

TRICYCLIC COMPOUNDS AND PHARMACEUTICAL USES THEREOF**CROSS-REFERENCE TO RELATED APPLICATION**

[001] This application claims the benefit of U.S. Provisional Application No. 61/243,107, filed on September 16, 2009 and entitled "TRICYCLIC COMPOUNDS AND PHARMACEUTICAL USES THEREOF", the contents of which are hereby incorporated by reference in their entirety for all purposes.

FIELD OF THE INVENTION

[002] The invention relates in part to molecules having certain biological activities that include, but are not limited to, inhibiting cell proliferation, and modulating certain protein kinase activities. The compounds of the invention have a tricyclic core comprising a five-membered aromatic nitrogen heterocyclic ring, with a polar group on that five-membered ring. Molecules of the invention modulate protein kinase CK2 activity formerly known as casein kinase activity and/or Pim kinase activity (e.g., Pim-1 activity), and are useful to treat cancers and inflammatory conditions as well as certain infectious disorders. The invention also relates in part to methods for using such compounds, and pharmaceutical compositions containing these compounds.

BACKGROUND OF THE INVENTION

[003] 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 are useful for treating certain types of cancers are described in PCT/US2007/077464, PCT/US2008/074820, PCT/US2009/35609.

[004] 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.

[005] 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.

[006] 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.*

[007] 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.*

[008] 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.

[009] 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.

[010] 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.

5 [011] 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.

10 [012] 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*,
15 *Plasmodium falciparum*, *Trypanosoma brucei*, *Toxoplasma gondii* and *Schistosoma mansoni*. Indeed, inhibition of CK2 has been shown to block infection by *T. cruzi*.

20 [013] 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., Epstein-Barr, 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. CK2 also phosphorylates HIV-2 Nef, and it phosphorylates Vpu protein, leading to rapid loss of circulating CD4+ T-cells.
25 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.

30 [014] 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.

5 **[015]** 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
10 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
15 and phosphorylates Cdc25A, which leads to an increase in its phosphatase activity and promotion of G1/S transition [reviewed in Losman et al., *JBC*, 278, 4800-4805 (1999)]. In addition, the cyclin kinase inhibitor p21^{Waf} which inhibits G1/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
20 which results in acceleration of G2/M transition [Bachman et al., *JBC*, 279, 48319-48 (2004)].

[016] Pim-1 appears to be an essential player in hematopoietic proliferation. Kinase active Pim-1 is required for the gpl30-mediated STAT3 proliferation signal [Hirano et al., *Oncogene* 19, 2548-2556, (2000)]. Pim-1 is overexpressed or even mutated in a number of
25 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
30 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.

[017] 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
5 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.

[018] The implication of a role for PIM-3 in cancer was first suggested by
10 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
15 hepatocellular cancer cell lines.

[019] 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
20 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 Ser112. 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
25 pancreatic cancer have a poor clinical outcome, PIM-3 could represent a new important molecular target towards successful control of this incurable disease.

[020] At the 2008 AACR Annual Meeting, SuperGen announced that it has identified a lead PIM kinase inhibitor, SGI-1776, which causes tumor regression in acute myelogenous leukemia (AML) xenograft models (Abstract No. 4974). In an oral presentation entitled, "A
30 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.

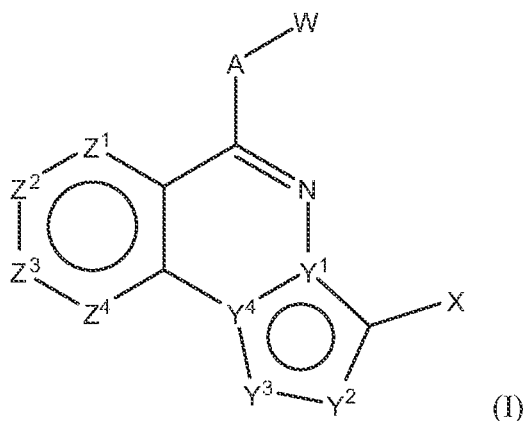
[021] Fedorov, et al., in *PNAS* vol. 104(51), 20523-28, showed that a selective inhibitor of Pim-1 kinase (Ly5333'531) suppressed cell growth and induced cell death in leukemic cells from AML patients. Pim-3 has been shown to be expressed in pancreatic cancer cells, while it is not expressed in normal pancreas cells, demonstrating that it should be a good target for pancreatic cancer. Li, et al., *Cancer Res.* 66(13), 6741-47 (2006).

[022] Because these two protein kinases have important functions in biochemical pathways associated with cancer and inflammation, and are also important in pathogenicity of many 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.

DISCLOSURE OF THE INVENTION

[023] 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 activities. These molecules modulate casein kinase 2 (CK2) activity and/or Pim kinase 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 these compounds. Also provided are compositions comprising the above-described molecules in combination with other materials, including other therapeutic agents and/or pharmaceutically acceptable excipients or diluents, and methods for using such compositions.

[024] In one aspect, the compounds of the invention are of Formula (I):



wherein:

each of Z^1 , Z^2 , Z^3 and Z^4 is independently CR^1 or N, provided no more than two of Z^1 to Z^4 are N, and the ring containing Z^1 - Z^4 is aromatic;

each R^1 is independently H, halo, CN, optionally substituted C1-C4 alkyl, optionally substituted C2-C4 alkenyl, optionally substituted C2-C4 alkynyl, optionally substituted C1-C4 alkoxy, SR, SO_2R , COOR, $COONR^7R^8$, or $-NR^7R^8$;

each of Y^1 and Y^4 is C or N, and Y^1 and Y^4 are not both simultaneously N; provided at least one of Y^1 to Y^4 is N;

Y^2 is N, NR^2 , CR^2 or CX^2 ,

wherein each R^2 is independently H, -OR, halo, CN, or optionally substituted C1-C4 alkyl,

and each X^2 is $-(CH_2)_{0-2}COOR$ or a polar group;

X is $-(CH_2)_{0-2}COOR$ or a polar group, or X is R^2 when Y^2 is CX^2 ;

each R is independently H or optionally substituted C1-C4 alkyl;

Y^3 is N, NR^3 , or CR^3 , and the ring containing Y^2 and Y^3 is aromatic;

wherein each R^3 is independently H, halo, -OR CN, or optionally substituted C1-C4 alkyl;

A is a bond, NR^4 , O or S, where R^4 is H or optionally substituted C1-C4 acyl;

W is optionally substituted aryl or arylalkyl; optionally substituted heteroaryl or heteroarylalkyl; optionally substituted heterocyclyl or heterocyclalkyl; or optionally substituted C3-C8 cycloalkyl or cycloalkylalkyl;

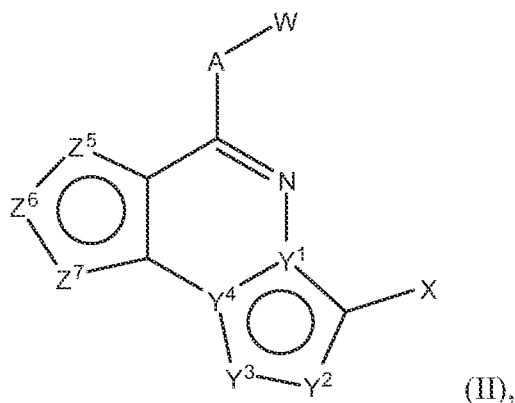
or alternatively, -A-W is NR^7R^8 ;

each R^7 and R^8 is independently selected from H, optionally substituted C1-C10 alkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, and optionally substituted heteroarylalkyl;

and wherein R^7 and R^8 in NR^7R^8 can be taken together along with N to form a 4-8 membered ring that can be optionally substituted, and can contain an additional heteroatom selected from N, O and S as a ring member.

[025] The invention also includes the pharmaceutically acceptable salts, solvates, and/or prodrugs of compounds of Formula (I).

[026] In another aspect, the invention provides a compound of Formula (II):



wherein:

each of Z^5 and Z^6 and Z^7 is independently CR^1 , NR^2 , N, O or S, provided at least one of Z^5 to Z^7 is not CR^1 , and no more than one of Z^5 to Z^7 is O or S, and the ring containing Z^5 - Z^7 is aromatic;

each of Y^1 and Y^4 is independently C or N, and Y^1 and Y^4 are not both simultaneously N; provided at least one of Y^1 to Y^4 is N;

Y^2 is N, CR^1 or CX^2 , where X^2 is $-(CH_2)_{0-2}COOR$ or a polar group;

Y^3 is CR^3 , and the ring containing Y^2 and Y^3 is aromatic;

each R^1 is independently H, halo, CN, optionally substituted C1-C4 alkyl, optionally substituted C2-C4 alkenyl, optionally substituted C2-C4 alkynyl, OR, SR, SO_2R , COOR, $COONR^7R^8$, or $-NR^7R^8$;

each R^2 is independently H, CN, -OR, COOR, $CONR_2$, SO_2R , or optionally substituted C1-C4 alkyl;

each R^3 is independently H, halo, CN, -OR, or optionally substituted C1-C4 alkyl;

X is $-(CH_2)_{0-2}COOR$ or a polar group, or X can be R^1 when Y^2 is CX^2 ;

R is independently at each occurrence H or an optionally substituted C1-C4 alkyl;

A is a bond, NR^4 , O or S;

wherein R^4 is H or optionally substituted C1-C4 acyl;

W is optionally substituted aryl or arylalkyl; optionally substituted heteroaryl or heteroarylalkyl; optionally substituted heterocyclyl or heterocyclalkyl; or optionally substituted C3-C8 cycloalkyl or cycloalkylalkyl;

or alternatively, -A-W is NR^7R^8 ;

each R^7 and R^8 is independently selected from H, optionally substituted C1-C10 alkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, and optionally substituted heteroarylalkyl;

and wherein R^7 and R^8 in NR^7R^8 can be taken together along with N to form a 4-8 membered ring that can be optionally substituted, and can contain an additional

heteroatom selected from N, O and S as a ring member;

and pharmaceutically acceptable salts, solvates, and/or prodrugs thereof.

[027] The compounds of Formula (I) and Formula (II) can be used as neutral compounds, or as salts. In certain embodiments, the compounds include pharmaceutically acceptable salts, solvates, and/or prodrugs of the compounds of Formula (I) or (II).

[028] The invention also provides pharmaceutical compositions containing such compounds of Formula (I) or (II), plus one or more pharmaceutically acceptable carriers or excipients, and methods of using these compounds and compositions for the treatment of specified conditions as further described herein.

[029] The compounds of the invention are characterized by a tricyclic heterocyclic ring system containing at least two nitrogen atoms: one in the central ring of the tricyclic system and at least one in the five-membered ring comprising Y^2 . Optionally, the tricyclic system can contain additional heteroatoms (N, O and/or S) as ring members. The five-membered ring comprising Y^2 has at least one polar group or COOR group as a substituent, either as the group X or on the atom represented by Y^2 .

[030] In Formulas (I) and (II), at least one of X and X^2 represents a group of formula - $(\text{CH}_2)_{0-2}\text{COOR}$ or a polar group present on the molecule. In some of these compounds, this group is COOR, where R can be H or an optionally substituted alkyl, e.g., C1-C4 alkyl. Frequently, R is H, Me or Et, or a substituted C1-C4 alkyl such as $-(\text{CH}_2)_{1-2}\text{-OMe}$ or $-\text{CH}_2\text{CF}_3$. In some embodiments, X is COOR or a polar group; in alternative embodiments, X is R^2 , and Y is C-X^2 , wherein X^2 is COOR or a polar group. Suitable polar groups are discussed further herein.

[031] In some embodiments of the compounds of Formulas I and II, A is NH, O or S. In certain embodiments, A is NH.

[032] W can represent a variety of groups that comprise a ring, and in some embodiments it is a C5-C10 aromatic or heteroaromatic ring, where the heteroaromatic ring comprises at least one heteroatom selected from N, O and S as a ring member. The aromatic and heteroaromatic rings are optionally substituted. Many substituents as disclosed herein for aromatic and heteroaromatic rings can be present. In some embodiments, the aromatic or heteroaromatic ring represented by W is substituted by at least one substituent selected from halo, optionally substituted C1-C4 alkyl, C1-C4 alkoxy, CN, or a group of the formula COOR', CONR'₂, NR'C(O)R', NR'C(O)OR', SR', S(O)R', or SO₂R'. In these substituents, R' is independently at each occurrence H or optionally substituted C1-C4 alkyl; preferably, each R' is independently H or C1-C4 alkyl; and if two R' are present on one substituent group, they can be taken together to form a 4-7 membered ring that can optionally include O, N or S as a ring member.

[033] Specific embodiments of the substituted phenyl that can be W include 3-chlorophenyl, 2-fluorophenyl, 3-fluorophenyl, 3-carboxyphenyl, and 3-(COOMe)-phenyl.

[034] The compounds of the invention include compounds of Formula (I) that contain the features specifically described below, or any combination of these features.

[035] Also provided herein are pharmaceutical compositions comprising a compound of Formula (I) or (II) as described herein and at least one pharmaceutically acceptable carrier or excipient, or two or more pharmaceutically acceptable carriers and/or excipients.

Pharmaceutical compositions comprising at least one of these compounds can be utilized in methods of treatment such as those described herein.

[036] The compounds of Formula (I) and (II) bind to certain kinase proteins, and without being bound by theory, this is believed to be the basis for their pharmaceutical activity.

[037] 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.

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 lvfehvntd
121 fkqlyqtlt d ydirfymyei lkaldychsm gimhrdvkph nvmidhehrk
lrlidwglae
181 fyhpgqeynv rvasryfkqp ellvdyqmyd ysldmwsllgc mlasimifrke
pffhghdnyd
241 qlvriakvlg tedlydyidk yniel dprfn dilgrhsrkr werfvhsenq
hlvspealdf

```

301 ldkllrydhq srltareame hpyfytvvkd qarmgssmp ggstpvssan
 mmsgissvpt
 361 pspgplags pviaaanplg mpvpaaagaq q

5 SEQ ID NO: 2 (NP_808227; casein kinase II alpha 1 subunit isoform a [Homo sapiens])

msgpvpsrar vytdvnthrp reywdyeshv vewgnqddyq lvrklgrgky
 sevfeainit
 nnekvvvki kpvkkkkikr eikilenlrg gpnitladi vkdpvsrtpa lvfehvntd
 121 fkqllyqtltd ydirfymyei lkaldychsm gimhrdvkph nvmidhehrk
 10 lrlidwglae
 181 fyhpgqeynv rvasryfkqp ellvdyqmyd ysldmwsllgc mlasmlfrke
 pffhghdnyd
 241 qlvriakvlq tedlydyidk ynielldprfn dilgrhsrkr werfvhsenq
 hlvspaldf
 15 301 ldkllrydhq srltareame hpyfytvvkd qarmgssmp ggstpvssan
 mmsgissvpt
 361 pspgplags pviaaanplg mpvpaaagaq q

20 SEQ ID NO: 3 (NP_808228; casein kinase II alpha 1 subunit isoform b [Homo sapiens])

myeilkalay chsmgimhrd vkphnmidh ehrklrlidw glaefyhpgq
 eynvrvasry
 fkgpellvdy qmydysldmw slgcm lasmi frkepfhgh dnydqlvria kvlgatedlyd
 121 yidkynield prfndilgrh srkrwerfvh senqhlvspe aldfldklr
 ydhqsrllar
 25 181 eamehpyfyt vvk dqarmgs ssmpggstpv ssanmmsgis svptpsplgp
 lagspvaaaa
 241 nplgmpvpaa agaqq

[038] Substantially identical variants of these include proteins having at least 90%

30 sequence homology with one of these, preferably at least 90% sequence identity; and having
 at least 50% of the level of *in vitro* kinase activity of the specified sequence under typical
 assay conditions.

[039] The invention includes methods to modulate the activity of CK2 protein, either in
 vitro or ex vivo. Suitable methods comprise contacting a system comprising the protein with
 35 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 comprising the amino acid sequence of SEQ ID NO: 1, 2 or 3 or a
 substantially identical variant thereof, for example. In certain embodiments the CK2 is in a
 cell or tissue; in other embodiments, it can be in a cell-free system.

40 [040] In some embodiments, the invention provides methods and compositions for
 modulating the activity of a Pim 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 system is a cell, and in other embodiments the

system is a cell-free system. In certain embodiments, the activity of the Pim protein is inhibited.

[041] 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, hemopoietic 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.

[042] 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 cancer of the breast, prostate, pancreas, lung, colorectum, skin, or ovary.

[043] In some embodiments, the cell proliferative condition is a non-tumor cancer, such as a hematopoietic cancer, for example, including leukemias and lymphomas.

[044] The cell proliferative condition is macular degeneration in some embodiments.

[045] The invention also includes methods for treating cancer 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 and/or Pim in an amount that is effective to enhance a desired effect of the therapeutic agent. In certain embodiments, the molecule that inhibits CK2 and/or Pim is a compound of Formula (I), including compounds of Formula (I)a and Ib, or a pharmaceutically acceptable salt, solvate, and/or prodrug thereof. In certain embodiments, the desired effect of the therapeutic agent that is enhanced by the molecule that inhibits CK2 and/or Pim is an increase in apoptosis in at least one type of cell.

[046] In some embodiments, the condition is a pathogenic infection such as those described herein.

[047] In some embodiments, the therapeutic agent and the molecule that inhibits CK2 and/or Pim are administered at substantially the same time. The therapeutic agent and molecule that inhibits CK2 and/or Pim sometimes are used concurrently by the subject. The therapeutic agent and the molecule that inhibits CK2 and/or Pim can be combined into one

pharmaceutical composition in certain embodiments; in other embodiments that are administered as separate compositions.

[048] Also provided are compositions of matter comprising a compound described herein and an isolated protein. The protein sometimes 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 some embodiments, the protein is a Pim protein. Certain compositions comprise a compound described herein in combination with a cell. The cell may be from a cell line, such as a cancer cell line. In the latter embodiments, the cancer cell line is sometimes a breast cancer, prostate cancer, pancreatic cancer, lung cancer, hematopoietic cancer, colorectal cancer, skin cancer, of ovary cancer cell line.

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

MODES OF CARRYING OUT THE INVENTION

[050] Compounds of Formula (I) and (II) exert biological activities that include, but are not limited to, inhibiting cell proliferation, reducing angiogenesis, preventing or reducing inflammatory responses and pain, modulating certain immune responses, and treating certain pathogenic infections. Compounds of these Formulae can modulate CK2 activity, Pim activity or both, as demonstrated herein. Such compounds therefore can be utilized in multiple applications by a person of ordinary skill in the art. For example, compounds described herein can be used, for example, for (i) modulation of protein kinase activity (e.g., CK2 activity), (ii) modulation of Pim activity (e.g., Pim-1 activity), (iii) modulation of cell proliferation, (iv) modulation of apoptosis, and (v) treatments of cell proliferation related disorders (e.g., administration alone or co-administration with another molecule), and (vi) treatment of certain pathogenic (viral, bacterial, etc.) infections.

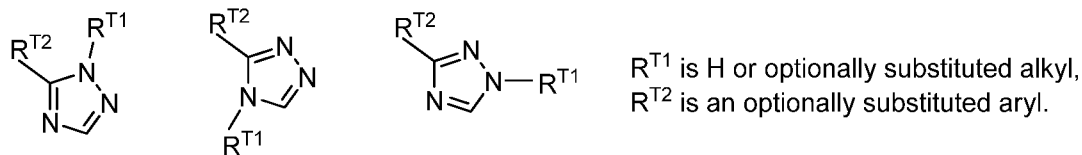
Definitions:

[051] 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.

[052] 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”.

[053] 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.

[054] 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:



[055] 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.

[056] "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.

[057] 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 alkoxy-carbonylalkyl 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; isopropylloxycarbonyloxyethyl 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, isopropylloxycarbonyloxyethyl esters and (5-methyl-2-oxo-1,3-dioxole-4-yl)methyl esters.

[058] 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.

[059] “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.

[060] 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.

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

[062] 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.

[063] 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-butylnyl, 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.

[064] 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.

[065] 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, NR₂, SR, SO₂R, SO₂NR₂, NRSO₂R, NRCONR₂, NRC₂SNR₂, NRC(=NR)NR₂, NR₂COOR, NRCOR, CN, C≡CR, COOR, CONR₂, OOCR, COR, and NO₂, 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, C3-C8 heterocyclyl, C4-C10 heterocyclylalkyl, 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', SO₂R', SO₂NR'₂, NR'SO₂R', NR'CONR'₂, NR'C₂SNR'₂, NR'C(=NR')NR'₂, NR'COOR', NR'COR', CN, C≡CR', COOR', CONR'₂, OOCR', COR', and NO₂, wherein each R' is independently H, C1-C8 alkyl, C2-C8 heteroalkyl, C1-C8 acyl, C3-C8 heterocyclyl, 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, C3-C8 cycloalkyl, C3-C8 heterocyclyl, or C5-C10 heteroaryl, each of which can be substituted by the substituents that are appropriate for the particular group. Where a substituent group contains two R or R' groups on the same or adjacent atoms (e.g., -NR₂, or -NR-C(O)R), the two R or R' groups can optionally be taken together with the atoms in the substituent group to which they are attached to form a ring having 5-8 ring members, which can be substituted as allowed for the R or R' itself, and can contain an additional heteroatom (N, O or S) as a ring member.

[066] "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.

5 **[067]** “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).

[068] Substituent groups useful for substituting saturated carbon atoms in the specified group or radical include, but are not limited to $-R^a$, halo, $-O^-$, $=O$, $-OR^b$, $-SR^b$, $-S^-$, $=S$,
 10 $-NR^cR^c$, $=NR^b$, $=N-OR^b$, trihalomethyl, $-CF_3$, $-CN$, $-OCN$, $-SCN$, $-NO$, $-NO_2$, $=N_2$, $-N_3$,
 $-S(O)_2R^b$, $-S(O)_2NR^b$, $-S(O)_2O^-$, $-S(O)_2OR^b$, $-OS(O)_2R^b$, $-OS(O)_2O^-$, $-OS(O)_2OR^b$, $-P(O)(O^-)_2$,
 $-P(O)(OR^b)(O^-)$, $-P(O)(OR^b)(OR^b)$, $-C(O)R^b$, $-C(S)R^b$, $-C(NR^b)R^b$, $-C(O)O^-$, $-C(O)OR^b$,
 $-C(S)OR^b$, $-C(O)NR^cR^c$, $-C(NR^b)NR^cR^c$, $-OC(O)R^b$, $-OC(S)R^b$, $-OC(O)O^-$, $-OC(O)OR^b$,
 $-OC(S)OR^b$, $-NR^bC(O)R^b$, $-NR^bC(S)R^b$, $-NR^bC(O)O^-$, $-NR^bC(O)OR^b$, $-NR^bC(S)OR^b$,
 15 $-NR^bC(O)NR^cR^c$, $-NR^bC(NR^b)R^b$ 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^c s 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
 20 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
 25 groups, taken together with the atoms to which they are bonded, may form a cyclic ring including cycloalkyl and cycloheteroalkyl.

[069] 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, $-CF_3$, $-CN$, $-OCN$, $-SCN$, $-NO$, $-NO_2$, $-N_3$, $-S(O)_2R^b$, $-S(O)_2O^-$,
 30 $-S(O)_2OR^b$, $-OS(O)_2R^b$, $-OS(O)_2O^-$, $-OS(O)_2OR^b$, $-P(O)(O^-)_2$, $-P(O)(OR^b)(O^-)$,
 $-P(O)(OR^b)(OR^b)$, $-C(O)R^b$, $-C(S)R^b$, $-C(NR^b)R^b$, $-C(O)O^-$, $-C(O)OR^b$, $-C(S)OR^b$,
 $-C(O)NR^cR^c$, $-C(NR^b)NR^cR^c$, $-OC(O)R^b$, $-OC(S)R^b$, $-OC(O)O^-$, $-OC(O)OR^b$, $-OC(S)OR^b$,
 $-NR^bC(O)R^b$, $-NR^bC(S)R^b$, $-NR^bC(O)O^-$, $-NR^bC(O)OR^b$, $-NR^bC(S)OR^b$, $-NR^bC(O)NR^cR^c$,
 $-NR^bC(NR^b)R^b$ and $-NR^bC(NR^b)NR^cR^c$, where R^a , R^b and R^c are as previously defined.

[070] 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.

[071] "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 , $COOR'$, $CONR'_2$, $OOOR'$, 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.

[072] "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.

[073] 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.

5 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
10 rings that contain a double bond or two, as long as the ring is not aromatic.

[074] 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
15 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.

[075] 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-
20 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.

25 [076] “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
30 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, cinnolyl, 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.

[077] 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, NR₂, SR, SO₂R, SO₂NR₂, NRSO₂R, NRCONR₂, NRCSNR₂, NRC(=NR)NR₂, NRCOOR, NRCOR, CN, C≡CR, COOR, CONR₂, OOCR, COR, and NO₂, wherein each R is independently H, C1-C8 alkyl, C2-C8 heteroalkyl, C2-C8 alkenyl, C2-C8 heteroalkenyl, C2-C8 alkynyl, C2-C8 heteroalkynyl, C3-C8 heterocyclyl, C4-C10 heterocyclylalkyl, 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. 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. Where a substituent group contains two R or R' groups on the same or adjacent atoms (e.g., -NR₂, or -NR-C(O)R), the two R or R' groups can optionally be taken together with the atoms in the substituent group to which they are attached to form a ring having 4-8 ring members, which can be substituted as allowed for the R or R' itself, and can contain an additional heteroatom (N, O or S) as a ring member.

[078] 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.

5 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
10 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.

[079] 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
15 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.

[080] "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
20 or similar linker. Thus a benzyl group is a C7-arylalkyl group, and phenylethyl is a C8-arylalkyl.

[081] "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
25 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.

30 [082] "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 alkenes, 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.

[083] 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, R⁷ is alkyl, this alkyl may optionally be substituted by the remaining substituents listed as embodiments for R⁷ 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.

[084] "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.

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

[086] "Amino" as used herein refers to NH₂, 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.

[087] As used herein, the term "carbocycle" or "carbocyclic" refers to a cyclic ring containing only carbon atoms in the ring, whereas the term "heterocycle" or "heterocyclic" refers to a ring comprising a heteroatom. The carbocyclic and heterocyclic structures encompass compounds having monocyclic, bicyclic or multiple ring systems.

[088] As used herein, the term "heteroatom" refers to any atom that is not carbon or hydrogen, such as nitrogen, oxygen or sulfur. When it is part of the backbone or skeleton of a chain or ring, a heteroatom must be at least divalent, and will typically be selected from N, O, P, and S.

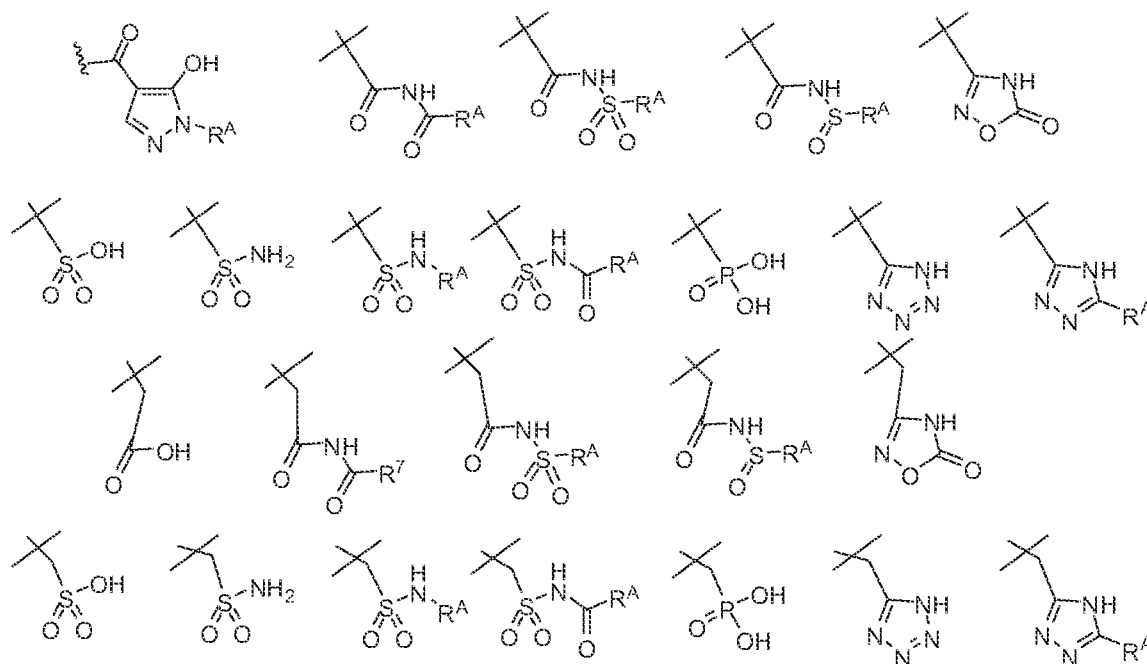
[089] Illustrative examples of heterocycles include but are not limited to tetrahydrofuran, 1,3-dioxolane, 2,3-dihydrofuran, pyran, tetrahydropyran, benzofuran, isobenzofuran, 1,3-dihydro-isobenzofuran, isoxazole, 4,5-dihydroisoxazole, piperidine, pyrrolidine, pyrrolidin-2-one, pyrrole, pyridine, pyrimidine, 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.

[090] The term "polar group" 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 groups 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 group is one that can accept or donate electrons in a non-covalent hydrogen bond with another chemical moiety. In certain embodiments, a polar group 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. Other polar groups 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.

[091] In some embodiments, the polar group represented by X or X² is a carboxylate or a carboxylate bioisostere.

- 5 [092] "Carboxylate bioisostere" or "carboxy bioisostere" as used here 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:



10

and salts and prodrugs of the foregoing, wherein each R^A is independently H or an optionally substituted member selected from the group consisting of C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ heteroalkyl, C₃₋₈ carbocyclic ring, and C₃₋₈ heterocyclic ring optionally fused to an additional optionally substituted carbocyclic or heterocyclic ring; or R^A is a C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, or C₂₋₁₀ heteroalkyl substituted with an optionally substituted C₃₋₈ carbocyclic ring or C₃₋₈ heterocyclic ring.

15

[093] In certain embodiments, the polar substituent is selected from the group consisting of carboxylic acid, carboxylic ester, carboxamide, tetrazole, triazole, carboxymethanesulfonamide, oxadiazole, oxothiadiazole, thiadiazole, thiazole, aminothiazole, and hydroxythiazole.

20

[094] In some embodiments, at least one of X or X² that is present is a carboxylic acid or a salt, or ester or a bioisostere thereof. In certain embodiments, at least one X or X² present is a carboxylic acid-containing substituent (-(CH₂)₀₋₂COOR) or a salt, ester or

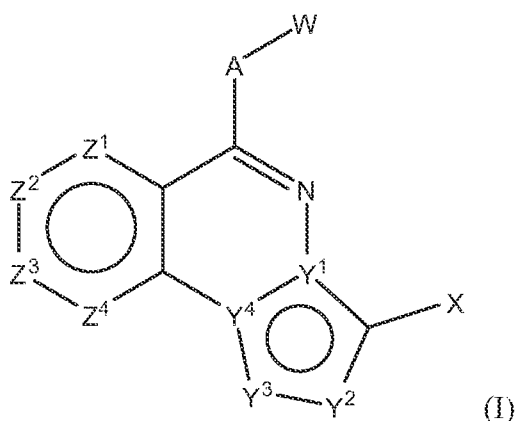
bioisostere thereof. In the latter embodiments, the polar group may be a C1-C10 alkyl or C1-C10 alkenyl linked to a carboxylic acid (or salt, ester or bioisostere thereof).

[095] 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.

[096] 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:

[097] The invention provides compounds of Formula (I):



wherein:

each of Z^1 , Z^2 , Z^3 and Z^4 is independently CR^1 or N, provided no more than two of Z^1 to Z^4 are N, and the ring containing Z^1 - Z^4 is aromatic;

each R^1 is independently H, halo, CN, optionally substituted C1-C4 alkyl, optionally substituted C2-C4 alkenyl, optionally substituted C2-C4 alkynyl, optionally substituted C1-C4 alkoxy, SR, SO_2R , COOR, $COONR^7R^8$, or $-NR^7R^8$;

each of Y^1 and Y^4 is C or N, and Y^1 and Y^4 are not both simultaneously N;
provided at least one of Y^1 to Y^4 is N;

Y^2 is N, NR^2 , CR^2 or CX^2 ,

wherein each R^2 is independently H, -OR, halo, CN, or optionally substituted C1-C4 alkyl,

and each X^2 is $-(CH_2)_{0-2}COOR$ or a polar group;

X is $-(CH_2)_{0-2}COOR$ or a polar group, or X is R^2 when Y^2 is CX^2 ;

each R is independently H or optionally substituted C1-C4 alkyl;

Y^3 is N, NR^3 , or CR^3 , and the ring containing Y^2 and Y^3 is aromatic;

wherein each R^3 is independently H, halo, -OR, CN, or optionally substituted C1-C4 alkyl;

A is a bond, NR^4 , O or S, where R^4 is H or optionally substituted C1-C4 acyl;

W is optionally substituted aryl or arylalkyl; optionally substituted heteroaryl or heteroarylalkyl; optionally substituted heterocyclyl or heterocyclalkyl; or optionally substituted C3-C8 cycloalkyl or cycloalkylalkyl;

or alternatively, -A-W is NR^7R^8 ;

each R^7 and R^8 is independently selected from H, optionally substituted C1-C10 alkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, and optionally substituted heteroarylalkyl;

and wherein R^7 and R^8 in NR^7R^8 can be taken together along with N to form a 4-8 membered ring that can be optionally substituted, and can contain an additional heteroatom selected from N, O and S as a ring member.

[098] The invention also includes the pharmaceutically acceptable salts, solvates, and/or prodrugs of compounds of formula (I), and pharmaceutical compositions as described herein that comprise a compound of Formula (I) and at least one pharmaceutically acceptable diluent or excipient.

[099] In some embodiments of the compounds of Formula (I), each of Z^1 to Z^4 is CR^1 . In other embodiments, one of Z^1 to Z^4 is N and the others are each CR^1 . In other embodiments, two of Z^1 to Z^4 are N and the others are each CR^1 . R^1 in these compounds can be, for example, H, halo (F, Cl), CF_3 , CN, Me, or OMe.

[0100] In some embodiments of the foregoing compounds of Formula (I), exactly one of Y^1 to Y^4 is N or NR^2 . In other embodiments, exactly two of Y^1 to Y^4 are selected from the group consisting of N and NR^2 . In still other embodiments, exactly three of Y^1 to Y^4 are selected from the group consisting of N and NR^2 . In certain of these embodiments, Y^1 is N and Y^4 is C; in others, Y^4 is N and Y^1 is C. In these embodiments, R^2 on each $Y^1 - Y^4$ is often H or C1-C4 alkyl.

[0101] The compounds of the invention have at least one group of the formula $-(CH_2)_{0-2}COOR$ or a polar group on the ring containing Y^2 and Y^3 . This group is often $COOR$, or a 5-membered heterocyclic ring comprising two or more nitrogen atoms as ring members and optionally substituted, or an amide ($-CONR_2$). Suitable $COOR$ groups include $-COOH$, $COOMe$, and $COOEt$, for example. Suitable amides include $CONH_2$, $CONHMe$, and the like. Suitable heterocyclic rings include imidazoles, triazoles, and tetrazoles. These rings are preferably attached to the five-membered ring of Formula (I) via a carbon-carbon bond, i.e., by a carbon atom of the heterocyclic ring bonded to a carbon atom of the five-membered ring in Formula (I).

[0102] In certain embodiments of the foregoing compounds, X is $-(CH_2)_{0-2}COOR$ or a polar group as described above. In some embodiments, X is $COOH$; in others it is a carboxylate bioisostere. In other embodiments of the foregoing compounds, X is R^2 (H, halo, or Me, for example), and Y^2 is CX^2 , wherein X^2 is $-(CH_2)_{0-2}COOR$ or a polar group, and in these embodiments, X^2 is often $COOR$, particularly $COOH$.

[0103] In any of the foregoing compounds of Formula (I), Y^1 can be N; or Y^4 can be N.

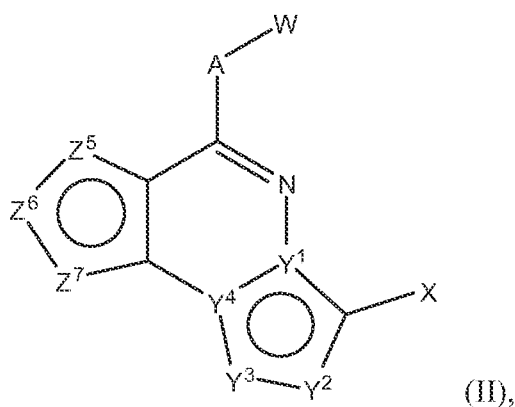
[0104] In any of the foregoing compounds of Formula (I), A can be a bond, or a one-atom linker (N, O or S). In some embodiments, A is NR^4 , such as NH . In other embodiments, A is O or S. In still other embodiments, A is a bond.

[0105] In any of the foregoing compounds of Formula (I), W comprises a ring. In some embodiments, it is an aryl or heteroaryl ring. In specific embodiments, W is optionally substituted aryl. In certain embodiments, W is optionally substituted phenyl.

[0106] Suitable substituents for the aryl or phenyl ring are described herein; in some instances, the aryl or heteroaryl ring is substituted with 1-2 groups selected from halo (F or Cl), Me, OMe, CF_3 , CN, $COOR$, $CONR_2$, and the like, where each R is independently H or C1-C4 alkyl. In specific embodiments of interest, W is substituted phenyl.

[0107] Specific embodiments of the substituted phenyl that can be W include 3-chlorophenyl, 2-fluorophenyl, 3-fluorophenyl, 3-carboxyphenyl, and 3-($COOMe$)-phenyl.

[0108] In another aspect, the invention provides a compound of Formula (II):



wherein:

each of Z^5 and Z^6 and Z^7 is independently CR^1 , NR^2 , N, O or S, provided at least one of Z^5 to Z^7 is not CR^1 , and no more than one of Z^5 to Z^7 is O or S, and the ring containing Z^5 - Z^7 is aromatic;

each of Y^1 and Y^4 is independently C or N, and Y^1 and Y^4 are not both simultaneously N; provided at least one of Y^1 to Y^4 is N;

Y^2 is N, CR^1 or CX^2 , where X^2 is $-(CH_2)_{0-2}COOR$ or a polar group;

Y^3 is CR^3 , and the ring containing Y^2 and Y^3 is aromatic;

each R^1 is independently H, halo, CN, optionally substituted C1-C4 alkyl, optionally substituted C2-C4 alkenyl, optionally substituted C2-C4 alkynyl, OR, SR, SO_2R , COOR, $COONR^7R^8$, or $-NR^7R^8$;

each R^2 is independently H, CN, -OR, COOR, $CONR_2$, SO_2R , or optionally substituted C1-C4 alkyl;

each R^3 is independently H, halo, CN, -OR, or optionally substituted C1-C4 alkyl;

X is $-(CH_2)_{0-2}COOR$ or a polar group, or X can be R^1 when Y^2 is CX^2 ;

R is independently at each occurrence H or an optionally substituted C1-C4 alkyl;

A is a bond, NR^4 , O or S;

wherein R^4 is H or optionally substituted C1-C4 acyl;

W is optionally substituted aryl or arylalkyl; optionally substituted heteroaryl or heteroarylalkyl; optionally substituted heterocyclyl or heterocyclylalkyl; or optionally substituted C3-C8 cycloalkyl or cycloalkylalkyl;

or alternatively, -A-W is NR^7R^8 ;

each R^7 and R^8 is independently selected from H, optionally substituted C1-C10 alkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, and optionally substituted heteroarylalkyl;

and wherein R^7 and R^8 in NR^7R^8 can be taken together along with N to form a 4-8 membered ring that can be optionally substituted, and can contain an additional heteroatom selected from N, O and S as a ring member.

[0109] The invention also includes the pharmaceutically acceptable salts, solvates, and/or prodrugs of compounds of Formula (II), and pharmaceutical compositions as described herein that comprise a compound of Formula (I) or (II) and at least one pharmaceutically acceptable diluent or excipient.

[0110] In some embodiments of the compounds of Formula (II), one of Z^5 - Z^7 is O, S or NR^2 , and the remaining two are CR^1 . In other embodiments, two of Z^5 - Z^7 are selected from O, S, NR^2 , and N, and the remaining one is CR^1 . This ring can thus be an imidazole, pyrazole, pyrrole, furan, thiophene, oxazole, isoxazole, thiazole, or isothiazole.

[0111] In some embodiments of the foregoing compounds of Formula (II), exactly one of Y^1 to Y^4 is N or NR^2 . In other embodiments, exactly two of Y^1 to Y^4 are selected from the group consisting of N and NR^2 . In still other embodiments, exactly three of Y^1 to Y^4 are selected from the group consisting of N and NR^2 . In certain of these embodiments, Y^1 is N and Y^4 is C; in others, Y^4 is N and Y^1 is C. In these embodiments, R^2 on each Y^1 — Y^4 is often H or C1-C4 alkyl.

[0112] The compounds of the invention have at least one group of the formula $-(CH_2)_0$ - $_2COOR$ or a polar group on the ring containing Y^2 and Y^3 . This group is often $COOR$, or a 5-membered heterocyclic ring comprising two or more nitrogen atoms as ring members and optionally substituted, or an amide ($-CONR_2$). Suitable $COOR$ groups include $-COOH$, $COOMe$, and $COOEt$, for example. Suitable amides include $CONH_2$, $CONHMe$, and the like. Suitable heterocyclic rings include imidazoles, triazoles, and tetrazoles. These rings are preferably attached to the five-membered ring of Formula (I) via a carbon-carbon bond, i.e., by a carbon atom of the heterocyclic ring bonded to a carbon atom of the five-membered ring in Formula (II).

[0113] In certain embodiments of the foregoing compounds, X is $COOR$ or a polar group as described above. In some embodiments, X is $COOH$; in others it is a carboxylate bioisostere. In other embodiments of the foregoing compounds, X is R^2 (H, halo, or Me, for example), and Y^2 is CX^2 , wherein X^2 is $COOR$ or a polar group.

[0114] In any of the foregoing compounds of Formula (II), Y^1 can be N; or Y^4 can be N.

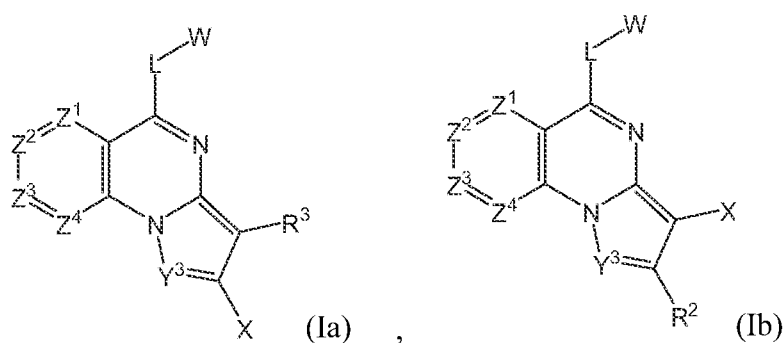
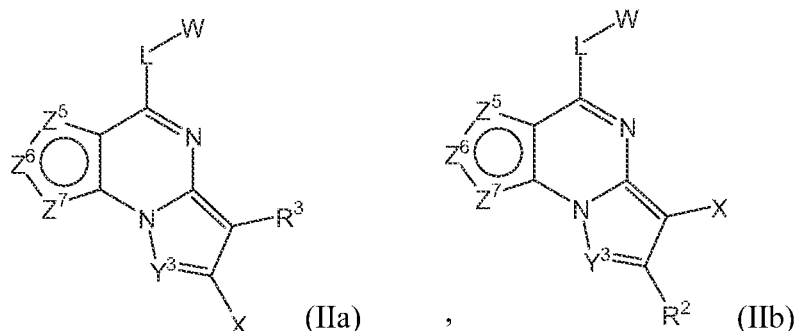
[0115] In any of the foregoing compounds of Formula (II), A can be a bond, or a one-atom linker (N, O or S). In some embodiments, A is NR^4 , such as NH. In other embodiments, A is O or S. In still other embodiments, A is a bond.

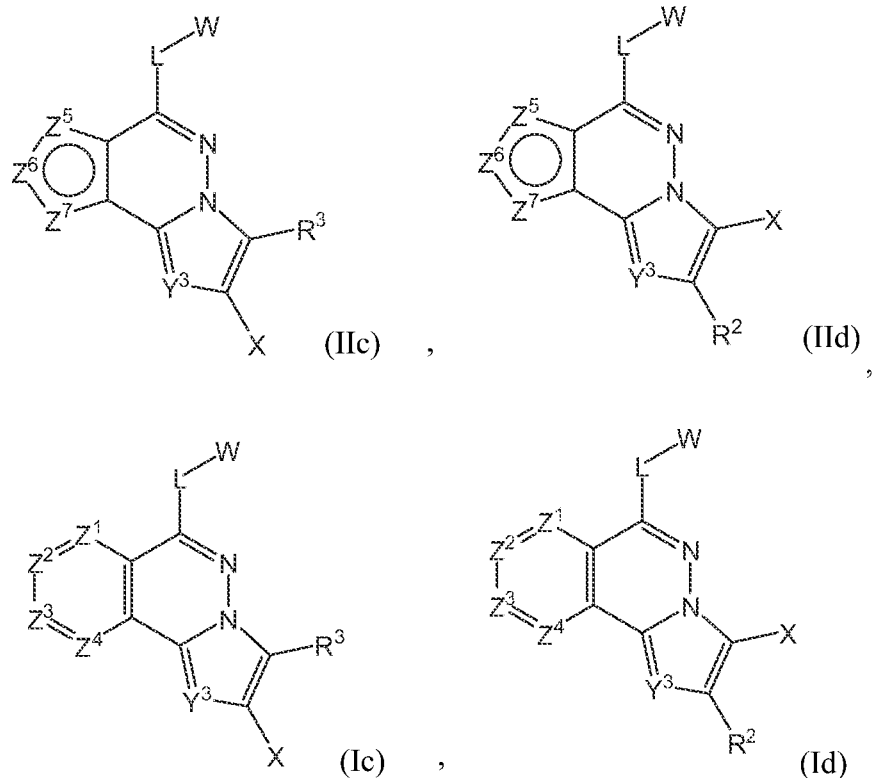
5 [0116] In any of the foregoing compounds of Formula (II), W comprises a ring. In some embodiments, it is an aryl or heteroaryl ring. In specific embodiments, W is optionally substituted aryl. In certain embodiments, W is optionally substituted phenyl.

[0117] Suitable substituents for the aryl or phenyl ring are described herein; in some instances, the aryl or heteroaryl ring is substituted with 1-2 groups selected from halo (F or Cl), Me, OMe, CF_3 , CN, COOR, $CONR_2$, and the like, where each R is independently H or
10 C1-C4 alkyl. In specific embodiments of interest, W is substituted phenyl.

[0118] Specific embodiments of the substituted phenyl that can be W include 3-chlorophenyl, 2-fluorophenyl, 3-fluorophenyl, 3-carboxyphenyl, and 3-(COOMe)-phenyl.

[0119] Some examples of compounds of specific interest include the following, where
15 Z^1 - Z^7 and Y^1 - Y^4 , and R^1 - R^4 , and X, L, R and W, etc., are as set forth for compounds of Formula (I) or (II):





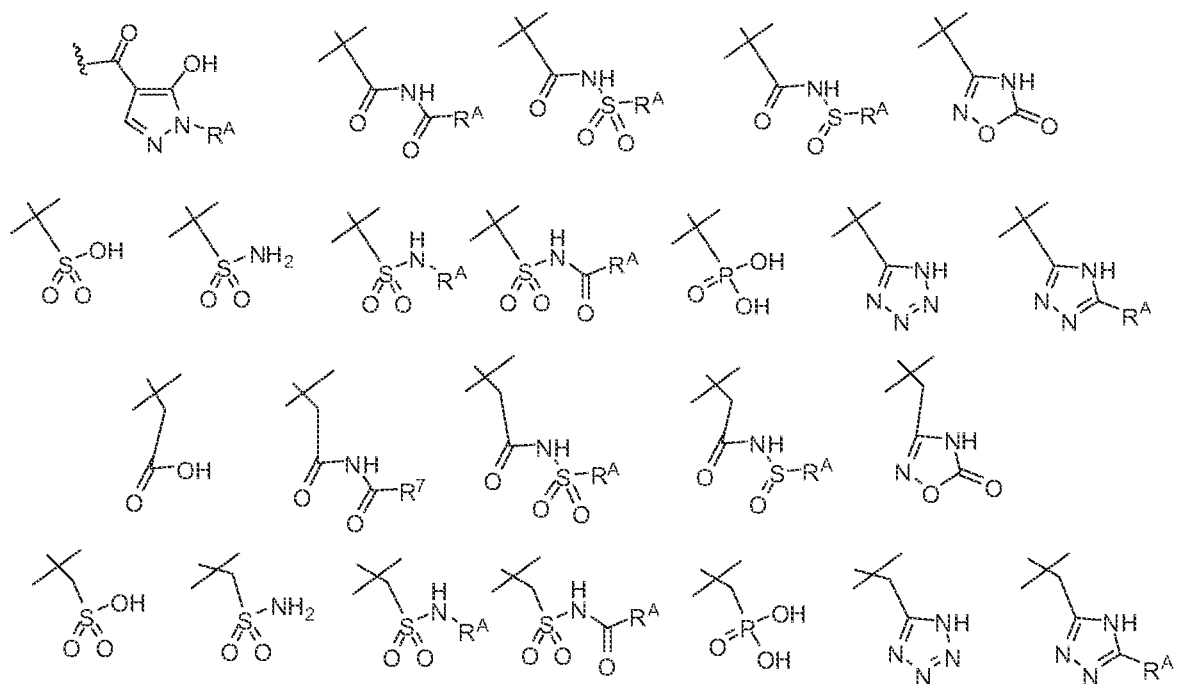
[0120] In one embodiment of Formula (Ia), (Ib), (Ic), (Id), (IIa), (IIb), (IIc), or (IId), A is NR⁴, O or S, where R⁴ is H or optionally substituted C1-C4 acyl; W is optionally substituted aryl or optionally substituted arylalkyl; optionally substituted heteroaryl or optionally substituted heteroarylalkyl; optionally substituted heterocyclyl or optionally substituted heterocyclylalkyl; or optionally substituted C3-C8 cycloalkyl or optionally substituted cycloalkylalkyl; and X is -COOR or a polar group.

[0121] In one embodiment of Formula (Ia), (Ib), (Ic), (Id), (IIa), (IIb), (IIc), or (IId), A is a bond; W is optionally substituted aryl; optionally substituted heteroaryl; optionally substituted heterocyclyl; or optionally substituted C3-C8 cycloalkyl; and X is -COOR or a polar group.

[0122] In one embodiment of Formula (Ia), (Ib), (Ic), (Id), (IIa), (IIb), (IIc), or (IId), A is a bond; W is optionally substituted arylalkyl; optionally substituted heteroarylalkyl; optionally substituted heterocyclylalkyl; or optionally substituted cycloalkylalkyl; and X is -COOR or a polar group.

[0123] In one embodiment of Formula (Ia), (Ib), (Ic), (Id), (IIa), (IIb), (IIc), or (IId), -A-W is -NR⁷R⁸; and X is COOR or a polar group.

[0124] In one embodiment of Formula (Ia), (Ib), (Ic), (Id), (IIa), (IIb), (IIc), or (IId), the polar group is selected from the group consisting of



Utilities of the Compounds:

[0125] 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.

[0126] The compounds of the invention are useful as medicaments, and are useful for the manufacture of medicaments, including medicaments to treat conditions disclosed herein, such as cancers, inflammatory conditions, infections, pain, and immunological disorders.

[0127] The compounds of Formula (I) and (II) are active as inhibitors of CK2 kinase, and are thus useful to treat infections by certain pathogens, including protozoans and viruses, whose life cycle, pathogenesis, etc. depend upon CK2 phosphorylations. As described above, CK2 inhibits phosphorylation of critical proteins in HIV-1 and other viruses, and 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. Antiviral activity following induction of viral expression with $\text{TNF}\alpha$, in this cell line, can be measured 72 hours after induction as a reduction of the HIV-1 reverse transcriptase activity to demonstrate the antiviral activity of the compounds of the invention.

[0128] Accordingly, the invention provides a method to treat viral infections by pathogenic viruses that depend on phosphorylation by CK2, including HIV-1, human papilloma virus, herpes simplex, Epstein-Barr virus, Hepatitis B and C, human Cytomegalovirus, adenovirus, coxsackievirus, and varicella zoster.

[0129] The invention provides methods for treating protozoal disorders such as protozoan parasitosis, including infection by parasitic protozoa responsible for neurological disorders such as schizophrenia, paranoia, and encephalitis in immunocompromised patients, as well as Chagas' disease. It also provides methods to treat various viral diseases, including human immunodeficiency virus type 1 (HIV-1), human papilloma viruses (HPVs), herpes simplex virus (HSV), Epstein-Barr virus (EBV), human cytomegalovirus, hepatitis C and B viruses, influenza virus, Borna disease virus, adenovirus, coxsackievirus, coronavirus and varicella zoster virus. The methods for treating these disorders comprise administering to a subject in need thereof an effective amount of a compound of Formula (I).

[0130] 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.

[0131] In addition, the invention in part provides methods for identifying a candidate molecule that interacts with a CK2 and/or Pim, which comprises contacting a composition containing a CK2 or Pim 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.

[0132] Also provided by the invention are methods for modulating certain protein kinase activities. 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.

[0133] 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
5 system comprising cells (e.g., *in vitro*).

[0134] 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
10 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.

[0135] 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. In some embodiments, the protein kinase in the composition
15 is, or contains a subunit (e.g., catalytic subunit, SH2 domain, SH3 domain) of, CK2 or a Pim subfamily protein kinase (e.g., PIM1, PIM2, PIM3). In certain embodiments the composition is cell free and sometimes the protein kinase is a recombinant protein.

[0136] 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
20 may potentially be inhibited, by compounds disclosed herein include without limitation human versions of CK2, CK2 α 2, and Pim subfamily kinases (e.g., PIM1, PIM2, PIM3). 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
25 of such protein kinases include without limitation human versions of CK2, STK10, HIPK2, HIPK3, DAPK3, DYK2 and Pim-1. 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
30 NP_002639.1 for PIM1; NM_006875.2 and NP_006866.2 for PIM2; XM_938171.2 and XP_943264.2 for PIM3.

[0137] 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).

[0138] Also provided are methods for treating a condition related to inflammation or pain. For example, methods are provided for 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 comprise 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 allergen 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.

[0139] Methods for determining and monitoring 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.

5 Compositions and Routes of Administration:

[0140] In another aspect, the invention provides pharmaceutical compositions (i.e., formulations). The pharmaceutical compositions can comprise a compound of any of Formulae (I), (Ia), (Ib), (Ic), (Id), (II), (IIa), (IIb), (IIc), and (IId), as described herein which is admixed with at least one pharmaceutically acceptable excipient or carrier. Frequently, the
10 composition comprises at least two pharmaceutically acceptable excipients or carriers.

[0141] 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,
15 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.

[0142] Pharmaceutical compositions suitable for use in the present invention include compositions wherein the active ingredients are contained in an effective amount to achieve
20 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.

[0143] 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
25 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,
30 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.

[0144] 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.

[0145] 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.

[0146] 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-C₁₋₅ 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.

[0147] 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.

[0148] 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.

[0149] Unless otherwise stated, structures depicted herein are also meant to include

5 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
10 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.

[0150] In addition to salt forms, the present invention provides compounds that are in a
15 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
20 transdermal patch reservoir with a suitable enzyme or chemical reagent.

[0151] 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
25 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.

30 [0152] A compound of the present invention can be formulated as a pharmaceutical composition. Such a pharmaceutical composition can then be administered orally, parenterally, by inhalation spray, rectally, or topically in dosage unit formulations containing conventional nontoxic pharmaceutically acceptable carriers, adjuvants, and vehicles as desired. Topical administration can also involve the use of transdermal administration such,

as transdermal patches or iontophoresis devices. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection, or infusion techniques. Formulation of drugs is discussed in, for example, Hoover, John E., REMINGTON'S PHARMACEUTICAL SCIENCES, Mack Publishing Co., Easton, Pa.; 1975. 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.

[0153] Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions can be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation can also be a sterile injectable solution or suspension in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that can be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables. Dimethyl acetamide, surfactants including ionic and non-ionic detergents, polyethylene glycols can be used. Mixtures of solvents and wetting agents such as those discussed above are also useful.

[0154] Suppositories for rectal administration of the drug can be prepared by mixing the drug with a suitable nonirritating excipient such as cocoa butter, synthetic mono- di- or triglycerides, fatty acids and polyethylene glycols that are solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum and release the drug.

[0155] Solid dosage forms for oral administration can include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the compounds of this invention are ordinarily combined with one or more adjuvants appropriate to the indicated route of administration. If administered per os, a compound of the invention can be admixed with lactose, sucrose, starch powder, cellulose esters of alkanolic acids, cellulose alkyl esters, talc, stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulfuric acids, gelatin, acacia gum, sodium alginate, polyvinylpyrrolidone, and/or polyvinyl alcohol, and then tableted or encapsulated for convenient administration. Such capsules or tablets can contain a controlled-release formulation as can be provided in a dispersion of active compound in hydroxypropylmethyl cellulose. In the case of capsules, tablets, and pills, the dosage forms can also comprise buffering agents such as sodium citrate, magnesium or calcium carbonate or bicarbonate. Tablets and pills can additionally be prepared with enteric coatings.

[0156] For therapeutic purposes, formulations for parenteral administration can be in the form of aqueous or non-aqueous isotonic sterile injection solutions or suspensions. These solutions and suspensions can be prepared from sterile powders or granules having one or more of the carriers or diluents mentioned for use in the formulations for oral administration.

5 A compound of the invention can be dissolved in water, polyethylene glycol, propylene glycol, ethanol, corn oil, cottonseed oil, peanut oil, sesame oil, benzyl alcohol, sodium chloride, and/or various buffers. Other adjuvants and modes of administration are well and widely known in the pharmaceutical art.

[0157] Liquid dosage forms for oral administration can include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art, such as water. Such compositions can also comprise adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavoring, and perfuming agents.

The amount of active ingredient that can be combined with the carrier materials to produce a single dosage form varies depending upon the mammalian host treated and the particular mode of administration.

[0158] The dosage regimen utilizing the compounds of the present invention in combination with an anticancer agent is selected in accordance with a variety of factors including type, species, age, weight, sex and medical condition of the patient; the severity of the condition to be treated; the route of administration; the renal and hepatic function of the patient; and the particular compound or salt or ester thereof employed. A consideration of these factors is well within the purview of the ordinarily skilled clinician for the purpose of determining the therapeutically effective dosage amounts to be given to a person in need of the instant combination therapy.

25 [0159] 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.

30 [0160] Thus in one aspect, the invention provides methods to treat each of these conditions, comprising administering to a subject in need of such treatment an effect amount of a CK2 inhibitor, such as a compound of Formula (I) as described herein.

[0161] The invention also in part pertains to methods for modulating an immune response in a subject, and methods for treating a condition associated with an aberrant immune response in a subject. Thus, provided are methods for determining whether a compound herein modulates an immune response, which comprise contacting a system with a compound described herein in an amount effective for modulating (e.g., inhibiting) an immune response or a signal associated with an immune response. Signals associated with immunomodulatory activity include, e.g., stimulation of T-cell proliferation, suppression or induction of cytokines, including, e.g., interleukins, interferon- γ and TNF. Methods of assessing immunomodulatory activity are known in the art.

[0162] 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.

[0163] In certain embodiments of the present invention, the compound is a compound of Formula (I)a, and in certain embodiments it is a compound of Formula (I)b.

[0164] Any suitable formulation of a compound described above can be prepared for administration by methods known in the art. Selection of useful excipients or carriers can be achieved without undue experimentation, based on the desired route of administration and the physical properties of the compound to be administered.

[0165] Any suitable route of administration may be used, as determined by a treating physician, 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

5 Pharmaceutical Sciences, latest edition, Mack Publishing Co., Easton, PA. The formulation of each substance or of the combination of two substances will frequently 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.

[0166] For injection, formulations can be prepared in conventional forms as liquid
10 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.

15 [0167] 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.

[0168] Systemic administration may also include relatively noninvasive methods such as the use of suppositories, transdermal patches, transmucosal delivery and intranasal
20 administration. Oral administration is also suitable for compounds of the invention. Suitable forms include syrups, capsules, tablets, as is understood in the art.

[0169] For administration to animal or human subjects, the appropriate dosage of a compound described above often is 0.01-15 mg/kg, and sometimes 0.1-10 mg/kg. In some
25 embodiments, a suitable dosage of the compound of the invention for an adult patient will be between 1 and 1000 mg per dose, frequently between 10 and 300 mg, and the dosage may be administered 1-4 times per day. 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; optimization of such parameters is within the ordinary level of skill in the art.

Therapeutic Combinations:

30 [0170] 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.

[0171] 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.

[0172] 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.

[0173] 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.

[0174] 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.

[0175] 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.

[0176] 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.

[0177] 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.

[0178] 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.

5 [0179] 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.

[0180] Diterpenoids, which are derived from natural sources, are phase specific anti -
10 cancer agents that are believed to operate at the G2/M phases of the cell cycle. It is believed that the diterpenoids stabilize the β -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.

[0181] Examples of diterpenoids include, but are not limited to, taxanes such as
15 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
20 TAXOTERE®.

[0182] 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
25 death following. Examples of vinca alkaloids include, but are not limited to, vinblastine, vincristine, vindesine, and vinorelbine. Vinblastine, vincalurekoblamine sulfate, is commercially available as VELBAN® as an injectable solution. Vincristine, vincalurekoblamine 22-oxo-sulfate, is commercially available as ONCOVIN® as an injectable solution. Vinorelbine, is commercially available as an injectable solution of vinorelbine
30 tartrate (NAVELBINE®), and is a semisynthetic vinca alkaloid derivative.

[0183] 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

5 PARAPLATIN® as an injectable solution.

[0184] 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, 10 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, 15 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 20 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 25 (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, 30 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.

[0185] 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- α -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, 7,8,9,10-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 verticillus*, is commercially available as BLENOXANE®.

[0186] Topoisomerase inhibitors include topoisomerase I inhibitors such as camptothecin, topotecan, irinotecan, rubitecan, and belotecan; and topoisomerase II inhibitors such as etoposide, teniposide, and amsacrine.

[0187] 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-O-(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-O-(R)-thenylidene- β -D- glucopyranoside], is commercially available as an injectable solution as VUMON® and is commonly known as VM-26.

[0188] 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-pyrano[3',4',6,7]indolizino[1,2-b]quinoline-3, 14(4H, 12H)-dione hydrochloride, is commercially available as the injectable solution CAMPT0SAR®. 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®.

[0189] 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- β -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®.

[0190] 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 toremifene;

(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, toremifene, droloxifene, and idoxifene, 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; 5 α -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.

[0191] 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 transduction 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, phosphatidylinositol-3 kinases, myo-inositol signaling, and Ras oncogenes.

[0192] 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
5 131I-tositumomab; and (g) cancer vaccines.

[0193] 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
10 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.

[0194] 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.
15 Consequently, inhibitors of such kinases could provide cancer treatment methods.

[0195] 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,
20 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.

[0196] Several inhibitors of growth receptors are under development and include ligand antagonists, antibodies, tyrosine kinase inhibitors and anti-sense oligonucleotides.
25 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 Loftis, 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
30 include, but are not limited to, sunitinib, erlotinib, gefitinib, and imatinib.

[0197] 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.

[0198] 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 Phosphatidylinositol-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.

[0199] 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.

[0200] 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).

[0201] 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 (alpha v 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).

[0202] 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.

[0203] 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.

[0204] 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.

[0205] 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.

[0206] 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 topoisomerase II enzyme; and creating iron-mediated free oxygen radicals that damage the DNA and cell membranes. Anthracyclines are generally characterized as topoisomerase II inhibitors.

[0207] 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

- 5 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,
- 10 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,
- 15 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,
- 20 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
- 25 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,
- 30 Tefibazumab, Tuvirumab, and Urtioxazumab. 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, Gavilimumab, Golimumab, Gomiliximab, Infliximab,
 Inolimomab, Keliximab, Lebrikizumab, Lerdelimumab, Mepolizumab, Metelimumab,
 Muromonab-CD3, Natalizumab, Ocrelizumab, Odulimumab, Omalizumab, Otelixizumab,
 5 Pascolizumab, Priliximab, Reslizumab, Rituximab, Rontalizumab, Rovelizumab,
 Ruplizumab, Sifalimumab, Siplizumab, Solanezumab, Stamulumab, Talizumab, Tanezumab,
 Teplizumab, Tocilizumab, Toralizumab, Ustekinumab, Vedolizumab, Vepalimumab,
 Visilizumab, Zanolimumab, and Zolimomab aritox. In yet another embodiment, such
 therapeutic antibodies include, but are not limited to adalimumab, basiliximab, certolizumab
 10 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.

[0208] Akt inhibitors include 1L6-Hydroxymethyl-chiro-inositol-2-(R)-2-O-methyl-3-O-
 15 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)Cl₂(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-
 20 (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
 25 (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-
 30 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.

- 5 **[0209]** 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
10 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.

- [0210]** Hsp90 inhibitors include benzoquinone ansamycins such as geldanamycin, 17-DMAG (17-Dimethylamino-ethylamino-17-demethoxygeldanamycin), tanespimycin
15 (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 radicicol; as well as BIIB021 (CNF2024), SNX-5422, STA-9090, and AUY922.

- 20 **[0211]** 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.

- [0212]** Biologic therapy agents include: interferons such as interferon- α 2a and interferon- α 2b, and interleukins such as aldesleukin, denileukin diftitox, and oprelvekin.
25

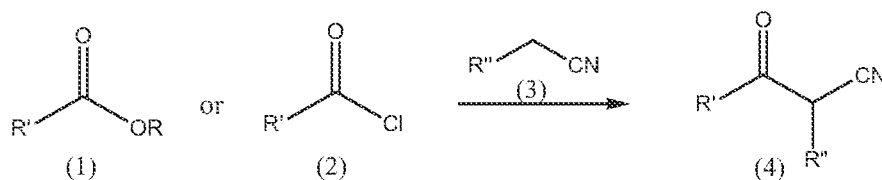
- [0213]** In addition to these anticancer agents intended to act against cancer cells, combination therapies including the use of protective or adjunctive agents, including: cytoprotective agents such as armifostine, dexrazoxane, and mesna, phosphonates such as pamidronate and zoledronic acid, and stimulating factors such as epoetin, darbepoetin,
30 filgrastim, PEG-filgrastim, and sargramostim, are also envisioned.

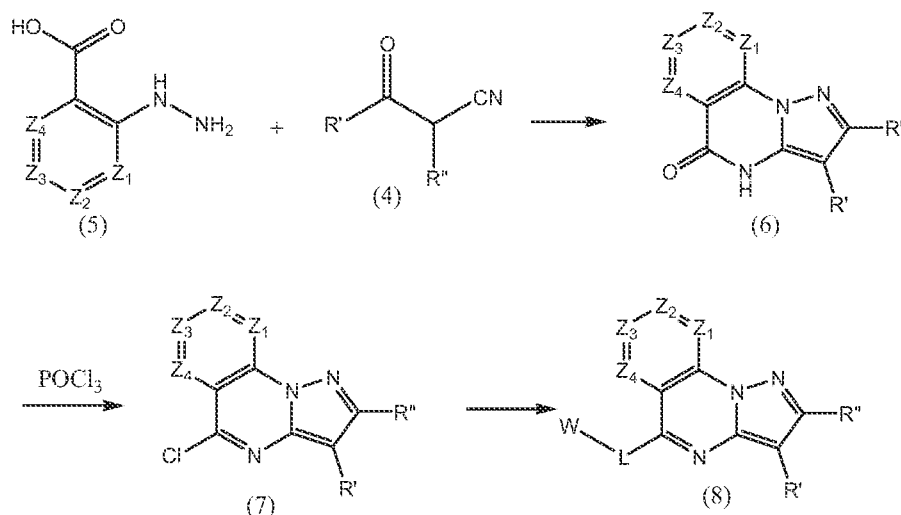
Examples:

[0214] The following examples illustrate and do not limit the invention. In specific
 5 embodiments, the invention includes any compound of Formula (I) or Formula (II) set forth
 in the following Reaction Schemes and Examples. By using the following general schemes
 and knowledge and reagents available in the art, a person of ordinary skill can easily prepare
 a wide array of compounds of Formula (I) and/or II. The depicted compounds should be
 understood to be within the scope of Formula (I) or (II) as stated, even if the atom labels used
 10 in the schemes differ from those used in Formulas (I) and (II).

Reaction Scheme 1

[0215] Certain compounds of formula (I) can be prepared by the general procedures
 illustrated in Scheme 1. Compounds of formula (8) can be obtained by (a) deprotonation of
 15 nitrile (3) with a base such as, but not limited to, n-butyl lithium and then (b) contacting the
 anion obtained from step (a) with an acid chloride (2) or an ester (1) to provide compound
 (4). Alternatively, the anion obtained from step (a) can be treated with (1) wherein R is
 hydrogen, in the presence of a coupling reagent such as, but not limited to, N,N'-
 carbonyldiimidazole or 1,3-dicyclohexylcarbodiimide to provide compound (4). Treatment of
 20 compound (5) and compound (4) in acetic acid, in a microwave reactor and at elevated
 temperature (for example, 150 °C) generates compound (6). Using POCl₃, compound (6) can
 be converted to compound (7) wherein one R' or R'' is the polar group of Formula (I), and the
 other is a suitable substituent within the scope of Formula (I) as described herein.

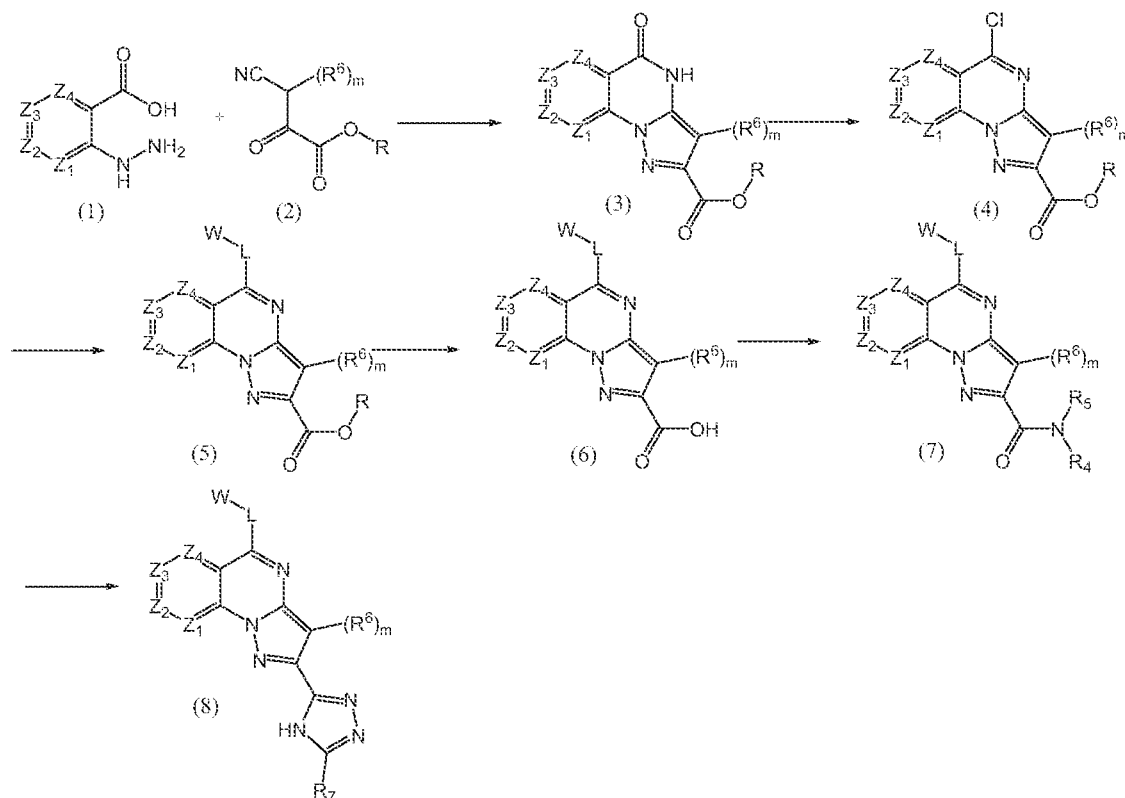
Scheme 1



Reaction Scheme 2

[0216] Additional compounds of Formula (I) can be prepared by the following reaction scheme. The reaction of reagent (2) with compound (1) under microwave irradiation as described in *Molecular Diversity* **2003**, 7, 161 can lead to compound (3). Compound (3) can react with POCl_3 at an appropriate temperature to give compound (4). Compound (5) can be obtained from compound (4) by reacting nucleophiles such as substituted amines or via Suzuki reaction with aryl boronic acids or esters. Subsequent hydrolysis of the ester (5) with NaOH followed by amide coupling of the resulting carboxylic acid (6) with amines lead to compound (7). Suitable coupling methods are those in the art as described in *Tetrahedron Lett.* **1974**, 15, 2695 and *Tetrahedron* **2004**, 6, 4579-4582 for the use of polymer-bound reagents and scavengers. Wherein R_4 and R_5 are hydrogen, triazole (8) can be prepared in two steps as described in patent application WO2005/9973. Wherein R_7 is hydrogen, the first step consists of the reaction of the amide (7) with N,N -dimethylformamide dimethyl acetal followed by hydrazine treatment at an appropriate temperature to give compound (8).

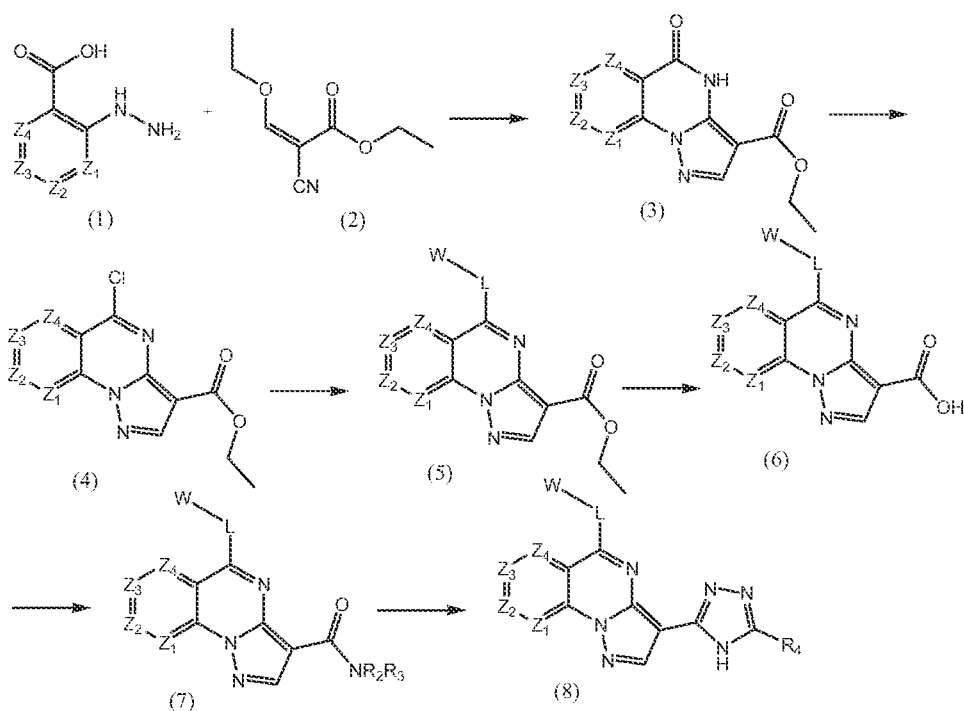
Scheme 2



Reaction Scheme 3

[0217] Compounds of Formula (I) can be prepared by the general procedure as illustrated in Scheme 3. Compound (3) can be obtained as described in patent US4105766 by reacting compound (1) with ethyl ethoxymethylenecyanoacetate (2) in the presence of sodium acetate. Compound (3) can react with POCl₃ at an appropriate temperature to give compound (4). Compound (5) can be obtained from compound (4) via a nucleophilic reaction with substituted amines or via Suzuki reaction with aryl boronic acids or esters. Subsequent hydrolysis of the ester (5) with NaOH followed by amide coupling of the resulting carboxylic acid (6) with amines can lead to compound (7). Wherein R₄ and R₅ are hydrogen, triazole (8) can be prepared in two steps as described in patent application WO2005/9973. Wherein R₇ is hydrogen, the first step consists of the reaction of the amide (7) with N,N-dimethylformamide dimethyl acetal followed by hydrazine treatment at an appropriate temperature to give compound (8).

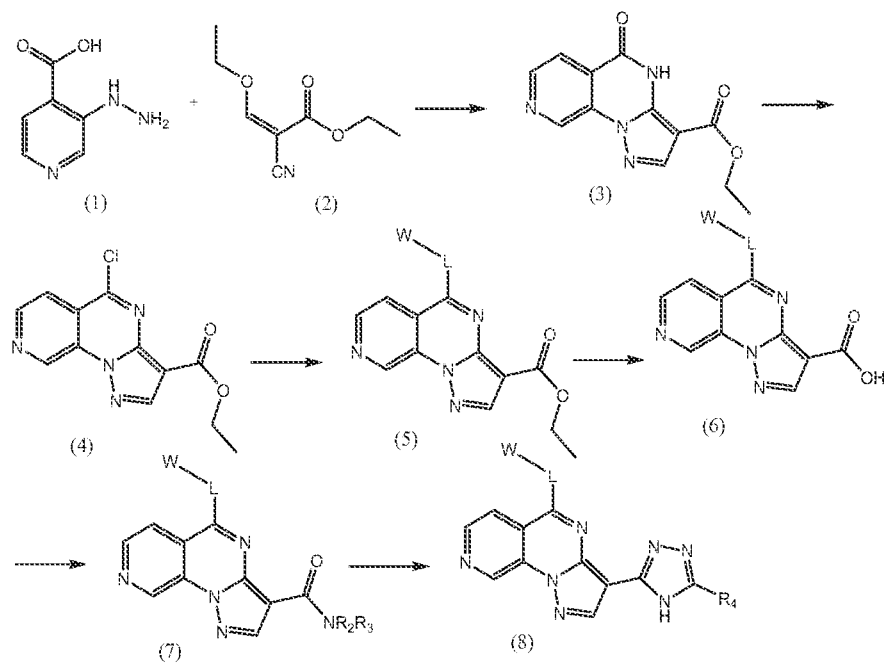
Scheme 3



Reaction Scheme 4

[0218] Compounds of Formula (I), such as compound (8) in Scheme 4, can be prepared as
 5 illustrated below, using conditions described with Scheme 3.

Scheme 4

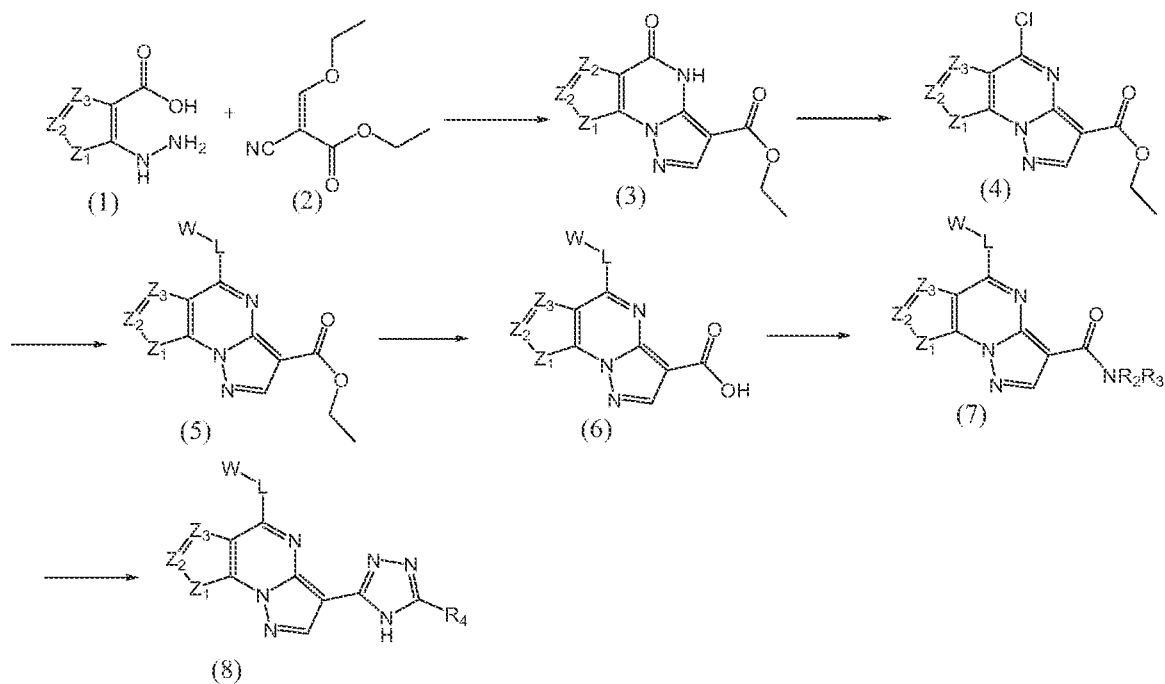


Reaction Scheme 5

[0219] Compounds of Formula (II), such as compound (8) in Scheme 5, can be prepared as described below, using transformations described for Scheme 3.

5

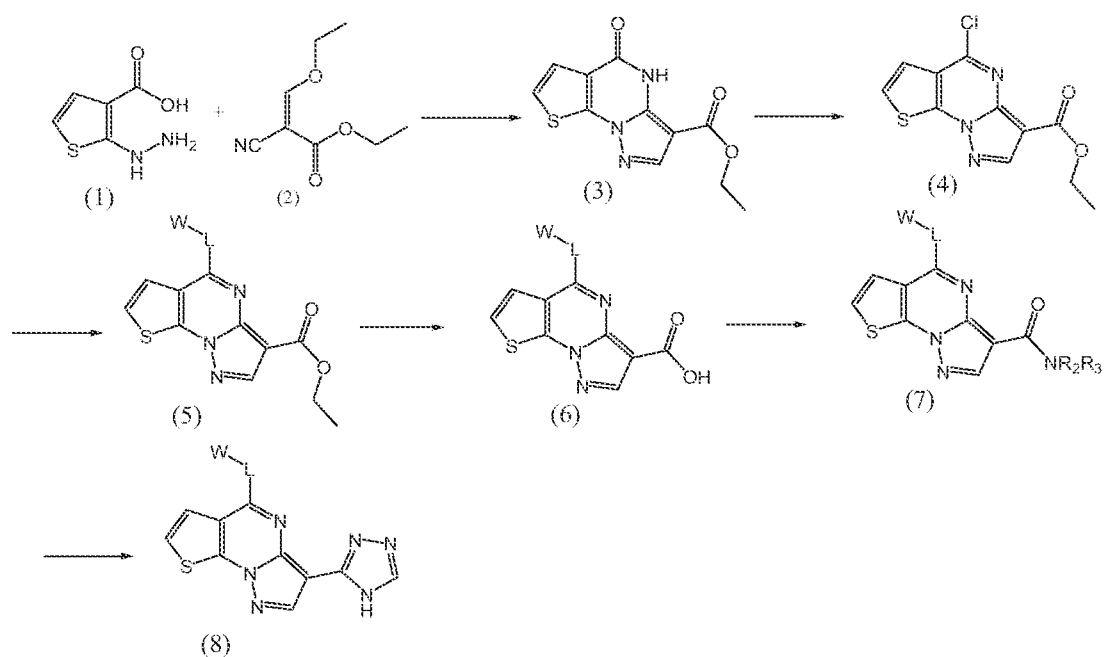
Scheme 5



Reaction Scheme 6

[0220] Compounds of Formula (II), such as compound (8) in Scheme 6, can be prepared as described below, using transformations described for Scheme 3.

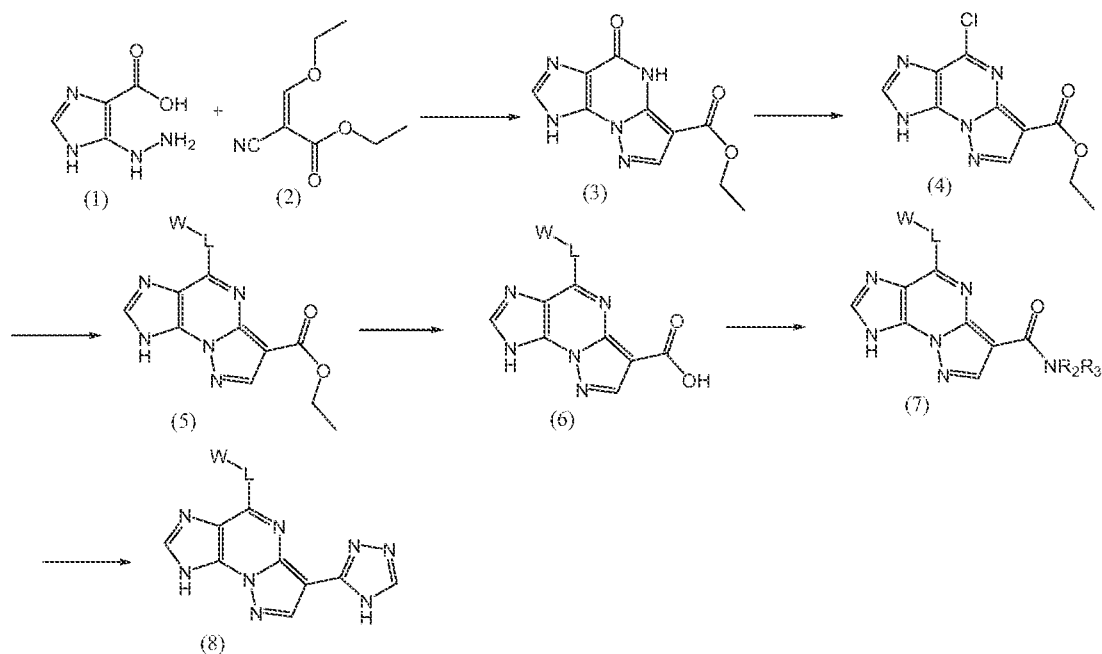
Scheme 6



Example 7

[0221] Compounds of Formula (II), such as compound (8) in Scheme 7, can be prepared as described below, using transformations described for Scheme 3.

Scheme 7

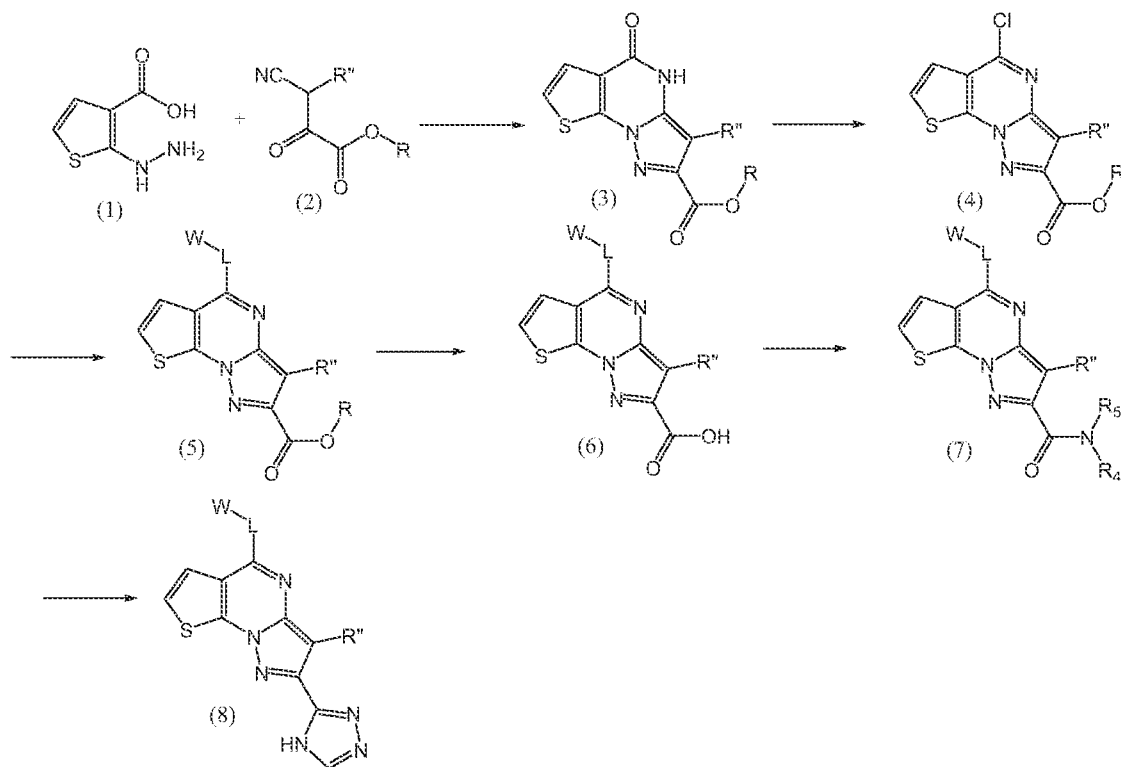


Reaction Scheme 8

[0222] Compounds of Formula (II), such as compound (8) in Scheme 8, can be prepared as described below, using transformations from Scheme 3.

5

Scheme 8

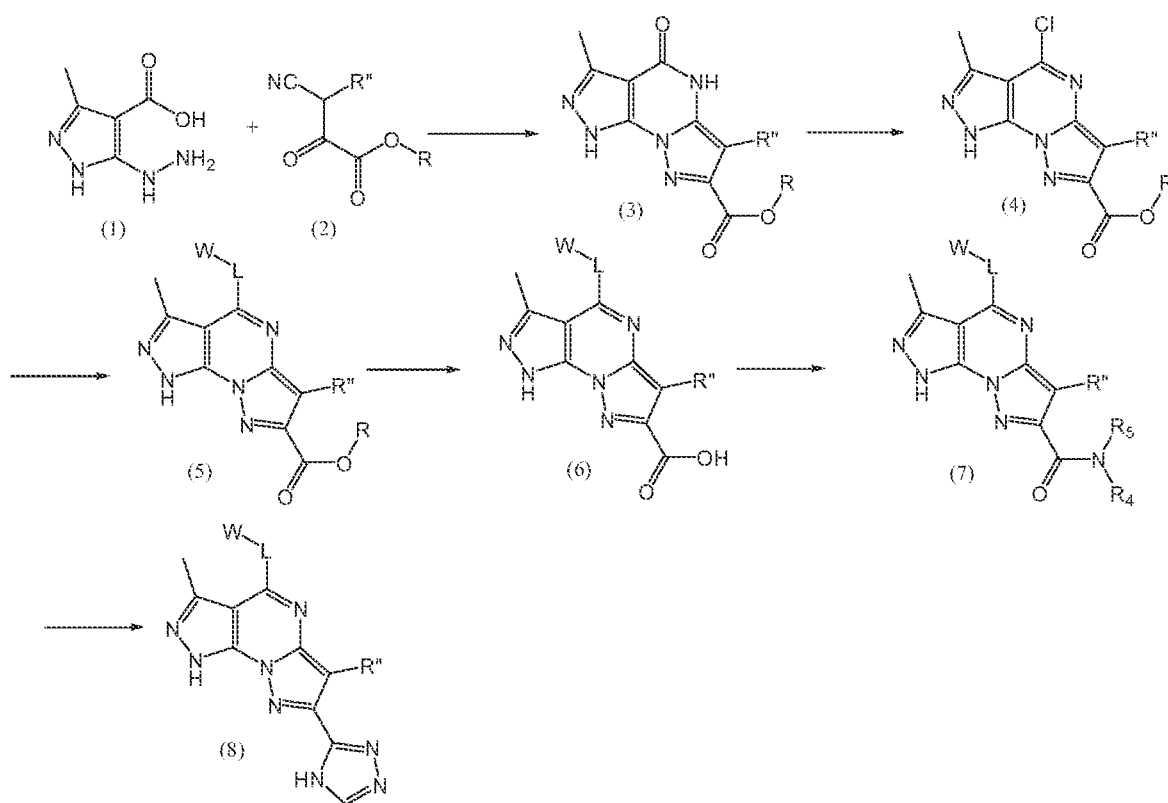


Reaction Scheme 9

[0223] Compounds of Formula (II), such as compound (8) in Scheme 9, can be prepared as described below, using transformations based on Scheme 3.

10

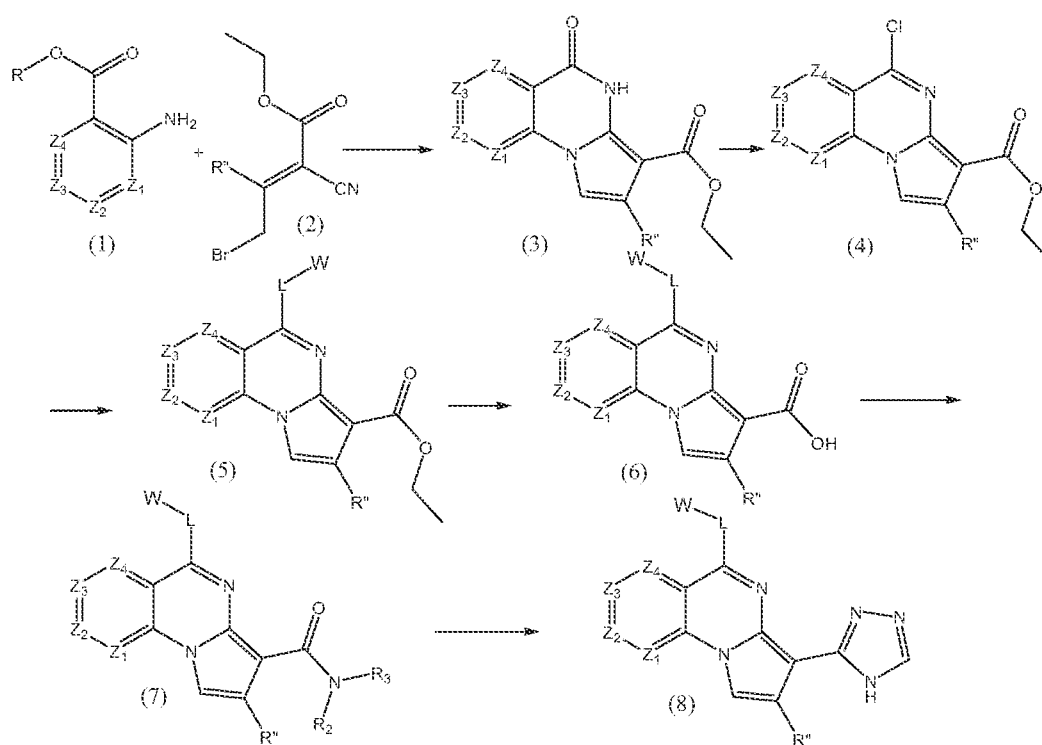
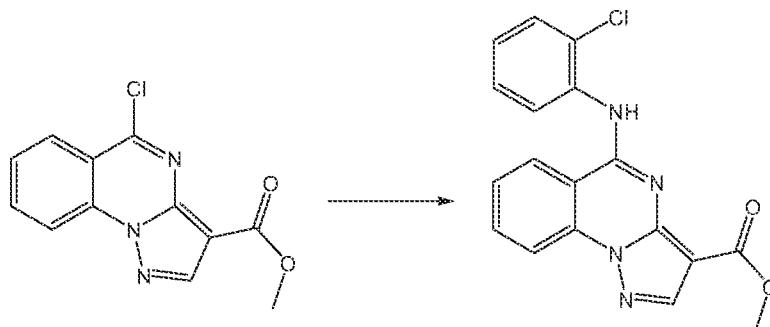
Scheme 9



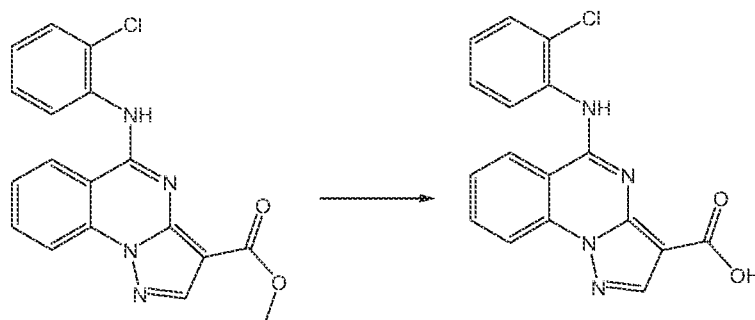
Reaction Scheme 10

[0224] Compounds of Formula (I), such as compound (3) in Scheme 10, can be prepared
 5 as described in *Journal fuer Praktische Chemie* **1981**, 323, 647-653. Compound (8) can be prepared from compound (3) as described for Scheme 3.

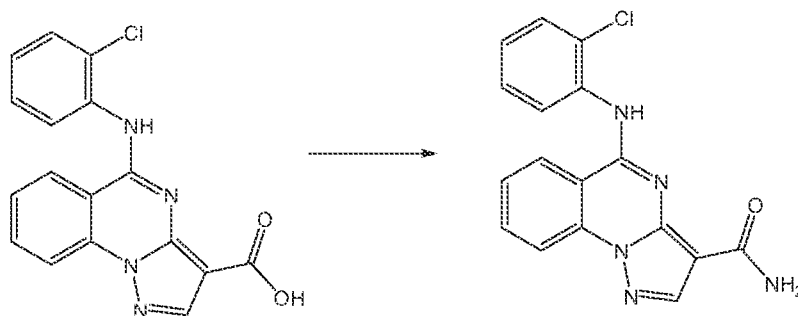
Scheme 10

**Example 1****5 Synthesis of methyl 5-(2-chlorophenylamino)pyrazolo[1,5-a]quinazoline-3-carboxylate.**

[0225] Methyl 5-chloropyrazolo[1,5-a]quinazoline-3-carboxylate can be obtained from commercial sources. To methyl 5-chloropyrazolo[1,5-a]quinazoline-3-carboxylate (200 mg, 0.872 mmol) in NMP (1 mL) was added 2-chloroaniline (183.5 μ L, 1.745 mmol). The mixture was heated at 140 $^{\circ}$ C for 30 min in the microwave. Methanol was added and the solid methyl 5-(2-chlorophenylamino)pyrazolo[1,5-a]quinazoline-3-carboxylate formed was isolated by filtration and used in the next step without further purification.

Example 2**Synthesis of 5-(2-chlorophenylamino)pyrazolo[1,5-a]quinazoline-3-carboxylic acid.**

[0226] To methyl 5-(2-chlorophenylamino)pyrazolo[1,5-a]quinazoline-3-carboxylate (163 mg) in EtOH (8 mL) was added NaOH (6 N, 1 mL). The mixture was heated over night at 60 °C. The reaction was acidified with HCl (6 N) and the solid formed was isolated by filtration and purified by preparative TLC eluting with 2.5% MeOH in dichloromethane to give 5-(2-chlorophenylamino)pyrazolo[1,5-a]quinazoline-3-carboxylic acid.

Example 3**Synthesis of 5-(2-chlorophenylamino)pyrazolo[1,5-a]quinazoline-3-carboxamide**

[0227] To 5-(2-chlorophenylamino)pyrazolo[1,5-a]quinazoline-3-carboxylic acid (270 mg, 0.799 mmol) in 1,4-Dioxane was added HOBT (216mg, 1.598mmol), EDCI (305 mg, 1.598 mmol), Ammonium Chloride (339 mg, 6.391 mmol), and DIEA (1114 µL, 6.391 mmol). The reaction was stirred at 80°C overnight. 3.195 mmol DIEA/Ammonium Chloride and 0.799 mmol HOBT/EDCI were added. The reaction was allowed to stir at 80°C for 2.5 hours, after which the solvent was removed under reduced pressure. The mixture was dissolved in

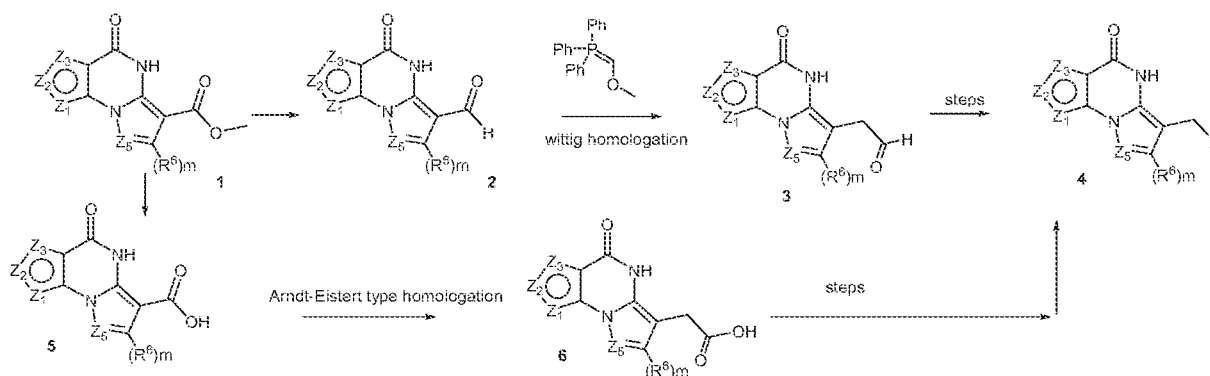
Methanol, and insolubilities were filtered off. The resulting filtrate was prepared by HPLC to yield 5-(2-chlorophenylamino)pyrazolo[1,5-a]quinazoline-3-carboxamide as a white solid. LCMS (M+1=338)

Example 4

Synthesis of Additional Compounds

[0228] Extended compounds of Formula (II), such as compound **4**, can be prepared by the general procedure as illustrated in Scheme 11. Compound **2** can be prepared by reacting compounds **1** in the presence of a reducing agent such as DIBALH. Compound **3** can be prepared by reacting **2** in the presence of methoxymethylenetriphenylphosphine using chemistry described in *J. Amer. Chem. Soc.* 1958, 80 (22), 6150-6151. Aldehyde **3** can be used to prepare various analogs **4** using chemistries known to a person skilled in the art. Alternatively ester **1** can be hydrolyzed to compound **5** by reacting in the presence of a base. Compound **5** can be transformed to an acyl chloride in the presence of oxalyl chloride. Compound **6** can be prepared using Arndt-Eistert type homologation using conditions described in literature (for example in *J. Org. Chem.* 2001, 66(16) pp 5606-5612). Compounds **6** can be transformed into various analogs **4** using chemistries known to a person skilled in the art.

Scheme 11

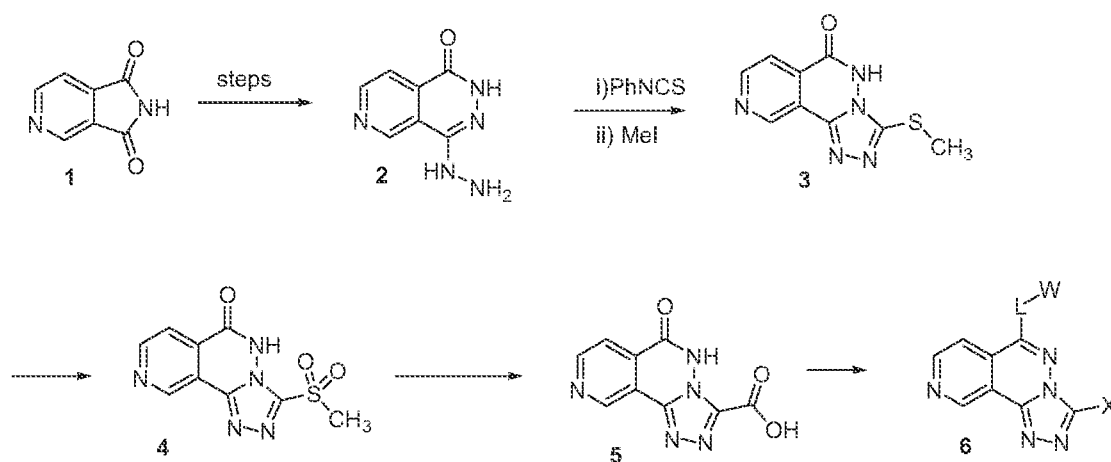


Example 5

[0229] Chemistry described in Scheme 12 can be used to prepare additional analogs of Formula (I). Compound **3** can be prepared in several steps from commercially available **1** using chemistries described in literature (*Tetrahedron*, 2002, 58, 8963-8972). Compound **3** can be transformed into compound **4** by reacting with m-chloroperbenzoic acid. Compound **4** can be transformed into compound **5** by reacting with DMF. Compound **5** can be transformed

into various analogs of general formula 6 using chemistries known to a person skilled in the art.

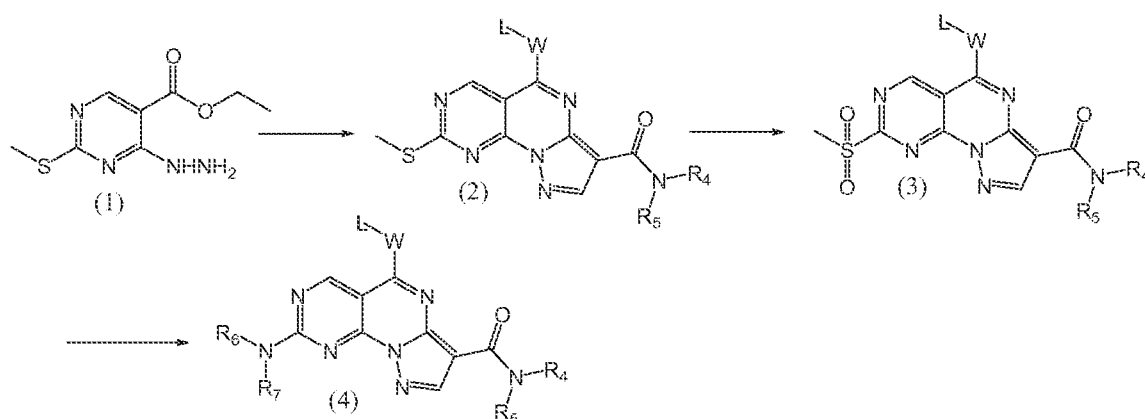
Scheme 12



Example 6

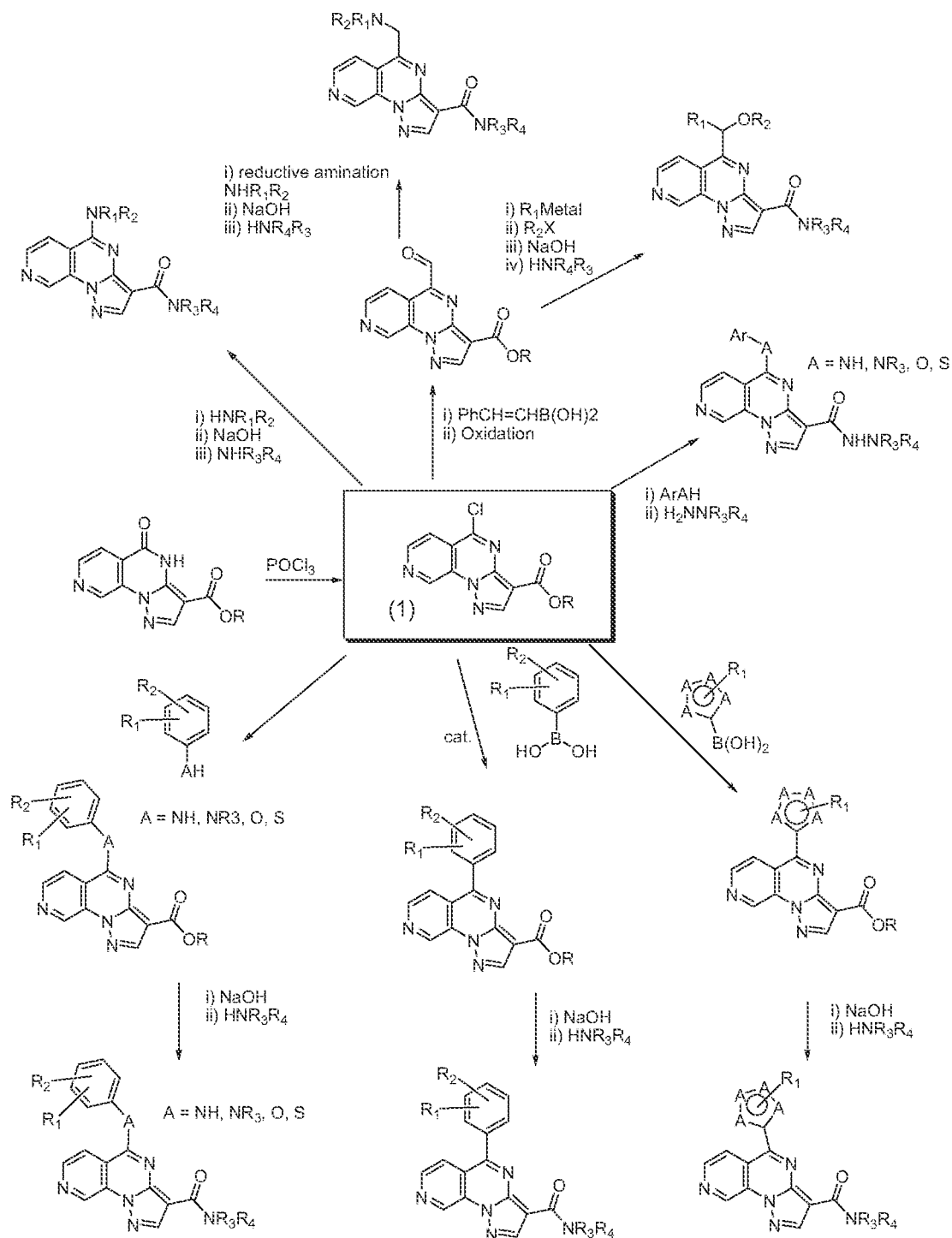
[0230] Chemistry described in Scheme 13 can be used to prepare additional compounds of Formula (I). Compound (2) can be prepared in several steps from commercially available (1) using chemistries described in scheme 4 (example 4). Compound (2) can be transformed into compound (3) by reacting with m-chloroperbenzoic acid. Compound (3) can be transformed into various analogs of general formula (4) using substituted nucleophiles such as substituted amines.

Scheme 13



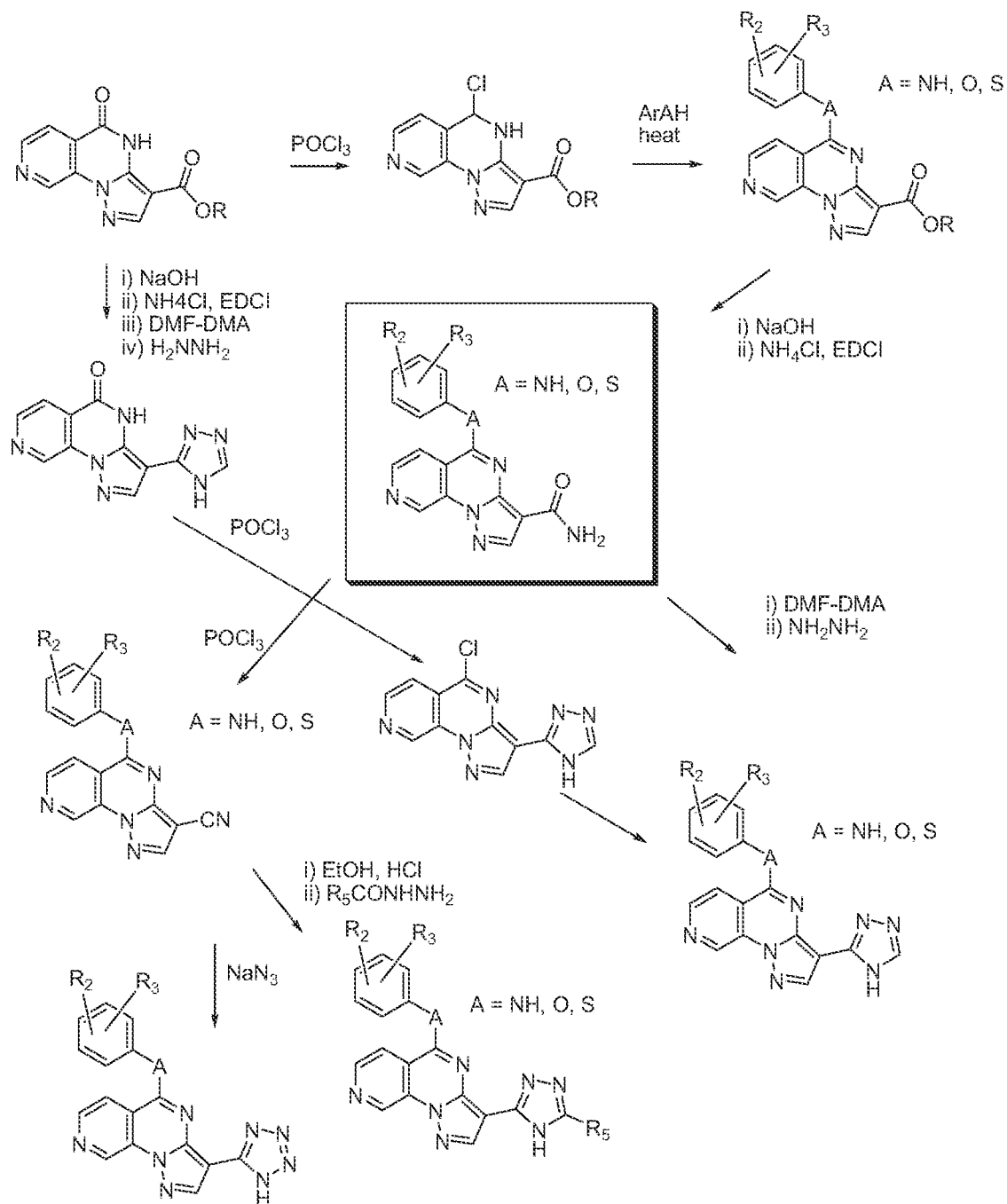
Example 7

[0231] The following are different chemistries useful to provide compounds of Formula (I) from available materials and those whose preparation is described herein:



Example 8

[0232] The following are different chemistries useful to provide compounds of Formula (I) from available materials and those whose preparation is described herein:



Biological Test Methods**Example 9****CK2 Assay Method**

[0188] Modulatory activity of compounds described herein was assessed *in vitro* in cell-free CK2 assays by the following method.

[0189] Test compounds in aqueous solution were added at a volume of 10 microliters, to a reaction mixture comprising 10 microliters Assay Dilution Buffer (ADB; 20mM MOPS, pH 7.2, 25 mM beta-glycerolphosphate, 5 mM EGTA, 1 mM sodium orthovanadate and 1 mM dithiothreitol), 10 microliters of substrate peptide (RRRDDDSDDD, dissolved in ADB at a concentration of 1 mM), 10 microliters of recombinant human CK2 (25 ng dissolved in ADB; Upstate). Reactions were initiated by the addition of 10 microliters of ATP Solution (90% 75 mM MgCl₂, 75 micromolar ATP dissolved in ADB; 10% [γ -³³P]ATP (stock 1 mCi/100 μ l; 3000 Ci/mmol (Perkin Elmer) and maintained for 10 minutes at 30 °C. The reactions were quenched with 100 microliters of 0.75% phosphoric acid, then transferred to and filtered through a phosphocellulose filter plate (Millipore). After washing each well 5 times with 0.75% phosphoric acid, the plate was dried under vacuum for 5 min and, following the addition of 15 μ l of scintillation fluid to each well, the residual radioactivity was measured using a Wallac luminescence counter.

Example 10**Pim-1 Assay Method**

[0190] The following procedure was used to assay the Pim-1 kinase activity of compounds of the invention. Other methods for assaying Pim-1 and other Pim kinases, as well as methods to assay for activity against the various kinases disclosed herein are known in the art.

[0191] In a final reaction volume of 50 μ l, recombinant Pim-1 (1 ng) was incubated with 12 mM MOPS pH 7.0, 0.4 mM EDTA, glycerol 1%, brij 35 0.002 %, 2-mercaptoethanol 0.02 %, BSA 0.2 mg/ml, 100 μ M KKRNRRLTK, 10 mM MgAcetate, 15 μ M ATP, [γ -³³P-ATP] (specific activity approx. 500 cpm/pmol), DMSO 4% and test inhibitor compound at the required concentration. The reaction was initiated by the addition of the magnesium ATP mixture. After 40 min incubation at 23 °C, the reactions were quenched by the addition of 100 μ l 0.75% Phosphoric acid, and the labeled peptide collected by filtration through a phosphocellulose filter plate. The plate was washed 4 times with 0.075% phosphoric acid

(100 ul per well) and then, after the addition of scintillation fluid (20 ul per well), the counts were measured by a scintillation counter.

Example 11

PIM-2 Assay Method

[0192] Test compounds dissolved and diluted in DMSO (2 µl) were added to a reaction mixture comprising 10 µl of 5X Reaction Buffer (40mM MOPS pH 7.0, 5mM EDTA), 10 µl of recombinant human Pim-2 solution (4 ng Pim-2 dissolved in dilution buffer (20 mM MOPS pH 7.0; EDTA 1 mM; 5% Glycerol; 0.01% Brij 35; 0.1%; 0.1% 2-mercaptoethanol; 1 mg/ml BSA)) and 8 ul of water. Reactions were initiated by the addition of 10 ul of ATP Solution (49% (15 mM MgCl₂; 75 uM ATP) 1% ([γ-33P]ATP: Stock 1mCi/100µl; 3000Ci/mmol (Perkin Elmer)) and 10 ul of substrate peptide solution (RSRSSYPAGT, dissolved in water at a concentration of 1 mM), Reactions were maintained for 10 min at 30 °C. The reactions were quenched with 100 ul of 0.75% phosphoric acid, then transferred to and filtered through a Phosphocellulose filter plate (Millipore, MSPH-N6B-50). After washing each well 4 times with 0.75% phosphoric acid, scintillation fluid (20 uL) was added to each well and the residual radioactivity was measured using a Wallac luminescence counter.

Example 12

Cell Proliferation Modulatory Activity

[0193] A representative cell-proliferation assay protocol using Alamar Blue dye (stored at 4°C, use 20ul per well) is described hereafter.

96-well plate setup and compound treatment

- a. Split and trypsinize cells.
- b. Count cells using hemocytometer.
- c. Plate 4,000-5,000 cells per well in 100 µl of medium and seed into a 96-well plate according to the following plate layout. Add cell culture medium only to wells B10 to B12. Wells B1 to B9 have cells but no compound added.

	1	2	3	4	5	6	7	8	9	10	11	12
A	EMPTY											
B	NO COMPOUND ADDED										Medium Only	
C	10nM		100nM		1uM		10uM		10uM		Control	
D	10nM		100nM		1uM		10uM		10uM		Comp1	
E	10nM		100nM		1uM		10uM		10uM		Comp2	
F	10nM		100nM		1uM		10uM		10uM		Comp3	
G	10nM		100nM		1uM		10uM		10uM		Comp4	
H	EMPTY											

d. Add 100 μ l of 2X drug dilution to each well in a concentration shown in the plate layout above. At the same time, add 100 μ l of media into the control wells (wells B10 to B12). Total volume is 200 μ l /well.

e. Incubate four (4) days at 37 °C, 5% CO₂ in a humidified incubator.

f. Add 20 μ l Alamar Blue reagent to each well.

g. Incubate for four (4) hours at 37 °C, 5% CO₂ in a humidified incubator.

h. Record fluorescence at an excitation wavelength of 544 nm and emission wavelength of 590 nm using a microplate reader.

[0194] In the assays, cells are cultured with a test compound for approximately four days, the dye is then added to the cells and fluorescence of non-reduced dye is detected after approximately four hours. Different types of cells can be utilized in the assays (e.g., HCT-116 human colorectal carcinoma cells, PC-3 human prostatic cancer cells, MDA-MB231 human breast cancer cells, K-562 human chronic myelogenous leukemia (CML) cells, MiaPaca human pancreatic carcinoma cells, MV-4 human acute myeloid leukemia cells, and BxPC3 human pancreatic adenocarcinoma cells).

[0195] Various compounds of the invention were tested in bioassay for enzyme inhibition and cell growth inhibition. These tested compounds showed desirable biological activity to inhibit one or more of the following enzymes or cells: CK2 IC₅₀ (μ M), PIM1 IC₅₀ (μ M), and

PIM2 IC₅₀ (μM). For example, all of the tested compounds showed CK2 IC₅₀, PIM1 IC₅₀, and/or PIM2 IC₅₀ of less than 50 μM; some of the tested compounds showed CK2 IC₅₀, PIM1 IC₅₀, and/or PIM2 IC₅₀ of less than 30 μM; some of the tested compounds showed CK2 IC₅₀, PIM1 IC₅₀, and/or PIM2 IC₅₀ of less than 20 μM; some of the tested compounds showed CK2 IC₅₀, PIM1 IC₅₀, and/or PIM2 IC₅₀ of less than 10 μM; some of the tested compounds showed CK2 IC₅₀, PIM1 IC₅₀, and/or PIM2 IC₅₀ of less than 5 μM; some of the tested compounds showed CK2 IC₅₀, PIM1 IC₅₀, and/or PIM2 IC₅₀ of less than 2.5 μM; and some of the tested compounds showed CK2 IC₅₀, PIM1 IC₅₀, and/or PIM2 IC₅₀ of less than 1 μM.

[0188] Biological activities for various compounds are summarized in the following tables, wherein Compounds A and B are Examples and specific compounds (i.e., species) as described herein above. For example, Compound B is described above as Example 3.

Table 1. Bioactivity of Selected Compounds.

Compound	CK2: IC ₅₀ (μM)	PIM1: IC ₅₀ (μM)	PIM2: IC ₅₀ (μM)
Compound A	> 5.0000	> 2.5000	> 2.5000
Compound B		< 1	< 1

[0189] 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. Furthermore, the contents of the patents, patent applications, publications and documents cited herein are

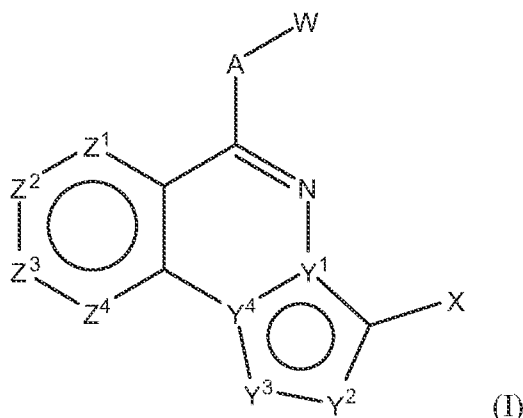
incorporated by reference in their entirety for all purposes to the same extent as each and everyone of them is incorporated by references specifically.

[0190] 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.

15

CLAIMS

1. A compound of Formula (I):



or a pharmaceutically acceptable salt, solvate, and/or prodrug thereof;
wherein:

each of Z^1 , Z^2 , Z^3 and Z^4 is independently CR^1 or N, provided no more than two of Z^1 to Z^4 are N, and the ring containing Z^1 to Z^4 is aromatic;

each R^1 is independently H, halo, CN, optionally substituted C1-C4 alkyl, optionally substituted C2-C4 alkenyl, optionally substituted C2-C4 alkynyl, optionally substituted C1-C4 alkoxy, SR, SO_2R , COOR, $COONR^7R^8$, or $-NR^7R^8$;

each of Y^1 and Y^4 is C or N, and Y^1 and Y^4 are not both simultaneously N; provided at least one of Y^1 to Y^4 is N;

Y^2 is N, NR^2 , CR^2 or CX^2 ,

wherein each R^2 is independently H, -OR, halo, CN, or optionally substituted C1-C4 alkyl,

and each X^2 is $-(CH_2)_{0-2}COOR$ or a polar group;

X is $-(CH_2)_{0-2}COOR$ or a polar group, or X is R^2 when Y^2 is CX^2 ;

each R is independently H or optionally substituted C1-C4 alkyl;

Y^3 is N, NR^3 , or CR^3 , and the ring containing Y^2 and Y^3 is aromatic;

wherein each R^3 is independently H, halo, -OR CN, or optionally substituted C1-C4 alkyl;

A is a bond, NR^4 , O or S, where R^4 is H or optionally substituted C1-C4 acyl;

W is optionally substituted aryl or optionally substituted arylalkyl; optionally substituted heteroaryl or optionally substituted heteroarylalkyl; optionally substituted heterocyclyl or optionally substituted heterocyclylalkyl; or optionally substituted C3-C8 cycloalkyl or optionally substituted cycloalkylalkyl;

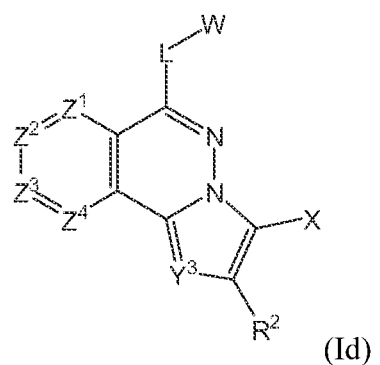
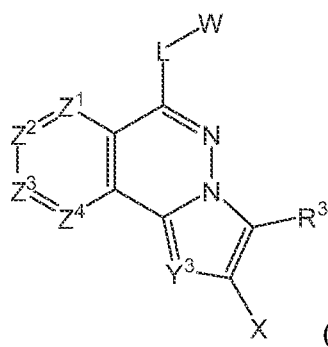
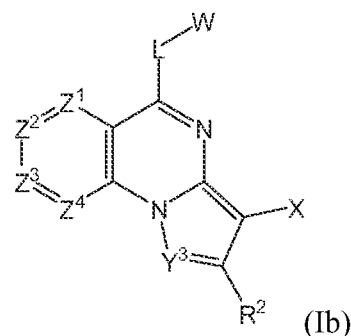
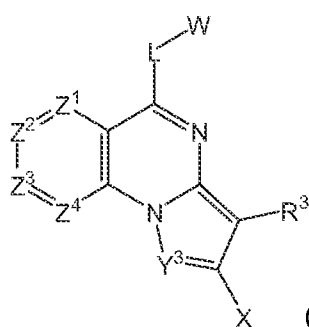
or alternatively, -A-W is -NR⁷R⁸;

each R⁷ and R⁸ is independently selected from H, optionally substituted C1-C10 alkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, and optionally substituted heteroarylalkyl;

and wherein R⁷ and R⁸ in NR⁷R⁸ can be taken together along with N to form a 4-8 membered ring that can be optionally substituted, and can contain an additional heteroatom selected from N, O and S as a ring member.

2. The compound of claim 1, wherein each of Z¹ to Z⁴ is CR¹.
3. The compound of claim 1 or 2, wherein one of Z¹ to Z⁴ is N and the others are each CR¹.
4. The compound of any one of claims 1 to 3, wherein exactly one of Y¹ to Y⁴ is N or NR².
5. The compound of any one of claims 1 to 3, wherein exactly two of Y¹ to Y⁴ are selected from the group consisting of N and NR².
6. The compound of claim 1 or 2, wherein X is COOR or a polar group.
7. The compound of any one of claims 1 to 5, wherein X is R², and Y² is CX², wherein X² is COOR or a polar group.
8. The compound of any one of claims 1 to 7, wherein Y¹ is N.
9. The compound of any one of claims 1 to 7, wherein Y⁴ is N.
10. The compound of any one of claims 1 to 9, wherein A is NH.
11. The compound of any one of claims 1 to 10, wherein W is optionally substituted aryl.
12. The compound of claim 11, wherein W is optionally substituted phenyl.

13. The compound of claim 1, wherein Formula (I) is represented by Formula (Ia), (Ib), (Ic), or (Id):



14. The compound of claim 13, wherein

A is NR^4 , O or S, where R^4 is H or optionally substituted C1-C4 acyl;

W is optionally substituted aryl or optionally substituted arylalkyl; optionally substituted heteroaryl or optionally substituted heteroarylalkyl; optionally substituted heterocyclyl or optionally substituted heterocyclalkyl; or optionally substituted C3-C8 cycloalkyl or optionally substituted cycloalkylalkyl; and

X is -COOR or a polar group.

15. The compound of claim 13, wherein

A is a bond;

W is optionally substituted aryl; optionally substituted heteroaryl; optionally substituted heterocyclyl; or optionally substituted C3-C8 cycloalkyl; and

X is COOR or a polar group.

16. The compound of claim 13, wherein

A is a bond;

W is optionally substituted arylalkyl; optionally substituted heteroarylalkyl; optionally substituted heterocyclalkyl; or optionally substituted cycloalkylalkyl; and

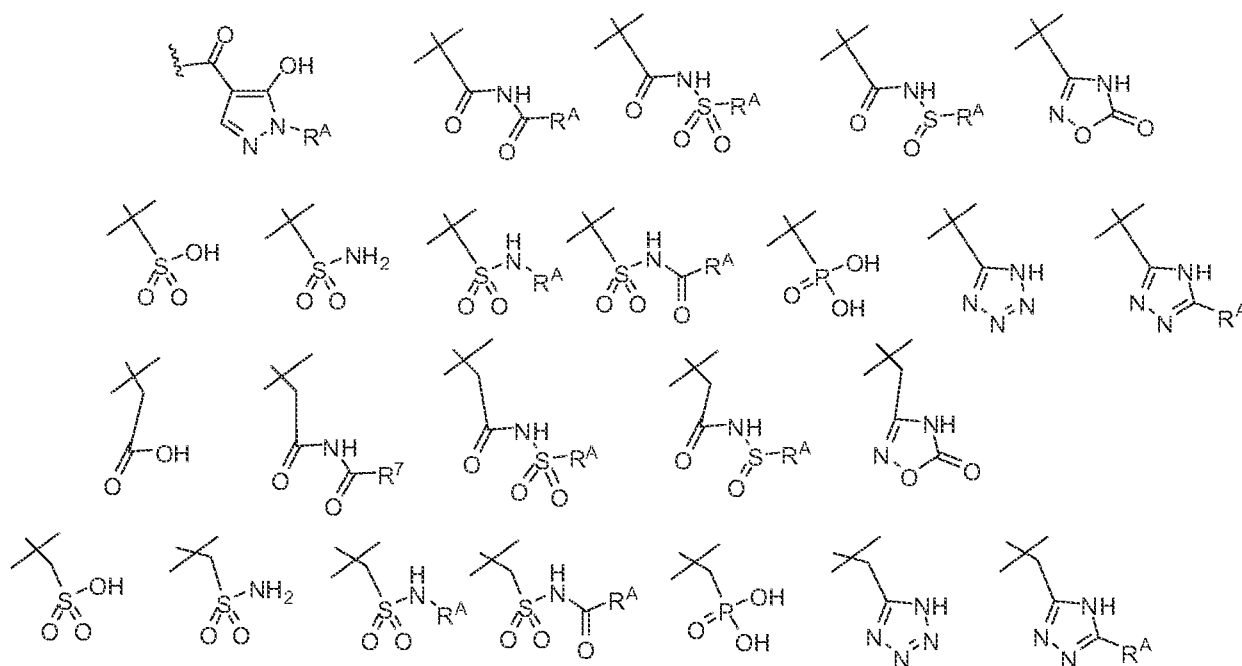
X is COOR or a polar group.

17. The compound of claim 13, wherein

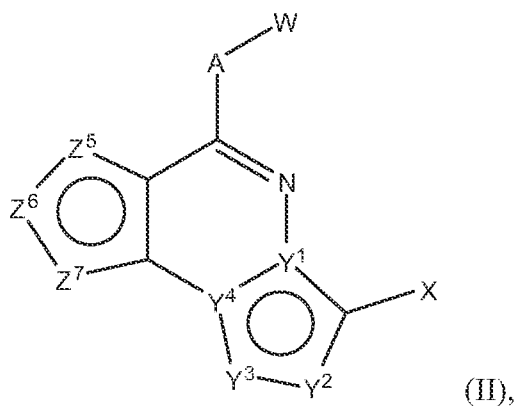
-A-W is -NR⁷R⁸; and

X is COOR or a polar group.

18. The compound of any one of claims 1 and 14 to 17, wherein the polar group is selected from the group consisting of



19. A compound of Formula (II):



or a pharmaceutically acceptable salt, solvate, and/or prodrug thereof;
wherein:

each of Z^5 and Z^6 and Z^7 is independently CR^1 , NR^2 , N, O or S, provided at least one of Z^5 to Z^7 is not CR^1 , and no more than one of Z^5 to Z^7 is O or S, and the ring containing Z^5 - Z^7 is aromatic;

each of Y^1 and Y^4 is independently C or N, and Y^1 and Y^4 are not both simultaneously N; provided at least one of Y^1 to Y^4 is N;

Y^2 is N, CR^1 or CX^2 , where X^2 is $-(CH_2)_{0-2}COOR$ or a polar group;

Y^3 is CR^3 , and the ring containing Y^2 and Y^3 is aromatic;

each R^1 is independently H, halo, CN, optionally substituted C1-C4 alkyl, optionally substituted C2-C4 alkenyl, optionally substituted C2-C4 alkynyl, OR, SR, SO_2R , COOR, $COONR^7R^8$, or $-NR^7R^8$;

each R^2 is independently H, CN, -OR, COOR, $CONR_2$, SO_2R , or optionally substituted C1-C4 alkyl;

each R^3 is independently H, halo, CN, -OR, or optionally substituted C1-C4 alkyl;

X is $-(CH_2)_{0-2}COOR$ or a polar group, or X can be R^1 when Y^2 is CX^2 ;

R is independently at each occurrence H or an optionally substituted C1-C4 alkyl;

A is a bond, NR^4 , O or S;

wherein R^4 is H or optionally substituted C1-C4 acyl;

W is optionally substituted aryl or arylalkyl; optionally substituted heteroaryl or heteroarylalkyl; optionally substituted heterocyclyl or heterocyclalkyl; or optionally substituted C3-C8 cycloalkyl or cycloalkylalkyl;

or alternatively, -A-W is $-NR^7R^8$;

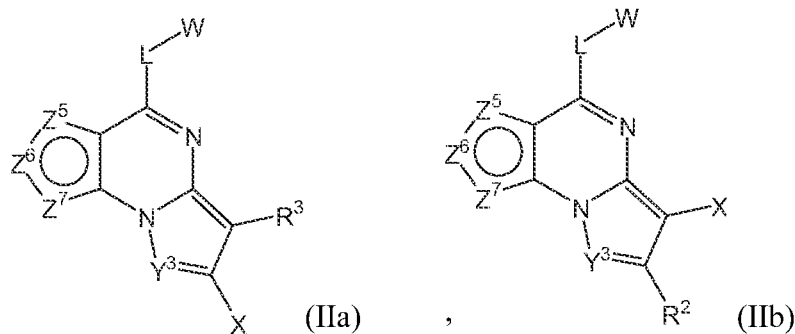
each R^7 and R^8 is independently selected from H, optionally substituted C1-C10 alkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, and optionally substituted heteroarylalkyl;

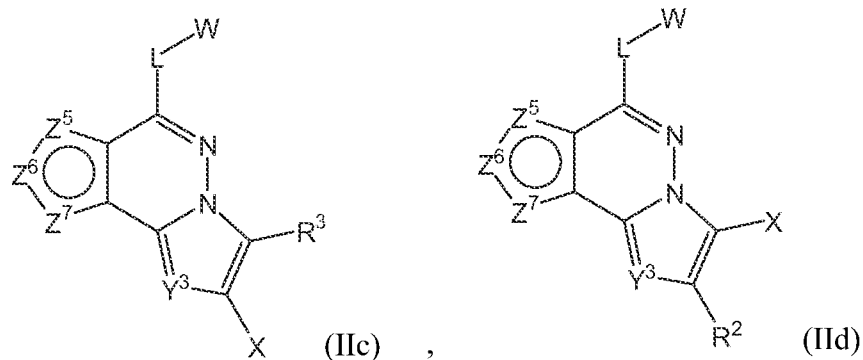
and wherein R^7 and R^8 in NR^7R^8 can be taken together along with N to form a 4-8 membered ring that can be optionally substituted, and can contain an additional heteroatom selected from N, O and S as a ring member.

20. The compound of claim 19, wherein Z^5 is N, O or S.

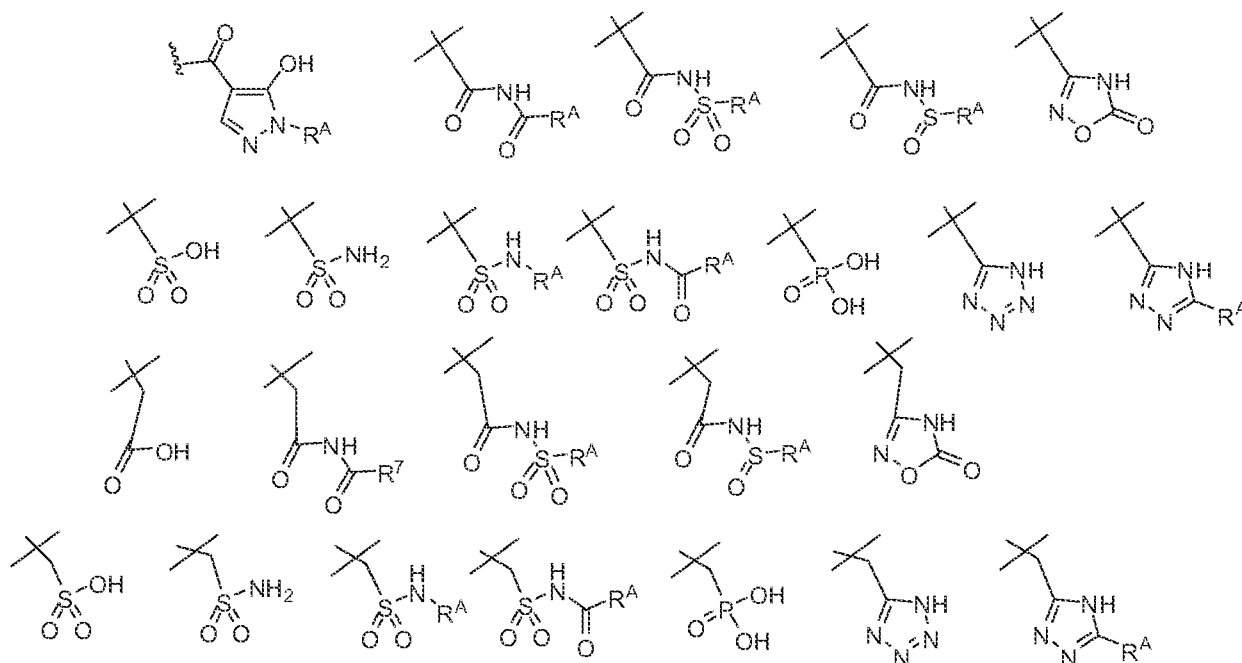
21. The compound of claim 19, wherein Z^6 is N, O or S.

22. The compound of claim 19, wherein Z^7 is N, O or S.
23. The compound of any one of claims 19 to 22, wherein exactly one of Y^1 to Y^4 is N or NR^2 .
24. The compound of any one of claims 19 to 22, wherein exactly two of Y^1 to Y^4 are N or NR^2 .
25. The compound of any of claims 19 to 24, wherein X is COOR or a polar group.
26. The compound of any one of claims 19 to 24, wherein X is R^2 , and X^2 is COOR or a polar group.
27. The compound of any one of claims 19 to 26, wherein Y^1 is N.
28. The compound of any one of claims 19 to 26, wherein Y^4 is N.
29. The compound of claim 27 or 28, wherein A is NH.
30. The compound of any one of claims 19 to 29, wherein W is optionally substituted aryl.
31. The compound of any one of claims 19 to 30, wherein W is optionally substituted phenyl.
32. The compound of claim 19, wherein Formula (II) is respresented by Formula (IIa), (IIb), (IIc), or (IId):





33. The compound of claim 19, wherein
 A is NR^4 , O or S, where R^4 is H or optionally substituted C1-C4 acyl;
 W is optionally substituted aryl or optionally substituted arylalkyl; optionally substituted heteroaryl or optionally substituted heteroarylalkyl; optionally substituted heterocyclyl or optionally substituted heterocyclalkyl; or optionally substituted C3-C8 cycloalkyl or optionally substituted cycloalkylalkyl;
 X is -COOR or a polar group.
34. The compound of claim 19, wherein
 A is a bond;
 W is optionally substituted aryl; optionally substituted heteroaryl; optionally substituted heterocyclyl; or optionally substituted C3-C8 cycloalkyl; and
 X is COOR or a polar group.
35. The compound of claim 19, wherein
 A is a bond;
 W is optionally substituted arylalkyl; optionally substituted heteroarylalkyl; optionally substituted heterocyclalkyl; or optionally substituted cycloalkylalkyl; and
 X is COOR or a polar group.
36. The compound of claim 19, wherein
 -A-W is $-\text{NR}^7\text{R}^8$; and
 X is COOR or a polar group.
37. The compound of any one of claims 19 and 33 to 36, wherein the polar group is selected from the group consisting of



38. A pharmaceutical composition comprising a compound of any one of claims 1 to 37, and a pharmaceutically acceptable excipient.

39. A method of modulating casein kinase 2 activity and/or Pim kinase activity in a cell comprising contacting the cell with an effective amount of a compound of any one of claims 1 to 37.

40. A method of treating a condition or disease associated with casein kinase 2 activity and/or Pim kinase activity in a patient comprising administering to the patient a therapeutically effective amount of the compound of any one of claims 1 to 37.

41. The method of claim 40, wherein the condition or disease associated with casein kinase 2 activity and/or Pim kinase activity is selected from the group consisting of a cancer, a vascular disorder, a inflammation, a pathogenic infection, a immunological disorder, and a combination thereof.

42. Ther method of claim 41, the cancer is of the colorectum, breast, lung, liver, pancreas, lymph node, colon, prostate, brain, head and neck, skin, liver, kidney, blood and heart.

43. A method for inhibiting cell proliferation, which comprises contacting cells with the compound of any one of claims 1 to 37, in an amount effective to inhibit proliferation of the cells.

44. The method of claim 43, wherein the cells are in a cancer cell line or in a tumor in a subject.

45. A compound according to any one of claims 1 to 37 for use as a medicament.

46. A pharmaceutical composition comprising a compound of any of one of claims 1 to 37, or a pharmaceutically acceptable salt, solvate, and/or prodrug thereof; and at least one additional therapeutic agent.

47. A method to treat a condition or disease 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 37, or a pharmaceutically acceptable salt, solvate, and/or prodrug thereof; and at least one additional therapeutic agent.