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(54) **Title**: NOVEL TRICYCLIC PROTEIN KINASE MODULATORS

(57) **Abstract**: The invention provides compounds that inhibit CK2 and/or Pim kinases and compositions containing such compounds. These tricyclic compounds and compositions containing them are useful for treating proliferative disorders such as cancer, as well as other kinase-associated conditions including inflammation, pain, pathogenic infections, and certain immunological disorders.

NOVEL TRICYCLIC PROTEIN KINASE MODULATORS

CROSS-REFERENCE TO RELATED APPLICATION

[0001] This application claims the benefit of U.S. Provisional Application No. 61/243,104, filed on September 16, 2009 and entitled "NOVEL TRICYCLIC PROTEIN KINASE MODULATORS", the contents of which are hereby incorporated by reference in their entirety for all purposes.

FIELD OF THE INVENTION

[0002] The invention relates in part to molecules having certain biological activities that include, but are not limited to, inhibiting cell proliferation, modulating serine-threonine protein kinase activity and modulating tyrosine kinase activity. Molecules of the invention can modulate casein kinase (CK) activity (e.g., CK2 activity) and/or Pim kinase activity (e.g., PIM-1 activity), and/or Fms-like tyrosine kinase (Flt) activity (e.g., Flt-3 activity). These compounds are useful in treatment of various physiological disorders, due to their activity as kinase inhibitors. The invention also relates in part to methods for using such molecules, and compositions containing them.

BACKGROUND OF THE INVENTION

[0003] The PIM protein kinases, which include the closely related PIM-1, -2, and -3, have been implicated in diverse biological processes such as cell survival, proliferation, and differentiation. PIM-1 is involved in a number of signaling pathways that are highly relevant to tumorigenesis [reviewed in Bachmann & Moroy, Internat. J. Biochem. Cell Biol., 37, 726-730 (2005)]. Many of these are involved in cell cycle progression and apoptosis. It has been shown that PIM-1 acts as an anti-apoptotic factor via inactivation of the pro-apoptotic factor BAD (Bcl2 associated death promoter, an apoptosis initiator). This finding suggested a direct role of PIM-1 in preventing cell death, since the inactivation of BAD can enhance Bcl-2 activity and can thereby promote cell survival [Aho et al., FEBS Letters, 571, 43-49 (2004)]. PIM-1 has also been recognized as a positive regulator of cell cycle progression. PIM-1 binds and phosphorylates Cdc25A, which leads to an increase in its phosphatase activity and promotion of Gl/S transition [reviewed in Losman et al., JBC, 278, 4800-4805 (1999)]. In addition, the cyclin kinase inhibitor p21Waf which inhibits Gl/S progression, was found to be inactivated by PIM-1 [Wang et al., Biochim. Biophys. Acta. 1593, 45-55 (2002)]. Furthermore, by means of

phosphorylation, PIM-1 inactivates C-TAK1 and activates Cdc25C which results in acceleration of G2/M transition [Bachman et al., JBC, 279, 48319-48 (2004)].

[0004] PIM-1 appears to be an essential player in hematopoietic proliferation. Kinase active PIM-1 is required for the gp130-mediated STAT3 proliferation signal [Hirano et al., Oncogene 19, 2548-2556, (2000)]. PIM-1 is overexpressed or even mutated in a number of tumors and different types of tumor cell lines and leads to genomic instability. Fedorov, et al., concluded that a Phase III compound in development for treating leukemia, LY333'531, is a selective PIM-1 inhibitor. O. Fedorov, et al., PNAS 104(51), 20523-28 (Dec. 2007). Evidence has been published to show that PIM-1 is involved in human tumors including prostate cancer, oral cancer, and Burkitt lymphoma (Gaidano & Dalla Faver, 1993). All these findings point to an important role of PIM-1 in the initiation and progression of human cancers, including various tumors and hematopoietic cancers, thus small molecule inhibitors of PIM-1 activity are a promising therapeutic strategy.

[0005] Additionally, PIM-2 and PIM-3 have overlapping functions with PIM-1 and inhibition of more than one isoform may provide additional therapeutic benefits. However, it is sometimes preferable for inhibitors of PIM to have little or no in vivo impact through their inhibition of various other kinases, since such effects are likely to cause side effects or unpredictable results. See, e.g., O. Fedorov, et al., PNAS 104(51), 20523-28 (Dec. 2007), discussing the effects that non-specific kinase inhibitors can produce. Accordingly, in some embodiments, the invention provides compounds that are selective inhibitors of at least one of PIM-1, PIM-2, and PIM-3, or some combination of these, while having substantially less activity on certain other human kinases, as described further herein, although the compounds of Formula I are typically active on CK2 as well as one or more Pim proteins.

[0006] The implication of a role for PIM-3 in cancer was first suggested by transcriptional profiling experiments showing that PIM3 gene transcription was upregulated in EWS/ETS-induced malignant transformation of NIH 3T3 cells. These results were extended to show that PIM-3 is selectively expressed in human and mouse hepatocellular and pancreatic carcinomas but not in normal liver or pancreatic tissues. In addition, PIM-3 mRNA and protein are constitutively expressed in multiple human pancreatic and hepatocellular cancer cell lines.

[0007] The link between PIM-3 overexpression and a functional role in promoting tumorigenesis came from RNAi studies in human pancreatic and hepatocellular cancer cell lines overexpressing PIM-3. In these studies the ablation of endogenous PIM-3 protein promoted apoptosis of these cells. The molecular mechanism by which PIM-3 suppresses apoptosis is in

part carried out through the modulation of phosphorylation of the pro-apoptotic protein BAD. Similar to both PIM-1 & 2 which phosphorylate BAD protein, the knockdown of PIM-3 protein by siRNA results in a decrease in BAD phosphorylation at Serll2. Thus, similar to PIM-1 and 2, PIM-3 acts a suppressor of apoptosis in cancers of endodermal origin, e.g., pancreatic and liver cancers. Moreover, as conventional therapies in pancreatic cancer have a poor clinical outcome, PIM-3 could represent a new important molecular target towards successful control of this incurable disease.

[0008] At the 2008 AACR Annual Meeting, SuperGen announced that it has identified a lead PIM kinase inhibitor, SGI-1776, that causes tumor regression in acute myelogenous leukemia (AML) xenograft models (Abstract No. 4974). In an oral presentation entitled, "A potent small molecule PIM kinase inhibitor with activity in cell lines from hematological and solid malignancies," Dr. Steven Warner detailed how scientists used SuperGen's CLIMB(TM) technology to build a model that allowed for the creation of small molecule PIM kinase inhibitors. SGI-1776 was identified as a potent and selective inhibitor of the PIM kinases, inducing apoptosis and cell cycle arrest, thereby causing a reduction in phospho-BAD levels and enhancement of mTOR inhibition in vitro. Most notably, SGI-1776 induced significant tumor regression in MV-4-11 (AML) and MOLM-13 (AML) xenograft models. This demonstrates that inhibitors of PIM kinases can be used to treat leukemias.

[0009] Fedorov, et al., in PNAS vol. 104(51), 20523-28, showed that a selective inhibitor of PIM-1 kinase (Ly5333'531) suppressed cell growth and induced cell death in leukemic cells from AML patients. PIM-3 has been shown to be expressed in pancreatic cancer cells, while it is not expressed in normal pancreas cells, demonstrating that it should be a good target for pancreatic cancer. Li, et al., Cancer Res. 66(13), 6741-47 (2006). Inhibitors of PIM kinases that are useful for treating certain types of cancers are described in PCT/US2008/012829.

[0010] Protein kinase CK2 (formerly called Casein kinase II, referred to herein as "CK2") is a ubiquitous and highly conserved protein serine/threonine kinase. The holoenzyme is typically found in tetrameric complexes consisting of two catalytic (alpha and/or alpha') subunits and two regulatory (beta) subunits. CK2 has a number of physiological targets and participates in a complex series of cellular functions including the maintenance of cell viability. The level of CK2 in normal cells is tightly regulated, and it has long been considered to play a role in cell growth and proliferation. Inhibitors of CK2 that described as are useful for treating certain types of cancers are described in PCT/US2007/077464, PCT/US2008/074820, PCT/US2009/35609.

[0011] Both the prevalence and the importance of CK2 suggest it is an ancient enzyme on the evolutionary scale, as does an evolutionary analysis of its sequence; its longevity may explain why it has become important in so many biochemical processes, and why CK2 from hosts have even been co-opted by infectious pathogens (e.g., viruses, protozoa) as an integral part of their survival and life cycle biochemical systems. These same characteristics explain why inhibitors of CK2 are believed to be useful in a variety of medical treatments as discussed herein. Because it is central to many biological processes, as summarized by Guerra & Issinger, Curr. Med. Chem., 2008, 15:1870-1886, inhibitors of CK2, including the compounds described herein, should be useful in the treatment of a variety of diseases and disorders.

[0012] Cancerous cells show an elevation of CK2, and recent evidence suggests that CK2 exerts potent suppression of apoptosis in cells by protecting regulatory proteins from caspase-mediated degradation. The anti-apoptotic function of CK2 may contribute to its ability to participate in transformation and tumorigenesis. In particular, CK2 has been shown to be associated with acute and chronic myelogenous leukemia, lymphoma and multiple myeloma. In addition, enhanced CK2 activity has been observed in solid tumors of the colon, rectum and breast, squamous cell carcinomas of the lung and of the head and neck (SCCHN), adenocarcinomas of the lung, colon, rectum, kidney, breast, and prostate. Inhibition of CK2 by a small molecule is reported to induce apoptosis of pancreatic cancer cells, and hepatocellular carcinoma cells (HegG2, Hep3, HeLa cancer cell lines); and CK2 inhibitors dramatically sensitized RMS (Rhabdomyosarcoma) tumors toward apoptosis induced by TRAIL. Thus an inhibitor of CK2 alone, or in combination with TRAIL or a ligand for the TRAIL receptor, would be useful to treat RMS, the most common soft-tissue sarcoma in children. In addition, elevated CK2 has been found to be highly correlated with aggressiveness of neoplasias, and treatment with a CK2 inhibitor of the invention should thus reduce tendency of benign lesions to advance into malignant ones, or for malignant ones to metastasize.

[0013] Unlike other kinases and signaling pathways, where mutations are often associated with structural changes that cause loss of regulatory control, increased CK2 activity level appears to be generally caused by upregulation or overexpression of the active protein rather than by changes that affect activation levels. Guerra and Issinger postulate this may be due to regulation by aggregation, since activity levels do not correlate well with mRNA levels. Excessive activity of CK2 has been shown in many cancers, including SCCHN tumors, lung tumors, breast tumors, and others. Id.

[0014] Elevated CK2 activity in colorectal carcinomas was shown to correlate with increased malignancy. Aberrant expression and activity of CK2 have been reported to promote increase nuclear levels of NF-kappaB in breast cancer cells. CK2 activity is markedly increased in patients with AML and CML during blast crisis, indicating that an inhibitor of CK2 should be particularly effective in these conditions. Multiple myeloma cell survival has been shown to rely on high activity of CK2, and inhibitors of CK2 were cytotoxic to MM cells. Similarly, a CK2 inhibitor inhibited growth of murine p190 lymphoma cells. Its interaction with Bcr/Abl has been reported to play an important role in proliferation of Bcr/Abl expressing cells, indicating inhibitors of CK2 may be useful in treatment of Bcr/Abl-positive leukemias. Inhibitors of CK2 have been shown to inhibit progression of skin papillomas, prostate and breast cancer xenografts in mice, and to prolong survival of transgenic mice that express prostate-promoters. Id.

[0015] The role of CK2 in various non-cancer disease processes has been recently reviewed. See Guerra & Issinger, Curr. Med. Chem., 2008, 15:1870-1886. Increasing evidence indicates that CK2 is involved in critical diseases of the central nervous system, including, for example, Alzheimer's disease, Parkinson's disease, and rare neurodegenerative disorders such as Guam-Parkinson dementia, chromosome 18 deletion syndrome, progressive supranuclear palsy, Kuf's disease, or Pick's disease. It is suggested that selective CK2-mediated phosphorylation of tau proteins may be involved in progressive neurodegeneration of Alzheimer's. In addition, recent studies suggest that CK2 plays a role in memory impairment and brain ischemia, the latter effect apparently being mediated by CK2's regulatory effect on the PI3K survival pathways.

[0016] CK2 has also been shown to be involved in the modulation of inflammatory disorders, for example, acute or chronic inflammatory pain, glomerulonephritis, and autoimmune diseases, including, e.g., multiple sclerosis (MS), systemic lupus erythematosus, rheumatoid arthritis, and juvenile arthritis. It positively regulates the function of the serotonin 5-HT3 receptor channel, activates heme oxygenase type 2, and enhances the activity of neuronal nitric oxide synthase. A selective CK2 inhibitor was reported to strongly reduce pain response of mice when administered to spinal cord tissue prior to pain testing. It phosphorylates secretory type IIA phospholipase A2 from synovial fluid of RA patients, and modulates secretion of DEK (a nuclear DNA-binding protein), which is a proinflammatory molecule found in synovial fluid of patients with juvenile arthritis. Thus inhibition of CK2 is expected to control progression of inflammatory pathologies such as those described here, and the inhibitors disclosed herein have been shown to effectively treat pain in animal models.

[0017] Protein kinase CK2 has also been shown to play a role in disorders of the vascular system, such as, e.g., atherosclerosis, laminar shear stress, and hypoxia. CK2 has also been shown to play a role in disorders of skeletal muscle and bone tissue, such as cardiomyocyte hypertrophy, impaired insulin signaling and bone tissue mineralization. In one study, inhibitors of CK2 were effective at slowing angiogenesis induced by growth factor in cultured cells. Moreover, in a retinopathy model, a CK2 inhibitor combined with octreotide (a somatostatin analog) reduced neovascular tufts; thus the CK2 inhibitors described herein would be effective in combination with a somatostatin analog to treat retinopathy.

[0018] CK2 has also been shown to phosphorylate GSK, troponin and myosin light chain; thus it is important in skeletal muscle and bone tissue physiology, and is linked to diseases affecting muscle tissue.

[0019] Evidence suggests that CK2 is also involved in the development and life cycle regulation of protozoal parasites, such as, for example, *Theileria parva, Trypanosoma cruzi, Leishmania donovani, Herpetomonas muscarum muscarum, Plasmodium falciparum, Trypanosoma brucei, Toxoplasma gondii* and *Schistosoma mansoni*. Numerous studies have confirmed the role of CK2 in regulation of cellular motility of protozoan parasites, essential to invasion of host cells. Activation of CK2 or excessive activity of CK2 has been shown to occur in hosts infected with *Leishmania donovani, Herpetomonas muscarum muscarum, Plasmodium falciparum, Trypanosoma brucei, Toxoplasma gondii* and *Schistosoma mansoni*. Indeed, inhibition of CK2 has been shown to block infection by *T. cruzi*.

[0020] CK2 has also been shown to interact with and/or phosphorylate viral proteins associated with human immunodeficiency virus type 1 (HIV-1), human papilloma virus, and herpes simplex virus, in addition to other virus types (e.g. human cytomegalovirus, hepatitis C and B viruses, Borna disease virus, adenovirus, coxsackievirus, coronavirus, influenza, and varicella zoster virus). CK2 phosphorylates and activates HIV-1 reverse transcriptase and proteases in vitro and in vivo, and promotes pathogenicity of simian-human immunodeficiency virus (SHIV), a model for HIV. Inhibitors of CK2 are thus able to reduce reduce pathogenic effects of a model of HIV infection. CK2 also phosphorylates numerous proteins in herpes simplex virus and numerous other viruses, and some evidence suggests viruses have adopted CK2 as a phosphorylating enzyme for their essential life cycle proteins. Inhibition of CK2 is thus expected to deter infection and progression of viral infections, which rely upon the host's CK2 for their own life cycles.

[0021] CK2 is unusual in the diversity of biological processes that it affects, and it differs from most kinases in other ways as well: it is constitutively active, it can use ATP or GTP, and it is elevated in most tumors and rapidly proliferating tissues. It also has unusual structural features that may distinguish it from most kinases, too, enabling its inhibitors to be highly specific for CK2 while many kinase inhibitors affect multiple kinases, increasing the likelihood of off-target effects, or variability between individual subjects. For all of these reasons, CK2 is a particularly interesting target for drug development, and the invention provides highly effective inhibitors of CK2 that are useful in treating a variety of different diseases and disorders mediated by or associated with excessive, aberrant or undesired levels of CK2 activity.

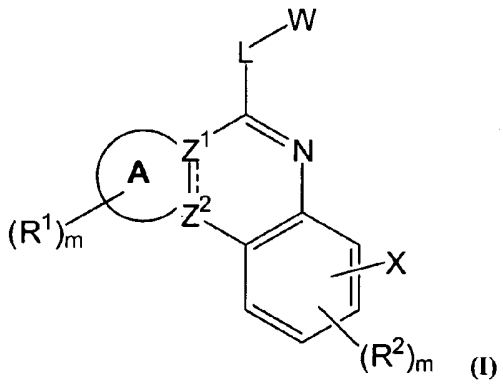
[0022] Because these protein kinases have important functions in biochemical pathways associated with cancer, immunological responses, and inflammation, and are also important in pathogenicity of certain microorganisms, inhibitors of their activity have many medicinal applications. The present invention provides novel compounds that inhibit CK2 or PIM or both, as well as compositions and methods of use utilizing these compounds. These compounds possess therapeutic utilities that are believed to derive from their activity as inhibitors of one or more of these protein kinases.

DISCLOSURE OF THE INVENTION

[0023] The present invention in part provides chemical compounds having certain biological activities that include, but are not limited to, inhibiting cell proliferation, inhibiting angiogenesis, and modulating protein kinase activity. These molecules can modulate Pim kinase activity, and also casein kinase 2 (CK2) activity, and in some cases also Fms-like tyrosine kinase 3 (Flt) activity, and thus affect biological functions that include but are not limited to, inhibiting gamma phosphate transfer from ATP to a protein or peptide substrate, inhibiting angiogenesis, inhibiting cell proliferation and inducing cell apoptosis, for example. The present invention also in part provides methods for preparing novel chemical compounds, and analogs thereof, and methods of using the foregoing. Also provided are compositions comprising the above-described molecules in combination with other agents, and methods for using such molecules in combination with other agents.

[0024] In one aspect, the invention provides compounds that inhibit at least one kinase selected from Pim-1, Pim-2, Pim-3, CK2, and Flt.

[0025] In one aspect, the invention provides compounds of Formula I:



(I)

wherein:

A is a saturated or partially saturated optionally substituted 5, 6 or 7 membered ring;

----- represents a single bond or a double bond;

Z^1 and Z^2 are independently N or C when ----- represents a single bond, provided Z^1 and Z^2 are not both N; and

Z^1 and Z^2 are C when ----- represents a double bond;

L is a linker selected from a bond, NR^3, O, S, CR^4R^5, CR^4R^5-NR^3, CR^4R^5-O-, and CR^4R^5-S;

each R^1, R^2, R^3, R^4 and R^5 is independently H, or an optionally substituted member selected from the group consisting of C1-C8 alkyl, C2-C8 heteroalkyl, C2-C8 alkenyl, C2-C8 heteroalkenyl, C2-C8 alkynyl, C2-C8 heteroalkynyl, C1-C8 acyl, C2-C8 heteroacyl, C6-C10 aryl, C5-C12 heteroaryl, C7-C12 arylalkyl, and C6-C12 heteroarylalkyl group,

or halo, OR, NR_2, NROR, $NRNR_2$, SR, SOR, SO_2R, SO_2NR_2, $NRSO_2R$, $NRCONR_2$, $NRCSNR_2$, $NRC(=NR)NR_2$, NRCOOR, NRCOR, CN, COOR, $CONR_2$, OOCR, COR, or NO_2,

wherein each R is independently H or C1-C8 alkyl, C2-C8 heteroalkyl, C2-C8 alkenyl, C2-C8 heteroalkenyl, C2-C8 alkynyl, C2-C8 heteroalkynyl, C1-C8 acyl, C2-C8 heteroacyl, C6-C10 aryl, C5-C10 heteroaryl, C7-C12 arylalkyl, or C6-C12 heteroarylalkyl,

and wherein two R on the same atom or on adjacent atoms can be linked to form a 3-8 membered ring, optionally containing one or more N, O or S;

and each R group, and each ring formed by linking two R groups together, is optionally substituted with one or more substituents selected from halo, =O, =N-CN, =N-OR', =NR', OR', NR'_2, SR', SO_2R',

$SO_2NR'_2$, $NR'SO_2R'$, $NR'CONR'_2$, $NR'CSNR'_2$, $NR'C(=NR')NR'_2$, NR'COOR', NR'COR', CN, COOR', $CONR'_2$, OOCR', COR', and NO_2,

wherein each R' is independently H, C1-C6 alkyl, C2-C6 heteroalkyl, C1-C6 acyl, C2-C6 heteroacyl, C6-C10 aryl, C5-C10 heteroaryl, C7-12 arylalkyl, or C6-12 heteroarylalkyl, each of which is optionally substituted with one or more groups selected from halo, C1-C4 alkyl, C1-C4 heteroalkyl, C1-C6 acyl, C1-C6 heteroacyl, hydroxy, amino, and =O;

and wherein two R' on the same atom or on adjacent atoms can be linked to form a 3-7 membered ring optionally containing up to three heteroatoms selected from N, O and S;

and R^1 can be =O, or two R^1 groups on the same atom or on adjacent connected atoms, can optionally be linked together to form a 3-8 membered cycloalkyl or heterocycloalkyl, which is optionally substituted;

and R^4 and R^5, when on the same atom or on adjacent connected atoms, can optionally be linked together to form a 3-8 membered cycloalkyl or heterocycloalkyl, which is optionally substituted;

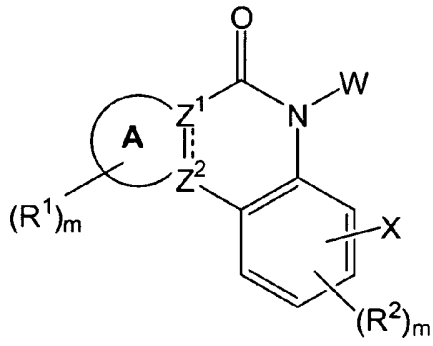
W is alkyl, heteroalkyl, aryl, heteroaryl, cycloalkyl, heterocyclyl, arylalkyl or heteroarylalkyl, each of which can be optionally substituted;

X is a polar substituent;

and each m is independently 0-3;

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

[0026] In another aspect, the invention provides compounds of Formula II:



(II)

wherein:

A is a saturated or partially saturated optionally substituted 5, 6 or 7 membered ring;

----- represents a single bond or a double bond;

Z^1 and Z^2 are independently N or C when ----- represents a single bond, provided Z^1 and Z^2 are not both N; and

Z^1 and Z^2 are C when ----- represents a double bond;

each of R^1 and R^2 is independently H, or an optionally substituted member selected from the group consisting of C1-C8 alkyl, C2-C8 heteroalkyl, C2-C8 alkenyl, C2-C8 heteroalkenyl, C2-C8 alkynyl, C2-C8 heteroalkynyl, C1-C8 acyl, C2-C8 heteroacyl, C6-C10 aryl, C5-C12 heteroaryl, C7-C12 arylalkyl, and C6-C12 heteroarylalkyl group,

or halo, OR, NR_2, NROR, $NRNR_2$, SR, SOR, SO_2R, SO_2NR_2, $NRSO_2R$, $NRCONR_2$, $NRCSNR_2$, $NRC(=NR)NR_2$, NRCOOR, NRCOR, CN, COOR, $CONR_2$, OOCR, COR, or NO_2,

wherein each R is independently H or C1-C8 alkyl, C2-C8 heteroalkyl, C2-C8 alkenyl, C2-C8 heteroalkenyl, C2-C8 alkynyl, C2-C8 heteroalkynyl, C1-C8 acyl, C2-C8 heteroacyl, C6-C10 aryl, C5-C10 heteroaryl, C7-C12 arylalkyl, or C6-C12 heteroarylalkyl,

and wherein two R on the same atom or on adjacent atoms can be linked to form a 3-8 membered ring, optionally containing one or more N, O or S;

and each R group, and each ring formed by linking two R groups together, is optionally substituted with one or more substituents selected from halo, =O, =N-CN, =N-OR', =NR', OR', NR'_2, SR', SO_2R', $SO_2NR'_2$, $NR'SO_2R'$, $NR'CONR'_2$, $NR'CSNR'_2$, $NR'C(=NR')NR'_2$, NR'COOR', NR'COR', CN, COOR', $CONR'_2$, OOCR', COR', and NO_2,

wherein each R' is independently H, C1-C6 alkyl, C2-C6 heteroalkyl, C1-C6 acyl, C2-C6 heteroacyl, C6-C10 aryl, C5-C10 heteroaryl, C7-12 arylalkyl, or C6-12 heteroarylalkyl, each of which is optionally substituted with one or more groups selected from halo, C1-C4 alkyl, C1-C4 heteroalkyl, C1-C6 acyl, C1-C6 heteroacyl, hydroxy, amino, and =O;

and wherein two R' on the same atom or on adjacent atoms can be linked to form a 3-7 membered ring optionally containing up to three heteroatoms selected from N, O and S;

and R^1 can be =O, or two R^1 groups on the same atom or on adjacent connected atoms, can optionally be linked together to form a 3-8 membered cycloalkyl or heterocycloalkyl, which is optionally substituted;

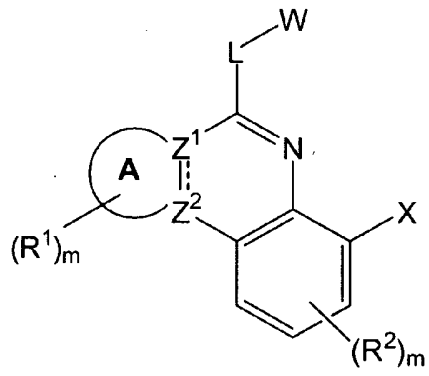
W is alkyl, heteroalkyl, aryl, heteroaryl, cycloalkyl, heterocyclyl, arylalkyl or heteroarylalkyl, each of which can be optionally substituted;

X is a polar substituent;

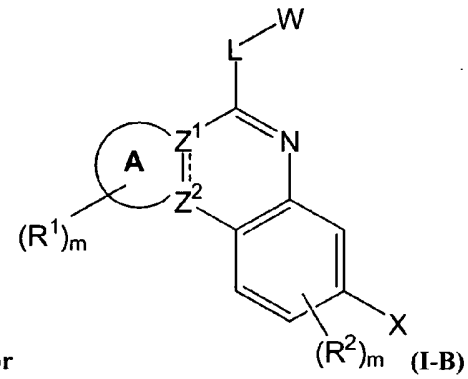
and each m is independently 0-3;

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

[0027] In some embodiments of Formula I, the compound has the structure of Formula I-A or I-B:



(I-A) or

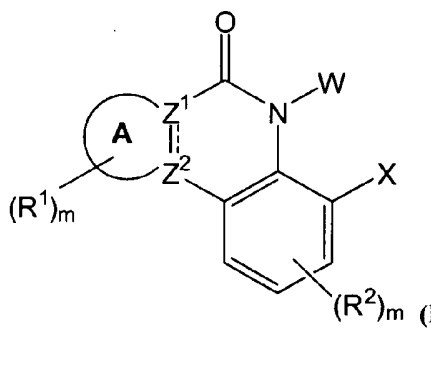


(I-B)

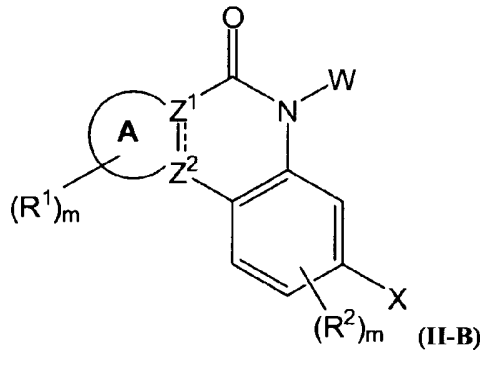
or a pharmaceutically acceptable salt, solvate, and/or prodrug thereof,

wherein A, Z^1, Z^2, L, W, X, R^1, R^2 and m are defined as in Formula I.

[0028] In some embodiments of Formula II, the compound has the structure of Formula II-A or II-B:



(II-A) or



(II-B)

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

wherein A, Z^1, Z^2, W, X, R^1, R^2 and m are defined as in Formula II.

[0029] In other aspects, the invention provides compositions comprising these compounds, and methods of using these compounds to treat various medical conditions, such as cancer, immunological disorders, pathogenic infections, inflammation, pain, angiogenesis-related disorders, and the like, as further described herein.

[0030] Also provided herein are pharmaceutical compositions comprising a compound of on one of the Formulae described herein and at least one pharmaceutically acceptable carrier or excipient, or two or more pharmaceutically acceptable carriers and/or excipients. Pharmaceutical compositions of these compounds can be utilized in treatments described herein.

[0031] The compounds of the invention bind to and interact with kinases, and in one aspect the invention provides a compound of the invention complexed with a kinase protein.

[0032] In certain embodiments, the protein is a CK2 protein, such as a CK2 protein comprising the amino acid sequence of SEQ ID NO: 1, 2 or 3 or a substantially identical variant thereof, for example. 'Substantially identical' means the sequence shares at least 90% homology to the specified sequence (SEQ ID NO: 1, 2 or 3), and preferably shares at least 90% sequence identity with the specified sequence.

SEQ ID NO: 1 (NP_001886; casein kinase II alpha 1 subunit isoform a [Homo sapiens])

```
      msgpvpsrar vytdvnthrp reywdyeshv vewgnqddyq lvrklgrgky sevfeainit
      nnekvvvkil kpvkkkkikr eikilenlrg gpniitladi vkdpvsrtpa lvfehvnntd
  121 fkqlyqtltd ydirfymyei lkaldychsm gimhrdvkph nvmidhehrk lrlidwglae
  181 fyhpgqeynv rvasryfkgp ellvdyqmyd ysldmwslgc mlasmifrke pffhghdnyd
  241 qlvriakvlg tedlydyidk ynieldprfn dilgrhsrkr werfvhsenq hlvspealdf
  301 ldkllrydhq srltareame hpyfytvvkd qarmgsssmp ggstpvssan mmsgissvpt
  361 psplgplags pviaaanplg mpvpaaagaq q
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SEQ ID NO: 2 (NP_808227; casein kinase II alpha 1 subunit isoform a [Homo sapiens])

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      msgpvpsrar vytdvnthrp reywdyeshv vewgnqddyq lvrklgrgky sevfeainit
      nnekvvvkil kpvkkkkikr eikilenlrg gpniitladi vkdpvsrtpa lvfehvnntd
  121 fkqlyqtltd ydirfymyei lkaldychsm gimhrdvkph nvmidhehrk lrlidwglae
  181 fyhpgqeynv rvasryfkgp ellvdyqmyd ysldmwslgc mlasmifrke pffhghdnyd
  241 qlvriakvlg tedlydyidk ynieldprfn dilgrhsrkr werfvhsenq hlvspealdf
  301 ldkllrydhq srltareame hpyfytvvkd qarmgsssmp ggstpvssan mmsgissvpt
  361 psplgplags pviaaanplg mpvpaaagaq q
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SEQ ID NO: 3 (NP_808228; casein kinase II alpha 1 subunit isoform b [Homo sapiens])

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      myeilkaldy chsmgimhrd vkphnvmidh ehrklrlidw glaefyhpgq eynvrvasry
      fkgpellvdy qmydysldmw slgcmlasmi frkepffhgh dnydqlvria kvlgtedlyd
  121 yidkynield prfndilgrh srkrwerfvh senqhlvspe aldfldkllr ydhqsrltar
  181 eamehpyfyt vvkdqarmgs ssmpggstpv ssanmmsgis svptpsplgp lagspviaaa
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241 nplgmpvpaa agaqq

[0033] In certain embodiments the protein is in a cell or in a cell-free system. The protein, the compound or the molecule in some embodiments is in association with a solid phase. In certain embodiments, the interaction between the compound and the protein is detected via a detectable label, where in some embodiments the protein comprises a detectable label and in certain embodiments the compound comprises a detectable label. The interaction between the compound and the protein sometimes is detected without a detectable label.

[0034] Also provided are methods for modulating the activity of a Pim protein, CK2 protein, or Flt protein which comprise contacting a system comprising the protein with a compound described herein in an amount effective for modulating the activity of the protein. In certain embodiments the activity of the protein is inhibited, and sometimes the protein is a CK2 protein, such as a CK2 protein comprising the amino acid sequence of SEQ ID NO: 1, 2 or 3 or a substantially identical variant thereof, for example. In other embodiments the protein is a Pim protein or a Flt protein. In certain embodiments, the system is a cell, and in other embodiments the system is a cell-free system. The protein or the compound may be in association with a solid phase in certain embodiments.

[0035] Provided also are methods for inhibiting cell proliferation, which comprise contacting cells with a compound described herein in an amount effective to inhibit proliferation of the cells. The cells sometimes are in a cell line, such as a cancer cell line (e.g., breast cancer, prostate cancer, pancreatic cancer, lung cancer, hematopoietic cancer, colorectal cancer, skin cancer, ovary cancer cell line), for example. In some embodiments, the cancer cell line is a breast cancer, prostate cancer or pancreatic cancer cell line. The cells sometimes are in a tissue, can be in a subject, at times are in a tumor, and sometimes are in a tumor in a subject. In certain embodiments, the method further comprises inducing cell apoptosis. Cells sometimes are from a subject having macular degeneration.

[0036] Also provided are methods for treating a condition related to aberrant cell proliferation, which comprise administering a compound described herein to a subject in need thereof in an amount effective to treat the cell proliferative condition. In certain embodiments the cell proliferative condition is a tumor-associated cancer. The cancer sometimes is of the breast, prostate, pancreas, lung, colorectum, skin, or ovary. In some embodiments, the cell proliferative condition is a non-tumor cancer, such as a hematopoietic cancer, for example. The cell proliferative condition is macular degeneration in some embodiments.

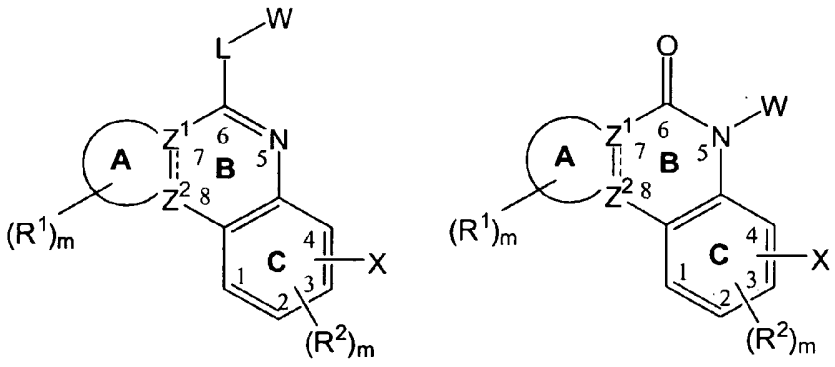
[0037] Provided also are methods for treating an immunological disorder, pain, or an inflammatory disorder in a subject in need of such treatment, comprising: administering to the subject a therapeutically effective amount of a therapeutic agent useful for treating such disorder; and administering to the subject a molecule that inhibits CK2, Pim or Flt in an amount that is effective to enhance a desired effect of the therapeutic agent. In certain embodiments, the molecule that inhibits CK2, Pim or Flt is a compound of Formula I or II as described herein, or a pharmaceutically acceptable salt thereof. In some embodiments, the molecule that inhibits CK2, Pim or Flt is a specific compound in one of the lists of compounds provided herein, or a pharmaceutically acceptable salt of one of these compounds. In some embodiments, the desired effect of the therapeutic agent that is enhanced by the molecule that inhibits CK2, Pim or Flt is a reduction in cell proliferation. In certain embodiments, the desired effect of the therapeutic agent that is enhanced by the molecule that inhibits CK2, Pim or Flt is an increase in apoptosis in at least one type of cell.

[0038] In some embodiments, the therapeutic agent and the molecule that inhibits CK2, Pim or Flt are administered at substantially the same time. The therapeutic agent and molecule that inhibits CK2, Pim or Flt sometimes are used concurrently by the subject. The therapeutic agent and the molecule that inhibits CK2, Pim or Flt are combined into one pharmaceutical composition in certain embodiments.

[0039] These and other embodiments of the invention are described in the description that follows.

MODES OF CARRYING OUT THE INVENTION

[0040] For convenience, and without regard to standard nomenclature, when the position of groups on the bicyclic core portion of Formula I and Formula II need to be described, the ring positions will be identified by number using the following numbering scheme:



(I) (II)

[0041] In this scheme, positions 1-4 are in the lower (phenyl) ring, and positions 5 (Nitrogen) through 8 are in the second ring. So, for example, the position of the polar substituent X on the phenyl ring may be described as position 4 if that group is attached to the unsubstituted carbon adjacent to the phenyl ring carbon attached to N in the second ring. Also for convenience, the phenyl ring is labeled as the C-ring in this structure and throughout the application, while the second ring containing N is referred to as the B-ring. The same relative numbering scheme will be used for other compounds that share the B and C ring bicyclic structure, while the additional ring containing Z^1-Z^2 fused to this bicyclic group will be referred to as the A-ring herein.

Definitions:

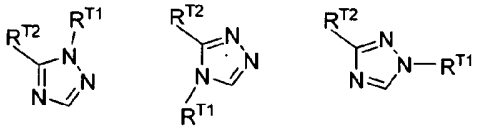
[0001] The terms "a" and "an" do not denote a limitation of quantity, but rather denote the presence of at least one of the referenced item. The terms "a" and "an" are used interchangeable with "one or more" or "at least one". The term "or" or "and/or" is used as a function word to indicate that two words or expressions are to be taken together or individually. The terms "comprising", "having", "including", and "containing" are to be construed as open-ended terms (i.e., meaning "including, but not limited to"). The endpoints of all ranges directed to the same component or property are inclusive and independently combinable.

[0002] The terms "compound(s) of the invention", "these compounds", "such compound(s)", "the compound(s)", and "the present compound(s)" refer to compounds encompassed by structural formulae disclosed herein, e.g., Formula (I), (Ia), (Ib), (Ic), (Id), (II), (IIa), (IIb), (IIc), and (Id), includes any specific compounds within these formulae whose structure is disclosed herein. Compounds may be identified either by their chemical structure and/or chemical name. When the chemical structure and chemical name conflict, the chemical structure is determinative of the identity of the compound. Furthermore, the present compounds can modulate, i.e., inhibit or enhance, the biological activity of a CK2 protein, a Pim protein or both, and thereby is also referred to herein as a "modulator(s)" or "CK2 and/or Pim modulator(s)". Compounds of Formula (I), (Ia), (Ib), (Ic), (Id), (II), (IIa), (IIb), (IIc), and (Id), including any specific compounds described herein are exemplary "modulators".

[0003] The compounds described herein may contain one or more chiral centers and/or double bonds and therefore, may exist as stereoisomers, such as double-bond isomers (*i.e.*, geometric isomers such as *E* and *Z*), enantiomers or diastereomers. The invention includes each of the isolated stereoisomeric forms as well as mixtures of stereoisomers in varying degrees of chiral purity, including racemic mixtures and mixtures of diastereomers. Accordingly, the chemical structures depicted herein encompass all possible enantiomers and stereoisomers of the illustrated compounds including the stereoisomerically pure form (*e.g.*, geometrically pure, enantiomerically pure or diastereomerically pure)

and enantiomeric and stereoisomeric mixtures. Enantiomeric and stereoisomeric mixtures can be resolved into their component enantiomers or stereoisomers using separation techniques or chiral synthesis techniques well known to the skilled artisan. The invention includes each of the isolated stereoisomeric forms as well as mixtures of stereoisomers in varying degrees of chiral purity, including racemic mixtures. It also encompasses the various diastereomers. Other structures may appear to depict a specific isomer, but that is merely for convenience, and is not intended to limit the invention to the depicted olefin isomer.

[0004] The compounds may also exist in several tautomeric forms, and the depiction herein of one tautomer is for convenience only, and is also understood to encompass other tautomers of the form shown. Accordingly, the chemical structures depicted herein encompass all possible tautomeric forms of the illustrated compounds. The term "tautomer" as used herein refers to isomers that change into one another with great ease so that they can exist together in equilibrium. For example, ketone and enol are two tautomeric forms of one compound. In another example, a substituted 1,2,4-triazole derivative may exist in at least three tautomeric forms as shown below:



R^{T1} is H or optionally substituted alkyl,
R^{T2} is an optionally substituted aryl.

[0042] The compounds of the invention often have ionizable groups so as to be capable of preparation as salts. In that case, wherever reference is made to the compound, it is understood in the art that a pharmaceutically acceptable salt may also be used. These salts may be acid addition salts involving inorganic or organic acids or the salts may, in the case of acidic forms of the compounds of the invention be prepared from inorganic or organic bases. Frequently, the compounds are prepared or used as pharmaceutically acceptable salts prepared as addition products of pharmaceutically acceptable acids or bases. Suitable pharmaceutically acceptable acids and bases are well-known in the art, such as hydrochloric, sulphuric, hydrobromic, acetic, lactic, citric, or tartaric acids for forming acid addition salts, and potassium hydroxide, sodium hydroxide, ammonium hydroxide, caffeine, various amines, and the like for forming basic salts. Methods for preparation of the appropriate salts are well-established in the art. In some cases, the compounds may contain both an acidic and a basic functional group, in which case they may have two ionized groups and yet have no net charge. Standard methods for the preparation of pharmaceutically acceptable salts and their formulations are well known in the art, and are disclosed in various references, including for example, "Remington: The Science and Practice of Pharmacy", A. Gennaro, ed., 20th edition, Lippincott, Williams & Wilkins, Philadelphia, PA.

[0043] "Solvate", as used herein, means a compound formed by solvation (the combination of solvent molecules with molecules or ions of the solute), or an aggregate that consists of a solute ion or molecule, i.e., a compound of the invention, with one or more solvent molecules. When water is the

solvent, the corresponding solvate is "hydrate". Examples of hydrate include, but are not limited to, hemihydrate, monohydrate, dihydrate, trihydrate, hexahydrate, etc. It should be understood by one of ordinary skill in the art that the pharmaceutically acceptable salt, and/or prodrug of the present compound may also exist in a solvate form. The solvate is typically formed via hydration which is either part of the preparation of the present compound or through natural absorption of moisture by the anhydrous compound of the present invention.

[0044] The term "ester" means any ester of a present compound in which any of the -COOH functions of the molecule is replaced by a -COOR function, in which the R moiety of the ester is any carbon-containing group which forms a stable ester moiety, including but not limited to alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclyl, heterocyclylalkyl and substituted derivatives thereof. The hydrolysable esters of the present compounds are the compounds whose carboxyls are present in the form of hydrolysable ester groups. That is, these esters are pharmaceutically acceptable and can be hydrolyzed to the corresponding carboxyl acid *in vivo*. These esters may be conventional ones, including lower alkanoyloxyalkyl esters, e.g. pivaloyloxymethyl and 1-pivaloyloxyethyl esters; lower alkoxycarbonylalkyl esters, e.g., methoxycarbonyloxymethyl, 1-ethoxycarbonyloxyethyl, and 1-isopropylcarbonyloxyethyl esters; lower alkoxymethyl esters, e.g., methoxymethyl esters, lactonyl esters, benzofuran keto esters, thiobenzofuran keto esters; lower alkanoylaminomethyl esters, e.g., acetylaminomethyl esters. Other esters can also be used, such as benzyl esters and cyano methyl esters. Other examples of these esters include: (2,2-dimethyl-1-oxypropyloxy)methyl esters; (1RS)-1-acetoxyethyl esters, 2-[(2-methylpropyloxy)carbonyl]-2-pentenyl esters, 1-[[(1-methylethoxy)carbonyl]- oxy]ethyl esters; isopropyloxycarbonyloxyethyl esters, (5-methyl-2-oxo-1,3- dioxole-4-yl) methyl esters, 1-[[(cyclohexyloxy)carbonyl]oxy]ethyl esters; 3,3-dimethyl-2-oxobutyl esters. It is obvious to those skilled in the art that hydrolysable esters of the compounds of the present invention can be formed at free carboxyls of said compounds by using conventional methods. Representative esters include pivaloyloxymethyl esters, isopropyloxycarbonyloxyethyl esters and (5-methyl-2-oxo-1,3-dioxole-4-yl)methyl esters.

[0045] The term "prodrug" refers to a precursor of a pharmaceutically active compound wherein the precursor itself may or may not be pharmaceutically active but, upon administration, will be converted, either metabolically or otherwise, into the pharmaceutically active compound or drug of interest. For example, prodrug can be an ester, ether, or amide form of a pharmaceutically active compound. Various types of prodrug have been prepared and disclosed for a variety of pharmaceuticals. See, for example, Bundgaard, H. and Moss, J., J. Pharm. Sci. 78: 122-126 (1989). Thus, one of ordinary skill in the art knows how to prepare these prodrugs with commonly employed techniques of organic synthesis.

[0046] "Protecting group" refers to a grouping of atoms that when attached to a reactive functional group in a molecule masks, reduces or prevents reactivity of the functional group. Examples of protecting groups can be found in Green *et al.*, "Protective Groups in Organic Chemistry", (Wiley, 2nd ed.

1991) and Harrison *et al.*, "Compendium of Synthetic Organic Methods", Vols. 1-8 (John Wiley and Sons, 1971-1996). Representative amino protecting groups include, but are not limited to, formyl, acetyl, trifluoroacetyl, benzyl, benzyloxycarbonyl ("CBZ"), *tert*-butoxycarbonyl ("Boc"), trimethylsilyl ("TMS"), 2-trimethylsilyl-ethanesulfonyl ("SES"), trityl and substituted trityl groups, allyloxycarbonyl, 9-fluorenylmethyloxycarbonyl ("FMOC"), nitro-veratryloxycarbonyl ("NVOC") and the like. Representative hydroxy protecting groups include, but are not limited to, those where the hydroxy group is either acylated or alkylated such as benzyl, and trityl ethers as well as alkyl ethers, tetrahydropyranyl ethers, trialkylsilyl ethers and allyl ethers.

[0047] As used herein, "pharmaceutically acceptable" means suitable for use in contact with the tissues of humans and animals without undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio, and effective for their intended use within the scope of sound medical judgment.

[0048] "Excipient" refers to a diluent, adjuvant, vehicle, or carrier with which a compound is administered.

[0049] An "effective amount" or "therapeutically effective amount" is the quantity of the present compound in which a beneficial outcome is achieved when the compound is administered to a patient or alternatively, the quantity of compound that possesses a desired activity in vivo or in vitro. In the case of proliferative disorders, a beneficial clinical outcome includes reduction in the extent or severity of the symptoms associated with the disease or disorder and/or an increase in the longevity and/or quality of life of the patient compared with the absence of the treatment. For example, for a subject with cancer, a "beneficial clinical outcome" includes a reduction in tumor mass, a reduction in the rate of tumor growth, a reduction in metastasis, a reduction in the severity of the symptoms associated with the cancer and/or an increase in the longevity of the subject compared with the absence of the treatment. The precise amount of compound administered to a subject will depend on the type and severity of the disease or condition and on the characteristics of the patient, such as general health, age, sex, body weight and tolerance to drugs. It will also depend on the degree, severity and type of proliferative disorder. The skilled artisan will be able to determine appropriate dosages depending on these and other factors.

[0050] As used herein, the terms "alkyl," "alkenyl" and "alkynyl" include straight-chain, branched-chain and cyclic monovalent hydrocarbyl radicals, and combinations of these, which contain only C and H when they are unsubstituted. Examples include methyl, ethyl, isobutyl, cyclohexyl, cyclopentylethyl, 2-propenyl, 3-butynyl, and the like. The total number of carbon atoms in each such group is sometimes described herein, *e.g.*, when the group can contain up to ten carbon atoms it can be represented as 1-10C or as C1-C10 or C1-10. When heteroatoms (N, O and S typically) are allowed to replace carbon atoms as in heteroalkyl groups, for example, the numbers describing the group, though still written as *e.g.* C1-C6, represent the sum of the

number of carbon atoms in the group plus the number of such heteroatoms that are included as replacements for carbon atoms in the backbone of the ring or chain being described.

[0051] Typically, the alkyl, alkenyl and alkynyl substituents of the invention contain 1-10C (alkyl) or 2-10C (alkenyl or alkynyl). Preferably they contain 1-8C (alkyl) or 2-8C (alkenyl or alkynyl). Sometimes they contain 1-4C (alkyl) or 2-4C (alkenyl or alkynyl). A single group can include more than one type of multiple bond, or more than one multiple bond; such groups are included within the definition of the term "alkenyl" when they contain at least one carbon-carbon double bond, and are included within the term "alkynyl" when they contain at least one carbon-carbon triple bond.

[0052] Alkyl, alkenyl and alkynyl groups are often optionally substituted to the extent that such substitution makes sense chemically. Typical substituents include, but are not limited to, halo, =O, =N-CN, =N-OR, =NR, OR, NR_2, SR, SO_2R, SO_2NR_2, $NRSO_2R$, $NRCONR_2$, $NRCSNR_2$, $NRC(=NR)NR_2$, NRCOOR, NRCOR, CN, C≡CR, COOR, $CONR_2$, OOCR, COR, and NO_2, wherein each R is independently H, C1-C8 alkyl, C2-C8 heteroalkyl, C1-C8 acyl, C2-C8 heteroacyl, C2-C8 alkenyl, C2-C8 heteroalkenyl, C2-C8 alkynyl, C2-C8 heteroalkynyl, C6-C10 aryl, or C5-C10 heteroaryl, and each R is optionally substituted with halo, =O, =N-CN, =N-OR', =NR', OR', NR'_2, SR', SO_2R', $SO_2NR'_2$, $NR'SO_2R'$, $NR'CONR'_2$, $NR'CSNR'_2$, $NR'C(=NR')NR'_2$, NR'COOR', NR'COR', CN, C≡CR', COOR', $CONR'_2$, OOCR', COR', and NO_2, wherein each R' is independently H, C1-C8 alkyl, C2-C8 heteroalkyl, C1-C8 acyl, C2-C8 heteroacyl, C6-C10 aryl or C5-C10 heteroaryl. Alkyl, alkenyl and alkynyl groups can also be substituted by C1-C8 acyl, C2-C8 heteroacyl, C6-C10 aryl or C5-C10 heteroaryl, each of which can be substituted by the substituents that are appropriate for the particular group. Where two R or R' are present on the same atom (e.g., NR_2), or on adjacent atoms that are bonded together (e.g., -NR-C(O)R), the two R or R; groups can be taken together with the atoms they are connected to to form a 5-8 membered ring, which can be substituted with C1-C4 alkyl, C1-C4 acyl, halo, C1-C4 alkoxy, and the like, and can contain an additional heteroatom selected from N, O and S as a ring member.

[0053] "Optionally substituted" as used herein indicates that the particular group or groups being described may have no non-hydrogen substituents, or the group or groups may have one or more non-hydrogen substituents. If not otherwise specified, the total number of such substituents that may be present is equal to the number of H atoms present on the unsubstituted form of the group being described. Where an optional substituent is attached via a double bond,

such as a carbonyl oxygen (=O), the group takes up two available valences, so the total number of substituents that may be included is reduced according to the number of available valences.

[0054] "Substituted," when used to modify a specified group or radical, means that one or more hydrogen atoms of the specified group or radical are each, independently of one another, replaced with the same or different substituent(s).

[0055] Substituent groups useful for substituting saturated carbon atoms in the specified group or radical include, but are not limited to $-R^a$, halo, $-O^-$, =O, $-OR^b$, $-SR^b$, $-S^-$, =S, $-NR^cR^c$, $=NR^b$, $=N-OR^b$, trihalomethyl, $-CF_3$, -CN, -OCN, -SCN, -NO, $-NO_2$, $=N_2$, $-N_3$, $-S(O)_2R^b$, $-S(O)_2NR^b$, $-S(O)_2O^-$, $-S(O)_2OR^b$, $-OS(O)_2R^b$, $-OS(O)_2O^-$, $-OS(O)_2OR^b$, $-P(O)(O^-)_2$, $-P(O)(OR^b)(O^-)$, $-P(O)(OR^b)(OR^b)$, $-C(O)R^b$, $-C(S)R^b$, $-C(NR^b)R^b$, $-C(O)O^-$, $-C(O)OR^b$, $-C(S)OR^b$, $-C(O)NR^cR^c$, $-C(NR^b)NR^cR^c$, $-OC(O)R^b$, $-OC(S)R^b$, $-OC(O)O^-$, $-OC(O)OR^b$, $-OC(S)OR^b$, $-NR^bC(O)R^b$, $-NR^bC(S)R^b$, $-NR^bC(O)O^-$, $-NR^bC(O)OR^b$, $-NR^bC(S)OR^b$, $-NR^bC(O)NR^cR^c$, $-NR^bC(NR^b)R^b$ and $-NR^bC(NR^b)NR^cR^c$, where R^a is selected from the group consisting of alkyl, cycloalkyl, heteroalkyl, cycloheteroalkyl, aryl, arylalkyl, heteroaryl and heteroarylalkyl; each R^b is independently hydrogen or R^a; and each R^c is independently R^b or alternatively, the two R^cs may be taken together with the nitrogen atom to which they are bonded form a 4-, 5-, 6- or 7-membered cycloheteroalkyl which may optionally include from 1 to 4 of the same or different additional heteroatoms selected from the group consisting of O, N and S. As specific examples, $-NR^cR^c$ is meant to include $-NH_2$, -NH-alkyl, N-pyrrolidinyl and N-morpholinyl. As another specific example, a substituted alkyl is meant to include –alkylene-O-alkyl, -alkylene-heteroaryl, -alkylene-cycloheteroalkyl, -alkylene-$C(O)OR^b$, -alkylene-$C(O)NR^bR^b$, and $-CH_2-CH_2-C(O)-CH_3$. The one or more substituent groups, taken together with the atoms to which they are bonded, may form a cyclic ring including cycloalkyl and cycloheteroalkyl.

[0056] Similarly, substituent groups useful for substituting unsaturated carbon atoms in the specified group or radical include, but are not limited to, $-R^a$, halo, $-O^-$, $-OR^b$, $-SR^b$, $-S^-$, $-NR^cR^c$, trihalomethyl, $-CF_3$, -CN, -OCN, -SCN, -NO, $-NO_2$, $-N_3$, $-S(O)_2R^b$, $-S(O)_2O^-$, $-S(O)_2OR^b$, $-OS(O)_2R^b$, $-OS(O)_2O^-$, $-OS(O)_2OR^b$, $-P(O)(O^-)_2$, $-P(O)(OR^b)(O^-)$, $-P(O)(OR^b)(OR^b)$, $-C(O)R^b$, $-C(S)R^b$, $-C(NR^b)R^b$, $-C(O)O^-$, $-C(O)OR^b$, $-C(S)OR^b$, $-C(O)NR^cR^c$, $-C(NR^b)NR^cR^c$, $-OC(O)R^b$, $-OC(S)R^b$, $-OC(O)O^-$, $-OC(O)OR^b$, $-OC(S)OR^b$, $-NR^bC(O)R^b$, $-NR^bC(S)R^b$, $-NR^bC(O)O^-$, $-NR^bC(O)OR^b$, $-NR^bC(S)OR^b$, $-NR^bC(O)NR^cR^c$, $-NR^bC(NR^b)R^b$ and $-NR^bC(NR^b)NR^cR^c$, where R^a, R^b and R^c are as previously defined.

[0057] Substituent groups useful for substituting nitrogen atoms in heteroalkyl and cycloheteroalkyl groups include, but are not limited to, $-R^a$, $-O^-$, $-OR^b$, $-SR^b$, $-S^-$, $-NR^cR^c$, trihalomethyl, $-CF_3$, -CN, -NO, $-NO_2$, $-S(O)_2R^b$, $-S(O)_2O^-$, $-S(O)_2OR^b$, $-OS(O)_2R^b$, $-OS(O)_2O^-$, $-OS(O)_2OR^b$, $-P(O)(O^-)_2$, $-P(O)(OR^b)(O^-)$, $-P(O)(OR^b)(OR^b)$, $-C(O)R^b$, $-C(S)R^b$, $-C(NR^b)R^b$, $-C(O)OR^b$, $-C(S)OR^b$, $-C(O)NR^cR^c$, $-C(NR^b)NR^cR^c$, $-OC(O)R^b$, $-OC(S)R^b$, $-OC(O)OR^b$, $-OC(S)OR^b$, $-NR^bC(O)R^b$, $-NR^bC(S)R^b$, $-NR^bC(O)OR^b$,

$-NR^bC(S)OR^b$, $-NR^bC(O)NR^cR^c$, $-NR^bC(NR^b)R^b$ and $-NR^bC(NR^b)NR^cR^c$, where R^a, R^b and R^c are as previously defined.

[0058] "Acetylene" substituents are 2-10C alkynyl groups that are optionally substituted, and are of the formula $-C\equiv C-R^a$, wherein R^a is H or C1-C8 alkyl, C2-C8 heteroalkyl, C2-C8 alkenyl, C2-C8 heteroalkenyl, C2-C8 alkynyl, C2-C8 heteroalkynyl, C1-C8 acyl, C2-C8 heteroacyl, C6-C10 aryl, C5-C10 heteroaryl, C7-C12 arylalkyl, or C6-C12 heteroarylalkyl, and each R^a group is optionally substituted with one or more substituents selected from halo, =O, =N-CN, =N-OR', =NR', OR', NR'_2, SR', SO_2R', $SO_2NR'_2$, NR'SO_2R', NR'CONR'$_2$, NR'CSNR'$_2$, NR'C(=NR')NR'$_2$, NR'COOR', NR'COR', CN, COOR', CONR'$_2$, OOCR', COR', and NO_2, wherein each R' is independently H, C1-C6 alkyl, C2-C6 heteroalkyl, C1-C6 acyl, C2-C6 heteroacyl, C6-C10 aryl, C5-C10 heteroaryl, C7-12 arylalkyl, or C6-12 heteroarylalkyl, each of which is optionally substituted with one or more groups selected from halo, C1-C4 alkyl, C1-C4 heteroalkyl, C1-C6 acyl, C1-C6 heteroacyl, hydroxy, amino, and =O; and wherein two R' can be linked to form a 3-7 membered ring optionally containing up to three heteroatoms selected from N, O and S. In some embodiments, R^a of $-C\equiv C-R^a$ is H or Me. Where two R or R' are present on the same atom (e.g., NR_2), or on adjacent atoms that are bonded together (e.g., -NR-C(O)R), the two R or R; groups can be taken together with the atoms they are connected to to form a 5-8 membered ring, which can be substituted with C1-C4 alkyl, C1-C4 acyl, halo, C1-C4 alkoxy, and the like, and can contain an additional heteroatom selected from N, O and S as a ring member.

[0059] "Heteroalkyl", "heteroalkenyl", and "heteroalkynyl" and the like are defined similarly to the corresponding hydrocarbyl (alkyl, alkenyl and alkynyl) groups, but the 'hetero' terms refer to groups that contain 1-3 O, S or N heteroatoms or combinations thereof within the backbone residue; thus at least one carbon atom of a corresponding alkyl, alkenyl, or alkynyl group is replaced by one of the specified heteroatoms to form a heteroalkyl, heteroalkenyl, or heteroalkynyl group. The typical and preferred sizes for heteroforms of alkyl, alkenyl and alkynyl groups are generally the same as for the corresponding hydrocarbyl groups, and the substituents that may be present on the heteroforms are the same as those described above for the hydrocarbyl groups. For reasons of chemical stability, it is also understood that, unless otherwise specified, such groups do not include more than two contiguous heteroatoms except where an oxo group is present on N or S as in a nitro or sulfonyl group.

[0060] While "alkyl" as used herein includes cycloalkyl and cycloalkylalkyl groups, the term "cycloalkyl" may be used herein to describe a carbocyclic non-aromatic group that is

connected via a ring carbon atom, and "cycloalkylalkyl" may be used to describe a carbocyclic non-aromatic group that is connected to the molecule through an alkyl linker. Similarly, "heterocyclyl" may be used to describe a non-aromatic cyclic group that contains at least one heteroatom as a ring member and that is connected to the molecule via a ring atom, which may be C or N; and "heterocyclylalkyl" may be used to describe such a group that is connected to another molecule through a linker. The sizes and substituents that are suitable for the cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl groups are the same as those described above for alkyl groups. As used herein, these terms also include rings that contain a double bond or two, as long as the ring is not aromatic.

[0061] As used herein, "acyl" encompasses groups comprising an alkyl, alkenyl, alkynyl, aryl or arylalkyl radical attached at one of the two available valence positions of a carbonyl carbon atom, and heteroacyl refers to the corresponding groups wherein at least one carbon other than the carbonyl carbon has been replaced by a heteroatom chosen from N, O and S. Thus heteroacyl includes, for example, -C(=O)OR and $-C(=O)NR_2$ as well as –C(=O)-heteroaryl.

[0062] Acyl and heteroacyl groups are bonded to any group or molecule to which they are attached through the open valence of the carbonyl carbon atom. Typically, they are C1-C8 acyl groups, which include formyl, acetyl, pivaloyl, and benzoyl, and C2-C8 heteroacyl groups, which include methoxyacetyl, ethoxycarbonyl, and 4-pyridinoyl. The hydrocarbyl groups, aryl groups, and heteroforms of such groups that comprise an acyl or heteroacyl group can be substituted with the substituents described herein as generally suitable substituents for each of the corresponding component of the acyl or heteroacyl group.

[0063] "Aromatic" moiety or "aryl" moiety refers to a monocyclic or fused bicyclic moiety having the well-known characteristics of aromaticity; examples include phenyl and naphthyl. Similarly, "heteroaromatic" and "heteroaryl" refer to such monocyclic or fused bicyclic ring systems which contain as ring members one or more heteroatoms selected from O, S and N. The inclusion of a heteroatom permits aromaticity in 5-membered rings as well as 6-membered rings. Typical heteroaromatic systems include monocyclic C5-C6 aromatic groups such as pyridyl, pyrimidyl, pyrazinyl, thienyl, furanyl, pyrrolyl, pyrazolyl, thiazolyl, oxazolyl, and imidazolyl and the fused bicyclic moieties formed by fusing one of these monocyclic groups with a phenyl ring or with any of the heteroaromatic monocyclic groups to form a C8-C10 bicyclic group such as indolyl, benzimidazolyl, indazolyl, benzotriazolyl, isoquinolyl, quinolyl, benzothiazolyl, benzofuranyl, pyrazolopyridyl, quinazolinyl, quinoxalinyl, cinnolinyl, and the like. Any monocyclic or fused ring bicyclic system which has the characteristics of aromaticity in terms of

electron distribution throughout the ring system is included in this definition. It also includes bicyclic groups where at least the ring which is directly attached to the remainder of the molecule has the characteristics of aromaticity. Typically, the ring systems contain 5-12 ring member atoms. Preferably the monocyclic heteroaryls contain 5-6 ring members, and the bicyclic heteroaryls contain 8-10 ring members.

[0064] Aryl and heteroaryl moieties may be substituted with a variety of substituents including C1-C8 alkyl, C2-C8 alkenyl, C2-C8 alkynyl, C5-C12 aryl, C1-C8 acyl, and heteroforms of these, each of which can itself be further substituted; other substituents for aryl and heteroaryl moieties include halo, OR, NR_2, SR, SO_2R, SO_2NR_2, $NRSO_2R$, $NRCONR_2$, $NRCSNR_2$, $NRC(=NR)NR_2$, NRCOOR, NRCOR, CN, C≡CR, COOR, $CONR_2$, OOCR, COR, and NO_2, wherein each R is independently H, C1-C8 alkyl, C2-C8 heteroalkyl, C2-C8 alkenyl, C2-C8 heteroalkenyl, C2-C8 alkynyl, C2-C8 heteroalkynyl, C6-C10 aryl, C5-C10 heteroaryl, C7-C12 arylalkyl, or C6-C12 heteroarylalkyl, and each R is optionally substituted as described above for alkyl groups. Where two R or R' are present on the same atom (e.g., NR_2), or on adjacent atoms that are bonded together (e.g., -NR-C(O)R), the two R or R; groups can be taken together with the atoms they are connected to to form a 5-8 membered ring, which can be substituted with C1-C4 alkyl, C1-C4 acyl, halo, C1-C4 alkoxy, and the like, and can contain an additional heteroatom selected from N, O and S as a ring member.

[0065] The substituent groups on an aryl or heteroaryl group may of course be further substituted with the groups described herein as suitable for each type of such substituents or for each component of the substituent. Thus, for example, an arylalkyl substituent may be substituted on the aryl portion with substituents described herein as typical for aryl groups, and it may be further substituted on the alkyl portion with substituents described herein as typical or suitable for alkyl groups.

[0066] Similarly, "arylalkyl" and "heteroarylalkyl" refer to aromatic and heteroaromatic ring systems which are bonded to their attachment point through a linking group such as an alkylene, including substituted or unsubstituted, saturated or unsaturated, cyclic or acyclic linkers. Typically the linker is C1-C8 alkyl or a hetero form thereof. These linkers may also include a carbonyl group, thus making them able to provide substituents as an acyl or heteroacyl moiety. An aryl or heteroaryl ring in an arylalkyl or heteroarylalkyl group may be substituted with the same substituents described above for aryl groups. Preferably, an arylalkyl group includes a phenyl ring optionally substituted with the groups defined above for aryl groups and a C1-C4 alkylene that is unsubstituted or is substituted with one or two C1-C4 alkyl groups or heteroalkyl

groups, where the alkyl or heteroalkyl groups can optionally cyclize to form a ring such as cyclopropane, dioxolane, or oxacyclopentane. Similarly, a heteroarylalkyl group preferably includes a C5-C6 monocyclic heteroaryl group that is optionally substituted with the groups described above as substituents typical on aryl groups and a C1-C4 alkylene that is unsubstituted or is substituted with one or two C1-C4 alkyl groups or heteroalkyl groups, or it includes an optionally substituted phenyl ring or C5-C6 monocyclic heteroaryl and a C1-C4 heteroalkylene that is unsubstituted or is substituted with one or two C1-C4 alkyl or heteroalkyl groups, where the alkyl or heteroalkyl groups can optionally cyclize to form a ring such as cyclopropane, dioxolane, or oxacyclopentane.

[0067] Where an arylalkyl or heteroarylalkyl group is described as optionally substituted, the substituents may be on either the alkyl or heteroalkyl portion or on the aryl or heteroaryl portion of the group. The substituents optionally present on the alkyl or heteroalkyl portion are the same as those described above for alkyl groups generally; the substituents optionally present on the aryl or heteroaryl portion are the same as those described above for aryl groups generally.

[0068] "Arylalkyl" groups as used herein are hydrocarbyl groups if they are unsubstituted, and are described by the total number of carbon atoms in the ring and alkylene or similar linker. Thus a benzyl group is a C7-arylalkyl group, and phenylethyl is a C8-arylalkyl.

[0069] "Heteroarylalkyl" as described above refers to a moiety comprising an aryl group that is attached through a linking group, and differs from "arylalkyl" in that at least one ring atom of the aryl moiety or one atom in the linking group is a heteroatom selected from N, O and S. The heteroarylalkyl groups are described herein according to the total number of atoms in the ring and linker combined, and they include aryl groups linked through a heteroalkyl linker; heteroaryl groups linked through a hydrocarbyl linker such as an alkylene; and heteroaryl groups linked through a heteroalkyl linker. Thus, for example, C7-heteroarylalkyl would include pyridylmethyl, phenoxy, and N-pyrrolylmethoxy.

[0070] "Alkylene" as used herein refers to a divalent hydrocarbyl group; because it is divalent, it can link two other groups together. Typically it refers to $-(CH_2)_n-$ where n is 1-8 and preferably n is 1-4, though where specified, an alkylene can also be substituted by other groups, and can be of other lengths, and the open valences need not be at opposite ends of a chain. Thus $-CH(Me)-$ and $-C(Me)_2-$ may also be referred to as alkylenes, as can a cyclic group such as cyclopropan-1,1-diyl. Where an alkylene group is substituted, the substituents include those typically present on alkyl groups as described herein.

[0071] In general, any alkyl, alkenyl, alkynyl, acyl, or aryl or arylalkyl group or any heteroform of one of these groups that is contained in a substituent may itself optionally be substituted by additional substituents. The nature of these substituents is similar to those recited with regard to the primary substituents themselves if the substituents are not otherwise described. Thus, where an embodiment of, for example, R^7 is alkyl, this alkyl may optionally be substituted by the remaining substituents listed as embodiments for R^7 where this makes chemical sense, and where this does not undermine the size limit provided for the alkyl *per se*; *e.g.*, alkyl substituted by alkyl or by alkenyl would simply extend the upper limit of carbon atoms for these embodiments, and is not included. However, alkyl substituted by aryl, amino, alkoxy, =O, and the like would be included within the scope of the invention, and the atoms of these substituent groups are not counted in the number used to describe the alkyl, alkenyl, etc. group that is being described. Where no number of substituents is specified, each such alkyl, alkenyl, alkynyl, acyl, or aryl group may be substituted with a number of substituents according to its available valences; in particular, any of these groups may be substituted with fluorine atoms at any or all of its available valences, for example.

[0072] "Heteroform" as used herein refers to a derivative of a group such as an alkyl, aryl, or acyl, wherein at least one carbon atom of the designated carbocyclic group has been replaced by a heteroatom selected from N, O and S. Thus the heteroforms of alkyl, alkenyl, alkynyl, acyl, aryl, and arylalkyl are heteroalkyl, heteroalkenyl, heteroalkynyl, heteroacyl, heteroaryl, and heteroarylalkyl, respectively. It is understood that no more than two N, O or S atoms are ordinarily connected sequentially, except where an oxo group is attached to N or S to form a nitro or sulfonyl group.

[0073] "Halo", as used herein includes fluoro, chloro, bromo and iodo. Fluoro and chloro are often preferred.

[0074] "Amino" as used herein refers to NH_2, but where an amino is described as "substituted" or "optionally substituted", the term includes NR'R" wherein each R' and R" is independently H, or is an alkyl, alkenyl, alkynyl, acyl, aryl, or arylalkyl group or a heteroform of one of these groups, and each of the alkyl, alkenyl, alkynyl, acyl, aryl, or arylalkyl groups or heteroforms of one of these groups is optionally substituted with the substituents described herein as suitable for the corresponding group. The term also includes forms wherein R' and R" are linked together to form a 3-8 membered ring which may be saturated, unsaturated or aromatic and which contains 1-3 heteroatoms independently selected from N, O and S as ring members, and which is optionally substituted with the substituents described as suitable for alkyl

groups or, if NR'R" is an aromatic group, it is optionally substituted with the substituents described as typical for heteroaryl groups.

[0075] As used herein, the term "carbocycle" refers to a cyclic compound containing only carbon atoms in the ring, whereas a "heterocycle" refers to a cyclic compound comprising a heteroatom. The carbocyclic and heterocyclic structures encompass compounds having monocyclic, bicyclic or multiple ring systems. As used herein, these terms also include rings that contain a double bond or two, as long as the ring is not aromatic.

[0076] As used herein, the term "heteroatom" refers to any atom that is not carbon or hydrogen, such as nitrogen, oxygen or sulfur.

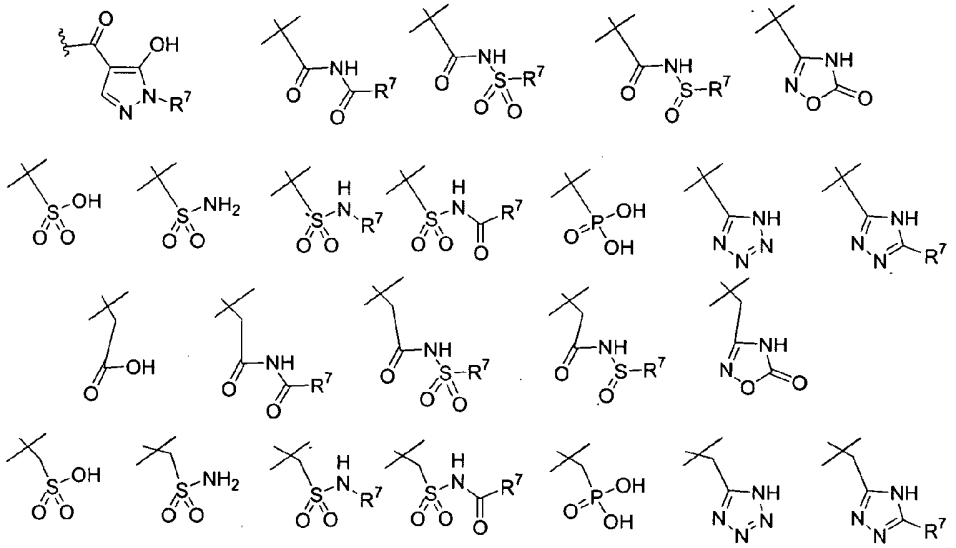
[0077] Illustrative examples of heterocycles include but are not limited to tetrahydrofuran, 1,3-dioxolane, 2,3-dihydrofuran, pyran, tetrahydropyran, benzofuran, isobenzofuran, 1,3-dihydro-isobenzofuran, isoxazole, 4,5-dihydroisoxazole, piperidine, pyrrolidine, pyrrolidin-2-one, pyrrole, pyridine, pyrimidine, octahydro-pyrrolo[3,4 b]pyridine, piperazine, pyrazine, morpholine, thiomorpholine, imidazole, imidazolidine 2,4-dione, 1,3-dihydrobenzimidazol-2-one, indole, thiazole, benzothiazole, thiadiazole, thiophene, tetrahydro thiophene 1,1-dioxide, diazepine, triazole, guanidine, diazabicyclo[2.2.1]heptane, 2,5- diazabicyclo[2.2.1]heptane, 2,3,4,4a,9,9a-hexahydro-1H-β-carboline, oxirane, oxetane, tetrahydropyran, dioxane, lactones, aziridine, azetidine, piperidine, lactams, and may also encompass heteroaryls. Other illustrative examples of heteroaryls include but are not limited to furan, pyrrole, pyridine, pyrimidine, imidazole, benzimidazole and triazole.

[0078] As used herein, the term "inorganic substituent" refers to substituents that do not contain carbon or contain carbon bound to elements other than hydrogen (e.g., elemental carbon, carbon monoxide, carbon dioxide, and carbonate). Examples of inorganic substituents include but are not limited to nitro, halogen, azido, cyano, sulfonyls, sulfinyls, sulfonates, phosphates, etc.

[0079] The term "polar substituent" as used herein refers to any substituent having an electric dipole, and optionally a dipole moment (e.g., an asymmetrical polar substituent has a dipole moment and a symmetrical polar substituent does not have a dipole moment). Polar substituents include substituents that accept or donate a hydrogen bond, and groups that would carry at least a partial positive or negative charge in aqueous solution at physiological pH levels. In certain embodiments, a polar substituent is one that can accept or donate electrons in a non-covalent hydrogen bond with another chemical moiety.

[0080] In certain embodiments, a polar substituent is selected from a carboxy, a carboxy bioisostere or other acid-derived moiety that exists predominately as an anion at a pH of about 7 to 8 or higher. Other polar substituents include, but are not limited to, groups containing an OH or NH, an ether oxygen, an amine nitrogen, an oxidized sulfur or nitrogen, a carbonyl, a nitrile, and a nitrogen-containing or oxygen-containing heterocyclic ring whether aromatic or non-aromatic. In some embodiments, the polar substituent (represented by X) is a carboxylate or a carboxylate bioisostere.

[0081] "Carboxylate bioisostere" or "carboxy bioisostere" as used herein refers to a moiety that is expected to be negatively charged to a substantial degree at physiological pH. In certain embodiments, the carboxylate bioisostere is a moiety selected from the group consisting of:



and salts of the foregoing, wherein each R^7 is independently H or an optionally substituted member selected from the group consisting of C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} heteroalkyl, C_{3-8} carbocyclic ring, and C_{3-8} heterocyclic ring optionally fused to an additional optionally substituted carbocyclic or heterocyclic ring; or R^7 is a C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} heteroalkyl substituted with an optionally substituted C_{3-8} carbocyclic ring or C_{3-8} heterocyclic ring.

[0082] In certain embodiments, the polar substituent is selected from the group consisting of carboxylic acid, carboxylic ester, carboxamide, tetrazole, triazole, oxadiazole, oxothiadiazole, thiazole, aminothiazole, hydroxythiazole, and carboxymethanesulfonamide,. In some embodiments of the compounds described herein, at least one polar substituent present is a

carboxylic acid or a salt, or ester or a bioisostere thereof. In certain embodiments, at least one polar substituent present is a carboxylic acid-containing substituent or a salt, ester or bioisostere thereof. In the latter embodiments, the polar substituent may be a C1-C10 alkyl or C1-C10 alkenyl linked to a carboxylic acid (or salt, ester or bioisostere thereof), for example.

[0083] The term 'solgroup' or 'solubility-enhancing group' as used herein refers to a molecular fragment selected for its ability to enhance physiological solubility of a compound that has otherwise relatively low solubility. Any substituent that can facilitate the dissolution of any particular molecule in water or any biological media can serve as a solubility-enhancing group. Examples of solubilizing groups are, but are not limited to: any substituent containing a group succeptible to being ionized in water at a pH range from 0 to 14; any ionizable group succeptible to form a salt; or any highly polar substituent, with a high dipolar moment and capable of forming strong interaction with molecules of water. Examples of solubilizing groups are, but are not limited to: substitued alkyl amines, substituted alkyl alcohols, alkyl ethers, aryl amines, pyridines, phenols, carboxylic acids, tetrazoles, sulfonamides, amides, sulfonylamides, sulfonic acids, sulfinic acids, phosphates, sulfonylureas.

[0084] Suitable groups for this purpose include, for example, groups of the formula -A-$(CH_2)_{0-4}$-G, where A is absent, O, or NR, where R is H or Me; and G can be a carboxy group, a carboxy bioisostere, hydroxy, phosphonate, sulfonate, or a group of the formula $-NR^y_2$ or $P(O)(OR^y)_2$, where each R^y is independently H or a C1-C4 alkyl that can be substituted with one or more (typically up to three) of these groups: NH_2, OH, NHMe, NMe_2, OMe, halo, or =O (carbonyl oxygen); and two Ry in one such group can be linked together to form a 5-7 membered ring, optionally containing an additional heteroatom (N, O or S) as a ring member, and optionally substituted with a C1-C4 alkyl, which can itself be substituted with one or more (typically up to three) of these groups: NH_2, OH, NHMe, NMe_2, OMe, halo, or =O (carbonyl oxygen).

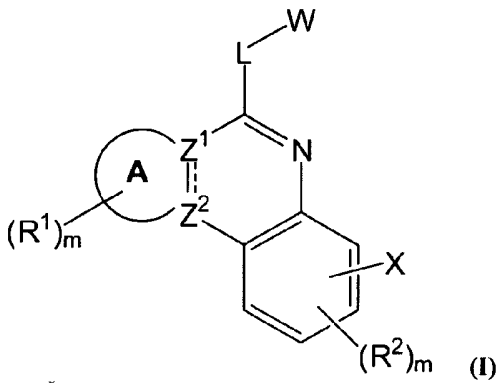
[0005] The terms "treat" and "treating" as used herein refer to ameliorating, alleviating, lessening, and removing symptoms of a disease or condition. A candidate molecule or compound described herein may be in a therapeutically effective amount in a formulation or medicament, which is an amount that can lead to a biological effect, such as apoptosis of certain cells (e.g., cancer cells), reduction of proliferation of certain cells, or lead to ameliorating, alleviating, lessening, or removing symptoms of a disease or condition, for example. The terms also can refer to reducing or stopping a cell proliferation rate (e.g., slowing or halting tumor growth) or reducing the number of proliferating cancer cells (e.g., removing part or all of a

tumor). These terms also are applicable to reducing a titre of a microorganism in a system (i.e., cell, tissue, or subject) infected with a microorganism, reducing the rate of microbial propagation, reducing the number of symptoms or an effect of a symptom associated with the microbial infection, and/or removing detectable amounts of the microbe from the system. Examples of microorganisms include but are not limited to virus, bacterium and fungus.

[0085] As used herein, the term "apoptosis" refers to an intrinsic cell self-destruction or suicide program. In response to a triggering stimulus, cells undergo a cascade of events including cell shrinkage, blebbing of cell membranes and chromatic condensation and fragmentation. These events culminate in cell conversion to clusters of membrane-bound particles (apoptotic bodies), which are thereafter engulfed by macrophages.

Embodiments of the Compounds:

[0086] In one aspect, the invention provides compounds of Formula I:



(I)

wherein:

A is a saturated or partially saturated optionally substituted 5, 6 or 7 membered ring;

----- represents a single bond or a double bond;

Z^1 and Z^2 are independently N or C when ----- represents a single bond, provided Z^1 and Z^2 are not both N; and

Z^1 and Z^2 are C when ----- represents a double bond;

L is a linker selected from a bond, NR^3, O, S, CR^4R^5, CR^4R^5-NR^3, CR^4R^5-O-, and CR^4R^5-S;

each R^1, R^2, R^3, R^4 and R^5 is independently H, or an optionally substituted member selected from the group consisting of C1-C8 alkyl, C2-C8 heteroalkyl, C2-C8 alkenyl, C2-C8 heteroalkenyl, C2-C8 alkynyl, C2-C8 heteroalkynyl, C1-C8 acyl, C2-C8 heteroacyl, C6-C10 aryl, C5-C12 heteroaryl, C7-C12 arylalkyl, and C6-C12 heteroarylalkyl group,

or halo, OR, NR_2, NROR, $NRNR_2$, SR, SOR, SO_2R, SO_2NR_2, $NRSO_2R$,

$NRCONR_2$, $NRCSNR_2$, $NRC(=NR)NR_2$, NRCOOR, NRCOR, CN, COOR, $CONR_2$, OOCR, COR, or NO_2,

wherein each R is independently H or C1-C8 alkyl, C2-C8 heteroalkyl, C2-C8 alkenyl, C2-C8 heteroalkenyl, C2-C8 alkynyl, C2-C8 heteroalkynyl, C1-C8 acyl, C2-C8 heteroacyl, C6-C10 aryl, C5-C10 heteroaryl, C7-C12 arylalkyl, or C6-C12 heteroarylalkyl,

and wherein two R on the same atom or on adjacent atoms can be linked to form a 3-8 membered ring, optionally containing one or more N, O or S;

and each R group, and each ring formed by linking two R groups together, is optionally substituted with one or more substituents selected from halo, =O, =N-CN, =N-OR', =NR', OR', NR'_2, SR', SO_2R', $SO_2NR'_2$, $NR'SO_2R'$, $NR'CONR'_2$, $NR'CSNR'_2$, $NR'C(=NR')NR'_2$, NR'COOR', NR'COR', CN, COOR', $CONR'_2$, OOCR', COR', and NO_2,

wherein each R' is independently H, C1-C6 alkyl, C2-C6 heteroalkyl, C1-C6 acyl, C2-C6 heteroacyl, C6-C10 aryl, C5-C10 heteroaryl, C7-12 arylalkyl, or C6-12 heteroarylalkyl, each of which is optionally substituted with one or more groups selected from halo, C1-C4 alkyl, C1-C4 heteroalkyl, C1-C6 acyl, C1-C6 heteroacyl, hydroxy, amino, and =O;

and wherein two R' on the same atom or on adjacent atoms can be linked to form a 3-7 membered ring optionally containing up to three heteroatoms selected from N, O and S;

and R^1 can be =O, or two R^1 groups on the same atom or on adjacent connected atoms, can optionally be linked together to form a 3-8 membered cycloalkyl or heterocycloalkyl, which is optionally substituted;

and R^4 and R^5, when on the same atom or on adjacent connected atoms, can optionally be linked together to form a 3-8 membered cycloalkyl or heterocycloalkyl, which is optionally substituted;

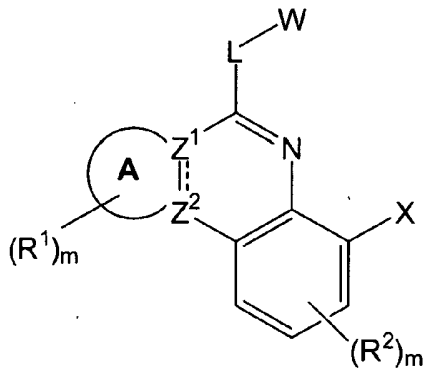
W is alkyl, heteroalkyl, aryl, heteroaryl, cycloalkyl, heterocyclyl, arylalkyl or heteroarylalkyl, each of which can be optionally substituted;

X is a polar substituent;

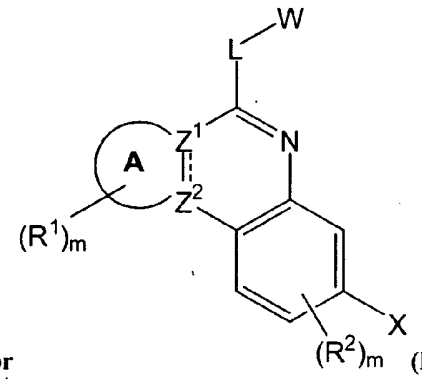
and each m is independently 0-3;

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

[0087] In some embodiments, the compound of Formula I has the structure of Formula I-A or I-B:



(I-A) or

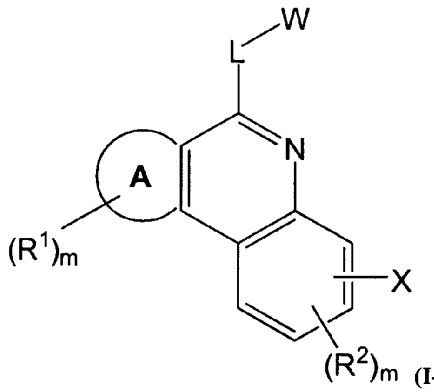


(I-B)

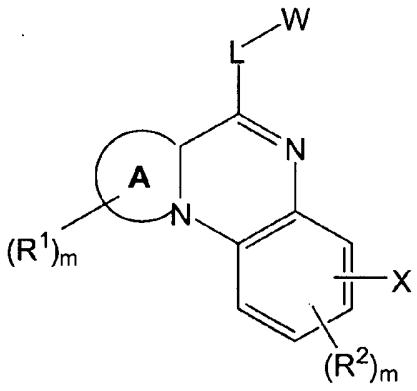
or a pharmaceutically acceptable salt, solvate, and/or prodrug thereof,

wherein A, Z^1, Z^2, L, W, X, R^1, R^2 and m are defined as in Formula I.

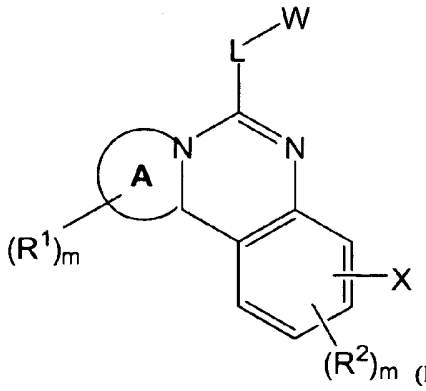
[0088] In other embodiments, the compound of Formula I has the structure of Formula I-C, I-D or I-E:



(I-C),



(I-D), or

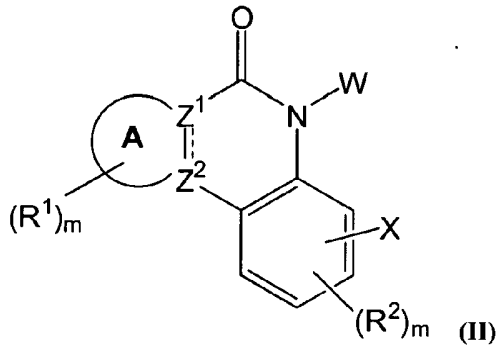


(I-E),

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

wherein A, L, W, X, R^1, R^2 and m are defined as in Formula I.

[0089] In another aspect, the invention provides compounds of Formula II:



(II)

wherein:

A is a saturated or partially saturated optionally substituted 5, 6 or 7 membered ring;

----- represents a single bond or a double bond;

Z^1 and Z^2 are independently N or C when ----- represents a single bond, provided Z^1 and Z^2 are not both N; and

Z^1 and Z^2 are C when ----- represents a double bond;

each of R^1 and R^2 is independently H, or an optionally substituted member selected from the group consisting of C1-C8 alkyl, C2-C8 heteroalkyl, C2-C8 alkenyl, C2-C8 heteroalkenyl, C2-C8 alkynyl, C2-C8 heteroalkynyl, C1-C8 acyl, C2-C8 heteroacyl, C6-C10 aryl, C5-C12 heteroaryl, C7-C12 arylalkyl, and C6-C12 heteroarylalkyl group,

or halo, OR, NR_2, NROR, $NRNR_2$, SR, SOR, SO_2R, SO_2NR_2, $NRSO_2R$, $NRCONR_2$, $NRCSNR_2$, $NRC(=NR)NR_2$, NRCOOR, NRCOR, CN, COOR, $CONR_2$, OOCR, COR, or NO_2,

wherein each R is independently H or C1-C8 alkyl, C2-C8 heteroalkyl, C2-C8 alkenyl, C2-C8 heteroalkenyl, C2-C8 alkynyl, C2-C8 heteroalkynyl, C1-C8 acyl, C2-C8 heteroacyl, C6-C10 aryl, C5-C10 heteroaryl, C7-C12 arylalkyl, or C6-C12 heteroarylalkyl,

and wherein two R on the same atom or on adjacent atoms can be linked to form a 3-8 membered ring, optionally containing one or more N, O or S;

and each R group, and each ring formed by linking two R groups together, is optionally substituted with one or more substituents selected from halo, =O, =N-CN, =N-OR', =NR', OR', NR'$_2$, SR', SO_2R',

$SO_2NR'_2$, $NR'SO_2R'$, $NR'CONR'_2$, $NR'CSNR'_2$, $NR'C(=NR')NR'_2$, NR'COOR', NR'COR', CN, COOR', $CONR'_2$, OOCR', COR', and NO_2,

wherein each R' is independently H, C1-C6 alkyl, C2-C6 heteroalkyl, C1-C6 acyl, C2-C6 heteroacyl, C6-C10 aryl, C5-C10 heteroaryl, C7-12 arylalkyl, or C6-12 heteroarylalkyl, each of which is optionally substituted with one or more groups selected from halo, C1-C4 alkyl, C1-C4 heteroalkyl, C1-C6 acyl, C1-C6 heteroacyl, hydroxy, amino, and =O;

and wherein two R' on the same atom or on adjacent atoms can be linked to form a 3-7 membered ring optionally containing up to three heteroatoms selected from N, O and S;

and R^1 can be =O, or two R^1 groups on the same atom or on adjacent connected atoms, can optionally be linked together to form a 3-8 membered cycloalkyl or heterocycloalkyl, which is optionally substituted;

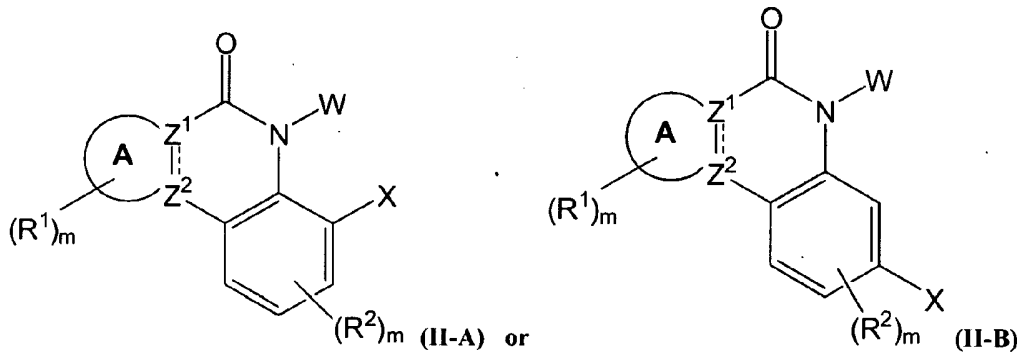
W is alkyl, heteroalkyl, aryl, heteroaryl, cycloalkyl, heterocyclyl, arylalkyl or heteroarylalkyl, each of which can be optionally substituted;

X is a polar substituent;

and each m is independently 0-3;

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

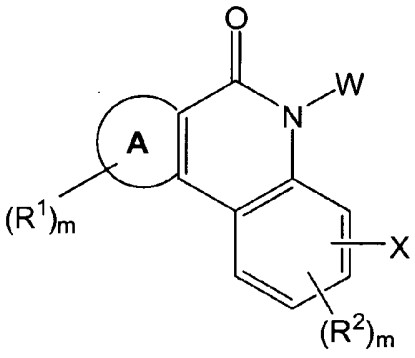
[0090] In some embodiments, the compound of Formula II has the structure of Formula II-A or II-B:



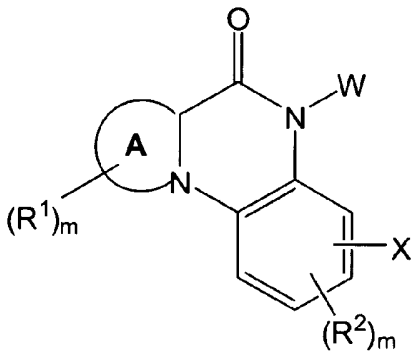
or a pharmaceutically acceptable salt, solvate, and/or prodrug thereof,

wherein A, Z^1, Z^2, W, X, R^1, R^2 and m are defined as in Formula II.

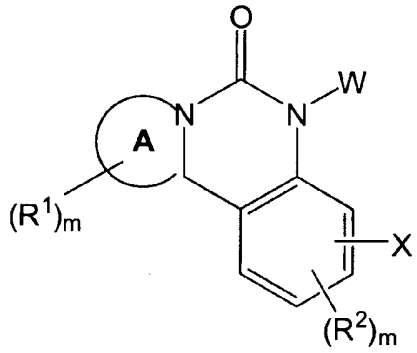
[0091] In other embodiments, the compound of Formula II has the structure of Formula II-C, II-D or II-E:



(II-C),



(II-D), or



(II-E),

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

wherein A, W, X, R^1, R^2 and m are defined as in Formula II.

[0092] It is understood that as described herein, compounds and embodiments of Formula I can include compounds of Formula I-A, I-B, I-C, I-D or I-E, and compounds of Formula II include compounds of Formula II-A, II-B, II-C, II-D and II-E.

[0093] In compounds of Formula I and II, A is a saturated or partially saturated optionally substituted 5-, 6- or 7-membered ring. The A-ring may be carbocyclic or heterocyclic ring that is saturated or partially saturated, and may be substituted by groups R^1 to the extent such groups make chemical sense.

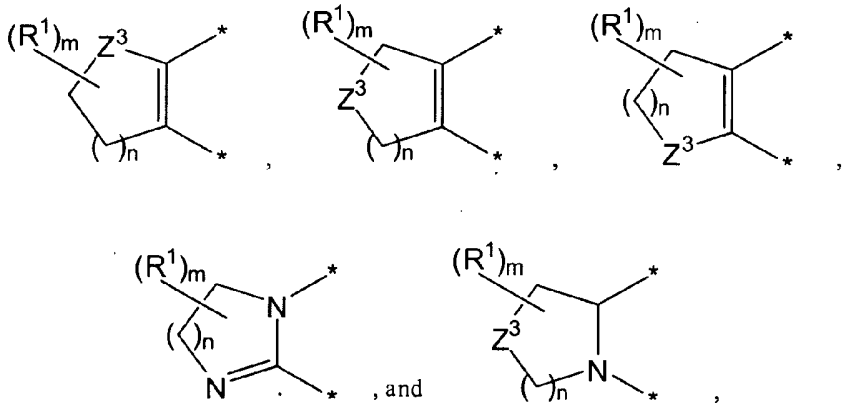
[0094] In some embodiments of Formula I and II, Z^1 and Z^2 are independently N or C and ----- represents a single bond, provided both of Z^1 and Z^2 are not N.

[0095] In other embodiments of Formula I and II, Z^1 and Z^2 are C and ----- represents a double bond.

[0096] In compounds of Formula I and II, the A-ring comprises an optionally substituted 5-7 membered ring. In some embodiments, the A-ring is an optionally substituted 5-7 membered ring carbocyclic ring. For example, ring A is an optionally substituted cyclopentane, cyclopentene, cyclohexane, cyclohexene, cycloheptane or cycloheptene ring.

[0097] In other embodiments, the A-ring comprises an optionally substituted 5-7 membered heterocyclic ring, containing at least one heteroatom selected from N, O, and S. In some such embodiments, one of Z^1 and Z^2 is N, and there are no additional heteroatoms in the A-ring. In other such embodiments, one of Z^1 and Z^2 is N, and there is an additional heteroatom selected from O, N and S in the A-ring. In certain embodiments, ring A is an optionally substituted dihydrofuran, tetrahydrofuran, dihydrothiophene, tetrahydrothiophene, dihydropyrrole, pyrrolidine, dihydropyran, tetrahydropyran, pyran, dihydrothiopyran, tetrahydrothiopyran, thiopyran, piperidine, dihydropyridine, tetrahydropyridine, imidazoline, thiazolidine, oxazolidine, dihydrothiazole, dihydrooxazole, morpholine, thiomorpholine, piperazine, dihydropyrimidine, azepine, dihydroazepine, tetrahydroazepine, hexahydroazepine ring, homomorpholine, homothiomorpholine, dizaepine, dihydrodiazepine, tetrahydrodiazepine, hexahydrodiazepine ring, oxepane, or thiooxepane ring.

[0098] Sometimes, the A-ring containing is selected from the group consisting of:



wherein Z^3 is CR^1_2, NR^1, $S(=O)_p$, or O;

n is 1-3; and

p is 0-2.

[0099] In compounds of Formula I, L is a linker selected from a bond, NR^3, O, S, CR^4R^5, CR^4R^5-NR^3, CR^4R^5-O-, and CR^4R^5-S. Where L is a two-atom linker, it can be attached to the ring system through either end, i.e., either the carbon atom or the heteroatom of CR^3R^4-NR^5, CR^3R^4-O-, and CR^3R^4-S can be attached to the ring, and the other atom is attached to L. In some embodiments, L is a bond, or a 1-2 atom linker, including $-N(R^3)$-, -O-, -S-, $-CH_2$- $N(R^3)$-

, - $N(R^3)$-CH_2-, -O-CH_2-, -CH_2-O-, -CH_2-S-, -S-CH_2-, -CMe_2 $N(R^3)$-, -CMe_2-O-, - $N(R^3)$-CMe_2, -O-CMe_2-, and the like. In certain embodiments, L is selected from a bond, NH, NMe, and - CH_2- $N(R^3)$- or - $N(R^3)$-CH_2-, where R^3 is H or Me.

[00100] In some embodiments of Formula I, L is NH or NMe. In other embodiments, L can be NAc, where Ac represents a C1-C10 acyl group, i.e., L is a group of the formula N-C(=O)-R^z, where R^z is H or a C1-C9 optionally substituted alkyl group. These can serve as pro-drugs for compounds where L is NH. In still other embodiments, L is a bond; in these embodiments, W is often an aryl or heteroaryl, which is optionally substituted.

[00101] In some embodiments of Formula I and II, W is selected from optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted arylalkyl, and optionally substituted heteroarylalkyl. For example, W can be an optionally substituted phenyl, pyridyl, pyrimidinyl, or pyrazinyl group; or a napthyl, indole; benzofuran, benzopyrazole, benzothiazole, quinoline, isoquinoline, quinazoline or quinoxaline group. Suitable substituents for these groups include, but are not limited to, halo, C1-C4 alkyl, C2-C4alkenyl or alkynyl, CN, OMe, COOMe, COOEt, $CONH_2$, CF_3, and the like, and typically the aryl group is substituted by up to 2 of these groups. In certain preferred embodiments, when W is aryl or heteroaryl, it is unsubstituted, or it is substituted by 1 or 2 substituents.

[00102] In some embodiments of Formula I and II, W is optionally substituted phenyl, optionally substituted heterocyclyl, or C1-C4 alkyl substituted with at least one member selected from the group consisting of optionally substituted phenyl, optionally substituted heteroalkyl, optionally substituted heteroaryl, halo, hydroxy and -$NR"_2$,

where each R" is independently H or optionally substituted C1-C6 alkyl;

and two R" taken together with the N to which they are attached can be linked together to form an optionally substituted 3-8 membered ring, which can contain another heteroatom selected from N, O and S as a ring member, and can be saturated, unsaturated or aromatic.

[00103] In some such compounds, W comprises at least one group of the formula $-(CH_2)_p$-NR^x_2,

where p is 1-4,

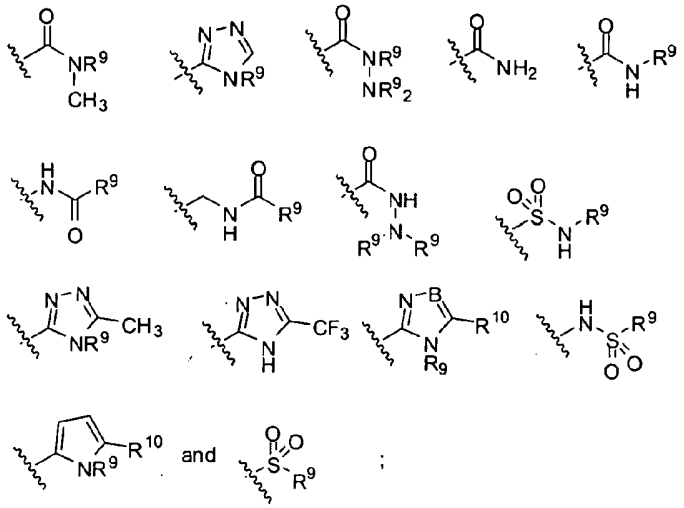
R^x is independently at each occurrence H or optionally substituted alkyl;

and two R^x taken together with the N to which they are attached can be linked together to form an optionally substituted 3-8 membered ring, which can contain another heteroatom selected from N, O and S as a ring member, and can be saturated, unsaturated or aromatic.

[00104] In some embodiments, W can be aryl (e.g., phenyl), heterocyclic (e.g., pyrrolidine, piperidine, morpholine, piperazine, thiomorpholine), or heteroaryl (e.g., pyrrole, pyridine, pyrazine, pyrimidine, furan, thiophene, thiazole, isothiazole, thiadiazole, oxazole, isoxazole, imidazole, pyrazole, triazole, triazine, tetrazole and the like, each of which can be substituted. In some such embodiments, it is selected from phenyl, pyrrolidine, piperidine, piperazine, morpholine, and the like. In other embodiments, W can be arylalkyl or heteroarylalkyl, where the aryl and heteroaryl moieties of these groups are selected from the groups described above, attached to a C_{1-6} and preferably a C_{1-4}alkylene or heteroalkylene moiety.

[00105] W can be substituted by a variety of substituents. In certain embodiments, W is an aryl ring substituted by a group of the formula $-(CH_2)_{0-4}-NR^x_2$, where each R^x can be H or C1-C4 alkyl, and can be substituted, and where two Rx can optionally cyclize into a ring. In some embodiments, this group is of the formula $-(CH_2)_{0-4}$-Az, where Az represents an azacyclic group such as pyrrolidine, piperidine, morpholine, piperazine, thiomorpholine, pyrrole, and the like. In some embodiments, this group is $-(CH_2)_{1-3}$-Az, where Az is 4-morpholinyl, 1-piperazinyl, 1-pyrrolidinyl, or 1-piperidinyl; $-CH_2-CH_2$-Az, where Az is 4-morpholinyl is one exemplary substituent for W, when W is substituted.

[00106] In some embodiments of Formula I and II, X is selected from the group consisting of $COOR^9$, $C(O)NR^9-OR^9$, triazole, tetrazole (preferably linked to the phenyl ring via the carbon atom of the tetrazole ring), CN, imidazole, carboxylate, a carboxylate bioisostere,



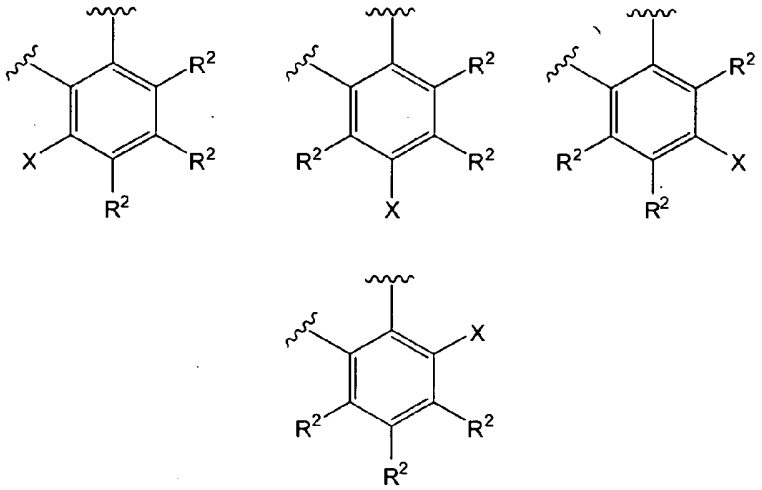
wherein each R^9 is independently H or an optionally substituted member selected from the group consisting of alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, arylalkyl, cycloalkylalkyl, heterocycloalkylalkyl, and heteroarylalkyl,

and two R^9 on the same or adjacent atoms can optionally be linked together to form an optionally substituted ring that can also contain an additional heteroatom selected from N, O and S as a ring member;

R^{10} is halo, CF_3, CN, SR, OR, NR_2, or R, where each R is independently H or optionally substituted C1-C6 alkyl, and two R on the same or adjacent atoms can optionally be linked together to form an optionally substituted ring that can also contain an additional heteroatom selected from N, O and S as a ring member;

and B is N or CR^{10}.

[00107] In compounds of Formula I and II, at least one polar substituent X may be at any position on the phenyl ring (C-ring), and the ring may include one, two, three or four polar substituents. In compounds of Formula I-A, I-B, II-A, and II-B, the molecule contains at least one polar group, X, at the position indicated by the structure, and the ring may include one, two, three or four polar substituents. In certain embodiments, there is one polar group, X, and each R^2 is H, or up to two R^2 are substituents described herein other than H, such as, for example only, Me, Et, halo (especially F or Cl), MeO, CF_3, $CONH_2$, or CN. A polar group can be at any position on the phenyl ring. In some embodiments, the phenyl ring is selected from the following options, which are oriented to match the orientation of Formula I herein, and depict the position of the polar substituent X:

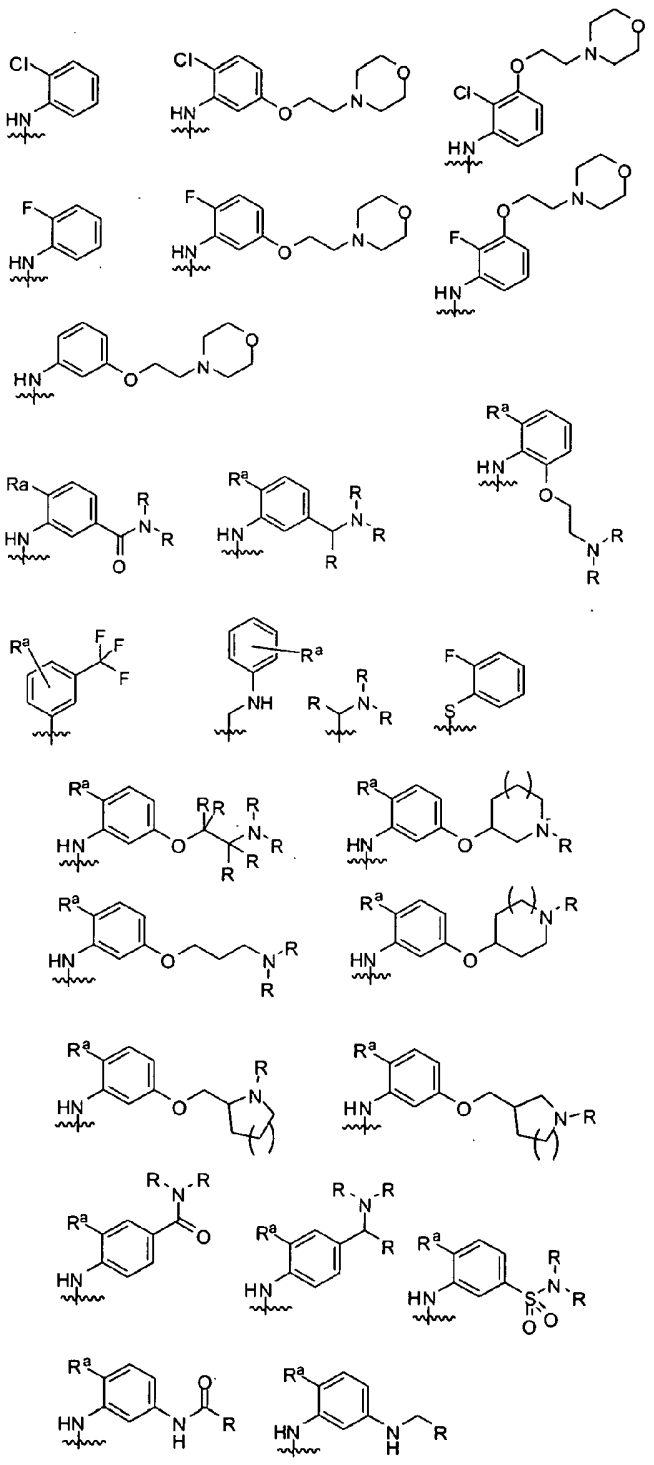


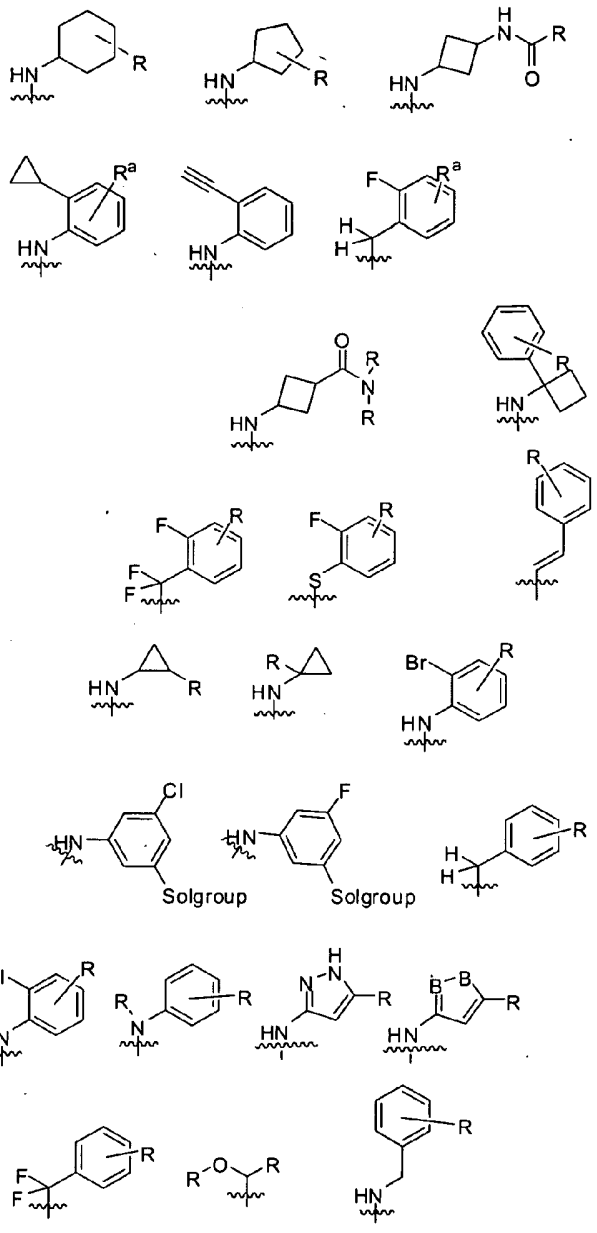
where X is a polar substituent and each R^2 is independently is selected from R^2 substituents, as defined above with respect to compounds of Formula I and II.

[00108] In some embodiments of the above-described compounds, the polar substituent X is located at position 4 on the phenyl ring. In alternative embodiments, the polar substituent X is located at position 3 on the phenyl ring. In certain embodiments, the polar substituent is a carboxylic acid or a tetrazole, and is at position 3 or 4 on the phenyl ring.

[00109] In some embodiments of these compounds, the phenyl ring (i.e., C-ring) is substituted by up to three additional substituents, in addition to the polar substituent X. Suitable substituents for the phenyl are described above. In some embodiments, these substituents are selected from halo, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 alkoxy, amino, C1-C4 alkylthio, and CN. In some embodiments, there is only one such substituent (i.e., m is 1), or there is no additional substituent besides the polar substituent X, i.e., m is 0.

[00110] In some embodiments of Formula I, –L-W is selected from:

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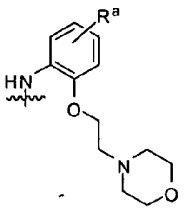
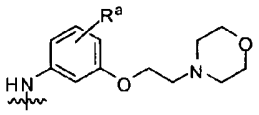
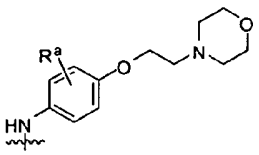
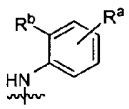
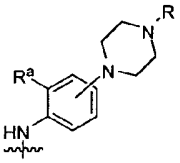
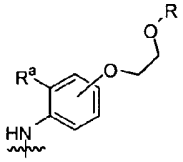
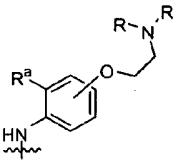








wherein each R^a is independently H, Cl or F;

each R^b is independently Me, F, or Cl;

each R is independently selected from H, halo, C1-C4 alkyl, C1-C4 alkoxy, and C1-C4 haloalkyl,

and two R groups on the same or adjacent connected atoms can optionally be linked together to form a 3-8 membered ring;

each B is N or CR;

and each Solgroup is a solubility-enhancing group.

Utilities of the Compounds:

[00111] In another aspect, the invention provides a method to treat cancer, a vascular disorder, inflammation, or a pathogenic infection, comprising administering to a subject in need of such treatment, an effective amount of any of the above-described compounds.

[0100] In another aspect, the invention provides a method to inhibit cell proliferation, which comprises contacting cells with a compound having a structure of Formula I or II, in an amount effective to inhibit proliferation of the cells. In certain embodiments, these cells are cells of a cancer cell line. In particular embodiments, the cancer cell line is a breast cancer, prostate cancer, pancreatic cancer, lung cancer, hemopoietic cancer, colorectal cancer, skin cancer, or an ovarian cancer cell line. Often, the cells are in a tumor in a subject, and the compound reduces the growth rate of the tumor, or reduces the size of the tumor, or reduces the aggressiveness of the tumor, or reduces the metastasis of the tumor. In some embodiments, the compound induces apoptosis.

[0101] In certain embodiments, the methods include contacting cells, especially tumor cells, with a compound having a structure of Formula I or II, which induces apoptosis.

[0102] In certain embodiments, the cells are from an eye of a subject having macular degeneration, and the treatment method reduces the severity or symptoms or further development of macular degeneration in the subject.

[0103] In another aspect, the invention provides a method to treat a condition related to aberrant cell proliferation, which comprises administering a compound having a structure of Formula I or II to a subject in need thereof, where the compound is administered in an amount effective to treat or ameliorate the cell proliferative condition. In certain embodiments, the cell proliferative condition is a tumor-associated cancer. Specific cancers for which the compounds are useful include breast cancer, prostate cancer, pancreatic cancer, lung cancer, hematopoietic cancer, colorectal cancer, skin cancer, and ovarian cancer, colorectum, liver, lymph node, colon, prostate, brain, head and neck, skin, kidney, blood and heart.

[0104] In other embodiments, the cell proliferative condition is a non-tumor cancer. Exemplary embodiments include hematopoietic cancers, such as lymphoma and leukemia.

[0105] In other embodiments, the cell proliferative condition is macular degeneration.

[0106] In another aspect, the invention provides a method for treating pain or inflammation in a subject, which comprises administering a compound of Formula I or II to a subject in need thereof, in an amount effective to treat or reduce the pain or the inflammation.

[0107] In another aspect, the invention provides a method for inhibiting angiogenesis in a subject, which comprises administering a compound of Formula I or II to a subject in need thereof in an amount effective to inhibit the angiogenesis.

[0108] The methods of treating these disorders comprise administering to a subject in need thereof an effective amount of an inhibitor compound of one of the formulae described herein.

[0109] The invention in part provides pharmaceutical compositions comprising at least one compound within the scope of the invention as described herein, and methods of using compounds described herein. For example, the invention in part provides methods for identifying a candidate molecule that interacts with a CK2, Pim or Flt protein, which comprises contacting a composition containing a CK2, Pim or Flt protein and a molecule described herein with a candidate molecule and determining whether the amount of the molecule described herein that interacts with the protein is modulated, whereby a candidate molecule that modulates the amount of the molecule described herein that interacts with the protein is identified as a candidate molecule that interacts with the protein.

[0110] Provided also are methods for modulating a protein kinase activity. Protein kinases catalyze the transfer of a gamma phosphate from adenosine triphosphate to a serine or threonine amino acid (serine/threonine protein kinase), tyrosine amino acid (tyrosine protein kinase), tyrosine, serine or threonine (dual specificity protein kinase) or histidine amino acid (histidine protein kinase) in a peptide or protein substrate. Thus, included herein are methods which comprise contacting a system comprising a protein kinase protein with a compound described herein in an amount effective for modulating (e.g., inhibiting) the activity of the protein kinase. In some embodiments, the activity of the protein kinase is the catalytic activity of the protein (e.g., catalyzing the transfer of a gamma phosphate from adenosine triphosphate to a peptide or protein substrate). In certain embodiments, provided are methods for identifying a candidate molecule that interacts with a protein kinase, which comprise: contacting a composition containing a protein kinase and a compound described herein with a candidate molecule under conditions in which the compound and the protein kinase interact, and determining whether the amount of the compound that interacts with the protein kinase is modulated relative to a control interaction between the compound and the protein kinase without the candidate molecule, whereby a candidate molecule that modulates the amount of the compound interacting with the protein kinase relative to the control interaction is identified as a candidate molecule that interacts with the protein kinase. Systems in such embodiments can be a cell-free system or a system comprising cells (e.g., *in vitro*). The protein kinase, the compound or the molecule in some embodiments is in association with a solid phase. In certain embodiments, the interaction between the compound and the protein kinase is detected via a detectable label, where in some embodiments the protein kinase comprises a detectable label and in certain embodiments the compound comprises a detectable label. The interaction between the compound and the protein kinase sometimes is detected without a detectable label.

[0111] Provided also are compositions of matter comprising a protein kinase and a compound described herein. In some embodiments, the protein kinase in the composition is a serine-threonine protein kinase or a tyrosine protein kinase. In certain embodiments, the protein kinase is a protein kinase fragment having compound-binding activity. In some embodiments, the protein kinase in the composition is, or contains a subunit (e.g., catalytic subunit, SH2 domain, SH3 domain) of, CK2, Pim subfamily protein kinase (e.g., PIM1, PIM2, PIM3) or Flt subfamily protein kinase (e.g, FLT1, FLT3, FLT4). In certain embodiments the composition is cell free and sometimes the protein kinase is a recombinant protein.

[0112] The protein kinase can be from any source, such as cells from a mammal, ape or human, for example. Examples of serine-threonine protein kinases that can be inhibited, or may potentially be inhibited, by compounds disclosed herein include without limitation human versions of CK2, CK2α2, Pim subfamily kinases (e.g., PIM1, PIM2, PIM3), CDK1/cyclinB, c-RAF, Mer, MELK, HIPK3, HIPK2 and ZIPK. A serine-threonine protein kinase sometimes is a member of a sub-family containing one or more of the following amino acids at positions corresponding to those listed in human CK2: leucine at position 45, methionine at position 163 and isoleucine at position 174. Examples of such protein kinases include without limitation human versions of CK2, STK10, HIPK2, HIPK3, DAPK3, DYK2 and PIM-1. Examples of tyrosine protein kinases that can be inhibited, or may potentially be inhibited, by compounds disclosed herein include without limitation human versions of Flt subfamily members (e.g., FLT1, FLT2, FLT3, FLT3 (D835Y), FLT4). An example of a dual specificity protein kinase that can be inhibited, or may potentially be inhibited, by compounds disclosed herein includes without limitation DYRK2. Nucleotide and amino acid sequences for protein kinases and reagents are publicly available (e.g., World Wide Web URLs ncbi.nlm.nih.gov/sites/entrez/ and Invitrogen.com). For example, various nucleotide sequences can be accessed using the following accession numbers: NM_002648.2 and NP_002639.1 for PIM1; NM_006875.2 and NP_006866.2 for PIM2; XM_938171.2 and XP_943264.2 for PIM3; NM_004119.2 and NP_004110.2 for FLT3; NM_002020.3 and NP_002011.2 for FLT4; and NM_002019.3 and NP_002010.2 for FLT1.

[0113] The invention also in part provides methods for treating a condition related to aberrant cell proliferation. For example, provided are methods of treating a cell proliferative condition in a subject, which comprises administering a compound described herein to a subject in need thereof in an amount effective to treat the cell proliferative condition. The subject may be a research animal (e.g., rodent, dog, cat, monkey), optionally containing a tumor such as a xenograft tumor (e.g., human tumor), for example, or may be a human. A cell proliferative condition sometimes is a tumor or non-tumor cancer, including but not limited to, cancers of the colorectum, breast, lung, liver, pancreas, lymph node, colon, prostate, brain, head and neck, skin, liver, kidney, blood and heart (e.g., leukemia, lymphoma, carcinoma).

[0114] Also provided are methods for treating a condition related to inflammation or pain. For example, provided are methods of treating pain in a subject, which comprise administering a compound described herein to a subject in need thereof in an amount effective to treat the pain. Provided also are methods of treating inflammation in a subject, which comprises administering

a compound described herein to a subject in need thereof in an amount effective to treat the inflammation. The subject may be a research animal (e.g., rodent, dog, cat, monkey), for example, or may be a human. Conditions associated with inflammation and pain include without limitation acid reflux, heartburn, acne, allergies and sensitivities, Alzheimer's disease, asthma, atherosclerosis, bronchitis, carditis, celiac disease, chronic pain, Crohn's disease, cirrhosis, colitis, dementia, dermatitis, diabetes, dry eyes, edema, emphysema, eczema, fibromyalgia, gastroenteritis, gingivitis, heart disease, hepatitis, high blood pressure, insulin resistance, interstitial cystitis, joint pain/arthritis/rheumatoid arthritis, metabolic syndrome (syndrome X), myositis, nephritis, obesity, osteopenia, glomerulonephritis (GN), juvenile cystic kidney disease, and type I nephronophthisis (NPHP), osteoporosis, Parkinson's disease, Guam-Parkinson dementia, supranuclear palsy, Kuf's disease, and Pick's disease, as well as memory impairment, brain ischemia, and schizophrenia, periodontal disease, polyarteritis, polychondritis, psoriasis, scleroderma, sinusitis, Sjögren's syndrome, spastic colon, systemic candidiasis, tendonitis, urinary track infections, vaginitis, inflammatory cancer (e.g., inflammatory breast cancer) and the like. Methods for determining effects of compounds herein on pain or inflammation are known. For example, formalin-stimulated pain behaviors in research animals can be monitored after administration of a compound described herein to assess treatment of pain (e.g., Li *et al., Pain 115(1-2)*: 182-90 (2005)). Also, modulation of pro-inflammatory molecules (e.g., IL-8, GRO-alpha, MCP-1, TNFalpha and iNOS) can be monitored after administration of a compound described herein to assess treatment of inflammation (e.g., Parhar *et al., Int J Colorectal Dis. 22(6)*: 601-9 (2006)), for example. Thus, also provided are methods for determining whether a compound herein reduces inflammation or pain, which comprise contacting a system with a compound described herein in an amount effective for modulating (e.g., inhibiting) the activity of a pain signal or inflammation signal. Provided also are methods for identifying a compound that reduces inflammation or pain, which comprise: contacting a system with a compound of one of the formulae described herein; and detecting a pain signal or inflammation signal, whereby a compound that modulates the pain signal relative to a control molecule is identified as a compound that reduces inflammation of pain. Non-limiting examples of pain signals are formalin-stimulated pain behaviors and examples of inflammation signals include without limitation a level of a pro-inflammatory molecule. The invention thus in part pertains to methods for modulating angiogenesis in a subject, and methods for treating a condition associated with aberrant angiogenesis in a subject. proliferative diabetic retinopathy.

[0115] CK2 has also been shown to play a role in the pathogenesis of atherosclerosis, and may prevent atherogenesis by maintaining laminar shear stress flow. CK2 plays a role in vascularization, and has been shown to mediate the hypoxia-induced activation of histone deacetylases (HDACs). CK2 is also involved in diseases relating to skeletal muscle and bone tissue, including, e.g., cardiomyocyte hypertrophy, heart failure, impaired insulin signaling and insulin resistance, hypophosphatemia and inadequate bone matrix mineralization.

[0116] Thus in one aspect, the invention provides methods to treat these conditions, comprising administering to a subject in need of such treatment an effect amount of a CK2 inhibitor, such as a compound of one of the formulae disclosed herein.

[0117] Also provided are methods for treating an angiogenesis condition, which comprise administering a compound described herein to a subject in need thereof, in an amount effective to treat the angiogenesis condition. Angiogenesis conditions include without limitation solid tumor cancers, varicose disease, and the like.

[0118] Also provided are methods for treating a condition associated with an aberrant immune response in a subject, which comprise administering a compound described herein to a subject in need thereof, in an amount effective to treat the condition. Conditions characterized by an aberrant immune response include without limitation, organ transplant rejection, asthma, autoimmune disorders, including rheumatoid arthritis, multiple sclerosis, myasthenia gravis, systemic lupus erythematosus, scleroderma, polymyositis, mixed connective tissue disease (MCTD),Crohn's disease, and ulcerative colitis. In certain embodiments, an immune response may be modulated by administering a compound herein in combination with a molecule that modulates (e.g., inhibits) the biological activity of an mTOR pathway member or member of a related pathway (e.g., mTOR, PI3 kinase, AKT). In certain embodiments the molecule that modulates the biological activity of an mTOR pathway member or member of a related pathway is rapamycin. In certain embodiments, provided herein is a composition comprising a compound described herein in combination with a molecule that modulates the biological activity of an mTOR pathway member or member of a related pathway, such as rapamycin, for example.

[0119] In preferred embodiments of the present invention, the compound is a compound of Formula I or II described in one of the lists of compounds provided herein, or a pharmaceutically acceptable salt of one of these compounds.

Compositions and Routes of Administration:

[0120] In another aspect, the invention provides pharmaceutical compositions (i.e., formulations). The pharmaceutical compositions can comprise a compound of the present invention, as described herein which is admixed with at least one pharmaceutically acceptable excipient or carrier. Frequently, the composition comprises at least two pharmaceutically acceptable excipients or carriers.

[0121] While the compositions and methods of the present invention will typically be used in therapy for human patients, they may also be used in veterinary medicine to treat similar or identical diseases. The compositions may, for example, be used to treat mammals, including, but not limited to, primates and domesticated mammals. The compositions may, for example be used to treat herbivores. The compositions of the present invention include geometric and optical isomers of one or more of the drugs, wherein each drug is a racemic mixture of isomers or one or more purified isomers.

[0122] Pharmaceutical compositions suitable for use in the present invention include compositions wherein the active ingredients are contained in an effective amount to achieve the intended purpose. Determination of the effective amounts is well within the capability of those skilled in the art, especially in light of the detailed disclosure provided herein.

[0123] The compounds of the present invention may exist as pharmaceutically acceptable salts. The present invention includes such salts. The term "pharmaceutically acceptable salts" is meant to include salts of active compounds which are prepared with relatively nontoxic acids or bases, depending on the particular substituent moieties found on the compounds described herein. When compounds of the present invention contain relatively acidic functionalities, base addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired base, either neat or in a suitable inert solvent. Included are base addition salts such as sodium, potassium, calcium, ammonium, organic amino, or magnesium salt, or a similar salt. When compounds of the present invention contain relatively basic functionalities, acid addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired acid, either neat or in a suitable inert solvent. Examples of acceptable acid addition salts include those derived from inorganic acids like hydrochloric, hydrobromic, nitric, carbonic, monohydrogencarbonic, phosphoric, monohydrogenphosphoric, dihydrogenphosphoric, sulfuric, monohydrogensulfuric, hydriodic, or phosphorous acids and the like, as well as the salts derived from relatively nontoxic organic acids, for example, acetic,

propionic, isobutyric, maleic, malonic, benzoic, succinic, suberic, fumaric, lactic, mandelic, phthalic, benzenesulfonic, p-tolylsulfonic, citric, tartaric, methanesulfonic, and the like. Also included are salts of amino acids such as arginate and the like, and salts of organic acids like glucuronic or galactunoric acids and the like (see, for example, Berge et al., "Pharmaceutical Salts", *Journal of Pharmaceutical Science*, 1977, 66, 1-19). Certain specific compounds of the present invention contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts.

[0124] Examples of applicable salt forms include hydrochlorides, hydrobromides, sulfates, methanesulfonates, nitrates, maleates, acetates, citrates, fumarates, tartrates (eg (+)-tartrates, (-)-tartrates or mixtures thereof, including racemic mixtures), succinates, benzoates and salts with amino acids such as glutamic acid. These salts may be prepared by methods known to those skilled in art.

[0125] The neutral forms of the compounds are preferably regenerated by contacting the salt with a base or acid and isolating the parent compound in the conventional manner. The parent form of the compound differs from the various salt forms in certain physical properties, such as solubility in polar solvents.

[0126] The pharmaceutically acceptable esters in the present invention refer to non-toxic esters, preferably the alkyl esters such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl or pentyl esters, of which the methyl ester is preferred. However, other esters such as phenyl-C_{1-5} alkyl may be employed if desired. Ester derivatives of certain compounds may act as prodrugs which, when absorbed into the bloodstream of a warm-blooded animal, may cleave in such a manner as to release the drug form and permit the drug to afford improved therapeutic efficacy.

[0127] Certain compounds of the present invention can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms are equivalent to unsolvated forms and are encompassed within the scope of the present invention. Certain compounds of the present invention may exist in multiple crystalline or amorphous forms. In general, all physical forms are equivalent for the uses contemplated by the present invention and are intended to be within the scope of the present invention.

[0128] When used as a therapeutic the compounds described herein often are administered with a physiologically acceptable carrier. A physiologically acceptable carrier is a formulation to which the compound can be added to dissolve it or otherwise facilitate its administration. Examples of physiologically acceptable carriers include, but are not limited to, water, saline, physiologically buffered saline.

[0129] Unless otherwise stated, structures depicted herein are also meant to include compounds which differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures except for the replacement of a hydrogen by a deuterium or tritium, or the replacement of a carbon by ^{13}C- or ^{14}C-enriched carbon are within the scope of this invention. The compounds of the present invention may also contain unnatural proportions of atomic isotopes at one or more of atoms that constitute such compounds. For example, the compounds may be radiolabeled with radioactive isotopes, such as for example tritium (3H), iodine-125 (^{125}I) or carbon-14 (^{14}C). All isotopic variations of the compounds of the present invention, whether radioactive or not, are encompassed within the scope of the present invention.

[0130] In addition to salt forms, the present invention provides compounds that are in a prodrug form. Prodrugs of the compounds described herein are those compounds that readily undergo chemical changes under physiological conditions to provide the compounds of the present invention. Additionally, prodrugs can be converted to the compounds of the present invention by chemical or biochemical methods in an ex vivo environment. For example, prodrugs can be slowly converted to the compounds of the present invention when placed in a transdermal patch reservoir with a suitable enzyme or chemical reagent.

[0131] The descriptions of compounds of the present invention are limited by principles of chemical bonding known to those skilled in the art. Accordingly, where a group may be substituted by one or more of a number of substituents, such substitutions are selected so as to comply with principles of chemical bonding and to give compounds which are not inherently unstable and/or would be known to one of ordinary skill in the art as likely to be unstable under ambient conditions, such as aqueous, neutral, and several known physiological conditions. For example, a heterocycloalkyl or heteroaryl is attached to the remainder of the molecule via a ring heteroatom in compliance with principles of chemical bonding known to those skilled in the art thereby avoiding inherently unstable compounds.

[0132] Any suitable formulation of a compound described above can be prepared for administration. Any suitable route of administration may be used, including, but not limited to, oral, parenteral, intravenous, intramuscular, transdermal, topical and subcutaneous routes. Depending on the subject to be treated, the mode of administration, and the type of treatment desired -- *e.g.*, prevention, prophylaxis, therapy; the compounds are formulated in ways consonant with these parameters. Preparation of suitable formulations for each route of administration are known in the art. A summary of such formulation methods and techniques is

found in Remington's Pharmaceutical Sciences, latest edition, Mack Publishing Co., Easton, PA, which is incorporated herein by reference. Other examples of drug formulations can be found in Liberman, H. A. and Lachman, L., Eds., Pharmaceutical Dosage Forms, Marcel Decker, New York, N.Y., 1980. The formulation of each substance or of the combination of two substances will generally include a diluent as well as, in some cases, adjuvants, buffers, preservatives and the like. The substances to be administered can be administered also in liposomal compositions or as microemulsions.

[0133] For injection, formulations can be prepared in conventional forms as liquid solutions or suspensions or as solid forms suitable for solution or suspension in liquid prior to injection or as emulsions. Suitable excipients include, for example, water, saline, dextrose, glycerol and the like. Such compositions may also contain amounts of nontoxic auxiliary substances such as wetting or emulsifying agents, pH buffering agents and the like, such as, for example, sodium acetate, sorbitan monolaurate, and so forth.

[0134] Various sustained release systems for drugs have also been devised, and can be applied to compounds of the invention. See, for example, U.S. patent No. 5,624,677, the methods of which are incorporated herein by reference.

[0135] Systemic administration may also include relatively noninvasive methods such as the use of suppositories, transdermal patches, transmucosal delivery and intranasal administration. Oral administration is also suitable for compounds of the invention. Suitable forms include syrups, capsules, tablets, as is understood in the art.

[0136] For administration to animal or human subjects, the appropriate dosage of the a compound described above often is 0.01 to 15 mg/kg, and sometimes 0.1 to 10 mg/kg. Dosage levels are dependent on the nature of the condition, drug efficacy, the condition of the patient, the judgment of the practitioner, and the frequency and mode of administration; however, optimization of such parameters is within the ordinary level of skill in the art.

Therapeutic Combinations:

[0137] Compounds of the invention may be used alone or in combination with another therapeutic agent. The invention provides methods to treat conditions such as cancer, inflammation and immune disorders by administering to a subject in need of such treatment a therapeutically effective amount of a therapeutic agent useful for treating said disorder and administering to the same subject a therapeutically effective amount of a modulator of the present invention, i.e., a compound of the invention. The therapeutic agent and the modulator

may be "co-administered", i.e, administered together, either as separate pharmaceutical compositions or admixed in a single pharmaceutical composition. By "administered together", the therapeutic agent and the modulator may also be administered separately, including at different times and with different frequencies. The modulator may be administered by any known route, such as orally, intravenously, intramuscularly, nasally, and the like; and the therapeutic agent may also be administered by any conventional route. In many embodiments, at least one and optionally both of the modulator and the therapeutic agent may be administered orally. Preferably, the modulator is an inhibitor, and it may inhibit either one of CK2 and Pim, or both of them to provide the treatment effects described herein.

[0138] In certain embodiments, a "modulator" as described above may be used in combination with a therapeutic agent that can act by binding to regions of DNA that can form certain quadruplex structures. In such embodiments, the therapeutic agents have anticancer activity on their own, but their activity is enhanced when they are used in combination with a modulator. This synergistic effect allows the therapeutic agent to be administered in a lower dosage while achieving equivalent or higher levels of at least one desired effect.

[0139] A modulator may be separately active for treating a cancer. For combination therapies described above, when used in combination with a therapeutic agent, the dosage of a modulator will frequently be two-fold to ten-fold lower than the dosage required when the modulator is used alone to treat the same condition or subject. Determination of a suitable amount of the modulator for use in combination with a therapeutic agent is readily determined by methods known in the art.

[0140] Compounds and compositions of the invention may be used in combination with anticancer or other agents, such as palliative agents, that are typically administered to a patient being treated for cancer. Such "anticancer agents" include, e.g., classic chemotherapeutic agents, as well as molecular targeted therapeutic agents, biologic therapy agents, and radiotherapeutic agents.

[0141] When a compound or composition of the invention is used in combination with an anticancer agent to another agent, the present invention provides, for example, simultaneous, staggered, or alternating treatment. Thus, the compound of the invention may be administered at the same time as an anticancer agent, in the same pharmaceutical composition; the compound of the invention may be administered at the same time as the anticancer agent, in separate pharmaceutical compositions; the compound of the invention may be administered before the

anticancer agent, or the anticancer agent may be administered before the compound of the invention, for example, with a time difference of seconds, minutes, hours, days, or weeks.

[0142] In examples of a staggered treatment, a course of therapy with the compound of the invention may be administered, followed by a course of therapy with the anticancer agent, or the reverse order of treatment may be used, and more than one series of treatments with each component may also be used. In certain examples of the present invention, one component, for example, the compound of the invention or the anticancer agent, is administered to a mammal while the other component, or its derivative products, remains in the bloodstream of the mammal. For example, a compound for formulae (I)-(IV) may be administered while the anticancer agent or its derivative products remains in the bloodstream, or the anticancer agent may be administered while the compound of formulae (I)-(IV) or its derivatives remains in the bloodstream. In other examples, the second component is administered after all, or most of the first component, or its derivatives, have left the bloodstream of the mammal.

[0143] The compound of the invention and the anticancer agent may be administered in the same dosage form, e.g., both administered as intravenous solutions, or they may be administered in different dosage forms, e.g., one compound may be administered topically and the other orally. A person of ordinary skill in the art would be able to discern which combinations of agents would be useful based on the particular characteristics of the drugs and the cancer involved.

[0144] Anticancer agents useful in combination with the compounds of the present invention may include agents selected from any of the classes known to those of ordinary skill in the art, including, but not limited to, antimicrotubule agents such as diterpenoids and vinca alkaloids; platinum coordination complexes; alkylating agents such as nitrogen mustards, oxazaphosphorines, alkylsulfonates, nitrosoureas, and triazenes; antibiotic agents such as anthracyclins, actinomycins and bleomycins; topoisomerase II inhibitors such as epipodophyllotoxins; antimetabolites such as purine and pyrimidine analogues and anti-folate compounds; topoisomerase I inhibitors such as camptothecins; hormones and hormonal analogues; signal transduction pathway inhibitors; nonreceptor tyrosine kinase angiogenesis inhibitors; immunotherapeutic agents; pro-apoptotic agents; and cell cycle signaling inhibitors; and other agents described below.

[0145] Anti-microtubule or anti-mitotic agents are phase specific agents that are typically active against the microtubules of tumor cells during M or the mitosis phase of the cell

cycle. Examples of anti-microtubule agents include, but are not limited to, diterpenoids and vinca alkaloids.

[0146] Plant alkaloid and terpenoid derived agents include mitotic inhibitors such as the vinca alkaloids vinblastine, vincristine, vindesine, and vinorelbine; and microtubule polymer stabilizers such as the taxanes, including, but not limited to paclitaxel, docetaxel, larotaxel, ortataxel, and tesetaxel.

[0147] Diterpenoids, which are derived from natural sources, are phase specific anti-cancer agents that are believed to operate at the G2/M phases of the cell cycle. It is believed that the diterpenoids stabilize the p-tubulin subunit of the microtubules, by binding with this protein. Disassembly of the protein appears then to be inhibited with mitosis being arrested and cell death following.

[0148] Examples of diterpenoids include, but are not limited to, taxanes such as paclitaxel, docetaxel, larotaxel, ortataxel, and tesetaxel. Paclitaxel is a natural diterpene product isolated from the Pacific yew tree *Taxus brevifolia* and is commercially available as an injectable solution TAXOL®. Docetaxel is a semisynthetic derivative of paclitaxel *q. v.*, prepared using a natural precursor, 10-deacetyl-baccatin III, extracted from the needle of the European Yew tree. Docetaxel is commercially available as an injectable solution as TAXOTERE®.

[0149] Vinca alkaloids are phase specific anti-neoplastic agents derived from the periwinkle plant. Vinca alkaloids that are believed to act at the M phase (mitosis) of the cell cycle by binding specifically to tubulin. Consequently, the bound tubulin molecule is unable to polymerize into microtubules. Mitosis is believed to be arrested in metaphase with cell death following. Examples of vinca alkaloids include, but are not limited to, vinblastine, vincristine, vindesine, and vinorelbine. Vinblastine, vincaleukoblastine sulfate, is commercially available as VELBAN® as an injectable solution. Vincristine, vincaleukoblastine 22-oxo-sulfate, is commercially available as ONCOVIN® as an injectable solution. Vinorelbine, is commercially available as an injectable solution of vinorelbine tartrate (NAVELBINE®), and is a semisynthetic vinca alkaloid derivative.

[0150] Platinum coordination complexes are non-phase specific anti-cancer agents, which are interactive with DNA. The platinum complexes are believed to enter tumor cells, undergo, aquation and form intra- and interstrand crosslinks with DNA causing adverse biological effects to the tumor. Platinum-based coordination complexes include, but are not limited to cisplatin, carboplatin, nedaplatin, oxaliplatin, satraplatin, and (SP-4-3)-(cis)-

amminedichloro-[2-methylpyridine] platinum(II). Cisplatin, cis-diamminedichloroplatinum, is commercially available as PLATINOL® as an injectable solution. Carboplatin, platinum, diammine [1, 1-cyclobutane-dicarboxylate(2-)-0,0'], is commercially available as PARAPLATIN® as an injectable solution.

[0151] Alkylating agents are generally non-phase specific agents and typically are strong electrophiles. Typically, alkylating agents form covalent linkages, by alkylation, to DNA through nucleophilic moieties of the DNA molecule such as phosphate, amino, sulfhydryl, hydroxyl, carboxyl, and imidazole groups. Such alkylation disrupts nucleic acid function leading to cell death. Examples of alkylating agents include, but are not limited to, alkyl sulfonates such as busulfan; ethyleneimine and methylmelamine derivatives such as altretamine and thiotepa; nitrogen mustards such as chlorambucil, cyclophosphamide, estramustine, ifosfamide, mechlorethamine, melphalan, and uramustine; nitrosoureas such as carmustine, lomustine, and streptozocin; triazenes and imidazotetrazines such as dacarbazine, procarbazine, temozolamide, and temozolomide. Cyclophosphamide, 2-[bis(2-chloroethyl)-amino]tetrahydro-2H-1,3,2-oxazaphosphorine 2-oxide monohydrate, is commercially available as an injectable solution or tablets as CYTOXAN®. Melphalan, 4-[bis(2-chloroethyl)amino]-L-phenylalanine, is commercially available as an injectable solution or tablets as ALKERAN®. Chlorambucil, 4-[bis(2-chloroethyl)amino]-benzenebutanoic acid, is commercially available as LEUKERAN® tablets. Busulfan, 1,4-butanediol dimethanesulfonate, is commercially available as MYLERAN® TABLETS. Carmustine, 1,3-[bis(2-chloroethyl)-1-nitrosourea, is commercially available as single vials of lyophilized material as BiCNU®, 5-(3,3-dimethyl-1-triazeno)-imidazole-4-carboxamide, is commercially available as single vials of material as DTIC-Dome®. Furthermore, alkylating agents include (a) alkylating-like platinum-based chemotherapeutic agents such as cisplatin, carboplatin, nedaplatin, oxaliplatin, satraplatin, and (SP-4-3)-(cis)-amminedichloro-[2-methylpyridine] platinum(II); (b) alkyl sulfonates such as busulfan; (c) ethyleneimine and methylmelamine derivatives such as altretamine and thiotepa; (d) nitrogen mustards such as chlorambucil, cyclophosphamide, estramustine, ifosfamide, mechlorethamine, trofosamide, prednimustine, melphalan, and uramustine; (e) nitrosoureas such as carmustine, lomustine, fotemustine, nimustine, ranimustine and streptozocin; (f) triazenes and imidazotetrazines such as dacarbazine, procarbazine, temozolamide, and temozolomide.

[0152] Anti-tumor antibiotics are non-phase specific agents which are believed to bind or intercalate with DNA. This may result in stable DNA complexes or strand breakage, which disrupts ordinary function of the nucleic acids, leading to cell death. Examples of anti-tumor

antibiotic agents include, but are not limited to, anthracyclines such as daunorubicin (including liposomal daunorubicin), doxorubicin (including liposomal doxorubicin), epirubicin, idarubicin, and valrubicin; streptomyces-related agents such as bleomycin, actinomycin, mithramycin, mitomycin, porfiromycin; and mitoxantrone. Dactinomycin, also know as Actinomycin D, is commercially available in injectable form as COSMEGEN®. Daunorubicin, (8S-cis-)-8-acetyl-10-[(3-amino-2,3,6-trideoxy-a-L-lyxohexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,8, 11-trihydroxy-1-methoxy-5, 12-naphthacenedione hydrochloride, is commercially available as a liposomal injectable form as DAUNOXOME® or as an injectable as CERUBIDINE®. Doxorubicin, (8S, 10S)-10-[(3-amino-2,3,6-trideoxy-α-L-lyxohexopyranosyl)oxy]-8-glycoloyl, 7,8,9,1 0-tetrahydro-6,8, 11-trihydroxy-1-methoxy-5,12-naphthacenedione hydrochloride, is commercially available in an injectable form as RUBEX® or ADRIAMYCIN RDF®. Bleomycin, a mixture of cytotoxic glycopeptide antibiotics isolated from a strain of *Streptomyces verticil/us*, is commercially available as BLENOXANE®.

[0153] Topoisomerase inhibitors include topoisomerase I inhibitors such as camptothecin, topotecan, irinotecan, rubitecan, and belotecan; and topoisomerase II inhibitors such as etoposide, teniposide, and amsacrine.

[0154] Topoisomerase II inhibitors include, but are not limited to, epipodophyllotoxins, which are phase specific anti-neoplastic agents derived from the mandrake plant. Epipodophyllotoxins typically affect cells in the S and G2 phases of the cell cycle by forming a ternary complex with topoisomerase II and DNA causing DNA strand breaks. The strand breaks accumulate and cell death follows. Examples of epipodophyllotoxins include, but are not limited to, etoposide, teniposide, and amsacrine. Etoposide, 4'-demethyl-epipodophyllotoxin 9[4,6-0-(R)-ethylidene-β-D- glucopyranoside], is commercially available as an injectable solution or capsules as VePESID® and is commonly known as VP-16. Teniposide, 4'-demethyl-epipodophyllotoxin 9[4,6-0-(R)-thenylidene-β-D-glucopyranoside], is commercially available as an injectable solution as VUMON® and is commonly known as VM-26.

[0155] Topoisomerase I inhibitors including, camptothecin and camptothecin derivatives. Examples of topoisomerase I inhibitors include, but are not limited to camptothecin, topotecan, irinotecan, rubitecan, belotecan and the various optical forms (i.e., (R), (S) or (R,S)) of 7-(4-methylpiperazino-methylene)-10, 11-ethylenedioxy-camptothecin, as described in U.S. Patent Nos. 6,063,923; 5,342,947; 5,559,235; 5,491,237 and pending U.S. patent Application No. 08/977,217 filed November 24, 1997. Irinotecan HCl, (4S)-4, 11-diethyl-4-hydroxy-9-[(4-piperidinopiperidino)-carbonyloxy]-1 H-yrano[3',4',6,7]indolizino[1,2-

b]quinoline-3, 14(4H, 12H)-dione hydrochloride, is commercially available as the injectable solution CAMPTOSAR®. Irinotecan is a derivative of camptothecin which binds, along with its active metabolite 8N-38, to the topoisomerase I-DNA complex. Topotecan HCl, (S)-10-[(dimethylamino)methyl]-4-ethyl-4,9-dihydroxy-1H-pyrano[3',4',6,7]indolizino[1 ,2-b]quinoline-3, 14-(4H, 12H)-dione monohydrochloride, is commercially available as the injectable solution HYCAMTIN®.

[0156] Anti-metabolites include (a) purine analogs such as fludarabine, cladribine, chlorodeoxyadenosine, clofarabine, mercaptopurine, pentostatin, and thioguanine; (b) pyrimidine analogs such as fluorouracil, gemcitabine, capecitabine, cytarabine, azacitidine, edatrexate, floxuridine, and troxacitabine; (c) antifolates, such as methotrexate, pemetrexed, raltitrexed, and trimetrexate. Anti-metabolites also include thymidylate synthase inhibitors, such as fluorouracil, raltitrexed, capecitabine, floxuridine and pemetrexed; and ribonucleotide reductase inhibitors such as claribine, clofarabine and fludarabine. Antimetabolite neoplastic agents are phase specific anti-neoplastic agents that typically act at S phase (DNA synthesis) of the cell cycle by inhibiting DNA synthesis or by inhibiting purine or pyrimidine base synthesis and thereby limiting DNA synthesis. Consequently, S phase does not proceed and cell death follows. Anti-metabolites, include purine analogs, such as fludarabine, cladribine, chlorodeoxyadenosine, clofarabine, mercaptopurine, pentostatin, erythrohydroxynonyladenine, fludarabine phosphate and thioguanine; pyrimidine analogs such as fluorouracil, gemcitabine, capecitabine, cytarabine, azacitidine, edatrexate, floxuridine, and troxacitabine; antifolates, such as methotrexate, pemetrexed, raltitrexed, and trimetrexate. Cytarabine, 4-amino-1-p-D-arabinofuranosyl-2 (1H)-pyrimidinone, is commercially available as CYTOSAR-U® and is commonly known as Ara-C. Mercaptopurine, 1,7-dihydro-6H-purine-6-thione monohydrate, is commercially available as PURINETHOL®. Thioguanine, 2-amino-1, 7-dihydro-6H-purine-6-thione, is commercially available as TABLOID®. Gemcitabine, 2'-deoxy-2', 2'-difluorocytidine monohydrochloride (p-isomer), is commercially available as GEMZAR®.

[0157] Hormonal therapies include (a) androgens such as fluoxymesterone and testolactone; (b) antiandrogens such as bicalutamide, cyproterone, flutamide, and nilutamide; (c) aromatase inhibitors such as aminoglutethimide, anastrozole, exemestane, formestane, and letrozole; (d) corticosteroids such as dexamethasone and prednisone; (e) estrogens such as diethylstilbestrol; (f) antiestrogens such as fulvestrant, raloxifene, tamoxifen, and toremifine; (g) LHRH agonists and antagonists such as buserelin, goserelin, leuprolide, and triptorelin; (h) progestins such as medroxyprogesterone acetate and megestrol acetate; and (i) thyroid

hormones such as levothyroxine and liothyronine. Hormones and hormonal analogues are useful compounds for treating cancers in which there is a relationship between the hormone(s) and growth and/or lack of growth of the cancer. Examples of hormones and hormonal analogues useful in cancer treatment include, but are not limited to, androgens such as fluoxymesterone and testolactone; antiandrogens such as bicalutamide, cyproterone, flutamide, and nilutamide; aromatase inhibitors such as aminoglutethimide, anastrozole, exemestane, formestane, vorazole, and letrozole; corticosteroids such as dexamethasone, prednisone and prednisolone; estrogens such as diethylstilbestrol; antiestrogens such as fulvestrant, raloxifene, tamoxifen, toremifine, droloxifene, and iodoxyfene, as well as selective estrogen receptor modulators (SERMS) such those described in U.S. Patent Nos. 5,681,835, 5,877,219, and 6,207,716; 5α-reductases such as finasteride and dutasteride; gonadotropin-releasing hormone (GnRH) and analogues thereof which stimulate the release of leutinizing hormone (LH) and/or follicle stimulating hormone (FSH), for example LHRH agonists and antagonists such as buserelin, goserelin, leuprolide, and triptorelin; progestins such as medroxyprogesterone acetate and megestrol acetate; and thyroid hormones such as levothyroxine and liothyronine.

[0158] Signal transduction pathway inhibitors are those inhibitors, which block or inhibit a chemical process which evokes an intracellular change, such as cell proliferation or differentiation. Signal tranduction inhibitors useful in the present invention include, e.g., inhibitors of receptor tyrosine kinases, non-receptor tyrosine kinases, SH2/SH3 domain blockers, serine/threonine kinases, phosphotidyl inositol-3 kinases, myo-inositol signaling, and Ras oncogenes.

[0159] Molecular targeted agents include (a) receptor tyrosine kinase ('RTK') inhibitors, such as inhibitors of EGFR, including erlotinib, gefitinib, and neratinib; inhibitors of VEGFR including vandetanib, semaxinib, and cediranib; and inhibitors of PDGFR; further included are RTK inhibitors that act at multiple receptor sites such as lapatinib, which inhibits both EGFR and HER2, as well as those inhibitors that act at each of C-kit, PDGFR and VEGFR, including but not limited to axitinib, sunitinib, sorafenib and toceranib; also included are inhibitors of BCR-ABL, c-kit and PDGFR, such as imatinib; (b) FKBP binding agents, such as an immunosuppressive macrolide antibiotic, including bafilomycin, rapamycin (sirolimus) and everolimus; (c) gene therapy agents, antisense therapy agents, and gene expression modulators such as the retinoids and rexinoids, e.g. adapalene, bexarotene, trans-retinoic acid, 9-cis-retinoic acid, and N-(4-hydroxyphenyl)retinamide; (d) phenotype-directed therapy agents, including monoclonal antibodies such as alemtuzumab, bevacizumab, cetuximab, ibritumomab tiuxetan,

rituximab, and trastuzumab; (e) immunotoxins such as gemtuzumab ozogamicin; (f) radioimmunoconjugates such as 131I-tositumomab; and (g) cancer vaccines.

[0160] Several protein tyrosine kinases catalyse the phosphorylation of specific tyrosyl residues in various proteins involved in the regulation of cell growth. Such protein tyrosine kinases can be broadly classified as receptor or non-receptor kinases. Receptor tyrosine kinases are transmembrane proteins having an extracellular ligand binding domain, a transmembrane domain, and a tyrosine kinase domain. Receptor tyrosine kinases are involved in the regulation of cell growth and are sometimes termed growth factor receptors.

[0161] Inappropriate or uncontrolled activation of many of these kinases, for example by over-expression or mutation, has been shown to result in uncontrolled cell growth. Accordingly, the aberrant activity of such kinases has been linked to malignant tissue growth. Consequently, inhibitors of such kinases could provide cancer treatment methods.

[0162] Growth factor receptors include, for example, epidermal growth factor receptor (EGFr), platelet derived growth factor receptor (PDGFr), erbB2, erbB4, vascular endothelial growth factor receptor (VEGFr), tyrosine kinase with immunoglobulin-like and epidermal growth factor homology domains (TIE-2), insulin growth factor -I (IGFI) receptor, macrophage colony stimulating factor (cfms), BTK, ckit, cmet, fibroblast growth factor (FGF) receptors, Trk receptors (TrkA, TrkB, and TrkC), ephrin (eph) receptors, and the RET protooncogene.

[0163] Several inhibitors of growth receptors are under development and include ligand antagonists, antibodies, tyrosine kinase inhibitors and anti-sense oligonucleotides. Growth factor receptors and agents that inhibit growth factor receptor function are described, for instance, in Kath, John C., *Exp. Opin. Ther. Patents* (2000) 10(6):803-818; Shawver et al., *Drug Discov. Today* (1997), 2(2):50-63; and Lofts, F. J. et al., "Growth factor receptors as targets", New Molecular Targets for Cancer Chemotherapy, ed. Workman, Paul and Kerr, David, CRC press 1994, London. Specific examples of receptor tyrosine kinase inhibitors include, but are not limited to, sunitinib, erlotinib, gefitinib, and imatinib.

[0164] Tyrosine kinases which are not growth factor receptor kinases are termed non-receptor tyrosine kinases. Non-receptor tyrosine kinases useful in the present invention, which are targets or potential targets of anti-cancer drugs, include cSrc, Lck, Fyn, Yes, Jak, cAbl, FAK (Focal adhesion kinase), Brutons tyrosine kinase, and Bcr-Abl. Such non-receptor kinases and agents which inhibit non-receptor tyrosine kinase function are described in Sinh, S. and Corey, S.J., *J. Hematotherapy & Stem Cell Res.* (1999) 8(5): 465 - 80; and Bolen, J.B., Brugge, J.S., *Annual Review of Immunology.* (1997) 15: 371-404.

[0165] SH2/SH3 domain blockers are agents that disrupt SH2 or SH3 domain binding in a variety of enzymes or adaptor proteins including, PI3-K p85 subunit, Src family kinases, adaptor molecules (Shc, Crk, Nck, Grb2) and Ras-GAP. SH2/SH3 domains as targets for anti-cancer drugs are discussed in Smithgall, T.E., *J. Pharmacol. Toxicol. Methods.* (1995), 34(3): 125-32. Inhibitors of Serine/Threonine Kinases including MAP kinase cascade blockers which include blockers of Raf kinases (rafk), Mitogen or Extracellular Regulated Kinase (MEKs), and Extracellular Regulated Kinases (ERKs); and Protein kinase C family member blockers including blockers of PKCs (alpha, beta, gamma, epsilon, mu, lambda, iota, zeta). IkB kinase family (IKKa, IKKb), PKB family kinases, AKT kinase family members, and TGF beta receptor kinases. Such Serine/Threonine kinases and inhibitors thereof are described in Yamamoto, T., Taya, S., Kaibuchi, K., *J. Biochemistry.* (1999) 126 (5): 799-803; Brodt, P, Samani, A, & Navab, R, *Biochem. Pharmacol.* (2000) 60:1101-1107; Massague, J., Weis-Garcia, F., *Cancer Surv.* (1996) 27:41-64; Philip, P.A, and Harris, AL, *Cancer Treat. Res.* (1995) 78: 3-27; Lackey, K. et al. *Bioorg. Med. Chem. Letters,* (2000) 10(3): 223-226; U.S. Patent No. 6,268,391; and Martinez-Lacaci, I., et al., *Int. J. Cancer* (2000), 88(1): 44-52. Inhibitors of Phosphotidyl inositol-3 Kinase family members including blockers of PI3- kinase, ATM, DNA-PK, and Ku are also useful in the present invention. Such kinases are discussed in Abraham, RT. *Current Opin. Immunol.* (1996), 8(3): 412-8; Canman, C.E., Lim, D.S., Oncogene (1998) 17(25): 3301-8; Jackson, S.P., *Int. J. Biochem. Cell Biol.* (1997) 29(7):935-8; and Zhong, H. et al., *Cancer Res.* (2000) 60(6):1541-5. Also useful in the present invention are Myo-inositol signaling inhibitors such as phospholipase C blockers and Myoinositol analogues. Such signal inhibitors are described in Powis, G., and Kozikowski A, (1994) New Molecular Targets for Cancer Chemotherapy, ed., Paul Workman and David Kerr, CRC Press 1994, London.

[0166] Another group of signal transduction pathway inhibitors are inhibitors of Ras Oncogene. Such inhibitors include inhibitors of farnesyltransferase, geranyl-geranyl transferase, and CAAX proteases as well as anti-sense oligonucleotides, ribozymes and immunotherapy. Such inhibitors have been shown to block ras activation in cells containing wild type mutant ras , thereby acting as antiproliferation agents. Ras oncogene inhibition is discussed in Scharovsky, O.G., Rozados, V.R, Gervasoni, SI, Matar, P., *J. Biomed. Sci.* (2000) 7(4): 292-8; Ashby, M.N., *Curr. Opin. Lipidol.* (1998) 9(2): 99 -102; and Oliff, A., *Biochim. Biophys. Acta,* (1999) 1423(3):C19-30.

[0167] As mentioned above, antibody antagonists to receptor kinase ligand binding may also serve as signal transduction inhibitors. This group of signal transduction pathway inhibitors

includes the use of humanized antibodies to the extracellular ligand binding domain of receptor tyrosine kinases. For example Imclone C225 EGFR specific antibody (*see* Green, M.C. et al., *Cancer Treat. Rev.*, (2000) 26(4): 269-286); Herceptin® erbB2 antibody (*see* Stern, DF, *Breast Cancer Res.* (2000) 2(3):176-183); and 2CB VEGFR2 specific antibody (*see* Brekken, R.A. et al., *Cancer Res.* (2000) 60(18):5117-24).

[0168] Non-receptor kinase angiogenesis inhibitors may also find use in the present invention. Inhibitors of angiogenesis related VEGFR and TIE2 are discussed above in regard to signal transduction inhibitors (both receptors are receptor tyrosine kinases). Angiogenesis in general is linked to erbB2/EGFR signaling since inhibitors of erbB2 and EGFR have been shown to inhibit angiogenesis, primarily VEGF expression. Thus, the combination of an erbB2/EGFR inhibitor with an inhibitor of angiogenesis makes sense. Accordingly, non-receptor tyrosine kinase inhibitors may be used in combination with the EGFR/erbB2 inhibitors of the present invention. For example, anti-VEGF antibodies, which do not recognize VEGFR (the receptor tyrosine kinase), but bind to the ligand; small molecule inhibitors of integrin (alphav beta3) that will inhibit angiogenesis; endostatin and angiostatin (non-RTK) may also prove useful in combination with the disclosed erb family inhibitors. (See Bruns, CJ et al., *Cancer Res.* (2000), 60(11): 2926-2935; Schreiber AB, Winkler ME, & Derynck R., *Science* (1986) 232(4755):1250-53; Yen L. et al., *Oncogene* (2000) 19(31): 3460-9).

[0169] Agents used in immunotherapeutic regimens may also be useful in combination with the compounds of formula (I). There are a number of immunologic strategies to generate an immune response against erbB2 or EGFR. These strategies are generally in the realm of tumor vaccinations. The efficacy of immunologic approaches may be greatly enhanced through combined inhibition of erbB2/EGFR signaling pathways using a small molecule inhibitor. Discussion of the immunologic/tumor vaccine approach against erbB2/EGFR are found in Reilly RT, et al., *Cancer Res.* (2000) 60(13):3569-76; and Chen Y, et al., *Cancer Res.* (1998) 58(9):1965-71.

[0170] Agents used in pro-apoptotic regimens (e.g., bcl-2 antisense oligonucleotides) may also be used in the combination of the present invention. Members of the Bcl-2 family of proteins block apoptosis. Upregulation of bcl-2 has therefore been linked to chemoresistance. Studies have shown that the epidermal growth factor (EGF) stimulates anti-apoptotic members of the bcl-2 family. Therefore, strategies designed to downregulate the expression of bcl-2 in tumors have demonstrated clinical benefit and are now in Phase II/III trials, namely Genta's G3139 bcl-2 antisense oligonucleotide. Such pro-apoptotic strategies using the antisense

oligonucleotide strategy for bcl-2 are discussed in Waters JS, et al., *J. Clin. Oncol.* (2000) 18(9): 1812-23; and Kitada S, et al. *Antisense Res. Dev.* (1994) 4(2): 71-9.

[0171] Cell cycle signalling inhibitors inhibit molecules involved in the control of the cell cycle. A family of protein kinases called cyclin dependent kinases (CDKs) and their interaction with a family of proteins termed cyclins controls progression through the eukaryotic cell cycle. The coordinate activation and inactivation of different cyclin/CDK complexes is necessary for normal progression through the cell cycle. Several inhibitors of cell cycle signalling are under development. For instance, examples of cyclin dependent kinases, including CDK2, CDK4, and CDK6 and inhibitors for the same are described in, for instance, RosaniaGR & Chang Y-T., *Exp. Opin. Ther. Patents* (2000) 10(2):215-30.

[0172] Other molecular targeted agents include FKBP binding agents, such as the immunosuppressive macrolide antibiotic, rapamycin; gene therapy agents, antisense therapy agents, and gene expression modulators such as the retinoids and rexinoids, e.g. adapalene, bexarotene, trans-retinoic acid, 9-cisretinoic acid, and N-(4 hydroxyphenyl)retinamide; phenotype-directed therapy agents, including: monoclonal antibodies such as alemtuzumab, bevacizumab, cetuximab, ibritumomab tiuxetan, rituximab, and trastuzumab; immunotoxins such as gemtuzumab ozogamicin, radioimmunoconjugates such as 131-tositumomab; and cancer vaccines.

[0173] Anti-tumor antibiotics include (a) anthracyclines such as daunorubicin (including liposomal daunorubicin), doxorubicin (including liposomal doxorubicin), epirubicin, idarubicin, and valrubicin; (b) streptomyces-related agents such as bleomycin, actinomycin, mithramycin, mitomycin, porfiromycin; and (c) anthracenediones, such as mitoxantrone and pixantrone. Anthracyclines have three mechanisms of action: intercalating between base pairs of the DNA/RNA strand; inhibiting topoiosomerase II enzyme; and creating iron-mediated free oxygen radicals that damage the DNA and cell membranes. Anthracyclines are generally characterized as topoisomerase II inhibitors.

[0174] Monoclonal antibodies include, but are not limited to, murine, chimeric, or partial or fully humanized monoclonal antibodies. Such therapeutic antibodies include, but are not limited to antibodies directed to tumor or cancer antigens either on the cell surface or inside the cell. Such therapeutic antibodies also include, but are not limited to antibodies directed to targets or pathways directly or indirectly associated with CK2. Therapeutic antibodies may further include, but are not limited to antibodies directed to targets or pathways that directly interact with targets or pathways associated with the compounds of the present invention. In one

variation, therapeutic antibodies include, but are not limited to anticancer agents such as Abagovomab, Adecatumumab, Afutuzumab, Alacizumab pegol, Alemtuzumab, Altumomab pentetate, Anatumomab mafenatox, Apolizumab, Bavituximab, Belimumab, Bevacizumab, Bivatuzumab mertansine, Blinatumomab, Brentuximab vedotin, Cantuzumab mertansine, Catumaxomab, Cetuximab, Citatuzumab bogatox, Cixutumumab, Clivatuzumab tetraxetan, Conatumumab, Dacetuzumab, Detumomab, Ecromeximab, Edrecolomab, Elotuzumab, Epratuzumab, Ertumaxomab, Etaracizumab, Farletuzumab, Figitumumab, Fresolimumab, Galiximab, Glembatumumab vedotin, Ibritumomab tiuxetan, Intetumumab, Inotuzumab ozogamicin, Ipilimumab, Iratumumab, Labetuzumab, Lexatumumab, Lintuzumab, Lucatumumab, Lumiliximab, Mapatumumab, Matuzumab, Milatuzumab, Mitumomab, Nacolomab tafenatox, Naptumomab estafenatox, Necitumumab, Nimotuzumab, Ofatumumab, Olaratumab, Oportuzumab monatox, Oregovomab, Panitumumab, Pemtumomab, Pertuzumab, Pintumomab, Pritumumab, Ramucirumab, Rilotumumab, Rituximab, Robatumumab, Sibrotuzumab, Tacatuzumab tetraxetan, Taplitumomab paptox, Tenatumomab, Ticilimumab, Tigatuzumab, Tositumomab, Trastuzumab, Tremelimumab, Tucotuzumab celmoleukin, Veltuzumab, Volociximab, Votumumab, Zalutumumab, and Zanolimumab. In some embodiments, such therapeutic antibodies include, alemtuzumab, bevacizumab, cetuximab, daclizumab, gemtuzumab, ibritumomab tiuxetan, pantitumumab, rituximab, tositumomab, and trastuzumab; in other embodiments, such monoclonal antibodies include alemtuzumab, bevacizumab, cetuximab, ibritumomab tiuxetan, rituximab, and trastuzumab; alternately, such antibodies include daclizumab, gemtuzumab, and pantitumumab. In yet another embodiment, therapeutic antibodies useful in the treatment of infections include but are not limited to Afelimomab, Efungumab, Exbivirumab, Felvizumab, Foravirumab, Ibalizumab, Libivirumab, Motavizumab, Nebacumab, Pagibaximab, Palivizumab, Panobacumab, Rafivirumab, Raxibacumab, Regavirumab, Sevirumab, Tefibazumab, Tuvirumab, and Urtoxazumab. In a further embodiment, therapeutic antibodies can be useful in the treatment of inflammation and/or autoimmune disorders, including, but are not limited to, Adalimumab, Atlizumab, Atorolimumab, Aselizumab, Bapineuzumab, Basiliximab, Benralizumab, Bertilimumab, Besilesomab, Briakinumab, Canakinumab, Cedelizumab, Certolizumab pegol, Clenoliximab, Daclizumab, Denosumab, Eculizumab, Edobacomab, Efalizumab, Erlizumab, Fezakinumab, Fontolizumab, Fresolimumab, Gantenerumab, Gavilimomab, Golimumab, Gomiliximab, Infliximab, Inolimomab, Keliximab, Lebrikizumab, Lerdelimumab, Mepolizumab, Metelimumab, Muromonab-CD3, Natalizumab, Ocrelizumab, Odulimomab, Omalizumab,

Otelixizumab, Pascolizumab, Priliximab, Reslizumab, Rituximab, Rontalizumab, Rovelizumab, Ruplizumab, Sifalimumab, Siplizumab, Solanezumab, Stamulumab, Talizumab, Tanezumab, Teplizumab, Tocilizumab, Toralizumab, Ustekinumab, Vedolizumab, Vepalimomab, Visilizumab, Zanolimumab, and Zolimomab aritox. In yet another embodiment, such therapeutic antibodies include, but are not limited to adalimumab, basiliximab, certolizumab pegol, eculizumab, efalizumab, infliximab, muromonab-CD3, natalizumab, and omalizumab. Alternately the therapeutic antibody can include abciximab or ranibizumab. Generally a therapeutic antibody is non-conjugated, or is conjugated with a radionuclide, cytokine, toxin, drug-activating enzyme or a drug-filled liposome.

[0175] Akt inhibitors include 1L6-Hydroxymethyl-chiro-inositol-2-(R)-2-O-methyl-3-O-octadecyl-*sn*-glycerocarbonate, SH-5 (Calbiochem Cat. No. 124008), SH-6 (Calbiochem Cat. No. Cat. No. 124009), Calbiochem Cat. No. 124011, Triciribine (NSC 154020, Calbiochem Cat. No. 124012), 10-(4'-(N-diethylamino)butyl)-2-chlorophenoxazine, Cu(II)Cl_2(3-Formylchromone thiosemicarbazone), 1,3-dihydro-1-(1-((4-(6-phenyl-1H-imidazo[4,5-g]quinoxalin-7-yl)phenyl)methyl)-4-piperidinyl)-2H-benzimidazol-2-one, GSK690693 (4-(2-(4-amino-1,2,5-oxadiazol-3-yl)-1-ethyl-7-{[(3S)-3-piperidinylmethyl]oxy}-1H-imidazo[4,5-c]pyridin-4-yl)-2-methyl-3-butyn-2-ol), SR13668 ((2,10-dicarbethoxy-6-methoxy-5,7-dihydro-indolo[2,3-b] carbazole), GSK2141795, Perifosine, GSK21110183, XL418, XL147, PF-04691502, BEZ-235 [2-Methyl-2-[4-(3-methyl-2-oxo-8-quinolin-3-yl-2,3-dihydro-imidazo[4,5-c]quinolin-1-yl)-phenyl]-propionitrile], PX-866 ((acetic acid (1S,4E,10R,11R,13S,14R)-[4-diallylaminomethylene-6-hydroxy-1-methoxymethyl-10,13-dimethyl-3,7,17-trioxo-1,3,4,7,10,11,12,13,14,15,16,17-dodecahydro-2-oxa-cyclopenta[a]phenanthren-11-yl ester)), D-106669, CAL-101, GDC0941 (2-(1H-indazol-4-yl)-6-(4-methanesulfonyl-piperazin-1-ylmethyl)-4-morpholin-4-yl-thieno[3,2-d]pyrimidine), SF1126, SF1188, SF2523, TG100-115 [3-[2,4-diamino-6-(3-hydroxyphenyl)pteridin-7-yl]phenol]. A number of these inhibitors, such as, for example, BEZ-235, PX-866, D 106669, CAL-101, GDC0941, SF1126, SF2523 are also identified in the art as PI3K/mTOR inhibitors; additional examples, such as PI-103 [3-[4-(4-morpholinylpyrido[3',2':4,5]furo[3,2-d]pyrimidin-2-yl]phenol hydrochloride] are well-known to those of skill in the art. Additional well-known PI3K inhibitors include LY294002 [2-(4-morpholinyl)-8-phenyl-4H-1-benzopyran-4-one] and wortmannin. mTOR inhibitors known to those of skill in the art include temsirolimus, deforolimus, sirolimus, everolimus, zotarolimus, and biolimus A9. A representative subset of such inhibitors includes temsirolimus, deforolimus, zotarolimus, and biolimus A9.

[0176] HDAC inhibitors include (i) hydroxamic acids such as Trichostatin A, vorinostat (suberoylanilide hydroxamic acid (SAHA)), panobinostat (LBH589) and belinostat (PXD101) (ii) cyclic peptides, such as trapoxin B, and depsipeptides, such as romidepsin (NSC 630176), (iii) benzamides, such as MS-275 (3-pyridylmethyl-N-{4-[(2-aminophenyl)-carbamoyl]-benzyl}-carbamate), CI994 (4-acetylamino-N-(2aminophenyl)-benzamide) and MGCD0103 (N-(2-aminophenyl)-4-((4-(pyridin-3-yl)pyrimidin-2-ylamino)methyl)benzamide), (iv) electrophilic ketones, (v) the aliphatic acid compounds such as phenylbutyrate and valproic acid.

[0177] Hsp90 inhibitors include benzoquinone ansamycins such as geldanamycin, 17-DMAG (17-Dimethylamino-ethylamino-17-demethoxygeldanamycin), tanespimycin (17-AAG, 17-allylamino-17-demethoxygeldanamycin), EC5, retaspimycin (IPI-504, 18,21-didehydro-17-demethoxy-18,21-dideoxo-18,21-dihydroxy-17-(2-propenylamino)-geldanamycin), and herbimycin; pyrazoles such as CCT 018159 (4-[4-(2,3-dihydro-1,4-benzodioxin-6-yl)-5-methyl-1H-pyrazol-3-yl]-6-ethyl-1,3-benzenediol); macrolides, such as radicocol; as well as BIIB021 (CNF2024), SNX-5422, STA-9090, and AUY922.

[0178] Miscellaneous agents include altretamine, arsenic trioxide, gallium nitrate, hydroxyurea, levamisole, mitotane, octreotide, procarbazine, suramin, thalidomide, lenalidomide, photodynamic compounds such as methoxsalen and sodium porfimer, and proteasome inhibitors such as bortezomib.

[0179] Biologic therapy agents include: interferons such as interferon-α2a and interferon-α2b, and interleukins such as aldesleukin, denileukin diftitox, and oprelvekin.

[0180] In addition to these anticancer agents intended to act against cancer cells, combination therapies including the use of protective or adjunctive agents, including: cytoprotective agents such as armifostine, dexrazonxane, and mesna, phosphonates such as parmidronate and zoledronic acid, and stimulating factors such as epoetin, darbepoetin, filgrastim, PEG-filgrastim, and sargramostim, are also envisioned.

[0181] Thus in one aspect, the invention provides a method to treat a condition described herein using a compound of the invention in combination therapy with any of the foregoing additional therapeutic agents and inhibitors and the like. The method comprises administering a compound of Formula I or II to a subject in need thereof, and an additional agent selected from the agents and inhibitors disclosed above, wherein the combined amounts of the compound of Formula I or II and of the additional therapeutic agent are effective to treat the cell proliferative condition. The invention further provides pharmaceutical compositions comprising at least one

compound of the invention, i.e., a compound of Formula I or II as described herein, admixed with at least one additional therapeutic agent selected from the foregoing agents and inhibitors. Optionally, these pharmaceutical compositions further comprise at least one pharmaceutically acceptable excipient.

Examples:

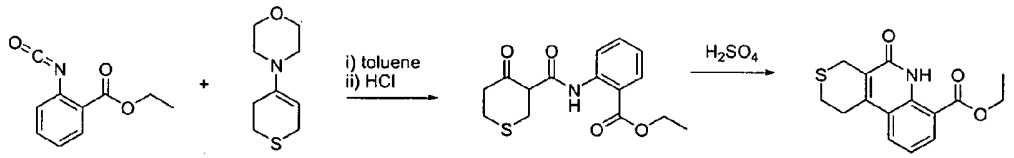
[0182] Compounds of the invention can be prepared using available methods and reagents, based on the ordinary level of skill in the art and methods in the schemes and examples provided below.

[0183] The following examples are offered to illustrate but not to limit the invention.

Example 1

[0184] The chemistry described in scheme 1 can be used to prepare intermediate **4** bearing a tetrahydrothiopyran ring. Compound **2** preparation was previously described in WO2009061131. Compound **3** can be formed by heating commercially available isocyanate **1** and compound **2** in toluene and by subsequently treating the reaction mixture with an acid, using a procedure described in WO2009061131. Compound **3** can be transformed into compound **4** using an acid such as sulfuric acid.

Scheme 1

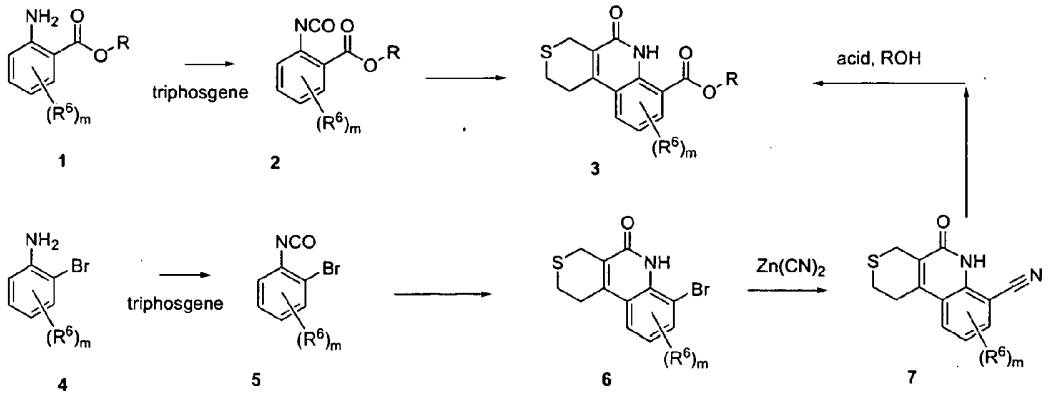


1 **2** **3** **4**

Example 2

[0185] The chemistry described in example 1 can be applied to other substituted isocyanates **2** (scheme 2) to prepare analogs **6** with various substitutions on the phenyl ring. Isocyanates **2** can be commercially available or prepared from commercially available anilines **1.**

Scheme 2

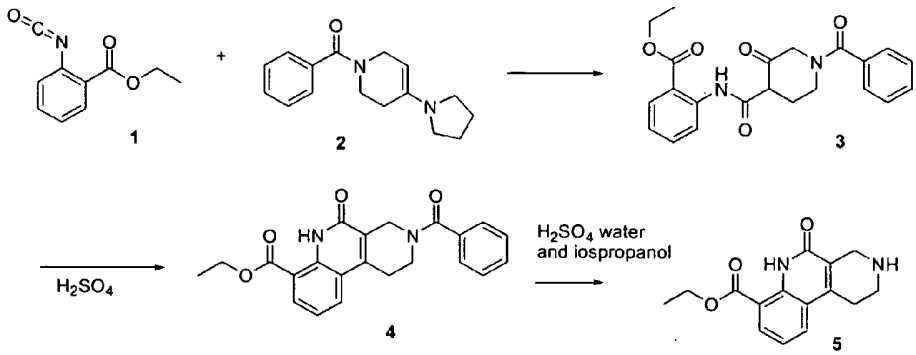


[0186] The chemistry can also be applied to substituted 2-bromo anilines **4** to obtain compounds **6**. Compounds **6** can be converted in two steps to compounds **3** by reacting with a cyanide reagent followed by subsequent hydrolysis and esterification.

Example 3

[0187] The chemistry described in scheme 3 can be used to prepare analogs bearing a piperidine ring. Compound **1** can be reacted with compound **2** (as described in US3,991,064 page 5) to obtain material **3**. Compound **3** can be cyclized to compound **4** using an acid such as sulfuric acid. The Amine in compound **4** can be deprotected using acidic conditions to afford **5**.

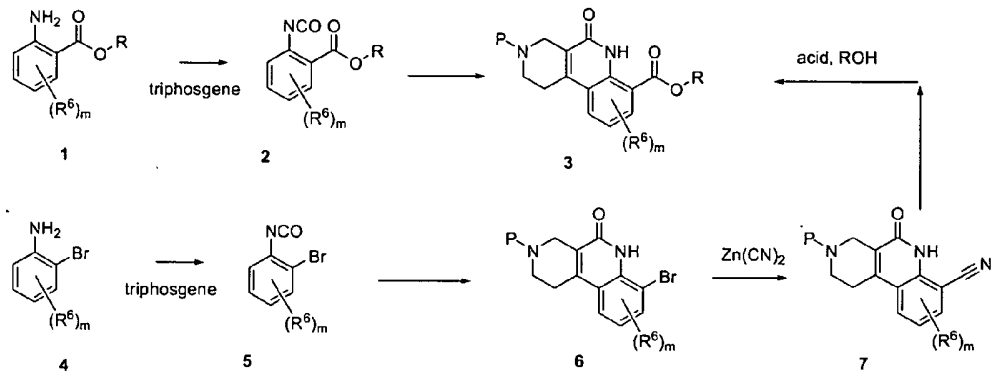
Scheme 3



Example 4

[0188] The chemistry described in scheme 4 described in example 2 can be applied to synthesize analogs **3** substituted on the phenyl ring.

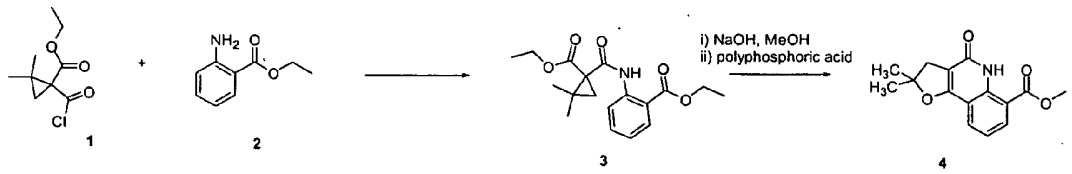
Scheme 4



Example 5

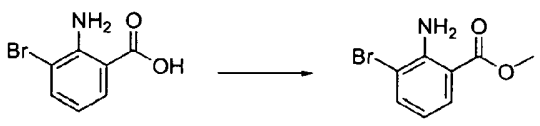
[0189] Compound **1** was described in literature (synthetic communications, 2006, vol. 36, 693-699). Compound **1** can be reacted with **2** to form compound **3.** Using conditions described in synthetic communications, 2006, vol. 36, 693-699, compound **4** can be formed from **3.**

Scheme 5



Example 6

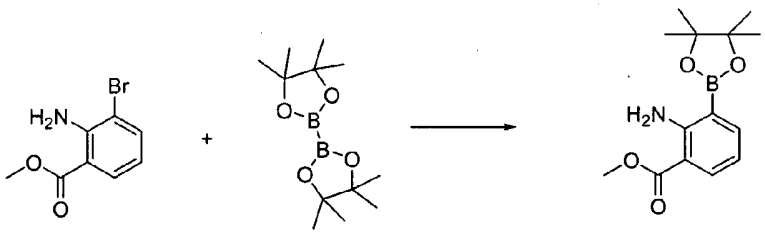
Process 1



[0190] 2-amino-3-bromobenzoic acid (1.00 g) was mixed with methanol (10 ml) and concentrated sulfuric acid (1ml). The mixture was stirred at reflux for 31 hours. The solvent were evaporated, and saturated aqueous sodium bicarbonate was carefully added. The solid was extracted with CH_2Cl_2 (3x). The combined extracts were dried over Na_2SO_4 and the solvents removed *in vacuo* to afford methyl 2-amino-3-bromobenzoate as a semi-crystalline solid (976 mg, 91% yield). LCMS (ES): >85% pure, m/z 230 $[M+1]^+$.

[0191] Alternatively, methyl 2-amino-3-bromobenzoate was prepared in two steps from 7-bromoindoline-2,3-dione using a procedure described in patent US 6,399,603 page 36.

Process 2



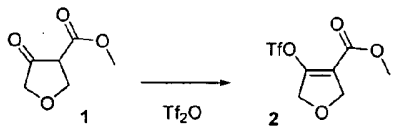
[0192] Methyl 2-amino-3-bromobenzoate (1.0 eq, 10.0 g, 43.46 mmol), dipinacol-diboron (1.4 eq, 15.42 g, 60.85 mmol) and potassium acetate (3.0 eq, 12.79 g, 130.4 mmol) were mixed in anhydrous toluene (220 ml). The reaction was degassed by bubbling nitrogen for 10 min through the solution. The catalyst $PdCl_2(dppf).CH_2Cl_2$ (0.05 eq, 1.77 g, 2.17 mmol) was added. The reaction was stirred under nitrogen atmosphere in an oil bath at 100°C for about 5 hours. The reaction was monitored by LCMS and TLC. On TLC (SiO_2, 20%AcOEt in hexanes) two spots appeared. The lower spot (Rf = 0.30) was a side product of unknown nature. The expected material constituted the higher spot (Rf = 0.5). The reaction was cooled down, diluted with EtOAc (300 ml) and filtered over a pad of celite. The pad was further washed with EtOAc (200 ml).The mixture was diluted with water (800 ml) and saturated $NaHCO_3$ (400 ml). The organic and aqueous phases were separated. The aqueous phase was washed with EtOAc (2x500 ml).The combined organics were washed with brine (1L). The organic phase was dried over Na_2SO_4, filtered and the concentrated in vacuo. The resulting dark brown/black oil was purified

by flash chromatography on silica gel using a gradient of EtOAc (1.5 to 2.5%) in hexanes. The resulting colorless oil solidified under vacuum to afford methyl 2-amino-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate as a yellowish semi-crystalline solid (5.44g, 45% yield). LCMS (ES): >95% pure, m/z 278 $[M+1]^+$, 246 $[M+1\text{-MeOH}]^+$. M.p. = 49-51°C.

Example 7

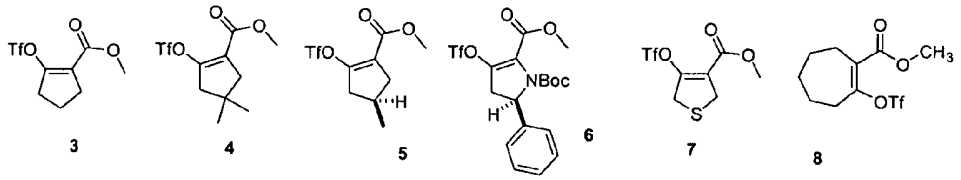
[0193] The compound **2** (scheme 7) can be prepared from compound **1** using a published procedure (bioorg. med. chem. lett. 2008, 18(3), 1124-1130).

Scheme 7



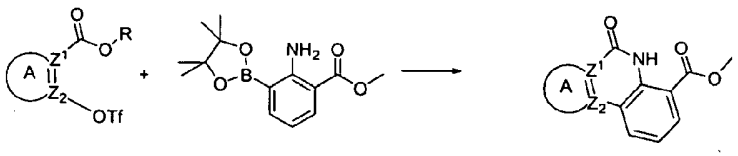
[0194] The following compounds on scheme 8 were already described in literature, respectively in J. Amer. Chem. Soc. 1990, 112, 5601 for compound **3**, Org. let. 2003, 59-62 for **4**, WO20049440 for **5**, Org. Lett. 2002, 4(9), 1599-1602 for **6** , Tetrahedron 1996, 52(9), 3117-3134 for **7** and Biorg. Med. Chem. Lett. 2002, 12(8), 2561-2564 for **8**.

Scheme 8



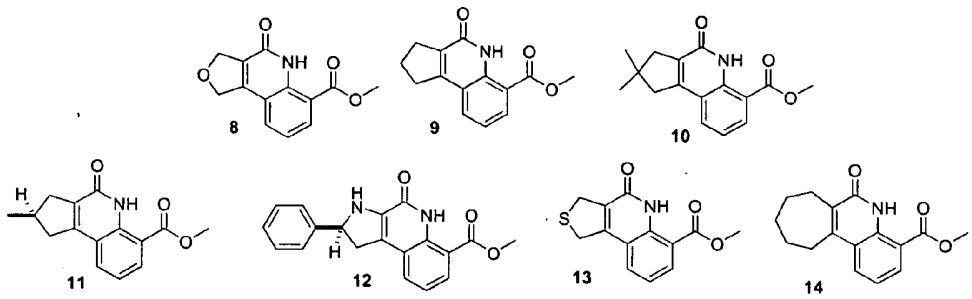
[0195] The general procedure on scheme 9 can be used to prepare useful lactam intermediates.

Scheme 9



[0196] Compounds **2-7** can be reacted with the boronic ester prepared in process 2 using conditions described in Bioorg. Med. Chem. Lett. 2002, 12(18), 2561-2564 or in Tetrahedron 1996, 52(9), 3117-3134 by using a catalyst such as $PdCl_2(dppf)$ to afford various useful lactam **8-13** (scheme 10).

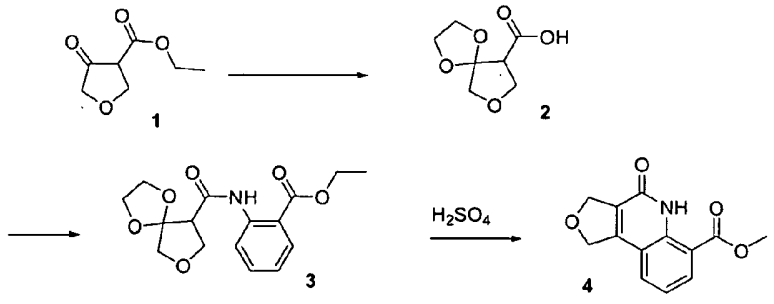
Scheme 10



Example 8

[0197] Compound **2** (scheme 11) can be prepared from compound **1** using chemistries described in WO200426864. Compound **3** can be prepared by reacting **2** and ethyl 2-aminobenzoate with a appropriate amide bond formation reagents. Compound **4** can be obtained by reacting compound **3** with acid such as sulfuric acid.

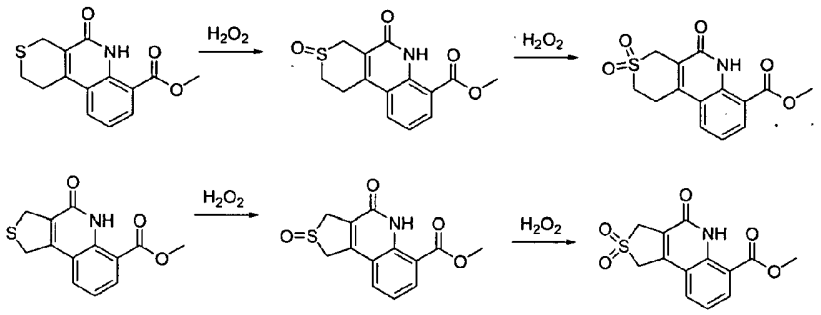
Scheme 11



Example 9

[0198] The thioethers in scheme 12 whose preparation is exemplified in examples 7 and example 1 can be transformed into the corresponding sulfoxides or sulfone using oxidants such as hydrogen peroxide.

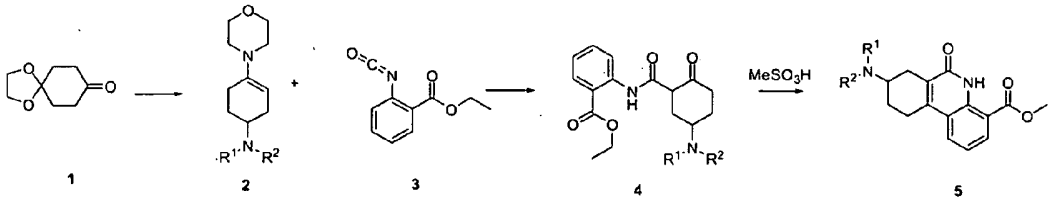
Scheme 12



Example 10

[0199] The chemistry described in scheme 13 can be used to prepare analogs bearing a six membered ring substituted by various amines. Compound 1 can be transformed into compound 2 using chemistries previously described in J. Heterocyclic chem. 1993, vol30, 4, 1125-1128. Compound 2 can be reacted with commercially available isocyanate 3 to form compound 4. Compound **4** can be cyclized into compound **5** by reacting with acids as described into J. Heterocyclic chem. 1993, vol30, 4, 1125-1128.

Scheme 13

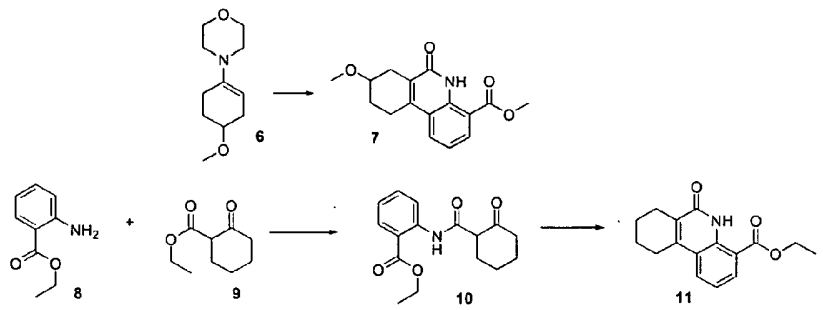


1 2 3 4 5

[0200] Similar chemistries can be applied to compound 6 to prepare compound 7 (scheme 14) as described in J. Med. Chem. 36, 1993, 3686-3692. Compound 10 can be prepared from commercially available compounds 8 and 9 . Compound 10 can be transformed into compound

11 using conditions similar to the ones used in Journal of the Indian chemical society 1929, 6, 313.

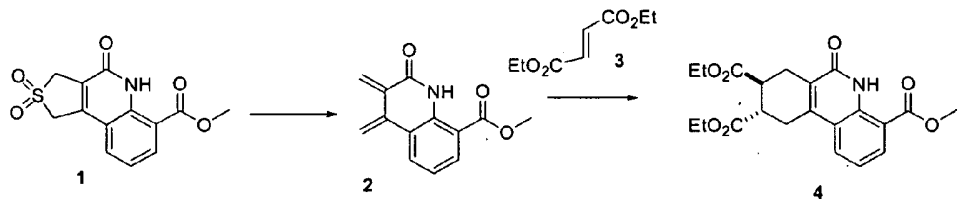
Scheme 14



Example 11

[0201] Compound **1** (scheme 15) can be prepared using chemistry similar to example 9. Compound **1** can be transformed into **2** by heating at a certain temperature as described with similar molecules in tetrahedron, 1996, 52(9) 3117-3134 and tetrahedron letters 1995, 36(33) 5983-5986. The intermediate **2** can react *in situ* with dienophiles such as **3** to form adduct **4**.

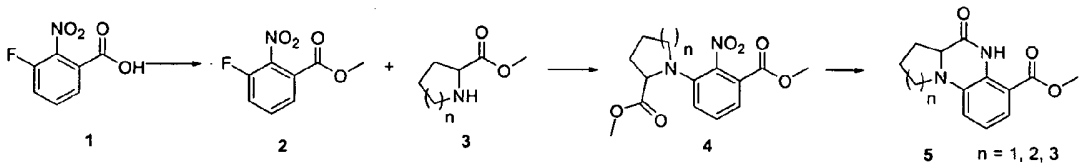
Scheme 15



Example 12

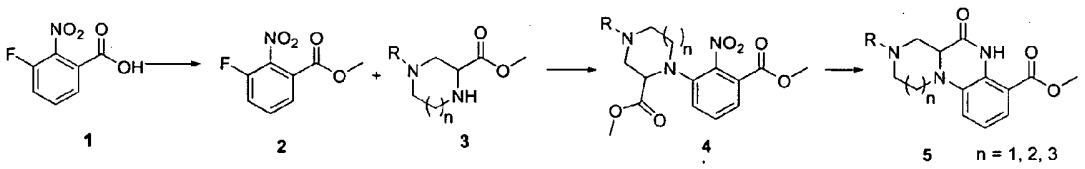
[0202] The chemistry exemplified in scheme 16 below can be used to prepare analogs **5** bearing a nitrogen at the junction of two rings. Commercially available compound **1** can be transformed into compound **2** using for example oxalyl chloride and methanol. Compound **2** can be reacted with various cyclic commercially available amino esters **3** using conditions described in US20080161292. Intermediates **4** can be transformed in several steps in compounds **5** through nitro reduction and cyclization by heating the product.

Scheme 16



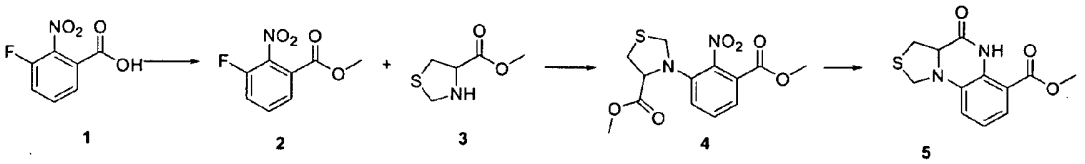
[0203] Similar chemistries can lead to molecules **5** (scheme 17).

Scheme 17



[0204] Using similar chemistries previously reported for close substrates (J. Heterocyclic Chem., 1983, 20, 1513, one can prepare analogs **5** (scheme 17) using commercially available **3**.

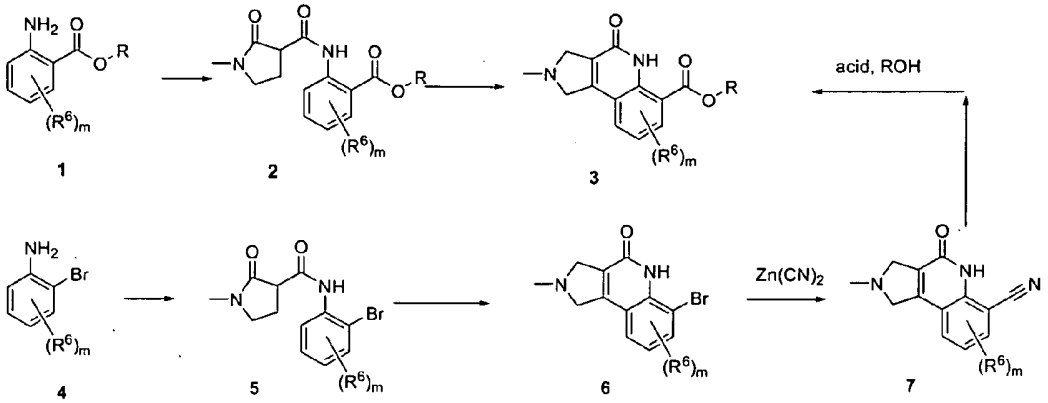
Scheme 18



Example 13

[0205] Using chemistries described in WO2004/26864 compounds **2** (scheme 19) can be prepared from commercially available **1**. Compound **3** can be prepared using conditions exemplified in WO2004/26864 and example 1-4. Compound **3** can also be prepared from commercially available **4** using procedure exemplified in examples 2 and 4.

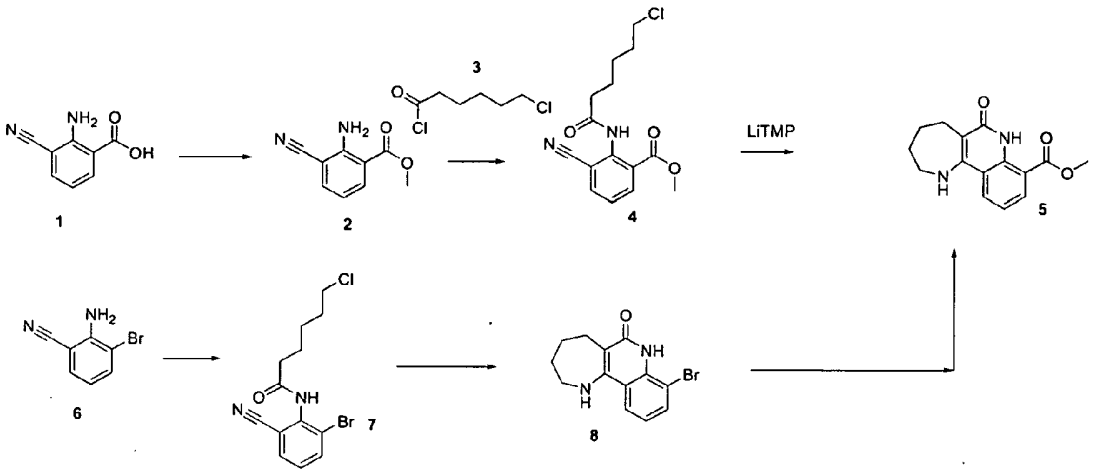
Scheme 19



Example 14

[0206] The chemistry summarized in scheme 20 can be used to prepare compounds bearing 7 membered rings. Compound **1** can be prepared according to Journal of the Chemical Society, **1959** , p. 1633 and can be transformed to ester **2** using for example oxalyl chloride and methanol. Compound **2** and **3** can be reacted to form **4** using chemistry similar to the one described in Tetrahedron lett. 1989, 30, 787-788. Compound **4** can be reacted with for example LiTMP using conditions similar to the one described in Tetrahedron lett. 1989, 30, 787-788 to form lactam **5**. Alternatively, compound **5** can be obtained from **6** (previously synthesized in Synthetic Communications, **1989** , vol. 19, # 13-14 p. 2255 – 2264) to form **8**. Compound **8** can be transformed in compound **5** using chemistries of example 2 and 4.

Scheme 20

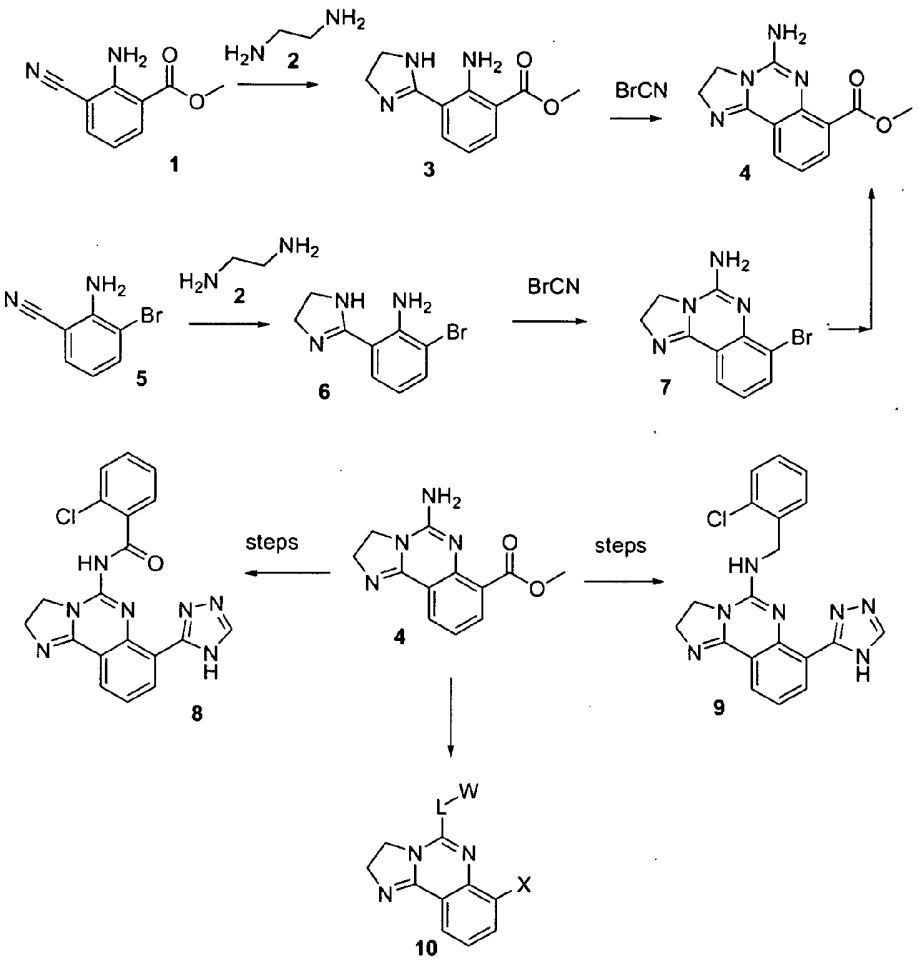


Example 15

[0207] The chemistry described in scheme 21 can be carried out using conditions similar to the one described in WO04029055, WO08070150 and WO09091550 and summarized in scheme 21.

[0208] Compound **1** and **5** can be prepared like in example 14. Compound **1** and **5** can be reacted with diamine **2** to form compounds **3** and **6** respectively which can be reacted with cyanogens bromide.

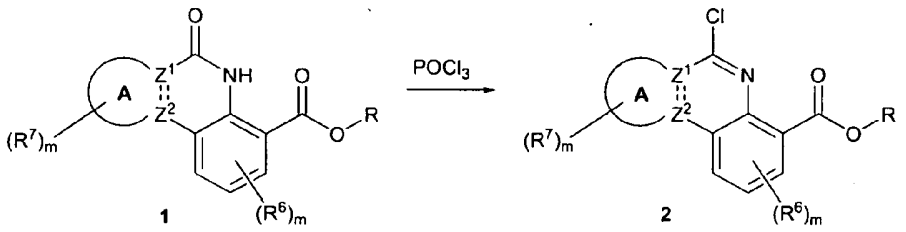
Scheme 21



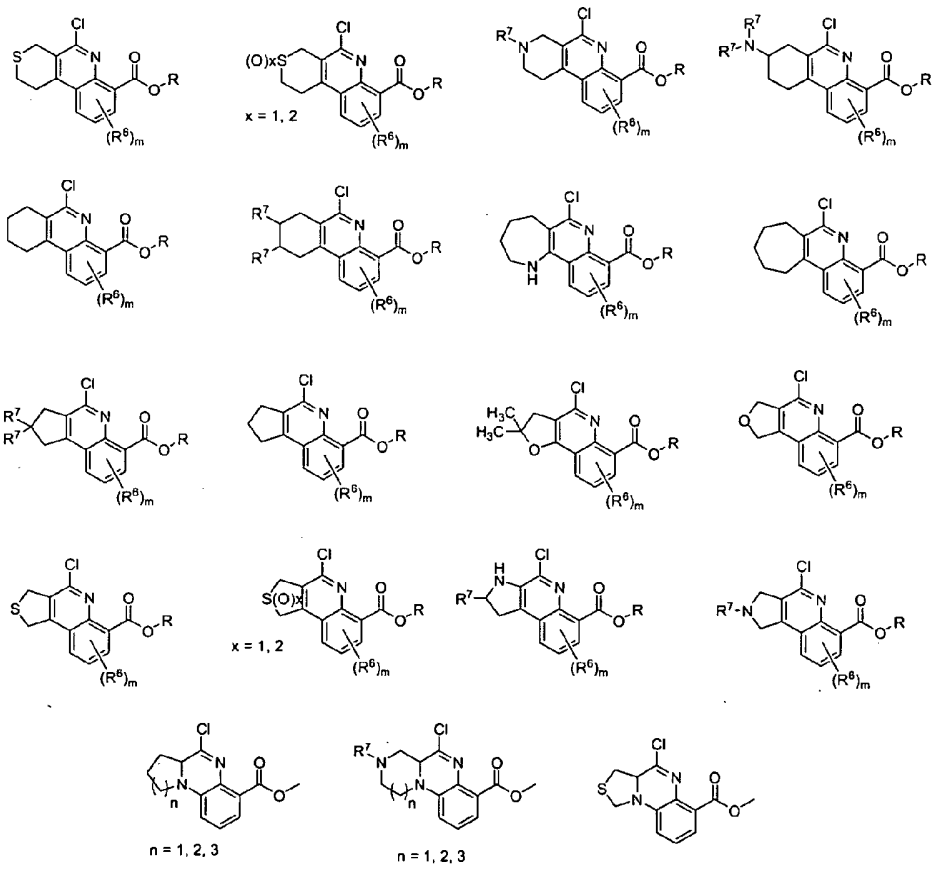
Example 16

[0209] The compounds of general formula **1** (scheme 22) can react for example with phosphorus oxychloride to be transformed into compounds of general formula **2**.

Scheme 22



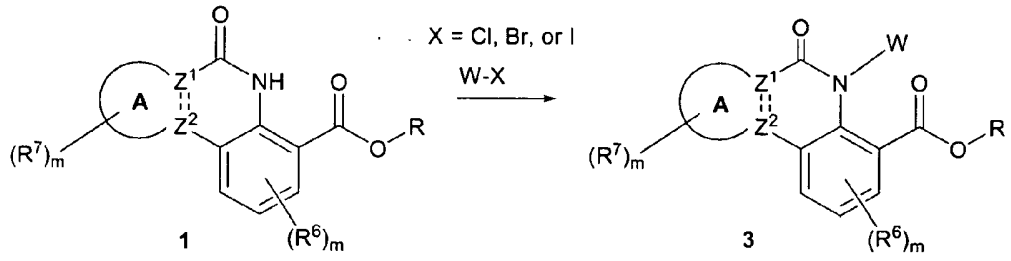
[0210] Examples of structures of compounds **2** are represented below:



Example 17

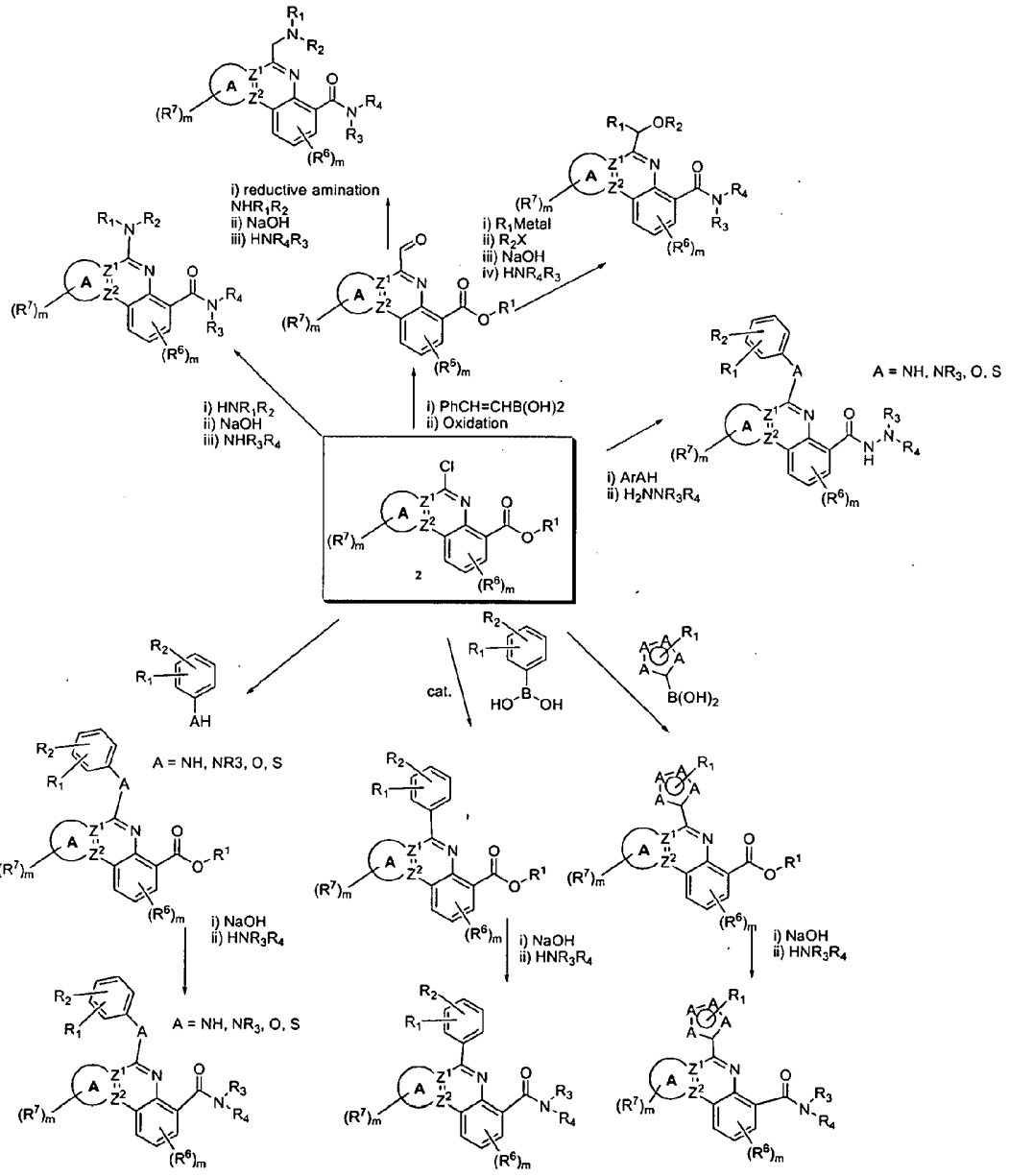
[0211] The compounds of general formula **1** (scheme 23) can react for example with halogenoalkyl reagents of general formula W-X to be transformed into N-substituted compound of general formula **3**.

Scheme 23



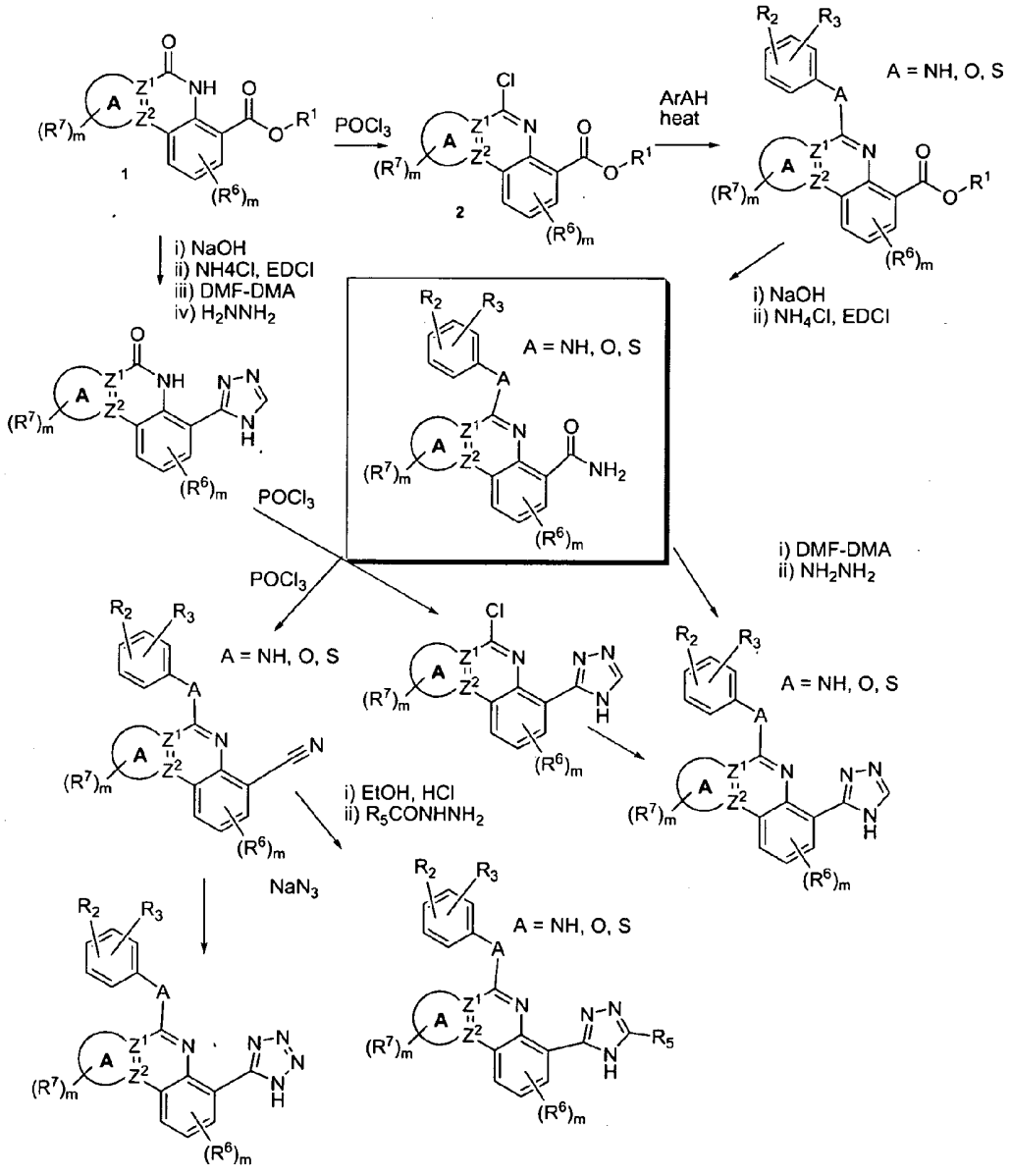
Example 18

[0212] The chemistry described below can be applied to compound **2** to prepare analogs with various functions:



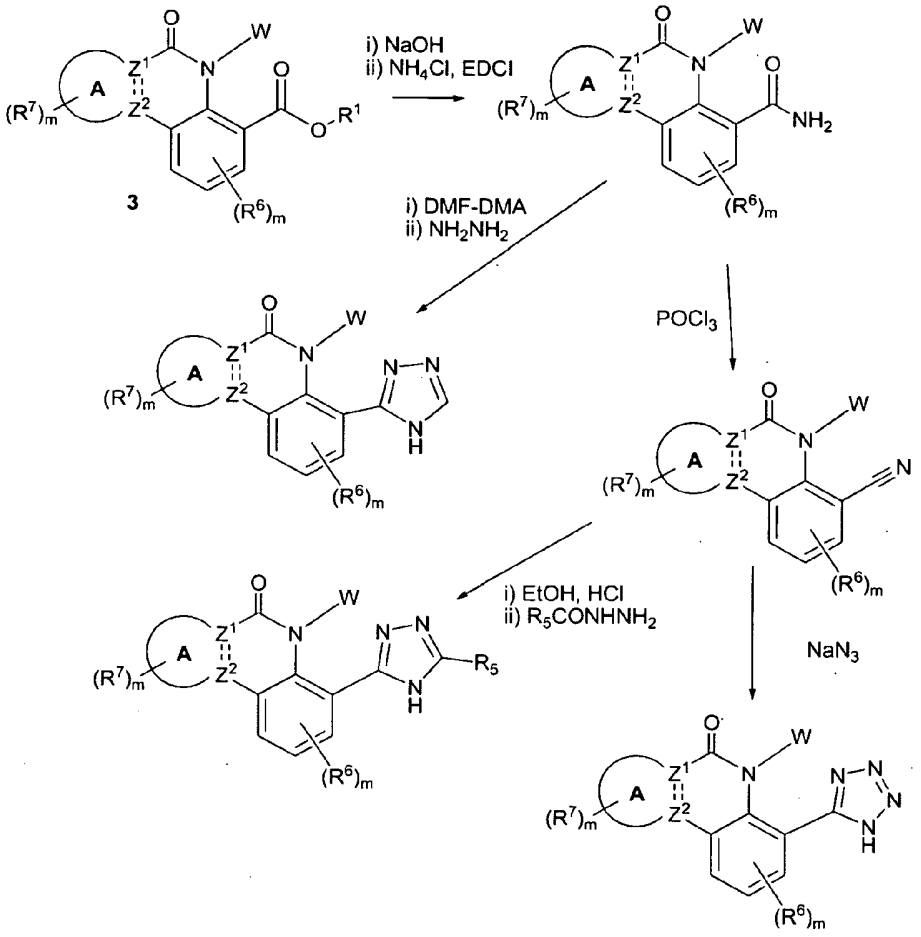
Example 19

[0213] The chemistry described below can be applied to modify the polar group:



Example 20

[0214] Similar chemistries can be applied to compound **3** as exemplified in the scheme below:



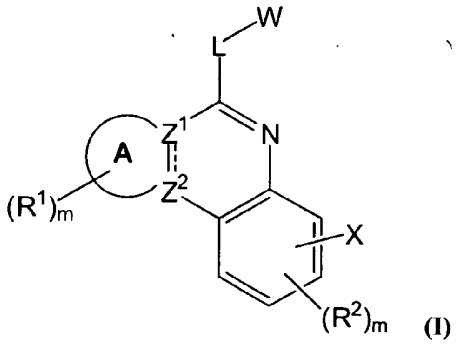
[0215] The entirety of each patent, patent application, publication and document referenced herein is hereby incorporated by reference. Citation of the above patents, patent applications, publications and documents is not an admission that any of the foregoing is pertinent prior art, nor does it constitute any admission as to the contents or date of these publications or documents.

[0216] Modifications may be made to the foregoing without departing from the basic aspects of the invention. Although the invention has been described in substantial detail with

reference to one or more specific embodiments, those of ordinary skill in the art will recognize that changes may be made to the embodiments specifically disclosed in this application, and yet these modifications and improvements are within the scope and spirit of the invention. The invention illustratively described herein suitably may be practiced in the absence of any element(s) not specifically disclosed herein. Thus, for example, in each instance herein any of the terms "comprising", "consisting essentially of", and "consisting of" may be replaced with either of the other two terms. Thus, the terms and expressions which have been employed are used as terms of description and not of limitation, equivalents of the features shown and described, or portions thereof, are not excluded, and it is recognized that various modifications are possible within the scope of the invention.

CLAIMS

1. A compound having a structure of Formula I:



(I)

wherein:

A is a saturated or partially saturated optionally substituted 5, 6 or 7 membered ring;

----- represents a single bond or a double bond;

Z^1 and Z^2 are independently N or C when ----- represents a single bond, provided Z^1 and Z^2 are not both N; and

Z^1 and Z^2 are C when ----- represents a double bond;

L is a linker selected from a bond, NR^3, O, S, CR^4R^5, CR^4R^5-NR^3, CR^4R^5-O-, and CR^4R^5-S;

each R^1, R^2, R^3, R^4 and R^5 is independently H, or an optionally substituted member selected from the group consisting of C1-C8 alkyl, C2-C8 heteroalkyl, C2-C8 alkenyl, C2-C8 heteroalkenyl, C2-C8 alkynyl, C2-C8 heteroalkynyl, C1-C8 acyl, C2-C8 heteroacyl, C6-C10 aryl, C5-C12 heteroaryl, C7-C12 arylalkyl, and C6-C12 heteroarylalkyl group,

or halo, OR, NR_2, NROR, $NRNR_2$, SR, SOR, SO_2R, SO_2NR_2, $NRSO_2R$, $NRCONR_2$, $NRCSNR_2$, $NRC(=NR)NR_2$, NRCOOR, NRCOR, CN, COOR, $CONR_2$, OOCR, COR, or NO_2,

wherein each R is independently H or C1-C8 alkyl, C2-C8 heteroalkyl, C2-C8 alkenyl, C2-C8 heteroalkenyl, C2-C8 alkynyl, C2-C8 heteroalkynyl, C1-C8 acyl, C2-C8 heteroacyl, C6-C10 aryl, C5-C10 heteroaryl, C7-C12 arylalkyl, or C6-C12 heteroarylalkyl,

and wherein two R on the same atom or on adjacent atoms can be linked to form a 3-8 membered ring, optionally containing one or more N, O or S;

and each R group, and each ring formed by linking two R groups together, is optionally substituted with one or more substituents selected from halo, =O, =N-CN, =N-OR', =NR', OR', NR'_2, SR', SO_2R', $SO_2NR'_2$, $NR'SO_2R'$, $NR'CONR'_2$, $NR'CSNR'_2$, $NR'C(=NR')NR'_2$, NR'COOR', NR'COR', CN, COOR', $CONR'_2$, OOCR', COR', and NO_2,

wherein each R' is independently H, C1-C6 alkyl, C2-C6 heteroalkyl, C1-C6 acyl, C2-C6 heteroacyl, C6-C10 aryl, C5-C10 heteroaryl, C7-12 arylalkyl, or C6-12 heteroarylalkyl, each of which is optionally substituted with one or more groups selected from halo, C1-C4 alkyl, C1-C4 heteroalkyl, C1-C6 acyl, C1-C6 heteroacyl, hydroxy, amino, and =O;

and wherein two R' on the same atom or on adjacent atoms can be linked to form a 3-7 membered ring optionally containing up to three heteroatoms selected from N, O and S;

and R^1 can be =O, or two R^1 groups on the same atom or on adjacent connected atoms, can optionally be linked together to form a 3-8 membered cycloalkyl or heterocycloalkyl, which is optionally substituted;

and R^4 and R^5, when on the same atom or on adjacent connected atoms, can optionally be linked together to form a 3 to 8 membered cycloalkyl or heterocycloalkyl, which is optionally substituted;

W is alkyl, heteroalkyl, aryl, heteroaryl, cycloalkyl, heterocyclyl, arylalkyl or heteroarylalkyl, each of which can be optionally substituted;

X is a polar substituent;

and each m is independently 0, 1, 2, or 3;

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

2. The compound of claim 1, wherein L is NH or NMe.

3. The compound of claim 1 or 2, wherein W is selected from the group consisting of optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl, and optionally substituted heterocyclyl.

4. The compound of claim 1, 2 or 3, wherein Z^1 and Z^2 are C and ----- represents a double bond.

5. The compound of claim 1, 2 or 3, wherein Z^1 is N, Z^2 is C and ----- represents a single bond.

6. The compound of claim 1, 2 or 3, wherein Z^1 is C, Z^2 is N and ----- represents a single bond.

7. The compound of any one of claims 1 to 6, wherein W is optionally substituted phenyl, optionally substituted heterocyclyl, or C1-C4 alkyl substituted with at least one member selected from the group consisting of optionally substituted phenyl, optionally substituted heteroalkyl, optionally substituted heteroaryl, halo, hydroxy and $-NR"_2$,

where each R" is independently H or optionally substituted C1-C6 alkyl;

and two R" taken together with the N to which they are attached can be linked together to form an optionally substituted 3 to 8 membered ring, which can contain another heteroatom selected from N, O and S as a ring member, and can be saturated, unsaturated or aromatic.

8. The compound of claim 7, wherein L is NH or NMe.

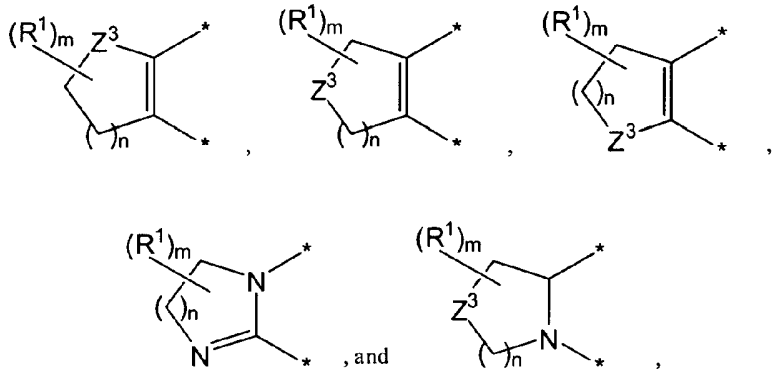
9. The compound of claim 7 or 8, wherein W comprises at least one group of the formula $-(CH_2)_p-NR^x_2$,

where p is 1, 2, 3, or 4,

R^x is independently at each occurrence H or optionally substituted alkyl;

and two R^x taken together with the N to which they are attached can be linked together to form an optionally substituted 3 to 8 membered ring, which can contain another heteroatom selected from N, O and S as a ring member, and can be saturated, unsaturated or aromatic.

10. The compound of any one of claims 1 to 9, wherein A is selected from the group consisting of:

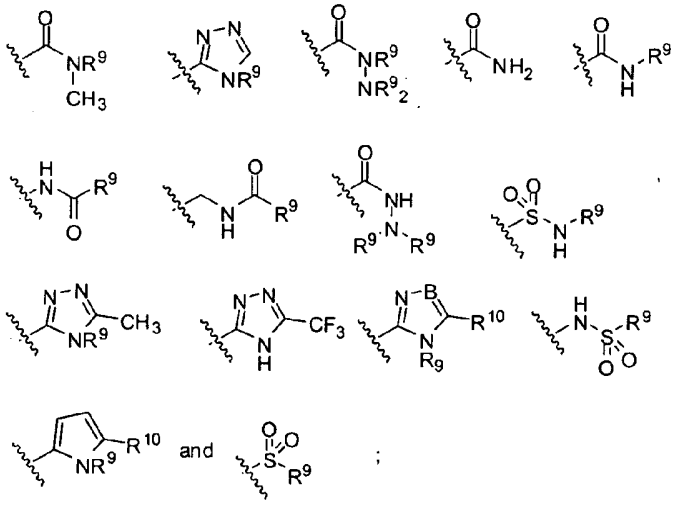


wherein Z^3 is CR^1_2, NR^1, $S(=O)_p$, or O;

n is 1, 2, or 3; and

p is 0,1, or 2.

11. The compound of any one of claims 1 to 10, wherein X is selected from the group consisting of $COOR^9$, $C(O)NR^9$-OR^9, triazole, tetrazole, CN, imidazole, carboxylate, a carboxylate bioisostere,



wherein each R^9 is independently H or an optionally substituted member selected from the group consisting of alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, arylalkyl, cycloalkylalkyl, heterocycloalkylalkyl, and heteroarylalkyl,

and two R^9 on the same or adjacent atoms can optionally be linked together to form an optionally substituted ring that can also contain an additional heteroatom selected from N, O and S as a ring member;

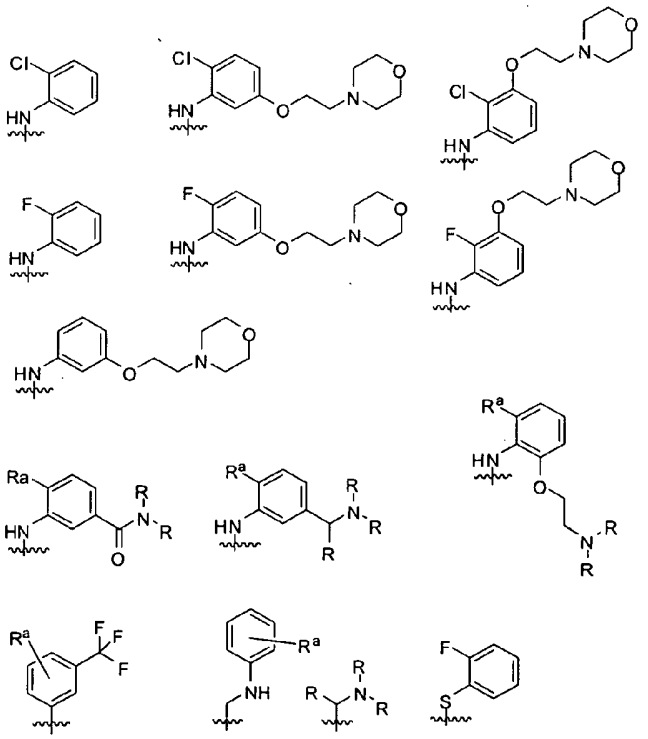
R^{10} is halo, CF_3, CN, SR, OR, NR_2, or R, where each R is independently H or optionally substituted C1-C6 alkyl, and two R on the same or adjacent atoms can optionally be linked together to form an optionally substituted ring that can also contain an additional heteroatom selected from N, O and S as a ring member;

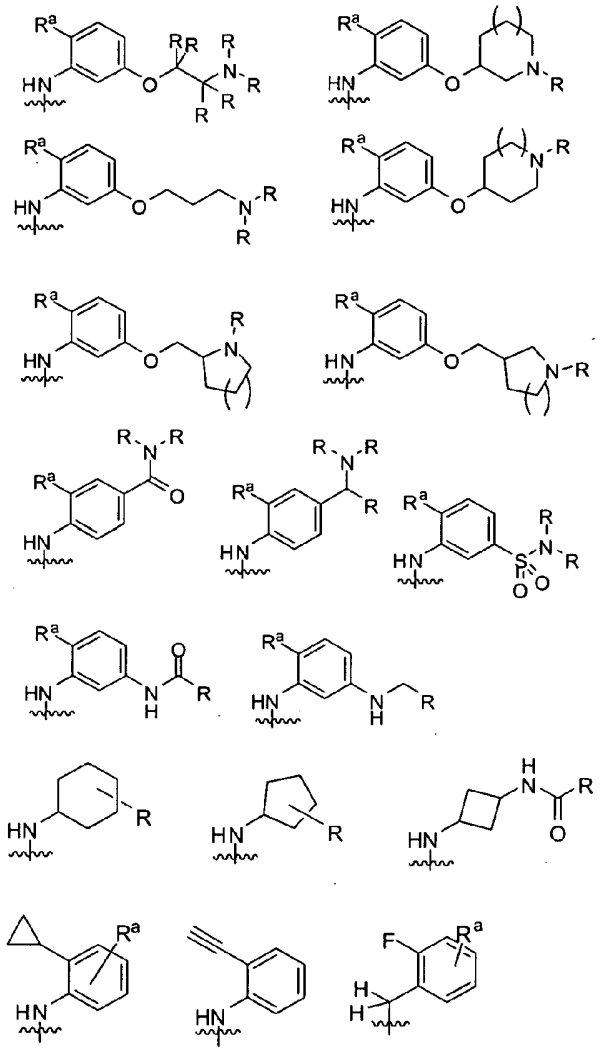
and B is N or CR^{10}.

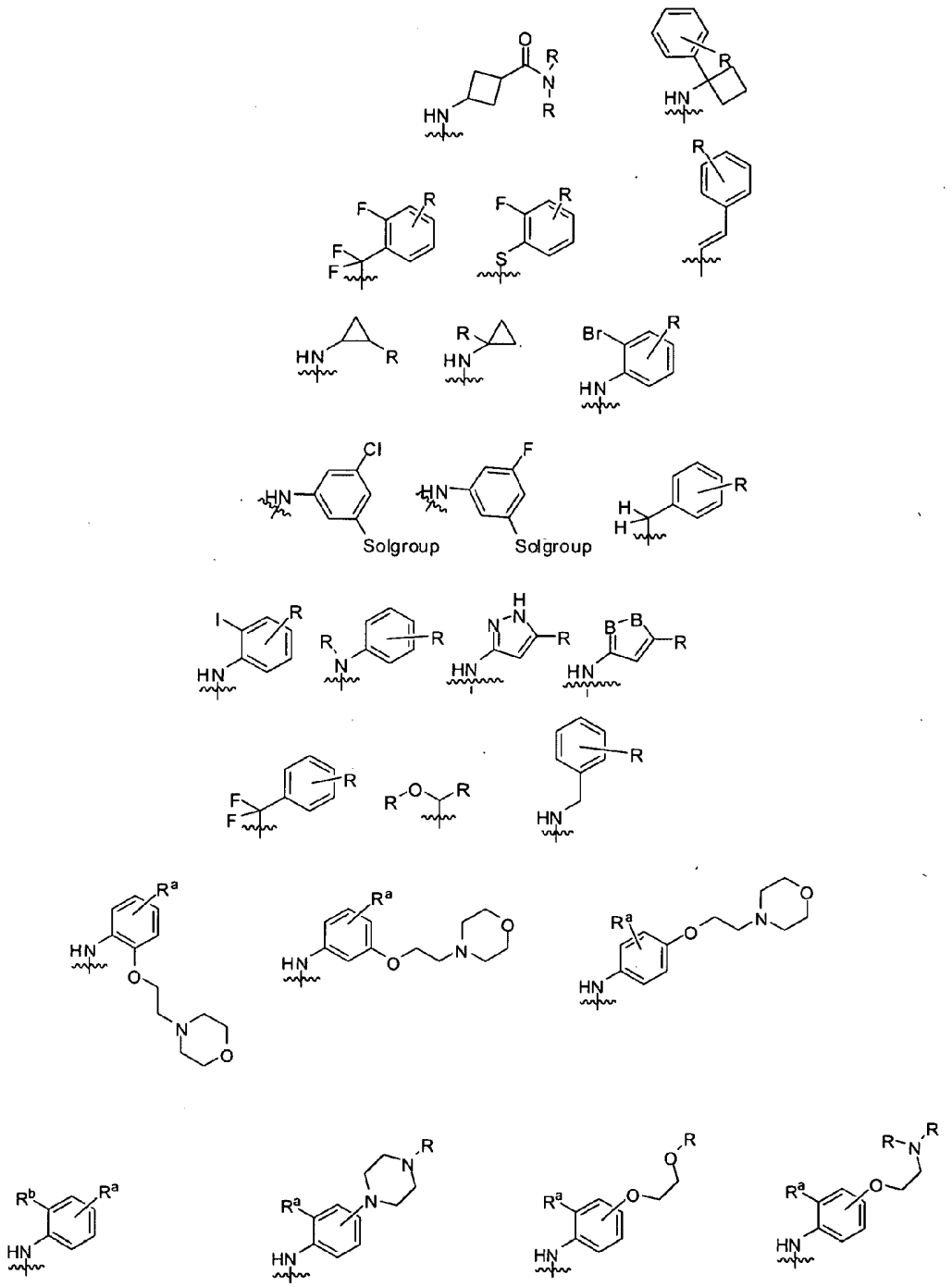
12. The compound of claim 11, wherein the polar substituent X is located at position 3 on the phenyl ring.

13. The compound of claim 11, wherein the polar substituent X is located at position 4 on the phenyl ring.

14. The compound of any one of claims 1 to 13, wherein –L-W is selected from:







wherein each R^a is independently H, Cl or F;

each R^b is independently Me, F, or Cl;

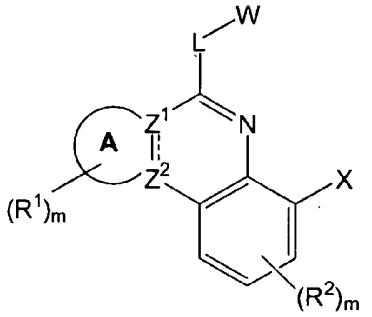
each R is independently selected from H, halo, C1-C4 alkyl, C1-C4 alkoxy, and C1-C4 haloalkyl,

and two R groups on the same or adjacent connected atoms can optionally be linked together to form a 3 to 8 membered ring;

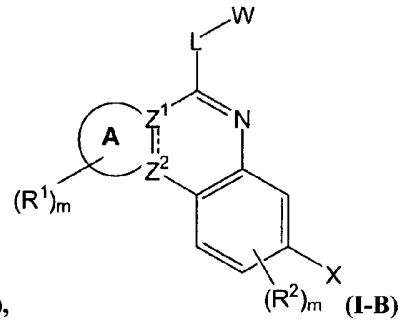
each B is N or CR;

and each Solgroup is a solubility-enhancing group.

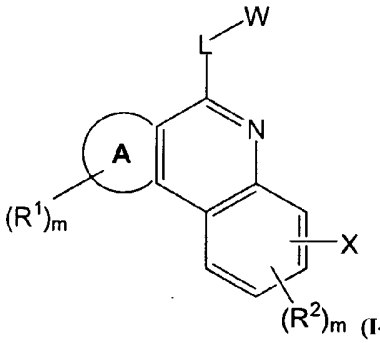
15. The compound of claim 1, having the Formula I-A, I-B, I-C, I-D or I-E:



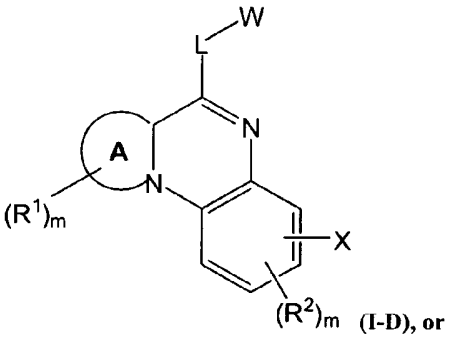
(I-A),



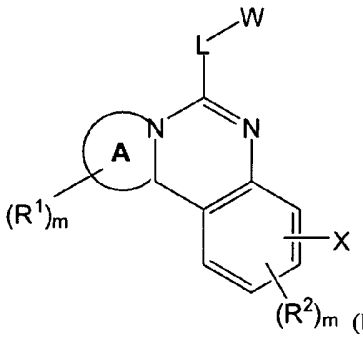
(I-B)



(I-C),



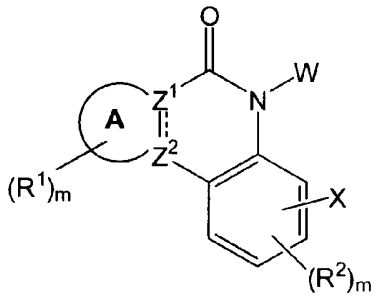
(I-D), or



(I-E),

or a pharmaceutically acceptable salt thereof.

16. A compound having a structure of Formula II:



(II)

wherein:

A is a saturated or partially saturated optionally substituted 5, 6 or 7 membered ring;

----- represents a single bond or a double bond;

Z^1 and Z^2 are independently N or C when ----- represents a single bond, provided Z^1 and Z^2 are not both N; and

Z^1 and Z^2 are C when ----- represents a double bond;

each of R^1 and R^2 is independently H, or an optionally substituted member selected from the group consisting of C1-C8 alkyl, C2-C8 heteroalkyl, C2-C8 alkenyl, C2-C8 heteroalkenyl, C2-C8 alkynyl, C2-C8 heteroalkynyl, C1-C8 acyl, C2-C8 heteroacyl, C6-C10 aryl, C5-C12 heteroaryl, C7-C12 arylalkyl, and C6-C12 heteroarylalkyl group,

or halo, OR, NR_2, NROR, $NRNR_2$, SR, SOR, SO_2R, SO_2NR_2, $NRSO_2R$, $NRCONR_2$, $NRCSNR_2$, $NRC(=NR)NR_2$, NRCOOR, NRCOR, CN, COOR, $CONR_2$, OOCR, COR, or NO_2,

wherein each R is independently H or C1-C8 alkyl, C2-C8 heteroalkyl, C2-C8 alkenyl, C2-C8 heteroalkenyl, C2-C8 alkynyl, C2-C8 heteroalkynyl, C1-

C8 acyl, C2-C8 heteroacyl, C6-C10 aryl, C5-C10 heteroaryl, C7-C12 arylalkyl, or C6-C12 heteroarylalkyl,

and wherein two R on the same atom or on adjacent atoms can be linked to form a 3 to 8 membered ring, optionally containing one or more N, O or S;

and each R group, and each ring formed by linking two R groups together, is optionally substituted with one or more substituents selected from halo, =O, =N-CN, =N-OR', =NR', OR', NR'_2, SR', SO_2R', $SO_2NR'_2$, NR'SO_2R', NR'CONR'$_2$, NR'CSNR'$_2$, NR'C(=NR')NR'$_2$, NR'COOR', NR'COR', CN, COOR', CONR'$_2$, OOCR', COR', and NO_2,

wherein each R' is independently H, C1-C6 alkyl, C2-C6 heteroalkyl, C1-C6 acyl, C2-C6 heteroacyl, C6-C10 aryl, C5-C10 heteroaryl, C7-12 arylalkyl, or C6-12 heteroarylalkyl, each of which is optionally substituted with one or more groups selected from halo, C1-C4 alkyl, C1-C4 heteroalkyl, C1-C6 acyl, C1-C6 heteroacyl, hydroxy, amino, and =O;

and wherein two R' on the same atom or on adjacent atoms can be linked to form a 3 to 7 membered ring optionally containing up to three heteroatoms selected from N, O and S;

and R^1 can be =O, or two R^1 groups on the same atom or on adjacent connected atoms, can optionally be linked together to form a 3 to 8 membered cycloalkyl or heterocycloalkyl, which is optionally substituted;

W is alkyl, heteroalkyl, aryl, heteroaryl, cycloalkyl, heterocyclyl, arylalkyl or heteroarylalkyl, each of which can be optionally substituted;

X is a polar substituent;

and each m is independently 0, 1, 2, or 3;

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

17. The compound of claim 16, wherein W is selected from the group consisting of optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl, and optionally substituted heterocyclyl.

18. The compound of claim 16 or 17, wherein Z^1 and Z^2 are C and ----- represents a double bond.

19. The compound of claim 16 or 17, wherein Z^1 is N, Z^2 is C and ----- represents a single bond.

20. The compound of claim 16 or 17, wherein Z^1 is C, Z^2 is N and ----- represents a single bond.

21. The compound of any one of claims 16 to 20, wherein W is optionally substituted phenyl, optionally substituted heterocyclyl, or C1-C4 alkyl substituted with at least one member selected from the group consisting of optionally substituted phenyl, optionally substituted heteroalkyl, optionally substituted heteroaryl, halo, hydroxy and $-NR"_2$,

where each R" is independently H or optionally substituted C1-C6 alkyl;

and two R" taken together with the N to which they are attached can be linked together to form an optionally substituted 3to 8 membered ring, which can contain another heteroatom selected from N, O and S as a ring member, and can be saturated, unsaturated or aromatic.

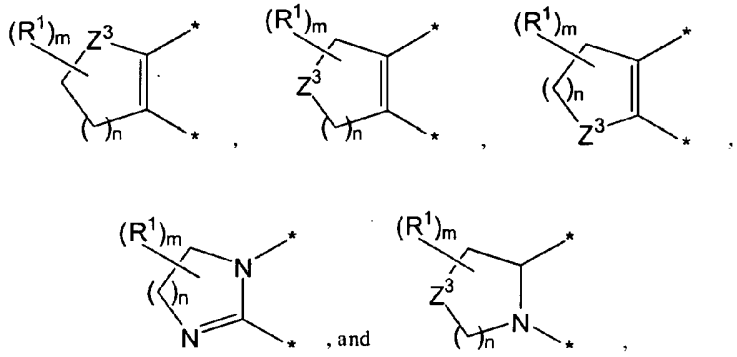
22. The compound of claim 21, wherein W comprises at least one group of the formula $-(CH_2)_p-NR^x_2$,

where p is 1, 2, 3, or 4,

R^x is independently at each occurrence H or optionally substituted alkyl;

and two R^x taken together with the N to which they are attached can be linked together to form an optionally substituted 3 to 8 membered ring, which can contain another heteroatom selected from N, O and S as a ring member, and can be saturated, unsaturated or aromatic.

23. The compound of any one of claims 16 to 22, wherein A is selected from the group consisting of:

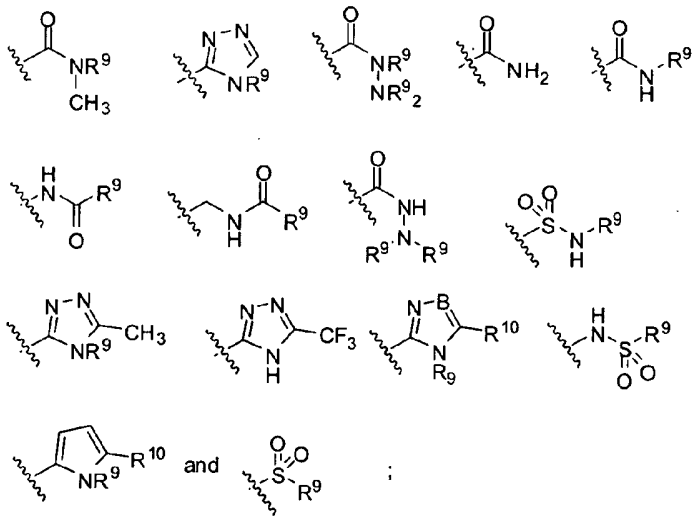


wherein Z^3 is CR^1_2, NR^1, $S(=O)_p$, or O;

n is 1, 2, or 3; and

p is 0, 1, or 2.

24. . The compound of any one of claims 16 to 23, wherein X is selected from the group consisting of $COOR^9$, $C(O)NR^9$-OR^9, triazole, tetrazole, CN, imidazole, carboxylate, a carboxylate bioisostere,



wherein each R^9 is independently H or an optionally substituted member selected from the group consisting of alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, arylalkyl, cycloalkylalkyl, heterocycloalkylalkyl, and heteroarylalkyl,

and two R^9 on the same or adjacent atoms can optionally be linked together to form an optionally substituted ring that can also contain an additional heteroatom selected from N, O and S as a ring member;

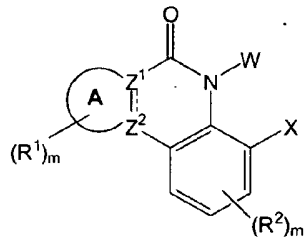
R^{10} is halo, CF_3, CN, SR, OR, NR_2, or R, where each R is independently H or optionally substituted C1-C6 alkyl, and two R on the same or adjacent atoms can optionally be linked together to form an optionally substituted ring that can also contain an additional heteroatom selected from N, O and S as a ring member;

and B is N or CR^{10}.

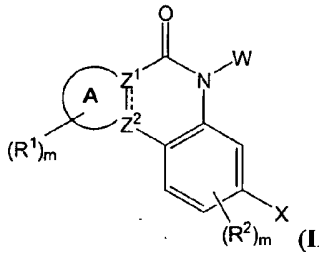
25. The compound of claim 24, wherein the polar substituent X is located at position 3 on the phenyl ring.

26. The compound of claim 24, wherein the polar substituent X is located at position 4 on the phenyl ring.

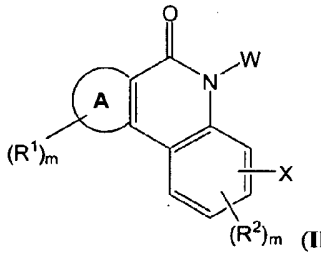
27. The compound of claim 1, having the Formula II-A, II-B, II-C, II-D or II-E:



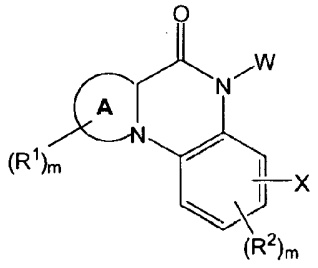
(II-A),



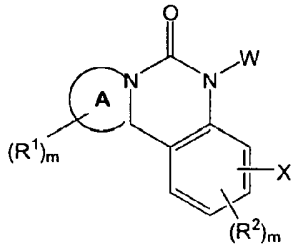
(II-B)



(II-C),



(II-D), or



(II-E),

or a pharmaceutically acceptable salt thereof.

28. A pharmaceutical composition comprising a compound of any one of claims 1 to 27, or a pharmaceutically acceptable salt, solvate, and/or prodrug thereof; and a pharmaceutically acceptable excipient.

29. A method of inhibiting cell proliferation, which comprises contacting cells with a compound of any one of claims 1 to 27, or a pharmaceutically acceptable salt, solvate, and/or prodrug thereof in an amount effective to inhibit proliferation of the cells.

30. The method of claim 29, wherein the cells are in a cancer cell line.

31. The method of claim 29, wherein the cells are in a tumor in a subject, or from an eye of a subject having macular degeneration, or in a subject having macular degeneration.

32. A method of treating a condition related to aberrant cell proliferation, which comprises administering a compound of any one of claims 1 to 27, or a pharmaceutically acceptable salt, solvate, and/or prodrug thereof, to a subject in need thereof in an amount effective to treat the cell proliferative condition.

33. The method of claim 32, wherein the cell proliferative condition is a tumor-associated cancer, a non-tumor cancer, or macular degeneration.

34. The method of claim 33, wherein the non-tumor cancer is a hematopoietic cancer.

35. A method of treating a condition or disease associated with casein kinase 2 activity, Pim kinase activity, and/or Fms-like tyrosine kinase activity comprising administering a

compound of any one of claims 1 to 27, or a pharmaceutically acceptable salt, solvate, and/or prodrug thereof, to a subject in need thereof in a therapeutically effective amount.

36. The method of claim 35, wherein the condition or disease is a cancer of colorectum, breast, lung, liver, pancreas, lymph node, colon, prostate, brain, head and neck, skin, liver, kidney, blood and heart.

37. A method of treating pain or inflammation in a subject, which comprises administering a compound of any one of claims 1 to 27, or a pharmaceutically acceptable salt, solvate, and/or prodrug thereof, to a subject in need thereof in an amount effective to treat the pain or the inflammation.

38. A method of inhibiting angiogenesis in a subject, which comprises administering a compound of any one of claims 1 to 27, or a pharmaceutically acceptable salt, solvate, and/or prodrug thereof, to a subject in need thereof in an amount effective to inhibit the angiogenesis.

39. A method of treating an infection in a subject, which comprises administering a compound of any one of claims 1 to 27, or a pharmaceutically acceptable salt, solvate, and/or prodrug thereof to a subject in need thereof, in an amount effective to treat the infection.

40. The method of claim 39, wherein the infection is selected from *Theileria parva, Trypanosoma cruzi, Leishmania donovani, Herpetomonas muscarum muscarum, Plasmodium falciparum, Trypanosoma brucei, Toxoplasma gondii* and *Schistosoma mansoni*, human immunodeficiency virus type 1 (HIV-1), human papilloma virus, herpes simplex virus, human cytomegalovirus, hepatitis C and B viruses, Epstein-Barr virus, Borna disease virus, adenovirus, coxsackievirus, coronavirus, influenza, and varicella zoster virus.

41. A method of modulating casein kinase 2 activity, Pim kinase activity, and/or Fms-like tyrosine kinase activity in a cell comprising contacting the cell with a compound any one of claims 1 to 27, or a pharmaceutically acceptable salt, solvate, and/or prodrug thereof.

42. A pharmaceutical composition comprising a compound of any of one of claims 1 to 27, or a pharmaceutically acceptable salt, solvate, and/or prodrug thereof; and at least one additional therapeutic agent.

43. A method to treat a condition related to aberrant cell proliferation, which comprises co-administering to a subject in need of treatment for such condition a compound of any of one of claims 1 to 27, or a pharmaceutically acceptable salt, solvate, and/or prodrug thereof; and at least one additional therapeutic agent.