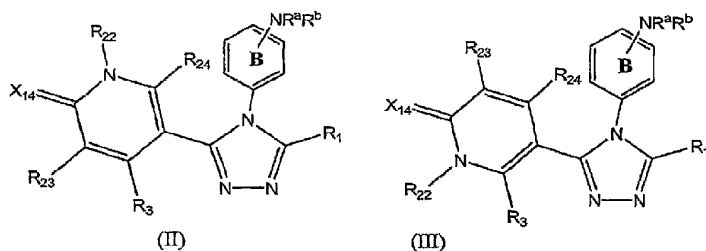
R_{26} is a C1-C6 alkyl;

p , for each occurrence, is independently, 0, 1 or 2; and

m , for each occurrence, is independently, 1, 2, 3 or 4.

In another embodiment, the present invention provides compounds

5 represented by a structural formula selected from (II) and (III):



or a tautomer, pharmaceutically acceptable salt, solvate, clathrate or a

10 prodrug thereof.

In formulas (II) and (III), ring B is further optionally substituted with one or more substituents in addition to $-NR^aR^b$;

R_1 is -OH, -SH, $-NR_7H$, $-OR_{26}$, $-SR_{26}$, $-NHR_{26}$, $-O(CH_2)_mOH$,
 $-O(CH_2)_mSH$, $-O(CH_2)_mNR_7H$, $-S(CH_2)_mOH$, $-S(CH_2)_mSH$, $-S(CH_2)_mNR_7H$,
 15 $-OC(O)NR_{10}R_{11}$, $-SC(O)NR_{10}R_{11}$, $-NR_7C(O)NR_{10}R_{11}$, $-OC(O)R_7$, $-SC(O)R_7$,
 $-NR_7C(O)R_7$, $-OC(O)OR_7$, $-SC(O)OR_7$, $-NR_7C(O)OR_7$, $-OCH_2C(O)R_7$,
 $-SCH_2C(O)R_7$, $-NR_7CH_2C(O)R_7$, $-OCH_2C(O)OR_7$, $-SCH_2C(O)OR_7$,
 $-NR_7CH_2C(O)OR_7$, $-OCH_2C(O)NR_{10}R_{11}$, $-SCH_2C(O)NR_{10}R_{11}$,
 $-NR_7CH_2C(O)NR_{10}R_{11}$, $-OS(O)_pR_7$, $-SS(O)_pR_7$, $-NR_7S(O)_pR_7$, $-OS(O)_pNR_{10}R_{11}$,
 20 $-SS(O)_pNR_{10}R_{11}$, $-NR_7S(O)_pNR_{10}R_{11}$, $-OS(O)_pOR_7$, $-SS(O)_pOR_7$, $-NR_7S(O)_pOR_7$,
 $-OC(S)R_7$, $-SC(S)R_7$, $-NR_7C(S)R_7$, $-OC(S)OR_7$, $-SC(S)OR_7$, $-NR_7C(S)OR_7$,
 $-OC(S)NR_{10}R_{11}$, $-SC(S)NR_{10}R_{11}$, $-NR_7C(S)NR_{10}R_{11}$, $-OC(NR_8)R_7$, $-SC(NR_8)R_7$,
 $-NR_7C(NR_8)R_7$, $-OC(NR_8)OR_7$, $-SC(NR_8)OR_7$, $-NR_7C(NR_8)OR_7$,
 $-OC(NR_8)NR_{10}R_{11}$, $-SC(NR_8)NR_{10}R_{11}$, or $-NR_7C(NR_8)NR_{10}R_{11}$, $-S(O)_pOR_7$,
 25 $-OP(O)(OR_7)_2$ or $-SP(O)(OR_7)_2$.

R_3 is -OH, -SH, $-NR_7H$, $-OR_{26}$, $-SR_{26}$, $-NHR_{26}$, $-O(CH_2)_mOH$,
 $-O(CH_2)_mSH$, $-O(CH_2)_mNR_7H$, $-S(CH_2)_mOH$, $-S(CH_2)_mSH$, $-S(CH_2)_mNR_7H$,

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- OC(O)NR₁₀R₁₁, -SC(O)NR₁₀R₁₁, -NR₇C(O)NR₁₀R₁₁, -OC(O)R₇, -SC(O)R₇,
 -NR₇C(O)R₇, -OC(O)OR₇, -SC(O)OR₇, -NR₇C(O)OR₇, -OCH₂C(O)R₇,
 -SCH₂C(O)R₇, -NR₇CH₂C(O)R₇, -OCH₂C(O)OR₇, -SCH₂C(O)OR₇,
 -NR₇CH₂C(O)OR₇, -OCH₂C(O)NR₁₀R₁₁, -SCH₂C(O)NR₁₀R₁₁,
 5 -NR₇CH₂C(O)NR₁₀R₁₁, -OS(O)_pR₇, -SS(O)_pR₇, -NR₇S(O)_pR₇, -OS(O)_pNR₁₀R₁₁,
 -SS(O)_pNR₁₀R₁₁, -NR₇S(O)_pNR₁₀R₁₁, -OS(O)_pOR₇, -SS(O)_pOR₇, -NR₇S(O)_pOR₇,
 -OC(S)R₇, -SC(S)R₇, -NR₇C(S)R₇, -OC(S)OR₇, -SC(S)OR₇, -NR₇C(S)OR₇,
 -OC(S)NR₁₀R₁₁, -SC(S)NR₁₀R₁₁, -NR₇C(S)NR₁₀R₁₁, -OC(NR₈)R₇, -SC(NR₈)R₇,
 -NR₇C(NR₈)R₇, -OC(NR₈)OR₇, -SC(NR₈)OR₇, -NR₇C(NR₈)OR₇,
 10 -OC(NR₈)NR₁₀R₁₁, -SC(NR₈)NR₁₀R₁₁, -NR₇C(NR₈)NR₁₀R₁₁, -C(O)OH,
 -C(O)NHR₈, -C(O)SH, -S(O)OH, -S(O)₂OH, -S(O)NHR₈, -S(O)₂NHR₈,
 -S(O)_pOR₇, -OP(O)(OR₇)₂, or -SP(O)(OR₇)₂;

- R₇ and R₈, for each occurrence, is independently, -H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl,
 15 an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteraralkyl;

- R₁₀ and R₁₁, for each occurrence, is independently -H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl,
 20 an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteraralkyl; or R₁₀ and R₁₁, taken together with the nitrogen to which they are
 25 attached, form an optionally substituted heterocyclyl or an optionally substituted heteroaryl;

- R₂₂, for each occurrence, is independently -H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an
 30 optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteraralkyl;

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heteraralkyl, a haloalkyl, $-C(O)R_7$, $-C(O)OR_7$, $-OC(O)R_7$, $-C(O)NR_{10}R_{11}$,
 $-NR_8C(O)R_7$, $-S(O)_pR_7$, $-S(O)_pOR_7$, or $-S(O)_pNR_{10}R_{11}$;

R_{23} and R_{24} , for each occurrence, is independently $-H$, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl,
 5 an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteraralkyl, halo, cyano, nitro, guanidino, a haloalkyl, a heteroalkyl, $-NR_{10}R_{11}$,
 $-OR_7$, $-C(O)R_7$, $-C(O)OR_7$, $-OC(O)R_7$, $-C(O)NR_{10}R_{11}$, $-NR_8C(O)R_7$, $-SR_7$,
 10 $-S(O)_pR_7$, $-OS(O)_pR_7$, $-S(O)_pOR_7$, $-NR_8S(O)_pR_7$, or $-S(O)_pNR_{10}R_{11}$;

R_{26} is a C1-C6 alkyl;

R^a and R^b , for each occurrence, is independently $-H$, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl or heteroaryl, an optionally substituted aralkyl; or R^a and R^b , taken together with the nitrogen to which they are attached, form an optionally substituted heteroaryl or heterocyclyl;

X_{14} is O, S, or NR_7 . Preferably, X_{14} is O;

p , for each occurrence, is independently, 0, 1 or 2; and

20 m , for each occurrence, is independently, 1, 2, 3, or 4.

In yet another embodiment, the present invention is a method of inhibiting Hsp90 in a mammal in need of such treatment. The method comprises administering to the mammal an effective amount of a Hsp90 inhibitor disclosed herein.

Yet another embodiment of the present invention is a method of inhibiting Hsp90 in a cell. The method comprises administering to the cell an effective amount of a Hsp90 inhibitor disclosed herein.

Yet another embodiment of the present invention is a method of treating a proliferative disorder in a mammal comprising administering an effective amount of a Hsp90 inhibitor disclosed herein.

30 Another embodiment of the present invention is a method of treating cancer in a mammal. The method comprises administering to the mammal an effective amount of a Hsp90 inhibitor disclosed herein.

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Yet another embodiment of the present invention is a pharmaceutical composition comprising a Hsp90 inhibitor disclosed herein and a pharmaceutically acceptable carrier. The pharmaceutical compositions can be used in therapy, e.g., to inhibit Hsp90 activity in a mammal in need of such inhibition, to treat a mammal with a proliferative disorder, or to treat a mammal with cancer.

Yet another embodiment of the present invention is the use of a Hsp90 inhibitor disclosed herein for the manufacture of a medicament for inhibiting Hsp90 in a mammal in need of such inhibition or for treating a mammal with cancer.

The compounds shown in Table 1 or compounds of any formula herein, or tautomers, pharmaceutically acceptable salts, solvates, clathrates, hydrates, polymorphs or prodrugs thereof, inhibit the activity of Hsp90 and, thereby cause the degradation of Hsp90 client proteins. Hsp90 is necessary for the survival of normal eukaryotic cells. However, Hsp90 is over expressed in many tumor types indicating that it may play a significant role in the survival of cancer cells and that cancer cells may be more sensitive to inhibition of Hsp90 than normal cells. Thus, the compounds shown in Table 1 or compounds of any formula herein, or tautomers, pharmaceutically acceptable salts, solvates, clathrates, hydrates, polymorphs or prodrugs thereof, are useful treating proliferative disorders such as cancer.

Although chemotherapeutic agents initially cause tumor regression, most agents that are currently used to treat cancer target only one pathway to tumor progression. Therefore, in many instances, after treatment with one or more chemotherapeutic agents, a tumor develops multidrug resistance and no longer responds positively to treatment. One of the advantages of inhibiting Hsp90 activity is that several of its client proteins, which are mostly protein kinases or transcription factors involved in signal transduction, have been shown to be involved in the progression of cancer. Thus, inhibition of Hsp90 provides a method of short circuiting several pathways for tumor progression simultaneously. Therefore, treatment of tumors with an Hsp90 inhibitor of the invention either alone, or in combination with other chemotherapeutic agents, is more likely to result in regression or elimination of the tumor, and less likely to result in the development of more aggressive multidrug resistant tumors than other currently available therapies.

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BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a graph showing an FACSCalibur flow cytometer analysis of the c-kit positive population of Kasumi-1 cells treated with Hsp90 inhibitors of the invention or 17AAG (as a positive control). The results indicate that the Hsp90 inhibitors of the invention induce c-kit degradation at a lower concentration than 17AAG, an Hsp90 inhibitor that is currently in phase II clinical trials.

Figure 2 is a Western blot analysis of the c-kit from Kasumi-1 cells treated with Hsp90 inhibitors of the invention or 17AAG (as a positive control).

Figure 3 is a Western blot analysis of the c-met from NCI-H1193 cells treated with Hsp90 inhibitors of the invention or 17AAG (as a positive control).

DETAILED DESCRIPTION OF THE INVENTION

A description of preferred embodiments of the invention follows.

The present invention provides compounds disclosed herein and uses of said compounds to inhibit Hsp90 activity and for the treatment of a proliferative disorder, such as cancer. In particular, the present invention encompasses the use of compounds of the invention to slow or stop the growth of cancerous cells or to reduce or eliminate cancerous cells in a subject, preferably the subject is a mammal.

In certain embodiments, the compounds of the invention can be used in combination with other chemotherapeutic agents and may help to prevent or reduce the development of multidrug resistant cancerous cells in a mammal. In this embodiment, the compounds of the invention may allow a reduced efficacious amount of a second chemotherapeutic agent given to a mammal, because compounds of the invention should inhibit the development of multidrug resistant cancerous cells.

A. Terminology

Unless otherwise specified, the below terms used herein are defined as follows:

As used herein, the term "alkyl" means a saturated straight chain or branched non-cyclic hydrocarbon having from 1 to 10 carbon atoms. Representative saturated

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straight chain alkyls include methyl, ethyl, n-propyl, n-butyl, n-pentyl, n-hexyl, n-heptyl, n-octyl, n-nonyl and n-decyl; while saturated branched alkyls include isopropyl, *sec*-butyl, isobutyl, *tert*-butyl, isopentyl, 2-methylbutyl, 3-methylbutyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 2-methylhexyl, 3-methylhexyl, 4-methylhexyl, 5-methylhexyl, 2,3-dimethylbutyl, 2,3-dimethylpentyl, 2,4-dimethylpentyl, 2,3-dimethylhexyl, 2,4-dimethylhexyl, 2,5-dimethylhexyl, 2,2-dimethylpentyl, 2,2-dimethylhexyl, 3,3-dimethylpentyl, 3,3-dimethylhexyl, 4,4-dimethylhexyl, 2-ethylpentyl, 3-ethylpentyl, 2-ethylhexyl, 3-ethylhexyl, 4-ethylhexyl, 2-methyl-2-ethylpentyl, 2-methyl-3-ethylpentyl, 2-methyl-4-ethylpentyl, 2-methyl-2-ethylhexyl, 2-methyl-3-ethylhexyl, 2-methyl-4-ethylhexyl, 2,2-diethylpentyl, 3,3-diethylhexyl, 2,2-diethylhexyl, 3,3-diethylhexyl and the like. The term "(C₁-C₆)alkyl" means a saturated straight chain or branched non-cyclic hydrocarbon having from 1 to 6 carbon atoms. Representative (C₁-C₆)alkyl groups are those shown above having from 1 to 6 carbon atoms. Alkyl groups included in compounds of this invention may be optionally substituted with one or more substituents.

As used herein, the term "alkenyl" means a saturated straight chain or branched non-cyclic hydrocarbon having from 2 to 10 carbon atoms and having at least one carbon-carbon double bond. Representative straight chain and branched (C₂-C₁₀)alkenyls include vinyl, allyl, 1-butenyl, 2-butenyl, isobutenyl, 1-pentenyl, 2-pentenyl, 3-methyl-1-butenyl, 2-methyl-2-butenyl, 2,3-dimethyl-2-butenyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 1-heptenyl, 2-heptenyl, 3-heptenyl, 1-octenyl, 2-octenyl, 3-octenyl, 1-nonenyl, 2-nonenyl, 3-nonenyl, 1-decenyl, 2-decenyl, 3-decenyl and the like. Alkenyl groups may be optionally substituted with one or more substituents.

As used herein, the term "alkynyl" means a saturated straight chain or branched non-cyclic hydrocarbon having from 2 to 10 carbon atoms and having at least one carbon-carbon triple bond. Representative straight chain and branched alkynyls include acetylenyl, propynyl, 1-butyne, 2-butyne, 1-pentyne, 2-pentyne, 3-methyl-1-butyne, 4-pentyne, 1-hexyne, 2-hexyne, 5-hexyne, 1-heptyne, 2-heptyne, 6-heptyne, 1-octyne, 2-octyne, 7-octyne, 1-nonyne, 2-nonyne, 8-

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nonyl, 1-decyl, 2-decyl, 9-decyl, and the like. Alkyl groups may be optionally substituted with one or more substituents.

As used herein, the term "cycloalkyl" means a saturated, mono- or polycyclic alkyl radical having from 3 to 20 carbon atoms. Representative cycloalkyls include cyclopropyl, 1-methylcyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl, octahydro-pentalenyl, and the like. Cycloalkyl groups may be optionally substituted with one or more substituents.

As used herein, the term "cycloalkenyl" means a mono- or poly- cyclic non-aromatic alkyl radical having at least one carbon-carbon double bond in the cyclic system and from 3 to 20 carbon atoms. Representative cycloalkenyls include cyclopentenyl, cyclopentadienyl, cyclohexenyl, cyclohexadienyl, cycloheptenyl, cycloheptadienyl, cycloheptatrienyl, cyclooctenyl, cyclooctadienyl, cyclooctatrienyl, cyclononatrienyl, cyclodecenyl, cyclodecadienyl, 1,2,3,4,5,8-hexahydronaphthalenyl and the like. Cycloalkenyl groups may be optionally substituted with one or more substituents.

As used herein, the term "haloalkyl" means an alkyl group, in which one or more (including all) the hydrogen radicals are replaced by a halo group, wherein each halo group is independently selected from -F, -Cl, -Br, and -I. The term "halomethyl" means a methyl in which one to three hydrogen radical(s) have been replaced by a halo group. Representative haloalkyl groups include trifluoromethyl, bromomethyl, 1,2-dichloroethyl, 4-iodobutyl, 2-fluoropentyl, and the like.

As used herein, an "alkoxy" is an alkyl group which is attached to another moiety via an oxygen linker.

As used herein, a "haloalkoxy" is a haloalkyl group which is attached to another moiety via an oxygen linker.

As used herein, the term an "aromatic ring" or "aryl" means a hydrocarbon monocyclic or polycyclic radical in which at least one ring is aromatic. Examples of suitable aryl groups include, but are not limited to, phenyl, tolyl, anthracenyl, fluorenyl, indenyl, azulenyl, and naphthyl, as well as benzo-fused carbocyclic moieties such as 5,6,7,8-tetrahydronaphthyl. Aryl groups may be optionally substituted with one or more substituents. In one embodiment, the aryl group is a

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monocyclic ring, wherein the ring comprises 6 carbon atoms, referred to herein as "(C₆)aryl."

As used herein, the term "aralkyl" means an aryl group that is attached to another group by a (C₁-C₆)alkylene group. Representative aralkyl groups include benzyl, 2-phenyl-ethyl, naphth-3-yl-methyl and the like. Aralkyl groups may be optionally substituted with one or more substituents.

As used herein, the term "alkylene" refers to an alkyl group that has two points of attachment. The term "(C₁-C₆)alkylene" refers to an alkylene group that has from one to six carbon atoms. Straight chain (C₁-C₆)alkylene groups are preferred. Non-limiting examples of alkylene groups include methylene (-CH₂-), ethylene (-CH₂CH₂-), n-propylene (-CH₂CH₂CH₂-), isopropylene (-CH₂CH(CH₃)-), and the like. Alkylene groups may be optionally substituted with one or more substituents.

As used herein, the term "heterocyclyl" means a monocyclic (typically having 3- to 10-members) or a polycyclic (typically having 7- to 20-members) heterocyclic ring system which is either a saturated ring or a unsaturated non-aromatic ring. A 3- to 10-membered heterocycle can contain up to 5 heteroatoms; and a 7- to 20-membered heterocycle can contain up to 7 heteroatoms. Typically, a heterocycle has at least one carbon atom ring member. Each heteroatom is independently selected from nitrogen, which can be oxidized (e.g., N(O)) or quaternized; oxygen; and sulfur, including sulfoxide and sulfone. The heterocycle may be attached via any heteroatom or carbon atom. Representative heterocycles include morpholinyl, thiomorpholinyl, pyrrolidinonyl, pyrrolidinyl, piperidinyl, piperazinyl, hydantoinyl, valerolactamyl, oxiranyl, oxetanyl, tetrahydrofuranyl, tetrahydropyranlyl, tetrahydropyrindinyl, tetrahydropyrimidinyl, tetrahydrothiophenyl, tetrahydrothiopyranlyl, and the like. A heteroatom may be substituted with a protecting group known to those of ordinary skill in the art, for example, the hydrogen on a nitrogen may be substituted with a tert-butoxycarbonyl group. Furthermore, the heterocyclyl may be optionally substituted with one or more substituents. Only stable isomers of such substituted heterocyclic groups are contemplated in this definition.

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- As used herein, the term "heteroaromatic", "heteroaryl" or like terms means a monocyclic or polycyclic heteroaromatic ring comprising carbon atom ring members and one or more heteroatom ring members. Each heteroatom is independently selected from nitrogen, which can be oxidized (e.g., N(O)) or
- 5 quaternized; oxygen; and sulfur, including sulfoxide and sulfone. Representative heteroaryl groups include pyridyl, 1-oxo-pyridyl, furanyl, benzo[1,3]dioxolyl, benzo[1,4]dioxinyl, thienyl, pyrrolyl, oxazolyl, imidazolyl, thiazolyl, a isoxazolyl, quinolinyl, pyrazolyl, isothiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, a triazinyl, triazolyl, thiadiazolyl, isoquinolinyl, indazolyl, benzoxazolyl, benzofuryl,
- 10 indoliziny, imidazopyridyl, tetrazolyl, benzimidazolyl, benzothiazolyl, benzothiadiazolyl, benzoxadiazolyl, indolyl, tetrahydroindolyl, azaindolyl, imidazopyridyl, quinazolinyl, purinyl, pyrrolo[2,3]pyrimidinyl, pyrazolo[3,4]pyrimidinyl, imidazo[1,2-a]pyridyl, and benzothienyl. In one embodiment, the heteroaromatic ring is selected from 5-8 membered monocyclic
- 15 heteroaryl rings. The point of attachment of a heteroaromatic or heteroaryl ring may be at either a carbon atom or a heteroatom of the heteroaromatic or heteroaryl rings. Heteroaryl groups may be optionally substituted with one or more substituents.
- As used herein, the term "(C₅)heteroaryl" means an aromatic heterocyclic ring of 5 members, wherein at least one carbon atom of the ring is replaced with a
- 20 heteroatom such as, for example, oxygen, sulfur or nitrogen. Representative (C₅)heteroaryls include furanyl, thienyl, pyrrolyl, oxazolyl, imidazolyl, thiazolyl, isoxazolyl, pyrazolyl, isothiazolyl, pyrazinyl, triazolyl, thiadiazolyl, and the like.
- As used herein, the term "(C₆)heteroaryl" means an aromatic heterocyclic ring of 6 members, wherein at least one carbon atom of the ring is replaced with a
- 25 heteroatom such as, for example, oxygen, nitrogen or sulfur. Representative (C₆)heteroaryls include pyridyl, pyridazinyl, pyrazinyl, triazinyl, tetrazinyl and the like.
- As used herein, the term "heteroaralkyl" means a heteroaryl group that is attached to another group by a (C₁-C₆)alkylene. Representative heteroaralkyls
- 30 include 2-(pyridin-4-yl)-propyl, 2-(thien-3-yl)-ethyl, imidazol-4-yl-methyl and the like. Heteroaralkyl groups may be optionally substituted with one or more substituents.

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As used herein, the term "halogen" or "halo" means -F, -Cl, -Br or -I.

As used herein the term "heteroalkyl" means a linear straight or branched chain alkyl group, wherein one or more of the internal carbon atoms in the chain is replaced by a heteroatom, such as, O, N or S, e.g., $-\text{[CH}_2\text{]}_x\text{-O-[CH}_2\text{]}_y\text{[CH}_3\text{]}$ wherein
 5 x is a positive integer and y is 0 or a positive integer, and wherein replacement of the carbon atom does not result in a unstable compound.

Suitable substituents for an alkyl, alkylene, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclyl, aryl, aralkyl, heteroaryl, and heteroaralkyl groups include arc those substituents which form a stable compound of the invention
 10 without significantly adversely affecting the reactivity or biological activity of the compound of the invention. Examples of substituents for an alkyl, alkylene, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclyl, aryl, aralkyl, heteroaryl, and heteroarylalkyl include an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an
 15 optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteraralkyl, an optionally substituted haloalkyl, an optionally substituted heteroalkyl, optionally substituted alkoxy,
 -C(O)NR₂₈R₂₉, -C(S)NR₂₈R₂₉, -C(NR₃₂)NR₂₈R₂₉, -NR₃₃C(O)R₃₁, -NR₃₃C(S)R₃₁,
 20 -NR₃₃C(NR₃₂)R₃₁, halo, -OR₃₃, cyano, nitro, haloalkoxy, -C(O)R₃₃, -C(S)R₃₃,
 -C(NR₃₂)R₃₃, -NR₂₈R₂₉, -C(O)OR₃₃, -C(S)OR₃₃, -C(NR₃₂)OR₃₃, -OC(O)R₃₃,
 -OC(S)R₃₃, -OC(NR₃₂)R₃₃, -NR₃₀C(O)NR₂₈R₂₉, -NR₃₃C(S)NR₂₈R₂₉,
 -NR₃₃C(NR₃₂)NR₂₈R₂₉, -OC(O)NR₂₈R₂₉, -OC(S)NR₂₈R₂₉, -OC(NR₃₂)NR₂₈R₂₉,
 -NR₃₃C(O)OR₃₁, -NR₃₃C(S)OR₃₁, -NR₃₃C(NR₃₂)OR₃₁, -S(O)_hR₃₃, -OS(O)_pR₃₃,
 25 -NR₃₃S(O)_pR₃₃, -S(O)_pNR₂₈R₂₉, -OS(O)_pNR₂₈R₂₉, or -NR₃₃S(O)_pNR₂₈R₂₉
 guanadino, -C(O)SR₃₁, -C(S)SR₃₁, -C(NR₃₂)SR₃₁, -OC(O)OR₃₁, -OC(S)OR₃₁,
 -OC(NR₃₂)OR₃₁, -SC(O)R₃₃, -SC(O)OR₃₁, -SC(NR₃₂)OR₃₁, -SC(S)R₃₃, -SC(S)OR₃₁,
 -SC(O)NR₂₈R₂₉, -SC(NR₃₂)NR₂₈R₂₉, -SC(S)NR₂₈R₂₉, -SC(NR₃₂)R₃₃, -OS(O)_pOR₃₁,
 -S(O)_pOR₃₁, -NR₃₀S(O)_pOR₃₁, -SS(O)_pR₃₃, -SS(O)_pOR₃₁, -SS(O)_pNR₂₈R₂₉,
 30 -OP(O)(OR₃₁)₂, or -SP(O)(OR₃₁)₂, (preferably the alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclyl, aryl, heteroaryl, aralkyl, heteroalkyl, alkoxy, heteroaralkyl and haloalkyl are unsubstituted); wherein R₂₈ and R₂₉, for each

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occurrence is independently, H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteraralkyl (preferably the alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclyl, aryl, heteroaryl, aralkyl and heteraralkyl are unsubstituted);

R_{33} and R_{31} for each occurrence is independently, H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteraralkyl (preferably the alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclyl, aryl, heteroaryl, aralkyl, and heteraralkyl are unsubstituted); and

R_{32} , for each occurrence is independently, H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteraralkyl, $-C(O)R_{33}$, $-C(O)NR_{28}R_{29}$, $-S(O)_pR_{33}$, or $-S(O)_pNR_{28}R_{29}$ (preferably the alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclyl, aryl, heteroaryl, aralkyl and heteraralkyl are unsubstituted);

p is 0, 1 or 2; and

h is 0, 1 or 2.

In addition, alkyl, cycloalkyl, alkylene, a heterocyclyl, and any saturated portion of a alkenyl, cycloalkenyl, alkynyl, aralkyl, and heteroaralkyl groups, may also be substituted with $=O$, $=S$, $=N-R_{32}$.

When a heterocyclyl, heteroaryl, or heteroaralkyl group contains a nitrogen atom, it may be substituted or unsubstituted. When a nitrogen atom in the aromatic ring of a heteroaryl group has a substituent the nitrogen may be a quaternary nitrogen.

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As used herein, the terms "subject", "patient" and "mammal" are used interchangeably. The terms "subject" and "patient" refer to an animal (*e.g.*, a bird such as a chicken, quail or turkey, or a mammal), preferably a mammal including a non-primate (*e.g.*, a cow, pig, horse, sheep, rabbit, guinea pig, rat, cat, dog, and mouse) and a primate (*e.g.*, a monkey, chimpanzee and a human), and more preferably a human. In one embodiment, the subject is a non-human animal such as a farm animal (*e.g.*, a horse, cow, pig or sheep), or a pet (*e.g.*, a dog, cat, guinea pig or rabbit). In a preferred embodiment, the subject is a human.

As used herein, the term "lower" refers to a group having up to four atoms. For example, a "lower alkyl" refers to an alkyl radical having from 1 to 4 carbon atoms, "lower alkoxy" refers to " $-\text{O}-(\text{C}_1-\text{C}_4)\text{alkyl}$ " and a "lower alkenyl" or "lower alkynyl" refers to an alkenyl or alkynyl radical having from 2 to 4 carbon atoms, respectively.

Unless indicated otherwise, the compounds of the invention containing reactive functional groups (such as (without limitation) carboxy, hydroxy, thiol, and amino moieties) also include protected derivatives thereof. "Protected derivatives" are those compounds in which a reactive site or sites are blocked with one or more protecting groups. Examples of suitable protecting groups for hydroxyl groups include benzyl, methoxymethyl, allyl, trimethylsilyl, tert-butyldimethylsilyl, acetate, and the like. Examples of suitable amine protecting groups include benzyloxycarbonyl, tert-butoxycarbonyl, tert-butyl, benzyl and fluorenylmethyloxycarbonyl (Fmoc). Examples of suitable thiol protecting groups include benzyl, tert-butyl, acetyl, methoxymethyl and the like. Other suitable protecting groups are well known to those of ordinary skill in the art and include those found in T. W. Greene, *Protecting Groups in Organic Synthesis*, John Wiley & Sons, Inc. 1981.

As used herein, the term "compound(s) of this invention" and similar terms refers to a compound of formula (I)- (XXXV), or Table 1, or a pharmaceutically acceptable salt, solvate, clathrate, hydrate, polymorph or prodrug thereof, and also include protected derivatives thereof.

The compounds of the invention may contain one or more chiral centers and/or double bonds and, therefore, exist as stereoisomers, such as double-bond isomers (*i.e.*, geometric isomers), enantiomers, or diastereomers. According to this

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invention, the chemical structures depicted herein, including the compounds of this invention, encompass all of the corresponding compounds' enantiomers, diastereomers and geometric isomers, that is, both the stereochemically pure form (e.g., geometrically pure, enantiomerically pure, or diastereomerically pure) and isomeric mixtures (e.g., enantiomeric, diastereomeric and geometric isomeric mixtures). In some cases, one enantiomer, diastereomer or geometric isomer will possess superior activity or an improved toxicity or kinetic profile compared to other isomers. In those cases, such enantiomers, diastereomers and geometric isomers of compounds of this invention are preferred.

10 As used herein, the term "polymorph" means solid crystalline forms of a compound of the present invention or complex thereof. Different polymorphs of the same compound can exhibit different physical, chemical and/or spectroscopic properties. Different physical properties include, but are not limited to stability (e.g., to heat or light), compressibility and density (important in formulation and product manufacturing), and dissolution rates (which can affect bioavailability).
15 Differences in stability can result from changes in chemical reactivity (e.g., differential oxidation, such that a dosage form discolors more rapidly when comprised of one polymorph than when comprised of another polymorph) or mechanical characteristics (e.g., tablets crumble on storage as a kinetically favored polymorph converts to thermodynamically more stable polymorph) or both (e.g., tablets of one polymorph are more susceptible to breakdown at high humidity).
20 Different physical properties of polymorphs can affect their processing. For example, one polymorph might be more likely to form solvates or might be more difficult to filter or wash free of impurities than another due to, for example, the shape or size distribution of particles of it.

25 As used herein, the term "hydrate" means a compound of the present invention or a salt thereof, that further includes a stoichiometric or non-stoichiometric amount of water bound by non-covalent intermolecular forces.

30 As used herein, the term "clathrate" means a compound of the present invention or a salt thereof in the form of a crystal lattice that contains spaces (e.g., channels) that have a guest molecule (e.g., a solvent or water) trapped within.

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As used herein and unless otherwise indicated, the term "prodrug" means a derivative of a compound that can hydrolyze, oxidize, or otherwise react under biological conditions (*in vitro* or *in vivo*) to provide a compound of this invention. Prodrugs may become active upon such reaction under biological conditions, or they may have activity in their unreacted forms. Examples of prodrugs contemplated in this invention include, but are not limited to, analogs or derivatives of compounds of formula (I) – (XXXV) or Table 1 that comprise biohydrolyzable moieties such as biohydrolyzable amides, biohydrolyzable esters, biohydrolyzable carbamates, biohydrolyzable carbonates, biohydrolyzable ureides, and biohydrolyzable phosphate analogues. Other examples of prodrugs include derivatives of compounds of formula (I) – (XXXV) or Table 1 that comprise -NO, -NO₂, -ONO, or -ONO₂ moieties. Prodrugs can typically be prepared using well-known methods, such as those described by 1 BURGER'S MEDICINAL CHEMISTRY AND DRUG DISCOVERY (1995) 172-178, 949-982 (Manfred E. Wolff ed., 5th ed).

As used herein and unless otherwise indicated, the terms "biohydrolyzable amide", "biohydrolyzable ester", "biohydrolyzable carbamate", "biohydrolyzable carbonate", "biohydrolyzable ureide" and "biohydrolyzable phosphate analogue" mean an amide, ester, carbamate, carbonate, ureide, or phosphate analogue, respectively, that either: 1) does not destroy the biological activity of the compound and confers upon that compound advantageous properties *in vivo*, such as improved water solubility, improved circulating half-life in the blood (e.g., because of reduced metabolism of the prodrug), improved uptake, improved duration of action, or improved onset of action; or 2) is itself biologically inactive but is converted *in vivo* to a biologically active compound. Examples of biohydrolyzable amides include, but are not limited to, lower alkyl amides, α -amino acid amides, alkoxyacyl amides, and alkylaminoalkylcarbonyl amides. Examples of biohydrolyzable esters include, but are not limited to, lower alkyl esters, alkoxyacyloxy esters, alkyl acylamino alkyl esters, and choline esters. Examples of biohydrolyzable carbamates include, but are not limited to, lower alkylamines, substituted ethylenediamines, aminoacids, hydroxyalkylamines, heterocyclic and heteroaromatic amines, and polyether amines.

As used herein, "Hsp90" includes each member of the family of heat shock proteins having a mass of about 90-kiloDaltons. For example, in humans the highly

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conserved Hsp90 family includes cytosolic Hsp90 α and Hsp90 β isoforms, as well as GRP94, which is found in the endoplasmic reticulum, and HSP75/TRAP1, which is found in the mitochondrial matrix.

The term "c-kit" or "c-kit kinase" refers to a membrane receptor protein tyrosine kinase which is preferably activated upon binding Stem Cell Factor (SCF) to its extracellular domain (Yarden et al., 1987; Qiu et al., 1988). The full length amino acid sequence of a c-kit kinase preferably is as set forth in Yarden, *et al.*, 1987, *EMBO J.*, 11:3341-3351; and Qiu, *et al.*, 1988, *EMBO J.*, 7:1003-1011, which are incorporated by reference herein in their entirety, including any drawings.

Mutant versions of c-kit kinase are encompassed by the term "c-kit" or "c-kit kinase" and include those that fall into two classes: (1) having a single amino acid substitution at codon 816 of the human c-kit kinase, or its equivalent position in other species (Ma *et al.*, 1999, *J. Invest Dermatol.*, 112:165-170), and (2) those which have mutations involving the putative juxtamembrane α -helix of the protein (Ma, *et al.*, 1999, *J. Biol. Chem.*, 274:13399-13402). Both of these publications are incorporated by reference herein in their entirety, including any drawings.

As used herein, "Bcr-Abl" is a fusion protein that results from the translocation of gene sequences from c-ABL protein tyrosine kinase on chromosome 9 into BCR sequences on chromosome 22 producing the Philadelphia chromosome.

A schematic representation of human Bcr, Abl, and Bcr-Abl can be seen in Figure 1 of U.S. patent application serial number 10/193,651, filed on July 9, 2002, the entire teachings of which are incorporated herein by reference. Depending on the breaking point in the Bcr gene, Bcr-Abl fusion proteins can vary in size from 185-230 kDa but they must contain at least the OLI domain from Bcr and the TK domain from Abl for transforming activity. The most common Bcr-Abl gene products found in humans are P230 Bcr-Abl, P210 Bcr-Abl, and P190 Bcr-Abl. P210 Bcr-Abl is characteristic of CML and P190 Bcr-Abl is characteristic of ALL.

FLT3 kinase is a tyrosine kinase receptor involved in the regulation and stimulation of cellular proliferation (see Gilliland *et al.*, *Blood* (2002), 100:1532-42, the entire teachings of which are incorporated herein by reference). The FLT3 kinase has five immunoglobulin-like domains in its extracellular region as well as an insert region of 75-100 amino acids in the middle of its cytoplasmic domain. FLT3 kinase

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is activated upon the binding of the FLT3 ligand, which causes receptor dimerization. Dimerization of the FLT3 kinase by FLT3 ligand activates the intracellular kinase activity as well as a cascade of downstream substrates including Stat5, Ras, phosphatidylinositol-3-kinase (PI3K), PLC γ , Erk2, Akt, MAPK, SHC, SHP2, and SHIP (see Rosnet *et al.*, *Acta Haematol.* (1996), 95:218; Hayakawa *et al.*, *Oncogene* (2000), 19:624; Mizuki *et al.*, *Blood* (2000), 96:3907; and Gilliland *et al.*, *Curr. Opin. Hematol.* (2002), 9: 274-81, the entire teachings of each of these references are incorporated herein by reference). Both membrane-bound and soluble FLT3 ligand bind, dimerize, and subsequently activate the FLT3 kinase.

Normal cells that express FLT3 kinase include immature hematopoietic cells, typically CD34+ cells, placenta, gonads, and brain (see Rosnet, *et al.*, *Blood* (1993), 82:1110-19; Small *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* (1994), 91:459-63; and Rosnet *et al.*, *Leukemia* (1996), 10:238-48, the entire teachings of each of these references are incorporated herein by reference). However, efficient stimulation of proliferation via FLT3 kinase typically requires other hematopoietic growth factors or interleukins. FLT3 kinase also plays a critical role in immune function through its regulation of dendritic cell proliferation and differentiation (see McKenna *et al.*, *Blood* (2000), 95:3489-97, the entire teachings of which are incorporated herein by reference).

Numerous hematologic malignancies express FLT3 kinase, the most prominent of which is AML (see Yokota *et al.*, *Leukemia* (1997), 11:1605-09, the entire teachings of which are incorporated herein by reference). Other FLT3 expressing malignancies include B-precursor cell acute lymphoblastic leukemias, myelodysplastic leukemias, T-cell acute lymphoblastic leukemias, and chronic myelogenous leukemias (see Rasko *et al.*, *Leukemia* (1995), 9:2058-66, the entire teachings of which are incorporated herein by reference).

FLT3 kinase mutations associated with hematologic malignancies are activating mutations. In other words, the FLT3 kinase is constitutively activated without the need for binding and dimerization by FLT3 ligand, and therefore stimulates the cell to grow continuously. Two types of activating mutations have been identified: internal tandem duplications (ITDs) and point mutation in the activating loop of the kinase domain. As used herein, the term "FLT3 kinase"

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refers to both wild type FLT3 kinase and mutant FLT3 kinases, such as FLT3 kinases that have activating mutations.

Compounds provided herein are useful in treating conditions characterized by inappropriate FLT3 activity such as proliferative disorders. Inappropriate FLT3 activity includes, but is not limited to, enhanced FLT3 activity resulting from increased or de novo expression of FLT3 in cells, increased FLT3 expression or activity, and FLT3 mutations resulting in constitutive activation. The existence of inappropriate or abnormal FLT3 ligand and FLT3 levels or activity can be determined using well known methods in the art. For example, abnormally high FLT3 levels can be determined using commercially available ELISA kits. FLT3 levels can be determined using flow cytometric analysis, immunohistochemical analysis, and in situ hybridization techniques.

By "epidermal growth factor receptor" or "EGFR" as used herein is meant, any epidermal growth factor receptor (EGFR) protein, peptide, or polypeptide having EGFR or EGFR family (e.g., HER1, HER2, HER3, and/or HER4) activity (such as encoded by EGFR Genbank Accession Nos. shown in Table I of U.S. Patent Application Serial No. 10/923,354, filed on August 20, 2004, the entire teachings of which are incorporated herein by reference), or any other EGFR transcript derived from a EGFR gene and/or generated by EGFR translocation. The term "EGFR" is also meant to include other EGFR protein, peptide, or polypeptide derived from EGFR isoforms (e.g., HER1, HER2, HER3, and/or HER4), mutant EGFR genes, splice variants of EGFR genes, and EGFR gene polymorphisms.

As used herein, a "proliferative disorder" or a "hyperproliferative disorder," and other equivalent terms, means a disease or medical condition involving pathological growth of cells. Proliferative disorders include cancer, smooth muscle cell proliferation, systemic sclerosis, cirrhosis of the liver, adult respiratory distress syndrome, idiopathic cardiomyopathy, lupus erythematosus, retinopathy, e.g., diabetic retinopathy or other retinopathies, cardiac hyperplasia, reproductive system associated disorders such as benign prostatic hyperplasia and ovarian cysts, pulmonary fibrosis, endometriosis, fibromatosis, hamartomas, lymphangiomatosis, sarcoidosis, desmoid tumors,

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Smooth muscle cell proliferation includes hyperproliferation of cells in the vasculature, for example, intimal smooth muscle cell hyperplasia, restenosis and vascular occlusion, particularly stenosis following biologically- or mechanically-mediated vascular injury, e.g., vascular injury associated with angioplasty.

5 Moreover, intimal smooth muscle cell hyperplasia can include hyperplasia in smooth muscle other than the vasculature, e.g., bile duct blockage, bronchial airways of the lung in patients with asthma, in the kidneys of patients with renal interstitial fibrosis, and the like.

10 Non-cancerous proliferative disorders also include hyperproliferation of cells in the skin such as psoriasis and its varied clinical forms, Reiter's syndrome, pityriasis rubra pilaris, and hyperproliferative variants of disorders of keratinization (e.g., actinic keratosis, senile keratosis), scleroderma, and the like.

In a preferred embodiment, the proliferative disorder is cancer. Cancers that can be treated or prevented by the methods of the present invention include, but are not limited to human sarcomas and carcinomas, e.g., fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilms' tumor, cervical cancer, testicular tumor, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendroglioma, meningioma, melanoma, neuroblastoma, retinoblastoma; leukemias, e.g., acute lymphocytic leukemia and acute myelocytic leukemia (myeloblastic, promyelocytic, myelomonocytic, monocytic and erythroleukemia); chronic leukemia (chronic myelocytic (granulocytic) leukemia and chronic lymphocytic leukemia); and

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polycythemia vera, lymphoma (Hodgkin's disease and non-Hodgkin's disease), multiple myeloma, Waldenstrom's macroglobulinemia, and heavy chain disease.

Other examples of leukemias include acute and/or chronic leukemias, e.g., lymphocytic leukemia (e.g., as exemplified by the p388 (murine) cell line), large
 5 granular lymphocytic leukemia, and lymphoblastic leukemia; T-cell leukemias, e.g., T-cell leukemia (e.g., as exemplified by the CEM, Jurkat, and HSB-2 (acute), YAC-1 (murine) cell lines), T-lymphocytic leukemia, and T-lymphoblastic leukemia; B cell leukemia (e.g., as exemplified by the SB (acute) cell line), and B-lymphocytic leukemia; mixed cell leukemias, e.g., B and T cell leukemia and B and T
 10 lymphocytic leukemia; myeloid leukemias, e.g., granulocytic leukemia, myelocytic leukemia (e.g., as exemplified by the HL-60 (promyelocyte) cell line), and myelogenous leukemia (e.g., as exemplified by the K562(chronic) cell line); neutrophilic leukemia; eosinophilic leukemia; monocytic leukemia (e.g., as exemplified by the THP-1(acute) cell line); myelomonocytic leukemia; Naegeli-type
 15 myeloid leukemia; and nonlymphocytic leukemia. Other examples of leukemias are described in Chapter 60 of *The Chemotherapy Sourcebook*, Michael C. Perry Ed., Williams & Williams (1992) and Section 36 of *Holland Frie Cancer Medicine* 5th Ed., Bast et al. Eds., B.C. Decker Inc. (2000). The entire teachings of the preceding references are incorporated herein by reference.

20 In one embodiment, the disclosed method is believed to be particularly effective in treating subject with non-solid tumors such as multiple myeloma. In another embodiment, the disclosed method is believed to be particularly effective against T-leukemia (e.g., as exemplified by Jurkat and CEM cell lines); B-leukemia (e.g., as exemplified by the SB cell line); promyelocytes (e.g., as exemplified by the
 25 HL-60 cell line); uterine sarcoma (e.g., as exemplified by the MES-SA cell line); monocytic leukemia (e.g., as exemplified by the THP-1(acute) cell line); and lymphoma (e.g., as exemplified by the U937 cell line).

In one embodiment, the disclosed method is believed to be particularly effective in treating subject with non-Hodgkin's lymphoma (NHL). Lymphomas are
 30 generally classified as either Hodgkin's disease (HD) or non-Hodgkin's lymphomas (NHL). NHL differs from HD by the absence of Reed-Sternberg cells. The course of NHL is less predictable than HD and is more likely to spread to areas beyond the

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lymph nodes. NHL can be further divided into B-cell NHL and T-cell NHL each of which can be further categorized into a variety of different subtypes. For example, B-cell NHL includes Burkitt's lymphoma, follicular lymphoma, diffuse large B-cell lymphoma, nodal marginal zone B-cell lymphoma, plasma cell neoplasms, small
 5 lymphocytic lymphoma/chronic lymphocytic leukemia, mantle cell lymphoma, extranodal marginal zone B-cell lymphoma, and lymphoplasmacytic lymphoma/Waldenstrom macroglobulinemia. T-cell NHL include anaplastic large-cell lymphoma, precursor-T-cell lymphoblastic leukemia/lymphoma, unspecified peripheral T-cell lymphoma, acute lymphoblastic leukemia/lymphoma,
 10 angioimmunoblastic T-cell lymphoma, and mycosis fungoides.

Without wishing to be bound by any theory, it is believed that the compounds of the invention are useful for treating NHLs, including B-cell and T-cell NHLs, since Hsp90 is upregulated in many NHLs. In particular, in a survey of 412 cases of NHL in B-cell NHL, Hsp90 was found to be moderately to strongly
 15 over expressed in all cases of Burkitt's lymphoma (5/5, 100%), and in a subset of follicular lymphoma (17/28, 61%), diffuse large B-cell lymphoma (27/46, 59%), nodal marginal zone B-cell lymphoma (6/16, 38%), plasma cell neoplasms (14/39, 36%), small lymphocytic lymphoma/chronic lymphocytic leukemia (3/9, 33%), mantle cell lymphoma (12/38, 32%), and lymphoplasmacytic
 20 lymphoma/Waldenstrom macroglobulinemia (3/10, 30%). In addition, in T-cell NHL, Hsp90 was found to be moderately to strongly over expressed in a subset of anaplastic large-cell lymphoma (14/24, 58%), precursor-T-cell lymphoblastic leukemia/lymphoma (20/65, 31%), unspecified peripheral T-cell lymphoma (8/43, 23%), and angioimmunoblastic T-cell lymphoma (2/17, 12%). (See Valbuena, *et al.*, *Modern Pathology* (2005), 18:1343-1349, the entire teachings of which are
 25 incorporated herein by reference.)

Some of the disclosed methods can be particularly effective at treating subjects whose cancer has become "multi-drug resistant". A cancer which initially responded to an anti-cancer drug becomes resistant to the anti-cancer drug when the
 30 anti-cancer drug is no longer effective in treating the subject with the cancer. For example, many tumors will initially respond to treatment with an anti-cancer drug by decreasing in size or even going into remission, only to develop resistance to the

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drug. Drug resistant tumors are characterized by a resumption of their growth and/or reappearance after having seemingly gone into remission, despite the administration of increased dosages of the anti-cancer drug. Cancers that have developed resistance to two or more anti-cancer drugs are said to be "multi-drug resistant". For example, it is common for cancers to become resistant to three or more anti-cancer agents, often five or more anti-cancer agents and at times ten or more anti-cancer agents.

In one embodiment, compounds of the invention are vascular targeting agents. In one aspect, compounds of the invention are effective for blocking, occluding, or otherwise disrupting blood flow in "neovasculature." In one aspect, the invention provides a novel treatment for diseases involving the growth of new blood vessels ("neovasculature"), including, but not limited to: cancer; infectious diseases; autoimmune disorders; benign tumors, *e.g.* hemangiomas, acoustic neuromas, neurofibromas, trachomas, and pyogenic granulomas; arteriosclerotic plaques; ocular angiogenic diseases, *e.g.*, diabetic retinopathy, retinopathy of prematurity, macular degeneration, corneal graft rejection, neovascular glaucoma, retrolental fibroplasia, rubeosis, retinoblastoma, persistent hyperplastic vitreous syndrome, choroidal neovascularization, uveitis and Pterygia (abnormal blood vessel growth) of the eye; rheumatoid arthritis; psoriasis; warts; allergic dermatitis; blistering disease; Kaposi sarcoma; delayed wound healing; endometriosis; uterine bleeding; ovarian cysts; ovarian hyperstimulation; vasculogenesis; granulations; hypertrophic scars (keloids); nonunion fractures; scleroderma; trachoma; vascular adhesions; vascular malformations; DiGeorge syndrome; HHT; transplant arteriopathy; restinosis; obesity; myocardial angiogenesis; coronary collaterals; cerebral collaterals; arteriovenous malformations; ischemic limb angiogenesis; primary pulmonary hypertension; pulmonary edema; asthma; nasal polyps; inflammatory bowel disease; periodontal disease; ascites; peritoneal adhesions; Osler-Webber Syndrome; plaque neovascularization; telangiectasia; hemophiliac joints; synovitis; osteomyelitis; osteophyte formation; angiofibroma; fibromuscular dysplasia; wound granulation; Crohn's disease; and atherosclerosis.

Vascular targeting can be demonstrated by any method known to those skilled in the art, such as the method described herein in Examples 44 and 45.

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As used herein, the term "angiogenesis" refers to a fundamental process of generating new blood vessels in tissues or organs. Angiogenesis is involved with or associated with many diseases or conditions, including, but not limited to: cancer; ocular neovascular disease; age-related macular degeneration; diabetic retinopathy, 5 retinopathy of prematurity; corneal graft rejection; neovascular glaucoma; retrolental fibroplasias; epidemic keratoconjunctivitis; Vitamin A deficiency; contact lens overwear; atopic keratitis; superior limbic keratitis; pterygium keratitis sicca; sjogrens; acne rosacea; warts; eczema; phlyctenulosis; syphilis; Mycobacteria infections; lipid degeneration; chemical burns; bacterial ulcers; fungal ulcers; Herpes 10 simplex infections; Herpes zoster infections; protozoan infections; Kaposi's sarcoma; Mooren's ulcer; Terrien's marginal degeneration; marginal keratolysis; rheumatoid arthritis; systemic lupus; polyarteritis; trauma; Wegener's sarcoidosis; scleritis; Stevens-Johnson disease; pemphigoid; radial keratotomy; corneal graft rejection; diabetic retinopathy; macular degeneration; sickle cell anemia; sarcoid; 15 syphilis; pseudoxanthoma elasticum; Paget's disease; vein occlusion; artery occlusion; carotid obstructive disease; chronic uveitis/vitritis; mycobacterial infections; Lyme's disease; systemic lupus erythematosus; retinopathy of prematurity; Eales' disease; Behcet's disease; infections causing a retinitis or choroiditis; presumed ocular histoplasmosis; Best's disease; myopia; optic pits; 20 Stargardt's disease; pars planitis; chronic retinal detachment; hyperviscosity syndromes; toxoplasmosis; trauma and post-laser complications; diseases associated with rubeosis (neovascularization of the angle); diseases caused by the abnormal proliferation of fibrovascular or fibrous tissue including all forms of proliferative vitreoretinopathy; rheumatoid arthritis; osteoarthritis; ulcerative colitis; Crohn's 25 disease; Bartonellosis; atherosclerosis; Osler-Weber-Rendu disease; hereditary hemorrhagic telangiectasia; pulmonary hemangiomatosis; pre-eclampsia; endometriosis; fibrosis of the liver and of the kidney; developmental abnormalities (organogenesis); skin discolorations (e.g., hemangioma, nevus flammeus, or nevus simplex); wound healing; hypertrophic scars, i.e., keloids; wound granulation; 30 vascular adhesions; cat scratch disease (Rochele ninalia quintosa); ulcers (Helicobacter pylori); keratoconjunctivitis; gingivitis; periodontal disease; epulis; hepatitis; tonsillitis; obesity; rhinitis; laryngitis; tracheitis; bronchitis; bronchiolitis;

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pneumonia; interstitial pulmonary fibrosis; pulmonary edema; neurodermitis; thyroiditis; thyroid enlargement; endometriosis; glomerulonephritis; gastritis; inflammatory bone and cartilage destruction; thromboembolic disease; and Buerger's disease.

5 Anti-angiogenesis can be demonstrated by any method known to those skilled in the art, such as the method described herein in Examples 46 and 47.

As used herein, the term "pharmaceutically acceptable salt," is a salt formed from, for example, an acid and a basic group of one of the compounds of formula (I) – (XXXV) or Table 1. Illustrative salts include, but are not limited, to sulfate,
 10 citrate, acetate, oxalate, chloride, bromide, iodide, nitrate, bisulfate, phosphate, acid phosphate, isonicotinate, lactate, salicylate, acid citrate, tartrate, oleate, tannate, pantothenate, bitartrate, ascorbate, succinate, maleate, besylate, gentisinate, fumarate, gluconate, glucuronate, saccharate, formate, benzoate, glutamate, methanesulfonate, ethanesulfonate, benzenesulfonate, *p*-toluenesulfonate, and
 15 pamoate (*i.e.*, 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)) salts. The term "pharmaceutically acceptable salt" also refers to a salt prepared from a compound of formula (I) – (XXXV) or Table 1 having an acidic functional group, such as a carboxylic acid functional group, and a pharmaceutically acceptable inorganic or organic base. Suitable bases include, but are not limited to, hydroxides of alkali
 20 metals such as sodium, potassium, and lithium; hydroxides of alkaline earth metal such as calcium and magnesium; hydroxides of other metals, such as aluminum and zinc; ammonia, and organic amines, such as unsubstituted or hydroxy-substituted mono-, di-, or trialkylamines; dicyclohexylamine; tributyl amine; pyridine; N-methyl-N-ethylamine; diethylamine; triethylamine; mono-, bis-, or tris-(2-hydroxy-
 25 lower alkyl amines), such as mono-, bis-, or tris-(2-hydroxyethyl)amine, 2-hydroxy-tert-butylamine, or tris-(hydroxymethyl)methylamine, N, N-di-lower alkyl-N-(hydroxy lower alkyl)-amines, such as N,N-dimethyl-N-(2-hydroxyethyl)amine, or tri-(2-hydroxyethyl)amine; N-methyl-D-glucamine; and amino acids such as arginine, lysine, and the like. The term "pharmaceutically acceptable salt" also
 30 refers to a salt prepared from a compound of formula (I) – (XXXV) or Table 1 having a basic functional group, such as an amine functional group, and a pharmaceutically acceptable inorganic or organic acid. Suitable acids include, but

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are not limited to, hydrogen sulfate, citric acid, acetic acid, oxalic acid, hydrochloric acid (HCl), hydrogen bromide (HBr), hydrogen iodide (HI), nitric acid, hydrogen bisulfide, phosphoric acid, lactic acid, salicylic acid, tartaric acid, bitartronic acid, ascorbic acid, succinic acid, maleic acid, besylic acid, fumaric acid, gluconic acid, 5 glucaronic acid, formic acid, benzoic acid, glutamic acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, and *p*-toluenesulfonic acid.

As used herein, the term "pharmaceutically acceptable solvate," is a solvate formed from the association of one or more pharmaceutically acceptable solvent molecules to one of the compounds of formula (I) – (XXXV) or Table 1. The term 10 solvate includes hydrates (*e.g.*, hemihydrate, monohydrate, dihydrate, trihydrate, tetrahydrate, and the like).

A pharmaceutically acceptable carrier may contain inert ingredients which do not unduly inhibit the biological activity of the compounds. The pharmaceutically acceptable carriers should be biocompatible, *i.e.*, non-toxic, non-inflammatory, non-immunogenic and devoid of other undesired reactions upon the 15 administration to a subject. Standard pharmaceutical formulation techniques can be employed, such as those described in Remington's Pharmaceutical Sciences, *ibid*. Suitable pharmaceutical carriers for parenteral administration include, for example, sterile water, physiological saline, bacteriostatic saline (saline containing about 0.9% 20 mg/ml benzyl alcohol), phosphate-buffered saline, Hank's solution, Ringer's-lactate and the like. Methods for encapsulating compositions (such as in a coating of hard gelatin or cyclodextran) are known in the art (Baker, *et al.*, "Controlled Release of Biological Active Agents", John Wiley and Sons, 1986).

As used herein, the term "effective amount" refers to an amount of a 25 compound of this invention which is sufficient to reduce or ameliorate the severity, duration, progression, or onset of a proliferative disorder, prevent the advancement of a proliferative disorder, cause the regression of a proliferative, prevent the recurrence, development, onset or progression of a symptom associated with a proliferative disorder, or enhance or improve the prophylactic or therapeutic 30 effect(s) of another therapy. The precise amount of compound administered to a subject will depend on the mode of administration, the type and severity of the disease or condition and on the characteristics of the subject, such as general health,

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age, sex, body weight and tolerance to drugs. It will also depend on the degree, severity and type of cell proliferation, and the mode of administration. The skilled artisan will be able to determine appropriate dosages depending on these and other factors. When co-administered with other agents, e.g., when co-administered with an anti-cancer agent, an "effective amount" of the second agent will depend on the type of drug used. Suitable dosages are known for approved agents and can be adjusted by the skilled artisan according to the condition of the subject, the type of condition(s) being treated and the amount of a compound of the invention being used. In cases where no amount is expressly noted, an effective amount should be assumed.

Non-limiting examples of an effective amount of a compound of the invention are provided herein below. In a specific embodiment, the invention provides a method of preventing, treating, managing, or ameliorating a proliferative disorder or one or more symptoms thereof, said methods comprising administering to a subject in need thereof a dose of at least 150 $\mu\text{g/kg}$, preferably at least 250 $\mu\text{g/kg}$, at least 500 $\mu\text{g/kg}$, at least 1 mg/kg, at least 5 mg/kg, at least 10 mg/kg, at least 25 mg/kg, at least 50 mg/kg, at least 75 mg/kg, at least 100 mg/kg, at least 125 mg/kg, at least 150 mg/kg, or at least 200 mg/kg or more of one or more compounds of the invention once every day, preferably, once every 2 days, once every 3 days, once every 4 days, once every 5 days, once every 6 days, once every 7 days, once every 8 days, once every 10 days, once every two weeks, once every three weeks, or once a month.

The dosages of a chemotherapeutic agents other than compounds of the invention, which have been or are currently being used to prevent, treat, manage, or ameliorate a proliferative disorder, or one or more symptoms thereof, can be used in the combination therapies of the invention. Preferably, dosages lower than those which have been or are currently being used to prevent, treat, manage, or ameliorate a proliferative disorder, or one or more symptoms thereof, are used in the combination therapies of the invention. The recommended dosages of agents currently used for the prevention, treatment, management, or amelioration of a proliferative disorder, or one or more symptoms thereof, can be obtained from any reference in the art including, but not limited to, Hardman *et al.*, eds., 1996,

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Goodman & Gilman's The Pharmacological Basis Of Therapeutics 9th Ed, Mc-Graw-Hill, New York; Physician's Desk Reference (PDR) 57th Ed., 2003, Medical Economics Co., Inc., Montvale, NJ, which are incorporated herein by reference in its entirety.

5 As used herein, the terms "treat", "treatment" and "treating" refer to the reduction or amelioration of the progression, severity and/or duration of a proliferative disorder, or the amelioration of one or more symptoms (preferably, one or more discernible symptoms) of a proliferative disorder resulting from the administration of one or more therapies (e.g., one or more therapeutic agents such as
10 a compound of the invention). In specific embodiments, the terms "treat", "treatment" and "treating" refer to the amelioration of at least one measurable physical parameter of a proliferative disorder, such as growth of a tumor, not necessarily discernible by the patient. In other embodiments the terms "treat", "treatment" and "treating" refer to the inhibition of the progression of a proliferative
15 disorder, either physically by, e.g., stabilization of a discernible symptom, physiologically by, e.g., stabilization of a physical parameter, or both. In other embodiments the terms "treat", "treatment" and "treating" refer to the reduction or stabilization of tumor size or cancerous cell count.

 As used herein, the terms "prevent", "prevention" and "preventing" refer to
20 the reduction in the risk of acquiring or developing a given proliferative disorder, or the reduction or inhibition of the recurrence of a proliferative disorder. In one embodiment, a compound of the invention is administered as a preventative measure to a patient, preferably a human, having a genetic predisposition to any of the disorders described herein.

25 As used herein, the terms "therapeutic agent" and "therapeutic agents" refer to any agent(s) which can be used in the treatment, management, or amelioration of a proliferative disorder or one or more symptoms thereof. In certain embodiments, the term "therapeutic agent" refers to a compound of the invention. In certain other embodiments, the term "therapeutic agent" refers does not refer to a compound of
30 the invention. Preferably, a therapeutic agent is an agent which is known to be useful for, or has been or is currently being used for the treatment, management,

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prevention, or amelioration a proliferative disorder or one or more symptoms thereof.

As used herein, the term "synergistic" refers to a combination of a compound of the invention and another therapy (*e.g.*, a prophylactic or therapeutic agent), which is more effective than the additive effects of the therapies. A synergistic effect of a combination of therapies (*e.g.*, a combination of prophylactic or therapeutic agents) permits the use of lower dosages of one or more of the therapies and/or less frequent administration of said therapies to a subject with a proliferative disorder. The ability to utilize lower dosages of a therapy (*e.g.*, a prophylactic or therapeutic agent) and/or to administer said therapy less frequently reduces the toxicity associated with the administration of said therapy to a subject without reducing the efficacy of said therapy in the prevention, management or treatment of a proliferative disorder. In addition, a synergistic effect can result in improved efficacy of agents in the prevention, management or treatment of a proliferative disorder. Finally, a synergistic effect of a combination of therapies (*e.g.*, a combination of prophylactic or therapeutic agents) may avoid or reduce adverse or unwanted side effects associated with the use of either therapy alone.

As used herein, the phrase "side effects" encompasses unwanted and adverse effects of a therapy (*e.g.*, a prophylactic or therapeutic agent). Side effects are always unwanted, but unwanted effects are not necessarily adverse. An adverse effect from a therapy (*e.g.*, prophylactic or therapeutic agent) might be harmful or uncomfortable or risky. Side effects include, but are not limited to fever, chills, lethargy, gastrointestinal toxicities (including gastric and intestinal ulcerations and erosions), nausea, vomiting, neurotoxicities, nephrotoxicities, renal toxicities (including such conditions as papillary necrosis and chronic interstitial nephritis), hepatic toxicities (including elevated serum liver enzyme levels), myelotoxicities (including leukopenia, myelosuppression, thrombocytopenia and anemia), dry mouth, metallic taste, prolongation of gestation, weakness, somnolence, pain (including muscle pain, bone pain and headache), hair loss, asthenia, dizziness, extra-pyramidal symptoms, akathisia, cardiovascular disturbances and sexual dysfunction.

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As used herein, the term "in combination" refers to the use of more than one therapies (*e.g.*, one or more prophylactic and/or therapeutic agents). The use of the term "in combination" does not restrict the order in which therapies (*e.g.*, prophylactic and/or therapeutic agents) are administered to a subject with a proliferative disorder. A first therapy (*e.g.*, a prophylactic or therapeutic agent such as a compound of the invention) can be administered prior to (*e.g.*, 5 minutes, 15 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours, 48 hours, 72 hours, 96 hours, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 8 weeks, or 12 weeks before), concomitantly with, or subsequent to (*e.g.*, 5 minutes, 15 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours, 48 hours, 72 hours, 96 hours, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 8 weeks, or 12 weeks after) the administration of a second therapy (*e.g.*, a prophylactic or therapeutic agent such as an anti-cancer agent) to a subject with a proliferative disorder, such as cancer.

As used herein, the terms "therapies" and "therapy" can refer to any protocol(s), method(s), and/or agent(s) that can be used in the prevention, treatment, management, or amelioration of a proliferative disorder or one or more symptoms thereof.

As used herein, a "protocol" includes dosing schedules and dosing regimens. The protocols herein are methods of use and include prophylactic and therapeutic protocols.

As used herein, the terms "manage," "managing," and "management" refer to the beneficial effects that a subject derives from a therapy (*e.g.*, a prophylactic or therapeutic agent), which does not result in a cure of the disease. In certain embodiments, a subject is administered one or more therapies (*e.g.*, one or more prophylactic or therapeutic agents) to "manage" a disease so as to prevent the progression or worsening of the disease.

As used herein, a composition that "substantially" comprises a compound means that the composition contains more than about 80% by weight, more preferably more than about 90% by weight, even more preferably more than about 95% by weight, and most preferably more than about 97% by weight of the compound.

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As used herein, a reaction that is "substantially complete" means that the reaction contains more than about 80% by weight of the desired product, more preferably more than about 90% by weight of the desired product, even more preferably more than about 95% by weight of the desired product, and most
5 preferably more than about 97% by weight of the desired product.

As used herein, a racemic mixture means about 50% of one enantiomer and about 50% of its corresponding enantiomer relative to a chiral center in the molecule. The invention encompasses all enantiomerically-pure, enantiomerically-enriched, diastereomerically pure, diastereomerically enriched, and racemic mixtures of the
10 compounds of the invention.

Enantiomeric and diastereomeric mixtures can be resolved into their component enantiomers or diastereomers by well known methods, such as chiral-phase gas chromatography, chiral-phase high performance liquid chromatography, crystallizing the compound as a chiral salt complex, or crystallizing the compound in
15 a chiral solvent. Enantiomers and diastereomers can also be obtained from diastereomerically- or enantiomerically-pure intermediates, reagents, and catalysts by well known asymmetric synthetic methods.

The compounds of the invention are defined herein by their chemical structures and/or chemical names. Where a compound is referred to by both a
20 chemical structure and a chemical name, and the chemical structure and chemical name conflict, the chemical structure is determinative of the compound's identity.

When administered to a patient, *e.g.*, to a non-human animal for veterinary use or for improvement of livestock, or to a human for clinical use, the compounds of the invention are administered in isolated form or as the isolated form in a
25 pharmaceutical composition. As used herein, "isolated" means that the compounds of the invention are separated from other components of either (a) a natural source, such as a plant or cell, preferably bacterial culture, or (b) a synthetic organic chemical reaction mixture. Preferably, the compounds of the invention are purified via conventional techniques. As used herein, "purified" means that when isolated,
30 the isolate contains at least 95%, preferably at least 98%, of a compound of the invention by weight of the isolate either as a mixture of stereoisomers or as a diastereomeric or enantiomeric pure isolate.

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As used herein, a composition that is "substantially free" of a compound means that the composition contains less than about 20% by weight, more preferably less than about 10% by weight, even more preferably less than about 5% by weight, and most preferably less than about 3% by weight of the compound.

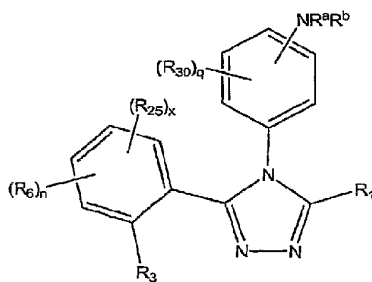
5 Only those choices and combinations of substituents that result in a stable structure are contemplated. Such choices and combinations will be apparent to those of ordinary skill in the art and may be determined without undue experimentation.

The invention can be understood more fully by reference to the following detailed description and illustrative examples, which are intended to exemplify non-
 10 limiting embodiments of the invention.

B. The Compounds of the Invention

In one embodiment the present invention provides compounds having
 15 formula (I) as described above or a tautomer, pharmaceutically acceptable salt, solvate, clathrate or a prodrug thereof.

In another embodiment the compounds of the present invention provides compounds represented by structural formula (IV):



(IV)

20 or a tautomer, pharmaceutically acceptable salt, solvate, clathrate or a prodrug thereof.

In formula (IV), R₁ is -OH, -SH, -NR₇H, -OR₂₆, -SR₂₆, -NHR₂₆,
 -O(CH₂)_mOH, -O(CH₂)_mSH, -O(CH₂)_mNR₇H, -S(CH₂)_mOH, -S(CH₂)_mSH,
 25 -S(CH₂)_mNR₇H, -OC(O)NR₁₀R₁₁, -SC(O)NR₁₀R₁₁, -NR₇C(O)NR₁₀R₁₁, -OC(O)R₇,
 -SC(O)R₇, -NR₇C(O)R₇, -OC(O)OR₇, -SC(O)OR₇, -NR₇C(O)OR₇,

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- OCH₂C(O)R₇, -SCH₂C(O)R₇, -NR₇CH₂C(O)R₇, -OCH₂C(O)OR₇,
 -SCH₂C(O)OR₇, -NR₇CH₂C(O)OR₇, -OCH₂C(O)NR₁₀R₁₁, -SCH₂C(O)NR₁₀R₁₁,
 -NR₇CH₂C(O)NR₁₀R₁₁, -OS(O)_pR₇, -SS(O)_pR₇, -S(O)_pOR₇, -NR₇S(O)_pR₇,
 -OS(O)_pNR₁₀R₁₁, -SS(O)_pNR₁₀R₁₁, -NR₇S(O)_pNR₁₀R₁₁, -OS(O)_pOR₇, -SS(O)_pOR₇,
 5 -NR₇S(O)_pOR₇, -OC(S)R₇, -SC(S)R₇, -NR₇C(S)R₇, -OC(S)OR₇, -SC(S)OR₇,
 -NR₇C(S)OR₇, -OC(S)NR₁₀R₁₁, -SC(S)NR₁₀R₁₁, -NR₇C(S)NR₁₀R₁₁, -OC(NR₈)R₇,
 -SC(NR₈)R₇, -NR₇C(NR₈)R₇, -OC(NR₈)OR₇, -SC(NR₈)OR₇, -NR₇C(NR₈)OR₇,
 -OC(NR₈)NR₁₀R₁₁, -SC(NR₈)NR₁₀R₁₁, or -NR₇C(NR₈)NR₁₀R₁₁, -OP(O)(OR₇)₂,
 -SP(O)(OR₇)₂. Preferably, R₁ is -OH, -SH, -NHR₇, -OC(O)NR₁₀R₁₁,
 10 -SC(O)NR₁₀R₁₁, -OC(O)R₇, -SC(O)R₇, -OC(O)OR₇, -SC(O)OR₇, -OS(O)_pR₇,
 -S(O)_pOR₇, -SS(O)_pR₇, -OS(O)_pOR₇, -SS(O)_pOR₇, -OC(S)R₇, -SC(S)R₇, -OC(S)OR₇,
 -SC(S)OR₇, -OC(S)NR₁₀R₁₁, -SC(S)NR₁₀R₁₁, -OC(NR₈)R₇, -SC(NR₈)R₇,
 -OC(NR₈)OR₇, -SC(NR₈)OR₇, -OP(O)(OR₇)₂ or -SP(O)(OR₇)₂. More preferably, R₁
 is -OH, -SH, or -NHR₇. Even more preferably, R₁ is -SH or -OH;
 15 R₃ is -OH, -SH, -NR₇H, -NHR₂₆, -O(CH₂)_mOH, -O(CH₂)_mSH,
 -O(CH₂)_mNR₇H, -S(CH₂)_mOH, -S(CH₂)_mSH, -S(CH₂)_mNR₇H, -OC(O)NR₁₀R₁₁,
 -SC(O)NR₁₀R₁₁, -NR₇C(O)NR₁₀R₁₁, -OC(O)R₇, -SC(O)R₇, -NR₇C(O)R₇,
 -OC(O)OR₇, -SC(O)OR₇, -NR₇C(O)OR₇, -OCH₂C(O)R₇, -SCH₂C(O)R₇,
 -NR₇CH₂C(O)R₇, -OCH₂C(O)OR₇, -SCH₂C(O)OR₇, -NR₇CH₂C(O)OR₇,
 20 -OCH₂C(O)NR₁₀R₁₁, -SCH₂C(O)NR₁₀R₁₁, -NR₇CH₂C(O)NR₁₀R₁₁, -OS(O)_pR₇,
 -SS(O)_pR₇, -S(O)_pOR₇, -NR₇S(O)_pR₇, -OS(O)_pNR₁₀R₁₁, -SS(O)_pNR₁₀R₁₁,
 -NR₇S(O)_pNR₁₀R₁₁, -OS(O)_pOR₇, -SS(O)_pOR₇, -NR₇S(O)_pOR₇, -OC(S)R₇,
 -SC(S)R₇, -NR₇C(S)R₇, -OC(S)OR₇, -SC(S)OR₇, -NR₇C(S)OR₇, -OC(S)NR₁₀R₁₁,
 -SC(S)NR₁₀R₁₁, -NR₇C(S)NR₁₀R₁₁, -OC(NR₈)R₇, -SC(NR₈)R₇, -NR₇C(NR₈)R₇,
 25 -OC(NR₈)OR₇, -SC(NR₈)OR₇, -NR₇C(NR₈)OR₇, -OC(NR₈)NR₁₀R₁₁,
 -SC(NR₈)NR₁₀R₁₁, -NR₇C(NR₈)NR₁₀R₁₁, -C(O)OH, -C(O)NHR₈, -C(O)SH,
 -S(O)OH, -S(O)₂OH, -S(O)NHR₈, -S(O)₂NHR₈, -OP(O)(OR₇)₂, or -SP(O)(OR₇)₂.
 In another embodiment, -OR₂₆ and -SR₂₆, are additional values for R₃. Preferably,
 R₃ is -OH, -SH, -NHR₇, -OC(O)NR₁₀R₁₁, -SC(O)NR₁₀R₁₁, -OC(O)R₇, -SC(O)R₇,
 30 -OC(O)OR₇, -SC(O)OR₇, -OS(O)_pR₇, -S(O)_pOR₇, -SS(O)_pR₇, -OS(O)_pOR₇,
 -SS(O)_pOR₇, -OC(S)R₇, -SC(S)R₇, -OC(S)OR₇, -SC(S)OR₇, -OC(S)NR₁₀R₁₁,
 -SC(S)NR₁₀R₁₁, -OC(NR₈)R₇, -SC(NR₈)R₇, -OC(NR₈)OR₇, -SC(NR₈)OR₇,

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-OP(O)(OR₇)₂ or -SP(O)(OR₇)₂. More preferably, R₃ is -OH, -SH, or -NHR₇.
Even more preferably, R₃ is -SH or -OH;

- R₆ for each occurrence, is independently an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteroaralkyl, halo, cyano, nitro, guanidino, a haloalkyl, a heteroalkyl, alkoxy, haloalkoxy, -NR₁₀R₁₁, -OR₇, -C(O)R₇, -C(O)OR₇, -C(S)R₇, -C(O)SR₇, -C(S)SR₇, -C(S)OR₇, -C(S)NR₁₀R₁₁, -C(NR₈)OR₇, -C(NR₈)R₇, -C(NR₈)NR₁₀R₁₁, -C(NR₈)SR₇, -OC(O)R₇, -OC(O)OR₇, -OC(S)OR₇, -OC(NR₈)OR₇, -SC(O)R₇, -SC(O)OR₇, -SC(NR₈)OR₇, -OC(S)R₇, -SC(S)R₇, -SC(S)OR₇, -OC(O)NR₁₀R₁₁, -OC(S)NR₁₀R₁₁, -OC(NR₈)NR₁₀R₁₁, -SC(O)NR₁₀R₁₁, -SC(NR₈)NR₁₀R₁₁, -SC(S)NR₁₀R₁₁, -OC(NR₈)R₇, -SC(NR₈)R₇, -C(O)NR₁₀R₁₁, -NR₈C(O)R₇, -NR₇C(S)R₇, -NR₇C(S)OR₇, -NR₇C(NR₈)R₇, -NR₇C(O)OR₇, -NR₇C(NR₈)OR₇, -NR₇C(O)NR₁₀R₁₁, -NR₇C(S)NR₁₀R₁₁, -NR₇C(NR₈)NR₁₀R₁₁, -SR₇, -S(O)_pR₇, -OS(O)_pR₇, -OS(O)_pOR₇, -OS(O)_pNR₁₀R₁₁, -S(O)_pOR₇, -NR₈S(O)_pR₇, -NR₇S(O)_pNR₁₀R₁₁, -NR₇S(O)_pOR₇, -S(O)_pNR₁₀R₁₁, -SS(O)_pR₇, -SS(O)_pOR₇, -SS(O)_pNR₁₀R₁₁, -OP(O)(OR₇)₂, or -SP(O)(OR₇)₂. Preferably, R₆ for each occurrence, is independently an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, cyano, halo, nitro, an optionally substituted cycloalkyl, haloalkyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteroaralkyl, -OR₇, -SR₇, -NR₁₀R₁₁, -OC(O)NR₁₀R₁₁, -SC(O)NR₁₀R₁₁, -NR₇C(O)NR₁₀R₁₁, -OC(O)R₇, -SC(O)R₇, -NR₇C(O)R₇, -OC(O)OR₇, -SC(O)OR₇, -NR₇C(O)OR₇, -OCH₂C(O)R₇, -SCH₂C(O)R₇, -NR₇CH₂C(O)R₇, -OCH₂C(O)OR₇, -SCH₂C(O)OR₇, -NR₇CH₂C(O)OR₇, -OCH₂C(O)NR₁₀R₁₁, -SCH₂C(O)NR₁₀R₁₁, -NR₇CH₂C(O)NR₁₀R₁₁, -OS(O)_pR₇, -SS(O)_pR₇, -NR₇S(O)_pR₇, -OS(O)_pNR₁₀R₁₁, -SS(O)_pNR₁₀R₁₁, -NR₇S(O)_pNR₁₀R₁₁, -OS(O)_pOR₇, -SS(O)_pOR₇, -NR₇S(O)_pOR₇, -OC(S)R₇, -SC(S)R₇, -NR₇C(S)R₇, -OC(S)OR₇, -SC(S)OR₇, -NR₇C(S)OR₇, -OC(S)NR₁₀R₁₁, -SC(S)NR₁₀R₁₁, -NR₇C(S)NR₁₀R₁₁, -OC(NR₈)R₇, -SC(NR₈)R₇,

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- $-\text{NR}_7\text{C}(\text{NR}_8)\text{R}_7$, $-\text{OC}(\text{NR}_8)\text{OR}_7$, $-\text{SC}(\text{NR}_8)\text{OR}_7$, $-\text{NR}_7\text{C}(\text{NR}_8)\text{OR}_7$,
 $-\text{OC}(\text{NR}_8)\text{NR}_{10}\text{R}_{11}$, $-\text{SC}(\text{NR}_8)\text{NR}_{10}\text{R}_{11}$, $-\text{NR}_7\text{C}(\text{NR}_8)\text{NR}_{10}\text{R}_{11}$, $-\text{C}(\text{O})\text{R}_7$,
 $-\text{C}(\text{O})\text{OR}_7$, $-\text{C}(\text{O})\text{NR}_{10}\text{R}_{11}$, $-\text{C}(\text{O})\text{SR}_7$, $-\text{C}(\text{S})\text{R}_7$, $-\text{C}(\text{S})\text{OR}_7$, $-\text{C}(\text{S})\text{NR}_{10}\text{R}_{11}$,
 $-\text{C}(\text{S})\text{SR}_7$, $-\text{C}(\text{NR}_8)\text{OR}_7$, $-\text{C}(\text{NR}_8)\text{R}_7$, $-\text{C}(\text{NR}_8)\text{NR}_{10}\text{R}_{11}$, $-\text{C}(\text{NR}_8)\text{SR}_7$, $-\text{S}(\text{O})_p\text{OR}_7$,
5 $-\text{S}(\text{O})_p\text{NR}_{10}\text{R}_{11}$, or $-\text{S}(\text{O})_p\text{R}_7$. More preferably, R_6 for each occurrence, is independently a C1-C6 alkyl, a C1-C6 haloalkyl, a C1-C6 alkoxy, a C1-C6 haloalkoxy, a C1-C6 alkyl sulfanyl or a C3-C6 cycloalkyl. Even more preferably, R_6 for each occurrence, is independently cyclopropyl or isopropyl;
 R_7 and R_8 , for each occurrence, is independently, -H, an optionally
10 substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteroaralkyl. Preferably, R_7 and R_8 , for each occurrence, is independently -H, C1-
15 C3 alkyl, C1-C6 cycloalkyl, an optionally substituted aryl or an optionally substituted heteroaryl. More preferably, R_7 and R_8 , for each occurrence, is independently -H or C1-C3 alkyl.

- R_{10} and R_{11} , for each occurrence, is independently -H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl,
20 an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteroaralkyl. Preferably, R_{10} and R_{11} , for each occurrence, is independently -H, C1-C3 alkyl, C1-C6 cycloalkyl, an optionally substituted aryl or an optionally
25 substituted heteroaryl. More preferably, R_{10} and R_{11} , for each occurrence, is independently -H or C1-C3 alkyl.

- Alternatively, R_{10} and R_{11} , taken together with the nitrogen to which they are attached, form an optionally substituted heterocyclyl or an optionally substituted heteroaryl. Preferably R_{10} and R_{11} , taken together with the nitrogen to which they are
30 attached, form an optionally substituted imidazolyl, pyrrolyl, pyrazolyl, triazolyl, tetrazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl, pyrrolidinyl, piperidinyl,

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morpholinyl, pyrazinyl, thiomorpholinyl, pyrrolidinyl, piperidinyl, pyranziny, thiomorpholinyl, tetrahydroquinolinyl or tetrahydroisoquinolinyl. More preferably R_{10} and R_{11} , taken together with the nitrogen to which they are attached, form an optionally substituted pyrrolidinyl, piperidinyl, piperazinyl, tetrahydroisoquinolinyl, morpholinyl or pyrazolyl.

R_{25} for each occurrence, is independently an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteraralkyl, halo, cyano, nitro, guanadino, a haloalkyl, a heteroalkyl, alkoxy, haloalkoxy, $-NR_{10}R_{11}$, $-OR_7$, $-C(O)R_7$, $-C(O)OR_7$, $-C(S)R_7$, $-C(O)SR_7$, $-C(S)SR_7$, $-C(S)OR_7$, $-C(S)NR_{10}R_{11}$, $-C(NR_8)OR_7$, $-C(NR_8)R_7$, $-C(NR_8)NR_{10}R_{11}$, $-C(NR_8)SR_7$, $-OC(O)R_7$, $-OC(O)OR_7$, $-OC(S)OR_7$, $-OC(NR_8)OR_7$, $-SC(O)R_7$, $-SC(O)OR_7$, $-SC(NR_8)OR_7$, $-OC(S)R_7$, $-SC(S)OR_7$, $-OC(O)NR_{10}R_{11}$, $-OC(S)NR_{10}R_{11}$, $-OC(NR_8)NR_{10}R_{11}$, $-SC(O)NR_{10}R_{11}$, $-SC(NR_8)NR_{10}R_{11}$, $-SC(S)NR_{10}R_{11}$, $-OC(NR_8)R_7$, $-SC(NR_8)R_7$, $-C(O)NR_{10}R_{11}$, $-NR_8C(O)R_7$, $-NR_7C(S)R_7$, $-NR_7C(S)OR_7$, $-NR_7C(NR_8)R_7$, $-NR_7C(O)OR_7$, $-NR_7C(NR_8)OR_7$, $-NR_7C(O)NR_{10}R_{11}$, $-NR_7C(S)NR_{10}R_{11}$, $-NR_7C(NR_8)NR_{10}R_{11}$, $-SR_7$, $-S(O)_pR_7$, $-OS(O)_pR_7$, $-OS(O)_pOR_7$, $-OS(O)_pNR_{10}R_{11}$, $-S(O)_pOR_7$, $-NR_8S(O)_pR_7$, $-NR_7S(O)_pNR_{10}R_{11}$, $-NR_7S(O)_pOR_7$, $-S(O)_pNR_{10}R_{11}$, $-SS(O)_pR_7$, $-SS(O)_pOR_7$, $-SS(O)_pNR_{10}R_{11}$, $-OP(O)(OR_7)_2$, or $-SP(O)(OR_7)_2$. Preferably R_{25} for each occurrence, is independently $-OH$, $-SH$, $-NHR_7$, $-(CH_2)_kOH$, $-(CH_2)_kSH$, $-(CH_2)_kNR_7H$, $-OCH_3$, $-SCH_3$, $-NHCH_3$, $-OCH_2CH_2OH$, $-OCH_2CH_2SH$, $-OCH_2CH_2NR_7H$, $-SCH_2CH_2OH$, $-SCH_2CH_2SH$, $-SCH_2CH_2NR_7H$, $-OC(O)NR_{10}R_{11}$, $-SC(O)NR_{10}R_{11}$, $-NR_7C(O)NR_{10}R_{11}$, $-OC(O)R_7$, $-SC(O)R_7$, $-NR_7C(O)R_7$, $-OC(O)OR_7$, $-SC(O)OR_7$, $-NR_7C(O)OR_7$, $-OCH_2C(O)R_7$, $-SCH_2C(O)R_7$, $-NR_7CH_2C(O)R_7$, $-OCH_2C(O)OR_7$, $-SCH_2C(O)OR_7$, $-NR_7CH_2C(O)OR_7$, $-OCH_2C(O)NR_{10}R_{11}$, $-SCH_2C(O)NR_{10}R_{11}$, $-NR_7CH_2C(O)NR_{10}R_{11}$, $-OS(O)_pR_7$, $-SS(O)_pR_7$, $-NR_7S(O)_pR_7$, $-OS(O)_pNR_{10}R_{11}$, $-SS(O)_pNR_{10}R_{11}$, $-NR_7S(O)_pNR_{10}R_{11}$, $-OS(O)_pOR_7$, $-SS(O)_pOR_7$, $-NR_7S(O)_pOR_7$, $-OC(S)R_7$, $-SC(S)R_7$, $-NR_7C(S)R_7$, $-OC(S)OR_7$, $-SC(S)OR_7$, $-NR_7C(S)OR_7$,

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- OC(S)NR₁₀R₁₁, -SC(S)NR₁₀R₁₁, -NR₇C(S)NR₁₀R₁₁, -OC(NR₈)R₇, -SC(NR₈)R₇,
 -NR₇C(NR₈)R₇, -OC(NR₈)OR₇, -SC(NR₈)OR₇, -NR₇C(NR₈)OR₇,
 -OC(NR₈)NR₁₀R₁₁, -SC(NR₈)NR₁₀R₁₁, -NR₇C(NR₈)NR₁₀R₁₁, -C(O)R₇,
 -C(O)OR₇, -C(O)NR₁₀R₁₁, -C(O)SR₇, -C(S)R₇, -C(S)OR₇, -C(S)NR₁₀R₁₁,
 5 -C(S)SR₇, -C(NR₈)OR₇, -C(NR₈)R₇, -C(NR₈)NR₁₀R₁₁, -C(NR₈)SR₇, -S(O)_pOR₇,
 -S(O)_pNR₁₀R₁₁, or -S(O)_pR₇. More preferably, R₂₃ for each occurrence, is
 independently -OH, -SH, -NHR₇, -OC(O)NR₁₀R₁₁, -SC(O)NR₁₀R₁₁, -OC(O)R₇,
 -SC(O)R₇, -OC(O)OR₇, -SC(O)OR₇, -OS(O)_pR₇, -S(O)_pOR₇, -SS(O)_pR₇,
 -OS(O)_pOR₇, -SS(O)_pOR₇, -OC(S)R₇, -SC(S)R₇, -OC(S)OR₇, -SC(S)OR₇,
 10 -OC(S)NR₁₀R₁₁, -SC(S)NR₁₀R₁₁, -OC(NR₈)R₇, -SC(NR₈)R₇, -OC(NR₈)OR₇,
 -SC(NR₈)OR₇, -OP(O)(OR₇)₂ or -SP(O)(OR₇)₂. Even more preferably, R₂₃ for each
 occurrence, is independently -SH or -OH;

R₂₆ is a C1-C6 alkyl;

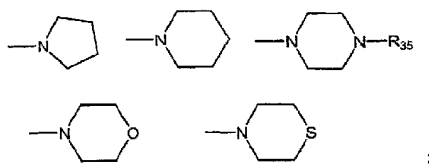
- R₃₀ for each occurrence, is independently an optionally substituted alkyl, an
 15 optionally substituted alkenyl, an optionally substituted alkynyl, an optionally
 substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally
 substituted heterocyclyl, an optionally substituted aryl, an optionally substituted
 heteroaryl, an optionally substituted aralkyl, an optionally substituted heteraralkyl,
 halo, cyano, nitro, guanadino, a haloalkyl, a heteroalkyl, alkoxy, haloalkoxy,
 20 -NR₁₀R₁₁, -OR₇, -C(O)R₇, -C(O)OR₇, -C(S)R₇, -C(O)SR₇, -C(S)SR₇, -C(S)OR₇,
 -C(S)NR₁₀R₁₁, -C(NR₈)OR₇, -C(NR₈)R₇, -C(NR₈)NR₁₀R₁₁, -C(NR₈)SR₇, -OC(O)R₇,
 -OC(O)OR₇, -OC(S)OR₇, -OC(NR₈)OR₇, -SC(O)R₇, -SC(O)OR₇, -SC(NR₈)OR₇,
 -OC(S)R₇, -SC(S)R₇, -SC(S)OR₇, -OC(O)NR₁₀R₁₁, -OC(S)NR₁₀R₁₁,
 -OC(NR₈)NR₁₀R₁₁, -SC(O)NR₁₀R₁₁, -SC(NR₈)NR₁₀R₁₁, -SC(S)NR₁₀R₁₁,
 25 -OC(NR₈)R₇, -SC(NR₈)R₇, -C(O)NR₁₀R₁₁, -NR₈C(O)R₇, -NR₇C(S)R₇,
 -NR₇C(S)OR₇, -NR₇C(NR₈)R₇, -NR₇C(O)OR₇, -NR₇C(NR₈)OR₇,
 -NR₇C(O)NR₁₀R₁₁, -NR₇C(S)NR₁₀R₁₁, -NR₇C(NR₈)NR₁₀R₁₁, -SR₇, -S(O)_pR₇,
 -OS(O)_pR₇, -OS(O)_pOR₇, -OS(O)_pNR₁₀R₁₁, -S(O)_pOR₇, -NR₈S(O)_pR₇,
 -NR₇S(O)_pNR₁₀R₁₁, -NR₇S(O)_pOR₇, -S(O)_pNR₁₀R₁₁, -SS(O)_pR₇, -SS(O)_pOR₇,
 30 -SS(O)_pNR₁₀R₁₁, -OP(O)(OR₇)₂, or -SP(O)(OR₇)₂. Preferably R₃₀ for each
 occurrence, is independently an optionally substituted alkyl, an optionally
 substituted alkenyl, an optionally substituted alkynyl, cyano, halo, nitro, an

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- optionally substituted cycloalkyl, haloalkyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteroaralkyl, -OR₇, -SR₇, -NR₁₀R₁₁, -OC(O)NR₁₀R₁₁, -SC(O)NR₁₀R₁₁, -NR₇C(O)NR₁₀R₁₁, -OC(O)R₇, -SC(O)R₇,
5 -NR₇C(O)R₇, -OC(O)OR₇, -SC(O)OR₇, -NR₇C(O)OR₇, -OCH₂C(O)R₇, -SCH₂C(O)R₇, -NR₇CH₂C(O)R₇, -OCH₂C(O)OR₇, -SCH₂C(O)OR₇, -NR₇CH₂C(O)OR₇, -OCH₂C(O)NR₁₀R₁₁, -SCH₂C(O)NR₁₀R₁₁, -NR₇CH₂C(O)NR₁₀R₁₁, -OS(O)_pR₇, -SS(O)_pR₇, -NR₇S(O)_pR₇, -OS(O)_pNR₁₀R₁₁, -SS(O)_pNR₁₀R₁₁, -NR₇S(O)_pNR₁₀R₁₁, -OS(O)_pOR₇, -SS(O)_pOR₇, -NR₇S(O)_pOR₇,
10 -OC(S)R₇, -SC(S)R₇, -NR₇C(S)R₇, -OC(S)OR₇, -SC(S)OR₇, -NR₇C(S)OR₇, -OC(S)NR₁₀R₁₁, -SC(S)NR₁₀R₁₁, -NR₇C(S)NR₁₀R₁₁, -OC(NR₈)R₇, -SC(NR₈)R₇, -NR₇C(NR₈)R₇, -OC(NR₈)OR₇, -SC(NR₈)OR₇, -NR₇C(NR₈)OR₇, -OC(NR₈)NR₁₀R₁₁, -SC(NR₈)NR₁₀R₁₁, -NR₇C(NR₈)NR₁₀R₁₁, -C(O)R₇, -C(O)OR₇, -C(O)NR₁₀R₁₁, -C(O)SR₇, -C(S)R₇, -C(S)OR₇, -C(S)NR₁₀R₁₁,
15 -C(S)SR₇, -C(NR₈)OR₇, -C(NR₈)R₇, -C(NR₈)NR₁₀R₁₁, -C(NR₈)SR₇, -S(O)_pOR₇, -S(O)_pNR₁₀R₁₁, or -S(O)_pR₇. More preferably, R₃₀ for each occurrence, is independently a hydrogen, -OH, -SH, halogen, cyano, a C1-C6 alkyl, C1-C6 haloalkyl, C1-C6 alkoxy, C1-C6 haloalkoxy or C1-C6 alkyl sulfanyl. Even more preferably, R₃₀ for each occurrence, is independently a hydrogen, methyl, ethyl,
20 propyl, isopropyl, methoxy or ethoxy;
R₃₅ is -H, a C1-C4 alkyl or a C1-C4 acyl;
R^a and R^b, for each occurrence, is independently -H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an
25 optionally substituted heterocyclyl, an optionally substituted aryl or heteroaryl, an optionally substituted aralkyl. Preferably, R^a and R^b for each occurrence, is independently a hydrogen, a C1-C6 straight or branched alkyl, optionally substituted by -OH, -CN, -SH, amino, a C1-C6 alkoxy, alkylsulfanyl, alkylamino, dialkylamino or a cycloalkyl. More preferably, R^a and R^b for each occurrence, is independently a
30 hydrogen, methyl, ethyl, propyl, isopropyl;
Alternatively, R^a and R^b, taken together with the nitrogen to which they are attached, form an optionally substituted heteroaryl or heterocyclyl. Preferably, R^a

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and R^b taken together with the nitrogen to which they are attached form a substituted or unsubstituted nonaromatic, nitrogen-containing heterocyclyl. More preferably, R^a and R^b taken together with the nitrogen to which they are attached, are:



5 k is 1, 2, 3 or 4;

p, for each occurrence, is independently, 0, 1 or 2;

m, for each occurrence, is independently, 1, 2, 3 or 4;

n and q for each occurrence, is independently an integer from 0 to 4.

Preferably n and q for each occurrence, is independently 0, 1, or 2. More preferably

10 n and q for each occurrence, is independently 0 or 1; and

x is 0 or 1, provided that n+x is less than or equal to 4.

In a first preferred embodiment, the values for the variables in formula (IV) are as described in the following paragraphs;

15 R₆, R₂₅ and R₃₀, for each occurrence, is independently an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteraralkyl, halo, cyano, nitro, guanadino, a haloalkyl, a heteroalkyl, alkoxy, haloalkoxy, -NR₁₀R₁₁, -OR₇, -C(O)R₇, -C(O)OR₇, -C(S)R₇, -C(O)SR₇, -C(S)SR₇, -C(S)OR₇, -C(S)NR₁₀R₁₁, -C(NR₈)OR₇, -C(NR₈)R₇, -C(NR₈)NR₁₀R₁₁, -C(NR₈)SR₇, -OC(O)R₇, -OC(O)OR₇, -OC(S)OR₇, -OC(NR₈)OR₇, -SC(O)R₇, -SC(O)OR₇, -SC(NR₈)OR₇, -OC(S)R₇, -SC(S)R₇, -SC(S)OR₇, -OC(O)NR₁₀R₁₁, -OC(S)NR₁₀R₁₁, -OC(NR₈)NR₁₀R₁₁, -SC(O)NR₁₀R₁₁, -SC(NR₈)NR₁₀R₁₁, -SC(S)NR₁₀R₁₁, -OC(NR₈)R₇, -SC(NR₈)R₇, -C(O)NR₁₀R₁₁, -NR₈C(O)R₇, -NR₇C(S)R₇, -NR₇C(S)OR₇, -NR₇C(NR₈)R₇, -NR₇C(O)OR₇, -NR₇C(NR₈)OR₇, -NR₇C(O)NR₁₀R₁₁, -NR₇C(S)NR₁₀R₁₁, -NR₇C(NR₈)NR₁₀R₁₁, -SR₇, -S(O)_pR₇, -OS(O)_pR₇, -OS(O)_pOR₇, -OS(O)_pNR₁₀R₁₁, -S(O)_pOR₇, -NR₈S(O)_pR₇,

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- $-\text{NR}_7\text{S}(\text{O})_p\text{NR}_{10}\text{R}_{11}$, $-\text{NR}_7\text{S}(\text{O})_p\text{OR}_7$, $-\text{S}(\text{O})_p\text{NR}_{10}\text{R}_{11}$, $-\text{SS}(\text{O})_p\text{R}_7$, $-\text{SS}(\text{O})_p\text{OR}_7$,
 $-\text{SS}(\text{O})_p\text{NR}_{10}\text{R}_{11}$, $-\text{OP}(\text{O})(\text{OR}_7)_2$, or $-\text{SP}(\text{O})(\text{OR}_7)_2$. Preferably, R_6 and R_{30} are as just
described and R_{25} is $-\text{OH}$, $-\text{SH}$, $-\text{NHR}_7$, $-(\text{CH}_2)_k\text{OH}$, $-(\text{CH}_2)_k\text{SH}$, $-(\text{CH}_2)_k\text{NR}_7\text{H}$,
 $-\text{OCH}_3$, $-\text{SCH}_3$, $-\text{NHCH}_3$, $-\text{OCH}_2\text{CH}_2\text{OH}$, $-\text{OCH}_2\text{CH}_2\text{SH}$, $-\text{OCH}_2\text{CH}_2\text{NR}_7\text{H}$,
5 $-\text{SCH}_2\text{CH}_2\text{OH}$, $-\text{SCH}_2\text{CH}_2\text{SH}$, $-\text{SCH}_2\text{CH}_2\text{NR}_7\text{H}$, $-\text{OC}(\text{O})\text{NR}_{10}\text{R}_{11}$,
 $-\text{SC}(\text{O})\text{NR}_{10}\text{R}_{11}$, $-\text{NR}_7\text{C}(\text{O})\text{NR}_{10}\text{R}_{11}$, $-\text{OC}(\text{O})\text{R}_7$, $-\text{SC}(\text{O})\text{R}_7$, $-\text{NR}_7\text{C}(\text{O})\text{R}_7$,
 $-\text{OC}(\text{O})\text{OR}_7$, $-\text{SC}(\text{O})\text{OR}_7$, $-\text{NR}_7\text{C}(\text{O})\text{OR}_7$, $-\text{OCH}_2\text{C}(\text{O})\text{R}_7$, $-\text{SCH}_2\text{C}(\text{O})\text{R}_7$,
 $-\text{NR}_7\text{CH}_2\text{C}(\text{O})\text{R}_7$, $-\text{OCH}_2\text{C}(\text{O})\text{OR}_7$, $-\text{SCH}_2\text{C}(\text{O})\text{OR}_7$, $-\text{NR}_7\text{CH}_2\text{C}(\text{O})\text{OR}_7$,
 $-\text{OCH}_2\text{C}(\text{O})\text{NR}_{10}\text{R}_{11}$, $-\text{SCH}_2\text{C}(\text{O})\text{NR}_{10}\text{R}_{11}$, $-\text{NR}_7\text{CH}_2\text{C}(\text{O})\text{NR}_{10}\text{R}_{11}$, $-\text{OS}(\text{O})_p\text{R}_7$,
10 $-\text{SS}(\text{O})_p\text{R}_7$, $-\text{NR}_7\text{S}(\text{O})_p\text{R}_7$, $-\text{OS}(\text{O})_p\text{NR}_{10}\text{R}_{11}$, $-\text{SS}(\text{O})_p\text{NR}_{10}\text{R}_{11}$, $-\text{NR}_7\text{S}(\text{O})_p\text{NR}_{10}\text{R}_{11}$,
 $-\text{OS}(\text{O})_p\text{OR}_7$, $-\text{SS}(\text{O})_p\text{OR}_7$, $-\text{NR}_7\text{S}(\text{O})_p\text{OR}_7$, $-\text{OC}(\text{S})\text{R}_7$, $-\text{SC}(\text{S})\text{R}_7$, $-\text{NR}_7\text{C}(\text{S})\text{R}_7$,
 $-\text{OC}(\text{S})\text{OR}_7$, $-\text{SC}(\text{S})\text{OR}_7$, $-\text{NR}_7\text{C}(\text{S})\text{OR}_7$, $-\text{OC}(\text{S})\text{NR}_{10}\text{R}_{11}$, $-\text{SC}(\text{S})\text{NR}_{10}\text{R}_{11}$,
 $-\text{NR}_7\text{C}(\text{S})\text{NR}_{10}\text{R}_{11}$, $-\text{OC}(\text{NR}_8)\text{R}_7$, $-\text{SC}(\text{NR}_8)\text{R}_7$, $-\text{NR}_7\text{C}(\text{NR}_8)\text{R}_7$, $-\text{OC}(\text{NR}_8)\text{OR}_7$,
 $-\text{SC}(\text{NR}_8)\text{OR}_7$, $-\text{NR}_7\text{C}(\text{NR}_8)\text{OR}_7$, $-\text{OC}(\text{NR}_8)\text{NR}_{10}\text{R}_{11}$, $-\text{SC}(\text{NR}_8)\text{NR}_{10}\text{R}_{11}$,
15 $-\text{NR}_7\text{C}(\text{NR}_8)\text{NR}_{10}\text{R}_{11}$, $-\text{C}(\text{O})\text{R}_7$, $-\text{C}(\text{O})\text{OR}_7$, $-\text{C}(\text{O})\text{NR}_{10}\text{R}_{11}$, $-\text{C}(\text{O})\text{SR}_7$, $-\text{C}(\text{S})\text{R}_7$,
 $-\text{C}(\text{S})\text{OR}_7$, $-\text{C}(\text{S})\text{NR}_{10}\text{R}_{11}$, $-\text{C}(\text{S})\text{SR}_7$, $-\text{C}(\text{NR}_8)\text{OR}_7$, $-\text{C}(\text{NR}_8)\text{R}_7$, $-\text{C}(\text{NR}_8)\text{NR}_{10}\text{R}_{11}$,
 $-\text{C}(\text{NR}_8)\text{SR}_7$, $-\text{S}(\text{O})_p\text{OR}_7$, $-\text{S}(\text{O})_p\text{NR}_{10}\text{R}_{11}$, or $-\text{S}(\text{O})_p\text{R}_7$;

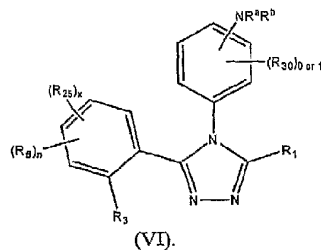
k is 1, 2, 3, or 4;

n and q for each occurrence, is independently an integer from 0 to 4;

- 20 x is 0 or 1, provided that $n+x$ less than or equal to 4; and

the values and preferred values for the remainder of the variables in formula (IV) are as described immediately above.

In a second preferred embodiment, the present invention provides compounds represented by structural formula (VI):

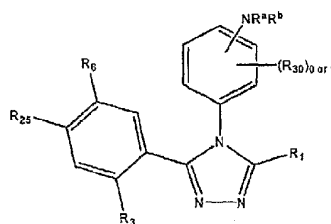


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The values and preferred values for the variables in formula (VI) are as described above for formula (IV). Alternatively, the values and preferred values for the variables in formula (VI) are as described in the first preferred embodiment for formula (IV) immediately above.

- 5 In a third preferred embodiment, the present invention provides compounds represented by structural formula (VII):



(VII)

- or a tautomer, pharmaceutically acceptable salt, solvate, clathrate or a
10 prodrug thereof.

The values and preferred values for the variables in formula (VII) are as described above for formula (IV). Preferably, the values and preferred values for the variables in formula (VII) are as described for formula (VI). More preferably, the values for the variables in formula (VII) are described in the following paragraphs:

- 15 R₃₀ is an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, cyano, halo, nitro, an optionally substituted cycloalkyl, haloalkyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteroaralkyl, -OR₇, -SR₇, -NR₁₀R₁₁,
20 -OC(O)NR₁₀R₁₁, -SC(O)NR₁₀R₁₁, -NR₇C(O)NR₁₀R₁₁, -OC(O)R₇, -SC(O)R₇, -NR₇C(O)R₇, -OC(O)OR₇, -SC(O)OR₇, -NR₇C(O)OR₇, -OCH₂C(O)R₇, -SCH₂C(O)R₇, -NR₇CH₂C(O)R₇, -OCH₂C(O)OR₇, -SCH₂C(O)OR₇, -NR₇CH₂C(O)OR₇, -OCH₂C(O)NR₁₀R₁₁, -SCH₂C(O)NR₁₀R₁₁, -NR₇CH₂C(O)NR₁₀R₁₁, -OS(O)_pR₇, -SS(O)_pR₇, -NR₇S(O)_pR₇, -OS(O)_pNR₁₀R₁₁,
25 -SS(O)_pNR₁₀R₁₁, -NR₇S(O)_pNR₁₀R₁₁, -OS(O)_pOR₇, -SS(O)_pOR₇, -NR₇S(O)_pOR₇, -OC(S)R₇, -SC(S)R₇, -NR₇C(S)R₇, -OC(S)OR₇, -SC(S)OR₇, -NR₇C(S)OR₇, -OC(S)NR₁₀R₁₁, -SC(S)NR₁₀R₁₁, -NR₇C(S)NR₁₀R₁₁, -OC(NR₈)R₇, -SC(NR₈)R₇,

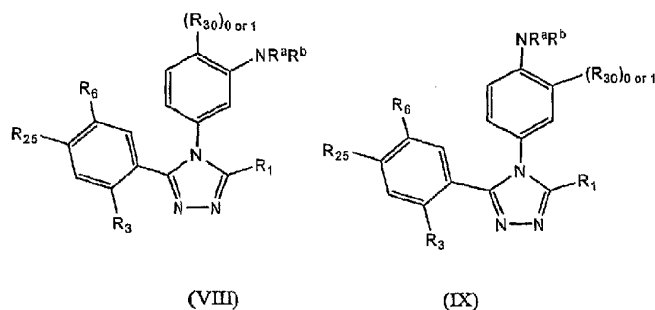
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-NR₇C(NR₈)R₇, -OC(NR₈)OR₇, -SC(NR₈)OR₇, -NR₇C(NR₈)OR₇,
 -OC(NR₈)NR₁₀R₁₁, -SC(NR₈)NR₁₀R₁₁, -NR₇C(NR₈)NR₁₀R₁₁, -C(O)R₇,
 -C(O)OR₇, -C(O)NR₁₀R₁₁, -C(O)SR₇, -C(S)R₇, -C(S)OR₇, -C(S)NR₁₀R₁₁,
 -C(S)SR₇, -C(NR₈)OR₇, -C(NR₈)R₇, -C(NR₈)NR₁₀R₁₁, -C(NR₈)SR₇, -S(O)_pOR₇,
 5 -S(O)_pNR₁₀R₁₁, or -S(O)_pR₇; and the values and preferred values for the remainder
 of the variables are as described above for formula (IV). Preferably, the values and
 preferred values for the remainder of the variables in formula (VII) are as described
 for formula (VI).

More preferably for formula (VII), R₆ is an optionally substituted alkyl, an
 10 optionally substituted alkenyl, an optionally substituted alkynyl, cyano, halo, nitro,
 an optionally substituted cycloalkyl, haloalkyl, an optionally substituted
 heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an
 optionally substituted aralkyl, an optionally substituted heteroaralkyl, -OR₇, -SR₇,
 -NR₁₀R₁₁, -OC(O)NR₁₀R₁₁, -SC(O)NR₁₀R₁₁, -NR₇C(O)NR₁₀R₁₁, -OC(O)R₇,
 15 -SC(O)R₇, -NR₇C(O)R₇, -OC(O)OR₇, -SC(O)OR₇, -NR₇C(O)OR₇,
 -OCH₂C(O)R₇, -SCH₂C(O)R₇, -NR₇CH₂C(O)R₇, -OCH₂C(O)OR₇,
 -SCH₂C(O)OR₇, -NR₇CH₂C(O)OR₇, -OCH₂C(O)NR₁₀R₁₁, -SCH₂C(O)NR₁₀R₁₁,
 -NR₇CH₂C(O)NR₁₀R₁₁, -OS(O)_pR₇, -SS(O)_pR₇, -NR₇S(O)_pR₇, -OS(O)_pNR₁₀R₁₁,
 -SS(O)_pNR₁₀R₁₁, -NR₇S(O)_pNR₁₀R₁₁, -OS(O)_pOR₇, -SS(O)_pOR₇, -NR₇S(O)_pOR₇,
 20 -OC(S)R₇, -SC(S)R₇, -NR₇C(S)R₇, -OC(S)OR₇, -SC(S)OR₇, -NR₇C(S)OR₇,
 -OC(S)NR₁₀R₁₁, -SC(S)NR₁₀R₁₁, -NR₇C(S)NR₁₀R₁₁, -OC(NR₈)R₇, -SC(NR₈)R₇,
 -NR₇C(NR₈)R₇, -OC(NR₈)OR₇, -SC(NR₈)OR₇, -NR₇C(NR₈)OR₇,
 -OC(NR₈)NR₁₀R₁₁, -SC(NR₈)NR₁₀R₁₁, -NR₇C(NR₈)NR₁₀R₁₁, -C(O)R₇,
 -C(O)OR₇, -C(O)NR₁₀R₁₁, -C(O)SR₇, -C(S)R₇, -C(S)OR₇, -C(S)NR₁₀R₁₁,
 25 -C(S)SR₇, -C(NR₈)OR₇, -C(NR₈)R₇, -C(NR₈)NR₁₀R₁₁, -C(NR₈)SR₇, -S(O)_pOR₇,
 -S(O)_pNR₁₀R₁₁, or -S(O)_pR₇; the values for R₃₀ are as described in the preceding
 paragraph; and the values and preferred values for the remainder of the variables are
 as described above for formula (IV). Preferably, the values and preferred values for
 the variables in formula (VII) are as described for formula (VI).

30 In a fourth preferred embodiment, the present invention provides compounds
 represented by a structural formula selected from (VIII) and (IX)

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or a tautomer, pharmaceutically acceptable salt, solvate, clathrate or a
 5 prodrug thereof.

The values and preferred values for formulas (VIII) and (IX) are as described
 above for formula (IV). Preferably, the values and preferred values for formulas
 (VIII) and (IX) are as described above for formula (VII). More preferably, the values
 for the variables in formulas (VIII) and (IX) are described in the following
 10 paragraphs:

R_1 , R_3 or R_{25} are each independently -OH, -SH, -NHR₇, -OC(O)NR₁₀R₁₁,
 -SC(O)NR₁₀R₁₁, -OC(O)R₇, -SC(O)R₇, -OC(O)OR₇, -SC(O)OR₇, -OS(O)_pR₇,
 -S(O)_pOR₇, -SS(O)_pR₇, -OS(O)_pOR₇, -SS(O)_pOR₇, -OC(S)R₇, -SC(S)R₇, -OC(S)OR₇,
 -SC(S)OR₇, -OC(S)NR₁₀R₁₁, -SC(S)NR₁₀R₁₁, -OC(NR₈)R₇, -SC(NR₈)R₇,
 15 -OC(NR₈)OR₇, -SC(NR₈)OR₇, -OP(O)(OR₇)₂ or -SP(O)(OR₇)₂. Preferably, R_7 and
 R_3 are each, independently, -OH, -SH, or -NHR₇ and R_{25} is as just described; and
 the values and preferred values for the remainder of the variables are as
 described above for formula (IV) or formula (VII).

In a first more preferred embodiment for formulas (VIII) and (IX), R_1 , R_3
 20 and R_{25} are as described in the immediately preceding two paragraphs: and

R^a and R^b are each independently a hydrogen, a C1-C6 straight or branched
 alkyl, optionally substituted by -OH, -CN, -SH, amino, a C1-C6 alkoxy,
 alkylsulfanyl, alkylamino, dialkylamino or a cycloalkyl; or R^a and R^b taken together
 with the nitrogen to which they are attached form a substituted or unsubstituted
 25 nonaromatic, nitrogen-containing heterocyclyl; and

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the values and preferred values for the remainder of the variables are as described above for formula (IV) formula (VII).

In a second more preferred embodiment for formulas (VIII) and (IX), R_6 is a C1-C6 alkyl, a C1-C6 haloalkyl, a C1-C6 alkoxy, a C1-C6 haloalkoxy, a C1-C6 alkyl sulfanyl or a C3-C6 cycloalkyl; and the values and preferred values for the remainder of the variables are as described above for first more preferred embodiment for formulas (VIII) and (IX).

In a third more preferred embodiment for formulas (VIII) and (IX):

R_1 and R_3 are each, independently, -OH, -SH, or -NHR₇;
 R_6 is a C1-C6 alkyl, a C1-C6 haloalkyl, a C1-C6 alkoxy, a C1-C6 haloalkoxy, a C1-C6 alkyl sulfanyl or a C3-C6 cycloalkyl;
 R_{25} is -OH, -SH, -NHR₇, -OC(O)NR₁₀R₁₁, -SC(O)NR₁₀R₁₁, -OC(O)R₇, -SC(O)R₇, -OC(O)OR₇, -SC(O)OR₇, -OS(O)_pR₇, -S(O)_pOR₇, -SS(O)_pR₇, -OS(O)_pOR₇, -SS(O)_pOR₇, -OC(S)R₇, -SC(S)R₇, -OC(S)OR₇, -SC(S)OR₇, -OC(S)NR₁₀R₁₁, -SC(S)NR₁₀R₁₁, -OC(NR₈)R₇, -SC(NR₈)R₇, -OC(NR₈)OR₇, -SC(NR₈)OR₇, -OP(O)(OR₇)₂ or -SP(O)(OR₇)₂;

R_{30} is -OH, -SH, halogen, cyano, a C1-C6 alkyl, C1-C6 haloalkyl, C1-C6 alkoxy, C1-C6 haloalkoxy or C1-C6 alkyl sulfanyl. Preferably, R_{30} is methyl, ethyl, propyl, isopropyl, methoxy or ethoxy;
 R^a and R^b are each independently a hydrogen, a C1-C6 straight or branched alkyl, optionally substituted by -OH, -CN, -SH, amino, a C1-C6 alkoxy, alkylsulfanyl, alkylamino, dialkylamino or a cycloalkyl; or R^a and R^b taken together with the nitrogen to which they are attached form a substituted or unsubstituted nonaromatic, nitrogen-containing heterocyclyl; and

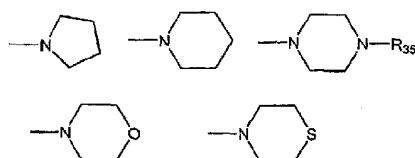
the values and preferred values for the remainder of the variables are as described above for formula (VII).

In a fourth more preferred embodiment for formulas (VIII) and (IX):

R_1 , R_3 and R_{25} for each occurrence, is independently -SH or -OH;
 R_6 is cyclopropyl or isopropyl; and
the remainder of the variables are as described for the third more preferred embodiment for formulas (VIII) and (IX). More preferably R_{30} is methyl, ethyl, propyl, isopropyl, methoxy or ethoxy. Even more preferably, R_{30} is methyl, ethyl,

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propyl, isopropyl, methoxy or ethoxy and R^a and R^b are each independently a hydrogen, methyl, ethyl, propyl, isopropyl, or taken together with the nitrogen to which they are attached, are:



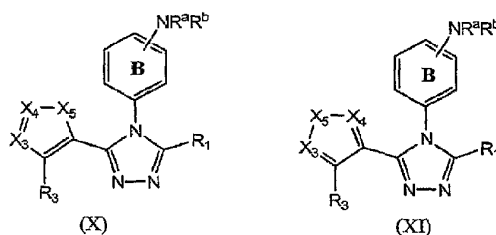
5 wherein R_{35} is -H, a C1-C4 alkyl or a C1-C4 acyl; and

the values and preferred values for the remainder of the variables are as described above for formula (VII).

In another preferred embodiment, the present invention is a compound represented by formula (IV), (VI), (VII), (VIII) or (IX), wherein R_1 , R_3 and R_{25} are -

10 SH or -OH and R_6 is cyclopropyl or isopropyl and the remainder of the variables are as described for Formula (IV), (VI), (VII), (VIII) or (IX), respectively.

In another embodiment, the present invention provides compounds represented by a structural formula selected from (X) and (XI):



15

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

In formulas (X) and (XI), ring B is further optionally substituted with one or more substituents in addition to NR^aR^b . Preferably ring B is substituted with $(R_{30})_q$

20 where q is 0, 1, 2, 3 or 4, preferably q is 0 or 1;

R_1 is -OH, -SH, -NR₇H, -OR₂₆, -SR₂₆, -NHR₂₆, -O(CH₂)_mOH, -O(CH₂)_mSH, -O(CH₂)_mNR₇H, -S(CH₂)_mOH, -S(CH₂)_mSH, -S(CH₂)_mNR₇H, -OC(O)NR₁₀R₁₁, -SC(O)NR₁₀R₁₁, -NR₇C(O)NR₁₀R₁₁, -OC(O)R₇, -SC(O)R₇, -NR₇C(O)R₇, -OC(O)OR₇, -SC(O)OR₇, -NR₇C(O)OR₇, -OCH₂C(O)R₇,

$-SCH_2C(O)R_7$, $-NR_7CH_2C(O)R_7$, $-OCH_2C(O)OR_7$, $-SCH_2C(O)OR_7$,
 $-NR_7CH_2C(O)OR_7$, $-OCH_2C(O)NR_{10}R_{11}$, $-SCH_2C(O)NR_{10}R_{11}$,
 $-NR_7CH_2C(O)NR_{10}R_{11}$, $-OS(O)_pR_7$, $-SS(O)_pR_7$, $-S(O)_pOR_7$, $-NR_7S(O)_pR_7$,
 $-OS(O)_pNR_{10}R_{11}$, $-SS(O)_pNR_{10}R_{11}$, $-NR_7S(O)_pNR_{10}R_{11}$, $-OS(O)_pOR_7$, $-SS(O)_pOR_7$,
 $-NR_7S(O)_pOR_7$, $-OC(S)R_7$, $-SC(S)R_7$, $-NR_7C(S)R_7$, $-OC(S)OR_7$, $-SC(S)OR_7$,
 $-NR_7C(S)OR_7$, $-OC(S)NR_{10}R_{11}$, $-SC(S)NR_{10}R_{11}$, $-NR_7C(S)NR_{10}R_{11}$, $-OC(NR_8)R_7$,
 $-SC(NR_8)R_7$, $-NR_7C(NR_8)R_7$, $-OC(NR_8)OR_7$, $-SC(NR_8)OR_7$, $-NR_7C(NR_8)OR_7$,
 $-OC(NR_8)NR_{10}R_{11}$, $-SC(NR_8)NR_{10}R_{11}$, or $-NR_7C(NR_8)NR_{10}R_{11}$, $-OP(O)(OR_7)_2$ or
 $-SP(O)(OR_7)_2$. Preferably, R_1 is $-OH$, $-SH$, $-HNR_7$, $-OC(O)NR_{10}R_{11}$,
 $-SC(O)NR_{10}R_{11}$, $-OC(O)R_7$, $-SC(O)R_7$, $-OC(O)OR_7$, $-SC(O)OR_7$, $-OS(O)_pR_7$,
 $-S(O)_pOR_7$, $-SS(O)_pR_7$, $-OS(O)_pOR_7$, $-SS(O)_pOR_7$, $-OC(S)R_7$, $-SC(S)R_7$, $-OC(S)OR_7$,
 $-SC(S)OR_7$, $-OC(S)NR_{10}R_{11}$, $-SC(S)NR_{10}R_{11}$, $-OC(NR_8)R_7$, $-SC(NR_8)R_7$,
 $-OC(NR_8)OR_7$, $-SC(NR_8)OR_7$, $-OP(O)(OR_7)_2$ or $-SP(O)(OR_7)_2$. More preferably, R_1
is $-OH$, $-SH$, or $-NHR_7$. Even more preferably, R_1 is $-SH$ or $-OH$;
 R_3 is $-OH$, $-SH$, $-NR_7H$, $-OR_{26}$, $-SR_{26}$, $-NHR_{26}$, $-O(CH_2)_mOH$,
 $-O(CH_2)_mSH$, $-O(CH_2)_mNR_7H$, $-S(CH_2)_mOH$, $-S(CH_2)_mSH$, $-S(CH_2)_mNR_7H$,
 $-OC(O)NR_{10}R_{11}$, $-SC(O)NR_{10}R_{11}$, $-NR_7C(O)NR_{10}R_{11}$, $-OC(O)R_7$, $-SC(O)R_7$,
 $-NR_7C(O)R_7$, $-OC(O)OR_7$, $-SC(O)OR_7$, $-NR_7C(O)OR_7$, $-OCH_2C(O)R_7$,
 $-SCH_2C(O)R_7$, $-NR_7CH_2C(O)R_7$, $-OCH_2C(O)OR_7$, $-SCH_2C(O)OR_7$,
 $-NR_7CH_2C(O)OR_7$, $-OCH_2C(O)NR_{10}R_{11}$, $-SCH_2C(O)NR_{10}R_{11}$,
 $-NR_7CH_2C(O)NR_{10}R_{11}$, $-OS(O)_pR_7$, $-SS(O)_pR_7$, $-S(O)_pOR_7$, $-NR_7S(O)_pR_7$,
 $-OS(O)_pNR_{10}R_{11}$, $-SS(O)_pNR_{10}R_{11}$, $-NR_7S(O)_pNR_{10}R_{11}$, $-OS(O)_pOR_7$, $-SS(O)_pOR_7$,
 $-NR_7S(O)_pOR_7$, $-OC(S)R_7$, $-SC(S)R_7$, $-NR_7C(S)R_7$, $-OC(S)OR_7$, $-SC(S)OR_7$,
 $-NR_7C(S)OR_7$, $-OC(S)NR_{10}R_{11}$, $-SC(S)NR_{10}R_{11}$, $-NR_7C(S)NR_{10}R_{11}$, $-OC(NR_8)R_7$,
 $-SC(NR_8)R_7$, $-NR_7C(NR_8)R_7$, $-OC(NR_8)OR_7$, $-SC(NR_8)OR_7$, $-NR_7C(NR_8)OR_7$,
 $-OC(NR_8)NR_{10}R_{11}$, $-SC(NR_8)NR_{10}R_{11}$, $-NR_7C(NR_8)NR_{10}R_{11}$, $-C(O)OH$,
 $-C(O)NHR_8$, $-C(O)SH$, $-S(O)OH$, $-S(O)_2OH$, $-S(O)NHR_8$, $-S(O)_2NHR_8$,
 $-OP(O)(OR_7)_2$, or $-SP(O)(OR_7)_2$. Preferably, R_3 is $-OH$, $-SH$, $-HNR_7$,
 $-OC(O)NR_{10}R_{11}$, $-SC(O)NR_{10}R_{11}$, $-OC(O)R_7$, $-SC(O)R_7$, $-OC(O)OR_7$, $-SC(O)OR_7$,
 $-OS(O)_pR_7$, $-S(O)_pOR_7$, $-SS(O)_pR_7$, $-OS(O)_pOR_7$, $-SS(O)_pOR_7$, $-OC(S)R_7$, $-SC(S)R_7$,
 $-OC(S)OR_7$, $-SC(S)OR_7$, $-OC(S)NR_{10}R_{11}$, $-SC(S)NR_{10}R_{11}$, $-OC(NR_8)R_7$, $-SC(NR_8)R_7$,

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$-\text{OC}(\text{NR}_8)\text{OR}_7$, $-\text{SC}(\text{NR}_8)\text{OR}_7$, $-\text{OP}(\text{O})(\text{OR}_7)_2$ or $-\text{SP}(\text{O})(\text{OR}_7)_2$. More preferably, R_3 is $-\text{OH}$, $-\text{SH}$, or $-\text{NHR}_7$. Even more preferably, R_3 is $-\text{SH}$ or $-\text{OH}$;

- R_6 , for each occurrence, is independently an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteraralkyl, halo, cyano, nitro, guanidino, a haloalkyl, a heteroalkyl, alkoxy, haloalkoxy, $-\text{NR}_{10}\text{R}_{11}$, $-\text{OR}_7$, $-\text{C}(\text{O})\text{R}_7$, $-\text{C}(\text{O})\text{OR}_7$, $-\text{C}(\text{S})\text{R}_7$, $-\text{C}(\text{O})\text{SR}_7$, $-\text{C}(\text{S})\text{SR}_7$, $-\text{C}(\text{S})\text{OR}_7$, $-\text{C}(\text{S})\text{NR}_{10}\text{R}_{11}$, $-\text{C}(\text{NR}_8)\text{OR}_7$, $-\text{C}(\text{NR}_8)\text{R}_7$, $-\text{C}(\text{NR}_8)\text{NR}_{10}\text{R}_{11}$, $-\text{C}(\text{NR}_8)\text{SR}_7$, $-\text{OC}(\text{O})\text{R}_7$, $-\text{OC}(\text{O})\text{OR}_7$, $-\text{OC}(\text{S})\text{OR}_7$, $-\text{OC}(\text{NR}_8)\text{OR}_7$, $-\text{SC}(\text{O})\text{R}_7$, $-\text{SC}(\text{O})\text{OR}_7$, $-\text{SC}(\text{NR}_8)\text{OR}_7$, $-\text{OC}(\text{S})\text{R}_7$, $-\text{SC}(\text{S})\text{R}_7$, $-\text{SC}(\text{S})\text{OR}_7$, $-\text{OC}(\text{O})\text{NR}_{10}\text{R}_{11}$, $-\text{OC}(\text{S})\text{NR}_{10}\text{R}_{11}$, $-\text{OC}(\text{NR}_8)\text{NR}_{10}\text{R}_{11}$, $-\text{SC}(\text{O})\text{NR}_{10}\text{R}_{11}$, $-\text{SC}(\text{NR}_8)\text{NR}_{10}\text{R}_{11}$, $-\text{SC}(\text{S})\text{NR}_{10}\text{R}_{11}$, $-\text{OC}(\text{NR}_8)\text{R}_7$, $-\text{SC}(\text{NR}_8)\text{R}_7$, $-\text{C}(\text{O})\text{NR}_{10}\text{R}_{11}$, $-\text{NR}_8\text{C}(\text{O})\text{R}_7$, $-\text{NR}_7\text{C}(\text{S})\text{R}_7$, $-\text{NR}_7\text{C}(\text{S})\text{OR}_7$, $-\text{NR}_7\text{C}(\text{NR}_8)\text{R}_7$, $-\text{NR}_7\text{C}(\text{O})\text{OR}_7$, $-\text{NR}_7\text{C}(\text{NR}_8)\text{OR}_7$, $-\text{NR}_7\text{C}(\text{O})\text{NR}_{10}\text{R}_{11}$, $-\text{NR}_7\text{C}(\text{S})\text{NR}_{10}\text{R}_{11}$, $-\text{NR}_7\text{C}(\text{NR}_8)\text{NR}_{10}\text{R}_{11}$, $-\text{SR}_7$, $-\text{S}(\text{O})_p\text{R}_7$, $-\text{OS}(\text{O})_p\text{R}_7$, $-\text{OS}(\text{O})_p\text{OR}_7$, $-\text{OS}(\text{O})_p\text{NR}_{10}\text{R}_{11}$, $-\text{S}(\text{O})_p\text{OR}_7$, $-\text{NR}_8\text{S}(\text{O})_p\text{R}_7$, $-\text{NR}_7\text{S}(\text{O})_p\text{NR}_{10}\text{R}_{11}$, $-\text{NR}_7\text{S}(\text{O})_p\text{OR}_7$, $-\text{S}(\text{O})_p\text{NR}_{10}\text{R}_{11}$, $-\text{SS}(\text{O})_p\text{R}_7$, $-\text{SS}(\text{O})_p\text{OR}_7$ or $-\text{SS}(\text{O})_p\text{NR}_{10}\text{R}_{11}$. Preferably, R_6 is for each occurrence, is independently an optionally substituted C1-C6 alkyl, an optionally substituted C3-C6 cycloalkyl, an optionally substituted C3-C6 cycloalkenyl, an optionally substituted heterocyclyl, a halo, a haloalkyl, a haloalkoxy, a heteroalkyl, an alkoxy, an alkylsulfanyl, $-\text{OH}$, $-\text{SH}$, $-\text{NHR}_7$, $-(\text{CH}_2)_k\text{OH}$, $-(\text{CH}_2)_k\text{SH}$, $-(\text{CH}_2)_k\text{NR}_7\text{H}$, $-\text{OCH}_3$, $-\text{SCH}_3$, $-\text{NHCH}_3$, $-\text{OCH}_2\text{CH}_2\text{OH}$, $-\text{OCH}_2\text{CH}_2\text{SH}$, $-\text{OCH}_2\text{CH}_2\text{NR}_7\text{H}$, $-\text{SCH}_2\text{CH}_2\text{OH}$, $-\text{SCH}_2\text{CH}_2\text{SH}$, $-\text{SCH}_2\text{CH}_2\text{NR}_7\text{H}$, $-\text{OC}(\text{O})\text{NR}_{10}\text{R}_{11}$, $-\text{SC}(\text{O})\text{NR}_{10}\text{R}_{11}$, $-\text{NR}_7\text{C}(\text{O})\text{NR}_{10}\text{R}_{11}$, $-\text{OC}(\text{O})\text{R}_7$, $-\text{SC}(\text{O})\text{R}_7$, $-\text{NR}_7\text{C}(\text{O})\text{R}_7$, $-\text{OC}(\text{O})\text{OR}_7$, $-\text{SC}(\text{O})\text{OR}_7$, $-\text{NR}_7\text{C}(\text{O})\text{OR}_7$, $-\text{OCH}_2\text{C}(\text{O})\text{R}_7$, $-\text{SCH}_2\text{C}(\text{O})\text{R}_7$, $-\text{NR}_7\text{CH}_2\text{C}(\text{O})\text{R}_7$, $-\text{OCH}_2\text{C}(\text{O})\text{OR}_7$, $-\text{SCH}_2\text{C}(\text{O})\text{OR}_7$, $-\text{NR}_7\text{CH}_2\text{C}(\text{O})\text{OR}_7$, $-\text{OCH}_2\text{C}(\text{O})\text{NR}_{10}\text{R}_{11}$, $-\text{SCH}_2\text{C}(\text{O})\text{NR}_{10}\text{R}_{11}$, $-\text{NR}_7\text{CH}_2\text{C}(\text{O})\text{NR}_{10}\text{R}_{11}$, $-\text{OS}(\text{O})_p\text{R}_7$, $-\text{SS}(\text{O})_p\text{R}_7$, $-\text{NR}_7\text{S}(\text{O})_p\text{R}_7$, $-\text{OS}(\text{O})_p\text{NR}_{10}\text{R}_{11}$, $-\text{SS}(\text{O})_p\text{NR}_{10}\text{R}_{11}$, $-\text{NR}_7\text{S}(\text{O})_p\text{NR}_{10}\text{R}_{11}$, $-\text{OS}(\text{O})_p\text{OR}_7$, $-\text{SS}(\text{O})_p\text{OR}_7$, $-\text{NR}_7\text{S}(\text{O})_p\text{OR}_7$, $-\text{OC}(\text{S})\text{R}_7$, $-\text{SC}(\text{S})\text{R}_7$, $-\text{NR}_7\text{C}(\text{S})\text{R}_7$, $-\text{OC}(\text{S})\text{OR}_7$, $-\text{SC}(\text{S})\text{OR}_7$, $-\text{NR}_7\text{C}(\text{S})\text{OR}_7$, $-\text{OC}(\text{S})\text{NR}_{10}\text{R}_{11}$, $-\text{SC}(\text{S})\text{NR}_{10}\text{R}_{11}$, $-\text{NR}_7\text{C}(\text{S})\text{NR}_{10}\text{R}_{11}$, $-\text{OC}(\text{NR}_8)\text{R}_7$, $-\text{SC}(\text{NR}_8)\text{R}_7$,

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$-\text{NR}_7\text{C}(\text{NR}_8)\text{R}_7$, $-\text{OC}(\text{NR}_8)\text{OR}_7$, $-\text{SC}(\text{NR}_8)\text{OR}_7$, $-\text{NR}_7\text{C}(\text{NR}_8)\text{OR}_7$,
 $-\text{OC}(\text{NR}_8)\text{NR}_{10}\text{R}_{11}$, $-\text{SC}(\text{NR}_8)\text{NR}_{10}\text{R}_{11}$, $-\text{NR}_7\text{C}(\text{NR}_8)\text{NR}_{10}\text{R}_{11}$, $-\text{C}(\text{O})\text{R}_7$,
 $-\text{C}(\text{O})\text{OR}_7$, $-\text{C}(\text{O})\text{NR}_{10}\text{R}_{11}$, $-\text{C}(\text{O})\text{SR}_7$, $-\text{C}(\text{S})\text{R}_7$, $-\text{C}(\text{S})\text{OR}_7$, $-\text{C}(\text{S})\text{NR}_{10}\text{R}_{11}$,
 $-\text{C}(\text{S})\text{SR}_7$, $-\text{C}(\text{NR}_8)\text{OR}_7$, $-\text{C}(\text{NR}_8)\text{R}_7$, $-\text{C}(\text{NR}_8)\text{NR}_{10}\text{R}_{11}$, $-\text{C}(\text{NR}_8)\text{SR}_7$, $-\text{S}(\text{O})_p\text{OR}_7$,
5 $-\text{S}(\text{O})_p\text{NR}_{10}\text{R}_{11}$, $-\text{S}(\text{O})_p\text{R}_7$, $-\text{OP}(\text{O})(\text{OR}_7)_2$ or $-\text{SP}(\text{O})(\text{OR}_7)_2$. More preferably, R_6 , for
each occurrence, is independently an optionally substituted alkyl, an optionally
substituted alkenyl, an optionally substituted alkynyl, an optionally substituted
cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted
heterocyclyl, $-\text{OH}$, $-\text{SH}$, $-\text{HNR}_7$, $-\text{OC}(\text{O})\text{NR}_{10}\text{R}_{11}$, $-\text{SC}(\text{O})\text{NR}_{10}\text{R}_{11}$, $-\text{OC}(\text{O})\text{R}_7$,
10 $-\text{SC}(\text{O})\text{R}_7$, $-\text{OC}(\text{O})\text{OR}_7$, $-\text{SC}(\text{O})\text{OR}_7$, $-\text{OS}(\text{O})_p\text{R}_7$, $-\text{S}(\text{O})_p\text{OR}_7$, $-\text{SS}(\text{O})_p\text{R}_7$,
 $-\text{OS}(\text{O})_p\text{OR}_7$, $-\text{SS}(\text{O})_p\text{OR}_7$, $-\text{OC}(\text{S})\text{R}_7$, $-\text{SC}(\text{S})\text{R}_7$, $-\text{OC}(\text{S})\text{OR}_7$, $-\text{SC}(\text{S})\text{OR}_7$,
 $-\text{OC}(\text{S})\text{NR}_{10}\text{R}_{11}$, $-\text{SC}(\text{S})\text{NR}_{10}\text{R}_{11}$, $-\text{OC}(\text{NR}_8)\text{R}_7$, $-\text{SC}(\text{NR}_8)\text{R}_7$, $-\text{OC}(\text{NR}_8)\text{OR}_7$,
 $-\text{SC}(\text{NR}_8)\text{OR}_7$, $-\text{OP}(\text{O})(\text{OR}_7)_2$ or $-\text{SP}(\text{O})(\text{OR}_7)_2$. Even more preferably, R_6 is for
each occurrence, is independently a C1-C6 alkyl, a C1-C6 haloalkyl, a C1-C6
15 alkoxy, a C1-C6 haloalkoxy, a C1-C6 alkyl sulfanyl or a C3-C6 cycloalkyl. Still
more preferably, R_6 for each occurrence, is independently a cyclopropyl or
isopropyl;

R_7 and R_8 , for each occurrence, is independently, $-\text{H}$, an optionally
substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl,
20 an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an
optionally substituted heterocyclyl, an optionally substituted aryl, an optionally
substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted
heteroaralkyl. Preferably, R_7 and R_8 , for each occurrence, is independently $-\text{H}$, C1-
C3 alkyl, C1-C6 cycloalkyl, an optionally substituted aryl or an optionally
25 substituted heteroaryl. More preferably, R_7 and R_8 , for each occurrence, is
independently $-\text{H}$ or C1-C3 alkyl;

R_{10} and R_{11} , for each occurrence, is independently $-\text{H}$, an optionally
substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl,
an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an
30 optionally substituted heterocyclyl, an optionally substituted aryl, an optionally
substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted
heteroaralkyl. Preferably, R_{10} and R_{11} , for each occurrence, is independently $-\text{H}$,

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C1-C3 alkyl, C1-C6 cycloalkyl, an optionally substituted aryl or an optionally substituted heteroaryl. More preferably, R₁₀ and R₁₁, for each occurrence, is independently -H or C1-C3 alkyl;

alternatively, R₁₀ and R₁₁, taken together with the nitrogen to which they are
 5 attached, form an optionally substituted heterocyclyl or an optionally substituted heteroaryl. Preferably R₁₀ and R₁₁, taken together with the nitrogen to which they are attached, form an optionally substituted imidazolyl, pyrrolyl, pyrazolyl, triazolyl, tetrazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl, pyrrolidinyl, piperidinyl,
 10 morpholinyl, pyrazinyl, thiomorpholinyl, pyrrolidinyl, piperidinyl, pyranzyl, thiomorpholinyl, tetrahydroquinolyl or tetrahydroisoquinolyl. More preferably R₁₀ and R₁₁, taken together with the nitrogen to which they are attached, form an optionally substituted pyrrolidinyl, piperidinyl, piperazinyl, tetrahydroisoquinolyl, morpholinyl or pyrazolyl;

15 R₁₇, for each occurrence, is independently an alkyl or an aralkyl. Preferably R₁₇ for each occurrence is independently a C1-C6 alkyl;

R₂₆ is a C1-C6 alkyl;

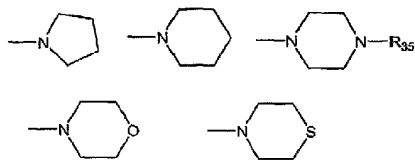
R₃₀, for each occurrence, is independently an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally
 20 substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteraralkyl, halo, cyano, nitro, guanadino, a haloalkyl, a heteroalkyl, alkoxy, haloalkoxy, -H, -NR₁₀R₁₁, -OR₇, -C(O)R₇, -C(O)OR₇, -C(S)R₇, -C(O)SR₇, -C(S)SR₇, -C(S)OR₇,
 25 -C(S)NR₁₀R₁₁, -C(NR₈)OR₇, -C(NR₈)R₇, -C(NR₈)NR₁₀R₁₁, -C(NR₈)SR₇, -OC(O)R₇, -OC(O)OR₇, -OC(S)OR₇, -OC(NR₈)OR₇, -SC(O)R₇, -SC(O)OR₇, -SC(NR₈)OR₇, -OC(S)R₇, -SC(S)R₇, -SC(S)OR₇, -OC(O)NR₁₀R₁₁, -OC(S)NR₁₀R₁₁, -OC(NR₈)NR₁₀R₁₁, -SC(O)NR₁₀R₁₁, -SC(NR₈)NR₁₀R₁₁, -SC(S)NR₁₀R₁₁, -OC(NR₈)R₇, -SC(NR₈)R₇, -C(O)NR₁₀R₁₁, -NR₈C(O)R₇, -NR₇C(S)R₇,
 30 -NR₇C(S)OR₇, -NR₇C(NR₈)R₇, -NR₇C(O)OR₇, -NR₇C(NR₈)OR₇, -NR₇C(O)NR₁₀R₁₁, -NR₇C(S)NR₁₀R₁₁, -NR₇C(NR₈)NR₁₀R₁₁, -SR₇, -S(O)_pR₇, -OS(O)_pR₇, -OS(O)_pOR₇, -OS(O)_pNR₁₀R₁₁, -S(O)_pOR₇, -NR₈S(O)_pR₇,

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- $-\text{NR}_7\text{S}(\text{O})_p\text{NR}_{10}\text{R}_{11}$, $-\text{NR}_7\text{S}(\text{O})_p\text{OR}_7$, $-\text{S}(\text{O})_p\text{NR}_{10}\text{R}_{11}$, $-\text{SS}(\text{O})_p\text{R}_7$, $-\text{SS}(\text{O})_p\text{OR}_7$, or
 $-\text{SS}(\text{O})_p\text{NR}_{10}\text{R}_{11}$. Preferably R_{30} for each occurrence, is independently an optionally
 substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl,
 cyano, halo, nitro, an optionally substituted cycloalkyl, haloalkyl, an optionally
 5 substituted heterocyclyl, an optionally substituted aryl, an optionally substituted
 heteroaryl, an optionally substituted aralkyl, an optionally substituted heteroaralkyl,
 $-\text{OR}_7$, $-\text{SR}_7$, $-\text{NR}_{10}\text{R}_{11}$, $-\text{OC}(\text{O})\text{NR}_{10}\text{R}_{11}$, $-\text{SC}(\text{O})\text{NR}_{10}\text{R}_{11}$, $-\text{NR}_7\text{C}(\text{O})\text{NR}_{10}\text{R}_{11}$,
 $-\text{OC}(\text{O})\text{R}_7$, $-\text{SC}(\text{O})\text{R}_7$, $-\text{NR}_7\text{C}(\text{O})\text{R}_7$, $-\text{OC}(\text{O})\text{OR}_7$, $-\text{SC}(\text{O})\text{OR}_7$, $-\text{NR}_7\text{C}(\text{O})\text{OR}_7$,
 $-\text{OCH}_2\text{C}(\text{O})\text{R}_7$, $-\text{SCH}_2\text{C}(\text{O})\text{R}_7$, $-\text{NR}_7\text{CH}_2\text{C}(\text{O})\text{R}_7$, $-\text{OCH}_2\text{C}(\text{O})\text{OR}_7$,
 10 $-\text{SCH}_2\text{C}(\text{O})\text{OR}_7$, $-\text{NR}_7\text{CH}_2\text{C}(\text{O})\text{OR}_7$, $-\text{OCH}_2\text{C}(\text{O})\text{NR}_{10}\text{R}_{11}$, $-\text{SCH}_2\text{C}(\text{O})\text{NR}_{10}\text{R}_{11}$,
 $-\text{NR}_7\text{CH}_2\text{C}(\text{O})\text{NR}_{10}\text{R}_{11}$, $-\text{OS}(\text{O})_p\text{R}_7$, $-\text{SS}(\text{O})_p\text{R}_7$, $-\text{NR}_7\text{S}(\text{O})_p\text{R}_7$, $-\text{OS}(\text{O})_p\text{NR}_{10}\text{R}_{11}$,
 $-\text{SS}(\text{O})_p\text{NR}_{10}\text{R}_{11}$, $-\text{NR}_7\text{S}(\text{O})_p\text{NR}_{10}\text{R}_{11}$, $-\text{OS}(\text{O})_p\text{OR}_7$, $-\text{SS}(\text{O})_p\text{OR}_7$, $-\text{NR}_7\text{S}(\text{O})_p\text{OR}_7$,
 $-\text{OC}(\text{S})\text{R}_7$, $-\text{SC}(\text{S})\text{R}_7$, $-\text{NR}_7\text{C}(\text{S})\text{R}_7$, $-\text{OC}(\text{S})\text{OR}_7$, $-\text{SC}(\text{S})\text{OR}_7$, $-\text{NR}_7\text{C}(\text{S})\text{OR}_7$,
 $-\text{OC}(\text{S})\text{NR}_{10}\text{R}_{11}$, $-\text{SC}(\text{S})\text{NR}_{10}\text{R}_{11}$, $-\text{NR}_7\text{C}(\text{S})\text{NR}_{10}\text{R}_{11}$, $-\text{OC}(\text{NR}_8)\text{R}_7$, $-\text{SC}(\text{NR}_8)\text{R}_7$,
 15 $-\text{NR}_7\text{C}(\text{NR}_8)\text{R}_7$, $-\text{OC}(\text{NR}_8)\text{OR}_7$, $-\text{SC}(\text{NR}_8)\text{OR}_7$, $-\text{NR}_7\text{C}(\text{NR}_8)\text{OR}_7$,
 $-\text{OC}(\text{NR}_8)\text{NR}_{10}\text{R}_{11}$, $-\text{SC}(\text{NR}_8)\text{NR}_{10}\text{R}_{11}$, $-\text{NR}_7\text{C}(\text{NR}_8)\text{NR}_{10}\text{R}_{11}$, $-\text{C}(\text{O})\text{R}_7$,
 $-\text{C}(\text{O})\text{OR}_7$, $-\text{C}(\text{O})\text{NR}_{10}\text{R}_{11}$, $-\text{C}(\text{O})\text{SR}_7$, $-\text{C}(\text{S})\text{R}_7$, $-\text{C}(\text{S})\text{OR}_7$, $-\text{C}(\text{S})\text{NR}_{10}\text{R}_{11}$,
 $-\text{C}(\text{S})\text{SR}_7$, $-\text{C}(\text{NR}_8)\text{OR}_7$, $-\text{C}(\text{NR}_8)\text{R}_7$, $-\text{C}(\text{NR}_8)\text{NR}_{10}\text{R}_{11}$, $-\text{C}(\text{NR}_8)\text{SR}_7$, $-\text{S}(\text{O})_p\text{OR}_7$,
 $-\text{S}(\text{O})_p\text{NR}_{10}\text{R}_{11}$ or $-\text{S}(\text{O})_p\text{R}_7$. More preferably, R_{30} for each occurrence, is
 20 independently a hydrogen, $-\text{OH}$, $-\text{SH}$, halogen, cyano, a C1-C6 alkyl, C1-C6
 haloalkyl, C1-C6 alkoxy, C1-C6 haloalkoxy or C1-C6 alkyl sulfanyl. Even more
 preferably, R_{30} for each occurrence, is independently a hydrogen, methyl, ethyl,
 propyl, isopropyl, methoxy or ethoxy;
 R^a and R^b , for each occurrence, is independently $-\text{H}$, an optionally substituted
 25 alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an
 optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an
 optionally substituted heterocyclyl, an optionally substituted aryl or heteroaryl, an
 optionally substituted aralkyl. Preferably, R^a and R^b for each occurrence, is
 independently a hydrogen, a C1-C6 straight or branched alkyl, optionally substituted
 30 by $-\text{OH}$, $-\text{CN}$, $-\text{SH}$, amino, a C1-C6 alkoxy, alkylsulfanyl, alkylamino, dialkylamino
 or a cycloalkyl. More preferably, R^a and R^b for each occurrence, is independently a
 hydrogen, methyl, ethyl, propyl, isopropyl;

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- Alternatively, R^a and R^b , taken together with the nitrogen to which they are attached, form an optionally substituted heteroaryl or heterocyclyl. Preferably, R^a and R^b taken together with the nitrogen to which they are attached form a substituted or unsubstituted nonaromatic, nitrogen-containing heterocyclyl. More preferably, R^a and R^b taken together with the nitrogen to which they are attached, are:



X_3 and X_4 are each, independently, N, N(O), $N^+(R_{17})$, CH or CR₆;

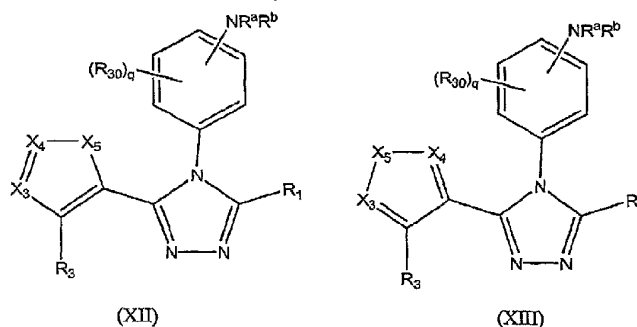
- X_5 is O, S, NR₁₇, CH₂, CH(R₆), C(R₆)₂, CH=CH, CH=CR₆, CR₆=CH, CR₆=CR₆, CH=N, CR₆=N, CH=N(O), CR₆=N(O), N=CH, N=CR₆, N(O)=CH, N(O)=CR₆, $N^+(R_{17})$ =CH, $N^+(R_{17})$ =CR₆, CH= $N^+(R_{17})$, CR₆= $N^+(R_{17})$, or N=N, provided that at least one X_3 , X_4 or X_5 is a heteroatom;

k is 1, 2, 3, or 4;

p , for each occurrence, is independently, 0, 1 or 2; and

m , for each occurrence, is independently, 1, 2, 3, or 4.

- In a fifth preferred embodiment, the present invention provides a compound represented by a structural formula selected from (XII) and (XIII):



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

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Preferably the values and preferred values for formulas (XII) and (XIII) are as described above for formulas (X) and (XI), and more preferably:

- R_9 is for each occurrence, is independently an optionally substituted C1-C6 alkyl, an optionally substituted C3-C6 cycloalkyl, an optionally substituted C3-C6 cycloalkenyl, an optionally substituted heterocyclyl, a halo, a haloalkyl, a haloalkoxy, a heteroalkyl, an alkoxy, an alkylsulfanyl, -OH, -SH, -NHR₇, -(CH₂)_kOH, -(CH₂)_kSH, -(CH₂)_kNR₇H, -OCH₃, -SCH₃, -NHCH₃, -OCH₂CH₂OH, -OCH₂CH₂SH, -OCH₂CH₂NR₇H, -SCH₂CH₂OH, -SCH₂CH₂SH, -SCH₂CH₂NR₇H, -OC(O)NR₁₀R₁₁, -SC(O)NR₁₀R₁₁, -NR₇C(O)NR₁₀R₁₁,
 10 -OC(O)R₇, -SC(O)R₇, -NR₇C(O)R₇, -OC(O)OR₇, -SC(O)OR₇, -NR₇C(O)OR₇, -OCH₂C(O)R₇, -SCH₂C(O)R₇, -NR₇CH₂C(O)R₇, -OCH₂C(O)OR₇, -SCH₂C(O)OR₇, -NR₇CH₂C(O)OR₇, -OCH₂C(O)NR₁₀R₁₁, -SCH₂C(O)NR₁₀R₁₁, -NR₇CH₂C(O)NR₁₀R₁₁, -OS(O)_pR₇, -SS(O)_pR₇, -NR₇S(O)_pR₇, -OS(O)_pNR₁₀R₁₁, -SS(O)_pNR₁₀R₁₁, -NR₇S(O)_pNR₁₀R₁₁, -OS(O)_pOR₇, -SS(O)_pOR₇, -NR₇S(O)_pOR₇,
 15 -OC(S)R₇, -SC(S)R₇, -NR₇C(S)R₇, -OC(S)OR₇, -SC(S)OR₇, -NR₇C(S)OR₇, -OC(S)NR₁₀R₁₁, -SC(S)NR₁₀R₁₁, -NR₇C(S)NR₁₀R₁₁, -OC(NR₈)R₇, -SC(NR₈)R₇, -NR₇C(NR₈)R₇, -OC(NR₈)OR₇, -SC(NR₈)OR₇, -NR₇C(NR₈)OR₇, -OC(NR₈)NR₁₀R₁₁, -SC(NR₈)NR₁₀R₁₁, -NR₇C(NR₈)NR₁₀R₁₁, -C(O)R₇, -C(O)OR₇, -C(O)NR₁₀R₁₁, -C(O)SR₇, -C(S)R₇, -C(S)OR₇, -C(S)NR₁₀R₁₁,
 20 -C(S)SR₇, -C(NR₈)OR₇, -C(NR₈)R₇, -C(NR₈)NR₁₀R₁₁, -C(NR₈)SR₇, -S(O)_pOR₇, -S(O)_pNR₁₀R₁₁, -S(O)_pR₇, -OP(O)(OR₇)₂ or -SP(O)(OR₇)₂;

- R_{10} , for each occurrence, is independently an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteroaralkyl, halo, cyano, nitro, guanidino, a haloalkyl, a heteroalkyl, alkoxy, haloalkoxy,
 25 -NR₁₀R₁₁, -OR₇, -C(O)R₇, -C(O)OR₇, -C(S)R₇, -C(O)SR₇, -C(S)SR₇, -C(S)OR₇, -C(S)NR₁₀R₁₁, -C(NR₈)OR₇, -C(NR₈)R₇, -C(NR₈)NR₁₀R₁₁, -C(NR₈)SR₇, -OC(O)R₇,
 30 -OC(O)OR₇, -OC(S)OR₇, -OC(NR₈)OR₇, -SC(O)R₇, -SC(O)OR₇, -SC(NR₈)OR₇, -OC(S)R₇, -SC(S)R₇, -SC(S)OR₇, -OC(O)NR₁₀R₁₁, -OC(S)NR₁₀R₁₁, -OC(NR₈)NR₁₀R₁₁, -SC(O)NR₁₀R₁₁, -SC(NR₈)NR₁₀R₁₁, -SC(S)NR₁₀R₁₁,

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-OC(NR₈)R₇, -SC(NR₈)R₇, -C(O)NR₁₀R₁₁, -NR₈C(O)R₇, -NR₇C(S)R₇,
 -NR₇C(S)OR₇, -NR₇C(NR₈)R₇, -NR₇C(O)OR₇, -NR₇C(NR₈)OR₇,
 -NR₇C(O)NR₁₀R₁₁, -NR₇C(S)NR₁₀R₁₁, -NR₇C(NR₈)NR₁₀R₁₁, -SR₇, -S(O)_pR₇,
 -OS(O)_pR₇, -OS(O)_pOR₇, -OS(O)_pNR₁₀R₁₁, -S(O)_pOR₇, -NR₈S(O)_pR₇,
 5 -NR₇S(O)_pNR₁₀R₁₁, -NR₇S(O)_pOR₇, -S(O)_pNR₁₀R₁₁, -SS(O)_pR₇, -SS(O)_pOR₇ or
 -SS(O)_pNR₁₀R₁₁;

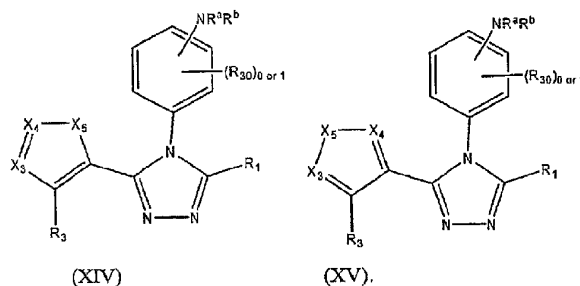
q is 0, 1, 2, 3 or 4;

k is 1, 2, 3, or 4; and

the values and preferred values for the remainder of the variables are as

10 described above for formulas (X) and (XI).

In a sixth preferred embodiment, the present invention provides a compound represented by a structural formula selected from (XIV) and (XV):



15 or a tautomer, pharmaceutically acceptable salt, solvate, clathrate or a prodrug thereof.

The values and preferred values for formulas (XIV) and (XV) are as described above for formulas (X) and (XI). Preferably the values and preferred values for formulas (XIV) and (XV) are as described in the are as described for
 20 formulas (XII) and (XIII). More preferably, the values for formulas (XIV) and (XV) are described in the following paragraphs:

R₃₀ is an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, cyano, halo, nitro, an optionally substituted cycloalkyl, haloalkyl, an optionally substituted heterocyclyl, an optionally
 25 substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteroaralkyl, -OR₇, -SR₇, -NR₁₀R₁₁,

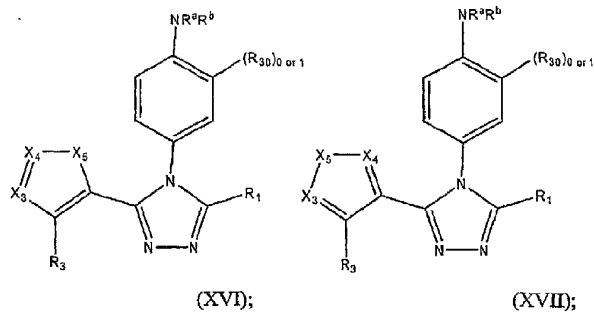
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- $-\text{OC}(\text{O})\text{NR}_{10}\text{R}_{11}$, $-\text{SC}(\text{O})\text{NR}_{10}\text{R}_{11}$, $-\text{NR}_7\text{C}(\text{O})\text{NR}_{10}\text{R}_{11}$, $-\text{OC}(\text{O})\text{R}_7$, $-\text{SC}(\text{O})\text{R}_7$,
 $-\text{NR}_7\text{C}(\text{O})\text{R}_7$, $-\text{OC}(\text{O})\text{OR}_7$, $-\text{SC}(\text{O})\text{OR}_7$, $-\text{NR}_7\text{C}(\text{O})\text{OR}_7$, $-\text{OCH}_2\text{C}(\text{O})\text{R}_7$,
 $-\text{SCH}_2\text{C}(\text{O})\text{R}_7$, $-\text{NR}_7\text{CH}_2\text{C}(\text{O})\text{R}_7$, $-\text{OCH}_2\text{C}(\text{O})\text{OR}_7$, $-\text{SCH}_2\text{C}(\text{O})\text{OR}_7$,
 $-\text{NR}_7\text{CH}_2\text{C}(\text{O})\text{OR}_7$, $-\text{OCH}_2\text{C}(\text{O})\text{NR}_{10}\text{R}_{11}$, $-\text{SCH}_2\text{C}(\text{O})\text{NR}_{10}\text{R}_{11}$,
5 $-\text{NR}_7\text{CH}_2\text{C}(\text{O})\text{NR}_{10}\text{R}_{11}$, $-\text{OS}(\text{O})_p\text{R}_7$, $-\text{SS}(\text{O})_p\text{R}_7$, $-\text{NR}_7\text{S}(\text{O})_p\text{R}_7$, $-\text{OS}(\text{O})_p\text{NR}_{10}\text{R}_{11}$,
 $-\text{SS}(\text{O})_p\text{NR}_{10}\text{R}_{11}$, $-\text{NR}_7\text{S}(\text{O})_p\text{NR}_{10}\text{R}_{11}$, $-\text{OS}(\text{O})_p\text{OR}_7$, $-\text{SS}(\text{O})_p\text{OR}_7$, $-\text{NR}_7\text{S}(\text{O})_p\text{OR}_7$,
 $-\text{OC}(\text{S})\text{R}_7$, $-\text{SC}(\text{S})\text{R}_7$, $-\text{NR}_7\text{C}(\text{S})\text{R}_7$, $-\text{OC}(\text{S})\text{OR}_7$, $-\text{SC}(\text{S})\text{OR}_7$, $-\text{NR}_7\text{C}(\text{S})\text{OR}_7$,
 $-\text{OC}(\text{S})\text{NR}_{10}\text{R}_{11}$, $-\text{SC}(\text{S})\text{NR}_{10}\text{R}_{11}$, $-\text{NR}_7\text{C}(\text{S})\text{NR}_{10}\text{R}_{11}$, $-\text{OC}(\text{NR}_8)\text{R}_7$, $-\text{SC}(\text{NR}_8)\text{R}_7$,
 $-\text{NR}_7\text{C}(\text{NR}_8)\text{R}_7$, $-\text{OC}(\text{NR}_8)\text{OR}_7$, $-\text{SC}(\text{NR}_8)\text{OR}_7$, $-\text{NR}_7\text{C}(\text{NR}_8)\text{OR}_7$,
10 $-\text{OC}(\text{NR}_8)\text{NR}_{10}\text{R}_{11}$, $-\text{SC}(\text{NR}_8)\text{NR}_{10}\text{R}_{11}$, $-\text{NR}_7\text{C}(\text{NR}_8)\text{NR}_{10}\text{R}_{11}$, $-\text{C}(\text{O})\text{R}_7$,
 $-\text{C}(\text{O})\text{OR}_7$, $-\text{C}(\text{O})\text{NR}_{10}\text{R}_{11}$, $-\text{C}(\text{O})\text{SR}_7$, $-\text{C}(\text{S})\text{R}_7$, $-\text{C}(\text{S})\text{OR}_7$, $-\text{C}(\text{S})\text{NR}_{10}\text{R}_{11}$,
 $-\text{C}(\text{S})\text{SR}_7$, $-\text{C}(\text{NR}_8)\text{OR}_7$, $-\text{C}(\text{NR}_8)\text{R}_7$, $-\text{C}(\text{NR}_8)\text{NR}_{10}\text{R}_{11}$, $-\text{C}(\text{NR}_8)\text{SR}_7$, $-\text{S}(\text{O})_p\text{OR}_7$,
 $-\text{S}(\text{O})_p\text{NR}_{10}\text{R}_{11}$, or $-\text{S}(\text{O})_p\text{R}_7$; and

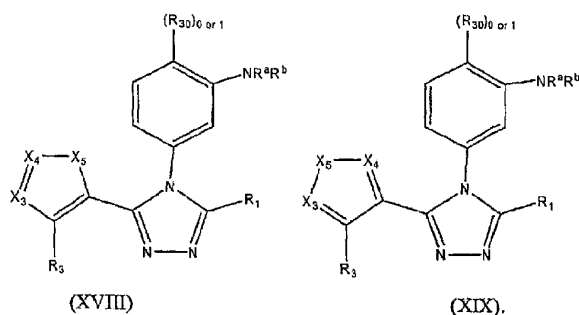
- the values and preferred values for the remainder of the variables are as
 15 described above for formulas (XIV) and (XV) are as described above for formulas
 (X) and (XI). Preferably the values and preferred values for the remainder of the
 variables in formulas (XIV) and (XV) are as described for formulas (XII) and (XIII).

In a seventh more preferred embodiment, the present invention provides a
 compound represented by a structural formula selected from (XVI) - (XIX):

20



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

- 5 The values and preferred values for formulas (XVI) - (XIX) are as described above for formulas (X) and (XI). Preferably the values and preferred values for formulas (XVI) - (XIX) are as described above for formulas (XIV) and (XV). More preferably, the values for formulas (XVI)-(XIX) are provided below in the following paragraphs:
- 10 R_1 and R_3 are each independently -OH, -SH, -HNR₇, -OC(O)NR₁₀R₁₁, -SC(O)NR₁₀R₁₁, -OC(O)R₇, -SC(O)R₇, -OC(O)OR₇, -SC(O)OR₇, -OS(O)_pR₇, -S(O)_pOR₇, -SS(O)_pR₇, -OS(O)_pOR₇, -SS(O)_pOR₇, -OC(S)R₇, -SC(S)R₇, -OC(S)OR₇, -SC(S)OR₇, -OC(S)NR₁₀R₁₁, -SC(S)NR₁₀R₁₁, -OC(NR₈)R₇, -SC(NR₈)R₇, -OC(NR₈)OR₇, -SC(NR₈)OR₇, -OP(O)(OR₇)₂ or -SP(O)(OR₇)₂; and
- 15 R_6 , for each occurrence, is independently an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, -OH, -SH, -HNR₇, -OC(O)NR₁₀R₁₁, -SC(O)NR₁₀R₁₁, -OC(O)R₇, -SC(O)R₇, -OC(O)OR₇, -SC(O)OR₇, -OS(O)_pR₇, -S(O)_pOR₇, -SS(O)_pR₇, -OS(O)_pOR₇, -SS(O)_pOR₇, -OC(S)R₇, -SC(S)R₇, -OC(S)OR₇, -SC(S)OR₇, -OC(S)NR₁₀R₁₁, -SC(S)NR₁₀R₁₁, -OC(NR₈)R₇, -SC(NR₈)R₇, -OC(NR₈)OR₇, -SC(NR₈)OR₇, -OP(O)(OR₇)₂ or -SP(O)(OR₇)₂; and
- 20 the values and preferred values for the remainder of the variables are as described for formulas (XIV) and (XV).

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Still more preferably for formulas (XVI) - (XIX), R_1 , R_3 and R_6 are as described in the immediately preceding paragraphs; and

R^a and R^b are each independently a hydrogen, a C1-C6 straight or branched alkyl, optionally substituted by -OH, -CN, -SH, amino, a C1-C6 alkoxy, alkylsulfanyl, alkylamino, dialkylamino or a cycloalkyl; or R^a and R^b taken together with the nitrogen to which they are attached form a substituted or unsubstituted nonaromatic, nitrogen-containing heterocyclyl; and

the values and preferred values for the remainder of the variables are as described for formulas (XIV) and (XV).

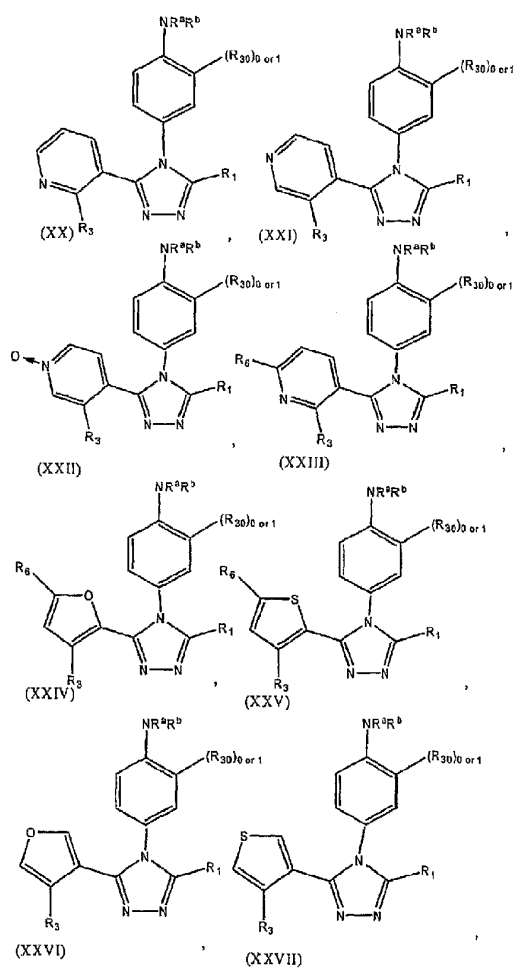
10 Still more preferably for formulas (XVI) - (XIX), R_1 , R_3 , R_6 , R^a and R^b are as described in the immediately preceding paragraphs; and

R_6 is a C1-C6 alkyl, a C1-C6 haloalkyl, a C1-C6 alkoxy, a C1-C6 haloalkoxy, a C1-C6 alkyl sulfanyl or a C3-C6 cycloalkyl; and

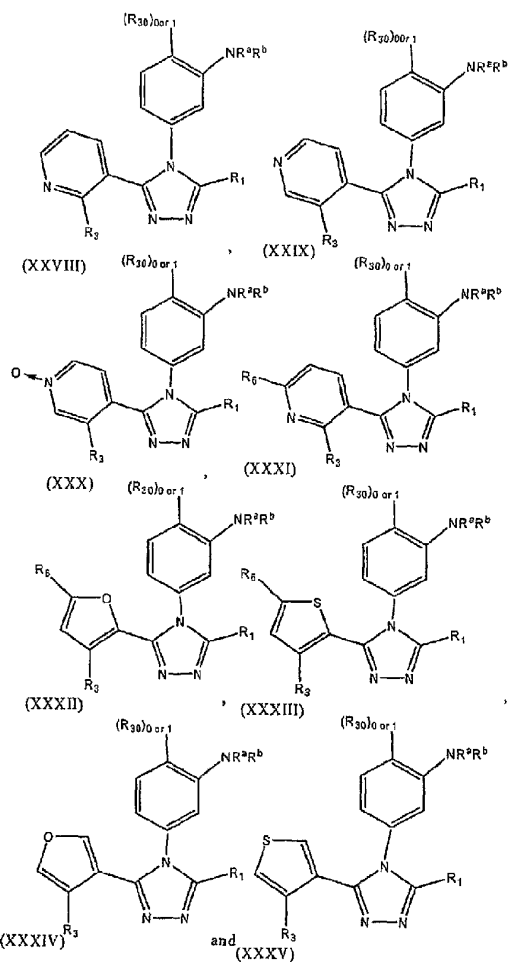
15 the values and preferred values for the remainder of the variables are as described above for formulas (X) and (XI). More preferably the values and preferred values for the remainder of the variables are as described above for formulas (XIV) and (XV).

In an eighth preferred embodiment, the present invention provides a compound represented by a structural formula selected from (XX) - (XXXV):

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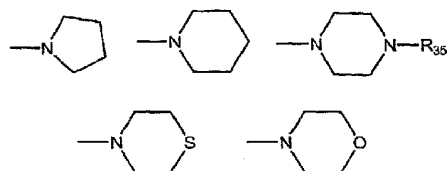


or a tautomer, pharmaceutically acceptable salt, solvate, clathrate or a prodrug thereof.

The values and preferred values for formulas (XX) - (XXXV) are as described above for formulas (X) and (XI). Preferably the values and preferred values for formulas (XVI) - (XIX) are as described for formulas (XVI)-(XIX). More

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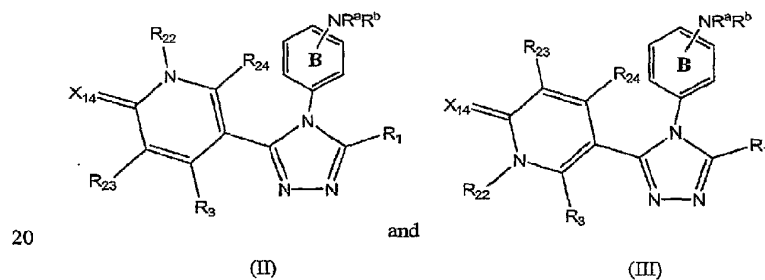
preferably, R_1 and R_3 are each, independently, -OH, -SH, or -NHR₇. Even more preferable, R_1 and R_3 are each, independently, -OH, -SH, or -NHR₇; and R_{30} is -OH, -SH, halogen, cyano, a C1-C6 alkyl, C1-C6 haloalkyl, C1-C6 alkoxy, C1-C6 haloalkoxy or C1-C6 alkyl sulfanyl (preferably methyl, ethyl, propyl, isopropyl, methoxy or ethoxy). Even more preferably, R_1 and R_3 for each occurrence, is independently -SH or -OH; R_6 is cyclopropyl or isopropyl; and R_{30} is -OH, -SH, halogen, cyano, a C1-C6 alkyl, C1-C6 haloalkyl, C1-C6 alkoxy, C1-C6 haloalkoxy or C1-C6 alkyl sulfanyl (preferably methyl, ethyl, propyl, isopropyl, methoxy or ethoxy). Even more preferably yet, R_1 , R_3 , R_6 and R_{30} are as just described and R^a and R^b are each independently a hydrogen, methyl, ethyl, propyl, isopropyl, or taken together with the nitrogen to which they are attached, are:



R_{35} is -H, a C1-C4 alkyl or a C1-C4 acyl; and

the values and preferred values for the remainder of the variables are as defined for formulas (XVI)-(XIX).

In another embodiment the compounds of the present invention are represented by a structural formula selected from (II) and (III):



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

In formulas (II) and (III), ring B is further optionally substituted with one or more substituents in addition to $-NR^aR^b$. Preferably ring B is further substituted

5 with $(R_{30})_q$ where q is 0, 1, 2, 3 or 4, preferably q is 0 or 1;

R_1 is $-OH$, $-SH$, $-NR_7H$, $-OR_{26}$, $-SR_{26}$, $-NHR_{26}$, $-O(CH_2)_mOH$,
 $-O(CH_2)_mSH$, $-O(CH_2)_mNR_7H$, $-S(CH_2)_mOH$, $-S(CH_2)_mSH$, $-S(CH_2)_mNR_7H$,
 $-OC(O)NR_{10}R_{11}$, $-SC(O)NR_{10}R_{11}$, $-NR_7C(O)NR_{10}R_{11}$, $-OC(O)R_7$, $-SC(O)R_7$,
 $-NR_7C(O)R_7$, $-OC(O)OR_7$, $-SC(O)OR_7$, $-NR_7C(O)OR_7$, $-OCH_2C(O)R_7$,
10 $-SCH_2C(O)R_7$, $-NR_7CH_2C(O)R_7$, $-OCH_2C(O)OR_7$, $-SCH_2C(O)OR_7$,
 $-NR_7CH_2C(O)OR_7$, $-OCH_2C(O)NR_{10}R_{11}$, $-SCH_2C(O)NR_{10}R_{11}$,
 $-NR_7CH_2C(O)NR_{10}R_{11}$, $-OS(O)_pR_7$, $-SS(O)_pR_7$, $-S(O)_pOR_7$, $-NR_7S(O)_pR_7$,
 $-OS(O)_pNR_{10}R_{11}$, $-SS(O)_pNR_{10}R_{11}$, $-NR_7S(O)_pNR_{10}R_{11}$, $-OS(O)_pOR_7$, $-SS(O)_pOR_7$,
 $-NR_7S(O)_pOR_7$, $-OC(S)R_7$, $-SC(S)R_7$, $-NR_7C(S)R_7$, $-OC(S)OR_7$, $-SC(S)OR_7$,
15 $-NR_7C(S)OR_7$, $-OC(S)NR_{10}R_{11}$, $-SC(S)NR_{10}R_{11}$, $-NR_7C(S)NR_{10}R_{11}$, $-OC(NR_8)R_7$,
 $-SC(NR_8)R_7$, $-NR_7C(NR_8)R_7$, $-OC(NR_8)OR_7$, $-SC(NR_8)OR_7$, $-NR_7C(NR_8)OR_7$,
 $-OC(NR_8)NR_{10}R_{11}$, $-SC(NR_8)NR_{10}R_{11}$, or $-NR_7C(NR_8)NR_{10}R_{11}$, $-OP(O)(OR_7)_2$ or
 $-SP(O)(OR_7)_2$. Preferably, R_1 is $-OH$, $-SH$, $-HNR_7$, $-OC(O)NR_{10}R_{11}$,
 $-SC(O)NR_{10}R_{11}$, $-OC(O)R_7$, $-SC(O)R_7$, $-OC(O)OR_7$, $-SC(O)OR_7$, $-OS(O)_pR_7$,
20 $-S(O)_pOR_7$, $-SS(O)_pR_7$, $-OS(O)_pOR_7$, $-SS(O)_pOR_7$, $-OC(S)R_7$, $-SC(S)R_7$, $-OC(S)OR_7$,
 $-SC(S)OR_7$, $-OC(S)NR_{10}R_{11}$, $-SC(S)NR_{10}R_{11}$, $-OC(NR_8)R_7$, $-SC(NR_8)R_7$,
 $-OC(NR_8)OR_7$, $-SC(NR_8)OR_7$, $-OP(O)(OR_7)_2$ or $-SP(O)(OR_7)_2$. More preferably, R_1
is $-OH$, $-SH$, or $-NHR_7$. Even more preferably, R_1 is $-SH$ or $-OH$;

R_3 is $-OH$, $-SH$, $-NR_7H$, $-OR_{26}$, $-SR_{26}$, $-NHR_{26}$, $-O(CH_2)_mOH$,
25 $-O(CH_2)_mSH$, $-O(CH_2)_mNR_7H$, $-S(CH_2)_mOH$, $-S(CH_2)_mSH$, $-S(CH_2)_mNR_7H$,
 $-OC(O)NR_{10}R_{11}$, $-SC(O)NR_{10}R_{11}$, $-NR_7C(O)NR_{10}R_{11}$, $-OC(O)R_7$, $-SC(O)R_7$,
 $-NR_7C(O)R_7$, $-OC(O)OR_7$, $-SC(O)OR_7$, $-NR_7C(O)OR_7$, $-OCH_2C(O)R_7$,
 $-SCH_2C(O)R_7$, $-NR_7CH_2C(O)R_7$, $-OCH_2C(O)OR_7$, $-SCH_2C(O)OR_7$,
 $-NR_7CH_2C(O)OR_7$, $-OCH_2C(O)NR_{10}R_{11}$, $-SCH_2C(O)NR_{10}R_{11}$,
30 $-NR_7CH_2C(O)NR_{10}R_{11}$, $-OS(O)_pR_7$, $-SS(O)_pR_7$, $-S(O)_pOR_7$, $-NR_7S(O)_pR_7$,
 $-OS(O)_pNR_{10}R_{11}$, $-SS(O)_pNR_{10}R_{11}$, $-NR_7S(O)_pNR_{10}R_{11}$, $-OS(O)_pOR_7$, $-SS(O)_pOR_7$,
 $-NR_7S(O)_pOR_7$, $-OC(S)R_7$, $-SC(S)R_7$, $-NR_7C(S)R_7$, $-OC(S)OR_7$, $-SC(S)OR_7$,

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- NR₇C(S)OR₇, -OC(S)NR₁₀R₁₁, -SC(S)NR₁₀R₁₁, -NR₇C(S)NR₁₀R₁₁, -OC(NR₈)R₇,
 -SC(NR₈)R₇, -NR₇C(NR₈)R₇, -OC(NR₈)OR₇, -SC(NR₈)OR₇, -NR₇C(NR₈)OR₇,
 -OC(NR₈)NR₁₀R₁₁, -SC(NR₈)NR₁₀R₁₁, -NR₇C(NR₈)NR₁₀R₁₁, -C(O)OH,
 -C(O)NHR₈, -C(O)SH, -S(O)OH, -S(O)₂OH, -S(O)NHR₈, -S(O)₂NHR₈,
 5 -OP(O)(OR₇)₂, or -SP(O)(OR₇)₂. Preferably, R₃ is -OH, -SH, -HNR₇,
 -OC(O)NR₁₀R₁₁, -SC(O)NR₁₀R₁₁, -OC(O)R₇, -SC(O)R₇, -OC(O)OR₇, -SC(O)OR₇,
 -OS(O)_pR₇, -S(O)_pOR₇, -SS(O)_pR₇, -OS(O)_pOR₇, -SS(O)_pOR₇, -OC(S)R₇, -SC(S)R₇,
 -OC(S)OR₇, -SC(S)OR₇, -OC(S)NR₁₀R₁₁, -SC(S)NR₁₀R₁₁, -OC(NR₈)R₇, -SC(NR₈)R₇,
 -OC(NR₈)OR₇, -SC(NR₈)OR₇, -OP(O)(OR₇)₂ or -SP(O)(OR₇)₂. More preferably, R₃
 10 is -OH, -SH, or -NHR₇. Even more preferably, R₃ is -SH or -OH;
- R₇ and R₈, for each occurrence, is independently, -H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteroaralkyl. Preferably, R₇ and R₈, for each occurrence, is independently -H, C1-C3 alkyl, C1-C6 cycloalkyl, an optionally substituted aryl or an optionally substituted heteroaryl. More preferably, R₇ and R₈, for each occurrence, is independently -H or C1-C3 alkyl;
- 20 R₁₀ and R₁₁, for each occurrence, is independently -H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteroaralkyl. Preferably, R₁₀ and R₁₁, for each occurrence, is independently -H, C1-C3 alkyl, C1-C6 cycloalkyl, an optionally substituted aryl or an optionally substituted heteroaryl. More preferably, R₁₀ and R₁₁, for each occurrence, is independently -H or C1-C3 alkyl;
- 25 Alternatively, R₁₀ and R₁₁, taken together with the nitrogen to which they are attached, form an optionally substituted heterocyclyl or an optionally substituted heteroaryl. Preferably R₁₀ and R₁₁, taken together with the nitrogen to which they are attached, form an optionally substituted imidazolyl, pyrrolyl, pyrazolyl, triazolyl,
- 30

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tetrazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl, pyrrolidinyl, piperidinyl, morpholinyl, pyrazinyl, thiomorpholinyl, pyrrolidinyl, piperidinyl, pyranzyl, thiomorpholinyl, tetrahydroquinolinyl or tetrahydroisoquinolinyl. More preferably

5 R₁₀ and R₁₁, taken together with the nitrogen to which they are attached, form an optionally substituted pyrrolidinyl, piperidinyl, piperazinyl, tetrahydroisoquinolinyl, morpholinyl or pyrazolyl;

R₂₂, for each occurrence, is independently -H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteroaralkyl, a haloalkyl, -C(O)R₇, -C(O)OR₇, -OC(O)R₇, -C(O)NR₁₀R₁₁, -NR₈C(O)R₇, -S(O)_pR₇, -S(O)_pOR₇, or -S(O)_pNR₁₀R₁₁. Preferably, R₂₂ is -H, an

10 alkyl, an aralkyl, -C(O)R₇, -C(O)OR₇, or -C(O)NR₁₀R₁₁;

R₂₃ and R₂₄, for each occurrence, is independently -H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteroaralkyl, halo, cyano, nitro, guanidino, a haloalkyl, a heteroalkyl, -NR₁₀R₁₁, -OR₇, -C(O)R₇, -C(O)OR₇, -OC(O)R₇, -C(O)NR₁₀R₁₁, -NR₈C(O)R₇, -SR₇, -S(O)_pR₇, -OS(O)_pR₇, -S(O)_pOR₇, -NR₈S(O)_pR₇, or -S(O)_pNR₁₀R₁₁. Preferably,

20 R₂₃ and R₂₄ for each occurrence is independently -H;

25 R₂₆ is a C1-C6 alkyl;

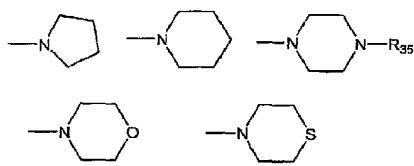
R^a and R^b, for each occurrence, is independently -H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl or heteroaryl, an optionally substituted aralkyl. Preferably, R^a and R^b for each occurrence, is

30 independently a hydrogen, a C1-C6 straight or branched alkyl, optionally substituted by -OH, -CN, -SH, amino, a C1-C6 alkoxy, alkylsulfanyl, alkylamino, dialkylamino

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or a cycloalkyl. More preferably, R^a and R^b for each occurrence, is independently a hydrogen, methyl, ethyl, propyl or isopropyl;

- Alternatively, R^a and R^b , taken together with the nitrogen to which they are attached, form an optionally substituted heteroaryl or heterocyclyl. Preferably, R^a and R^b taken together with the nitrogen to which they are attached form a substituted or unsubstituted nonaromatic, nitrogen-containing heterocyclyl. More preferably, R^a and R^b taken together with the nitrogen to which they are attached, are:



X_{14} is O, S, or NR_7 . Preferably, X_{14} is O;

- p , for each occurrence, is independently, 0, 1 or 2; and
 m , for each occurrence, is independently, 1, 2, 3, or 4.

- Preferably for the compound represented by formulas (II) and (III), R_1 is -OH, -SH, or -NHR₇; and R_{22} is -H, an alkyl, an aralkyl, -C(O)R₇, -C(O)OR₇, or -C(O)NR₁₀R₁₁. More preferably, R_1 is -OH, -SH, or -NHR₇; R_{22} is -H, an alkyl, an aralkyl, -C(O)R₇, -C(O)OR₇, or -C(O)NR₁₀R₁₁; and X_{14} is O. The values and preferred values for the remainder of the variables are as described above.

Exemplary compounds of the invention are depicted in Table 1 below, including tautomers, pharmaceutically acceptable salts, solvates, clathrates, hydrates, polymorphs or prodrugs thereof.

20

| NO. | Structure | Tautomeric structure | Name |
|-----|-----------|----------------------|---|
| | | | 4-(4-(3-(diethylamino)-4-methoxyphenyl)-5-mercapto-4H-1,2,4-triazol-3-yl)-6-ethylbenzene-1,3-diol |

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| | | |
|---|--|--|
| 2 | | 4-(4-(3-(N-isopropyl-N-propylamino)-4-methoxyphenyl)-5-mercapto-4H-1,2,4-triazol-3-yl)-6-ethylbenzene-1,3-diol |
| 3 | | 4-(4-(3-(N-methylamino)-4-methoxyphenyl)-5-mercapto-4H-1,2,4-triazol-3-yl)-6-ethylbenzene-1,3-diol |
| 4 | | 4-(4-(3-(N-ethyl-N-methylamino)-4-methoxyphenyl)-5-mercapto-4H-1,2,4-triazol-3-yl)-6-ethylbenzene-1,3-diol |
| 5 | | 4-(4-(3-(dimethylamino)-4-methoxyphenyl)-5-mercapto-4H-1,2,4-triazol-3-yl)-6-ethylbenzene-1,3-diol |
| 6 | | 4-(4-(3-(dimethylamino)phenyl)-5-mercapto-4H-1,2,4-triazol-3-yl)-6-ethylbenzene-1,3-diol |

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| | | |
|----|--|--|
| 7 | | 4-(4-(3-(N-ethyl-N-isopropylamino)-4-methoxyphenyl)-5-mercapto-4H-1,2,4-triazol-3-yl)-6-ethylbenzene-1,3-diol |
| 8 | | 4-ethyl-6-(5-mercapto-4-(3-(pyrrolidin-1-yl)phenyl)-4H-1,2,4-triazol-3-yl)benzene-1,3-diol |
| 9 | | 4-ethyl-6-(5-mercapto-4-(4-methoxy-3-morpholinophenyl)-4H-1,2,4-triazol-3-yl)benzene-1,3-diol |
| 10 | | 4-(4-(3-(N-isopropyl-N-propylamino)-4-methoxyphenyl)-5-mercapto-4H-1,2,4-triazol-3-yl)-6-isopropylbenzene-1,3-diol |
| 11 | | 4-(4-(3-(N-methyl-N-propylamino)-4-methoxyphenyl)-5-mercapto-4H-1,2,4-triazol-3-yl)-6-isopropylbenzene-1,3-diol |

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| | | | |
|----|--|--|--|
| 12 | | | 4-(4-(3-(N-methyl-N-ethylamino)-4-methoxyphenyl)-5-mercapto-4H-1,2,4-triazol-3-yl)-6-isopropylbenzene-1,3-diol |
| 13 | | | 4-(4-(4-(dimethylamino)-3-methoxyphenyl)-5-mercapto-4H-1,2,4-triazol-3-yl)-6-ethylbenzene-1,3-diol |
| 14 | | | |
| 15 | | | 4-(4-(3-aminophenyl)-5-mercapto-4H-1,2,4-triazol-3-yl)-6-ethylbenzene-1,3-diol |
| 16 | | | |
| 17 | | | 4-(4-(3-(N-isopentyl-N-methylamino)-4-methoxyphenyl)-5-mercapto-4H-1,2,4-triazol-3-yl)-6-ethylbenzene-1,3-diol |

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| | | | |
|----|--|--|---|
| | | | isopropylbenzene-1,3-diol |
| 18 | | | |
| 19 | | | 4-(4-(3-(N-(2-(dimethylamino)ethyl)-N-methylamino)-4-methoxyphenyl)-5-mercapto-4H-1,2,4-triazol-3-yl)-6-isopropylbenzene-1,3-diol |
| 20 | | | 4-(4-(3-(N-(2-methoxyethyl)-N-methylamino)-4-methoxyphenyl)-5-mercapto-4H-1,2,4-triazol-3-yl)-6-isopropylbenzene-1,3-diol |
| 21 | | | 4-(4-(3-(N-(cyclopropylmethyl)-N-methylamino)-4-methoxyphenyl)-5-mercapto-4H-1,2,4-triazol-3-yl)-6-isopropylbenzene-1,3-diol |

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| | | | |
|----|--|--|--|
| 22 | | | 4-(4-(3-(N-butyl-N-methylamino)-4-methoxyphenyl)-5-mercapto-4H-1,2,4-triazol-3-yl)-6-isopropylbenzene-1,3-diol |
| 23 | | | 4-(4-(3-(N-isobutyl-N-methylamino)-4-methoxyphenyl)-5-mercapto-4H-1,2,4-triazol-3-yl)-6-isopropylbenzene-1,3-diol |
| 24 | | | 4-(4-(3-(N-(2-(1H-imidazol-1-yl)ethyl)-N-methylamino)-4-methoxyphenyl)-5-mercapto-4H-1,2,4-triazol-3-yl)-6-isopropylbenzene-1,3-diol |
| 25 | | | 4-(4-(3-(N-methyl-N-propylamino)-4-methoxyphenyl)-5-mercapto-4H-1,2,4-triazol-3-yl)-6-isopropylbenzene-1,3-diol |

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| | | | |
|----|--|--|---|
| 26 | | | 4-(4-(3-(dimethylamino)-4-(methylthio)phenyl)-5-mercapto-4H-1,2,4-triazol-3-yl)-6-isopropylbenzene-1,3-diol |
| 27 | | | 4-(4-(3-(1H-pyrrol-1-yl)phenyl)-5-hydroxy-4H-1,2,4-triazol-3-yl)-6-ethylbenzene-1,3-diol |
| 28 | | | 4-(4-(3-(1H-imidazol-1-yl)phenyl)-5-mercapto-4H-1,2,4-triazol-3-yl)-6-isopropylbenzene-1,3-diol |
| 29 | | | |
| 30 | | | |

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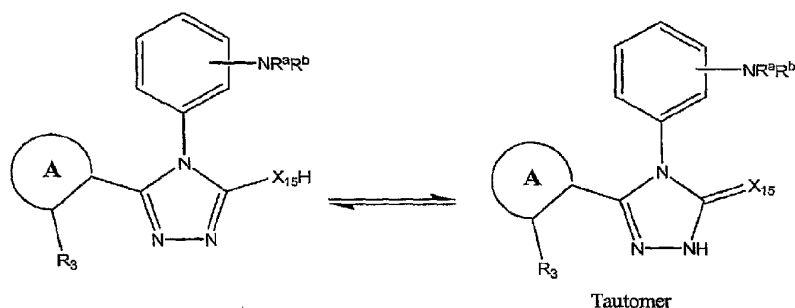
| | | | |
|----|--|--|--|
| 31 | | | 4-(4-(4-(dimethylamino)phenyl)-5-mercapto-4H-1,2,4-triazol-3-yl)-6-ethylbenzene-1,3-diol |
| 32 | | | 4-(4-(4-(diethylamino)phenyl)-5-mercapto-4H-1,2,4-triazol-3-yl)-6-ethylbenzene-1,3-diol |
| 33 | | | 4-ethyl-6-(5-mercapto-4-(4-morpholinophenyl)-4H-1,2,4-triazol-3-yl)benzene-1,3-diol |
| 34 | | | 4-(4-(4-(1H-imidazol-1-yl)phenyl)-5-mercapto-4H-1,2,4-triazol-3-yl)-6-ethylbenzene-1,3-diol |
| 35 | | | 4-(4-(2,5-diethoxy-4-morpholinophenyl)-5-mercapto-4H-1,2,4-triazol-3-yl)-6-ethylbenzene-1,3-diol |

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| | | | |
|----|--|--|---|
| 36 | | | 4-(4-(3-(1H-pyrrol-1-yl)phenyl)-5-mercapto-4H-1,2,4-triazol-3-yl)-6-ethylbenzene-1,3-diol |
| 37 | | | 4-(4-(4-(1H-pyrazol-1-yl)phenyl)-5-mercapto-4H-1,2,4-triazol-3-yl)-6-ethylbenzene-1,3-diol |
| 38 | | | 4-(4-(4-(amino)-3-hydroxyphenyl)-5-mercapto-4H-1,2,4-triazol-3-yl)-6-ethylbenzene-1,3-diol |
| 39 | | | 4-(4-(4-(methylamino)-3-hydroxyphenyl)-5-mercapto-4H-1,2,4-triazol-3-yl)-6-ethylbenzene-1,3-diol |
| 40 | | | 4-(4-(4-(dimethylamino)-3-methylphenyl)-5-mercapto-4H-1,2,4-triazol-3-yl)-6-ethylbenzene-1,3-diol |

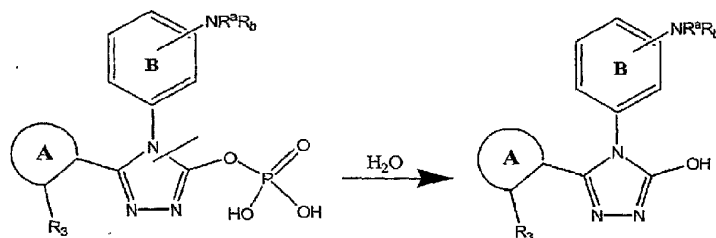
In certain instances tautomeric forms of the disclosed compound exist, such as the tautomeric structures shown below:

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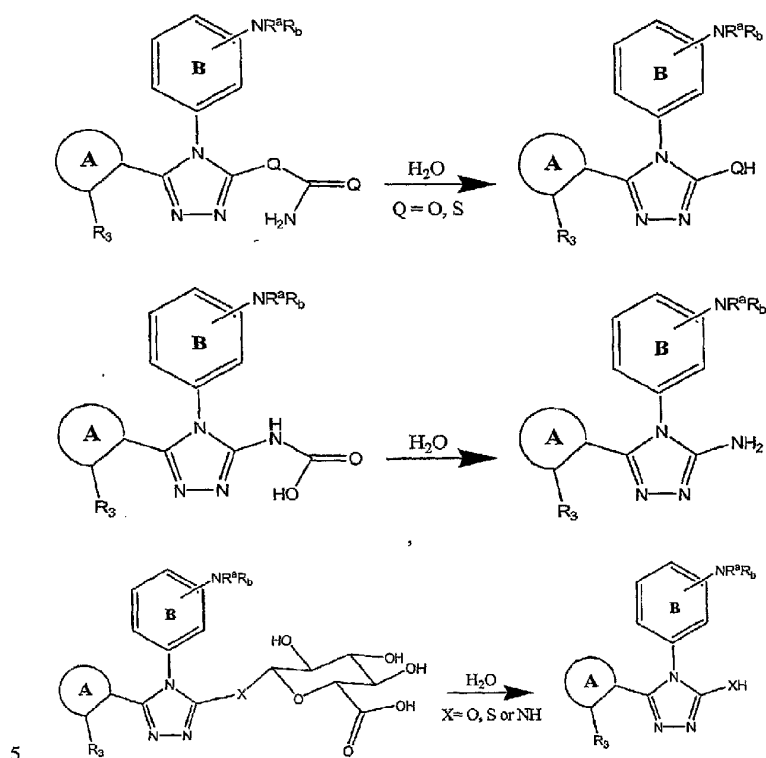

 $X_{15} = O, S \text{ or } NR_7$

It is to be understood that when a compound is represented by a structural formula herein, all other tautomeric forms which may exist for the compound are encompassed the structural formula. Compounds represented by formulas disclosed herein that can form analogous tautomeric structures to the one shown above are also preferred.

Similarly, prodrugs, *i.e.* compounds which can be metabolized or hydrolyzed *in vivo* to a compound of the present invention are encompassed by the present description. For example, the following embodiments of a compound of the present invention can be produced *in vivo* in the following reaction:



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One skilled in the art will understand that other hydrolyzable protecting groups can be employed with the compounds of the present invention to obtain prodrugs encompassed by the present description.

Without wishing to be bound by any theory, it is believed that the compounds of the invention preferentially bind to Hsp90 in the tautomeric form shown above, and thereby inhibit the activity of Hsp90.

C. Methods for Making Compounds of the Invention

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Compounds of the invention can be obtained via standard, well-known synthetic methodology, see *e.g.*, March, J. Advanced Organic Chemistry; Reactions Mechanisms, and Structure, 4th ed., 1992.

Compounds of the invention can also be made as in the following provisional
5 applications: 60/808,376, filed May 25, 2006; 60/808,342, filed May 25, 2006; and 60/808,375, filed May 25, 2006, which are incorporated by reference herein in their entirety.

In particular, compounds of the invention can be obtained by heating a benzoic acid (1) with an aminophenyl (2) to give a phenyl benzamide (3) which can
10 then be reacted with hydrazine to give a triazole (4) (see Scheme I below). Starting materials useful for preparing compounds of the invention and intermediates therefore, are commercially available or can be prepared from commercially available materials using known synthetic methods and reagents.

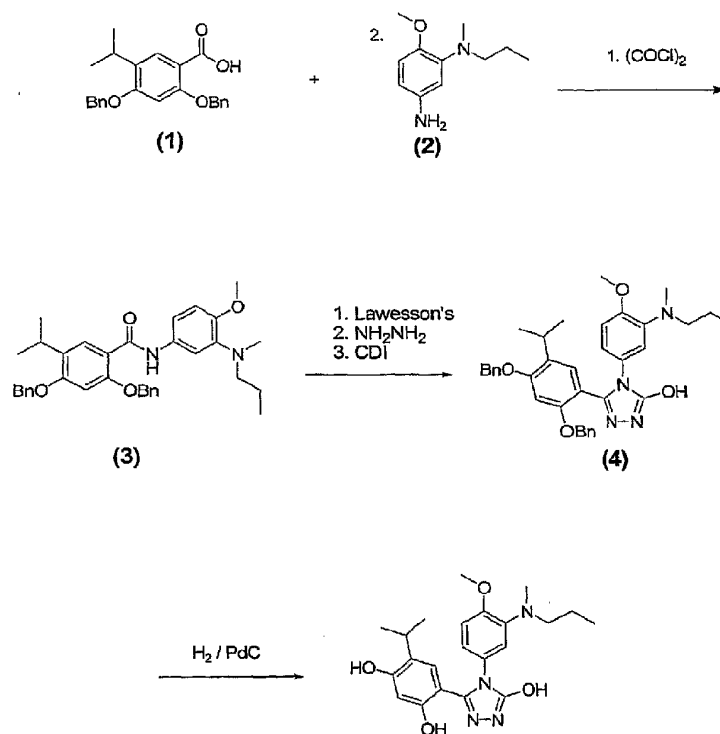
Reactive functional groups can be protected during one or more reaction
15 step, then deprotected to restore the original functionality. Examples of suitable protecting groups for hydroxyl groups include benzyl, methoxymethyl, allyl, trimethylsilyl, tert-butyldimethylsilyl, acetate, and the like. Examples of suitable amine protecting groups include benzyloxycarbonyl, tert-butoxycarbonyl, tert-butyl, benzyl and fluorenylmethyloxy-carbonyl (Fmoc). Examples of suitable thiol
20 protecting groups include benzyl, tert-butyl, acetyl, methoxymethyl and the like. Other suitable protecting groups are well known to those of ordinary skill in the art and include those found in T. W. Greene, Protecting Groups in Organic Synthesis, John Wiley & Sons, Inc. 1981.

Scheme I:

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Scheme I: Synthesis of triazole compounds of the invention.

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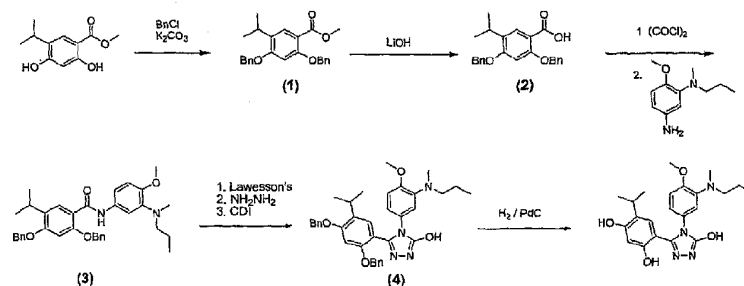


In addition, compounds of the invention can also be prepared as shown below in Schemes II, III, IV and Examples 1-40.

In one embodiment, the compounds can be prepared as shown in Scheme II. A dihydroxy benzoic acid methyl ester is reacted with benzyl chloride, to produce a
 5 Bis-benzyloxy benzoic acid methyl ester (1). The Bis-benzyloxy benzoic acid methyl ester can then be heated with LiOH to give a Bis-benzyloxy benzoic acid (2). The Bis-benzyloxy benzoic acid (2) is then reacted with an aminophenyl to produce a phenyl-benzamide (3). The phenyl-benzamide (3) is then reacted with hydrazine to give a triazol (4). The hydroxy groups can then be unprotectcd in the presence
 10 of palladium on charcoal to give the final product.

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Scheme II



5 In another embodiment the compounds can be prepared as shown in Scheme III. A nitroaniline (1) can be reacted with propionyl chloride to yield nitro-phenyl-propionamide (2). NaH can then be added to a solution of (2) in anhydrous THF followed by iodomethane to give pure product nitro-phenyl-N-methyl-propionamide (3).

10 The nitro-phenyl-N-methyl-propionamide (3) and borane-methyl sulfide complex are heated to give the nitro-phenyl-methyl-propyl-amine (4). A solution of (4) in MeOH/EtOAc containing Pd-C can be subjected to hydrogenation to give the N-methyl-N-propyl-benzene-1,3-diamine (5).

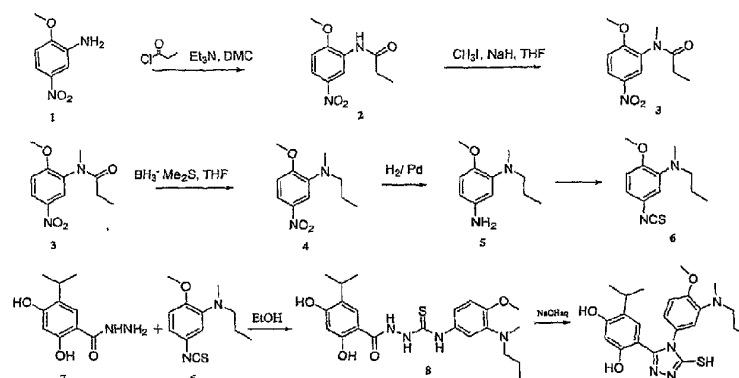
To a stirred solution of (5) in CH_2Cl_2 can be added 1,1'-thiocarbonyldiimidazole to give the (5-Isothiocyanato-2-methoxy-phenyl)-methyl-propyl-amine (6).

The isothiocyanate (6) can be reacted with the hydrazide (7) to give the intermediate (8). A solution of NaOH in water can be added to the intermediate (8), which can then be flushed with nitrogen and heated. The reaction mixture can then be cooled and acidified. The mixture can then be filtered and purified to give 4-isopropyl-6-(5-mercapto-4-[4-methoxy-3-(methyl-propyl-amino)-phenyl]-4H-[1,2,4]triazol-3-yl)-benzene-1,3-diol.

Scheme III

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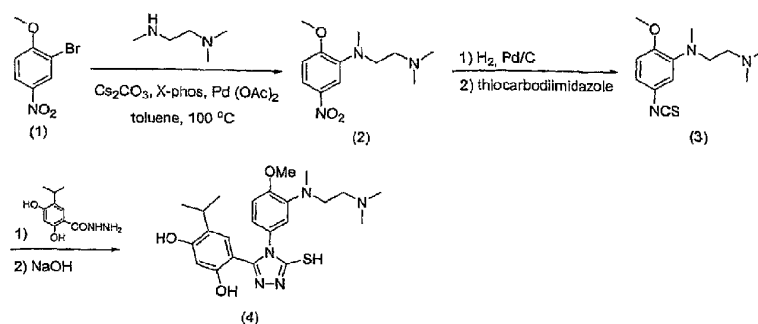


- In another embodiment the compounds can be prepared as shown in Scheme IV. A bromo-nitrobenzene (1) can be reacted with *N*¹, *N*², *N*³-trimethylethane-1,2-diamine to give *N*¹-(nitrophenyl)-*N*¹, *N*², *N*²-trimethylethane-1,2-diamine (2). A solution of (2) in can be subjected to hydrogenation, passed through a short pad of celite, washed with MeOH and evaporated under reduced pressure. Thiocarbodiimidazole can then be added to (2) to give the *N*¹-(isothiocyanato-phenyl)- *N*¹, *N*², *N*²-trimethylethane-1,2-diamine (3).
- The isothiocyanate (3) can then be reacted with a benzoic acid hydrazide to give the final product 4-(4-(3-((2-(dimethylamino)ethyl)(methyl)amino)-4-methoxyphenyl)-5-mercapto-4H-1,2,4-triazol-3-yl)-6-isopropylbenzene-1,3-diol (4).

Scheme IV

15

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D. Uses of Compounds of the Invention

The present invention is directed to therapies which involve administering one of more compounds of the invention, and compositions comprising said compounds to a subject, preferably a human subject, to inhibit the activity of Hsp90 or to prevent, treat, manage, or ameliorate a proliferative disorder, such as cancer, or one or more symptoms thereof.

In one aspect, the invention provides a method of inhibiting the activity of Hsp90 in a cell, comprising administering to the cell an effective amount of a compound represented by formula (I) – (XXXV) or Table 1. In one embodiment, the compound is administered to a cell in a subject, preferably a mammal, and more preferably a human.

In one embodiment, the present invention is directed to treating cancers in which aberrant expression and/or activation of c-kit has been implicated as a contributing factor. The method comprises administering to a patient an effective amount of a compound represented by formula (I) – (XXXV), or any embodiment thereof, or a compound shown in Table 1.

In one embodiment, the present invention is directed to treating cancers in which expression of Bcr-Abl has been implicated as a contributing factor. The method comprises administering to a patient an effective amount of a compound represented by formula (I) – (XXXV), or any embodiment thereof, or a compound shown in Table 1.

In one embodiment, the present invention is directed to treating cancers in which aberrant expression and/or activation of *flt-3* has been implicated as a

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contributing factor. The method comprises administering to a patient an effective amount of a compound represented by formula (I) – (XXXV), or any embodiment thereof, or a compound shown in Table 1.

5 In one embodiment, the present invention is directed to treating cancers in which aberrant expression and/or activation of EGFR has been implicated as a contributing factor. The method comprises administering to a patient an effective amount of a compound represented by formula (I) – (XXXV), or any embodiment thereof, or a compound shown in Table 1.

10 In one embodiment, the present invention is directed to treating cancers in which Hsp90 is over expressed compared with normal cells. The method comprises administering to a patient an effective amount of a compound represented by formula (I) – (XXXV), or any embodiment thereof, or a compound shown in Table 1. Examples of cancers in which Hsp90 is over expressed include diffuse large B-cell lymphomas (DLBCL).

15 In one aspect, the invention provides a method of inhibiting the activity of Hsp90 in a cell, comprising administering to the cell an effective amount of a compound represented by formula (I) – (XXXV), or any embodiment thereof, or a compound shown in Table 1. In one embodiment, the compound is administered to a cell in a subject, preferably a mammal, and more preferably a human.

20 In another aspect, the invention provides a method of treating or preventing a proliferation disorder in a mammal, comprising administering to the mammal an effective amount of a compound represented by formula (I) – (XXXV), or any embodiment thereof, or a compound shown in Table 1. In one embodiment, the compound is administered to a human to treat or prevent a proliferative disorder. In another embodiment, the proliferation disorder is cancer. In another embodiment, the compound is administered with one or more additional therapeutic agents. In a preferred embodiment, the additional therapeutic agent is an anticancer agent.

25 In another aspect, the invention provides a method for treating cancer in a mammal, comprising administering to the mammal an effective amount of a compound represented by formula (I) – (XXXV), or any embodiment thereof, or a compound shown in Table 1. In one embodiment, the compound is administered to a human to treat or prevent cancer. In another embodiment, the compound is

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administered with one or more additional therapeutic agents. In a preferred embodiment, the one or more additional therapeutic agents are anticancer agents.

In another aspect, the invention provides a method for treating a c-kit associated cancer in a mammal, comprising administering to the mammal an effective amount of a compound represented by formula (I) – (XXXV), or any embodiment thereof, or a compound shown in Table 1. In one embodiment, the compound is administered to a human to treat or prevent the c-kit associated cancer. In another embodiment, the compound is administered with one or more additional therapeutic agents. In a preferred embodiment, the one or more additional therapeutic agents are anticancer agents.

In another aspect, the invention provides a method for treating a Bcr-Abl associated cancer in a mammal, comprising administering to the mammal an effective amount of a compound represented by formula (I) – (XXXV), or any embodiment thereof, or a compound shown in Table 1. In one embodiment, the compound is administered to a human to treat or prevent the Bcr-Abl associated cancer. In another embodiment, the compound is administered with one or more additional therapeutic agents. In a preferred embodiment, the one or more additional therapeutic agents are anticancer agents.

In another aspect, the invention provides a method for treating a flt3 associated cancer in a mammal, comprising administering to the mammal an effective amount of a compound represented by formula (I) – (XXXV), or any embodiment thereof, or a compound shown in Table 1. In one embodiment, the compound is administered to a human to treat or prevent the flt3 associated cancer. In another embodiment, the compound is administered with one or more additional therapeutic agents. In a preferred embodiment, the one or more additional therapeutic agents are anticancer agents.

In another aspect, the invention provides a method for treating an EGFR associated cancer in a mammal, comprising administering to the mammal an effective amount of a compound represented by formula (I) – (XXXV), or any embodiment thereof, or a compound shown in Table 1. In one embodiment, the compound is administered to a human to treat or prevent the EGFR associated cancer. In another embodiment, the compound is administered with one or more

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additional therapeutic agents. In a preferred embodiment, the one or more additional therapeutic agents are anticancer agents.

In another aspect, the invention provides a method for treating a cancer in a mammal which is characterized by the upregulation of Hsp90 compared to normal
 5 cells of the same type, comprising administering to the mammal an effective amount of a compound represented by formula (I) – (XXXV), or any embodiment thereof, or a compound shown in Table 1. In one embodiment, the compound is administered to a human to treat or prevent the cancer associated with the upregulation of Hsp90. In another embodiment, the cancer associated with the upregulation of Hsp90 is
 10 DLBCL. In another embodiment, the compound is administered with one or more additional therapeutic agents. In a preferred embodiment, the one or more additional therapeutic agents are anticancer agents.

In another aspect, the invention provides a method for treating or inhibiting angiogenesis in a subject in need thereof, comprising administering to the subject an
 15 effective amount of a compound represented by formula (I) – (XXXV), or any embodiment thereof, or a compound shown in Table 1.

In another aspect, the invention provides a method of blocking, occluding, or otherwise disrupting blood flow in neovasculature, comprising contacting the neovasculature with an effective amount of a compound represented by formula (I) –
 20 (XXXV), or any embodiment thereof, or a compound shown in Table 1. In one aspect, the neovasculature is in a subject and blood flow in the neovasculature is blocked, occluded, or otherwise disrupted in the subject by administering to the subject an effective amount of a compound represented by formula (I) – (XXXV), or any embodiment thereof, or a compound shown in Table 1. In one aspect, the
 25 subject is human.

1. c-Kit Associated Cancers

SCF binding to the c-kit protects hematopoietic stem and progenitor cells from apoptosis (Lee, *et al.*, 1997, *J. Immunol.*, 159:3211-3219), thereby contributing to colony formation and hematopoiesis. Expression of c-kit is frequently observed
 30 in acute myelocytic leukemia (AML) and sometimes observed in acute lymphocytic leukemia (ALL) (for reviews, see Sperling, *et al.*, 1997, *Haemat.*, 82:617-621; Escribano, *et al.*, 1998, *Leuk. Lymph.*, 30:459-466). Although c-kit is expressed in

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the majority of AML cells, its expression does not appear to be prognostic of disease progression (Sperling, *et al*, 1997, *Haemat.* 82:617-621). However, SCF protected AML cells from apoptosis induced by chemotherapeutic agents (Hassan, *et al.*, 1996, *Acta. Hem.*, 95:257-262). Therefore, degradation of c-kit caused by the
5 inhibition of Hsp90 by the compounds of the invention will enhance the efficacy of these agents and may induce apoptosis of AML cells.

The clonal growth of cells from patients with myelodysplastic syndrome (Sawada, *et al.*, 1996, *Blood*, 88:319-327) or chronic myelogenous leukemia (CML) (Sawai, *et al.*, 1996, *Exp. Hem.*, 2:116-122) was found to be significantly enhanced
10 by SCF in combination with other cytokines. CML is characterized by expansion of Philadelphia chromosome positive cells of the marrow (Verfaillie, *et al.*, 1998, *Leuk.*, 12:136-138), which appears to primarily result from inhibition of apoptotic death (Jones, 1997, *Curr. Opin. Onc.*, 9:3-7). The product of the Philadelphia chromosome, p210.sup.BCR-ABL, has been reported to mediate inhibition of
15 apoptosis (Bedi, *et al.*, 1995, *Blood*, 86:1148-1158). Since p210.sup.BCR-ABL and the c-kit RTK both inhibit apoptosis and p62.sup.dok has been suggested as a substrate (Carpino, *et al.*, 1997, *Cell*, 88:197-204), it is possible that clonal expansion mediated by these kinases occurs through a common signaling pathway. However, c-kit has also been reported to interact directly with p210.sup.BCR-ABL
20 (Hallek, *et al.*, 1996, *Brit. J Haem.*, 94:5-16), which suggests that c-kit may have a more causative role in CML pathology. Therefore, degradation of c-kit caused by the inhibition of Hsp90 by the compounds of the invention will prove useful in the treatment of CML.

Normal colorectal mucosa does not express c-kit (Bellone, *et al.*, 1997, *J. Cell Physiol.*, 172:1-11). However, c-kit is frequently expressed in colorectal carcinoma (Bellone, *et al.*, 1997, *J. Cell Physiol.*, 172: 1-11), and autocrine loops of SCF and c-kit have been observed in several colon carcinoma cell lines (Toyota, *et al.*, 1993, *Turn. Biol.*, 14:295-302; Lahm, *et al.*, 1995, *Cell Growth & Differ.*, 6:1111-1118; Bellone, *et al.*, 1997, *J. Cell Physiol.*, 172:1-11). Furthermore,
30 disruption of the autocrine loop by the use of neutralizing antibodies (Lahm, *et al.*, 1995, *Cell Growth & Differ.*, 6:1111-1118) and downregulation of c-kit and/or SCF

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significantly inhibits cell proliferation (Lahm, *et al.*, 1995, *Cell Growth & Differl.*, 6:1111-1118; Bellone, *et al.*, 1997, *J. Cell Physiol.*, 172:1-11).

SCF/c-kit autocrine loops have been observed in gastric carcinoma cell lines (Turner, *et al.*, 1992, *Blood*, 80:374-381; Hassan, *et al.*, 1998, *Digest. Dis. Science*, 43:8-14), and constitutive c-kit activation also appears to be important for gastrointestinal stromal tumors (GISTs). GISTs are the most common mesenchymal tumor of the digestive system. More than 90% of GISTs express c-kit, which is consistent with the putative origin of these tumor cells from interstitial cells of Cajal (ICCs) (Hirota, *et al.*, 1998, *Science*, 279:577-580). The c-kit expressed in GISTs from several different patients was observed to have mutations in the intracellular juxtamembrane domain leading to constitutive activation (Hirota, *et al.*, 1998, *Science* 279:577-580). Therefore, degradation of c-kit caused by the inhibition of Hsp90 by the compounds of the invention will be an efficacious means for the treatment of these cancers.

Male germ cell tumors have been histologically categorized into seminomas, which retain germ cell characteristics, and nonseminomas which can display characteristics of embryonal differentiation. Both seminomas and nonseminomas are thought to initiate from a preinvasive stage designated carcinoma in situ (CIS) (Murty, *et al.*, 1998, *Sem. Oncol.*, 25:133-144). Both c-kit and SCF have been reported to be essential for normal gonadal development during embryogenesis (Loveland, *et al.*, 1997, *J. Endocrinol.*, 153:337-344). Loss of either the receptor or the ligand resulted in animals devoid of germ cells. In postnatal testes, c-kit has been found to be expressed in Leydig cells and spermatogonia, while SCF was expressed in Sertoli cells (Loveland, *et al.*, 1997, *J. Endocrinol.*, 153:337-344). Testicular tumors develop from Leydig cells with high frequency in transgenic mice expressing human papilloma virus 16 (HPV16) E6 and E7 oncogenes (Kondoh, *et al.*, 1991, *J. Virol.*, 65:3335-3339; Kondoh, *et al.*, 1994, *J. Urol.*, 152:2151-2154). These tumors express both c-kit and SCF, and an autocrine loop may contribute to the tumorigenesis (Kondoh, *et al.*, 1995, *Oncogene*, 10:341-347) associated with cellular loss of functional p53 and the retinoblastoma gene product by association with E6 and E7 (Dyson, *et al.*, 1989, *Science*, 243:934-937; Werness, *et al.*, 1990, *Science*, 248:76-79; Scheffner, *et al.*, 1990, *Cell*, 63:1129-1136). Defective signaling

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mutants of SCF (Kondoh, *et al.*, 1995, *Oncogene*, 10:341-347) or c-kit (Li, *et al.*, 1996, *Canc. Res.*, 56:4343-4346) inhibited formation of testicular tumors in mice expressing HPV16 E6 and E7. Since c-kit kinase activation is pivotal to tumorigenesis in these animals, the compounds of the invention which inhibit Hsp90
5 and thereby cause the degradation of c-kit will be useful for preventing or treating testicular tumors associated with human papilloma virus.

Expression of c-kit on germ cell tumors shows that the receptor is expressed by the majority of carcinomas in situ and seminomas, but c-kit is expressed in only a minority of nonseminomas (Strohmeyer, *et al.*, 1991, *Canc. Res.*, 51:1811-1816;
10 Rajpert-de Meyts, *et al.*, 1994, *Int. J. Androl.*, 17:85-92; Izquierdo, *et al.*, 1995, *J. Pathol.*, 177:253-258; Strohmeyer, *et al.*, 1995, *J. Urol.*, 153:511-515; Bokenmeyer, *et al.*, 1996, *J. Cance. Res., Clin. Oncol.*, 122:301-306; Sandlow, *et al.*, 1996, *J. Androl.*, 17:403-408). Therefore, degradation of c-kit caused by the inhibition of Hsp90 by the compounds of the invention will be an efficacious means for the
15 treatment of these cancers.

SCF and c-kit are expressed throughout the central nervous system of developing rodents, and the pattern of expression suggests a role in growth, migration and differentiation of neuroectodermal cells. Expression of SCF and c-kit have also been reported in the adult brain (Hamel, *et al.*, 1997, *J. Neuro-Onc.*,
20 35:327-333). Expression of c-kit has also been observed in normal human brain tissue (Tada, *et al.* 1994, *J. Neuro.*, 80:1063-1073). Glioblastoma and astrocytoma, which define the majority of intracranial tumors, arise from neoplastic transformation of astrocytes (Levin, *et al.*, 1997, *Principles & Practice of Oncology*, 2022-2082). Expression of c-kit has been observed in glioblastoma cell lines and
25 tissues (Berdal, *et al.*, 1992, *Canc. Res.*, 52:3498-3502; Tada, *et al.*, 1994, *J. Neuro.*, 80:1063-1073; Stanulla, *et al.*, 1995, *Act. Neuropath.*, 89:158-165).

The association of c-kit with astrocytoma pathology is less clear. Reports of expression of c-kit in normal astrocytes have been made (Natali, *et al.*, 1992, *Int. J. Canc.*, 52:197-201), (Tada, *et al.* 1994, *J. Neuro.*, 80:1063-1073), while others
30 report it is not expressed (Kristt, *et al.*, 1993, *Neuro.*, 33:106-115). In the former case, high levels of c-kit expression in high grade tumors were observed (Kristt, *et al.*, 1993, *Neuro.*, 33:106-115), whereas in the latter case researchers were unable to

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detect any expression in astrocytomas. In addition, contradictory reports of c-kit and SCF expression in neuroblastomas also exist. One study found that neuroblastoma cell lines often express SCF, but rarely express c-kit. In primary tumors, c-kit was detected in about 8% of neuroblastomas, while SCF was found in 18% of tumors (Beck, et al., 1995, *Blood*, 86:3132-3138). In contrast, other studies (Cohen, et al., 1994, *Blood*, 84:3465-3472) have reported that all 14 neuroblastoma cell lines examined contained c-kit/SCF autocrine loops, and expression of both the receptor and ligand were observed in 45% of tumor samples examined. In two cell lines, anti-c-kit antibodies inhibited cell proliferation, suggesting that the SCF/c-kit autocrine loop contributed to growth (Cohen, et al., 1994, *Blood*, 84:3465-3472). Therefore, degradation of c-kit caused by the inhibition of Hsp90 by the compounds of the invention will be an efficacious means for treating some cancers of the central nervous system.

2. Bcr-Abl Associated Cancers

The Philadelphia chromosome which generates the fusion protein Bcr-Abl is associated with the bulk of chronic myelogenous leukemia (CML) patients (more than 95%), 10-25% of acute lymphocytic leukemia (ALL) patients, and about 2-3% of acute myelogenous leukemias (AML). In addition, Bcr-Abl is a factor in a variety of other hematological malignancies, including granulocytic hyperplasia resembling CML, myelomonocytic leukemia, lymphomas, and erythroid leukemia (see Lugo, et al., MCB (1989), 9:1263-1270; Daley, et al., Science (1990), 247:824-830; and Honda, Blood (1998), 91:2067-2075, the entire teachings of each of these references are incorporated herein by reference).

A number of different kinds of evidence support the contention that Bcr-Abl oncoproteins, such as p210 and p185 BCR-ABL, are causative factors in these leukemias (Campbell and Arlinghaus, "Current Status of Bcr Gene Involvement with Human Leukemia", In: Advances in Cancer Research, Eds. Klein, VandeWoude, Orlando, Fla. Academic Press, Inc., 57:227-256, 1991, the entire teachings of which are incorporated herein by reference). The malignant activity is due in large part to the Bcr-Abl protein's highly activated protein tyrosine kinase activity and its abnormal interaction with protein substrates (Arlinghaus et al., In:

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UCLA Symposia on Molecular and Cellular Biology New Series, Acute Lymphoblastic Leukemia, Eds. R. P. Gale, D. Hoelzer, New York, N.Y., Alan R. Liss, Inc., 108:81-90, 1990, the entire teachings of which are incorporated herein by reference). The Bcr-Abl oncoprotein p210 Bcr-Abl is associated with both CML and
 5 ALL, whereas the smaller oncoprotein, p185 BCR-ABL, is associated with ALL patients, although some CML patients also express p185 (Campbell et al., 1991).

3. FLT3 Associated Cancers

FLT3 associated cancers are cancers in which inappropriate FLT3 activity is detected. FLT3 associated cancers include hematologic malignancies such as
 10 leukemia and lymphoma. In some embodiments FLT3 associated cancers include acute myelogenous leukemia (AML), B-precursor cell acute lymphoblastic leukemia, myelodysplastic leukemia, T-cell acute lymphoblastic leukemia, mixed lineage leukemia (MLL), or chronic myelogenous leukemia (CML).

4. EGFR Associated Cancers

EGFR associated cancers are cancers in which inappropriate EGFR activity (e.g., overexpression of EGFR or mutation of EGFR which causes constitutive tyrosine kinase activity) has been implicated as a contributing factor. Inappropriate EGFR activity has been associated with an adverse prognosis in a number of human
 20 cancers, such as neuroblastoma, intestine carcinoma such as rectum carcinoma, colon carcinoma, familial adenomatous polyposis carcinoma and hereditary non-polyposis colorectal cancer, esophageal carcinoma, labial carcinoma, larynx carcinoma, hypopharynx carcinoma, tongue carcinoma, salivary gland carcinoma, gastric carcinoma, adenocarcinoma, medullary thyroid carcinoma, papillary
 25 thyroid carcinoma, renal carcinoma, kidney parenchym carcinoma, ovarian carcinoma, cervix carcinoma, uterine corpus carcinoma, endometrium carcinoma, chorion carcinoma, pancreatic carcinoma, prostate carcinoma, testis carcinoma, breast carcinoma, urinary carcinoma, melanoma, brain tumors such as glioblastoma, astrocytoma, meningioma, medulloblastoma and peripheral neuroectodermal tumors,
 30 Hodgkin lymphoma, non-Hodgkin lymphoma, Burkitt lymphoma, acute lymphatic leukemia (ALL), chronic lymphatic leukemia (CLL), acute myeloid leukemia (AML), chronic myeloid leukemia (CML), adult T-cell leukemia lymphoma,

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hepatocellular carcinoma, gall bladder carcinoma, bronchial carcinoma, small cell lung carcinoma, non-small cell lung carcinoma, multiple myeloma, basalioma, teratoma, retinoblastoma, choroidea melanoma, seminoma, rhabdomyo sarcoma, craniopharyngeoma, osteosarcoma, chondrosarcoma, myosarcoma, liposarcoma, fibrosarcoma, Ewing sarcoma and plasmocytoma.

In particular, EGFR appears to have an important role in the development of human brain tumors. A high incidence of overexpression, amplification, deletion and structural rearrangement of the gene coding for EGFR has been found in biopsies of brain tumors. In fact, the amplification of the EGFR gene in glioblastoma multiforme tumors is one of the most consistent genetic alterations known, with EGFR being overexpressed in approximately 40% of malignant gliomas and EGFRvIII mutation being found in about 50% of all glioblastomas.

In addition to gliomas, abnormal EGFR expression has also been reported in a number of squamous epidermoid cancers and breast cancers. Interestingly, evidence also suggests that many patients with tumors that over-express EGFR have a poorer prognosis than those having tumors that do not over-express EGFR.

Non-small cell lung cancer (NSCLC) includes squamous cell carcinomas, adenocarcinoma, bronchioloalveolar carcinoma (BAC), and large cell undifferentiated carcinoma. A subset of patients with NSCLC have been shown to have mutations in the tyrosine kinase domain of EGFR which is thought to be necessary for the maintenance of the disease. Treatment of this subset of patients with NSCLC with gefitinib, a tyrosine kinase inhibitor which targets EGFR, has shown rapid and dramatic clinical response.

Consequently, therapeutic strategies that can potentially inhibit or reduce the aberrant expression of EGFR are of great interest as potential anti-cancer agents.

3. Combination Therapies and Treatment of Refractory Cancers

The prophylactic or therapeutic agents of the combination therapies of the invention can be administered sequentially or concurrently. In a specific embodiment, the combination therapies of the invention comprise one or more compounds and at least one other therapy (*e.g.*, another prophylactic or therapeutic agent) which has the same mechanism of action as said compounds. In another

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specific embodiment, the combination therapies of the invention comprise one or more compounds of the invention and at least one other therapy (*e.g.*, another prophylactic or therapeutic agent) which has a different mechanism of action than said compounds. In certain embodiments, the combination therapies of the present invention improve the prophylactic or therapeutic effect of one or more compounds of the invention by functioning together with the compounds to have an additive or synergistic effect. In certain embodiments, the combination therapies of the present invention reduce the side effects associated with the therapies (*e.g.*, prophylactic or therapeutic agents). In certain embodiments, the combination therapies of the present invention reduce the effective dosage of one or more of the therapies.

The prophylactic or therapeutic agents of the combination therapies can be administered to a subject, preferably a human subject, in the same pharmaceutical composition. In alternative embodiments, the prophylactic or therapeutic agents of the combination therapies can be administered concurrently to a subject in separate pharmaceutical compositions. The prophylactic or therapeutic agents may be administered to a subject by the same or different routes of administration.

In a specific embodiment, a pharmaceutical composition comprising one or more compounds of the invention is administered to a subject, preferably a human, to prevent, treat, manage, or ameliorate a proliferative disorder, such as cancer, or one or more symptom thereof. In accordance with the invention, pharmaceutical compositions of the invention may also comprise one or more other agents (*e.g.*, prophylactic or therapeutic agents which are currently being used, have been used, or are known to be useful in the prevention, treatment or amelioration of a proliferative disorder or a symptom thereof).

The invention provides methods for preventing, managing, treating or ameliorating a proliferative disorder, such as cancer, or one or more symptoms thereof in a subject refractory (either completely or partially) to existing agent therapies for such a proliferative disorder, said methods comprising administering to said subject a dose of an effective amount of one or more compounds of the invention and a dose of an effective amount of one or more therapies (*e.g.*, one or more prophylactic or therapeutic agents useful for the prevention, treatment, management, or amelioration of a proliferative disorder or a symptom thereof). The

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invention also provides methods for preventing, treating, managing, or ameliorating a proliferative disorder or a symptom thereof by administering one or more compounds of the invention in combination with any other therapy(ies) to patients who have proven refractory to other therapies but are no longer on these therapies.

5 The compounds of the invention and/or other therapies can be administered to a subject by any route known to one of skill in the art. Examples of routes of administration include, but are not limited to, parenteral, *e.g.*, intravenous, intradermal, subcutaneous, oral (*e.g.*, inhalation), intranasal, transdermal (topical), transmucosal, and rectal administration.

10

1) Agents Useful In Combination With the Compounds of the Invention

Without wishing to be bound by theory, it is believed that the compounds of the invention can be particularly effective at treating subjects whose cancer has become multi-drug resistant. Although chemotherapeutic agents initially cause tumor regression, most agents that are currently used to treat cancer target only one pathway to tumor progression. Therefore, in many instances, after treatment with one or more chemotherapeutic agents, a tumor develops multidrug resistance and no longer responds positively to treatment. One of the advantages of inhibiting Hsp90 activity is that several of its client proteins, which are mostly protein kinases or transcription factors involved in signal transduction, have been shown to be involved in the progression of cancer. Thus, inhibition of Hsp90 provides a method of short circuiting several pathways for tumor progression simultaneously. Therefore, it is believed that treatment of cancer with an Hsp90 inhibitor of the invention either alone, or in combination with other chemotherapeutic agents, is more likely to result in regression or elimination of the tumor, and less likely to result in the development of more aggressive multidrug resistant tumors than other currently available therapies.

30 In one embodiment, the compounds of the invention can be administered with agents that are tyrosine kinase inhibitors (*e.g.*, gefitinib or erlotinib which inhibit EGFR tyrosine kinase activity). In another embodiment, the compounds of the invention can be administered to patients whose cancer has become resistant to a

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tyrosine kinase inhibitor (e.g., gefitinib or erlotinib). In this embodiment, the compounds of the invention can be administered either alone or in combination with the tyrosine kinase inhibitor.

In another embodiment, the compounds of the invention are useful for
 5 treating patients with hematological cancers that have become resistant to Imatinib, a chemotherapeutic agent that acts by inhibiting tyrosine kinase activity of Bcr-Abl. In patients with CML in the chronic phase, as well as in a blast crisis, treatment with Imatinib typically will induce remission. However, in many cases, particularly in
 10 those patients who were in a blast crisis before remission, the remission is not durable because the Bcr-Abl fusion protein develops mutations in the tyrosine kinase domain that cause it to be resistance to Imatinib. (See Nimmanapalli, *et al.*, *Cancer Research* (2001), 61:1799-1804; and Gorre, *et al.*, *Blood* (2002), 100:3041-3044, the entire teachings of each of these references are incorporated herein by reference). Compounds of the invention act by inhibiting the activity of Hsp90 which disrupt
 15 Bcr-Abl/Hsp90 complexes. When Bcr-Abl is not complex to Hsp90 it is rapidly degraded. Therefore, compounds of the invention are effective in treating Imatinib resistant leukemias since they act through a different mechanism than Imatinib. Compounds of the invention can be administered alone or with Imatinib in patients who have a Bcr-Abl associated cancer that is not resistant to Imatinib or to patients
 20 whose cancer has become resistant to Imatinib.

Anticancer agents that can be co-administered with the compounds of the invention include TaxolTM, also referred to as "paclitaxel", is a well-known anti-cancer drug which acts by enhancing and stabilizing microtubule formation, and
 25 analogs of TaxolTM, such as TaxotereTM. Compounds that have the basic taxane skeleton as a common structure feature, have also been shown to have the ability to arrest cells in the G2-M phases due to stabilization or inhibition of microtubules.

Other anti-cancer agents that can be employed in combination with the compounds of the invention include Avastin, Adriamycin, Dactinomycin, Bleomycin, Vinblastine, Cisplatin, acivicin; aclerubicin; acodazole hydrochloride;
 30 acronine; adozelesin; aldesleukin; altretamine; ambomycin; ametantrone acetate; aminoglutethimide; amsacrine; anastrozole; anthramycin; asparaginase; asperlin; azacitidine; azetepa; azotomycin; batimastat; benzodepa; bicalutamide; bisantrene

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- hydrochloride; bisnafide dimesylate; bizelesin; bleomycin sulfate; brequinar sodium; broprimine; busulfan; cactinomycin; calusterone; caracemide; carbetimer; carboplatin; carmustine; carubicin hydrochloride; carzelesin; cedefingol; chlorambucil; cirolemycin; cladribine; crisnatol mesylate; cyclophosphamide; cytarabine; dacarbazine; daunorubicin hydrochloride; decitabine; dexormaplatin; dezaguanine; dezaguanine mesylate; diaziquone; doxorubicin; doxorubicin hydrochloride; droloxifene; droloxifene citrate; dromostanolone propionate; duazomycin; edatrexate; eflomithine hydrochloride; elsamitrucin; enloplatin; enpromate; epipropidine; epirubicin hydrochloride; erbulozole; esorubicin hydrochloride; estramustine; estramustine phosphate sodium; etanidazole; etoposide; etoposide phosphate; etoprine; fadrozole hydrochloride; fazarabine; fenretinide; floxuridine; fludarabine phosphate; fluorouracil; flurocitabine; fosquidone; fostriecin sodium; gemcitabine; gemcitabine hydrochloride; hydroxyurea; idarubicin hydrochloride; ifosfamide; ilmofofine; interleukin II (including recombinant interleukin II, or rIL2), interferon alfa-2a; interferon alfa-2b; interferon alfa-n1 ; interferon alfa-n3; interferon beta-I a; interferon gamma-I b; iproplatin; irinotecan hydrochloride; lanreotide acetate; letrozole; leuprolide acetate; liarozole hydrochloride; lometrexol sodium; lomustine; losoxantrone hydrochloride; masoprocol; maytansine; mechlorethamine hydrochloride; megestrol acetate; melengestrol acetate; melphalan; menogarl; mercaptopurine; methotrexate; methotrexate sodium; metoprine; meturedapa; mitindomide; mitocarcin; mitocromin; mitogillin; mitomalcin; mitomycin; mitosper; mitotane; mitoxantrone hydrochloride; mycophenolic acid; nocodazole; nogalamycin; ormaplatin; oxisuran; pegaspargase; peliomycin; pentamustine; peplomycin sulfate; perfosfamide; pipobroman; piposulfan; piroxantrone hydrochloride; plicamycin; plomestane; porfimer sodium; porfiromycin; prednimustine; procarbazine hydrochloride; puromycin; puromycin hydrochloride; pyrazofurin; riboprime; rogletimide; safingol; safingol hydrochloride; semustine; simtrazene; sparfosate sodium; sparsomycin; spirogermanium hydrochloride; spiromustine; spiroplatin; streptonigrin; streptozocin; sulofenur; talisomycin; tecogalan sodium; tegafur; teloxantrone hydrochloride; temoporfin; teniposide; teroxirone; testolactone; thiamiprine; thioguanine; thiotepa; tiazofurin; tirapazamine; toremifene citrate; trestolone acetate;

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

Other anti-cancer drugs that can be employed in combination with the compounds of the invention include: 20-epi-1,25 dihydroxyvitamin D3; 5-ethynyluracil; abiraterone; aclarubicin; acylfulvene; adecypenol; adozelesin; aldesleukin; ALL-TK antagonists; altretamine; ambamustine; amidox; amifostine; aminolevulinic acid; amrubicin; amsacrine; anagrelide; anastrozole; andrographolide; angiogenesis inhibitors; antagonist D; antagonist G; antarelix; anti-dorsalizing morphogenetic protein-1; antiandrogen, prostatic carcinoma; antiestrogen; antineoplaston; antisense oligonucleotides; aphidicolin glycinate; apoptosis gene modulators; apoptosis regulators; apurinic acid; ara-CDP-DL-PTBA; arginine deaminase; asulacrine; atamestane; atrimustine; axinastatin 1; axinastatin 2; arginine deaminase; asulacrine; atamestane; atrimustine; axinastatin 1; axinastatin 2; axinastatin 3; azasetron; azatoxin; azatyrosine; baccatin III derivatives; balanol; batimastat; BCR/ABL antagonists; benzochlorins; benzoylstauroporine; beta lactam derivatives; beta-alethine; betaclamycin B; betulinic acid; bFGF inhibitor; bicalutamide; bisantrene; bisaziridinylspermine; bisnafide; bistratene A; bizelesin; breflate; broprimine; budotitane; buthionine sulfoximine; calcipotriol; calphostin C; camptothecin derivatives; canarypox IL-2; capecitabine; carboxamide-amino-triazole; carboxyamidotriazole; CaRest M3; CARN 700; cartilage derived inhibitor; carzelesin; casein kinase inhibitors (ICOS); castanospermine; cecropin B; cetrorelix; chlorlins; chloroquinoxaline sulfonamide; cicaprost; cis-porphyrin; cladribine; clomifene analogues; clotrimazole; collismycin A; collismycin B; combretastatin A4; combretastatin analogue; conagenin; crambescidin 816; crisnatol; cryptophycin 8; cryptophycin A derivatives; curacin A; cyclopentantraquinones; cycloplatam; cypemycin; cytarabine ocfosfate; cytolytic factor; cytostatin; dacliximah; decitabine; dehydridemnin B; deslorelin; dexamethasone; dexifosfamide; dexrazoxane; dexverapamil; diaziquone; didemnin B; didox; diethylnorspermine; dihydro-5-azacytidine; 9-dioxamycin; diphenyl spiromustine; docosanol; dolasetron; doxifluridine; droloxifene; dronabinol; duocarmycin SA; ebselen; ecomustine;

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- edelfosine; edrecolomab; eflornithine; elemene; emitefur; epirubicin; epristeride; estramustine analogue; estrogen agonists; estrogen antagonists; etanidazole; etoposide phosphate; exemestane; fadrozole; fazarabine; fenretinide; filgrastim; finasteride; flavopiridol; flezelastine; fluasterone; fludarabine; fluorodaunorubicin
- 5 hydrochloride; forfenimex; formestane; fostriecin; fotemustine; gadolinium texaphyrin; gallium nitrate; galocitabine; ganirelix; gelatinase inhibitors; gemcitabine; glutathione inhibitors; hepsulfam; heregulin; hexamethylene bisacetamide; hypericin; ibandronic acid; idarubicin; idoxifene; idramantone; ilmofofosine; ilomastat; imidazoacridones; imiquimod; immunostimulant peptides;
- 10 insulin-like growth factor-1 receptor inhibitor; interferon agonists; interferons; interleukins; iobenguane; iododoxorubicin; ipomeanol, 4-; iroplact; irsogladine; isobengazole; isohomohalicondrin B; itasetron; jasplakinolide; kahalalide F; lamellarin-N triacetate; lanreotide; leinamycin; lenograstim; lentinan sulfate; leptolstatin; letrozole; leukemia inhibiting factor; leukocyte alpha interferon;
- 15 leuprolide+estrogen+progesterone; leuprorelin; levamisole; liarazole; linear polyamine analogue; lipophilic disaccharide peptide; lipophilic platinum compounds; lissoclinamide 7; lobaplatin; lombricine; lometrexol; lonidamine; losoxantrone; lovastatin; loxoribine; lurtotecan; lutetium texaphyrin; lysofylline; lytic peptides; maitansine; mannosatin A; marimastat; masoprocol; maspin;
- 20 matrilysin inhibitors; matrix metalloproteinase inhibitors; menogaril; merbarone; meterelin; methioninase; metoclopramide; MIF inhibitor; mifepristone; miltefosine; mirimostim; mismatched double stranded RNA; mitoguazone; mitolactol; mitomycin analogues; mitonafide; mitotoxin fibroblast growth factor-saporin; mitoxantrone; mofarotene; molgramostim; monoclonal antibody, human chorionic
- 25 gonadotrophin; monophosphoryl lipid A+myobacterium cell wall sk; mopidamol; multiple drug resistance gene inhibitor; multiple tumor suppressor 1-based therapy; mustard anticancer agent; mycaperoxide B; mycobacterial cell wall extract; myriaporone; N-acetyldinaline; N-substituted benzamides; nafarelin; nagrestip; naloxone+pentazocine; napavin; naphterpin; nartograstim; nedaplatin; nemorubicin;
- 30 neridronic acid; neutral endopeptidase; nilutamide; nisamycin; nitric oxide modulators; nitroxide antioxidant; nitrullyn; O6-benzylguanine; octreotide; okicenone; oligonucleotides; onapristone; ondansetron; ondansetron; oracin; oral

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- cytokine inducer; ormaplatin; osaterone; oxaliplatin; oxanornomycin; palauamine;
 palmitoylrhizoxin; pamidronic acid; panaxytriol; panomifene; parabactin;
 pazelliptine; pegaspargase; peldesine; pentosan polysulfate sodium; pentostatin;
 pentozole; perflubron; perfosfamide; perillyl alcohol; phenazinomycin;
 5 phenylacetate; phosphatase inhibitors; picibanil; pilocarpine hydrochloride;
 pirarubicin; piritrexim; placetin A; placetin B; plasminogen activator inhibitor;
 platinum complex; platinum compounds; platinum-triamine complex; porfimer
 sodium; porfiromycin; prednisone; propyl bis-acridone; prostaglandin J2;
 proteasome inhibitors; protein A-based immune modulator; protein kinase C
 10 inhibitor; protein kinase C inhibitors, microalgal; protein tyrosine phosphatase
 inhibitors; purine nucleoside phosphorylase inhibitors; purpurins; pyrazoloacridine;
 pyridoxylated hemoglobin polyoxyethylene conjugate; raf antagonists; raltitrexed;
 ramosetron; ras farnesyl protein transferase inhibitors; ras inhibitors; ras-GAP
 inhibitor; retelliptine demethylated; rhenium Re 186 etidronate; rhizoxin; ribozymes;
 15 RII retinamide; rogletimide; rohitukine; romurtide; roquinimex; rubiginone B1;
 ruboxyl; safinol; saintopin; SarCNU; sarcophytol A; sargramostim; Sdi 1 mimetics;
 semustine; senescence derived inhibitor 1; sense oligonucleotides; signal
 transduction inhibitors; signal transduction modulators; single chain antigen-binding
 protein; sizofiran; sobuzoxane; sodium borocaptate; sodium phenylacetate; solverol;
 20 somatomedin binding protein; sonermin; sparfosic acid; spicamycin D;
 spiromustine; splenopentin; spongistatin 1; squalamine; stem cell inhibitor; stem-cell
 division inhibitors; stipiamide; stromelysin inhibitors; sulfinosine; superactive
 vasoactive intestinal peptide antagonist; suradista; suramin; swainsonine; synthetic
 glycosaminoglycans; tallimustine; tamoxifen methiodide; tauromustine; tazarotene;
 25 tecogalan sodium; tegafur; tellurapyrylium; telomerase inhibitors; temoporfin;
 temozolomide; teniposide; tetrachlorodecaoxide; tetrazomine; thaliblastine;
 thiocoraline; thrombopoietin; thrombopoietin mimetic; thymalfasin; thymopoietin
 receptor agonist; thymotrinan; thyroid stimulating hormone; tin ethyl etiopurpurin;
 tirapazamine; titanocene bichloride; topsentin; toremifene; totipotent stem cell
 30 factor; translation inhibitors; tretinoin; triacetyluridine; tricinibine; trimetrexate;
 triptorelin; tropisetron; turosteride; tyrosine kinase inhibitors; tyrphostins; UBC
 inhibitors; ubenimex; urogenital sinus-derived growth inhibitory factor; urokinase

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receptor antagonists; vapreotide; variolin B; vector system, erythrocyte gene therapy; velaresol; veramine; verdins; verteporfin; vinorelbine; vinxaltine; vitaxin; vorozole; zanoterone; zeniplatin; zilascorb; and zinostatin stimalamer. Preferred anti-cancer drugs are 5-fluorouracil and leucovorin.

- 5 Other chemotherapeutic agents that can be employed in combination with the compounds of the invention include but are not limited to alkylating agents, antimetabolites, natural products, or hormones. Examples of alkylating agents useful for the treatment or prevention of T-cell malignancies in the methods and compositions of the invention include but are not limited to, nitrogen mustards (*e.g.*,
 10 mechloroethamine, cyclophosphamide, chlorambucil, *etc.*), alkyl sulfonates (*e.g.*, busulfan), nitrosoureas (*e.g.*, carmustine, lomustine, *etc.*), or triazenes (decabazine, *etc.*). Examples of antimetabolites useful for the treatment or prevention of T-cell malignancies in the methods and compositions of the invention include but are not limited to folic acid analog (*e.g.*, methotrexate), or pyrimidine analogs (*e.g.*,
 15 Cytarabine), purine analogs (*e.g.*, mercaptopurine, thioguanine, pentostatin). Examples of natural products useful for the treatment or prevention of T-cell malignancies in the methods and compositions of the invention include but are not limited to vinca alkaloids (*e.g.*, vinblastin, vincristine), epipodophyllotoxins (*e.g.*, etoposide), antibiotics (*e.g.*, daunorubicin, doxorubicin, bleomycin), enzymes (*e.g.*,
 20 L-asparaginase), or biological response modifiers (*e.g.*, interferon alpha).

- Examples of alkylating agents that can be employed in combination with the compounds of the invention include but are not limited to, nitrogen mustards (*e.g.*, mechloroethamine, cyclophosphamide, chlorambucil, melphalan, *etc.*), ethylenimine and methylmelamines (*e.g.*, hexamethylmelamine, thiotepa), alkyl sulfonates (*e.g.*,
 25 busulfan), nitrosoureas (*e.g.*, carmustine, lomustine, semustine, streptozocin, *etc.*), or triazenes (decabazine, *etc.*). Examples of antimetabolites useful for the treatment or prevention of cancer in the methods and compositions of the invention include but are not limited to folic acid analog (*e.g.*, methotrexate), or pyrimidine analogs (*e.g.*, fluorouracil, floxouridine, Cytarabine), purine analogs (*e.g.*, mercaptopurine,
 30 thioguanine, pentostatin). Examples of natural products useful for the treatment or prevention of cancer in the methods and compositions of the invention include but are not limited to vinca alkaloids (*e.g.*, vinblastin, vincristine), epipodophyllotoxins

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- (*e.g.*, etoposide, teniposide), antibiotics (*e.g.*, actinomycin D, daunorubicin, doxorubicin, bleomycin, plicamycin, mitomycin), enzymes (*e.g.*, L-asparaginase), or biological response modifiers (*e.g.*, interferon alpha). Examples of hormones and antagonists useful for the treatment or prevention of cancer in the methods and compositions of the invention include but are not limited to adrenocorticosteroids (*e.g.*, prednisone), progestins (*e.g.*, hydroxyprogesterone caproate, megestrol acetate, medroxyprogesterone acetate), estrogens (*e.g.*, diethylstilbestrol, ethinyl estradiol), antiestrogen (*e.g.*, tamoxifen), androgens (*e.g.*, testosterone propionate, fluoxymesterone), antiandrogen (*e.g.*, flutamide), gonadotropin releasing hormone analog (*e.g.*, leuprolide). Other agents that can be used in the methods and compositions of the invention for the treatment or prevention of cancer include platinum coordination complexes (*e.g.*, cisplatin, carboplatin), anthracenedione (*e.g.*, mitoxantrone), substituted urea (*e.g.*, hydroxyurea), methyl hydrazine derivative (*e.g.*, procarbazine), adrenocortical suppressant (*e.g.*, mitotane, aminoglutethimide).
- Examples of anti-cancer agents which act by arresting cells in the G2-M phases due to stabilization or inhibition of microtubules and which can be used in combination with the compounds of the invention include without limitation the following marketed drugs and drugs in development: Erbulozole (also known as R-55104), Dolastatin 10 (also known as DLS-10 and NSC-376128), Mivobulin isethionate (also known as CI-980), Vincristine, NSC-639829, Discodermolide (also known as NVP-XX-A-296), ABT-751 (Abbott, also known as E-7010), Altorhyrtins (such as Altorhyrtin A and Altorhyrtin C), Spongistatins (such as Spongistatin 1, Spongistatin 2, Spongistatin 3, Spongistatin 4, Spongistatin 5, Spongistatin 6, Spongistatin 7, Spongistatin 8, and Spongistatin 9), Cemadotin hydrochloride (also known as LU-103793 and NSC-D-669356), Epothilones (such as Epothilone A, Epothilone B, Epothilone C (also known as desoxyepothilone A or dEpoA), Epothilone D (also referred to as KOS-862, dEpoB, and desoxyepothilone B), Epothilone E, Epothilone F, Epothilone B N-oxide, Epothilone A N-oxide, 16-aza-epothilone B, 21-aminoepothilone B (also known as BMS-310705), 21-hydroxyepothilone D (also known as Desoxyepothilone F and dEpoF), 26-fluoroepothilone), Auristatin PE (also known as NSC-654663), Soblidotin (also known as TZT-1027), LS-4559-P (Pharmacia, also known as LS-4577), LS-4578

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- (Pharmacia, also known as LS-477-P), LS-4477 (Pharmacia), LS-4559 (Pharmacia), RPR-112378 (Aventis), Vincristine sulfate, DZ-3358 (Daiichi), FR-182877 (Fujisawa, also known as WS-9885B), GS-164 (Takeda), GS-198 (Takeda), KAR-2 (Hungarian Academy of Sciences), BSF-223651 (BASF, also known as ILX-651 and LU-223651), SAH-49960 (Lilly/Novartis), SDZ-268970 (Lilly/Novartis), AM-97 (Armada/Kyowa Hakko), AM-132 (Armada), AM-138 (Armada/Kyowa Hakko), IDN-5005 (Indena), Cryptophycin 52 (also known as LY-355703), AC-7739 (Ajinomoto, also known as AVE-8063A and CS-39.HCl), AC-7700 (Ajinomoto, also known as AVE-8062, AVE-8062A, CS-39-L-Ser.HCl, and RPR-258062A),
- 10 Vitilevuamide, Tubulysin A, Canadensol, Centaureidin (also known as NSC-106969), T-138067 (Tularik, also known as T-67, TL-138067 and TI-138067), COBRA-1 (Parker Hughes Institute, also known as DDE-261 and WHI-261), H10 (Kansas State University), H16 (Kansas State University), Oncocidin A1 (also known as BTO-956 and DIME), DDE-313 (Parker Hughes Institute), Fijianolide B,
- 15 Laulimalide, SPA-2 (Parker Hughes Institute), SPA-1 (Parker Hughes Institute, also known as SPIKET-P), 3-IAABU (Cytoskeleton/Mt. Sinai School of Medicine, also known as MF-569), Narcosine (also known as NSC-5366), Nascapine, D-24851 (Asta Medica), A-105972 (Abbott), Hemiasterlin, 3-BAABU (Cytoskeleton/Mt. Sinai School of Medicine, also known as MF-191), TMPN (Arizona State
- 20 University), Vanadocene acetylacetonate, T-138026 (Tularik), Monsatrol, Inanocine (also known as NSC-698666), 3-IAABE (Cytoskeleton/Mt. Sinai School of Medicine), A-204197 (Abbott), T-607 (Tularik, also known as T-900607), RPR-115781 (Aventis), Eleutherobins (such as Desmethyleleutherobin, Desacetylleutherobin, Isoeleutherobin A, and Z-Eleutherobin), Caribacoxide,
- 25 Caribaeolin, Halichondrin B, D-64131 (Asta Medica), D-68144 (Asta Medica), Diazonamide A, A-293620 (Abbott), NPI-2350 (Nereus), Taccalonolide A, TUB-245 (Aventis), A-259754 (Abbott), Diozostatin, (-)-Phenylhistin (also known as NSCL-96F037), D-68838 (Asta Medica), D-68836 (Asta Medica), Myoseverin B, D-43411 (Zentaris, also known as D-81862), A-289099 (Abbott), A-318315
- 30 (Abbott), HTI-286 (also known as SPA-110, trifluoroacetate salt) (Wyeth), D-82317 (Zentaris), D-82318 (Zentaris), SC-12983 (NCI), Resverastatin phosphate sodium, BPR-0Y-007 (National Health Research Institutes), and SSR-250411 (Sanofi).

E. Compositions and Methods for Administering Therapies

The present invention provides compositions for the treatment, prophylaxis, and amelioration of proliferative disorders, such as cancer. In a specific embodiment, a composition comprises one or more compounds of the invention, or a pharmaceutically acceptable salt, solvate, clathrate, hydrate or prodrug thereof. In another embodiment, a composition of the invention comprises one or more prophylactic or therapeutic agents other than a compound of the invention, or a pharmaceutically acceptable salt, solvate, clathrate, hydrate, prodrug thereof. In another embodiment, a composition of the invention comprises one or more compounds of the invention, or a pharmaceutically acceptable salt, solvate, clathrate, hydrate or prodrug thereof, and one or more other prophylactic or therapeutic agents. In another embodiment, the composition comprises a compound of the invention, or a pharmaceutically acceptable salt, solvate, clathrate, hydrate, or prodrug thereof, and a pharmaceutically acceptable carrier, diluent or excipient.

In a preferred embodiment, a composition of the invention is a pharmaceutical composition or a single unit dosage form. Pharmaceutical compositions and dosage forms of the invention comprise one or more active ingredients in relative amounts and formulated in such a way that a given pharmaceutical composition or dosage form can be used to treat or prevent proliferative disorders, such as cancer. Preferred pharmaceutical compositions and dosage forms comprise a compound of formula (I) – (XXXV) or a pharmaceutically acceptable prodrug, salt, solvate, clathrate, hydrate, or prodrug thereof, optionally in combination with one or more additional active agents.

A pharmaceutical composition of the invention is formulated to be compatible with its intended route of administration. Examples of routes of administration include, but are not limited to, parenteral, *e.g.*, intravenous, intradermal, subcutaneous, oral (*e.g.*, inhalation), intranasal, transdermal (topical), transmucosal, and rectal administration. In a specific embodiment, the composition is formulated in accordance with routine procedures as a pharmaceutical composition adapted for intravenous, subcutaneous, intramuscular, oral, intranasal or topical administration to human beings. In a preferred embodiment, a

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pharmaceutical composition is formulated in accordance with routine procedures for subcutaneous administration to human beings.

Single unit dosage forms of the invention are suitable for oral, mucosal (*e.g.*, nasal, sublingual, vaginal, buccal, or rectal), parenteral (*e.g.*, subcutaneous, intravenous, bolus injection, intramuscular, or intraarterial), or transdermal administration to a patient. Examples of dosage forms include, but are not limited to: tablets; caplets; capsules, such as soft elastic gelatin capsules; cachets; troches; lozenges; dispersions; suppositories; ointments; cataplasms (poultices); pastes; powders; dressings; creams; plasters; solutions; patches; aerosols (*e.g.*, nasal sprays or inhalers); gels; liquid dosage forms suitable for oral or mucosal administration to a patient, including suspensions (*e.g.*, aqueous or non-aqueous liquid suspensions, oil-in-water emulsions, or a water-in-oil liquid emulsions), solutions, and elixirs; liquid dosage forms suitable for parenteral administration to a patient; and sterile solids (*e.g.*, crystalline or amorphous solids) that can be reconstituted to provide liquid dosage forms suitable for parenteral administration to a patient.

The composition, shape, and type of dosage forms of the invention will typically vary depending on their use. For example, a dosage form suitable for mucosal administration may contain a smaller amount of active ingredient(s) than an oral dosage form used to treat the same indication. This aspect of the invention will be readily apparent to those skilled in the art. *See, e.g.*, Remington's Pharmaceutical Sciences (1990) 18th ed., Mack Publishing, Easton PA.

Typical pharmaceutical compositions and dosage forms comprise one or more excipients. Suitable excipients are well known to those skilled in the art of pharmacy, and non-limiting examples of suitable excipients are provided herein. Whether a particular excipient is suitable for incorporation into a pharmaceutical composition or dosage form depends on a variety of factors well known in the art including, but not limited to, the way in which the dosage form will be administered to a patient. For example, oral dosage forms such as tablets may contain excipients not suited for use in parenteral dosage forms.

The suitability of a particular excipient may also depend on the specific active ingredients in the dosage form. For example, the decomposition of some active ingredients can be accelerated by some excipients such as lactose, or when

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exposed to water. Active ingredients that comprise primary or secondary amines (e.g., N-desmethylvenlafaxine and N,N-didesmethylvenlafaxine) are particularly susceptible to such accelerated decomposition. Consequently, this invention encompasses pharmaceutical compositions and dosage forms that contain little, if any, lactose. As used herein, the term "lactose-free" means that the amount of lactose present, if any, is insufficient to substantially increase the degradation rate of an active ingredient. Lactose-free compositions of the invention can comprise excipients that are well known in the art and are listed, for example, in the U.S. Pharmacopia (USP) SP (XXI)/NF (XVI). In general, lactose-free compositions comprise active ingredients, a binder/filler, and a lubricant in pharmaceutically compatible and pharmaceutically acceptable amounts. Preferred lactose-free dosage forms comprise active ingredients, microcrystalline cellulose, pre-gelatinized starch, and magnesium stearate.

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

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

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

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

1) Oral Dosage Forms

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

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

Because of their ease of administration, tablets and capsules represent the most advantageous oral dosage unit forms, in which case solid excipients are

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employed. If desired, tablets can be coated by standard aqueous or nonaqueous techniques. Such dosage forms can be prepared by any of the methods of pharmacy. In general, pharmaceutical compositions and dosage forms are prepared by uniformly and intimately admixing the active ingredients with liquid carriers, finely divided solid carriers, or both, and then shaping the product into the desired presentation if necessary.

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

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

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

Examples of fillers suitable for use in the pharmaceutical compositions and dosage forms disclosed herein include, but are not limited to, talc, calcium carbonate (*e.g.*, granules or powder), microcrystalline cellulose, powdered cellulose, dextrates, kaolin, mannitol, silicic acid, sorbitol, starch, pre-gelatinized starch, and mixtures

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thereof. The binder or filler in pharmaceutical compositions of the invention is typically present in from about 50 to about 99 weight percent of the pharmaceutical composition or dosage form.

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

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

Lubricants that can be used in pharmaceutical compositions and dosage
20 forms of the invention include, but are not limited to, calcium stearate, magnesium stearate, mineral oil, light mineral oil, glycerin, sorbitol, mannitol, polyethylene glycol, other glycols, stearic acid, sodium lauryl sulfate, talc, hydrogenated vegetable oil (e.g., peanut oil, cottonseed oil, sunflower oil, sesame oil, olive oil,
25 corn oil, and soybean oil), zinc stearate, ethyl oleate, ethyl laureate, agar, and mixtures thereof. Additional lubricants include, for example, a syloid silica gel (AEROSIL 200, manufactured by W.R. Grace Co. of Baltimore, MD), a coagulated aerosol of synthetic silica (marketed by Degussa Co. of Plano, TX), CAB-O-SIL (a pyrogenic silicon dioxide product sold by Cabot Co. of Boston, MA), and mixtures
30 thereof. If used at all, lubricants are typically used in an amount of less than about 1 weight percent of the pharmaceutical compositions or dosage forms into which they are incorporated.

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2) Controlled Release Dosage Forms

Active ingredients of the invention can be administered by controlled release means or by delivery devices that are well known to those of ordinary skill in the art. Examples include, but are not limited to, those described in U.S. Patent Nos.: 3,845,770; 3,916,899; 3,536,809; 3,598,123; and 4,008,719, 5,674,533, 5,059,595, 5,591,767, 5,120,548, 5,073,543, 5,639,476, 5,354,556, and 5,733,566, each of which is incorporated herein by reference. Such dosage forms can be used to provide slow or controlled-release of one or more active ingredients using, for example, hydropropylmethyl cellulose, other polymer matrices, gels, permeable membranes, osmotic systems, multilayer coatings, microparticles, liposomes, microspheres, or a combination thereof to provide the desired release profile in varying proportions. Suitable controlled-release formulations known to those of ordinary skill in the art, including those described herein, can be readily selected for use with the active ingredients of the invention. The invention thus encompasses single unit dosage forms suitable for oral administration such as, but not limited to, tablets, capsules, gelcaps, and caplets that are adapted for controlled-release.

All controlled-release pharmaceutical products have a common goal of improving drug therapy over that achieved by their non-controlled counterparts. Ideally, the use of an optimally designed controlled-release preparation in medical treatment is characterized by a minimum of drug substance being employed to cure or control the condition in a minimum amount of time. Advantages of controlled-release formulations include extended activity of the drug, reduced dosage frequency, and increased patient compliance.

Most controlled-release formulations are designed to initially release an amount of drug (active ingredient) that promptly produces the desired therapeutic effect, and gradually and continually release of other amounts of drug to maintain this level of therapeutic or prophylactic effect over an extended period of time. In order to maintain this constant level of drug in the body, the drug must be released from the dosage form at a rate that will replace the amount of drug being metabolized and excreted from the body. Controlled-release of an active ingredient

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can be stimulated by various conditions including, but not limited to, pH, temperature, enzymes, water, or other physiological conditions or compounds.

A particular extended release formulation of this invention comprises a therapeutically or prophylactically effective amount of a compound of formula (I) – (XXXV), or a pharmaceutically acceptable salt, solvate, hydrate, clathrate, or prodrug thereof, in spheroids which further comprise microcrystalline cellulose and, optionally, hydroxypropylmethyl-cellulose coated with a mixture of ethyl cellulose and hydroxypropylmethylcellulose. Such extended release formulations can be prepared according to U.S. Patent No. 6,274,171, the entirety of which is incorporated herein by reference.

A specific controlled-release formulation of this invention comprises from about 6% to about 40% a compound of formula (I) – (XXXV), or a pharmaceutically acceptable salt, solvate, hydrate, clathrate, or prodrug thereof, by weight, about 50% to about 94% microcrystalline cellulose, NF, by weight, and optionally from about 0.25% to about 1% by weight of hydroxypropyl-methylcellulose, USP, wherein the spheroids are coated with a film coating composition comprised of ethyl cellulose and hydroxypropylmethylcellulose.

3) Parenteral Dosage Forms

Parenteral dosage forms can be administered to patients by various routes including, but not limited to, subcutaneous, intravenous (including bolus injection), intramuscular, and intraarterial. Because their administration typically bypasses patients' natural defenses against contaminants, parenteral dosage forms are preferably sterile or capable of being sterilized prior to administration to a patient. Examples of parenteral dosage forms include, but are not limited to, solutions ready for injection, dry products ready to be dissolved or suspended in a pharmaceutically acceptable vehicle for injection, suspensions ready for injection, and emulsions.

Suitable vehicles that can be used to provide parenteral dosage forms of the invention are well known to those skilled in the art. Examples include, but are not limited to: Water for Injection USP; aqueous vehicles such as, but not limited to, Sodium Chloride Injection, Ringer's Injection, Dextrose Injection, Dextrose and Sodium Chloride Injection, and Lactated Ringer's Injection; water-miscible vehicles

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such as, but not limited to, ethyl alcohol, polyethylene glycol, and polypropylene glycol; and non-aqueous vehicles such as, but not limited to, corn oil, cottonseed oil, peanut oil, sesame oil, ethyl oleate, isopropyl myristate, and benzyl benzoate.

Compounds that increase the solubility of one or more of the active ingredients disclosed herein can also be incorporated into the parenteral dosage forms of the invention.

4) Transdermal, Topical, and Mucosal Dosage Forms

Transdermal, topical, and mucosal dosage forms of the invention include, but are not limited to, ophthalmic solutions, sprays, aerosols, creams, lotions, ointments, gels, solutions, emulsions, suspensions, or other forms known to one of skill in the art. *See, e.g.*, Remington's Pharmaceutical Sciences (1980 & 1990) 16th and 18th eds., Mack Publishing, Easton PA and Introduction to Pharmaceutical Dosage Forms (1985) 4th ed., Lea & Febiger, Philadelphia. Dosage forms suitable for treating mucosal tissues within the oral cavity can be formulated as mouthwashes or as oral gels. Further, transdermal dosage forms include "reservoir type" or "matrix type" patches, which can be applied to the skin and worn for a specific period of time to permit the penetration of a desired amount of active ingredients.

Suitable excipients (*e.g.*, carriers and diluents) and other materials that can be used to provide transdermal, topical, and mucosal dosage forms encompassed by this invention are well known to those skilled in the pharmaceutical arts, and depend on the particular tissue to which a given pharmaceutical composition or dosage form will be applied. With that fact in mind, typical excipients include, but are not limited to, water, acetone, ethanol, ethylene glycol, propylene glycol, butane-1,3-diol, isopropyl myristate, isopropyl palmitate, mineral oil, and mixtures thereof to form lotions, tinctures, creams, emulsions, gels or ointments, which are non-toxic and pharmaceutically acceptable. Moisturizers or humectants can also be added to pharmaceutical compositions and dosage forms if desired. Examples of such additional ingredients are well known in the art. *See, e.g.*, Remington's Pharmaceutical Sciences (1980 & 1990) 16th and 18th eds., Mack Publishing, Easton PA.

Depending on the specific tissue to be treated, additional components may be used prior to, in conjunction with, or subsequent to treatment with active ingredients

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of the invention. For example, penetration enhancers can be used to assist in delivering the active ingredients to the tissue. Suitable penetration enhancers include, but are not limited to: acetone; various alcohols such as ethanol, oleyl, and tetrahydrofuryl; alkyl sulfoxides such as dimethyl sulfoxide; dimethyl acetamide; 5 dimethyl formamide; polyethylene glycol; pyrrolidones such as polyvinylpyrrolidone; Kollidon grades (Povidone, Polyvidone); urea; and various water-soluble or insoluble sugar esters such as Tween 80 (polysorbate 80) and Span 60 (sorbitan monostearate).

The pH of a pharmaceutical composition or dosage form, or of the tissue to 10 which the pharmaceutical composition or dosage form is applied, may also be adjusted to improve delivery of one or more active ingredients. Similarly, the polarity of a solvent carrier, its ionic strength, or tonicity can be adjusted to improve delivery. Compounds such as stearates can also be added to pharmaceutical compositions or dosage forms to advantageously alter the hydrophilicity or 15 lipophilicity of one or more active ingredients so as to improve delivery. In this regard, stearates can serve as a lipid vehicle for the formulation, as an emulsifying agent or surfactant, and as a delivery-enhancing or penetration-enhancing agent. Different salts, hydrates or solvates of the active ingredients can be used to further adjust the properties of the resulting composition.

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5) Dosage & Frequency of Administration

The amount of the compound or composition of the invention which will be effective in the prevention, treatment, management, or amelioration of a proliferative disorders, such as cancer, or one or more symptoms thereof, will vary with the 25 nature and severity of the disease or condition, and the route by which the active ingredient is administered. The frequency and dosage will also vary according to factors specific for each patient depending on the specific therapy (e.g., therapeutic or prophylactic agents) administered, the severity of the disorder, disease, or condition, the route of administration, as well as age, body, weight, response, and 30 the past medical history of the patient. Effective doses may be extrapolated from dose-response curves derived from *in vitro* or animal model test systems. Suitable regimens can be selected by one skilled in the art by considering such factors and

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by following, for example, dosages reported in the literature and recommended in the *Physician's Desk Reference* (57th ed., 2003).

Exemplary doses of a small molecule include milligram or microgram amounts of the small molecule per kilogram of subject or sample weight (*e.g.*, about 5 1 microgram per kilogram to about 500 milligrams per kilogram, about 100 micrograms per kilogram to about 5 milligrams per kilogram, or about 1 microgram per kilogram to about 50 micrograms per kilogram).

In general, the recommended daily dose range of a compound of the invention for the conditions described herein lie within the range of from about 0.01 10 mg to about 1000 mg per day, given as a single once-a-day dose preferably as divided doses throughout a day. In one embodiment, the daily dose is administered twice daily in equally divided doses. Specifically, a daily dose range should be from about 5 mg to about 500 mg per day, more specifically, between about 10 mg and about 200 mg per day. In managing the patient, the therapy should be initiated at a 15 lower dose, perhaps about 1 mg to about 25 mg, and increased if necessary up to about 200 mg to about 1000 mg per day as either a single dose or divided doses, depending on the patient's global response. It may be necessary to use dosages of the active ingredient outside the ranges disclosed herein in some cases, as will be apparent to those of ordinary skill in the art. Furthermore, it is noted that the 20 clinician or treating physician will know how and when to interrupt, adjust, or terminate therapy in conjunction with individual patient response.

Different therapeutically effective amounts may be applicable for different proliferative disorders, as will be readily known by those of ordinary skill in the art. Similarly, amounts sufficient to prevent, manage, treat or ameliorate such 25 proliferative disorders, but insufficient to cause, or sufficient to reduce, adverse effects associated with the compounds of the invention are also encompassed by the above described dosage amounts and dose frequency schedules. Further, when a patient is administered multiple dosages of a compound of the invention, not all of the dosages need be the same. For example, the dosage administered to the patient 30 may be increased to improve the prophylactic or therapeutic effect of the compound or it may be decreased to reduce one or more side effects that a particular patient is experiencing.

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In a specific embodiment, the dosage of the composition of the invention or a compound of the invention administered to prevent, treat, manage, or ameliorate a proliferative disorders, such as cancer, or one or more symptoms thereof in a patient is 150 $\mu\text{g/kg}$, preferably 250 $\mu\text{g/kg}$, 500 $\mu\text{g/kg}$, 1 mg/kg, 5 mg/kg, 10 mg/kg, 25 mg/kg, 50 mg/kg, 75 mg/kg, 100 mg/kg, 125 mg/kg, 150 mg/kg, or 200 mg/kg or more of a patient's body weight. In another embodiment, the dosage of the composition of the invention or a compound of the invention administered to prevent, treat, manage, or ameliorate a proliferative disorders, such as cancer, or one or more symptoms thereof in a patient is a unit dose of 0.1 mg to 20 mg, 0.1 mg to 15 mg, 0.1 mg to 12 mg, 0.1 mg to 10 mg, 0.1 mg to 8 mg, 0.1 mg to 7 mg, 0.1 mg to 5 mg, 0.1 to 2.5 mg, 0.25 mg to 20 mg, 0.25 to 15 mg, 0.25 to 12 mg, 0.25 to 10 mg, 0.25 to 8 mg, 0.25 mg to 7 mg, 0.25 mg to 5 mg, 0.5 mg to 2.5 mg, 1 mg to 20 mg, 1 mg to 15 mg, 1 mg to 12 mg, 1 mg to 10 mg, 1 mg to 8 mg, 1 mg to 7 mg, 1 mg to 5 mg, or 1 mg to 2.5 mg.

The dosages of prophylactic or therapeutic agents other than compounds of the invention, which have been or are currently being used to prevent, treat, manage, or proliferative disorders, such as cancer, or one or more symptoms thereof can be used in the combination therapies of the invention. Preferably, dosages lower than those which have been or are currently being used to prevent, treat, manage, or ameliorate a proliferative disorders, or one or more symptoms thereof, are used in the combination therapies of the invention. The recommended dosages of agents currently used for the prevention, treatment, management, or amelioration of a proliferative disorders, such as cancer, or one or more symptoms thereof, can be obtained from any reference in the art including, but not limited to, Hardman *et al.*, eds., 1996, Goodman & Gilman's The Pharmacological Basis Of Basis Of Therapeutics 9th Ed, Mc-Graw-Hill, New York; Physician's Desk Reference (PDR) 57th Ed., 2003, Medical Economics Co., Inc., Montvale, NJ, which are incorporated herein by reference in its entirety.

In certain embodiments, when the compounds of the invention are administered in combination with another therapy, the therapies (*e.g.*, prophylactic or therapeutic agents) are administered less than 5 minutes apart, less than 30 minutes apart, 1 hour apart, at about 1 hour apart, at about 1 to about 2 hours apart,

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at about 2 hours to about 3 hours apart, at about 3 hours to about 4 hours apart, at about 4 hours to about 5 hours apart, at about 5 hours to about 6 hours apart, at about 6 hours to about 7 hours apart, at about 7 hours to about 8 hours apart, at about 8 hours to about 9 hours apart, at about 9 hours to about 10 hours apart, at about 10 hours to about 11 hours apart, at about 11 hours to about 12 hours apart, at about 12 hours to about 18 hours apart, 18 hours to 24 hours apart, 24 hours to 36 hours apart, 36 hours to 48 hours apart, 48 hours to 52 hours apart, 52 hours to 60 hours apart, 60 hours to 72 hours apart, 72 hours to 84 hours apart, 84 hours to 96 hours apart, or 96 hours to 120 hours apart. In one embodiment, two or more therapies (e.g., prophylactic or therapeutic agents) are administered within the same patent visit.

In certain embodiments, one or more compounds of the invention and one or more other the therapies (e.g., prophylactic or therapeutic agents) are cyclically administered. Cycling therapy involves the administration of a first therapy (e.g., a first prophylactic or therapeutic agents) for a period of time, followed by the administration of a second therapy (e.g., a second prophylactic or therapeutic agents) for a period of time, followed by the administration of a third therapy (e.g., a third prophylactic or therapeutic agents) for a period of time and so forth, and repeating this sequential administration, i.e., the cycle in order to reduce the development of resistance to one of the agents, to avoid or reduce the side effects of one of the agents, and/or to improve the efficacy of the treatment.

In certain embodiments, administration of the same compound of the invention may be repeated and the administrations may be separated by at least 1 day, 2 days, 3 days, 5 days, 10 days, 15 days, 30 days, 45 days, 2 months, 75 days, 3 months, or 6 months. In other embodiments, administration of the same prophylactic or therapeutic agent may be repeated and the administration may be separated by at least at least 1 day, 2 days, 3 days, 5 days, 10 days, 15 days, 30 days, 45 days, 2 months, 75 days, 3 months, or 6 months.

In a specific embodiment, the invention provides a method of preventing, treating, managing, or ameliorating a proliferative disorders, such as cancer, or one or more symptoms thereof, said methods comprising administering to a subject in need thereof a dose of at least 150 $\mu\text{g/kg}$, preferably at least 250 $\mu\text{g/kg}$, at least 500 $\mu\text{g/kg}$, at least 1 mg/kg, at least 5 mg/kg, at least 10 mg/kg, at least 25 mg/kg, at

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least 50 mg/kg, at least 75 mg/kg, at least 100 mg/kg, at least 125 mg/kg, at least 150 mg/kg, or at least 200 mg/kg or more of one or more compounds of the invention once every day, preferably, once every 2 days, once every 3 days, once every 4 days, once every 5 days, once every 6 days, once every 7 days, once every 8 days, once every 10 days, once every two weeks, once every three weeks, or once a month.

F. Other Embodiments

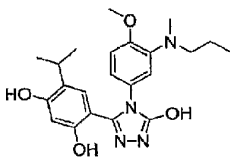
The compounds of the invention may be used as research tools (for example, to evaluate the mechanism of action of new drug agents, to isolate new drug discovery targets using affinity chromatography, as antigens in an ELISA or ELISA-like assay, or as standards in *in vitro* or *in vivo* assays). These and other uses and embodiments of the compounds and compositions of this invention will be apparent to those of ordinary skill in the art.

The invention is further defined by reference to the following examples describing in detail the preparation of compounds of the invention. It will be apparent to those skilled in the art that many modifications, both to materials and methods, may be practiced without departing from the purpose and interest of this invention. The following examples are set forth to assist in understanding the invention and should not be construed as specifically limiting the invention described and claimed herein. Such variations of the invention, including the substitution of all equivalents now known or later developed, which would be within the purview of those skilled in the art, and changes in formulation or minor changes in experimental design, are to be considered to fall within the scope of the invention incorporated herein.

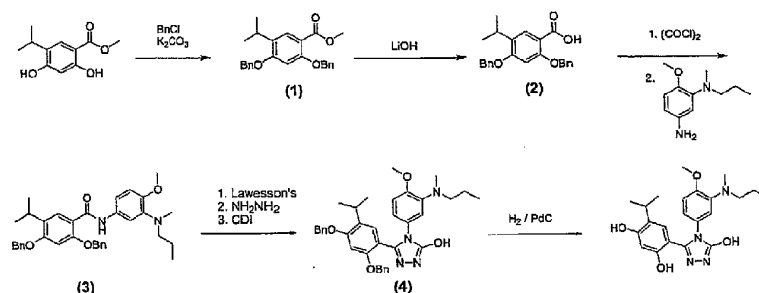
EXAMPLES

Example 1: 4-{5-Hydroxy-4-[4-methoxy-3-(methylpropylamino)phenyl]-4H-[1,2,4]triazol-3-yl}-6-isopropyl-benzene-1,3-diol

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Scheme 1



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To a solution of 2,4-dihydroxy-5-isopropylbenzoic acid methyl ester (1.63 g, 7.75 mmol) in dimethylformamide (DMF) (100 mL) was added potassium carbonate (3.21 g, 23 mmol) then benzyl chloride (1.95 mL, 17 mmol). The suspension was heated to 80°C for 16 hrs under a nitrogen atmosphere. Ethyl acetate (100 mL) and water (100 mL) were added, and then the ethyl acetate layer was washed with water (3x50 mL), and then dried over magnesium sulfate, filtered and evaporated to dryness to produce the desired compound as brown oil (2.9 g, 97%).

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2,4-Bis-benzyloxy-5-isopropylbenzoic acid methyl ester (3.23 g, 8.27 mmol) and LiOH (1.0 g, 24.8 mmol) were heated in a mixture of tetrahydrofuran (THF)/methanol/water (100 mL, 3:1:1) for 16 hrs. Ethyl acetate (100 mL) and water (100 mL) were added, then the ethyl acetate layer was washed with water (3x50 mL), dried over magnesium sulfate, filtered and evaporated to dryness to produce the desired compound as a yellow solid (2.6 g, 83%).

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2,4-Bis-benzyloxy-5-isopropylbenzoic acid (1.25 g, 3.32 mmol) was dissolved in dichloromethane (50 mL) and cooled in an ice bath. Oxalyl chloride (0.32 mL, 3.65 mmol) was added followed by the dropwise addition of DMF (0.1

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mL). The reaction was stirred at room temperature for 1hr then evaporated to dryness under reduced pressure to produce a brown solid. This solid was dissolved in THF (50 mL) and cooled in an ice bath. A solution of 4-Methoxy-N³-methyl-N³-propyl-benzene-1,3-diamine (0.71 g, 3.65 mmol) in THF (20 mL) was added dropwisely followed by the triethylamine (1.6 mL) and the reaction was stirred at room temperature for 16 hrs. Ethyl acetate (50 mL) and water (100 mL) were added. The ethyl acetate layer was washed with water (3x50 mL), dried over magnesium sulfate, filtered and evaporated to dryness to produce the crude product as a brown solid. Purification by silicagel chromatography (elution with 25 % ethyl acetate/hexane) provided the desired compound as a white solid (1.8 g, 93%).

2,4-Bis-benzyloxy-5-isopropyl-N-[4-methoxy-3-(methylpropylamino)phenyl]benzamide (700 mg, 1.27 mmol) and Lawesson's reagent (0.31 g, 0.76 mmol) were dissolved in toluene (20 mL) and heated to 110°C for 3 hrs then evaporated to dryness under reduced pressure to produce a yellow oil. This crude product was dissolved in dioxane (10 mL), anhydrous hydrazine (0.6 mL) was added and the reaction was heated to 80°C for 30 min. After cooling, ethyl acetate (50 mL) and water (50 mL) were added. The ethyl acetate layer was washed with water (3x50 mL), dried over magnesium sulfate, filtered and evaporated to dryness to produce the crude product as a brown solid. This solid was dissolved in ethyl acetate (50 mL), CDI (0.66 g, 4.08 mmol) was added then the reaction was heated to reflux for 3 hrs. Removal of the solvent under reduced pressure followed by purification by silicagel chromatography (elution with 50 % ethyl acetate/hexane) provided the desired compound as a white solid (250 mg, 33% over 3 steps).

5-(2,4-Bis-benzyloxy-5-isopropyl-phenyl)-4-[4-methoxy-3-(methylpropylamino)phenyl]-4H-[1,2,4]triazol-3-ol (240 mg, 0.4 mmol) was dissolved in methanol (10 mL) then 10% palladium on charcoal (200 mg) was added and the reaction was stirred under an atmosphere of hydrogen for 16hrs. Filtration was carried out through a silica gel plug and removal of the solvent under reduced pressure produced the desired compound as a white solid (150 mg, 94%).

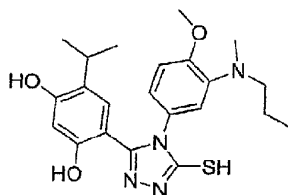
¹H NMR (300 MHz, DMSO-d₆), δ (ppm): 11.8 (s, 1H), 9.55 (s, 1H), 9.39 (s, 1H), 6.88 (d, J = 8.7 Hz, 1H), 6.77-6.79 (m, 2H), 6.5 (s, 1H), 6.24 (s, 1H), 3.73 (s,

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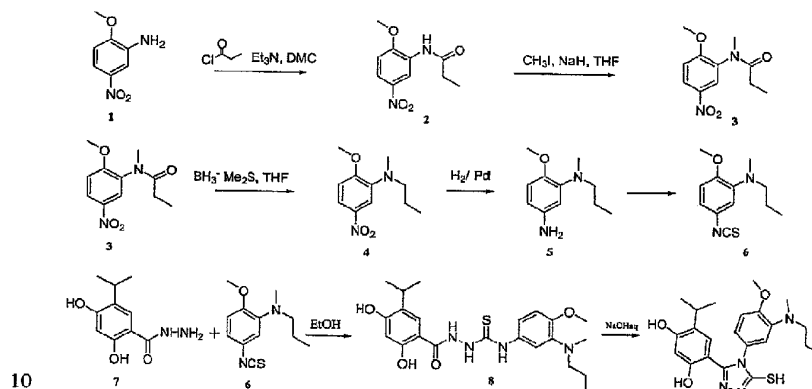
3H), 2.97 (qn, $J = 6.9$ Hz, 1H), 2.79 (t, $J = 7.5$ Hz, 2H), 2.48 (s, 3H), 1.30 (m, 2H), 0.97 (d, $J = 6.9$ Hz, 6H), 0.73 (t, $J = 7.5$ Hz, 3H).

ESMS calcd for $C_{22}H_{28}N_4O_4$: 412.21; Found: 413.2 (M+H)⁺.

Example 2: 4-Isopropyl-6-{5-mercapto-4-[4-methoxy-3-(methyl-propyl-amino)-phenyl]-4H-[1,2,4]triazol-3-yl}-benzene-1,3-diol



Scheme 2



2-methoxy-5-nitroaniline (1) (10.1 g, 60.0 mmol) in 250 mL dichloromethane at 0°- 5°C was treated with triethylamine (10.0 g, 100.0 mmol) and propionyl chloride (6.7g, 6.3 mL, 72.0 mmol) for 1 hour and 0.5 h at room temperature (RT). Normal aqueous workup and removal of solvent gave a light yellow solid which was washed with hexane/EtOAc (9:1) to yield solid N-(2-Methoxy-5-nitro-phenyl)-propionamide (2) (13.2 g, 98%).

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To a stirred solution of 11.2 g (50.0 mmol) of (2) in 150 mL of anhydrous THF at 0°C under the nitrogen, was added 3.0g (75mmol) of NaH (60% in oil). The suspension was stirred for 0.5h at 0°C and 10mL (150mmol) of iodomethane was added at 0°C. After the mixture warmed to room temperature and stirred for 3h, the reaction was quenched by ice brine and extracted with EtOAc (200mL). The organic phase was washed with brine, dried (Na₂SO₄), filtered, evaporated in *vacuo* and the solid was washed with hexane/EtOAc (9:1) to give pure product N-(2-Methoxy-5-nitro-phenyl)-N-methyl-propionamide (3) as a light yellow solid (11.3 g, 95% yield).

N-(2-Methoxy-5-nitro-phenyl)-N-methyl-propionamide (3) (10.0g 42mmol) and borane-methyl sulfide complex (21 mL of 2.0M solution in tetrahydrofurane) in 50 mL THF were heated under reflux for 30 min, cooled and quenched by ice-water (slowly). Extraction with EtOAc and the organic layer washed with brine dried (Na₂SO₄), filtered and evaporated in *vacuo* to give (9.1g, 96%) (2-Methoxy-5-nitro-phenyl)-methyl-propyl-amine (4) as a yellow oil.

A solution of 9.0 g (40.1mmol) of (2-Methoxy-5-nitro-phenyl)-methyl-propyl-amine (4) in 200 mL of MeOH/EtOAc (1:1) containing 5% w/w of Pd-C (10%) was subjected to hydrogenation (1 atm, balloon) overnight. The contents of the flask were passed through a short pad of celite and washed with EtOAc. The filtrate was evaporated under reduced pressure to give 7.7 g (92%) of crude amine 4-Methoxy-N3-methyl-N3-propyl-benzene-1,3-diamine (5) of an oil.

To a stirred solution of 6.8 g (35.0 mmol) of (5) in 150 mL of CH₂Cl₂ at RT was added 6.4g (35mmol) of 1,1'-thiocarbonyldiimidazole. The mixture was stirred at room temperature for 15 minutes and then evaporated under reduced pressure and the residue was passed through a short pad of silica gel, eluting with a gradient of hexane/EtOAc, which gave (5-Isothiocyanato-2-methoxy-phenyl)-methyl-propyl-amine (6) (7.85g, 95%) as a colorless oil.

To a stirred solution of 4.5g (19.0mmol) of the isothiocyanate (6) in 60mL of ethanol was added 4.0 g (19.0mmol) of the hydrazide (7) portion wise. The resultant mixture was then heated at 70 °C for 1h, then cooled. Solvent was removed on rotary evaporator and the residue was treated with hexane/EtOAc (9:1). The white

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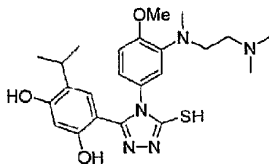
precipitate thus obtained was filtered, washed with ether (2 X 50 mL) and vacuum dried to 7.6 g (90%) of (8) as white solid.

To a solution of 1.36 g (34mmol) of NaOH in 80 mL of water was added 7.5g (16.8mmol) of the intermediate (8) portion-wise. After the dissolution of the solid (1-2 min), the flask was flushed with nitrogen and heated to 110 °C for 3h. The reaction mixture was cooled, an additional 100 mL of water was added and the whole mixture was acidified with conc. HCl to pH 7. The white precipitate thus obtained was filtered, washed with water (3 X 75 mL) and dried. The crude product was then re-dissolved in a mixture of 200 mL of ethyl acetate, dried over anhydrous Na₂SO₄ and passed through a short pad of silica gel with an additional 150 mL of ethyl acetate as eluent. The filtrates were concentrated and crude product was re-precipitated in 3:1 hexane/ethyl acetate to give 6.83 g (95%) of 4-isopropyl-6-{5-mercapto-4-[4-methoxy-3-(methyl-propyl-amino)-phenyl]-4H-[1,2,4]triazol-3-yl}-benzene-1,3-diol as white solid.

¹H NMR (300 MHz, DMSO-d₆), (ppm): 9.58 (s, 1H); 9.39 (s, 1H); 6.92-6.83 (m, 3H); 6.56(d, J=1.8 Hz, 1H); 6.23 (s, 1H); 3.74 (s, 3H); 3.0-2.93(m, 1H); 2.81(t, J=6.9 Hz, 2H); 2.48(s, 3H); 1.31-1.24 (m, 2H); 0.96 (d, J= 6.9 Hz, 6H); 0.72 (t, J=7.2 Hz, 3H);

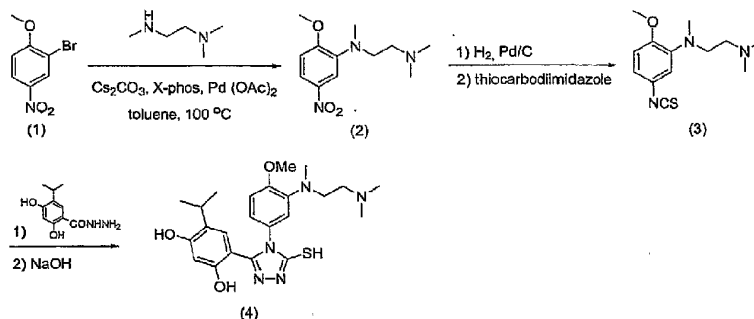
ESMS calcd for C₂₂H₂₈N₄O₃S: 428.19; Found: 429.2 (M+H)⁺.

Example 3: 4-(4-{3-[(2-Dimethylamino-ethyl)-methyl-amino]-4-methoxy-phenyl}-5-mercapto-4H-[1,2,4]triazol-3-yl)-6-isopropyl-benzene-1,3-diol



25 Scheme 3,

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An oven-dried flask was charged with cesium carbonate (2.28 g, 7 mmol, 1.4 eq), Pd(OAc)₂ (79 mg, 0.35 mmol, 0.07 eq), and X-phos (238 mg, 0.5 mmol, 0.1 eq) under nitrogen. 2-bromo-1-methoxy-4-nitrobenzene (1.16 g, 5 mmol, 1 eq), *N'*, *N''*, *N''*-trimethylethane-1,2-diamine (613 mg, 6 mmol, 1.2 eq) and toluene (20 mL, 0.25 M) were added, and the mixture was heated to 100 °C with stirring overnight. The reaction mixture was cooled to room temperature and concentrated. The crude product was then purified by flash chromatography on silica gel to give *N'*-(2-methoxy-5-nitrophenyl)-*N'*, *N''*, *N''*-trimethylethane-1,2-diamine (2) (340 mg, 1.34 mmol, 27%).

A solution of 340 mg of *N'*-(2-methoxy-5-nitrophenyl)-*N'*, *N''*, *N''*-trimethylethane-1,2-diamine (2) in 20 mL of ethanol containing 5% w/w of Pd-C (10%) was subjected to hydrogenation (1 atm, balloon) for 1.5 h. The contents of the flask were passed through a short pad of celite and washed with MeOH. The filtrate was evaporated under reduced pressure and crude amine obtained was carried over to the next reaction without further purification. Thiocarbonylimidazole (260 mg, 1.46 mmol) was added to the crude amine in dichloromethane (10 mL) at room temperature. The reaction mixture was stirred at room temperature for 1 h, and concentrated. The crude product was then purified by flash chromatography on silica gel to give *N'*-(5-isothiocyanto-2-methoxyphenyl)-*N'*, *N''*, *N''*-trimethylethane-1,2-diamine (3) (110 mg, 0.42 mmol, 31%).

To a stirred solution of 110 mg (0.54 mmol) of the isothiocyanate (3) in 5 mL of ethanol was added 105 mg (0.54 mmol) of 2,4-dihydroxy-5-isopropylbenzoic acid hydrazide portion wise. The resultant mixture was then heated at 80 °C for 1 h,

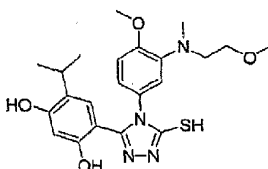
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and then cooled. Solvent was removed on rotary evaporator and the residue was treated with hexane/EtOAc (9:1). The white precipitate thus obtained was filtered, washed with ether (2 X 20 mL) and vacuum dried to crude product as white solid. This solid was added to a solution of 44 mg (1.08 mmol) of NaOH in 5 mL of water portion-wise. After the dissolution of the solid (1-2 min), the flask was flushed with nitrogen and heated to 110 °C for 1.5 h. The reaction mixture was cooled, an additional 20 mL of water was added and the whole mixture was acidified with conc. HCl to pH 7. The white precipitate thus obtained was filtered, washed with water (3 X 20 mL) and dried. The crude product was then re-dissolved in a mixture of 20 mL of ethyl acetate, dried over anhydrous Na₂SO₄ and passed through a short pad of silica gel with an additional 15 mL of ethyl acetate as eluent. The filtrates were concentrated and crude product was re-precipitated in 3:1 hexane/ethyl acetate to give 97 mg of 4-(4-(3-((2-(dimethylamino)ethyl)(methyl)amino)-4-methoxyphenyl)-5-mercapto-4H-1,2,4-triazol-3-yl)-6-isopropylbenzene-1,3-diol (4) as white solid.

¹H-NMR (300 MHz, DMSO-d₆) δ (ppm): 9.80 (s, 1H), 9.62 (br s, 1H), 6.85 (m, 3H), 6.63 (m, 1H), 6.41 (s, 1H), 3.78 (s, 3H), 3.06 (m, 2H), 2.97 (q, J = 6.9 Hz, 1H), 2.55 (s, 3H), 2.47 (m, 2H), 2.24 (s, 6H), 0.99 (s, 3H), 0.97 (s, 3H).

ESMS calcd for C₂₃H₃₁N₅O₃S: 457.21; Found: 458.2 (M+H)⁺.

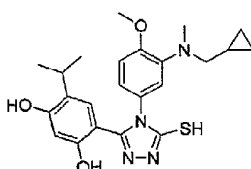
Example 4: 4-Isopropyl-6-(5-mercapto-4-{4-methoxy-3-[(2-methoxyethyl)methylamino]phenyl}-4H-[1,2,4]triazol-3-yl)-benzene-1,3-diol



¹H NMR (300 MHz, DMSO-d₆) δ (ppm): 9.57 (s, 1H), 9.39 (s, 1H), 6.83-6.90 (m, 3H), 6.59 (d, J = 2.1 Hz, 1H), 6.23 (s, 1H), 3.74 (s, 3H), 3.39 (t, J = 6 Hz, 2H), 3.14 (s, 3H), 3.07 (t, J = 6 Hz, 2H), 2.96 (qn, J = 6.9 Hz, 1H), 2.54 (s, 3H), 0.97 (d, J = 6.9 Hz, 6H). ESMS calcd for C₂₇H₂₈N₄O₄S: 444.18; Found: 445.2 (M+H)⁺.

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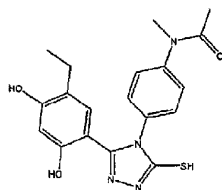
Example 5: 4-{4-[3-(Cyclopropylmethylmethylamino)-4-methoxy-phenyl]-5-mercapto-4H-[1,2,4]triazol-3-yl}-6-isopropylbenzene-1,3-diol



¹H NMR (300 MHz, DMSO-d₆) δ (ppm): 9.56 (s, 1H), 9.39 (s, 1H), 6.85-6.90 (m, 3H), 6.58 (d, *J* = 2.1 Hz, 1H), 6.23 (s, 1H), 3.76 (s, 3H), 2.96 (qn, *J* = 6.9 Hz, 1H), 2.76 (d, *J* = 6.3 Hz, 2H), 2.57 (s, 3H), 0.99 (d, *J* = 6.9 Hz, 6H), 0.58-0.64 (m, 1H), 0.32-0.34 (m, 2H), -0.03-0.01 (m, 2H).

ESMS calcd for C₂₃H₂₈N₄O₃S: 440.19; Found: 441.1 (M+H)⁺.

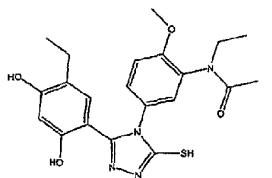
Example 6: N-{4-[3-(5-Ethyl-2,4-dihydroxy-phenyl)-5-mercapto-[1,2,4]triazol-4-yl]-phenyl}-N-methyl-acetamide,



ESMS calcd for C₁₉H₂₀N₄O₃S: 384.13; Found: 385.1 (M+H)⁺.

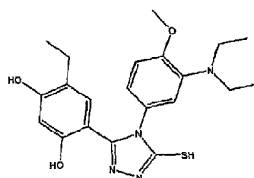
Example 7: N-Ethyl-N-{5-[3-(5-ethyl-2,4-dihydroxy-phenyl)-5-mercapto-[1,2,4]triazol-4-yl]-2-methoxy-phenyl}-acetamide,

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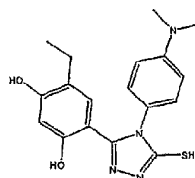
ESMS calcd for $C_{21}H_{24}N_4O_4S$: 428.15; Found: 429.2 (M+H)⁺.

- 5 Example 8: 4-[4-(3-Diethylamino-4-methoxy-phenyl)-5-mercapto-4H-[1,2,4]triazol-3-yl]-6-ethyl-benzene-1,3-diol



- 10 ESMS calcd for $C_{21}H_{26}N_4O_3S$: 414.17; Found: 415.2 (M+H)⁺.

Example 9: 4-[4-(4-Dimethylamino-phenyl)-5-mercapto-4H-[1,2,4]triazol-3-yl]-6-ethyl-benzene-1,3-diol

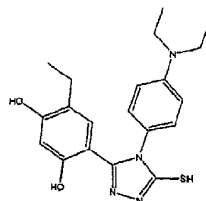


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ESMS calcd for $C_{18}H_{20}N_4O_2S$: 356.13; Found: 357.2 (M+H)⁺.

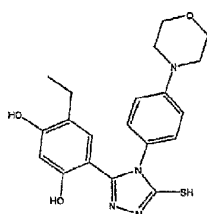
- 20 Example 10: 4-[4-(4-Diethylamino-phenyl)-5-mercapto-4H-[1,2,4]triazol-3-yl]-6-ethyl-benzene-1,3-diol

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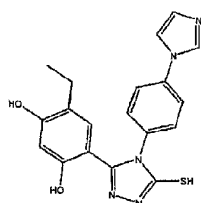
ESMS cld for $C_{20}H_{24}N_4O_2S$: 384.16; Found: 385.2 (M+H)⁺.

- 5 Example 11: 4-Ethyl-6-[5-mercapto-4-(4-morpholin-4-yl-phenyl)-4H-[1,2,4]triazol-3-yl]-benzene-1,3-diol



- 10 ESMS cld for $C_{20}H_{22}N_4O_3S$: 398.14; Found: 399.2 (M+H)⁺.

Example 12: 4-Ethyl-6-[4-(4-imidazol-1-yl-phenyl)-5-mercapto-4H-[1,2,4]triazol-3-yl]-benzene-1,3-diol

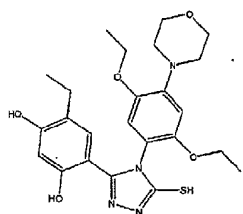


15

ESMS cld for $C_{19}H_{17}N_5O_2S$: 379.11; Found: 380.2 (M+H)⁺.

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Example 13: 4-[4-(2,5-Diethoxy-4-morpholin-4-yl-phenyl)-5-mercapto-4H-[1,2,4]triazol-3-yl]-6-ethyl-benzene-1,3-diol

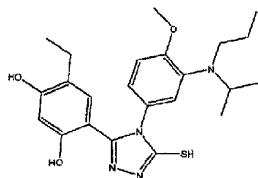


5

ESMS calcd for $C_{24}H_{30}N_4O_5S$: 486.19; Found: 487.3 ($M+H$)⁺.

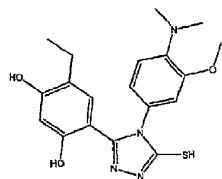
Example 14: 4-Ethyl-6-{4-[3-(isopropyl-propyl-amino)-4-methoxy-phenyl]-5-mercapto-4H-[1,2,4]triazol-3-yl}-benzene-1,3-diol

10



ESMS calcd for $C_{23}H_{30}N_4O_3S$: 442.20; Found: 443.3 ($M+H$)⁺.

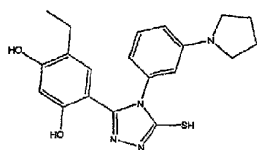
15 Example 15: 4-[4-(4-Dimethylamino-3-methoxy-phenyl)-5-mercapto-4H-[1,2,4]triazol-3-yl]-6-ethyl-benzene-1,3-diol



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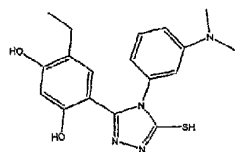
ESMS cld for $C_{19}H_{22}N_4O_3S$: 386.14; Found: 387.2 (M+H)⁺.

Example 16: 4-Ethyl-6-[5-mercapto-4-(3-pyrrolidin-1-yl-phenyl)-4H-[1,2,4]triazol-3-yl]-benzene-1,3-diol

ESMS cld for $C_{20}H_{22}N_4O_2S$: 382.15; Found: 383.2 (M+H)⁺.

10

Example 17: 4-[4-(3-Dimethylamino-phenyl)-5-mercapto-4H-[1,2,4]triazol-3-yl]-6-ethyl-benzene-1,3-diol

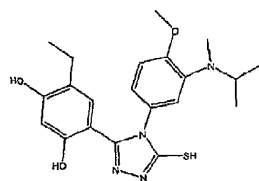


15

ESMS cld for $C_{18}H_{20}N_4O_2S$: 356.13; Found: 357.2 (M+H)⁺.

Example 18: 4-Ethyl-6-{4-[3-(isopropyl-methyl-amino)-4-methoxy-phenyl]-5-mercapto-4H-[1,2,4]triazol-3-yl}-benzene-1,3-diol

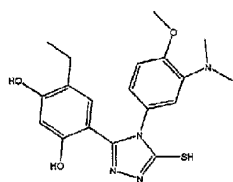
20



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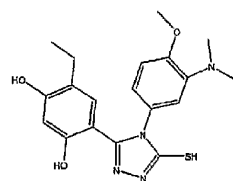
ESMS cld for $C_{21}H_{26}N_4O_3S$: 414.17; Found: 415.2 (M+H)⁺.

Example 19: 4-[4-(3-Dimethylamino-4-methoxy-phenyl)-5-mercapto-4H-
5 [1,2,4]triazol-3-yl]-6-ethyl-benzene-1,3-diol



10 ESMS cld for $C_{19}H_{22}N_4O_3S$: 386.14; Found: 387.2 (M+H)⁺.

Example 20: 4-Ethyl-6-{4-[3-(ethyl-methyl-amino)-4-methoxy-phenyl]-5-mercapto-
4H-[1,2,4]triazol-3-yl}-benzene-1,3-diol

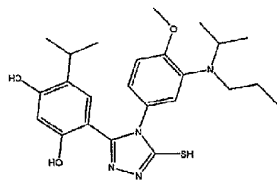


15

ESMS cld for $C_{26}H_{24}N_4O_3S$: 400.16; Found: 401.2 (M+H)⁺.

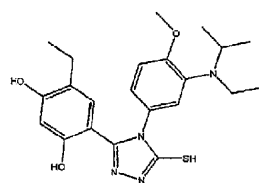
Example 21: 4-Isopropyl-6-{4-[3-(isopropyl-propyl-amino)-4-methoxy-phenyl]-5-
20 mercapto-4H-[1,2,4]triazol-3-yl}-benzene-1,3-diol

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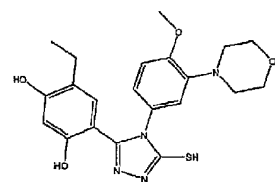
ESMS calcd for $C_{24}H_{32}N_4O_3S$: 456.22; Found: 457.3 ($M+H$)⁺.

- 5 Example 22: 4-Ethyl-6-{4-[3-(ethyl-isopropyl-amino)-4-methoxy-phenyl]-5-mercapto-4H-[1,2,4]triazol-3-yl}-benzene-1,3-diol



- 10 ESMS calcd for $C_{22}H_{28}N_4O_3S$: 428.19; Found: 429.3 ($M+H$)⁺.

Example 23: 4-Ethyl-6-[5-mercapto-4-(4-methoxy-3-morpholin-4-yl-phenyl)-4H-[1,2,4]triazol-3-yl]-benzene-1,3-diol

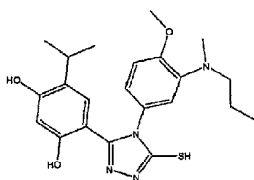


15

ESMS calcd for $C_{21}H_{24}N_4O_4S$: 428.15; Found: 429.2 ($M+H$)⁺.

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Example 24: 4-Isopropyl-6-{5-mercapto-4-[4-methoxy-3-(methyl-propyl-amino)-phenyl]-4H-[1,2,4]triazol-3-yl}-benzene-1,3-diol

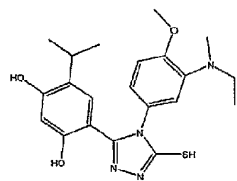


5

^1H NMR (300 MHz, DMSO- d_6) δ (ppm): 9.58 (s, 1H); 9.39 (s, 1H); 6.92- 6.83 (m, 3H); 6.56(d, $J=1.8$ Hz, 1H); 6.23 (s, 1H); 3.74 (s, 3H); 3.0-2.93(m, 1H); 2.81(t, $J=6.9$ Hz, 2H); 2.48(s, 3H); 1.31-1.24 (m, 2H); 0.96 (d, $J=6.9$ Hz, 6H); 0.72 (t, $J=7.2$ Hz, 3H);

10 ESMS clcd for $\text{C}_{22}\text{H}_{28}\text{N}_4\text{O}_3\text{S}$: 428.19; Found: 429.2 ($\text{M}+\text{H}$) $^+$.

Example 25: 4-{4-[3-(Ethyl-methyl-amino)-4-methoxy-phenyl]-5-mercapto-4H-[1,2,4]triazol-3-yl}-6-isopropyl-benzene-1,3-diol



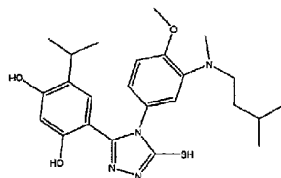
15

^1H NMR (300 MHz, DMSO- d_6) δ (ppm): 9.58 (s, 1H); 9.40 (s, 1H); 6.92-6.85 (m, 3H); 6.58 (d, $J=1.8$ Hz, 1H); 6.24 (s, 1H); 3.76 (s, 3H); 3.02-2.90 (m, 3H); 2.49(s, 3H) 0.99 (d, $J=6.9$ Hz, 6H); 0.86 (t, $J=7.2$ Hz, 3H).

20 ESMS clcd for $\text{C}_{21}\text{H}_{26}\text{N}_4\text{O}_3\text{S}$: 414.17; Found: 415.1 ($\text{M}+\text{H}$) $^+$.

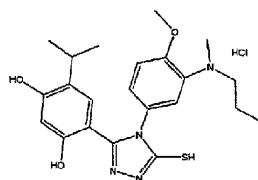
Example 26: 4-Isopropyl-6-(5-mercapto-4-{4-methoxy-3-[methyl-(3-methyl-butyl)-amino]-phenyl}-4H-[1,2,4]triazol-3-yl)-benzene-1,3-diol

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ESMS cld for $C_{24}H_{32}N_4O_3S$: 456.22; Found: 457.2 (M+H)⁺.

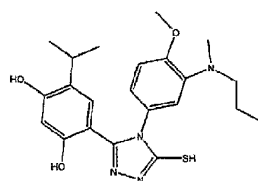
- 5 Example 27: 4-Isopropyl-6-{5-mercapto-4-[4-methoxy-3-(methyl-propyl-amino)-phenyl]-4H-[1,2,4]triazol-3-yl}-benzene-1,3-diol; compound with hydrogen chloride



10

ESMS cld for $C_{22}H_{29}ClN_4O_3S$: 464.16; Found: 429.3 (M+H)⁺.

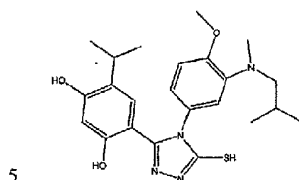
- 15 Example 28: 4-{4-[3-(Butyl-methyl-amino)-4-methoxy-phenyl]-5-mercapto-4H-[1,2,4]triazol-3-yl}-6-isopropyl-benzene-1,3-diol



ESMS cld for $C_{23}H_{30}N_4O_3S$: 442.20; Found: 443.3 (M+H)⁺.

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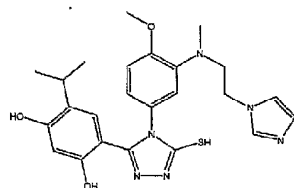
Example 29: 4-{4-[3-(Isobutyl-methyl-amino)-4-methoxy-phenyl]-5-mercapto-4H-[1,2,4]triazol-3-yl}-6-isopropyl-benzene-1,3-diol



ESMS cld for $C_{23}H_{30}N_4O_3S$: 442.20; Found: 443.1 ($M+H$)⁺.

Example 30: 4-(4-{3-[(2-Imidazol-1-yl-ethyl)-methyl-amino]-4-methoxy-phenyl}-5-mercapto-4H-[1,2,4]triazol-3-yl)-6-isopropyl-benzene-1,3-diol

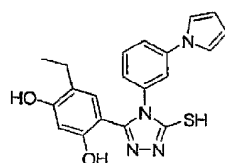
10



ESMS cld for $C_{24}H_{28}N_6O_3S$: 480.19; Found: 481.1 ($M+H$)⁺.

15

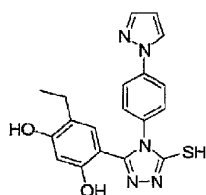
Example 31: 4-(4-{3-(1H-pyrrol-1-yl)phenyl}-5-mercapto-4H-1,2,4-triazol-3-yl)-6-ethylbenzene-1,3-diol



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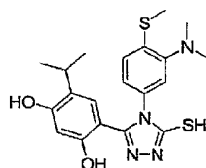
ESMS calcd for $C_{20}H_{18}N_4O_2S$: 378.12; Found: 379.1 $(M+H)^+$.

Example 32: 4-(4-(4-(1H-pyrazol-1-yl)phenyl)-5-mercapto-4H-1,2,4-triazol-3-yl)-6-ethylbenzene-1,3-diol



ESMS calcd for $C_{19}H_{17}N_5O_2S$: 379.11; Found: 380.1 $(M+H)^+$.

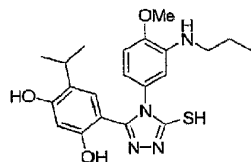
Example 33: 4-(4-(3-(dimethylamino)-4-(methylthio)phenyl)-5-mercapto-4H-1,2,4-triazol-3-yl)-6-isopropylbenzene-1,3-diol



ESMS calcd for $C_{20}H_{24}N_4O_2S_2$: 416.13; Found: 417.1 $(M+H)^+$.

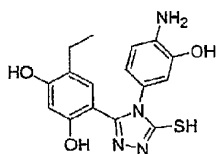
Example 34: 4-isopropyl-6-(5-mercapto-4-(4-methoxy-3-(propylamino)phenyl)-4H-1,2,4-triazol-3-yl)benzene-1,3-diol

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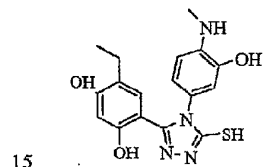
ESMS cld for $C_{21}H_{26}N_4O_3S$: 414.17; Found: 415.1 (M+H)⁺.

- 5 Example 35: 4-[4-(4-Amino-3-hydroxy-phenyl)-5-mercapto-4H-[1,2,4]triazol-3-yl]-6-ethyl-benzene-1,3-diol



- 10 ESMS cld for $C_{16}H_{16}N_4O_3S$: 344.09; Found: 345.1 (M+H)⁺.

Example 36: 4-ethyl-6-(4-(3-hydroxy-4-(methylamino)phenyl)-5-mercapto-4H-1,2,4-triazol-3-yl)benzene-1,3-diol

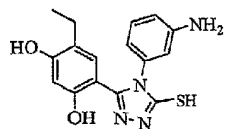


15

ESMS cld for $C_{17}H_{18}N_4O_3S$: 358.11; Found: 359.1 (M+H)⁺

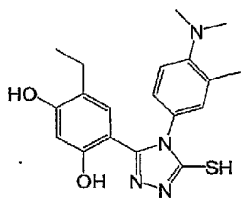
- 20 Example 37: 4-(4-(3-aminophenyl)-5-mercapto-4H-1,2,4-triazol-3-yl)-6-ethylbenzene-1,3-diol

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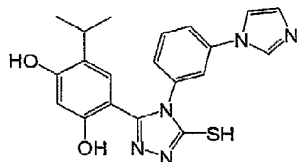
ESMS clcd for $C_{16}H_{16}N_4O_2S$: 328.10; Found: 329.1 (M+H)⁺.

- 5 Example 38: 4-[4-(4-Dimethylamino-3-methyl-phenyl)-5-mercapto-4H-[1,2,4]triazol-3-yl]-6-ethyl-benzene-1,3-diol



- 10 ESMS clcd for $C_{19}H_{23}N_4O_2S$: 371.1; Found: 371.1 (M + H)⁺.

Example 39: 4-[4-(3-Imidazol-1-yl-phenyl)-5-mercapto-4H-[1,2,4]triazol-3-yl]-6-isopropyl-benzene-1,3-diol



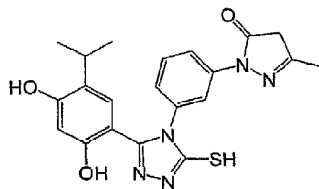
15

ESMS clcd. for $C_{20}H_{20}N_3O_2S$: 394.1; Found: 394.1 (M + H)⁺.

Example 40: 4-[4-(3-Imidazol-1-yl-phenyl)-5-mercapto-4H-[1,2,4]triazol-3-yl]-6-isopropyl-benzene-1,3-diol

20

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2-{3-[3-(2,4-Dihydroxy-5-isopropyl-phenyl)-5-mercapto-[1,2,4]triazol-4-yl]-phenyl}-5-methyl-2,4-dihydro-pyrazol-3-one

¹H NMR (300 MHz, DMSO-d₆) δ (ppm): 9.63 (br s, 1H); 7.70-7.80 (m, 2H); 7.37-

5 7.43 (m, 1H); 6.99-7.02 (m, 1H); 6.91 (s, 1H); 6.25 (s, 1H); 5.35 (s, 1H); 3.70 (s, 2H); 2.96 (hept, *J* = 6.9 Hz, 1H); 2.09 (s, 3H); 0.99 (d, *J* = 6.9 Hz, 6H);

ESMS calcd. for C₂₁H₂₂N₅O₃S: 424.1; Found: 424.1 (M + H)⁺.

Example 41: Inhibition of Hsp90

10 A) Malachite Green Assay:

Hsp90 protein is obtained from Stressgen (Cat#SPP-770). Assay buffer: 100 mM Tris-HCl, Ph7.4, 20 mM KCl, 6 mM MgCl₂. Malachite green (0.0812% w/v) (M9636) and polyvinyl alcohol USP (2.32% w/v) (P1097) are obtained from Sigma. A Malachite Green Assay (see Methods Mol Med, 2003, 85:149 for method details) is used for examination of ATPase activity of Hsp90 protein. Briefly, Hsp90 protein in assay buffer (100 mM Tris-HCl, Ph7.4, 20 mM KCl, 6 mM MgCl₂) is mixed with ATP alone (negative control) or in the presence of Geldanamycin (a positive control) or a compound of the invention in a 96-well plate. Malachite green reagent is added to the reaction. The mixtures are incubated at 37°C for 4 hours and sodium citrate buffer (34% w/v sodium citrate) is added to the reaction. The plate is read by an ELISA reader with an absorbance at 620 nm.

Example 42: Degradation of Hsp90 Client Proteins via Inhibition of Hsp90 Activity

25

A. Cells and Cell Culture

Human high-Her2 breast carcinoma BT474 (HTB-20), SK-BR-3 (HTB-30) and MCF-7 breast carcinoma (HTB-22) from American Type Culture Collection,

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VA, USA were grown in Dulbecco's modified Eagle's medium with 4 mM L-glutamine and antibiotics (100IU/ml penicillin and 100 ug/ml streptomycin; GibcoBRL). To obtain exponential cell growth, cells were trypsinized, counted and seeded at a cell density of 0.5×10^6 cells /ml regularly, every 3 days. All experiments were performed on day 1 after cell passage.

B. Degradation of Her2 in Cells after Treatment with a Compound of the Invention

1. Method 1

BT-474 cells are treated with 0.5 μ M, 2 μ M, or 5 μ M of 17AAG (a positive control) or 0.5 μ M, 2 μ M, or 5 μ M of a compound of the invention overnight in DMEM medium. After treatment, each cytoplasmic sample is prepared from 1×10^6 cells by incubation of cell lysis buffer (#9803, cell Signaling Technology) on ice for 10 minutes. The resulting supernatant used as the cytosol fractions is dissolved with sample buffer for SDS-PAGE and run on a SDS-PAGE gel, blotted onto a nitrocellulose membrane by using semi-dry transfer. Non-specific binding to nitrocellulose is blocked with 5% skim milk in TBS with 0.5% Tween at room temperature for 1 hour, then probed with anti-Her2/ErB2 mAb (rabbit IgG, #2242, Cell Signaling) and anti-Tubulin (T9026, Sigma) as housekeeping control protein. HRP-conjugated goat anti-rabbit IgG (H+L) and HRP-conjugated horse anti-mouse IgG (H+L) are used as secondary Ab (#7074, #7076, Cell Signaling) and LumiGLO reagent, 20x Peroxide (#7003, Cell Signaling) is used for visualization.

Her2, an Hsp90 client protein, is expected to be degraded when cells are treated with compounds of the invention. 0.5 μ M of 17AAG, a known Hsp90 inhibitor which is used as a positive control, causes partial degradation of Her2.

2. Method 2

MV-4-11 cells (20,000 cells/well) were cultured in 96-well plates and maintained at 37 °C for several hours. The cells were treated with a compound of the invention or 17AAG (a positive control) at various concentrations and incubated at 37 °C for 72 hours. Cell survival was measured with Cell Counting Kit-8 (Dojindo Laboratories, Cat. # CK04).

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The IC₅₀ range for Her2 degradation by compounds of the invention is listed below in Table 2.

Table 2: IC₅₀ range of compounds of the invention

| IC ₅₀ Range | Compound Number |
|------------------------|---------------------|
| < 1 μ M | 1, 2, 3, 4, 5, 6, 8 |
| 1 μ M to 3 μ M | 13 |

5

C. Fluorescent Staining of Her2 on the Surface of Cells Treated with a Compound of the Invention

After treatment with a compound of the invention, cells are washed twice with 1xPBS/1%FBS, and then stained with anti-Her2- FITC (#340553, BD) for 30 min at 4°C. Cells are then washed three times in FACS buffer before the fixation in 0.5 ml 1% paraformaldehyde. Data is acquired on a FACSCalibur system. Isotype-matched controls are used to establish the non-specific staining of samples and to set the fluorescent markers. A total 10,000 events are recorded from each sample. Data are analysed by using CellQuest software (BD Biosciences).

15

D. Degradation of c-Kit in Cells after Treatment with a Compound of the Invention

Leukemia cell line, Kasumi-1, was used for testing c-kit degradation induced by Hsp90 inhibitors of the invention. The cells (3X10⁵ per well) were treated with 17AAG (0.5 μ M) or Compound 11 (0.05 μ M or 0.5 μ M) for about 18 h. The cells were collected and centrifuged (SORVALL RT 6000D) at 1200 rpm for 5 min. The supernatants were discarded, and the cells were washed one time with 1X PBS. After centrifugation the cells were stained with FITC conjugated c-kit antibody (MBL International, Cat# K0105-4) in 100 mL 1X PBS at 4°C for 1 h. The samples were read and analyzed with FACSCalibur flow cytometer (Becton Dickinson).

25

c-Kit, a tyrosine kinase receptor and one of the Hsp90 client proteins, was selected and used in a FACS-based degradation assay. The results of the assay showed that Compound 11 induced c-kit degradation at 0.5 and 0.05 μ M in a dose-dependent manner. Surprisingly, 17-AAG, which is a potent Hsp90 inhibitor and is

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in phase 2 clinical trials, could not induce c-kit degradation at 0.5 μ M in Kasumi-1 cells (see fig. 1). Since the compounds of the invention cause c-kit degradation more efficiently than other Hsp90 inhibitors, the compounds of the invention are expected to be more effective in the treatment of c-kit associated tumors, such as leukemias, mast cell tumors, small cell lung cancer, testicular cancer, some cancers of the gastrointestinal tract (including GIST), and some central nervous system.

The results of the FACS analysis were confirmed with Western blot analysis (see Fig. 2). In Kasumi-1 cells (myelogenous leukemia), both Compound 11 (100 nM and 400 nM) and Compound 12 (100 nM and 400 nM) induced the degradation of c-Kit. In contrast, 17-AAG had no effect of c-Kit protein levels at either 100 nM or 400 nM.

E. Degradation of c-Met in Cells after Treatment with a Compound of the Invention

We examined the ability of the Hsp90 inhibitors of the invention to induce the degradation of c-Met, an Hsp90 client protein that is expressed at high levels in several types of non-small cell lung cancer. NCI-H1993 (ATCC, cat# CRL-5909) were seeded in 6-well plates at 5×10^5 cells/well. The cells were treated with 17AAG (100 nM or 400 nM), Compound 11 (100 nM or 400 nM) or Compound 12 (100 nM or 400 nM), and cell lysis was prepared 24 h after treatment. Equal amount of proteins were used for Western blot analysis. The compounds of the invention potentially induced degradation of c-Met in this cell line due to inhibition of Hsp90 (see Fig. 3).

Example 43: Apoptosis analysis

After treatment with the compounds of the invention, cells are washed once with 1xPBS/1%FBS, and then stained in binding buffer with FITC-conjugated Annexin V and Propidium iodide (PI) (all obtained from BD Biosciences) for 30 min at 4°C. Flow cytometric analysis is performed with FACSCalibur (BD Biosciences) and a total 10,000 events are recorded from each sample. Data are

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analyzed by using CellQuest software (BD Biosciences). The relative fluorescence is calculated after subtraction of the fluorescence of control.

Example 44: Necrosis in a *nude* Mouse Tumor Model

The mouse mammary carcinoma cell line, EMT6 (ATCC #CRL-2755), is
 5 obtained from the American Type Culture Collection (ATCC; Manassas, Virginia, USA). The cell line is cultured in growth media prepared from 50% Dulbecco's Modified Eagle Medium (high glucose), 50% RPMI Media 1640, 10% fetal bovine serum (FBS), 1% 100X L-glutamine, 1% 100X Penicillin-Streptomycin, 1% 100X sodium pyruvate and 1% 100X MEM non-essential amino acids. FBS is obtained
 10 from ATCC and all other reagents are obtained from Invitrogen Corp. (Carlsbad, California, USA). Approximately $4-5 \times 10^6$ cells that have been cryopreserved in liquid nitrogen are rapidly thawed at 37 °C and transferred to a 175 cm² tissue culture flask containing 50 ml of growth media and then incubated at 37°C in a 5% CO₂ incubator. The growth media is replaced every 2-3 days until the flask became
 15 90% confluent, typically in 5-7 days. To passage and expand the cell line, a 90% confluent flask is washed with 10 ml of room temperature phosphate buffered saline (PBS) and the cells are disassociated by adding 5 ml 1X Trypsin-EDTA (Invitrogen) and incubating at 37 °C until the cells detach from the surface of the flask. To inactivate the trypsin, 5 ml of growth media is added and then the
 20 contents of the flask are centrifuged to pellet the cells. The supernatant is aspirated and the cell pellet is resuspended in 10 ml of growth media and the cell number determined using a hemocytometer. Approximately $1-3 \times 10^6$ cells per flask are seeded into 175 cm² flasks containing 50 ml of growth media and incubated at 37 °C in a 5% CO₂ incubator. When the flasks reach 90% confluence, the above
 25 passaging process is repeated until sufficient cells have been obtained for implantation into mice.

Seven to eight week old, female Crl:CD-1-*nu*BR (*nude*) mice are obtained from Charles River Laboratories (Wilmington, Massachusetts, USA). Animals are
 housed 4-5/cage in micro-isolators, with a 12hr/12hr light/dark cycle, acclimated
 30 for at least 1 week prior to use and fed normal laboratory chow *ad libitum*. Studies are conducted on animals between 8 and 10 weeks of age at implantation. To implant EMT6 tumor cells into *nude* mice, the cells are trypsinized as above,

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washed in PBS and resuspended at a concentration of 10×10^6 cells/ml in PBS. Using a 27 gauge needle and 1 cc syringe, 0.1 ml of the cell suspension is injected subcutaneously into the flank of each *nude* mouse.

5 Tumors are then permitted to develop *in vivo* until the majority reached 75-125 mm³ in tumor volume, which typically requires 1 week following implantation. Animals with oblong, very small or large tumors are discarded, and only animals carrying tumors that display consistent growth rates are selected for studies. Tumor volumes (V) are calculated by caliper measurement of the width (W), length (L) and thickness (T) of tumors using the following formula: $V = 0.5236 \times (L \times W \times T)$. Animals are randomized into treatment groups so that each group had median
10 tumor volumes of ~100 mm³ at the start of dosing.

To formulate a compound of the invention in DRD, a stock solution of the test article is prepared by dissolving an appropriate amount of the compound in dimethyl sulfoxide (DMSO) by sonication in an ultrasonic water bath. A solution
15 of 20% Cremophore RH40 (polyoxyl 40 hydrogenated castor oil; BASF Corp., Aktiengesellschaft, Ludwigshafen, Germany) in 5% dextrose in water (Abbott Laboratories, North Chicago, Illinois, USA) is also prepared by first heating 100% Cremophore RH40 at 50-60°C until liquefied and clear, diluting 1:5 with 100% D5W, reheating again until clear and then mixing well. This solution is stored at
20 room temperature for up to 3 months prior to use. To prepare a DRD formulation for dosing, the DMSO stock solution is diluted 1:10 with 20% Cremophore RH40. The final DRD formulation for dosing contains 10% DMSO, 18% Cremophore RH40, 3.6% dextrose, 68.4% water and the appropriate amount of test article.

Tumor-bearing animals are given a single intravenous (i.v.) bolus injections
25 of either DRD vehicle or a compound of the invention formulated in DRD, both at 10 mL per kg body weight. Then, 4-24 hr after drug treatment, tumors are excised, cut in half and fixed overnight in 10% neutral-buffered formalin. Each tumor is embedded in paraffin with the cut surfaces placed downwards in the block, and rough cut until a complete section is obtained. From each tumor, 5 µM serial
30 sections are prepared and stained with hematoxylin and eosin. Slides are evaluated manually using light microscopy with a 10 x 10 square gridded reticle. The

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percentage of necrosis in a tumor is quantified at 200X magnification by scoring the total number of grid squares containing necrosis and the total number of grid squares containing viable tumor cells.

- 5 It is expected that compounds of the invention will result in an increase in necrotic tissue in the center of EMT6 tumors relative to the baseline necrosis observed in vehicle treated tumors. As would be expected for a vascular targeting mechanism of action, rapid onset of necrosis is consistent with there being a loss of blood flow to tumors resulting in hypoxia and tumor cell death.

Example 45: Vascular Disrupting Activities in a *nude* Mouse Tumor Model

- 10 The mouse mammary carcinoma cell line, EMT6 (ATCC #CRL-2755), is obtained from the American Type Culture Collection (ATCC; Manassas, Virginia, USA). The cell line is cultured in growth media prepared from 50% Dulbecco's Modified Eagle Medium (high glucose), 50% RPMI Media 1640, 10% fetal bovine serum (FBS), 1% 100X L-glutamine, 1% 100X Penicillin-Streptomycin, 1% 100X
15 sodium pyruvate and 1% 100X MEM non-essential amino acids. FBS is obtained from ATCC and all other reagents are obtained from Invitrogen Corp. (Carlsbad, California, USA). Approximately $4-5 \times 10^6$ cells that have been cryopreserved in liquid nitrogen are rapidly thawed at 37°C and transferred to a 175 cm² tissue culture flask containing 50 mL of growth media and then incubated at 37°C in a 5%
20 CO₂ incubator. The growth media is replaced every 2-3 days until the flask became 90% confluent, typically in 5-7 days. To passage and expand the cell line, a 90% confluent flask is washed with 10 mL of room temperature phosphate buffered saline (PBS) and the cells are disassociated by adding 5 mL 1X Trypsin-EDTA (Invitrogen) and incubating at 37°C until the cells detach from the surface of the
25 flask. To inactivate the trypsin, 5 mL of growth media is added and then the contents of the flask are centrifuged to pellet the cells. The supernatant is aspirated and the cell pellet is resuspended in 10 mL of growth media and the cell number determined using a hemocytometer. Approximately $1-3 \times 10^6$ cells per flask are seeded into 175 cm² flasks containing 50 mL of growth media and incubated at
30 37°C in a 5% CO₂ incubator. When the flasks reach 90% confluence, the above

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passaging process is repeated until sufficient cells have been obtained for implantation into mice.

Seven to eight week old, female Crl:CD-1-*nu*BR (*nude*) mice are obtained from Charles River Laboratories (Wilmington, Massachusetts, USA). Animals are housed 4-5/cage in micro-isolators, with a 12hr/12hr light/dark cycle, acclimated for at least 1 week prior to use and fed normal laboratory chow *ad libitum*. Studies are conducted on animals between 8 and 10 weeks of age at implantation. To implant EMT6 tumor cells into *nude* mice, the cells are trypsinized as above, washed in PBS and resuspended at a concentration of 10×10^6 cells/mL in PBS. Using a 27 gauge needle and 1 cc syringe, 0.1 mL of the cell suspension is injected subcutaneously into the flank of each *nude* mouse.

For the Evans Blue dye assay, tumors are permitted to develop *in vivo* until the majority reach 40-90 mm³ in tumor volume (to minimize the extent of tumor necrosis), which typically require 4-6 days following implantation. Animals with visibly necrotic, oblong, very small or very large tumors are discarded and only animals carrying tumors that display consistent growth rates are selected for use. Tumor volumes (V) are calculated by caliper measurement of the width (W), length (L) and thickness (T) of tumors using the following formula: $V = 0.5236 \times (L \times W \times T)$. Animals are randomized into treatment groups so that at the start of dosing each group have median tumor volumes of ~125 mm³ or ~55 mm³ for the Evans Blue dye assay.

To formulate compounds of the invention for dosing, the appropriate amount of compound is dissolved in 5% dextrose in water (D5W; Abbott Laboratories, North Chicago, Illinois, USA). Vehicle-treated animals are dosed with D5W.

To conduct the Evans Blue dye assay, tumor-bearing animals are dosed with vehicle or test article at 0 hr, and then i.v. injected with 100 µL of a 1% (w/v) Evan's Blue dye (Sigma #E-2129; St. Louis, Missouri, USA) solution in 0.9% NaCl at +1 hr. Tumors are excised at +4 hr, weighed and the tissue disassociated by incubation in 50 µL 1 N KOH at 60 °C for 16 hr. To extract the dye, 125 µL of a 0.6 N phosphoric acid and 325 µL acetone are added, and the samples vigorously

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vortexed and then microcentrifuged at 3000 RPM for 15 min to pellet cell debris. The optical absorbance of 200 μ L of supernatant is then measured at 620 nm in a Triad spectrophotometer (Dynex Technologies, Chantilly, Virginia, USA). Background OD₆₂₀ values from similarly sized groups of vehicle or test article-treated animals that have not been injected with dye are subtracted as background. OD₆₂₀ values are then normalized for tumor weight and dye uptake is calculated relative to vehicle-treated tumors.

To examine the vascular disrupting activity of a compound of the invention, the Evans Blue dye assay is employed as a measurement of tumor blood volume (Graff *et al.*, Eur J Cancer 36:1433-1440, 2000). Evans Blue dye makes a complex with serum albumin by electrostatic interaction between the sulphonic acid group of the dye and the terminal cationic nitrogens of the lysine residues in albumin. The dye leaves the circulation very slowly, principally by diffusion into extravascular tissues while still bound to albumin. Albumin-dye complex taken up by tumors is located in the extracellular space of non-necrotic tissue, and intracellular uptake and uptake in necrotic regions is negligible. The amount of dye present in a tumor is a measurement of the tumor blood volume and microvessel permeability. Compounds of the invention are expected to result in substantially decreased tumor dye uptake relative to vehicle-treated animals. Such a decrease in dye penetration into the tumor is consistent with there being a loss of blood flow to tumors due to blockage of tumor vasculature, consistent with a vascular disrupting mechanism of action.

Example 46: Inhibition of HUVEC cell migration

To examine if the compounds of the invention affect endothelial cell function, an *in vitro* human umbilical vein endothelial cell (HUVEC) migration assay is performed in the presence of a compound of the invention. HUVEC cells (passage number 4) are cultured on 12-well plates and time-lapse imaging is performed with the live cell imaging system on an inverted microscope supplied with 6-7% CO₂. The temperature is kept at 37°C. Images are taken every 30 minutes using the 2X objective for up to 106 hr or every 60 seconds using the 20X objective

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for 30 min. Confluent HUVEC cultures are scraped similarly to make a blank area, followed by culturing in HUVEC medium for 15 hr without treatment. The migration areas, which are imaged as time-lapse sequences for each well, are used as a basis to standardize/correct migration rates. Then, migration of cells under different treatments is imaged at the same time to generate time-lapse image sequences for each well. Time-lapse movies are further analyzed by measuring areas that are covered by migrating cells. During experiments, HUVEC cells are activated by the presence of VEGF and basic FGF. Compounds of the invention (e.g. 100 nM and 1 μ M) are expected to completely block migration of HUVEC cells to the blank area, indicating that compounds of the invention possesses potent inhibitory effect on the migration of activated HUVEC cell *in vitro* induced by VEGF and basic FGF.

It is also possible to track HUVEC behavior during above treatments. It is expected that HUVEC cells will begin to shrink after 24 hr treatment with compounds of the invention.

Example 47: Enhanced VE-cadherin junctions of HUVEC cells

An immunofluorescence study is performed by using anti-VE-cadherin antibodies to examine VE-cadherin junctions between HUVEC cells. HUVEC cells are treated with DMSO or a compound of the invention (e.g. 10, 100 and 1000nM) for 24 hrs and fixed for immunostaining. DMSO concentration is 1:100 for all treatments. To boost the immunofluorescence signal, cells are stained with a mixture of 2 polyclonal anti-human VE-cadherin Abs followed by staining with a mixture of fluorescent secondary antibodies. It is expected that with compounds of the invention, VE-cadherin staining will be extremely strong in cell-cell junction regions, but not the non-contacted regions compared to that in DMSO treated cultures. Compounds of the invention are expected to enhance the assembly of cell-cell junctions of activated human endothelial cells, likely through induction of the accumulation of VE-cadherin molecules at the junctions. This effect could result in limited motility of the cells and reducing permeability of the endothelium, thus contributing to the cell migration inhibition and the potential anti-angiogenesis effect of compounds of the invention.

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All publications, patent applications, patents, and other documents cited herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting.

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

Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" and "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

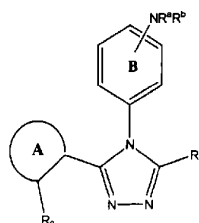
The reference in this specification to any prior publication (or information derived from it), or to any matter which is known, is not, and should not be taken as an acknowledgment or admission or any form of suggestion that that prior publication (or information derived from it) or known matter forms part of the common general knowledge in the field of endeavour to which this specification relates.

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THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A compound represented by the following structural formula:



or a tautomer, pharmaceutically acceptable salt or clathrate thereof,

wherein:

ring A is an aryl or a heteroaryl, wherein the aryl or the heteroaryl are optionally further substituted with one or more substituents in addition to R_3 ;

R_1 is -OH, -SH, -NR₇H, -OR₂₆, -SR₂₆, -NHR₂₆, -O(CH₂)_mOH, -O(CH₂)_mSH, -O(CH₂)_mNR₇H, -S(CH₂)_mOH, -S(CH₂)_mSH, -S(CH₂)_mNR₇H, -OC(O)NR₁₀R₁₁, -SC(O)NR₁₀R₁₁, -NR₇C(O)NR₁₀R₁₁, -OC(O)R₇, -SC(O)R₇, -NR₇C(O)R₇, -OC(O)OR₇, -SC(O)OR₇, -NR₇C(O)OR₇, -OCH₂C(O)R₇, -SCH₂C(O)R₇, -NR₇CH₂C(O)R₇, -OCH₂C(O)OR₇, -SCH₂C(O)OR₇, -NR₇CH₂C(O)OR₇, -OCH₂C(O)NR₁₀R₁₁, -SCH₂C(O)NR₁₀R₁₁, -NR₇CH₂C(O)NR₁₀R₁₁, -OS(O)_pR₇, -SS(O)_pR₇, -S(O)_pOR₇, -NR₇S(O)_pR₇, -OS(O)_pNR₁₀R₁₁, -SS(O)_pNR₁₀R₁₁, -NR₇S(O)_pNR₁₀R₁₁, -OS(O)_pOR₇, -SS(O)_pOR₇, -NR₇S(O)_pOR₇, -OC(S)R₇, -SC(S)R₇, -NR₇C(S)R₇, -OC(S)OR₇, -SC(S)OR₇, -NR₇C(S)OR₇, -OC(S)NR₁₀R₁₁, -SC(S)NR₁₀R₁₁, -NR₇C(S)NR₁₀R₁₁, -OC(NR₈)R₇, -SC(NR₈)R₇, -NR₇C(NR₈)R₇, -OC(NR₈)OR₇, -SC(NR₈)OR₇, -NR₇C(NR₈)OR₇, -OC(NR₈)NR₁₀R₁₁, -SC(NR₈)NR₁₀R₁₁, -NR₇C(NR₈)NR₁₀R₁₁, -OP(O)(OR₇)₂, or -SP(O)(OR₇)₂;

R_3 is -OH, -SH, -NR₇H, -OR₂₆, -SR₂₆, -NHR₂₆, -O(CH₂)_mOH, -O(CH₂)_mSH, -O(CH₂)_mNR₇H, -S(CH₂)_mOH, -S(CH₂)_mSH, -S(CH₂)_mNR₇H, -OC(O)NR₁₀R₁₁, -SC(O)NR₁₀R₁₁, -NR₇C(O)NR₁₀R₁₁, -OC(O)R₇, -SC(O)R₇, -NR₇C(O)R₇, -OC(O)OR₇, -SC(O)OR₇, -NR₇C(O)OR₇, -OCH₂C(O)R₇, -SCH₂C(O)R₇, -NR₇CH₂C(O)R₇, -OCH₂C(O)OR₇, -SCH₂C(O)OR₇,

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-NR₇CH₂C(O)OR₇, -OCH₂C(O)NR₁₀R₁₁, -SCH₂C(O)NR₁₀R₁₁,
 -NR₇CH₂C(O)NR₁₀R₁₁, -OS(O)_pR₇, -SS(O)_pR₇, -S(O)_pOR₇, -NR₇S(O)_pR₇,
 -OS(O)_pNR₁₀R₁₁, -SS(O)_pNR₁₀R₁₁, -NR₇S(O)_pNR₁₀R₁₁, -OS(O)_pOR₇,
 -SS(O)_pOR₇, -NR₇S(O)_pOR₇, -OC(S)R₇, -SC(S)R₇, -NR₇C(S)R₇, -OC(S)OR₇,
 -SC(S)OR₇, -NR₇C(S)OR₇, -OC(S)NR₁₀R₁₁, -SC(S)NR₁₀R₁₁,
 -NR₇C(S)NR₁₀R₁₁, -OC(NR₈)R₇, -SC(NR₈)R₇, -NR₇C(NR₈)R₇, -OC(NR₈)OR₇,
 -SC(NR₈)OR₇, -NR₇C(NR₈)OR₇, -OC(NR₈)NR₁₀R₁₁, -SC(NR₈)NR₁₀R₁₁,
 -NR₇C(NR₈)NR₁₀R₁₁, -C(O)OH, -C(O)NHR₈, -C(O)SH, -S(O)OH, -S(O)₂OH,
 -S(O)NHR₈, -S(O)₂NHR₈, -OP(O)(OR₇)₂ or -SP(O)(OR₇)₂;

ring B is further optionally substituted with one or more substituents in addition to -NR^aR^b;

R^a and R^b, for each occurrence, is independently -H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl or heteroaryl or an optionally substituted aralkyl; or R^a and R^b, taken together with the nitrogen to which they are attached, form an optionally substituted heteroaryl or heterocyclyl;

R₇ and R₈, for each occurrence, is independently, -H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteroaralkyl;

R₁₀ and R₁₁, for each occurrence, is independently -H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteroaralkyl; or R₁₀ and R₁₁, taken together with the

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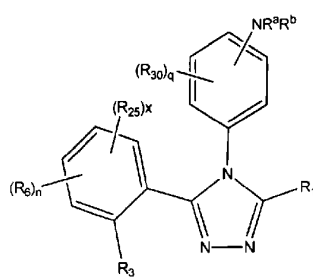
nitrogen to which they are attached, form an optionally substituted heterocyclyl or an optionally substituted heteroaryl;

R_{26} is a C1-C6 alkyl;

p , for each occurrence, is independently, 0, 1 or 2; and

m , for each occurrence, is independently, 1, 2, 3 or 4.

2. The compound of claim 1, wherein the compound is represented by the following structural formula:



or a tautomer, pharmaceutically acceptable salt, solvate, or clathrate thereof, wherein:

R_6 and R_{30} , for each occurrence, are independently an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteroaralkyl, halo, cyano, nitro, guanidino, a haloalkyl, a heteroalkyl, alkoxy, haloalkoxy, $-NR_{10}R_{11}$, $-OR_7$, $-C(O)R_7$, $-C(O)OR_7$, $-C(S)R_7$, $-C(O)SR_7$, $-C(S)SR_7$, $-C(S)OR_7$, $-C(S)NR_{10}R_{11}$, $-C(NR_8)OR_7$, $-C(NR_8)R_7$, $-C(NR_8)NR_{10}R_{11}$, $-C(NR_8)SR_7$, $-OC(O)R_7$, $-OC(O)OR_7$, $-OC(S)OR_7$, $-OC(NR_8)OR_7$, $-SC(O)R_7$, $-SC(O)OR_7$, $-SC(NR_8)OR_7$, $-OC(S)R_7$, $-SC(S)R_7$, $-SC(S)OR_7$, $-OC(O)NR_{10}R_{11}$, $-OC(S)NR_{10}R_{11}$, $-OC(NR_8)NR_{10}R_{11}$, $-SC(O)NR_{10}R_{11}$, $-SC(NR_8)NR_{10}R_{11}$, $-SC(S)NR_{10}R_{11}$, $-OC(NR_8)R_7$, $-SC(NR_8)R_7$, $-C(O)NR_{10}R_{11}$, $-NR_8C(O)R_7$, $-NR_7C(S)R_7$, $-NR_7C(S)OR_7$, $-NR_7C(NR_8)R_7$,

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-NR₇C(O)OR₇, -NR₇C(NR₈)OR₇, -NR₇C(O)NR₁₀R₁₁, -NR₇C(S)NR₁₀R₁₁,
 -NR₇C(NR₈)NR₁₀R₁₁, -SR₇, -S(O)_pR₇, -OS(O)_pR₇, -OS(O)_pOR₇,
 -OS(O)_pNR₁₀R₁₁, -S(O)_pOR₇, -NR₈S(O)_pR₇, -NR₇S(O)_pNR₁₀R₁₁, -NR₇S(O)_pOR₇,
 -S(O)_pNR₁₀R₁₁, -SS(O)_pR₇, -SS(O)_pOR₇, -SS(O)_pNR₁₀R₁₁, -OP(O)(OR₇)₂, or
 -SP(O)(OR₇)₂;

R₂₅ is -OH, -SH, -NHR₇, -(CH₂)_kOH, -(CH₂)_kSH, -(CH₂)_kNR₇H,
 -OCH₃, -SCH₃, -NHCH₃, -OCH₂CH₂OH, -OCH₂CH₂SH, -OCH₂CH₂NR₇H,
 -SCH₂CH₂OH, -SCH₂CH₂SH, -SCH₂CH₂NR₇H, -OC(O)NR₁₀R₁₁,
 -SC(O)NR₁₀R₁₁, -NR₇C(O)NR₁₀R₁₁, -OC(O)R₇, -SC(O)R₇, -NR₇C(O)R₇,
 -OC(O)OR₇, -SC(O)OR₇, -NR₇C(O)OR₇, -OCH₂C(O)R₇, -SCH₂C(O)R₇,
 -NR₇CH₂C(O)R₇, -OCH₂C(O)OR₇, -SCH₂C(O)OR₇, -NR₇CH₂C(O)OR₇,
 -OCH₂C(O)NR₁₀R₁₁, -SCH₂C(O)NR₁₀R₁₁, -NR₇CH₂C(O)NR₁₀R₁₁, -OS(O)_pR₇,
 -SS(O)_pR₇, -NR₇S(O)_pR₇, -OS(O)_pNR₁₀R₁₁, -SS(O)_pNR₁₀R₁₁,
 -NR₇S(O)_pNR₁₀R₁₁, -OS(O)_pOR₇, -SS(O)_pOR₇, -NR₇S(O)_pOR₇, -OC(S)R₇,
 -SC(S)R₇, -NR₇C(S)R₇, -OC(S)OR₇, -SC(S)OR₇, -NR₇C(S)OR₇,
 -OC(S)NR₁₀R₁₁, -SC(S)NR₁₀R₁₁, -NR₇C(S)NR₁₀R₁₁, -OC(NR₈)R₇,
 -SC(NR₈)R₇, -NR₇C(NR₈)R₇, -OC(NR₈)OR₇, -SC(NR₈)OR₇, -NR₇C(NR₈)OR₇,
 -OC(NR₈)NR₁₀R₁₁, -SC(NR₈)NR₁₀R₁₁, -NR₇C(NR₈)NR₁₀R₁₁, -C(O)R₇,
 -C(O)OR₇, -C(O)NR₁₀R₁₁, -C(O)SR₇, -C(S)R₇, -C(S)OR₇, -C(S)NR₁₀R₁₁,
 -C(S)SR₇, -C(NR₈)OR₇, -C(NR₈)R₇, -C(NR₈)NR₁₀R₁₁, -C(NR₈)SR₇,
 -S(O)_pOR₇, -S(O)_pNR₁₀R₁₁ or -S(O)_pR₇;

k is 1, 2, 3 or 4;

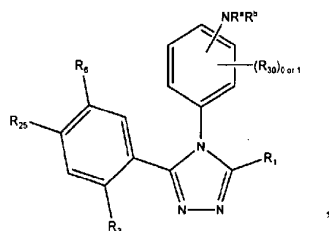
n and q for each occurrence, is independently an integer from 0 to 4; and

x is 0 or 1, provided that n+x is less than or equal to 4.

3. The compound of claim 2, wherein the compound is represented by the structural formula

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or a tautomer, pharmaceutically acceptable salt, solvate, or clathrate thereof, wherein:

R_6 is an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, cyano, halo, nitro, an optionally substituted cycloalkyl, haloalkyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteroaralkyl, $-OR_7$, $-SR_7$, $-NR_{10}R_{11}$, $-OC(O)NR_{10}R_{11}$, $-SC(O)NR_{10}R_{11}$, $-NR_7C(O)NR_{10}R_{11}$, $-OC(O)R_7$, $-SC(O)R_7$, $-NR_7C(O)R_7$, $-OC(O)OR_7$, $-SC(O)OR_7$, $-NR_7C(O)OR_7$, $-OCH_2C(O)R_7$, $-SCH_2C(O)R_7$, $-NR_7CH_2C(O)R_7$, $-OCH_2C(O)OR_7$, $-SCH_2C(O)OR_7$, $-NR_7CH_2C(O)OR_7$, $-OCH_2C(O)NR_{10}R_{11}$, $-SCH_2C(O)NR_{10}R_{11}$, $-NR_7CH_2C(O)NR_{10}R_{11}$, $-OS(O)_pR_7$, $-SS(O)_pR_7$, $-NR_7S(O)_pR_7$, $-OS(O)_pNR_{10}R_{11}$, $-SS(O)_pNR_{10}R_{11}$, $-NR_7S(O)_pNR_{10}R_{11}$, $-OS(O)_pOR_7$, $-SS(O)_pOR_7$, $-NR_7S(O)_pOR_7$, $-OC(S)R_7$, $-SC(S)R_7$, $-NR_7C(S)R_7$, $-OC(S)OR_7$, $-SC(S)OR_7$, $-NR_7C(S)OR_7$, $-OC(S)NR_{10}R_{11}$, $-SC(S)NR_{10}R_{11}$, $-NR_7C(S)NR_{10}R_{11}$, $-OC(NR_8)R_7$, $-SC(NR_8)R_7$, $-NR_7C(NR_8)R_7$, $-OC(NR_8)OR_7$, $-SC(NR_8)OR_7$, $-NR_7C(NR_8)OR_7$, $-OC(NR_8)NR_{10}R_{11}$, $-SC(NR_8)NR_{10}R_{11}$, $-NR_7C(NR_8)NR_{10}R_{11}$, $-C(O)R_7$, $-C(O)OR_7$, $-C(O)NR_{10}R_{11}$, $-C(O)SR_7$, $-C(S)R_7$, $-C(S)OR_7$, $-C(S)NR_{10}R_{11}$, $-C(S)SR_7$, $-C(NR_8)OR_7$, $-C(NR_8)R_7$, $-C(NR_8)NR_{10}R_{11}$, $-C(NR_8)SR_7$, $-S(O)_pOR_7$, $-S(O)_pNR_{10}R_{11}$ or $-S(O)_pR_7$;

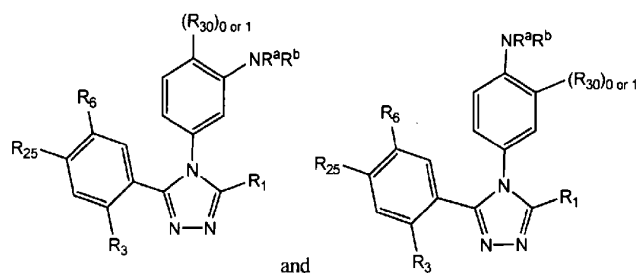
R_{30} is an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, cyano, halo, nitro, an optionally substituted cycloalkyl, haloalkyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteroaralkyl, $-OR_7$, $-SR_7$, $-NR_{10}R_{11}$,

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-OC(O)NR₁₀R₁₁, -SC(O)NR₁₀R₁₁, -NR₇C(O)NR₁₀R₁₁, -OC(O)R₇, -SC(O)R₇,
 -NR₇C(O)R₇, -OC(O)OR₇, -SC(O)OR₇, -NR₇C(O)OR₇, -OCH₂C(O)R₇,
 -SCH₂C(O)R₇, -NR₇CH₂C(O)R₇, -OCH₂C(O)OR₇, -SCH₂C(O)OR₇,
 -NR₇CH₂C(O)OR₇, -OCH₂C(O)NR₁₀R₁₁, -SCH₂C(O)NR₁₀R₁₁,
 -NR₇CH₂C(O)NR₁₀R₁₁, -OS(O)_pR₇, -SS(O)_pR₇, -NR₇S(O)_pR₇,
 -OS(O)_pNR₁₀R₁₁, -SS(O)_pNR₁₀R₁₁, -NR₇S(O)_pNR₁₀R₁₁, -OS(O)_pOR₇,
 -SS(O)_pOR₇, -NR₇S(O)_pOR₇, -OC(S)R₇, -SC(S)R₇, -NR₇C(S)R₇, -OC(S)OR₇,
 -SC(S)OR₇, -NR₇C(S)OR₇, -OC(S)NR₁₀R₁₁, -SC(S)NR₁₀R₁₁,
 -NR₇C(S)NR₁₀R₁₁, -OC(NR₈)R₇, -SC(NR₈)R₇, -NR₇C(NR₈)R₇, -OC(NR₈)OR₇,
 -SC(NR₈)OR₇, -NR₇C(NR₈)OR₇, -OC(NR₈)NR₁₀R₁₁, -SC(NR₈)NR₁₀R₁₁,
 -NR₇C(NR₈)NR₁₀R₁₁, -C(O)R₇, -C(O)OR₇, -C(O)NR₁₀R₁₁, -C(O)SR₇,
 -C(S)R₇, -C(S)OR₇, -C(S)NR₁₀R₁₁, -C(S)SR₇, -C(NR₈)OR₇, -C(NR₈)R₇,
 -C(NR₈)NR₁₀R₁₁, -C(NR₈)SR₇, -S(O)_pOR₇, -S(O)_pNR₁₀R₁₁ or -S(O)_pR₇.

4. The compound of claim 3, wherein the compound is represented by a structural formula selected from:



or a tautomer, pharmaceutically acceptable salt, solvate, or clathrate thereof.

5. The compound of claim 4, wherein:

R₁, R₃ or R₂₅ are each independently -OH, -SH, -NHR₇, -OC(O)NR₁₀R₁₁,
 -SC(O)NR₁₀R₁₁, -OC(O)R₇, -SC(O)R₇, -OC(O)OR₇, -SC(O)OR₇, -OS(O)_pR₇,
 -S(O)_pOR₇, -SS(O)_pR₇, -OS(O)_pOR₇, -SS(O)_pOR₇, -OC(S)R₇, -SC(S)R₇,
 -OC(S)OR₇, -SC(S)OR₇, -OC(S)NR₁₀R₁₁, -SC(S)NR₁₀R₁₁, -OC(NR₈)R₇,
 -SC(NR₈)R₇, -OC(NR₈)OR₇, -SC(NR₈)OR₇, -OP(O)(OR₇)₂ or -SP(O)(OR₇)₂;

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R^a and R^b are each independently a hydrogen, a C1-C6 straight or branched alkyl, optionally substituted by -OH, -CN, -SH, amino, a C1-C6 alkoxy, alkylsulfanyl, alkylamino, dialkylamino or a cycloalkyl; or R^a and R^b taken together with the nitrogen to which they are attached form a substituted or unsubstituted nonaromatic, nitrogen-containing heterocyclyl; and

R_6 is a C1-C6 alkyl, a C1-C6 haloalkyl, a C1-C6 alkoxy, a C1-C6 haloalkoxy, a C1-C6 alkyl sulfanyl or a C3-C6 cycloalkyl.

6. The compound of claim 5, wherein:

R_1 and R_3 are each, independently, -OH, -SH or -NHR₇; and

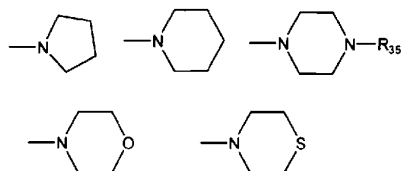
R_{30} is a -OH, -SH, halogen, cyano, a C1-C6 alkyl, C1-C6 haloalkyl, C1-C6 alkoxy, C1-C6 haloalkoxy or C1-C6 alkyl sulfanyl.

7. The compound of claim 6, wherein:

R_1 , R_3 and R_{25} for each occurrence, is independently -SH or -OH, and R_6 is cyclopropyl or isopropyl;

R_{30} is a methyl, ethyl, propyl, isopropyl, methoxy or ethoxy; and

R^a and R^b are each independently a hydrogen, methyl, ethyl, propyl, isopropyl, or taken together with the nitrogen to which they are attached, are:

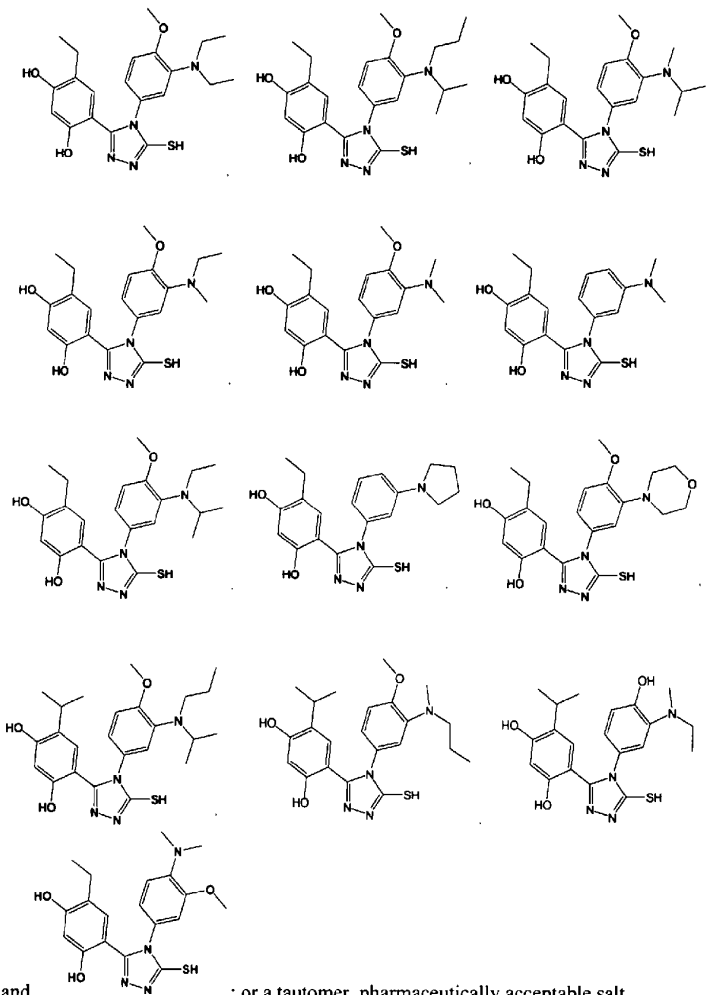


wherein R_{35} is -H, a C1-C4 alkyl or a C1-C4 acyl.

8. The compound of claim 2, wherein R_1 , R_3 and R_{25} are each independently -SH or -OH; and R_6 is cyclopropyl or isopropyl.
9. The compound of claim 7, wherein the compound is represented by a structural formula selected from:

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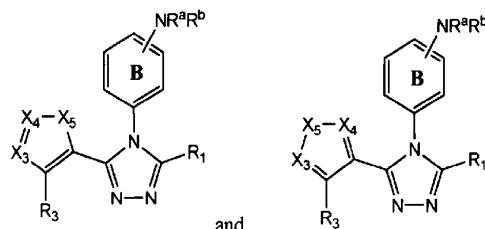


and ; or a tautomer, pharmaceutically acceptable salt, solvate, or clathrate thereof.

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10. The compound of claim 1, wherein the compound is represented by a structural formula selected from:



or a tautomer, pharmaceutically acceptable salt, solvate, or clathrate thereof, wherein:

X_3 and X_4 are each, independently, N, N(O), $N^+(R_{17})$ CH or CR_6 ;

X_5 is O, S, NR_{17} , CH_2 , $CH(R_6)$, $C(R_6)_2$, $CH=CH$, $CH=CR_6$, $CR_6=CH$, $CR_6=CR_6$, $CH=N$, $CR_6=N$, $CH=N(O)$, $CR_6=N(O)$, $N=CH$, $N=CR_6$, $N(O)=CH$, $N(O)=CR_6$, $N^+(R_{17})=CH$, $N^+(R_{17})=CR_6$, $CH=N^+(R_{17})$, $CR_6=N^+(R_{17})$ or $N=N$, provided that at least one X_3 , X_4 or X_5 is a heteroatom;

R_6 , for each occurrence, is independently an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteroaralkyl, halo, cyano, nitro, guanadino, a haloalkyl, a heteroalkyl, alkoxy, haloalkoxy, $-NR_{10}R_{11}$, $-OR_7$, $-C(O)R_7$, $-C(O)OR_7$, $-C(S)R_7$, $-C(O)SR_7$, $-C(S)SR_7$, $-C(S)OR_7$, $-C(S)NR_{10}R_{11}$, $-C(NR_8)OR_7$, $-C(NR_8)R_7$, $-C(NR_8)NR_{10}R_{11}$, $-C(NR_8)SR_7$, $-OC(O)R_7$, $-OC(O)OR_7$, $-OC(S)OR_7$, $-OC(NR_8)OR_7$, $-SC(O)R_7$, $-SC(O)OR_7$, $-SC(NR_8)OR_7$, $-OC(S)R_7$, $-SC(S)R_7$, $-SC(S)OR_7$, $-OC(O)NR_{10}R_{11}$, $-OC(S)NR_{10}R_{11}$, $-OC(NR_8)NR_{10}R_{11}$, $-SC(O)NR_{10}R_{11}$, $-SC(NR_8)NR_{10}R_{11}$, $-SC(S)NR_{10}R_{11}$, $-OC(NR_8)R_7$, $-SC(NR_8)R_7$, $-C(O)NR_{10}R_{11}$, $-NR_8C(O)R_7$, $-NR_7C(S)R_7$, $-NR_7C(S)OR_7$, $-NR_7C(NR_8)R_7$, $-NR_7C(O)OR_7$, $-NR_7C(NR_8)OR_7$, $-NR_7C(O)NR_{10}R_{11}$, $-NR_7C(S)NR_{10}R_{11}$, $-NR_7C(NR_8)NR_{10}R_{11}$, $-SR_7$, $-S(O)_pR_7$, $-OS(O)_pR_7$, $-OS(O)_pOR_7$, $-OS(O)_pNR_{10}R_{11}$, $-S(O)_pOR_7$, $-NR_8S(O)_pR_7$,

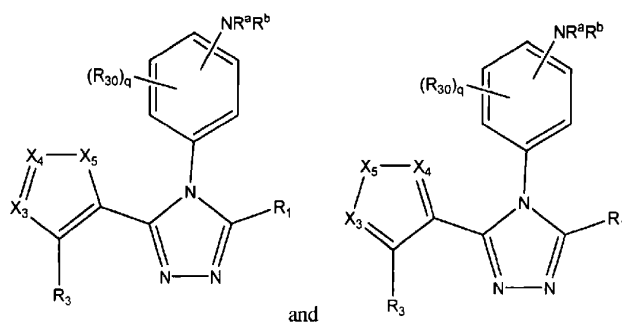
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$-\text{NR}_7\text{S}(\text{O})_p\text{NR}_{10}\text{R}_{11}$, $-\text{NR}_7\text{S}(\text{O})_p\text{OR}_7$, $-\text{S}(\text{O})_p\text{NR}_{10}\text{R}_{11}$, $-\text{SS}(\text{O})_p\text{R}_7$, $-\text{SS}(\text{O})_p\text{OR}_7$,
or $-\text{SS}(\text{O})_p\text{NR}_{10}\text{R}_{11}$; and

R_{17} , for each occurrence, is independently an alkyl or an aralkyl.

11. The compound of claim 10, wherein the compound is represented by a structural formula selected from:



or a tautomer, pharmaceutically acceptable salt, solvate, or clathrate thereof,
wherein:

R_6 is for each occurrence, is independently an optionally substituted C1-C6 alkyl, an optionally substituted C3-C6 cycloalkyl, an optionally substituted C3-C6 cycloalkenyl, an optionally substituted heterocyclyl, a halo, a haloalkyl, a haloalkoxy, a heteroalkyl, an alkoxy, an alkylsulfanyl, -OH, -SH, -NHR₇, -(CH₂)_kOH, -(CH₂)_kSH, -(CH₂)_kNR₇H, -OCH₃, -SCH₃, -NHCH₃, -OCH₂CH₂OH, -OCH₂CH₂SH, -OCH₂CH₂NR₇H, -SCH₂CH₂OH, -SCH₂CH₂SH, -SCH₂CH₂NR₇H, -OC(O)NR₁₀R₁₁, -SC(O)NR₁₀R₁₁, -NR₇C(O)NR₁₀R₁₁, -OC(O)R₇, -SC(O)R₇, -NR₇C(O)R₇, -OC(O)OR₇, -SC(O)OR₇, -NR₇C(O)OR₇, -OCH₂C(O)R₇, -SCH₂C(O)R₇, -NR₇CH₂C(O)R₇, -OCH₂C(O)OR₇, -SCH₂C(O)OR₇, -NR₇CH₂C(O)OR₇, -OCH₂C(O)NR₁₀R₁₁, -SCH₂C(O)NR₁₀R₁₁, -NR₇CH₂C(O)NR₁₀R₁₁, -OS(O)_pR₇, -SS(O)_pR₇, -NR₇S(O)_pR₇, -OS(O)_pNR₁₀R₁₁, -SS(O)_pNR₁₀R₁₁, -NR₇S(O)_pNR₁₀R₁₁, -OS(O)_pOR₇, -SS(O)_pOR₇, -NR₇S(O)_pOR₇, -OC(S)R₇, -SC(S)R₇, -NR₇C(S)R₇, -OC(S)OR₇, -SC(S)OR₇, -NR₇C(S)OR₇, -OC(S)NR₁₀R₁₁, -SC(S)NR₁₀R₁₁, -NR₇C(S)NR₁₀R₁₁, -OC(NR₈)R₇, -SC(NR₈)R₇, -NR₇C(NR₈)R₇, -OC(NR₈)OR₇,

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-SC(NR₈)OR₇, -NR₇C(NR₈)OR₇, -OC(NR₈)NR₁₀R₁₁, -SC(NR₈)NR₁₀R₁₁,
 -NR₇C(NR₈)NR₁₀R₁₁, -C(O)R₇, -C(O)OR₇, -C(O)NR₁₀R₁₁, -C(O)SR₇,
 -C(S)R₇, -C(S)OR₇, -C(S)NR₁₀R₁₁, -C(S)SR₇, -C(NR₈)OR₇, -C(NR₈)R₇,
 -C(NR₈)NR₁₀R₁₁, -C(NR₈)SR₇, -S(O)_pOR₇, -S(O)_pNR₁₀R₁₁, -S(O)_pR₇,
 -OP(O)(OR₇)₂ or -SP(O)(OR₇)₂;

k is 1, 2, 3, or 4;

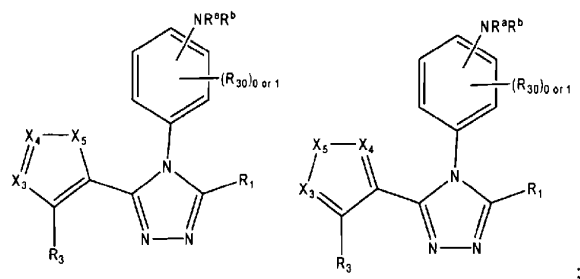
R₃₀, for each occurrence, is independently an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteraralkyl, halo, cyano, nitro, guanidino, a haloalkyl, a heteroalkyl, alkoxy, haloalkoxy, -NR₁₀R₁₁, -OR₇, -C(O)R₇, -C(O)OR₇, -C(S)R₇, -C(O)SR₇, -C(S)SR₇, -C(S)OR₇, -C(S)NR₁₀R₁₁, -C(NR₈)OR₇, -C(NR₈)R₇, -C(NR₈)NR₁₀R₁₁, -C(NR₈)SR₇, -OC(O)R₇, -OC(O)OR₇, -OC(S)OR₇, -OC(NR₈)OR₇, -SC(O)R₇, -SC(O)OR₇, -SC(NR₈)OR₇, -OC(S)R₇, -SC(S)R₇, -SC(S)OR₇, -OC(O)NR₁₀R₁₁, -OC(S)NR₁₀R₁₁, -OC(NR₈)NR₁₀R₁₁, -SC(O)NR₁₀R₁₁, -SC(NR₈)NR₁₀R₁₁, -SC(S)NR₁₀R₁₁, -OC(NR₈)R₇, -SC(NR₈)R₇, -C(O)NR₁₀R₁₁, -NR₈C(O)R₇, -NR₇C(S)R₇, -NR₇C(S)OR₇, -NR₇C(NR₈)R₇, -NR₇C(O)OR₇, -NR₇C(NR₈)OR₇, -NR₇C(O)NR₁₀R₁₁, -NR₇C(S)NR₁₀R₁₁, -NR₇C(NR₈)NR₁₀R₁₁, -SR₇, -S(O)_pR₇, -OS(O)_pR₇, -OS(O)_pOR₇, -OS(O)_pNR₁₀R₁₁, -S(O)_pOR₇, -NR₈S(O)_pR₇, -NR₇S(O)_pNR₁₀R₁₁, -NR₇S(O)_pOR₇, -S(O)_pNR₁₀R₁₁, -SS(O)_pR₇, -SS(O)_pOR₇, or -SS(O)_pNR₁₀R₁₁; and

q is 0, 1, 2, 3 or 4.

12. The compound of claim 11, wherein the compound is represented by a structural formula selected from:

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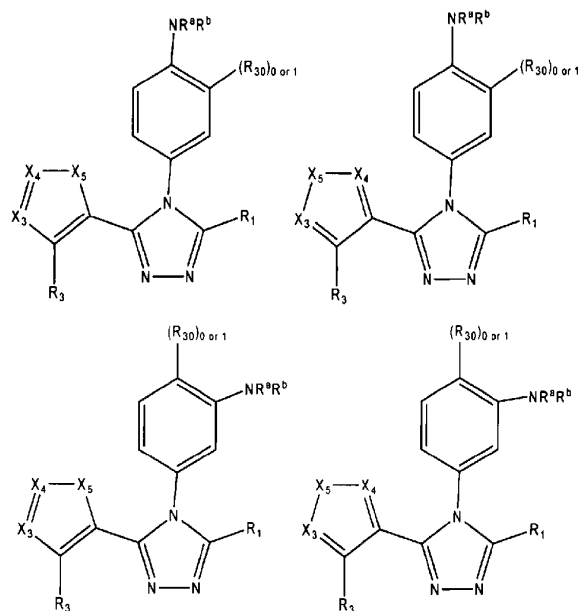
or a tautomer, pharmaceutically acceptable salt, solvate, or clathrate thereof, wherein:

R_{30} for each occurrence is independently an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, cyano, halo, nitro, an optionally substituted cycloalkyl, haloalkyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteroaralkyl, $-OR_7$, $-SR_7$, $-NR_{10}R_{11}$, $-OC(O)NR_{10}R_{11}$, $-SC(O)NR_{10}R_{11}$, $-NR_7C(O)NR_{10}R_{11}$, $-OC(O)R_7$, $-SC(O)R_7$, $-NR_7C(O)R_7$, $-OC(O)OR_7$, $-SC(O)OR_7$, $-NR_7C(O)OR_7$, $-OCH_2C(O)R_7$, $-SCH_2C(O)R_7$, $-NR_7CH_2C(O)R_7$, $-OCH_2C(O)OR_7$, $-SCH_2C(O)OR_7$, $-NR_7CH_2C(O)OR_7$, $-OCH_2C(O)NR_{10}R_{11}$, $-SCH_2C(O)NR_{10}R_{11}$, $-NR_7CH_2C(O)NR_{10}R_{11}$, $-OS(O)_pR_7$, $-SS(O)_pR_7$, $-NR_7S(O)_pR_7$, $-OS(O)_pNR_{10}R_{11}$, $-SS(O)_pNR_{10}R_{11}$, $-NR_7S(O)_pNR_{10}R_{11}$, $-OS(O)_pOR_7$, $-SS(O)_pOR_7$, $-NR_7S(O)_pOR_7$, $-OC(S)R_7$, $-SC(S)R_7$, $-NR_7C(S)R_7$, $-OC(S)OR_7$, $-SC(S)OR_7$, $-NR_7C(S)OR_7$, $-OC(S)NR_{10}R_{11}$, $-SC(S)NR_{10}R_{11}$, $-NR_7C(S)NR_{10}R_{11}$, $-OC(NR_8)R_7$, $-SC(NR_8)R_7$, $-NR_7C(NR_8)R_7$, $-OC(NR_8)OR_7$, $-SC(NR_8)OR_7$, $-NR_7C(NR_8)OR_7$, $-OC(NR_8)NR_{10}R_{11}$, $-SC(NR_8)NR_{10}R_{11}$, $-NR_7C(NR_8)NR_{10}R_{11}$, $-C(O)R_7$, $-C(O)OR_7$, $-C(O)NR_{10}R_{11}$, $-C(O)SR_7$, $-C(S)R_7$, $-C(S)OR_7$, $-C(S)NR_{10}R_{11}$, $-C(S)SR_7$, $-C(NR_8)OR_7$, $-C(NR_8)R_7$, $-C(NR_8)NR_{10}R_{11}$, $-C(NR_8)SR_7$, $-S(O)_pOR_7$, $-S(O)_pNR_{10}R_{11}$ or $-S(O)_pR_7$.

13. The compound of claim 12, wherein the compound is represented by a structural formula selected from:

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or a tautomer, pharmaceutically acceptable salt, solvate, or clathrate thereof, wherein:

R_1 and R_3 for each occurrence is independently -OH, -SH, -HNR₇, -OC(O)NR₁₀R₁₁, -SC(O)NR₁₀R₁₁, -OC(O)R₇, -SC(O)R₇, -OC(O)OR₇, -SC(O)OR₇, -OS(O)_pR₇, -S(O)_pOR₇, -SS(O)_pR₇, -OS(O)_pOR₇, -SS(O)_pOR₇, -OC(S)R₇, -SC(S)R₇, -OC(S)OR₇, -SC(S)OR₇, -OC(S)NR₁₀R₁₁, -SC(S)NR₁₀R₁₁, -OC(NR₈)R₇, -SC(NR₈)R₇, -OC(NR₈)OR₇, -SC(NR₈)OR₇, -OP(O)(OR₇)₂ or -SP(O)(OR₇)₂;

R_6 , for each occurrence, is independently an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, -OH, -SH, -HNR₇, -OC(O)NR₁₀R₁₁, -SC(O)NR₁₀R₁₁, -OC(O)R₇, -SC(O)R₇, -OC(O)OR₇, -SC(O)OR₇, -OS(O)_pR₇, -S(O)_pOR₇, -SS(O)_pR₇, -OS(O)_pOR₇, -SS(O)_pOR₇, -OC(S)R₇, -SC(S)R₇, -OC(S)OR₇,

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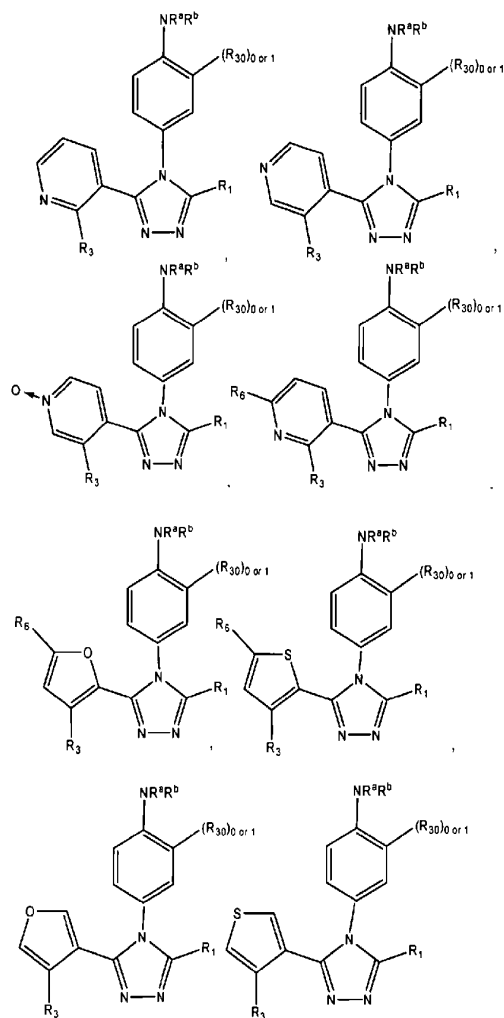
-SC(S)OR₇, -OC(S)NR₁₀R₁₁, -SC(S)NR₁₀R₁₁, -OC(NR₈)R₇, -SC(NR₈)R₇,
-OC(NR₈)OR₇, -SC(NR₈)OR₇, -OP(O)(OR₇)₂ or -SP(O)(OR₇)₂; and

R^a and R^b for each occurrence is independently a hydrogen, a C1-C6 straight or branched alkyl, optionally substituted by -OH, -CN, -SH, amino, a C1-C6 alkoxy, alkylsulfanyl, alkylamino, dialkylamino or a cycloalkyl; or R^a and R^b taken together with the nitrogen to which they are attached form a substituted or unsubstituted nonaromatic, nitrogen-containing heterocyclyl.

14. The compound of claim 13, wherein the compound is represented by a structural formula selected from:

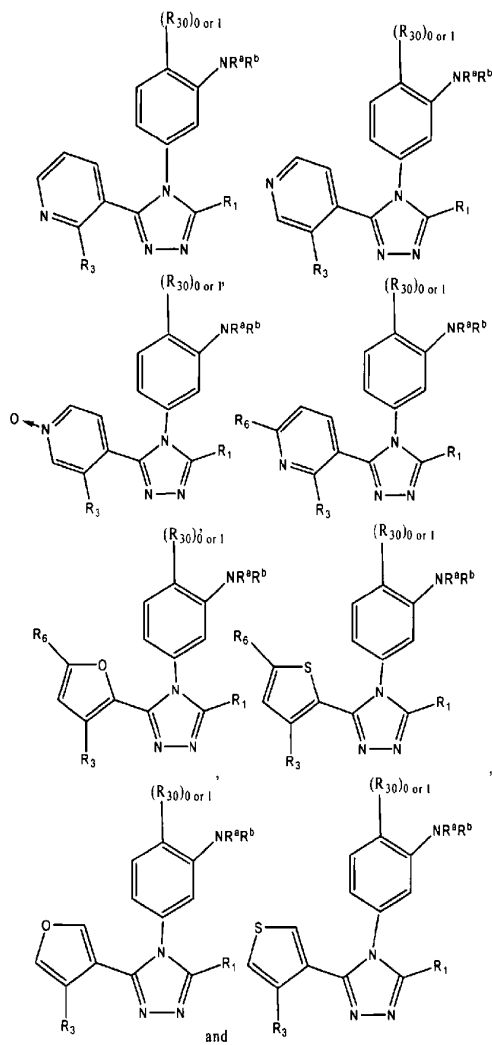
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or a tautomer, pharmaceutically acceptable salt, solvate, or clathrate thereof, wherein:

R_6 is a C1-C6 alkyl, a C1-C6 haloalkyl, a C1-C6 alkoxy, a C1-C6 haloalkoxy, a C1-C6 alkyl sulfanyl or a C3-C6 cycloalkyl;

R_1 and R_3 for each occurrence is independently, -OH, -SH, or -NHR₇; and

R_{30} for each occurrence is independently -OH, -SH, halogen, cyano, a C1-C6 alkyl, C1-C6 haloalkyl, C1-C6 alkoxy, C1-C6 haloalkoxy or C1-C6 alkyl sulfanyl.

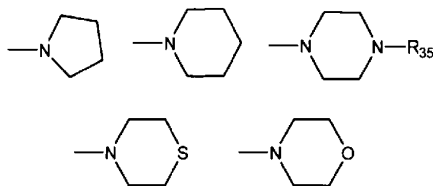
15. The compound of claim 14, wherein:

R_1 and R_3 for each occurrence, is independently -SH or -OH;

R_6 is cyclopropyl or isopropyl;

R_{30} for each occurrence is independently methyl, ethyl, propyl, isopropyl, methoxy or ethoxy; and.

R^a and R^b are each independently a hydrogen, methyl, ethyl, propyl, isopropyl, or taken together with the nitrogen to which they are attached, are:

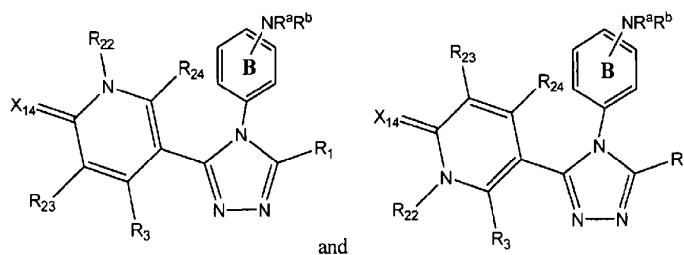


wherein R_{35} is -H, a C1-C4 alkyl or a C1-C4 acyl.

16. A compound represented by a structural formula selected from:

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or a tautomer, pharmaceutically acceptable salt, solvate or clathrate thereof,
wherein:

X_{14} is O, S or NR_7 ;

R_1 is -OH, -SH, $-NR_7H$, $-OR_{26}$, $-SR_{26}$, $-NHR_{26}$, $-O(CH_2)_mOH$,
 $-O(CH_2)_mSH$, $-O(CH_2)_mNR_7H$, $-S(CH_2)_mOH$, $-S(CH_2)_mSH$, $-S(CH_2)_mNR_7H$,
 $-OC(O)NR_{10}R_{11}$, $-SC(O)NR_{10}R_{11}$, $-NR_7C(O)NR_{10}R_{11}$, $-OC(O)R_7$, $-SC(O)R_7$,
 $-NR_7C(O)R_7$, $-OC(O)OR_7$, $-SC(O)OR_7$, $-NR_7C(O)OR_7$, $-OCH_2C(O)R_7$,
 $-SCH_2C(O)R_7$, $-NR_7CH_2C(O)R_7$, $-OCH_2C(O)OR_7$, $-SCH_2C(O)OR_7$,
 $-NR_7CH_2C(O)OR_7$, $-OCH_2C(O)NR_{10}R_{11}$, $-SCH_2C(O)NR_{10}R_{11}$,
 $-NR_7CH_2C(O)NR_{10}R_{11}$, $-OS(O)_pR_7$, $-SS(O)_pR_7$, $-NR_7S(O)_pR_7$,
 $-OS(O)_pNR_{10}R_{11}$, $-SS(O)_pNR_{10}R_{11}$, $-NR_7S(O)_pNR_{10}R_{11}$, $-OS(O)_pOR_7$,
 $-SS(O)_pOR_7$, $-NR_7S(O)_pOR_7$, $-OC(S)R_7$, $-SC(S)R_7$, $-NR_7C(S)R_7$, $-OC(S)OR_7$,
 $-SC(S)OR_7$, $-NR_7C(S)OR_7$, $-OC(S)NR_{10}R_{11}$, $-SC(S)NR_{10}R_{11}$,
 $-NR_7C(S)NR_{10}R_{11}$, $-OC(NR_8)R_7$, $-SC(NR_8)R_7$, $-NR_7C(NR_8)R_7$, $-OC(NR_8)OR_7$,
 $-SC(NR_8)OR_7$, $-NR_7C(NR_8)OR_7$, $-OC(NR_8)NR_{10}R_{11}$, $-SC(NR_8)NR_{10}R_{11}$,
 $-NR_7C(NR_8)NR_{10}R_{11}$, $-S(O)_pOR_7$, $-OP(O)(OR_7)_2$ or $-SP(O)(OR_7)_2$;

R_3 is -OH, -SH, $-NR_7H$, $-OR_{26}$, $-SR_{26}$, $-NHR_{26}$, $-O(CH_2)_mOH$,
 $-O(CH_2)_mSH$, $-O(CH_2)_mNR_7H$, $-S(CH_2)_mOH$, $-S(CH_2)_mSH$, $-S(CH_2)_mNR_7H$,
 $-OC(O)NR_{10}R_{11}$, $-SC(O)NR_{10}R_{11}$, $-NR_7C(O)NR_{10}R_{11}$, $-OC(O)R_7$, $-SC(O)R_7$,
 $-NR_7C(O)R_7$, $-OC(O)OR_7$, $-SC(O)OR_7$, $-NR_7C(O)OR_7$, $-OCH_2C(O)R_7$,
 $-SCH_2C(O)R_7$, $-NR_7CH_2C(O)R_7$, $-OCH_2C(O)OR_7$, $-SCH_2C(O)OR_7$,
 $-NR_7CH_2C(O)OR_7$, $-OCH_2C(O)NR_{10}R_{11}$, $-SCH_2C(O)NR_{10}R_{11}$,
 $-NR_7CH_2C(O)NR_{10}R_{11}$, $-OS(O)_pR_7$, $-SS(O)_pR_7$, $-NR_7S(O)_pR_7$,
 $-OS(O)_pNR_{10}R_{11}$, $-SS(O)_pNR_{10}R_{11}$, $-NR_7S(O)_pNR_{10}R_{11}$, $-OS(O)_pOR_7$,

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-SS(O)_pOR₇, -NR₇S(O)_pOR₇, -OC(S)R₇, -SC(S)R₇, -NR₇C(S)R₇, -OC(S)OR₇,
 -SC(S)OR₇, -NR₇C(S)OR₇, -OC(S)NR₁₀R₁₁, -SC(S)NR₁₀R₁₁,
 -NR₇C(S)NR₁₀R₁₁, -OC(NR₈)R₇, -SC(NR₈)R₇, -NR₇C(NR₈)R₇, -OC(NR₈)OR₇,
 -SC(NR₈)OR₇, -NR₇C(NR₈)OR₇, -OC(NR₈)NR₁₀R₁₁, -SC(NR₈)NR₁₀R₁₁,
 -NR₇C(NR₈)NR₁₀R₁₁, -C(O)OH, -C(O)NHR₈, -C(O)SH, -S(O)OH, -S(O)₂OH,
 -S(O)NHR₈, -S(O)₂NHR₈, -S(O)_pOR₇, -OP(O)(OR₇)₂ or -SP(O)(OR₇)₂;

R₇ and R₈, for each occurrence, is independently, -H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl or an optionally substituted heteraralkyl;

R₁₀ and R₁₁, for each occurrence, is independently -H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteraralkyl; or R₁₀ and R₁₁, taken together with the nitrogen to which they are attached, form an optionally substituted heterocyclyl or an optionally substituted heteroaryl;

ring B is further optionally substituted with one or more substituents in addition to -NR^aR^b;

R^a and R^b, for each occurrence, is independently -H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl or heteroaryl, an optionally substituted aralkyl; or R^a and R^b, taken together with the nitrogen to which they are attached, form an optionally substituted heteroaryl or heterocyclyl;

R₂₂, for each occurrence, is independently -H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an

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optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteraralkyl, a haloalkyl, $-C(O)R_7$, $-C(O)OR_7$, $-OC(O)R_7$, $-C(O)NR_{10}R_{11}$, $-NR_8C(O)R_7$, $-S(O)_pR_7$, $-S(O)_pOR_7$ or $-S(O)_pNR_{10}R_{11}$; and

R_{23} and R_{24} , for each occurrence, is independently $-H$, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteraralkyl, halo, cyano, nitro, guanidino, a haloalkyl, a heteroalkyl, $-NR_{10}R_{11}$, $-OR_7$, $-C(O)R_7$, $-C(O)OR_7$, $-OC(O)R_7$, $-C(O)NR_{10}R_{11}$, $-NR_8C(O)R_7$, $-SR_7$, $-S(O)_pR_7$, $-OS(O)_pR_7$, $-S(O)_pOR_7$, $-NR_8S(O)_pR_7$ or $-S(O)_pNR_{10}R_{11}$;

R_{26} is a C1-C6 alkyl;

p , for each occurrence, is independently, 0, 1 or 2; and

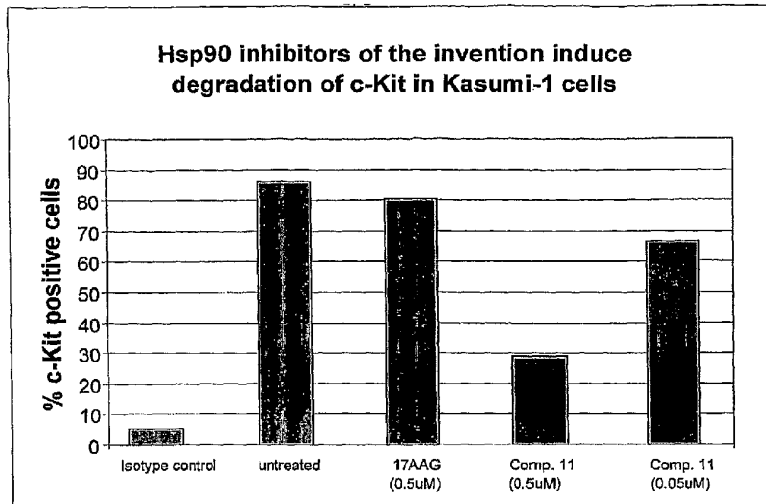
m , for each occurrence, is independently, 1, 2, 3 or 4.

17. The compound of claim 16, wherein:
 - R_1 is $-OH$, $-SH$, or $-NHR_7$;
 - R_{22} is $-H$, an alkyl, an aralkyl, $-C(O)R_7$, $-C(O)OR_7$ or $-C(O)NR_{10}R_{11}$; and
 - X_{14} is O .
18. A method of treating or preventing a proliferative disorder in a mammal, comprising administering to the mammal an effective amount of a compound according to any one of claims 1 to 17.
19. The method of claim 18, wherein the proliferation disorder is cancer.
20. The method of claim 19, wherein the cancer is selected from the group consisting of a c-kit associated cancer, a Bcr-Abl associated cancer, a FLT-3 associated cancer, or an EGFR associated cancer.

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21. A pharmaceutical composition, comprising a pharmaceutically acceptable carrier and one or more compounds of any one of claims 1 to 17.
22. A method of treating or inhibiting angiogenesis in a subject in need thereof, comprising administering to the subject an effective amount of a compound according to any one of claims 1 to 17.
23. Use of a compound according to any one of claims 1 to 17 in the manufacture of a medicament for the treatment or prevention of a proliferative disorder in a mammal.
24. Use of a compound according to any one of claims 1 to 17 in the manufacture of a medicament for inhibiting angiogenesis.
25. Compound according to claim 1 or claim 16 or pharmaceutical composition according to claim 21, substantially as hereinbefore described with reference to any one of the examples.
26. Method according to claim 18 or claim 22 or use according to claim 23 or claim 24, substantially as hereinbefore described with reference to any one of the examples.

**Fig. 1**

SUBSTITUTE SHEET (RULE 26)

Hsp90 inhibitors induce degradation of c-Kit in Kasumi-1 cells

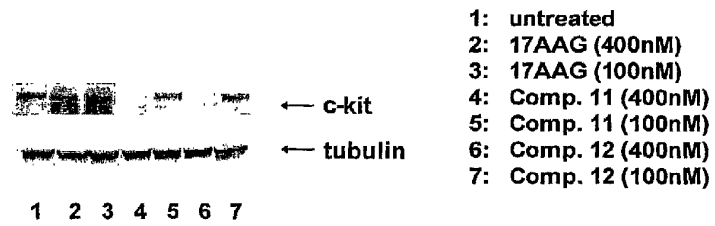
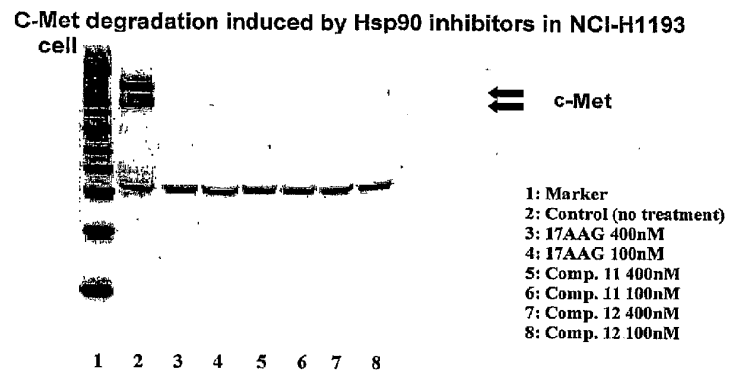


Fig. 2

SUBSTITUTE SHEET (RULE 26)

**Fig. 3**

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