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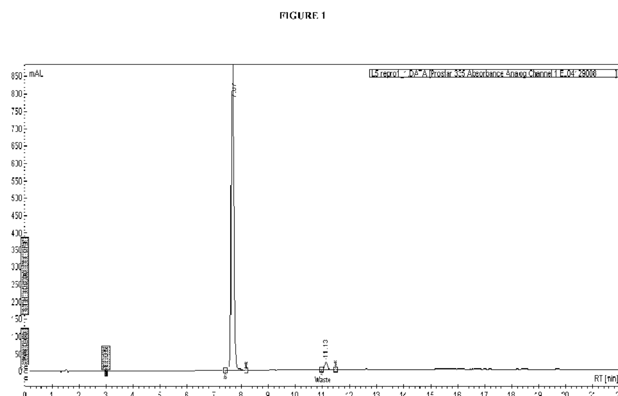
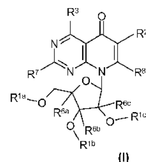
(54) Title: COMPOUNDS USEFUL AS AKT/PKB MODULATORS AND USES THEREOF

FIGURE 1





(57) Abstract: Compounds, and pharmaceutical compositions, and formulations thereof, are disclosed that have formula (I): where R^{1a}, R^{1b}, R^{1c}, R^2, R^3, R^{6a}, $R6^b$, R^{6c}, R^7, and R^8 are as defined herein. The compounds, pharmaceutical compositions, and pharmaceutical formulations thereof are useful for the prevention and treatment of a variety of conditions in mammals including humans, including by way of non-limiting example, cancer, and others. The manufacturing and analytical methods for LD- 101 are also disclosed.

WO 2012/158197 A2

COMPOUNDS USEFUL AS AKT/PKB MODULATORS AND USES THEREOF

FIELD OF THE INVENTION

[0001] This invention relates to novel pyrido[2,3-d]pyrimidine compounds that are capable of modulating Akt, also known as protein kinase B-PKB activities, the Akt pathways and to pharmaceutical compositions containing such compounds. The invention further relates to preparation of novel pyrido[2,3-d]pyrimidine compounds. The invention further relates to pharmaceutical formulations comprising the novel pyrido[2,3-d]pyrimidine compounds. In particular, the invention relates to pharmaceutical formulations and manufacturing and analytical methods of 4-amino-8-[3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-5-oxopyrido[2,3-d]pyrimidine-6-carboxamide. This invention also relates to methods for the prevention, prophylaxis and/or treatment of conditions that are causally related to increased Akt, overexpression of Akt, hyperactvation of Akt, amplification of Akt, constitutivelly active and aberrant Akt/PKB activity and its pathways or can be alleviated by modulating Akt/PKB activity and its pathways in diseases such as cancer, Huntington's disease, HIV infection, hemostasis, rheumatoid arthritis or other disorders.

BACKGROUND OF THE INVENTION

[0002] Akt/PKB, represents a subfamily of the serine/threonine kinase. Akt was first described as the cellular homologue of the product of the v-Akt oncogene (Bellacosa et al. 1991), and it has three members, Aktl/ PKBα, AkΛ2/PKBβ and Akt3/PKBy ((hereinafter referred to as 'Aktl ', 'Akt2' and 'Akt3'), respectively) (Cheng et al. 1992; Jones et al. 1991a; Jones et al. 1991b). Activation of Akt depends on the integrity of the pleckstrin homology (PH) domain, which mediates its membrane translocation, and on the phosphorylation of Thr^{308} in the activation loop and Ser^{473} (Konishi et al. 1995). Phosphoinositides, PtdIns-3,4-P2 and PtdIns-3,4,5-P3, produced by PI3 K bind directly to the PH domain of Akt, driving a conformational change in the molecule, which enables the activation loop of Akt to be phosphorylated by PDKl at Thr^{308} (Datta et al. 1999). Phosphorylation of Aktl occurs on two regulatory sites, Thr^{308} in the catalytic domain activation loop and on Ser^{473} near the carboxy terminus (D. R. Alessi et al. *EMBOJ.* 15:6541-6551 (1996) and R. Meier et al. *J. Biol. Chem.* 272:30491-30497 (1997)). Equivalent regulatory phosphorylation sites occur in Akt2 (Thr^{309} and Ser^{474}) and Akt3 (Thr^{306} and Ser^{472}). The upstream kinase, which phosphorylates Akt at the activation loop site has been cloned and termed 3'-phosphoinositide dependent protein kinase 1 (PDKl). PDKl phosphorylates not only Akt, but also p70 ribosomal S6 kinase, p90RSK, serum and glucocorticoid-regulated kinase (SGK), and protein kinase C. Full activation of Akt is also associated with phosphorylation by PDK2 (Peterson et al. 1999, Liu et al. 2005) at Ser^{473} within a C-terminal hydrophobic motif (Datta et al. 1999). Although the role of PDKl in Thr^{308} phosphorylation is well established, the mechanism of Ser^{473} phosphorylation by PDK2 has not been completely elucidated. A number of candidate enzymes designated PDK2 responsible for this phosphorylation have been put forward, including integrin-linked kinase (Persad et al. 2001), PDKl when

in a complex with the kinase PRK2 (Wick et al. 2000), Akt itself, through autophosphorylation (Toker et al. 2000), DNA-dependent kinase (Feng et al. 2004), and the rictor-mTOR complex (Sarbassoy et al. 2005). The activity of Akt is negatively regulated by tumor suppressor called phosphatase and tensin homolog (PTEN), which is frequently mutated in human malignancy (Vazquez et Al. 2000). PTEN encodes a dual-specificity protein and lipid phosphatase that reduces intracellular levels of phosphatidylinositol 3-kinase or PtdIns(3,4,5)P3 (PI3K) by converting them to phophatidylinositol 2-kinase or PtdIns(4,5)P2 (PI2K), thereby inhibiting the PI3K/Akt signaling transduction intracellular pathway (Stambolic et al. 1998).

[0003] Apoptosis (programmed cell death) plays essential roles in embryonic development and pathogenesis of various diseases, such as degenerative neuronal diseases, cardiovascular diseases and cancer. Recent work has led to the identification of various pro- and anti-apoptotic gene products that are involved in the regulation or execution of programmed cell death. Expression of anti-apoptotic genes, such as Bcl2 or Bcl-x.sub.L, inhibits apoptotic cell death induced by various stimuli. On the other hand, expression of pro-apoptotic genes, such as Bax or Bad, leads to programmed cell death (Adams et al. Science, 281:1322-1326 (1998)). The execution of programmed cell death is mediated by caspase-1 related proteinases, including caspase-3, caspase-7, caspase-8 and caspase-9 etc (Thornberry et al. Science, 281:1312-1316 (1998)).

[0004] The phosphatidylinositol 3'-OH kinase (PI3K)/Akt/PKB pathway appears important for regulating cell survival/cell death (Kulik et al. Mol. Cell. Biol. 17:1595-1606 (1997); Franke et al, Cell, 88:435-437 (1997); Kauffmann-Zeh et al. Nature 385:544-548 (1997) Hemmings Science, 275:628-630 (1997); Dudek et al., Science, 275:661-665 (1997)). Survival factors, such as platelet derived growth factor (PDGF), nerve growth factor (NGF) and insulin- like growth factor- 1 (IGF-1), promote cell survival under various conditions by inducing the activity of PI3K (Kulik et al. 1997, Hemmings 1997). Activated PI3K leads to the production of phosphatidylinositol (3,4,5)-triphosphatase (Ptdlns (3,4,5)—P3), which in turn binds to, and promotes the activation of, the serine/threonine kinase Akt, which contains a pleckstrin homology (PH)-domain (Franke et al Cell, 81:727-736 (1995); Hemmings Science, 277:534 (1997); Downward, Curr. Opin. Cell Biol. 10:262-267 (1998), Alessi et al., EMBO J. 15: 6541-6551 (1996)). Specific inhibitors of PI3K or dominant negative Akt/PKB mutants abolish survival-promoting activities of these growth factors or cytokines. It has been previously disclosed that inhibitors of PI3K (LY294002 or wortmannin) blocked the activation of Akt/PKB by upstream kinases. In addition, introduction of constitutively active PI3K or Akt/PKB mutants promotes cell survival under conditions in which cells normally undergo apoptotic cell death (Kulik et al. 1997, Dudek et al. 1997).

[0005] Three members of the Akt subfamily of second-messenger regulated serine/threonine protein kinases have been identified and termed Aktl/PKBa, Akt2/PKBβ, and Akt3/PKBy (hereinafter referred to as "Aktl", "Akt2" and "Akt3"), respectively. The isoforms are homologous, particularly in regions encoding the catalytic domains. Akts are activated by phosphorylation events occurring in response to PI3K signaling. PI3K phosphorylates membrane inositol phospholipids, generating the second messengers phosphatidyl-inositol 3,4,5-trisphosphate and phosphatidylinositol 3,4-bisphosphate, which have been shown to bind to the PH domain of Akt. The current model of Akt activation proposes

recruitment of the enzyme to the membrane by 3'-phosphorylated phosphoinositides, where phosphorylation of the regulatory sites of Akt by the upstream kinases occurs (B. A. Hemmings, *Science* 275:628-630 (1997); B. A. Hemmings, *Science* 276:534 (1997); J. Downward, *Science* 279:673-674 (1998)).

[0006] Phosphorylation of Aktl occurs on two regulatory sites, Thr^{308} in the catalytic domain activation loop and on Ser^{473} near the carboxy terminus (D. R. Alessi et al. *EMBOJ.* 15:6541-6551 (1996) and R. Meier et al. *J. Biol. Chem.* 272:30491-30497 (1997)). Equivalent regulatory phosphorylation sites occur in Akt2 and Akt3. The upstream kinase, which phosphorylates Akt at the activation loop site has been cloned and termed 3'-phosphoinositide dependent protein kinase 1 (PDK1). PDK1 phosphorylates not only Akt, but also p70 ribosomal S6 kinase, p90RSK, serum and glucocorticoid-regulated kinase (SGK), and protein kinase C. The upstream kinase phosphorylating the regulatory site of Akt near the carboxy terminus has not been identified yet, but recent reports imply a role for the integrin-linked kinase (ILK-1), a serine/threonine protein kinase, or autophosphorylation.

[0007] Akt phosphorylates and/or interacts with a number of molecules to exert its normal cellular functions, which include roles in cell proliferation, survival, migration and differentiation (Cheng et al. 2001). Many lines of evidence demonstrate that Akt is a critical player in tumor development and progression. In addition, overexpression of Akt and /or aberrant hyperactivation of Akt pathway has been detected in up to 50% all human tumors (Sun et al. 2001; Cheng et al. 1997) and is closely associated with chemoresistance (West et al. 2002). Therefore, Akt has been an attracting target for anti-cancer drug discovery (West et al. 2002). A recent study identified a recurring somatic mutation within PH domain of AKT1 in human breast, colorectal, lung and ovarian cancers that results in a glutamic acid to lysine substitution at amino acid 17 (E17K) in the lipid-binding pocket (18) which led to hyperactivated and constitutive ly active Aktl. Lys 17 alters the electrostatic interactions of the pocket and forms new hydrogen bonds with a phosphoinositide ligand. This mutation activates AKT1 through aberrant pathological localization to the plasma membrane, transforms cells and induces leukemia in mice (18). Further, the E17K substitution reduces the sensitivity to an allosteric Akt kinase inhibitor (18), but not to API-1 (or LD-101) which inhibits all isoforms of Akt in a non-PH domain dependent manner. Thus, the pharmacodynamic inhibitory activities of the compound of instant invention is not dependent of the length of amino acid chain, the order of amino acid sequence or the amount of amino acids on the PH-domain of the Akt..

[0008] Analysis of Akt levels in human tumors showed that Aktl is hyperactivated in gastric cancer *(Hill, MM., and Hemmings B.A. 2002. Pharmacol. Therap. 93, 243),* while Akt2 is overexpressed in a significant number of ovarian (J. Q. Cheng et al. *Proc. Natl. Acad. Sci. U.S.A.* 89:9267-9271 (1992)) and pancreatic cancers (J. Q. Cheng et al. *Proc, Natl. Acad. Sci. U.S.A.* 93:3636-3641 (1996)). Similarly, Akt3 was found to be overexpressed in breast and prostate cancer cell lines (Nakatani et al. *J. Biol. Chem.* 274:21528-21532 (1999).

[0009] The tumor suppressor PTEN, a protein and lipid phosphatase that specifically removes the 3' phosphate of Ptdlns(3,4,5)-P3, is a negative regulator of the PI3K/Akt pathway (Li et al. *Science* 275:1943-1947 (1997), Stambolic et al. *Cell* 95:29-39 (1998), Sun et al. *Proc. Natl. Acad. Sci. U.S.A.*

96:6199-6204 (1999)). Germline mutations of PTEN are responsible for human cancer syndromes such as Cowden disease (Liaw et al. *Nature Genetics* 16:64-67 (1997)). PTEN is deleted in a large percentage of human tumors and tumor cell lines without functional PTEN show elevated levels of activated Akt (Li et al. supra, Guldberg et al. *Cancer Research* 57:3660-3663 (1997), Risinger et al. *Cancer Research* 57:4736-4738 (1997)).

[0010] These observations demonstrate that the PI3K/Akt pathway plays important roles for regulating cell survival or apoptosis in tumorigenesis.

[0011] Inhibition of Akt activation and activity can be achieved by inhibiting PI3K with inhibitors such as LY294002 and or wortmannin. However, PI3K inhibition has the potential to indiscriminately affect not just all three Akt isozymes but also other PH domain-containing signaling molecules that are dependent on Pdtlns(3,4,5)-P3, such as the Tec family of tyrosine kinases, hence accompanied toxicities. Moreover, it has been disclosed that Akt can be activated by growth signals that are independent of PI3K.

[0012] Alternatively, Akt activity can be inhibited by blocking the activity of the upstream kinase PDK1. Some PDK1 inhibitors have been disclosed such as BX-795, BX-912, and BX-320 (Berlex Biosciences), AR12 (Arno Therapeutics) and 7-hydroxystaurosporine (UCN-01 - Abbott Labs). Again, inhibition of PDK1 would result in inhibition of multiple protein kinases whose activities depend on PDK1, such as AGC family protein kinases including PKC isoforms, SGK, and S6 kinases, thus accompanied by toxicities (Williams et al. *Curr. Biol.* 10:439-448 (2000).

[0013] Therefore, it is an object of the instant invention to provide novel compounds that are inhibitors of Akt. It is also an object of the present invention to provide pharmaceutical compositions that comprise the novel compounds that are inhibitors of Akt.

[0014] In the last several years, through combinatorial chemistry, high-throughput and virtual screening, and traditional medicinal chemistry, a dozen inhibitors of the Akt pathway have been identified. Lipid-based inhibitors of Akt were the first to be developed, including perifosine (Kondapaka et Al. 2003), PX-316 (Meuillet et al. 2004) and phosphatidylinositol ether lipid analogues (PLAs) (Castillo et al. 2004), which were designed to interact with the PH domain of Akt. In addition, several Akt antagonists have been identified using high-throughput screening of chemical libraries and rational design. These inhibitors include 9-methoxy-2-methylellipticinium acetate (Jin et al. 2004), the indazole-pyridine A-443654 (Luo et al. 2005), isoform-specific allosteric kinase inhibitors (Lindsley et al. 2005) and Akt/PKB signaling inhibitor-2 (API-2), also called triciribine/TCN (Yang et al. 2004). API-2/TCN is a tricyclic nucleoside that previously showed antitumor activity in phase I and phase II trials conducted, but multiple toxicities, including hepatotoxicity, hyperglycemia, thrombocytopenia, and hypertriglyceridemia, precluded further development (Feun et al. 1993; Hoffman et al. 1996). By screen of the NCI diversity set, Yang et al have previously shown that API-2 inhibit Akt kinase activity and stimulate apoptosis of xenografts of human cancer cells exhibiting high Akt activity (Yang et al. 2004). This finding has provided new interest in studying this drug and raises the possibility that lower doses may inhibit Akt and induce tumor cell apoptosis without the previously associated side effects (Yang et at. 2004; Cheng et ct. 2005).

[0015] Small molecule inhibitors of Akt are useful in the treatment of tumors, especially those with activated Akt (e.g. PTEN null tumors and tumors with ras mutations). PTEN is a critical negative regulator of Akt and its function is lost in many cancer cases, including breast and prostate carcinomas, glioblastomas, and several cancer syndromes including Bannayan-Zonana syndrome (Maehama, T. et al. Annual Review of Biochemistry, 70: 247 (2001)), Cowden disease (Parsons, R.; Simpson, L. Methods in Molecular Biology (Totowa, N.J., United States), 222 (Tumor Suppressor Genes, Volume 1): 147 (2003)), and Lhermitte-Duclos disease (Backman, S. et al. Current Opinion in Neurobiology, 12(5): 516 (2002)). Akt3 is up-regulated in estrogen receptor-deficient breast cancers and androgen-independent prostate cancer cell lines and Akt2 is over-expressed in pancreatic and ovarian carcinomas. Aktl is amplified in gastric cancers (Staal, Proc. Natl. Acad. Sci. USA 84: 5034-7 (1987) and upregulated in breast cancers (Stal et al. Breast Cancer Res. 5: R37-R44 (2003)). Therefore a small molecule Akt inhibitor is expected to be useful for the treatment of these types of cancer as well as other types of cancer. Akt inhibitors are also useful in combination with further chemotherapeutic and anticancer agents.

[0016] The US Patent application publication, US 2009/0028855, describes specific pyridopyrimidine derivatives as Akt inhibitors, with anti-tumor activity.

[0017] Accordingly, a need therefore exists for the development of agents, i.e. compounds, that are effective as modulators of Akt/PKB activity, and it is toward the fulfillment of that need, that the present invention is directed.

SUMMARY OF THE INVENTION

[0018] Compounds, and pharmaceutical compositions thereof, having potency, specificity and selectivity in the prevention, prophylaxis, and treatment of conditions that have been associated with elevation, overexpression, hyperactivation, amplification, increase, upregulation and or aberration of Akt and its pathways leading to disease conditions such as in oncological (cancer), neurological diseases (Huntington's disease, ataxia, macular degeneration), respiratory (idiopathic pulmonary fibrosis), immunology (rheumatoid arthritis), infection (HIV) and other related conditions described herein.

[0019] In particular, compounds, pharmaceutical compositions and methods provided are used to prevent, treat, or ameliorate a range of mammallian conditions in which Akt and / or its pathways is hyperactivated, elevated, overexpressed, amplified, constitutively or abberantly active such as (but not limited to); cancer, ataxia, Huntington's disease, orthostatic hypotension, hypovolemia, diabetic retinopathy, septic shock, HIV infection, influenza, wound healing and type I insulin-dependent diabetis mellitus and other related conditions. Furthermore, the compounds of the invention may be used for killing cancer cells, HIV, influenza virus or other cells in which expression of an Akt protein is elevated, amplified, hyperactivated, overexpressed, aberrantly or constitutively active, comprising contacting the cell with an effective amount of a compound of formula I.

[0020] The subject invention also concerns methods for treating cancer (or tumor), Huntington's disease, ataxia, macular degeneration, diabetic retinopathy, hypovolemia, wound, ulcerative dermatitis, burns, autoimmune disease, idiopathic pulmonary fibrosis and type I diabetis mellitus in a person or animal comprising administering an effective amount of a compound of formula I to the person or animal.

[0021] The serine/threonine kinase Akt/PKB pathway is frequently hyperactivated, overexpressed, elevated, increased and constitutively activated in many human diseases such as cancer, autoimmune, pulmonary fibrosis, macular degeneration, septic shock, etc. and functions as a cardinal nodal point for transducing extracellular and intracellular oncogenic and other metabolic signals, and thus it presents a target for molecular therapeutics. API- 1 (or LD- 101) inhibits the kinase activity and phosphorylation level of all the three members of Akt family (Aktl, Akt2 and Akt3). API-1 (or LD-101) inhibits constitutively active Akt, including naturally occurring AKT1-E40K and somatic mutant AKT1-E17K, and its downstream targets. API-1 (or LD-101) abrogates kinase activity and phosphorylation of all isoforms of Akt, thereby inhibits AktlE40K and AktlE17K because E40 and E17 are located in the PH domain. However, API-1 (or LD-101) has demonstrated no effect on the activity of the activators (enzymes) upstream of Akt in the Akt pathway such as; PI3K, PDK1 and PDK2. Further, the kinase activity and phosphorylation levels of constitutively active Akt were largely inhibited by API- 1 (or LD-101) in cell culture, while it had no effect on Akt kinase activity *in vitro.* API-1 (or LD-101) is very potent, highly selective and particularly specific for Akt, and does not inhibit the activation of other members of the AGC family of enzymes, including PKC, PKG, SGK, PKA, or enzymes and targets in other parallel oncogenic signal transduction pathways such as; STAT3, p38, ERK-1/2, or JNK and MAP-kinase. As a consequence of inhibition of Akt, API-1 (or LD-101) does indirectly (not directly) inhibit activation (or phosphorylation) of enzymes downstream of Akt such as inhibit p90 ribosomal S6 kinase and p70 S6K. API-1 (or LD-101) does not directly inhibit molecular targets on other physiologically important signal transduction pathways such as PKA, PLC and PKC-related kinases. Hence, absence of toxicities. The inhibition of Akt by API-1 (or LD-101) resulted in cell growth arrest, tumor growth inhibition and induction of apoptosis in cells that harbor constitutively activated Akt, aberrant Akt, hyperactivated Akt, overexpressed Akt, increased Akt, upregulated Akt, amplified Akt and overexpressed Akt for instance in human cancer cells. Significantly, API-1 (or LD-101) selectively inhibited tumor growth in nude mice of xenograpgh human cancer cells in which Akt is elevated, increased, hyperactivated or overexpressed but NOT of those cells in which it is not. Hence, lack of systemic toxicities. These data suggest that API-1 (or LD-101) is an Akt, and Akt pathway inhibitor with anti-tumor activity *in vitro* and *in vivo* and could be a potential anti-cancer agent for patients with cancer expressing hyperactivated Akt.

[0022] API- 1 (or LD- 10 1) directly inhibits Akt by directly binding to Akt Protein and inhibits Akt membrane translocation. Since Akt activation is initiated by PH domain binding to PI3K anchored to intracellular side of the cell membrane, API-1 (or LD-101) inhibits Akt through blockade of its membrane translocation. Immunofluorescence staining revealed that Akt membrane translocation induced by IGF1 was abrogated by API- 1 (or LD- 101). Furthermore, API- 1 (or LD- 101) inhibition of Akt through the targeting of the PH domain, that was examined under fluorescence miscropy demonstrates that IGF- 1 induced GFPAkt and GFP-PH membrane translocation was largely attenuated by API-1 (or LD-101). Moreover, endogenous AKT2 membrane translocation induced by EGF was also inhibited by API- 1 (or LD-101). SPR and NMR were also used to explore molecular interactions and structural activities relationship between API-1 (or LD-101) and PH domain of Akt. The results clearly indicte that API-1

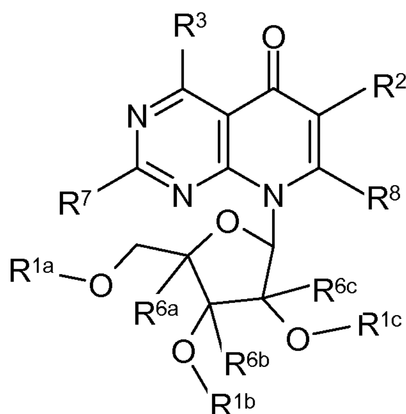
inhibits Akt function by binding to the PH domain of Akt, blocking its recruitment to the plasma membrane and subsequent inhibition of its phosphorylation. Collectively, these findings indicate that API-1 (or LD-101) inhibition of Akt through binding to the Akt-PH domain hence blocks Akt membrane translocation.

[0023] Akt is a major pathway and crutial nodal point regulating and modulating cell survival, growth, replication, cell cycle, cell progression, invasiveness, metastasis, chemoresistance and resistance to radiotherapy in all disease conditions associated with elevated, increased, hyperactivated, amplified, constitutively activated and overexpressed Akt and or its signaling transduction pathways. These conditions include (but not limited to) cancer, huntimgton's, ataxias, pulmonary fibrosis, HIV infection and other discussed herein. It has been well documented that elevated levels of Akt kinase contribute significantly to resistance observed during various cancer therapies, including cytotoxic chemotherapeutics, radiotherapy and small molecule inhibitors of; Bcr-Abl (Gleevec), Her2/Neu (Herceptin), and mTOR (rapamycin). Blocking Akt inhibits tumor growth in the cancer cells with hyperactivated Akt and renders cancer cells more sensitive to chemotherapy, radiotherapy and other therapeutic approaches. Combination of API-1 (or LD-101) with other anti-tumor therapies (chemo, radio, immuno, targeted, surgery) could provide potent synergistic anti-tumor effects.

[0024] The present invention relates to novel pyridopyrimidine compounds that are inhibitors of the activity of one or more or all of the isoforms of the serine/threonine kinase, Akt (also known as protein kinase B), suitably the compounds of the invention are inhibitors of the activity of all three isoforms of the serine/threonine kinase, Akt; name PKBα, PKBβ, PKBγ which are also respectively known as Aktl, Akt2, and Akt 3. The present invention also relates to pharmaceutical compositions, synthesis and manufacturing comprising such compounds and methods of using the compounds of the invention in the diagnosis of, prevention of, prophylaxis for, prognosis for and/or treatment of conditions that are causally related to increased Akt, overexpression of Akt, elevation of Akt, hyperactvation of Akt, amplification of Akt, constitutivelly active and or aberrant Akt/PKB activity and its pathways or can be alleviated by modulating Akt/PKB activity and its signaling transduction pathways.

[0025] The invention further relates to preparation of novel pyrido[2,3-d]pyrimidine compounds. The invention further relates to pharmaceutical formulations comprising the novel pyrido[2,3-d]pyrimidine compounds. In particular, the invention relates to pharmaceutical formulations and manufacturing and analytical methods of 4-amino-8-[3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-5-oxopyrido[2,3-d]pyrimidine-6-carboxamide.

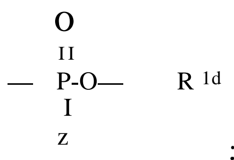
[0026] Accordingly, in one aspect, compounds are provided that have formula I:



I

wherein

each R^{1a}, R^{1b}, and R^{1c} is independently selected from H, an amino acid, a dipeptide, a tripeptide, and



;

R^{1d} is alkyl, aryl, or heteroaryl; Z is an amino acid, a dipeptide, or a tripeptide;

each R^2 and R^3 is independently selected from H, hydroxy, amino, alkyl, alkoxy, and C(0)-NH_2;

each R^{6a}, R^{6b}, R^{6c}, and R^8 is independently selected from H, alkyl, or hydroxyalkyl; or the group -OR^{1b} is absent;

R^7 is selected from H, alkyl, hydroxy, alkoxy, SMe, S(0)Me, or S(0)$_2$Me;

R^8 is selected from H, alkyl, hydroxy, alkoxy, or thioalkoxy;

or a pharmaceutically acceptable salt, solvate or prodrug thereof; and stereoisomers, isotopic variants and tautomers thereof;

provided that at least one of R^{1a}, R^{1b}, and R^{1c} is other than H.

[0027] In one embodiment, with respect to the compound of formula I, the invention covers all stereoisomers.

[0028] In one embodiment, with respect to the compound of formula I, the invention covers all isotopic varients.

[0029] In one embodiment, with respect to the compound of formula I, the invention covers all tautomers.

[0030] In one embodiment, with respect to the compound of formula I, each R^{6a}, R^{6b}, R^{6c}, R^7, and R^8 is H.

[00003311] In one embodiment, with respect to the compound of formula I, at least one of R^{6a}, R^{5b}, R^{6c}, R^7, and R^8 is other than H.

[[00003322]] IInn oonnee eemmbbooddiirment, with respect to the compound of formula I, R^2 is C(0)NH_2.

[0033] In one embodiment, with respect to the compound of formula I, R^3 is NH_2.

[0034] In another aspect, pharmaceutical compositions are provided comprising a compound of the invention, and a pharmaceutical carrier, excipient or diluent. The pharmaceutical composition can comprise one or more of the compounds described herein. In a further embodiment, the pharmaceutical compositions of the invention can comprise a compound in combination with one or more other compounds and/or compositions having a like therapeutic effect.

[0035] It will be understood that compounds of the present invention useful in the pharmaceutical compositions and treatment methods disclosed herein, can be pharmaceutically acceptable as prepared and used.

[0036] In another aspect, the invention provides preparation of novel pyrido[2,3-d]pyrimidine compounds. In particular, the invention relates to manufacturing methods for preparation of 4-amino-8-[3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-5-oxopyrido[2,3-d]pyrimidine-6-carboxamide.

[0037] In yet another aspect, the invention provides pharmaceutical formulations comprising the novel pyrido[2,3-d]pyrimidine compounds. In particular, the invention relates to pharmaceutical formulations of 4-amino-8-[3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-5-oxopyrido[2,3-d]pyrimidine-6-carboxamide.

[0038] In another aspect, methods are provided for preventing, treating or ameliorating a condition from among those listed herein, and particularly, such condition as may be associated with, cancer, which method comprises administering to a mammal in need thereof an amount of one or more of the compounds as provided herein, or pharmaceutical composition thereof, effective to prevent, treat or ameliorate the condition.

[0039] In yet another aspect, methods are provided for preventing, providing prophylaxis, treating or ameliorating a variety of disease states, including the diseases associated with cancer by administration of a compound such as those provided herein.

[0040] In addition to the methods of treatment set forth above, the present invention extends to the use of any of the compounds of the invention for the preparation of medicaments that may be administered for such treatments, as well as to such compounds for the treatments disclosed and specified.

[0041] In additional aspects, methods are provided for synthesizing the compounds described herein, with representative synthetic protocols and pathways described below.

[0042] Accordingly, it is a principal object of the invention to provide a novel series of compounds, which can modify any aberrant activity of Akt/PKB and thus may have the ability to treat certain of the conditions in which Akt/PKB is believed to play a role.

[0043] A still further object of the invention is to provide a method for the treatment of the disease states recited above, by the administration of a therapeutically effective amount of the compounds of the invention, and/or the pharmaceutical compositions of the invention.

[0044] A yet further object of the invention is to provide formulations for the treatment of the diseases as aforesaid, by the combination of at least one of the compounds of the invention, a pharmaceutical composition of the invention, combinations thereof with other compounds and or therapeutic modalities and such compositions having a like therapeutic effect.

[0045] Other objects and advantages will become apparent to those skilled in the art from a consideration of the ensuing detailed description.

BRIEF DESCRIPTION OF THE DRAWINGS

Figures:

[0046] **Fig. 1.** Typical API-1 HPLC chromatogram

[0047] **Fig. 2.** Typical HPLC reagent blank

[0048] **Fig. 3.** HPLC trace of L3, L4 and API- 1 (L5) test mix.

[0049] **Fig. 4.** HPLC trace of API- 1 reference material

[0050] **Fig. 5.** UV Spectrum of API-1

[0051] **Fig. 6.** LD- 101 Achieves Greater Apoptosis in Mantle Cell Lymphoma than Velcade®

[0052] **Fig. 7.** LD-101 Achieves Greater Apoptosis in Multiple Myeloma than Velcade®, and even Greater Apoptosis in Combination with Velcade®

[0053] **Fig. 8.** LD-101 Achieves Greater Inhibition of Cell Growth in Prostate Cancer than Rapamycin, and even Greater Inhibition in Combination with Rapamycin

[0054] **Fig. 9.** LD- 101 Achieves Greater Inhibition of Cell Growth in Breast Cancer than RAD00 1, and even Greater Inhibition in Combination with RADOOl

[0055] **Fig. 10.** LD-101 Enhances Inhibition of Cell Growth in Combination with Rapamycin in Ovarian Cancer

[0056] **Fig. 11.** LD-101 Achieves Greater Inhibition of Cell Survival in Resistant Ovarian Cancer (CI 3) than Cisplatin, and even Greater Inhibitionin Combination with Cisplatin

[0057] **Fig. 12.** LD-101 Achieves Greater Inhibition of Cell Growth in Resistant Ovarian Cancer (CI 3) than CDDP, and even Greater Inhibition in Combination with CDDP in Nude Mouse Xenografts

[0058] **Fig. 13.** LD-101 in Combination with Taxol® Achieves Greater Apoptosis in Resistant Ovarian Cancer than either Alone

[0059] **Fig. 14.** LD-101 Overcomes and Inhibits Rapamycin and RADOOl Feedback Activation of Akt

[0060] **Fig. 15.** Inhibition of Akt Downregulates VEGF, mTor Rictor and Sirtl

[0061] **Fig. 16.** Dose dependent inhibition of growth by AKt inhibitor on four renal cell carninoma cell lines CaKi-1, KU19-20, SW839, and Caki-2.

[0062] **Fig. 17.** LD-101 Overcomes CDDP Resistance in Ovarian Cancer

[0063] **Fig. 18.** Blockade of Akt Pathway Attenuates Radiation-Induced Akt Activation

[0064] **Fig. 19.** Inhibition of Akt Eliminates Radiation-Induced Akt Activation

[0065] **Fig. 20.** Inhibition of Akt Pathway Potentiates/Sensitizes Radiation-Induced Apoptosis

[0066] **Fig. 21.** LD-101 Achieves Greater Inhibition of Tumor Growth in Lung Cancer Cell H661 than CDDP, and even Greater Inhibition in Combination with CDDP.

[0067] **Fig. 22.** LD-101 Achieves Greater Inhibition of Tumor Growth in Lung Cancer Cell H661 than Etoposide®, and even Greater Inhibition in Combination with Etoposide®

[0068] **Fig. 23.** LD-101 Achieves Greater Inhibition of Tumor Growth in Lung Cancer Cell H661 than Rapamycin, and even Greater Inhibition in Combination with Rapamycin

[0069] **Fig. 24. shows the pharmacodynamic action of LD-101 in cancer cells**

DETAILED DESCRIPTION OF THE INVENTION

Definitions

[0070] The following terms are intended to have the meanings presented therewith below and are useful in understanding the description and intended scope of the present invention.

[0071] When describing the invention, which may include compounds, pharmaceutical compositions containing such compounds and methods of using such compounds and compositions, the following terms, if present, have the following meanings unless otherwise indicated. It should also be understood that when described herein any of the moieties defined forth below may be substituted with a variety of substituents, and that the respective definitions are intended to include such substituted moieties within their scope as set out below. Unless otherwise stated, the term 'substituted' is to be defined as set out below. It should be further understood that the terms 'groups' and 'radicals' can be considered interchangeable when used herein.

[0072] The articles 'a' and 'an' may be used herein to refer to one or to more than one (i.e. at least one) of the grammatical objects of the article. By way of example 'an analogue' means one analogue or more than one analogue.

[0073] 'Acyl' or 'Alkanoyl' refers to a radical -C(0)R ^{20}, where R^{20} is hydrogen, C_1-C_8 alkyl, C_3-Cio cycloalkyl, C_3-C_{10} cycloalkylmethyl, 4-10 membered heterocycloalkyl, aryl, arylalkyl, 5-10 membered heteroaryl or heteroarylalkyl as defined herein. Representative examples include, but are not limited to, formyl, acetyl, cyclohexylcarbonyl, cyclohexylmethylcarbonyl, benzoyl and benzylcarbonyl. Exemplary 'acyl' groups are -C(0)H, -C(0)-C_1-C_8 alkyl, -C(O)-$(CH_2)_t$(C_6-Ci$_0$ aryl), -C(O)-$(CH_2)_t$(5-10 membered heteroaryl), -C(O)-$(CH_2)_t$(C_3-Ci$_0$ cycloalkyl), and -C(O)-$(CH_2)_t$(4-10 membered heterocycloalkyl), wherein t is an integer from 0 to 4.

[0074] 'Substituted Acyl' or 'Substituted Alkanoyl' refers to a radical -C(0)R ^{21}, wherein R^{21} is independently

- Ci-Cg alkyl, substituted with halo or hydroxy; or
- C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl, arylalkyl, 5-10 membered heteroaryl or heteroarylalkyl, each of which is substituted with unsubstituted C_1-C_4 alkyl, halo, unsubstituted C_1-C_4 alkoxy, unsubstituted C_1-C_4 haloalkyl, unsubstituted C_1-C_4 hydroxyalkyl, or unsubstituted C_1-C_4 haloalkoxy or hydroxy.

[0075] 'Acylamino' refers to a radical -$NR^{22}C(0)R^{23}$, where R^{22} is hydrogen, C_1-C_8 alkyl, C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl, arylalkyl, 5-10 memberd heteroaryl or heteroarylalkyl and R^{23} is hydrogen, Ci-Cg alkyl, C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, Ce-C_{10} aryl, arylalkyl, 5-10 membered heteroaryl or heteroarylalkyl, as defined herein. Exemplary 'acylamino' include, but are not limited to, formylamino, acetylamino, cyclohexylcarbonylamino, cyclohexylmethyl-carbonylamino, benzoylamino and benzylcarbonylamino. Particular exemplary

'acylamino' groups are -NR ^{24}C(0)-C $_{1}$-C_8 alkyl, -NR ^{24}C(O)-$(CH_2)_t$(C_6-Ci$_0$ aryl), -NR ^{24}C(O)-$(CH_2)_t$(5-10 membered heteroaryl), -NR ^{24}C(O)-$(CH_2)_t$(C_3-Ci$_0$ cycloalkyl), and -NR ^{24}C(O)-$(CH_2)_t$(4-10 membered heterocycloalkyl), wherein t is an integer from 0 to 4, and each R^{24} independently represents H or C_1-C_8 alkyl.

[0076] 'Substituted Acylamino' refers to a radical -NR^{25}C(0)R ^{26}, wherein:

R^{25} is independently

- H, Ci-Cg alkyl, substituted with halo or hydroxy; or
- C3-C10 cycloalkyl, 4-10 membered heterocycloalkyl, C6-C10 aryl, arylalkyl, 5-10 membered heteroaryl or heteroarylalkyl, each of which is substituted with unsubstituted C1-C4 alkyl, halo, unsubstituted C1-C4 alkoxy, unsubstituted C1-C4 haloalkyl, unsubstituted C1-C4 hydroxyalkyl, or unsubstituted C1-C4 haloalkoxy or hydroxy; and

R^{26} is independently

- H, Ci-Cg alkyl, substituted with halo or hydroxy; or
- C3-C10 cycloalkyl, 4-10 membered heterocycloalkyl, C6-C10 aryl, arylalkyl, 5-10 membered heteroaryl or heteroarylalkyl, each of which is substituted with unsubstituted C1-C4 alkyl, halo, unsubstituted C1-C4 alkoxy, unsubstituted C1-C4 haloalkyl, unsubstituted C1-C4 hydroxyalkyl, or unsubstituted C1-C4 haloalkoxy or hydroxyl;

provided at least one of R^{25} and R^{26} is other than H.

[0077] 'Acyloxy' refers to a radical -OC(0)R ^{27}, where R^{27} is hydrogen, C_1-C_8 alkyl, C_3-C_{10} cycloalkyl, C3-C10 cycloalkylmethyl, 4-10 membered heterocycloalkyl, aryl, arylalkyl, 5-10 membered heteroaryl or heteroarylalkyl as defined herein. Representative examples include, but are not limited to, formyl, acetyl, cyclohexylcarbonyl, cyclohexylmethylcarbonyl, benzoyl and benzylcarbonyl. Exemplary 'acyl' groups are -C(0)H, -C(0)-C $_{1}$-C_8 alkyl, -C(O)-(CH $_{2})_t$(C_6-Ci$_0$ aryl), -C(O)-(CH $_{2})_t$(5-10 membered heteroaryl), -C(O)-(CH $_{2})_t$(C_3-Ci$_0$ cycloalkyl), and -C(O)-(CH $_{2})_t$(4-10 membered heterocycloalkyl), wherein t is an integer from 0 to 4.

[0078] 'Substituted Acyloxy' refers to a radical -OC(0)R ^{28}, wherein R^{28} is independently

- Ci-Cg alkyl, substituted with halo or hydroxy; or
- C3-C10 cycloalkyl, 4-10 membered heterocycloalkyl, C_6-Ci$_0$ aryl, arylalkyl, 5-10 membered heteroaryl or heteroarylalkyl, each of which is substituted with unsubstituted C1-C4 alkyl, halo, unsubstituted C1-C4 alkoxy, unsubstituted C1-C4 haloalkyl, unsubstituted C1-C4 hydroxyalkyl, or unsubstituted C1-C4 haloalkoxy or hydroxy.

[0079] 'Alkoxy' refers to the group -OR ^{29} where R^{29} is Ci-Cg alkyl. Particular alkoxy groups are methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, tert-butoxy, sec-butoxy, n-pentoxy, n-hexoxy, and 1,2-dimethylbutoxy. Particular alkoxy groups are lower alkoxy, i.e. with between 1 and 6 carbon atoms. Further particular alkoxy groups have between 1 and 4 carbon atoms.

[0080] 'Substituted alkoxy' refers to an alkoxy group substituted with one or more of those groups recited in the definition of 'substituted' herein, and particularly refers to an alkoxy group having 1 or more substituents, for instance from 1 to 5 substituents, and particularly from 1 to 3 substituents, in particular 1 substituent, selected from the group consisting of amino, substituted amino, C_6-Ci $_0$ aryl, aryloxy, carboxyl, cyano, C_3-Ci $_0$ cycloalkyl, 4-10 membered heterocycloalkyl, halogen, 5-10 membered heteroaryl, hydroxyl, nitro, thioalkoxy, thioaryloxy, thiol, alkyl-S(O)-, aryl-S(O)-, alkyl-S(0) $_2$- and aryl-S(0) $_2$-. Exemplary 'substituted alkoxy' groups are -0-(CH $_2$)$_t$(C_6-Cio aryl), -O-(CH $_2$)$_t$(5-10 membered heteroaryl), -0-(CH $_2$)$_t$(C_3-Cio cycloalkyl), and -0-(CH $_2$)$_t$(4- 10 membered heterocycloalkyl), wherein t is an integer from 0 to 4 and any aryl, heteroaryl, cycloalkyl or heterocycloalkyl groups present, may themselves be substituted by unsubstituted $C_{1\text{-}C4}$ alkyl, halo, unsubstituted $C_{1\text{-}C4}$ alkoxy, unsubstituted $C_{1\text{-}C4}$ haloalkyl, unsubstituted $C_{1\text{-}C4}$ hydroxyalkyl, or unsubstituted $C_{1\text{-}C4}$ haloalkoxy or hydroxy. Particular exemplary 'substituted alkoxy' groups are OCF_3, OCH_2CF_3, OCH_2Ph, OCH_2-cyclopropyl, OCH_2CH_2OH, and $OCH_2CH_2NMe_2$.

[0081] 'Alkoxycarbonyl' refers to a radical -C(0)-OR $^{3\circ}$ where R^{30} represents an C_1-C_8 alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkylalkyl, 4-10 membered heterocycloalkylalkyl, aralkyl, or 5-10 membered heteroarylalkyl as defined herein. Exemplary 'alkoxycarbonyl' groups are C(0)0-Ci-Cg alkyl, -C(0)0-(CH $_2$)$_t$(C_6-Cio aryl), -C(O)O-(CH $_2$)$_t$(5-10 membered heteroaryl), -C(O)O-(CH $_2$)$_t$(C_3-Ci $_0$ cycloalkyl), and -C(O)O-(CH_2)$_t$(4-10 membered heterocycloalkyl), wherein t is an integer from 1 to 4.

[0082] 'Substituted Alkoxycarbonyl' refers to a radical -C(0)-OR ^{31} where R^{31} represents:

- Ci-Cg alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkylalkyl, or 4-10 membered heterocycloalkylalkyl, each of which is substituted with halo, substituted or unsubstituted amino, or hydroxy; or
- C_6-C_{10} aralkyl, or 5- 10 membered heteroarylalkyl, each of which is substituted with unsubstituted $C_{1\text{-}C4}$ alkyl, halo, unsubstituted $C_{1\text{-}C4}$ alkoxy, unsubstituted $C_{1\text{-}C4}$ haloalkyl, unsubstituted $C_{1\text{-}C4}$ hydroxyalkyl, or unsubstituted $C_{1\text{-}C4}$ haloalkoxy or hydroxyl.

[0083] 'Aryloxycarbonyl' refers to a radical -C(0)-OR ^{32} where R^{32} represents an C_6-C_{10} aryl, as defined herein. Exemplary 'aryloxycarbonyl' groups is -C(0)0-(C6-Cio aryl).

[0084] 'Substituted Aryloxycarbonyl' refers to a radical -C(0)-OR ^{33} where R^{33} represents

- C_6-C_{10} aryl, substituted with unsubstituted $C_{1\text{-}C4}$ alkyl, halo, unsubstituted $C_{1\text{-}C4}$ alkoxy, unsubstituted $C_{1\text{-}C4}$ haloalkyl, unsubstituted $C_{1\text{-}C4}$ hydroxyalkyl, or unsubstituted $C_{1\text{-}C4}$ haloalkoxy or hydroxyl.

[0085] 'Heteroaryloxycarbonyl' refers to a radical -C(0)-OR ^{34} where R^{34} represents a 5-10 membered heteroaryl, as defined herein. An exemplary 'aryloxycarbonyl' group is -C(O)O-(5-10 membered heteroaryl).

[0086] 'Substituted Heteroaryloxycarbonyl' refers to a radical -C(0)-OR ^{35} where R^{35} represents:

- 5-10 membered heteroaryl, substituted with unsubstituted $C_{1\text{-}C4}$ alkyl, halo, unsubstituted Cr C_4 alkoxy, unsubstituted $C_{1\text{-}C4}$ haloalkyl, unsubstituted $C_{1\text{-}C4}$ hydroxyalkyl, or unsubstituted $C_{1\text{-}C4}$ haloalkoxy or hydroxyl.

[0087] 'Alkoxycarbonylamino' refers to the group $-NR^{36}C(0)OR^{37}$, where R^{36} is hydrogen, C_1-C_8 alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkylmethyl, 4-10 membered heterocycloalkyl, aryl, arylalkyl, 5-10 membered heteroaryl or heteroarylalkyl as defined herein, and R^{37} is Ci-Cg alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkylmethyl, 4-10 membered heterocycloalkyl, aryl, arylalkyl, 5-10 membered heteroaryl or heteroarylalkyl as defined herein.

[0088] 'Alkyl' means straight or branched aliphatic hydrocarbon having 1 to 20 carbon atoms. Particular alkyl has 1 to 12 carbon atoms. More particular is lower alkyl which has 1 to 6 carbon atoms. A further particular group has 1 to 4 carbon atoms. Exemplary straight chained groups include methyl, ethyl n-propyl, and n-butyl. Branched means that one or more lower alkyl groups such as methyl, ethyl, propyl or butyl is attached to a linear alkyl chain, exemplary branched chain groups include isopropyl, iso-butyl, t-butyl and isoamyl.

[0089] 'Substituted alkyl' refers to an alkyl group as defined above substituted with one or more of those groups recited in the definition of 'substituted' herein, and particularly refers to an alkyl group having 1 or more substituents, for instance from 1 to 5 substituents, and particularly from 1 to 3 substituents, in particular 1 substituent, selected from the group consisting of acyl, acylamino, acyloxy (-O-acyl or $-OC(0)R^{20}$), alkoxy, alkoxycarbonyl, alkoxycarbonylamino ($-NR''$-alkoxycarbonyl or $-NH-C(0)-OR^{27}$), amino, substituted amino, aminocarbonyl (carbamoyl or amido or $-C(0)-NR''_2$), aminocarbonylamino ($-NR''-C(0)-NR''_2$), aminocarbonyloxy ($-O-C(O)-NR''_2$), aminosulfonyl, sulfonylamino, aryl, aryloxy, azido, carboxyl, cyano, cycloalkyl, halogen, hydroxy, heteroaryl, nitro, thiol, -S-alkyl, -S-aryl, -S(0)-alkyl,-S(0)-aryl, -S(0)2-alkyl, and -S(0)2-aryl. In a particular embodiment 'substituted alkyl' refers to a Ci-Cg alkyl group substituted with halo, cyano, nitro, trifluoromethyl, trifluoromethoxy, azido, $-NR''SO_2R''$, $-SO_2NR''R'''$, $-C(0)R''$, $-C(0)OR''$, $-OC(0)R''$, $-NR''C(0)R''$, $-C(0)NR''R'''$, $-NR''R'''$, or $-(CR'''R'''')_mOR'''$; wherein each R'' is independently selected from H, C_1-C_8 alkyl, $-(CH_2)_t(C_6\text{-}C_{10}$ aryl), $-(CH_2)_t$(5-10 membered heteroaryl), $-(CH_2)_t(C_3\text{-}C_{10}$ cycloalkyl), and $-(CH_2)_t$(4-10 membered heterocycloalkyl), wherein t is an integer from 0 to 4 and any aryl, heteroaryl, cycloalkyl or heterocycloalkyl groups present, may themselves be substituted by unsubstituted C_1-C_4 alkyl, halo, unsubstituted C_1-C_4 alkoxy, unsubstituted C_1-C_4 haloalkyl, unsubstituted C_1-C_4 hydroxyalkyl, or unsubstituted C_1-C_4 haloalkoxy or hydroxy. Each of R''' and R'''' independently represents H or Ci-Cg alkyl.

[0090] 'Alkylene' refers to divalent saturated alkene radical groups having 1 to 11 carbon atoms and more particularly 1 to 6 carbon atoms which can be straight-chained or branched. This term is exemplified by groups such as methylene ($-CH_2-$), ethylene ($-CH_2CH_2-$), the propylene isomers *(e.g.,* $-CH_2CH_2CH_2-$ and $-CH(CH_3)CH_2-$) and the like.

[0091] 'Substituted alkylene' refers to those groups recited in the definition of 'substituted' herein, and particularly refers to an alkylene group having 1 or more substituents, for instance from 1 to 5 substituents, and particularly from 1 to 3 substituents, selected from the group consisting of acyl, acylamino, acyloxy, alkoxy, substituted alkoxy, alkoxycarbonyl, alkoxycarbonylamino, amino, substituted amino, aminocarbonyl, amino-carbonylamino, aminocarbonyloxy, aryl, aryloxy, azido, carboxyl, cyano,

halogen, hydroxyl, keto, nitro, thioalkoxy, substituted thioalkoxy, thioaryloxy, thioketo, thiol, alkyl-S(O)-, aryl-S(O)-, alkyl-S(0) $_2$- and aryl-S(0) $_2$-.

[0092] 'Alkenyl' refers to monovalent olefinically unsaturated hydrocarbyl groups preferably having 2 to 11 carbon atoms, particularly, from 2 to 8 carbon atoms, and more particularly, from 2 to 6 carbon atoms, which can be straight-chained or branched and having at least 1 and particularly from 1 to 2 sites of olefinic unsaturation. Particular alkenyl groups include ethenyl (-CH=CH_2), n-propenyl (-CH_2CH=CH_2), isopropenyl (-C(CH_3)=CH_2), vinyl and substituted vinyl, and the like.

[0093] 'Substituted alkenyl' refers to those groups recited in the definition of 'substituted' herein, and particularly refers to an alkenyl group having 1 or more substituents, for instance from 1 to 5 substituents, and particularly from 1 to 3 substituents, selected from the group consisting of acyl, acylamino, acyloxy, alkoxy, substituted alkoxy, alkoxycarbonyl, alkoxycarbonylamino, amino, substituted amino, aminocarbonyl, aminocarbonylamino, aminocarbonyloxy, aryl, aryloxy, azido, carboxyl, cyano, cycloalkyl, substituted cycloalkyl, halogen, hydroxyl, keto, nitro, thioalkoxy, substituted thioalkoxy, thioaryloxy, thioketo, thiol, alkyl-S(O)-, aryl-S(O)-, alkyl-S(0) $_2$- and aryl-S(0) $_2$-.

[0094] 'Alkenylene' refers to divalent olefinically unsaturated hydrocarbyl groups particularly having up to about 11 carbon atoms and more particularly 2 to 6 carbon atoms which can be straight-chained or branched and having at least 1 and particularly from 1 to 2 sites of olefinic unsaturation. This term is exemplified by groups such as ethenylene (-CH=CH-), the propenylene isomers *(e.g.,* -CH=$CHCH_2$- and -C(CH_3)=CH- and -CH=C(CH_3)-) and the like.

[0095] 'Alkynyl' refers to acetylenically or alkynically unsaturated hydrocarbyl groups particularly having 2 to 11 carbon atoms, and more particularly 2 to 6 carbon atoms which can be straight-chained or branched and having at least 1 and particularly from 1 to 2 sites of alkynyl unsaturation. Particular non-limiting examples of alkynyl groups include acetylenic, ethynyl (-C≡CH), propargyl (-CH_2C≡CH), and the like.

[0096] 'Substituted alkynyl' refers to those groups recited in the definition of 'substituted' herein, and particularly refers to an alkynyl group having 1 or more substituents, for instance from 1 to 5 substituents, and particularly from 1 to 3 substituents, selected from the group consisting of acyl, acylamino, acyloxy, alkoxy, substituted alkoxy, alkoxycarbonyl, alkoxycarbonylamino, amino, substituted amino, aminocarbonyl, aminocarbonylamino, aminocarbonyloxy, aryl, aryloxy, azido, carboxyl, cyano, cycloalkyl, substituted cycloalkyl, halogen, hydroxyl, keto, nitro, thioalkoxy, substituted thioalkoxy, thioaryloxy, thioketo, thiol, alkyl-S(O)-, aryl-S(O)-, alkyl-S(0) $_2$- and aryl-S(0) $_2$-.

[0097] 'Amino' refers to the radical -NH_2.

[0098] 'Substituted amino' refers to an amino group substituted with one or more of those groups recited in the definition of 'substituted' herein, and particularly refers to the group -N(R^{38})$_2$ where each Pv^{38} is independently selected from:

- hydrogen, C_1-C_8 alkyl, C_6-Ci_0 aryl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, or C_3-Ci_0 cycloalkyl; or
- Ci-Cg alkyl, substituted with halo or hydroxy; or

- $-(CH_2)_t(C_6-C_{10}$ aryl), $-(CH_2)_t$(5- 10 membered heteroaryl), $-(CH_2)_t(C_3-C_{10}$ cycloalkyl) or -$(CH_2)_t$(4-10 membered heterocycloalkyl) wherein t is an integer between 0 and 8, each of which is substituted by unsubstituted C_{1-C4} alkyl, halo, unsubstituted C_{1-C4} alkoxy, unsubstituted C_{1-C4} haloalkyl, unsubstituted C_{1-C4} hydroxyalkyl, or unsubstituted C_{1-C4} haloalkoxy or hydroxy; or
- both R^{38} groups are joined to form an alkylene group.

When both R^{38} groups are hydrogen, $-N(R^{38})_2$ is an amino group. Exemplary ' substituted amino' groups are $-NR^{39}-C_1-C_8$ alkyl, $-NR^{39}-(CH_2)_t(C_6$-Ci$_0$ aryl), $-NR^{39}-(CH_2)_t$(5- 10 membered heteroaryl), $-NR^{39}-(CH_2)_t(C_3$-Cio cycloalkyl), and $-NR^{39}-(CH_2)_t$(4- 10 membered heterocycloalkyl), wherein t is an integer from 0 to 4, each R^{39} independently represents H or Ci-Cg alkyl; and any alkyl groups present, may themselves be substituted by halo, substituted or unsubstituted amino, or hydroxy; and any aryl, heteroaryl, cycloalkyl or heterocycloalkyl groups present, may themselves be substituted by unsubstituted C_{1-C4} alkyl, halo, unsubstituted C_1-C4 alkoxy, unsubstituted C_1-C4 haloalkyl, unsubstituted C_1-C4 hydroxyalkyl, or unsubstituted C_1-C4 haloalkoxy or hydroxy. For the avoidance of doubt the term 'substituted amino' includes the groups alkylamino, substituted alkylamino, alkylarylamino, substituted alkylarylamino, arylamino, substituted arylamino, dialkylamino and substituted dialkylamino as defined below.

[0099] 'Alkylamino' refers to the group $-NHR^{40}$, wherein R^{40} is C_1-C_8 alkyl;

[00100] 'Substituted Alkylamino' refers to the group $-NHR^{41}$, wherein R^{41} is C_1-C_8 alkyl; and the alkyl group is substituted with halo, substituted or unsubstituted amino, hydroxy, C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, aralkyl or heteroaralkyl; and any aryl, heteroaryl, cycloalkyl or heterocycloalkyl groups present, may themselves be substituted by unsubstituted C_{1-C4} alkyl, halo, unsubstituted C_{1-C4} alkoxy, unsubstituted C_{1-C4} haloalkyl, unsubstituted C_{1-C4} hydroxyalkyl, or unsubstituted C_{1-C4} haloalkoxy or hydroxy.

[00101] 'Alkylarylamino' refers to the group $-NR^{42}R^{43}$, wherein R^{42} is aryl and R^{43} is C_1-C_8 alkyl.

[00102] 'Substituted Alkylarylamino' refers to the group -NR^R ^{45}, wherein R^{44} is aryl and R^{45} is Ci-Cg alkyl; and the alkyl group is substituted with halo, substituted or unsubstituted amino, hydroxy, C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, aralkyl or heteroaralkyl; and any aryl, heteroaryl, cycloalkyl or heterocycloalkyl groups present, may themselves be substituted by unsubstituted C_{1-C4} alkyl, halo, cyano, unsubstituted C_{1-C4} alkoxy, unsubstituted C_1-C4 haloalkyl, unsubstituted C_{1-C4} hydroxyalkyl, or unsubstituted C_{1-C4} haloalkoxy or hydroxy.

[00103] 'Arylamino' means a radical $-NHR^{46}$ where R^{46} is selected from C_6-C_{10} aryl and 5-10 membered heteroaryl as defined herein.

[00104] 'Substituted Arylamino' refers to the group $-NHR^{47}$, wherein R^{47} is independently selected from C_6-C_{10} aryl and 5-10 membered heteroaryl; and any aryl or heteroaryl groups present, may themselves be substituted by unsubstituted C_{1-C4} alkyl, halo, cyano, unsubstituted C_{1-C4} alkoxy, unsubstituted C_{1-C4} haloalkyl, unsubstituted C_{1-C4} hydroxyalkyl, or unsubstituted C_{1-C4} haloalkoxy or hydroxy.

[00105] 'Dialkylamino' refers to the group $-NR^{48}R^{49}$, wherein each of R^{48} and R^{49} are independently selected from C_1-C_8 alkyl.

[00106] 'Substituted Dialkylamino' refers to the group $-NR^{50}R^{51}$, wherein each of R^{59} and R^{51} are independently selected from C_1-C_8 alkyl; and at least one of the alkyl groups is independently substituted with halo, hydroxy, C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, aralkyl or heteroaralkyl; and any aryl, heteroaryl, cycloalkyl or heterocycloalkyl groups present, may themselves be substituted by unsubstituted C_1-C_4 alkyl, halo, unsubstituted C_1-C_4 alkoxy, unsubstituted C_1-C_4 haloalkyl, unsubstituted C_1-C_4 hydroxyalkyl, or unsubstituted C_1-C_4 haloalkoxy or hydroxy.

[00107] 'Diarylamino' refers to the group $-NR^{52}R^{53}$, wherein each of R^{52} and R^{53} are independently selected from C_6-C_{10} aryl.

[00108] 'Aminosulfonyl' or 'Sulfonamide' refers to the radical $-S(O_2)NH_2$.

[00109] 'Substituted aminosulfonyl' or 'substituted sulfonamide' refers to a radical such as -$S(O_2)N(R^{54})_2$ wherein each R^{548} is independently selected from:

- H, C_1-C_8 alkyl, C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl, aralkyl, 5-10 membered heteroaryl, and heteroaralkyl; or
- C_1-C_8 alkyl substituted with halo or hydroxy; or
- C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl, aralkyl, 5-10 membered heteroaryl, or heteroaralkyl, each of which is substituted by unsubstituted C_1-C_4 alkyl, halo, unsubstituted C_1-C_4 alkoxy, unsubstituted C_1-C_4 haloalkyl, unsubstituted C_1-C_4 hydroxyalkyl, or unsubstituted C_1-C_4 haloalkoxy or hydroxy;

provided that at least one R^{54} is other than H.

[00110] Exemplary 'substituted aminosulfonyl' or 'substituted sulfonamide' groups are -$S(O_2)N(R^{55})$-C_1-C_8 alkyl, -$S(O_2)N(R^{55})$-$(CH_2)_t$(C_6-C_{10} aryl), -$S(O_2)N(R^{55})$-$(CH_2)_t$(5-10 membered heteroaryl), -$S(O_2)N(R^{55})$-$(CH_2)_t$(C_3-C_{10} cycloalkyl), and -$S(O_2)N(R^{55})$-$(CH_2)_t$(4-10 membered heterocycloalkyl), wherein t is an integer from 0 to 4; each R^{55} independently represents H or C_1-C_8 alkyl; and any aryl, heteroaryl, cycloalkyl or heterocycloalkyl groups present, may themselves be substituted by unsubstituted C_1-C_4 alkyl, halo, unsubstituted C_1-C_4 alkoxy, unsubstituted C_1-C_4 haloalkyl, unsubstituted C_1-C_4 hydroxyalkyl, or unsubstituted C_1-C_4 haloalkoxy or hydroxy.

[00111] 'Aralkyl' or 'arylalkyl' refers to an alkyl group, as defined above, substituted with one or more aryl groups, as defined above. Particular aralkyl or arylalkyl groups are alkyl groups substituted with one aryl group.

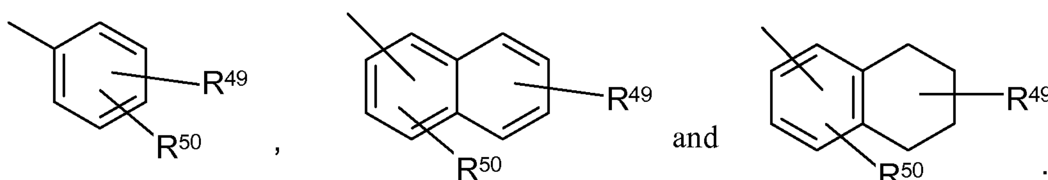
[00112] 'Substituted Aralkyl' or 'substituted arylalkyl' refers to an alkyl group, as defined above, substituted with one or more aryl groups; and at least one of the aryl groups present, may themselves be substituted by unsubstituted C_1-C_4 alkyl, halo, cyano, unsubstituted C_1-C_4 alkoxy, unsubstituted C_1-C_4 haloalkyl, unsubstituted C_1-C_4 hydroxyalkyl, or unsubstituted C_1-C_4 haloalkoxy or hydroxy.

[00113] 'Aryl' refers to a monovalent aromatic hydrocarbon group derived by the removal of one hydrogen atom from a single carbon atom of a parent aromatic ring system. In particular aryl refers to an

aromatic ring structure, mono-cyclic or poly-cyclic that includes from 5 to 12 ring members, more usually 6 to 10. Where the aryl group is a monocyclic ring system it preferentially contains 6 carbon atoms. Typical aryl groups include, but are not limited to, groups derived from aceanthrylene, acenaphthylene, acephenanthrylene, anthracene, azulene, benzene, chrysene, coronene, fluoranthene, fluorene, hexacene, hexaphene, hexalene, as-indacene, s-indacene, indane, indene, naphthalene, octacene, octaphene, octalene, ovalene, penta-2,4-diene, pentacene, pentalene, pentaphene, perylene, phenalene, phenanthrene, picene, pleiadene, pyrene, pyranthrene, rubicene, triphenylene and trinaphthalene. Particularly aryl groups include phenyl, naphthyl, indenyl, and tetrahydronaphthyl.

[00114] 'Substituted Aryl' refers to an aryl group substituted with one or more of those groups recited in the definition of 'substituted' herein, and particularly refers to an aryl group that may optionally be substituted with 1 or more substituents, for instance from 1 to 5 substituents, particularly 1 to 3 substituents, in particular 1 substituent. Particularly, 'Substituted Aryl' refers to an aryl group substituted with one or more of groups selected from halo, Ci-Cg alkyl, C_1-Cg haloalkyl, cyano, hydroxy, Ci-Cg alkoxy, and amino.

[00115] Examples of representative substituted aryls include the following



[00116] In these formulae one of R^{56} and R^{57} may be hydrogen and at least one of R^{56} and R^{57} is each independently selected from C_1-Cg alkyl, C_1-Cg haloalkyl, 4-10 membered heterocycloalkyl, alkanoyl, Ci-Cg alkoxy, heteroaryloxy, alkylamino, arylamino, heteroarylamino, $NR^{58}COR^{59}$, $NR^{58}SOR^{59}$, $NR^{58}SO_2R^{59}$, COOalkyl, COOaryl, $CONR^{58}R^{59}$, $CONR^{58}OR^{59}$, $NR^{58}R^{59}$, $SO_2NR^{58}R^{59}$, S-alkyl, SOalkyl, SO_2alkyl, Saryl, SOaryl, SC^aryl; or R^{56} and R^{57} may be joined to form a cyclic ring (saturated or unsaturated) from 5 to 8 atoms, optionally containing one or more heteroatoms selected from the group N, O or S. R^{60}, and R^{61} are independently hydrogen, Ci-Cg alkyl, C_{1-C4} haloalkyl, C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl, substituted aryl, 5-10 membered heteroaryl.

[00117] 'Fused Aryl' refers to an aryl having two of its ring carbon in common with a second aryl ring or with an aliphatic ring.

[00118] 'Arylalkyloxy' refers to an -O-alkylaryl radical where alkylaryl is as defined herein.

[00119] 'Substituted Arylalkyloxy' refers to an -O-alkylaryl radical where alkylaryl is as defined herein; and any aryl groups present, may themselves be substituted by unsubstituted C_{1-C4} alkyl, halo, cyano, unsubstituted C_{1-C4} alkoxy, unsubstituted C_{1-C4} haloalkyl, unsubstituted C_{1-C4} hydroxyalkyl, or unsubstituted C_{1-C4} haloalkoxy or hydroxy.

[00120] 'Azido' refers to the radical $-N_3$.

[00121] 'Carbamoyl or amido' refers to the radical $-C(0)NH_2$.

[00122] 'Substituted Carbamoyl' or 'substituted amido' refers to the radical $-C(0)N(R^{62})_2$ wherein each R^{62} is independently

- H, Ci-Cg alkyl, C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-Ci_0 aryl, aralkyl, 5-10 membered heteroaryl, and heteroaralkyl; or
- Ci-Cg alkyl substituted with halo or hydroxy; or
- C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl, aralkyl, 5-10 membered heteroaryl, or heteroaralkyl, each of which is substituted by unsubstituted $C_{1\text{-}C4}$ alkyl, halo, unsubstituted C_1-C4 alkoxy, unsubstituted $C_{1\text{-}C4}$ haloalkyl, unsubstituted $C_{1\text{-}C4}$ hydroxyalkyl, or unsubstituted $C_{1\text{-}C4}$ haloalkoxy or hydroxy;

provided that at least one R^{62} is other than H.

Exemplary 'Substituted Carbamoyl' groups are -C(0) NR^{64}-C_1-C_8 alkyl, -C(O)NR ^{64}-$(CH_2)_t$(C_6-C_{10} aryl), -C(O)N ^{64}-$(CH_2)_t$(5-10 membered heteroaryl), -C(O)NR ^{64}-$(CH_2)_t$(C_3-C_{10} cycloalkyl), and -C(0)NR ^{64}-$(CH_2)_t$(4- 10 membered heterocycloalkyl), wherein t is an integer from 0 to 4, each R^{64} independently represents H or Ci-Cg alkyl and any aryl, heteroaryl, cycloalkyl or heterocycloalkyl groups present, may themselves be substituted by unsubstituted C_1-C_4 alkyl, halo, unsubstituted C_1-C_4 alkoxy, unsubstituted C_1-C_4 haloalkyl, unsubstituted C_1-C_4 hydroxyalkyl, or unsubstituted C_1-C_4 haloalkoxy or hydroxy.

[00123] 'Carboxy' refers to the radical -C(0)OH.

[00124] 'Cycloalkyl' refers to cyclic non-aromatic hydrocarbyl groups having from 3 to 10 carbon atoms. Such cycloalkyl groups include, by way of example, single ring structures such as cyclopropyl, cyclobutyl, cyclopentyl, and cyclooctyl.

[00125] 'Substituted cycloalkyl' refers to a cycloalkyl group as defined above substituted with one or more of those groups recited in the definition of 'substituted' herein, and particularly refers to a cycloalkyl group having 1 or more substituents, for instance from 1 to 5 substituents, and particularly from 1 to 3 substituents, in particular 1 substituent.

[00126] 'Cyano' refers to the radical -CN.

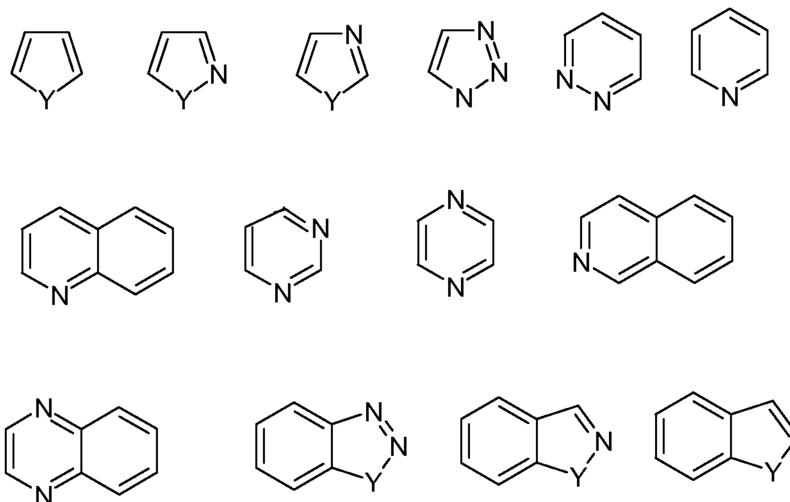
[00127] 'Halo' or 'halogen' refers to fluoro (F), chloro (CI), bromo (Br) and iodo (I). Particular halo groups are either fluoro or chloro.

[00128] 'Hetero' when used to describe a compound or a group present on a compound means that one or more carbon atoms in the compound or group have been replaced by a nitrogen, oxygen, or sulfur heteroatom. Hetero may be applied to any of the hydrocarbyl groups described above such as alkyl, e.g. heteroalkyl, cycloalkyl, e.g. heterocycloalkyl, aryl, e.g. heteroaryl, cycloalkenyl, e.g. cycloheteroalkenyl, and the like having from 1 to 5, and particularly from 1 to 3 heteroatoms.

[00129] 'Heteroaryl' means an aromatic ring structure, mono-cyclic or polycyclic, that includes one or more heteroatoms and 5 to 12 ring members, more usually 5 to 10 ring members. The heteroaryl group can be, for example, a five membered or six membered monocyclic ring or a bicyclic structure formed from fused five and six membered rings or two fused six membered rings or, by way of a further example, two fused five membered rings. Each ring may contain up to four heteroatoms typically selected from nitrogen, sulphur and oxygen. Typically the heteroaryl ring will contain up to 4 heteroatoms, more typically up to 3 heteroatoms, more usually up to 2, for example a single heteroatom. In one embodiment, the heteroaryl ring contains at least one ring nitrogen atom. The nitrogen atoms in the heteroaryl rings can

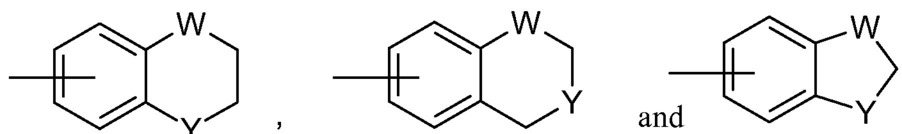
be basic, as in the case of an imidazole or pyridine, or essentially non-basic as in the case of an indole or pyrrole nitrogen. In general the number of basic nitrogen atoms present in the heteroaryl group, including any amino group substituents of the ring, will be less than five. Examples of five membered monocyclic heteroaryl groups include but are not limited to pyrrole, furan, thiophene, imidazole, furazan, oxazole, oxadiazole, oxatriazole, isoxazole, thiazole, isothiazole, pyrazole, triazole and tetrazole groups. Examples of six membered monocyclic heteroaryl groups include but are not limited to pyridine, pyrazine, pyridazine, pyrimidine and triazine. Particular examples of bicyclic heteroaryl groups containing a five membered ring fused to another five membered ring include but are not limited to imidazothiazole and imidazoimidazole. Particular examples of bicyclic heteroaryl groups containing a six membered ring fused to a five membered ring include but are not limited to benzfuran, benzthiophene, benzimidazole, benzoxazole, isobenzoxazole, benzisoxazole, benzthiazole, benzisothiazole, isobenzofuran, indole, isoindole, isoindolone, indolizine, indoline, isoindoline, purine (e.g., adenine, guanine), indazole, pyrazolopyrimidine, triazolopyrimidine, benzodioxole and pyrazolopyridine groups. Particular examples of bicyclic heteroaryl groups containing two fused six membered rings include but are not limited to quinoline, isoquinoline, chroman, thiochroman, chromene, isochromene, chroman, isochroman, benzodioxan, quinolizine, benzoxazine, benzodiazine, pyridopyridine, quinoxaline, quinazoline, cinnoline, phthalazine, naphthyridine and pteridine groups. Particular heteroaryl groups are those derived from thiophene, pyrrole, benzothiophene, benzofuran, indole, pyridine, quinoline, imidazole, oxazole and pyrazine.

[00130] Examples of representative heteroaryls include the following:



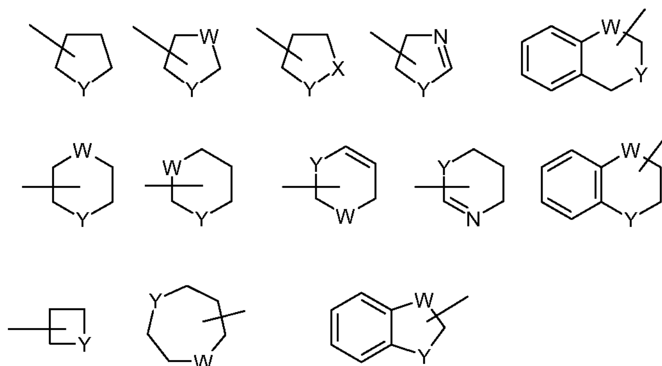
wherein each Y is selected from carbonyl, N, NR^{65}, O and S; and R^{55} is independently hydrogen, C_1-C_8 alkyl, C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-Ci_0 aryl, and 5-10 membered heteroaryl.

[00131] Examples of representative aryl having hetero atoms containing substitution include the following:



wherein each W is selected from $C(R^{66})_2$, NR^{66}, O and S; and each Y is selected from carbonyl, NR^{66}, O and S; and R^{66} is independently hydrogen, Ci-Cg alkyl, C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl, and 5-10 membered heteroaryl.

[00132] As used herein, the term 'heterocycloalkyl' refers to a 4-10 membered, stable heterocyclic non-aromatic ring and/or including rings containing one or more heteroatoms independently selected from N, O and S, fused thereto. A fused heterocyclic ring system may include carbocyclic rings and need only include one heterocyclic ring. Examples of heterocyclic rings include, but are not limited to, morpholine, piperidine (e.g. 1-piperidinyl, 2-piperidinyl, 3-piperidinyl and 4-piperidinyl), pyrrolidine (e.g. 1-pyrrolidinyl, 2-pyrrolidinyl and 3-pyrrolidinyl), pyrrolidone, pyran (2H-pyran or 4H-pyran), dihydrothiophene, dihydropyran, dihydrofuran, dihydrothiazole, tetrahydrofuran, tetrahydrothiophene, dioxane, tetrahydropyran (e.g. 4-tetrahydro pyranyl), imidazoline, imidazolidinone, oxazoline, thiazoline, 2-pyrazoline, pyrazolidine, piperazine, and N-alkyl piperazines such as N-methyl piperazine. Further examples include thiomorpholine and its S-oxide and S,S-dioxide (particularly thiomorpholine). Still further examples include azetidine, piperidone, piperazone, and N-alkyl piperidines such as N-methyl piperidine. Particular examples of heterocycloalkyl groups are shown in the following illustrative examples:



wherein each W is selected from CR^{67}, $C(R^{67})_2$, NR^{67}, O and S; and each Y is selected from NR^{67}, O and S; and R^{67} is independently hydrogen, C_1-C_8 alkyl, C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, These heterocycloalkyl rings may be optionally substituted with one or more groups selected from the group consisting of acyl, acylamino, acyloxy, alkoxy, alkoxycarbonyl, alkoxycarbonylamino, amino, substituted amino, aminocarbonyl (carbamoyl or amido), aminocarbonylamino, aminosulfonyl, sulfonylamino, aryl, aryloxy, azido, carboxyl, cyano, cycloalkyl, halogen, hydroxy, keto, nitro, thiol, -S-alkyl, -S-aryl, -S(0)-alkyl,-S(0)-aryl, $-S(0)_2$-alkyl, and $-S(0)_2$-aryl. Substituting groups include carbonyl or thiocarbonyl which provide, for example, lactam and urea derivatives.

[00133] 'Hydroxy' refers to the radical -OH.

[00134] 'Nitro' refers to the radical $-N0_2$.

[00135] 'Substituted' refers to a group in which one or more hydrogen atoms are each independently replaced with the same or different substituent(s). Typical substituents may be selected from the group consisting of:

halogen, $-R^{68}$, $-O^-$, =0, $-OR^{68}$, $-SR^{68}$, $-S^-$, =S, $-NR^{68}R^{69}$, $=NR^{68}$, $-CC1_3$, $-CF_3$, -CN, -OCN, -SCN, -NO, $-N0_2$, $=N_2$, $-N_3$, $-S(0)_20^-$, $-S(0)_2OH$, $-S(0)_2R^{68}$, $-OS(0_2)0^-$, $-OS(0)_2R^{68}$, $-P(0)(0^-)_2$, $-P(0)(OR^{68})(0^-)$, $-OP(0)(OR^{68})(OR^{69})$, $-C(0)R^{68}$, $-C(S)R^{68}$, $-C(0)OR^{68}$, $-C(0)NR^{68}R^{69}$, $-C(0)0^-$, $-C(S)OR^{68}$, $-NR^{70}C(O)NR^{68}R^{69}$, $-NR^{70}C(S)NR^{68}R^{69}$, $-NR^{71}C(NR^{70})NR^{68}R^{69}$ and $-C(NR^{70})NR^{68}R^{69}$;

wherein each R^{68}, R^{69}, R^{70} and R^{71} are independently:

- hydrogen, Ci-Cg alkyl, C6-C10 aryl, arylalkyl, C3-C10 cycloalkyl, 4-10 membered heterocycloalkyl, 5-10 membered heteroaryl, heteroarylalkyl; or
- Ci-Cg alkyl substituted with halo or hydroxy; or
- C_6-Cio aryl, 5-10 membered heteroaryl, C_6-Ci $_0$ cycloalkyl or 4- 10 membered heterocycloalkyl each of which is substituted by unsubstituted C_1-C_4 alkyl, halo, unsubstituted C_1-C_4 alkoxy, unsubstituted C1-C4 haloalkyl, unsubstituted C1-C4 hydroxyalkyl, or unsubstituted C1-C4 haloalkoxy or hydroxy.

[00136] In a particular embodiment, substituted groups are substituted with one or more substituents, particularly with 1 to 3 substituents, in particular with one substituent group.

[00137] In a further particular embodiment the substituent group or groups are selected from halo, cyano, nitro, trifluoromethyl, trifluoromethoxy, azido, $-NR^{72}S0_2R^{73}$, $-S0_2NR^{73}R^{72}$, $-C(0)R^{73}$, $-C(0)OR^{73}$, $-OC(0)R^{73}$, $-NR^{72}C(0)R^{73}$, $-C(0)NR^{73}R^{72}$, $-NR^{73}R^{72}$, $-(CR^{72}R^{72})_mOR^{72}$, wherein, each R^{73} is independently selected from H, Q-Cg alkyl, $-(CH_2)_t(C_6$-Ci $_0$ aryl), $-(CH_2)_t$(5-10 membered heteroaryl), $-(CH_2)_t(C_3$-Ci $_0$ cycloalkyl), and $-(CH_2)_t$(4-10 membered heterocycloalkyl), wherein t is an integer from 0 to 4; and

- any alkyl groups present, may themselves be substituted by halo or hydroxy; and
- any aryl, heteroaryl, cycloalkyl or heterocycloalkyl groups present, may themselves be substituted by unsubstituted C1-C4 alkyl, halo, unsubstituted C1-C4 alkoxy, unsubstituted C_1-C_4 haloalkyl, unsubstituted C1-C4 hydroxyalkyl, or unsubstituted C1-C4 haloalkoxy or hydroxy. Each $R^{"}$ independently represents H or C i-Cealkyl.

[00138] 'Substituted sulfanyl' refers to the group $-SR^{74}$, wherein R^{74} is selected from:

- Ci-Cg alkyl, C3-C10 cycloalkyl, 4-10 membered heterocycloalkyl, C6-C10 aryl, aralkyl, 5-10 membered heteroaryl, and heteroaralkyl; or
- Ci-Cg alkyl substituted with halo, substituted or unsubstituted amino, or hydroxy; or
- C3-C10 cycloalkyl, 4-10 membered heterocycloalkyl, C6-C10 aryl, aralkyl, 5-10 membered heteroaryl, or heteroaralkyl, each of which is substituted by unsubstituted C1-C4 alkyl, halo, unsubstituted C1-C4 alkoxy, unsubstituted C1-C4 haloalkyl, unsubstituted C1-C4 hydroxyalkyl, or unsubstituted C1-C4 haloalkoxy or hydroxy.

[00139] Exemplary 'substituted sulfanyl' groups are -S-(Ci-Cg alkyl) and -S-(C3-Cio cycloalkyl), $-S-(CH_2)_t(C_6-C_{10}$ aryl), $-S-(CH_2)_t$(5-10 membered heteroaryl), $-S-(CH_2)_t(C_3-C_{10}$ cycloalkyl), and $-S-(CH_2)_t$(4- 10 membered heterocycloalkyl), wherein t is an integer from 0 to 4 and any aryl, heteroaryl, cycloalkyl or heterocycloalkyl groups present, may themselves be substituted by unsubstituted C1-C4 alkyl, halo, unsubstituted C1-C4 alkoxy, unsubstituted C1-C4 haloalkyl, unsubstituted C1-C4 hydroxyalkyl, or unsubstituted C1-C4 haloalkoxy or hydroxy. The term 'substituted sulfanyl' includes the groups

'alkylsulfanyl' or 'alkylthio', 'substituted alkylthio' or 'substituted alkylsulfanyl', 'cycloalkylsulfanyl' or 'cycloalkylthio', 'substituted cycloalkylsulfanyl' or 'substituted cycloalkylthio', 'arylsulfanyl' or 'arylthio' and 'heteroarylsulfanyl' or 'heteroarylthio' as defined below.

[00140] 'Alkylthio' or 'Alkylsulfanyl' refers to a radical $-SR^{75}$ where R^{75} is a C_1-C_8 alkyl or group as defined herein. Representative examples include, but are not limited to, methylthio, ethylthio, propylthio and butylthio.

[00141] 'Substituted Alkylthio'or 'substituted alkylsulfanyl' refers to the group $-SR^{76}$ where R^{76} is a Ci-Cg alkyl, substituted with halo, substituted or unsubstituted amino, or hydroxy.

[00142] 'Cycloalkylthio' or 'Cycloalkylsulfanyl' refers to a radical $-SR^{77}$ where R^{77} is a C_3-C_{10} cycloalkyl or group as defined herein. Representative examples include, but are not limited to, cyclopropylthio, cyclohexylthio, and cyclopentylthio.

[00143] 'Substituted cycloalkylthio' or 'substituted cycloalkylsulfanyl' refers to the group $-SR^{78}$ where R^{78} is a C3-C10 cycloalkyl, substituted with halo, substituted or unsubstituted amino, or hydroxy.

[[0000114444]] 'Arylthio' or 'Arylsulfanyl' refers to a radical $-SR^{79}$ where R^{79} is a C6-C10 aryl group as defined herein.

[[0000114455]] 'Heteroarylthio' or 'Heteroarylsulfanyl' refers to a radical $-SR^{80}$ where R^{80} is a 5-10 membered heteroaryl group as defined herein.

[00146] 'Substituted sulfinyl' refers to the group $-S(0)R^{81}$, wherein R^{81} is selected from:

- Ci-Cg alkyl, C3-C10 cycloalkyl, 4-10 membered heterocycloalkyl, C_6-Ci $_0$ aryl, aralkyl, 5-10 membered heteroaryl, and heteroaralkyl; or
- Ci-Cg alkyl substituted with halo, substituted or unsubstituted amino, or hydroxy; or
- C3-C10 cycloalkyl, 4-10 membered heterocycloalkyl, C6-C10 aryl, aralkyl, 5-10 membered heteroaryl, or heteroaralkyl, each of which is substituted by unsubstituted C1-C4 alkyl, halo, unsubstituted C1-C4 alkoxy, unsubstituted C_1-C4haloalkyl, unsubstituted C1-C4 hydroxyalkyl, or unsubstituted C1-C4 haloalkoxy or hydroxy.

[00147] Exemplary 'substituted sulfinyl' groups are -S(0)-(C_1-C_8 alkyl) and -S(O)-(C_3-C_{10} cycloalkyl), -S(O)-(CH_2)$_t$(C_6-C_{10} aryl), -S(O)-(CH_2)$_t$(5-10 membered heteroaryl), -S(O)-(CH_2)$_t$(C_3-C_{10} cycloalkyl), and -S(O)-(CH_2)$_t$(4-10 membered heterocycloalkyl), wherein t is an integer from 0 to 4 and any aryl, heteroaryl, cycloalkyl or heterocycloalkyl groups present, may themselves be substituted by unsubstituted C1-C4 alkyl, halo, unsubstituted C1-C4 alkoxy, unsubstituted C1-C4 haloalkyl, unsubstituted C1-C4 hydroxyalkyl, or unsubstituted C1-C4 haloalkoxy or hydroxy. The term substituted sulfinyl includes the groups 'alkylsulfinyl', 'substituted alkylsulfinyl', 'cycloalkylsulfinyl', 'substituted cycloalkylsulfinyl', 'arylsulfinyl' and 'heteroarylsulfinyl' as defined herein.

[00148] 'Alkylsulfinyl' refers to a radical $-S(0)R^{82}$ where R^{82} is a C_1-C_8 alkyl group as defined herein. Representative examples include, but are not limited to, methylsulfinyl, ethylsulfinyl, propylsulfinyl and butylsulfinyl.

[00149] 'Substituted Alkylsulfinyl' refers to a radical $-S(0)R^{83}$ where R^{83} is a C_1-C_8 alkyl group as defined herein, substituted with halo, substituted or unsubstituted amino, or hydroxy.

[00150] 'Cycloalkylsulfmyl' refers to a radical -S(0)R [84] where R^{84} is a C3-C10 cycloalkyl or group as defined herein. Representative examples include, but are not limited to, cyclopropylsulfinyl, cyclohexylsulfinyl, and cyclopentylsulfinyl. Exemplary 'cycloalkylsulfinyl' groups are S(0)-C3-Cio cycloalkyl.

[00151] 'Substituted cycloalkylsulfmyl' refers to the group -S(0)R [85] where R^{85} is a C_3-C_{10} cycloalkyl, substituted with halo, substituted or unsubstituted amino, or hydroxy.

[00152] 'Arylsulfmyl' refers to a radical -S(0)R [86] where R^{86} is a C_6-C_{10} aryl group as defined herein.

[00153] 'Heteroarylsulfinyl' refers to a radical -S(0)R [87] where R^{87} is a 5-10 membered heteroaryl group as defined herein.

[00154] 'Substituted sulfonyl' refers to the group -S(0)2R [88], wherein R^{88} is selected from:

- Ci-Cg alkyl, C3-C10 cycloalkyl, 4-10 membered heterocycloalkyl, C6-C10 aryl, aralkyl, 5-10 membered heteroaryl, and heteroaralkyl; or
- Ci-Cg alkyl substituted with halo, substituted or unsubstituted amino, or hydroxy; or
- C3-C10 cycloalkyl, 4-10 membered heterocycloalkyl, C6-C10 aryl, aralkyl, 5-10 membered heteroaryl, or heteroaralkyl, each of which is substituted by unsubstituted C1-C4 alkyl, halo, unsubstituted C1-C4 alkoxy, unsubstituted C1-C4 haloalkyl, unsubstituted C1-C4 hydroxyalkyl, or unsubstituted C1-C4 haloalkoxy or hydroxy.

[00155] Exemplary 'substituted sulfonyl' groups are -S(0)2-(Ci-Cg alkyl) and -S(0)2-(C3-Cio cycloalkyl), -S(O) $_2$-(CH2)t(C $_6$-C_{10} aryl), -S(O) $_2$-$(CH_2)_t$(5-10 membered heteroaryl), -S(0) $_2$-(CH $_2$)t(C3-Cio cycloalkyl), and -S(O)2-$(CH_2)_t$(4-10 membered heterocycloalkyl), wherein t is an integer from 0 to 4 and any aryl, heteroaryl, cycloalkyl or heterocycloalkyl groups present, may themselves be substituted by unsubstituted C1-C4 alkyl, halo, unsubstituted C1-C4 alkoxy, unsubstituted C1-C4 haloalkyl, unsubstituted C1-C4 hydroxyalkyl, or unsubstituted C1-C4 haloalkoxy or hydroxy. The term substituted sulfonyl includes the groups alkylsulfonyl, substituted alkylsulfonyl, cycloalkylsulfonyl, substituted cycloalkylsulfonyl, arylsulfonyl and heteroarylsulfonyl.

[00156] 'Alkylsulfonyl' refers to a radical -S(0) $_2R^{89}$ where R^{89} is an C_1-C_8 alkyl group as defined herein. Representative examples include, but are not limited to, methylsulfonyl, ethylsulfonyl, propylsulfonyl and butylsulfonyl.

[00157] 'Substituted Alkylsulfonyl' refers to a radical -S(0) $_2R^{9\circ}$ where R^{90} is an C_1-C_8 alkyl group as defined herein, substituted with halo, substituted or unsubstituted amino, or hydroxy.

[00158] 'Cycloalkylsulfonyl' refers to a radical -S(0) $_2R^{91}$ where R^{91} is a C3-C10 cycloalkyl or group as defined herein. Representative examples include, but are not limited to, cyclopropylsulfonyl, cyclohexylsulfonyl, and cyclopentylsulfonyl.

[00159] 'Substituted cycloalkylsulfonyl' refers to the group -S(0) $_2R^{92}$ where R^{92} is a C3-C10 cycloalkyl, substituted with halo, substituted or unsubstituted amino, or hydroxy.

[00160] 'Arylsulfonyl' refers to a radical -S(0) $_2R^{93}$ where R^{93} is an C6-C10 aryl group as defined herein.

[00161] 'Heteroarylsulfonyl' refers to a radical $-S(0)2R^{94}$ where R^{94} is an 5-10 membered heteroaryl group as defined herein.

[00162] 'Sulfo' or 'sulfonic acid' refers to a radical such as $-SO_3H$.

[00163] 'Substituted sulfo' or 'sulfonic acid ester' refers to the group $-S(0)_2OR^{95}$, wherein R^{95} is selected from:

- Ci-Cg alkyl, C3-C10 cycloalkyl, 4-10 membered heterocycloalkyl, C6-C10 aryl, aralkyl, 5-10 membered heteroaryl, and heteroaralkyl; or
- Ci-Cg alkyl substituted with halo, substituted or unsubstituted amino, or hydroxy; or
- C3-C10 cycloalkyl, 4-10 membered heterocycloalkyl, C_6-Ci_0 aryl, aralkyl, 5-10 membered heteroaryl, or heteroaralkyl, each of which is substituted by unsubstituted C_1-C4 alkyl, halo, unsubstituted C1-C4 alkoxy, unsubstituted C1-C4 haloalkyl, unsubstituted C1-C4 hydroxyalkyl, or unsubstituted C1-C4 haloalkoxy or hydroxy.

[00164] Exemplary 'Substituted sulfo' or 'sulfonic acid ester' groups are $-S(0)_2$-0-(Ci-Cg alkyl) and $-S(0)_2$-0-(C_3-Cio cycloalkyl), $-S(0)_2$-0-(CH_2)$_t$(C_6-Cio aryl), $-S(O)_2$-O-(CH_2)$_t$(5-10 membered heteroaryl), $-S(O)_2$-O-(CH_2)$_t$(C_3-Ci_0 cycloalkyl), and $-S(O)_2$-O-(CH_2)$_t$(4-10 membered heterocycloalkyl), wherein t is an integer from 0 to 4 and any aryl, heteroaryl, cycloalkyl or heterocycloalkyl groups present, may themselves be substituted by unsubstituted C1-C4 alkyl, halo, unsubstituted C1-C4 alkoxy, unsubstituted C1-C4 haloalkyl, unsubstituted C1-C4 hydroxyalkyl, or unsubstituted C1-C4 haloalkoxy or hydroxy.

[00165] 'Thiol' refers to the group -SH.

[00166] 'Aminocarbonylamino' refers to the group $-NR^{96}C(0)NR^{96}R^{96}$ where each R^{96} is independently hydrogen C_1-Cg alkyl, C3-C10 cycloalkyl, 4-10 membered heterocycloalkyl, C6-C10 aryl, aralkyl, 5-10 membered heteroaryl, and heteroaralkyl, as defined herein; or where two R^{96} groups, when attached to the same N, are joined to form an alkylene group.

[00167] 'Bicycloaryl' refers to a monovalent aromatic hydrocarbon group derived by the removal of one hydrogen atom from a single carbon atom of a parent bicycloaromatic ring system. Typical bicycloaryl groups include, but are not limited to, groups derived from indane, indene, naphthalene, tetrahydronaphthalene, and the like. Particularly, an aryl group comprises from 8 to 11 carbon atoms.

[00168] 'Bicycloheteroaryl' refers to a monovalent bicycloheteroaromatic group derived by the removal of one hydrogen atom from a single atom of a parent bicycloheteroaromatic ring system. Typical bicycloheteroaryl groups include, but are not limited to, groups derived from benzofuran, benzimidazole, benzindazole, benzdioxane, chromene, chromane, cinnoline, phthalazine, indole, indoline, indolizine, isobenzofuran, isochromene, isoindole, isoindoline, isoquinoline, benzothiazole, benzoxazole, naphthyridine, benzoxadiazole, pteridine, purine, benzopyran, benzpyrazine, pyridopyrimidine, quinazoline, quinoline, quinolizine, quinoxaline, benzomorphan, tetrahydroisoquinoline, tetrahydroquinoline, and the like. Preferably, the bicycloheteroaryl group is between 9-11 membered bicycloheteroaryl, with 5-10 membered heteroaryl being particularly preferred. Particular

bicycloheteroaryl groups are those derived from benzothiophene, benzofuran, benzothiazole, indole, quinoline, isoquinoline, benzimidazole, benzoxazole and benzdioxane.

[00169] 'Compounds of the present invention', and equivalent expressions, are meant to embrace the compounds as hereinbefore described, in particular compounds according to any of the formulae herein recited and/or described, which expression includes the prodrugs, analogs, the pharmaceutically acceptable salts, and the solvates, e.g., hydrates, where the context so permits. Similarly, reference to intermediates, whether or not they themselves are claimed, is meant to embrace their salts, and solvates, where the context so permits.

[00170] 'Cycloalkylalkyl' refers to a radical in which a cycloalkyl group is substituted for a hydrogen atom of an alkyl group. Typical cycloalkylalkyl groups include, but are not limited to, cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, cycloheptylmethyl, cyclooctylmethyl, cyclopropylethyl, cyclobutylethyl, cyclopentylethyl, cyclohexylethyl, cycloheptylethyl, and cyclooctylethyl, and the like.

[00171] 'Heterocycloalkylalkyl' refers to a radical in which a heterocycloalkyl group is substituted for a hydrogen atom of an alkyl group. Typical heterocycloalkylalkyl groups include, but are not limited to, pyrrolidinylmethyl, piperidinylmethyl, piperazinylmethyl, morpholinylmethyl, pyrrolidinylethyl, piperidinylethyl, piperazinylethyl, morpholinylethyl, and the like.

[00172] 'Cycloalkenyl' refers to cyclic hydrocarbyl groups having from 3 to 10 carbon atoms and having a single cyclic ring or multiple condensed rings, including fused and bridged ring systems and having at least one and particularly from 1 to 2 sites of olefinic unsaturation. Such cycloalkenyl groups include, by way of example, single ring structures such as cyclohexenyl, cyclopentenyl, cyclopropenyl, and the like.

[00173] 'Substituted cycloalkenyl' refers to those groups recited in the definition of 'substituted' herein, and particularly refers to a cycloalkenyl group having 1 or more substituents, for instance from 1 to 5 substituents, and particularly from 1 to 3 substituents, selected from the group consisting of acyl, acylamino, acyloxy, alkoxy, substituted alkoxy, alkoxycarbonyl, alkoxycarbonylamino, amino, substituted amino, aminocarbonyl, aminocarbonylamino, aminocarbonyloxy, aryl, aryloxy, azido, carboxyl, cyano, cycloalkyl, substituted cycloalkyl, halogen, hydroxyl, keto, nitro, thioalkoxy, substituted thioalkoxy, thioaryloxy, thioketo, thiol, alkyl-S(O)-, aryl-S(O)-, alkyl-$S(0)_2$- and aryl-$S(0)_2$-.

[00174] 'Fused Cycloalkenyl' refers to a cycloalkenyl having two of its ring carbon atoms in common with a second aliphatic or aromatic ring and having its olefinic unsaturation located to impart aromaticity to the cycloalkenyl ring.

[00175] 'Ethenyl' refers to substituted or unsubstituted -(C=C)-.

[00176] 'Ethylene' refers to substituted or unsubstituted -(C-C)-.

[00177] 'Ethynyl' refers to -(C≡C)-.

[00178] 'Hydrogen bond donor' group refers to a group containg O-H, or N-H functionality. Examples of 'hydrogen bond donor' groups include -OH, -NH_2, and -NH-R^{97} and wherein R^{97} is alkyl, acyl, cycloalkyl, aryl, or heteroaryl.

[00179] 'Dihydroxyphosphoryl' refers to the radical -$PO(OH)_2$.

[00180] 'Substituted dihydroxyphosphoryl' refers to those groups recited in the definition of 'substituted' herein, and particularly refers to a dihydroxyphosphoryl radical wherein one or both of the hydroxyl groups are substituted. Suitable substituents are described in detail below.

[00181] 'Aminohydroxyphosphoryl' refers to the radical $-PO(OH)NH_2$.

[00182] 'Substituted aminohydroxyphosphoryl' refers to those groups recited in the definition of 'substituted' herein, and particularly refers to an aminohydroxyphosphoryl wherein the amino group is substituted with one or two substituents. Suitable substituents are described in detail below. In certain embodiments, the hydroxyl group can also be substituted.

[00183] 'Nitrogen-Containing Heterocycloalkyl' group means a 4 to 7 membered non-aromatic cyclic group containing at least one nitrogen atom, for example, but without limitation, morpholine, piperidine (e.g. 2-piperidinyl, 3-piperidinyl and 4-piperidinyl), pyrrolidine (e.g. 2-pyrrolidinyl and 3-pyrrolidinyl), azetidine, pyrrolidone, imidazoline, imidazolidinone, 2-pyrazoline, pyrazolidine, piperazine, and N-alkyl piperazines such as N-methyl piperazine. Particular examples include azetidine, piperidone and piperazone.

[00184] Thioketo' refers to the group =S.

[00185] One having ordinary skill in the art of organic synthesis will recognize that the maximum number of heteroatoms in a stable, chemically feasible heterocyclic ring, whether it is aromatic or non aromatic, is determined by the size of the ring, the degree of unsaturation and the valence of the heteroatoms. In general, a heterocyclic ring may have one to four heteroatoms so long as the heteroaromatic ring is chemically feasible and stable.

[00186] 'Pharmaceutically acceptable' means approved or approvable by a regulatory agency of the Federal or a state government or the corresponding agency in countries other than the United States, or that is listed in the U.S. Pharmacopoeia or other generally recognized pharmacopoeia for use in animals, and more particularly, in humans.

[00187] 'Pharmaceutically acceptable salt' refers to a salt of a compound of the invention that is pharmaceutically acceptable and that possesses the desired pharmacological activity of the parent compound. In particular, such salts are non-toxic may be inorganic or organic acid addition salts and base addition salts. Specifically, such salts include: (1) acid addition salts, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or formed with organic acids such as acetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, 3-(4-hydroxybenzoyl) benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethane-disulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, 4-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, 4-toluenesulfonic acid, camphorsulfonic acid, 4-methylbicyclo[2.2.2]-oct-2-ene-l-carboxylic acid, glucoheptonic acid, 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid, and the like; or (2) salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, e.g., an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base such as

ethanolamine, diethanolamine, triethanolamine, N-methylglucamine and the like. Salts further include, by way of example only, sodium, potassium, calcium, magnesium, ammonium, tetraalkylammonium, and the like; and when the compound contains a basic functionality, salts of non toxic organic or inorganic acids, such as hydrochloride, hydrobromide, tartrate, mesylate, acetate, maleate, oxalate and the like. The term 'pharmaceutically acceptable cation' refers to an acceptable cationic counter-ion of an acidic functional group. Such cations are exemplified by sodium, potassium, calcium, magnesium, ammonium, tetraalkylammonium cations, and the like.

[00188] 'Pharmaceutically acceptable vehicle' refers to a diluent, adjuvant, excipient or carrier with which a compound of the invention is administered.

[00189] 'Prodrugs' refers to compounds, including derivatives of the compounds of the invention, which have cleavable groups and become by solvolysis or under physiological conditions the compounds of the invention which are pharmaceutically active *in vivo*. Such examples include, but are not limited to, choline ester derivatives and the like, N-alkylmorpholine esters and the like.

[00190] 'Solvate' refers to forms of the compound that are associated with a solvent, usually by a solvolysis reaction. This physical association includes hydrogen bonding. Conventional solvents include water, ethanol, acetic acid and the like. The compounds of the invention may be prepared e.g. in crystalline form and may be solvated or hydrated. Suitable solvates include pharmaceutically acceptable solvates, such as hydrates, and further include both stoichiometric solvates and non-stoichiometric solvates. In certain instances the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. 'Solvate' encompasses both solution-phase and isolable solvates. Representative solvates include hydrates, ethanolates and methanolates.

[00191] 'Subject' includes humans. The terms 'human', 'patient' and 'subject' are used interchangeably herein.

[00192] 'Therapeutically effective amount' means the amount of a compound that, when administered to a subject for treating a disease, is sufficient to effect such treatment for the disease. The 'therapeutically effective amount' can vary depending on the compound, the intention of treatment *viz-a-viz* prevention, prophylaxis, intent-to-treat, treatment, the disease and its severity, and the age, co-morbidity, weight, gender, social habits such as smoking, alcohol consumption etc., of the subject to be treated.

[00193] 'Preventing' or 'prevention' refers to a reduction in risk of acquiring or developing a disease or disorder (i.e., causing at least one of the clinical symptoms of the disease not to develop in a subject that may be exposed to a disease-causing agent, or predisposed to the disease in advance of disease onset.

[00194] The term 'prophylaxis' is related to 'prevention', and refers to a measure or procedure the purpose of which is to prevent, rather than to treat or cure a disease. Non-limiting examples of prophylactic measures may include the administration of vaccines; the administration of low molecular weight heparin to hospital patients at risk for thrombosis due, for example, to immobilization; and the

administration of an anti-malarial agent such as chloroquine, in advance of a visit to a geographical region where malaria is endemic or the risk of contracting malaria is high.

[00195] 'Treating' or 'treatment' of any disease or disorder refers, in one embodiment, to ameliorating the disease or disorder (i.e., arresting the disease or reducing the manifestation, extent or severity of at least one of the clinical symptoms thereof). In another embodiment 'treating' or 'treatment' refers to ameliorating at least one physical parameter, which may not be discernible by the subject. In yet another embodiment, 'treating' or 'treatment' refers to modulating the disease or disorder, either physically, (e.g., stabilization of a discernible symptom), physiologically, (e.g., stabilization of a physical parameter), or both. In a further embodiment, 'treating' or 'treatment' relates to slowing the progression of the disease.

[00196] 'Compounds of the present invention', and equivalent expressions, are meant to embrace compounds of the Formula(e) as hereinbefore described, which expression includes the prodrugs, analogs, the pharmaceutically acceptable salts, and the solvates, e.g., hydrates, where the context so permits. Similarly, reference to intermediates, whether or not they themselves are claimed, is meant to embrace their salts, and solvates, where the context so permits.

[00197] When ranges are referred to herein, for example but without limitation, C_1-C_8 alkyl, the citation of a range should be considered a representation of each member of said range.

[00198] Other derivatives of the compounds of this invention have activity in both their acid and acid derivative forms, but in the acid sensitive form often offers advantages of solubility, tissue compatibility, or delayed release in the mammalian organism (see, Bundgard, H., Design of Prodrugs, pp. 7-9, 21-24, Elsevier, Amsterdam 1985). Prodrugs and or analogs include acid derivatives well know to practitioners of the art, such as, for example, esters prepared by reaction of the parent acid with a suitable alcohol, or amides prepared by reaction of the parent acid compound with a substituted or unsubstituted amine, or acid anhydrides, or mixed anhydrides. Simple aliphatic or aromatic esters, amides and anhydrides derived from acidic groups pendant on the compounds of this invention are particular prodrugs. In some cases it is desirable to prepare double ester type prodrugs such as (acyloxy)alkyl esters or ((alkoxycarbonyl)oxy)alkylesters. Particularly the C_1 to C_8 alkyl, C_2-C_8 alkenyl, aryl, C_7-Ci $_2$ substituted aryl, and C7-C12 arylalkyl esters of the compounds of the invention.

[00199] As used herein, the term 'isotopic variant' refers to a compound that contains unnatural proportions of isotopes at one or more of the atoms that constitute such compound. For example, an 'isotopic variant' of a compound can contain one or more non-radioactive isotopes, such as for example, deuterium (^{2}H or D), carbon- 13 (^{13}C), nitrogen- 15 (^{15}N), or the like. It will be understood that, in a compound where such isotopic substitution is made, the following atoms, where present, may vary, so that for example, any hydrogen may be ^{2}H/D, any carbon may be ^{13}C, or any nitrogen may be ^{15}N, and that the presence and placement of such atoms may be determined within the skill of the art. Likewise, the invention may include the preparation of isotopic variants with radioisotopes, in the instance for example, where the resulting compounds may be used for drug and/or substrate tissue distribution studies. The radioactive isotopes tritium, i.e. ^{3}H, and carbon-14, i.e. ^{14}C, are particularly useful for this purpose in view of their ease of incorporation and ready means of detection. Further, compounds may be prepared that are

substituted with positron emitting isotopes, such as ^{11}C, ^{18}F, $^{15}0$ and ^{13}N, and would be useful in Positron Emission Topography (PET) studies for examining substrate receptor occupancy.

[00200] All isotopic variants of the compounds provided herein, radioactive or not, are intended to be encompassed within the scope of the invention.

[00201] It is also to be understood that compounds that have the same molecular formula but differ in the nature or sequence of bonding of their atoms or the arrangement of their atoms in space are termed 'isomers'. Isomers that differ in the arrangement of their atoms in space are termed 'stereoisomers'.

[00202] Stereoisomers that are not mirror images of one another are termed 'diastereomers' and those that are non-superimposable mirror images of each other are termed 'enantiomers'. When a compound has an asymmetric center, for example, it is bonded to four different groups, a pair of enantiomers is possible. An enantiomer can be characterized by the absolute configuration of its asymmetric center and is described by the R- and S-sequencing rules of Cahn and Prelog, or by the manner in which the molecule rotates the plane of polarized light and designated as dextrorotatory or levorotatory (i.e., as (+) or (-)-isomers respectively). A chiral compound can exist as either individual enantiomer or as a mixture thereof. A mixture containing equal proportions of the enantiomers is called a 'racemic mixture'.

[00203] 'Tautomers' refer to compounds that are interchangeable forms of a particular compound structure, and that vary in the displacement of hydrogen atoms and electrons. Thus, two structures may be in equilibrium through the movement of π electrons and an atom (usually H). For example, enols and ketones are tautomers because they are rapidly interconverted by treatment with either acid or base. Another example of tautomerism is the aci- and nitro- forms of phenylnitromethane, that are likewise formed by treatment with acid or base.

[00204] Tautomeric forms may be relevant to the attainment of the optimal chemical reactivity and biological activity of a compound of interest.

[00205] As used herein a pure enantiomeric compound is substantially free from other enantiomers or stereoisomers of the compound *(i.e.,* in enantiomeric excess). In other words, an "S" form of the compound is substantially free from the "R" form of the compound and is, thus, in enantiomeric excess of the "R" form. The term "enantiomerically pure" or "pure enantiomer" denotes that the compound comprises more than 75% by weight, more than 80% by weight, more than 85% by weight, more than 90% by weight, more than 91% by weight, more than 92% by weight, more than 93% by weight, more than 94% by weight, more than 95% by weight, more than 96% by weight, more than 97% by weight, more than 98% by weight, more than 98.5% by weight, more than 99% by weight, more than 99.2% by weight, more than 99.5% by weight, more than 99.6% by weight, more than 99.7% by weight, more than 99.8% by weight or more than 99.9% by weight, of the enantiomer. In certain embodiments, the weights are based upon total weight of all enantiomers or stereoisomers of the compound.

[00206] As used herein and unless otherwise indicated, the term 'enantiomerically pure R-compound' refers to at least about 80% by weight R-compound and at most about 20% by weight S-compound, at least about 90% by weight R-compound and at most about 10% by weight S-compound, at

least about 95% by weight R-compound and at most about 5% by weight S-compound, at least about 99% by weight R-compound and at most about 1% by weight S-compound, at least about 99.9% by weight R-compound or at most about 0.1% by weight S-compound. In certain embodiments, the weights are based upon total weight of compound.

[00207] As used herein and unless otherwise indicated, the term 'enantiomerically pure S-compound' or 'S-compound' refers to at least about 80% by weight S-compound and at most about 20% by weight R-compound, at least about 90% by weight S-compound and at most about 10% by weight R-compound, at least about 95% by weight S-compound and at most about 5% by weight R-compound, at least about 99% by weight S-compound and at most about 1% by weight R-compound or at least about 99.9% by weight S-compound and at most about 0.1% by weight R-compound. In certain embodiments, the weights are based upon total weight of compound.

[00208] In the compositions provided herein, an enantiomerically pure compound or a pharmaceutically acceptable salt, solvate, hydrate, analog or prodrug thereof can be present with other active or inactive ingredients. For example, a pharmaceutical composition comprising enantiomerically pure R-compound can comprise, for example, about 90% excipient and about 10% enantiomerically pure R-compound. In certain embodiments, the enantiomerically pure R-compound in such compositions can, for example, comprise, at least about 95% by weight R-compound and at most about 5% by weight S-compound, by total weight of the compound. For example, a pharmaceutical composition comprising enantiomerically pure S-compound can comprise, for example, about 90% excipient and about 10% enantiomerically pure S-compound. In certain embodiments, the enantiomerically pure S-compound in such compositions can, for example, comprise, at least about 95% by weight S-compound and at most about 5% by weight R-compound, by total weight of the compound. In certain embodiments, the active ingredient can be formulated with little or no excipient or carrier.

[00209] The compounds of this invention may possess one or more asymmetric centers; such compounds can therefore be produced as individual (R)- or (S)- or Cis-trans or E-Z -stereoisomers or as mixtures thereof.

[00210] Unless indicated otherwise, the description or naming of a particular compound in the specification and claims is intended to include both individual enantiomers and mixtures, racemic or otherwise, thereof. The methods for the determination of stereochemistry and the separation of stereoisomers are well-known in the art.

THE COMPOUNDS

[00211] Compounds, and pharmaceutical compositions thereof, having potency, specificity and selectivity in the diagnosis, prophylaxis, prevention, treatment and prognosis of conditions such illnesses, diseases, ailment etc associated with increased or elevated levels of Akt including hyperactivation, overexpression, up-regulation, amplification of Akt in such conditions as in cancer, macular degeneration, Huntington's disease, ataxia, HIV infection, diabetic retinopathy, type I diabetis mellitus, hypovolemia, septic shock, wound healing, auto-immune disease, rheumatoid arthritisand other Akt-related conditions are described herein.

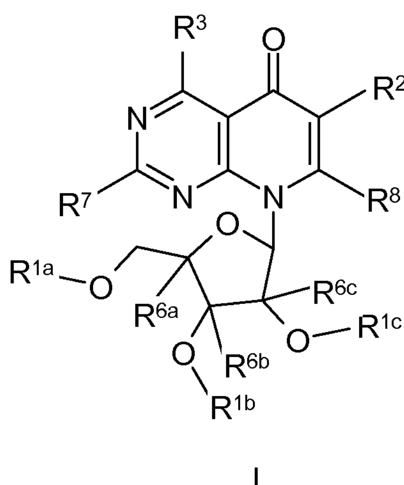
[00212] In particular, compounds, pharmaceutical compositions and methods provided are used to diagnose, prophylaxis, prevent, treat, prognose or ameliorate a range of conditions in mammals where inhibition of Akt and / or its pathways are indicated as molecular target or cause of such conditions resulting in illness, disease, ailment, etc. such as, but not limited to, cancer, macular degeneration, Huntington's disease, ataxia, HIV infection, diabetic retinopathy, diabetis mellitus, hypovolemia, septic shock, wound healing, ulcerative dermatitis, auto-immune disease, rheumatoid arthritis and other Akt-related conditions. Furthermore, the compounds of the invention may be used for killing a human cells or other cells in which expression of an Akt protein is elevated, hyperactivated, overexpressed, increased, up-regulated, amplified, aberrantly or constitutively actived, comprising contacting the cell with an effective amount of a compound of formula I in disease conditions such as (but not limited to); cancer, macular degeneration, Huntington's disease, ataxia, HIV infection, diabetic retinopathy, type I diabetis mellitus, hypovolemia, septic shock, wound healing, ulcerative dermatitis, auto-immune disease, rheumatoid arthritis and other Akt-related conditions.

[00213] The subject of invention also concerns methods for treating all conditions where Akt and or its pathways are either hyperactivated, amplified, elevated, increased, up-regulated, overexpressed, aberrantly or constitutively activated, or are affected in any combination of the aforementioned ways, resulting in disease conditions such as (but not limited to); cancer, macular degeneration, Huntington's disease, ataxia, HIV infection, diabetic retinopathy, diabetis mellitus, hypovolemia, septic shock, wound healing, ulcerative dermatitis, auto-immune disease, rheumatoid arthritis and other Akt-related conditions in a person or animal comprising administering an effective amount of a compound of formula I to the person or animal.

[00214] The Akt pathway is frequently hyperactivated in human cancer and functions as a cardinal nodal point for transducing extracellular and intracellular oncogenic signals, and thus presents an exciting target for molecular and targeted therapeutics. The present invention is related to the identification of a small molecule Akt/PKB inhibitor that is known as API-1 (or LD-101). API-1 (or LD-101) is neither an ATP-competitor nor a substrate mimetic not allosteric, because it binds to the pleckstrin homology (PH) domain of Akt in a non-dependent manner and blocks Akt membrane translocation. Further, API-1 (or LD-101) treatment of cancer cells results in inhibition of the kinase activities and phosphorylation levels of all isoforms of Akt family. In contrast, API-1 (or LD-101) had no effects on the activities of the upstream Akt activators such as PI3K, PDK1, PDK2 and rictor mTORC2. Notably, the kinase activity and phosphorylation (e.g., pT308 and pS473) levels of constitutively active Akt, including a naturally occurring AKT1-E40K and somatic mutant AKT1-E17K, were inhibited by API-1 (or LD- 101). API- 1 (or LD- 10 1) is selective for Akt and does not inhibit the activation of othe AGC family kinases such as PKC, SGK and PKA. API-1 (or LD-101) does not inhibit molecular targets in other parallel oncogenic signaling pathways such as STAT3, Erk-1/2, MAP-kinase or JNK. The inhibition of Akt by API-1 (or LD-101) resulted in cell growth arrest, tumor growth inhibition and induction of apoptosis selectively in human cancer cells that harbor constitutively activated Akt. Further, API-1 (or LD-101) inhibited tumor growth in nude mice of human cancer cells in which Akt is elevated but not in those cancer cells in which it is not. These data indicate that API-1 (or LD-101) directly

inhibits Akt through binding to Akt PH domain in a non-dependent way (i.e. non-dependent on the order or arrangement or sequence or number or amount of amino acids on the PH domain) and blocking Akt membrane translocation, and that API-1 (or **LD-101**) has anti-tumor activity *in vitro* (cell culture) and *in vivo* (xenograph tumor models) and could be a potential anti-cancer agent for patients whose tumors express hyperactivated Akt. Akt is a major pathway regulating cancer cell survival, growth and tumor progression. It has been well documented that elevated levels of Akt kinase contribute to resistance to various cancer therapies, including cytotoxic chemotherapeutics, radiatotherapy, immunotherapy, other targeted therapeutics and other small molecule inhibitors of Bcr-Abl (Gleevec), Her2/Neu (Hercptin), and mTOR (rapamycin). Blocking Akt inhibits tumor growth in the cancer cells with hyperactivated Akt and renders cancer cells more sensitive to chemotherapy, radio, immuno, surgical and other targeted therapies. Combination of API-1 (or **LD-101**) with other anti-tumor treatment modalities (chemo, radio, immuno, targeted, cellular, genetic and surgical) could provides for more potent and strong synergistic anti-tumor effects.

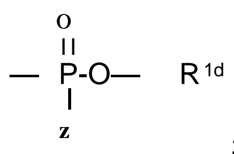
[00215] Accordingly, in one aspect, compounds are provided that have formula I:



I

wherein

each R^{1a}, R^{1b}, and R^{1c} is independently selected from H, an amino acid, a dipeptide, a tripeptide, and



;

R^{1d} is alkyl, aryl, or heteroaryl; Z is an amino acid, a dipeptide, or a tripeptide;

each R^2 and R^3 is independently selected from H, hydroxy, amino, alkyl, alkoxy, and C(0)-NH_2;

each R^{6a}, R^{6b}, R^{6c}, and R^8 is independently selected from H, alkyl, or hydroxyalkyl; or the group -OR^{1b} is absent;

R^7 is selected from H, alkyl, hydroxy, alkoxy, SMe, S(0)Me, or S(0)$_2$Me;

R^8 is selected from H, alkyl, hydroxy, alkoxy, or thioalkoxy;

or a pharmaceutically acceptable salt, solvate or prodrug thereof; and stereoisomers, isotopic variants and tautomers thereof;

provided that at least one of R^{1a}, R^{1b}, and R^{1c} is other than H.

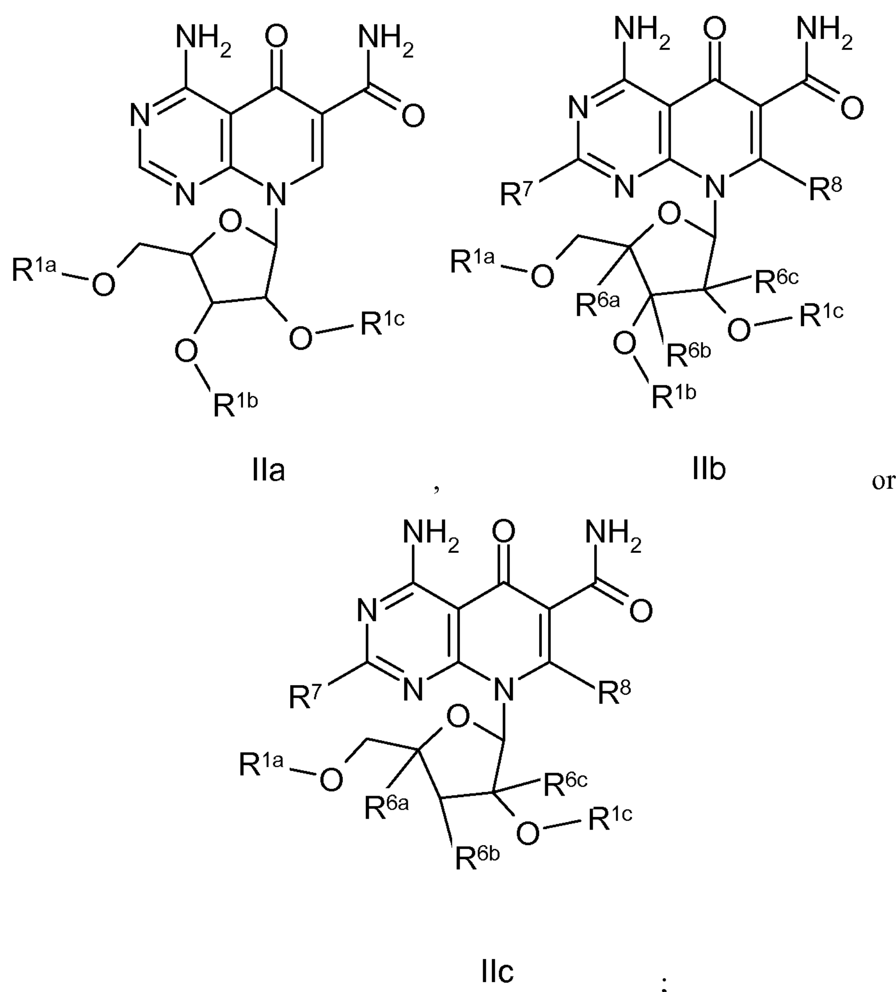
[00216] In one embodiment, with respect to the compound of formula I, each R^{6a}, R^{6b}, R^{6c}, R^7, and R^8 is H.

[00217] In one embodiment, with respect to the compound of formula I, at least one of R^{6a}, R^{6b}, R^{6c}, R^7, and R^8 is other than H.

[00218] In one embodiment, with respect to the compound of formula I, R^2 is C(0)NH $_2$.

[00219] In one embodiment, with respect to the compound of formula I, R^3 is NH_2.

[00220] In one embodiment, with respect to the compound of formula I, the compound is according to formula Ila, lib, or lie:



, or

;

and wherein R^{1a}, R^{1b}, R^{1c}, R^{6a}, R^{6b}, R^{6c}, R^7, and R^8 are as described for formula I.

[00221] In one embodiment, with respect to the compound of formulae I-IIc, at least one of R^{1a}, R^{1b}, and R^{1c} is an amino acid.

[00222] In another embodiment, with respect to the compound of formulae I-IIc, the amino acid is an L-amino acid.

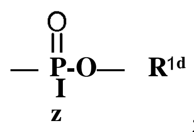
[00223] In another embodiment, with respect to the compound of formulae I-IIc, the amino acid is an D-amino acid.

[00224] In another embodiment, with respect to the compound of formulae I-IIc, at least one of R^{1a}, R^{1b}, and R^{1c} is selected from -D-isoleucyl; -L-isoleucyl; -D-valy; -L-valyl ; -glycyl; -D-phenylalanyl; -L-phenylalanyl; - D-leucyl; -L-leucyl; -L-aspartyl; -D-alpha-aspartyl; -L-alpha-aspartyl; -D-beta-aspartyl; -L-beta- aspartyl; and -L-prolyl.

[00225] In another embodiment, with respect to the compound of formulae I-IIc, at least one of R^{1a}, R^{1b}, and R^{1c} is a dipeptide.

[00226] In another embodiment, with respect to the compound of formulae I-IIc, at least one of R^{1a}, R^{1b}, and R^{1c} is a tripeptide.

[00227] In another embodiment, with respect to the compound of formulae I-IIc, at least one of R^{1a}, R^{1b}, and R^{1c} is



;

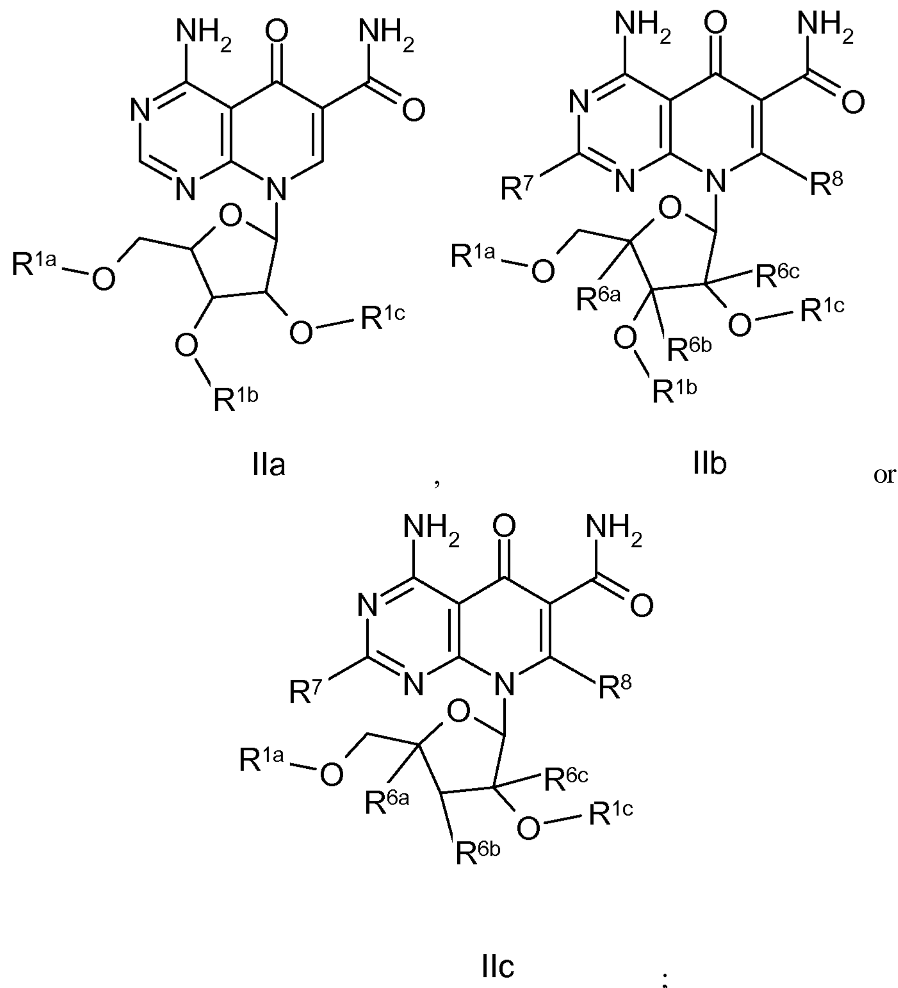
and wherein Z and R^{1d} are as described for formula I.

[00228] In another embodiment, with respect to the compound of formulae I-IIc, Z is an amino acid.

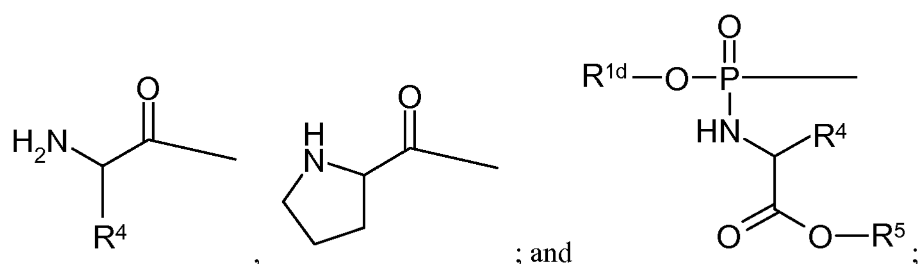
[00229] In another embodiment, with respect to the compound of formulae I-IIc, R^{1d} is benzyl.

[00230] In another embodiment, with respect to the compound of formulae I-IIc, at least one of R^{1a}, R^{1b}, and R^{1c} is selected from -D-isoleucyl phosphoramidate; -L-isoleucyl phosphoramidate; -D-valyl phosphoramidate; -L-valyl phosphoramidate; -glycyl phosphoramidate; -D-phenylalanyl phosphoramidate; -L-phenylalanyl phosphoramidate; 5'-0-L- leucyl phosphoramidate; 5'-0-L-aspartyl phosphoramidate; -D-alpha-aspartyl phosphoramidate; -L-alpha-aspartyl phosphoramidate; D-beta-aspartyl phosphoramidate; -L-beta- aspartyl phosphoramidate; and -L-prolyl phosphoramidate.

[00231] In one particular embodiment, with respect to the compound of formula I, the compound is according to formulae Ila, lib or lie:



and wherein each R^{1a}, R^{1b}, and R^{1c} is independently selected from H,



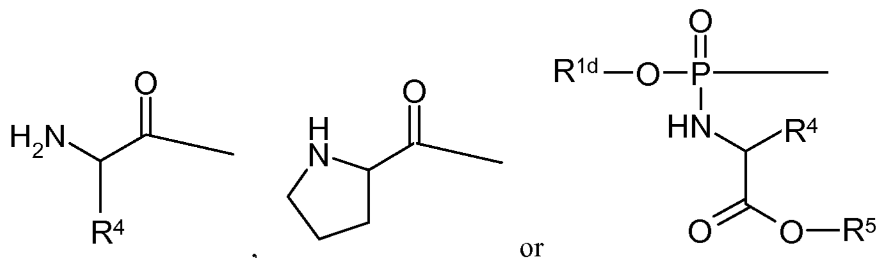
wherein R^{1d} is alkyl, aryl, or heteroaryl; R^4 is H, substituted or unstubstituted alkyl, or substituted or unsubstituted aryl; R^5 is H, or substituted or unstubstituted alkyl;
and R^{6a}, R^{6b}, R^{6c}, R^7, and R^8 are as described for formula I;
provided that at least one of R^{1a}, R^{1b}, and R^{1c} is other than H; and
at least one of R^{6a}, R^f , R^{6c}, R^7, and R^8 is other than H.

[00232] In one particular embodiment, with respect to the compound of formulae I-IIc, each R^{1b}, and R^{1c} is H.

[00233] In one particular embodiment, with respect to the compound of formulae I-IIc, each R^{1a}, and R^{1b} is H.

[00234] In one particular embodiment, with respect to the compound of formulae I-IIc, each R^{1a}, and R^{1c} is H.

[00235] In one particular embodiment, with respect to the compound of formulae I-IIc, R^{1a} is



and each R^{1b} and R^{1c} is H.

[00236] In one particular embodiment, with respect to the compound of formulae I-IIc, R^4 is a standard amino acid side chain.

[00237] In one particular embodiment, with respect to the compound of formulae I-IIc, R^4 is H.

[00238] In one particular embodiment, with respect to the compound of formulae I-IIc, R^4 is substituted or unstubstituted alkyl.

[00239] In one particular embodiment, with respect to the compound of formulae I-IIc, R^4 is alkyl, substituted with hydroxyl, amino, carboxy, SH, SMe, phenyl, hydroxyphenyl, amido, imidazolyl, indolyl, or -NH-C(=NH)-NH_2.

[00240] In one particular embodiment, with respect to the compound of formulae I-IIc, R^4 is Me, Et, i-Pr, n-Bu, i-Bu, sec-Bu, hydroxymethyl, hydroxyethyl, aminopropyl, carboxymethyl, carboxyethyl, amidomethyl, amidoethyl, thiomethyl, methylthioethyl, benzyl, (4-hydroxyphenyl)methyl, (3-indolyl)methyl, or imidazomethyl.

[00241] In one particular embodiment, with respect to the compound of formulae I-IIc, R^4 is -$(CH_2)_3$-NH-C(=NH)-NH_2.

[00242] In one particular embodiment, with respect to the compound of formulae I-IIc, R^5 is H, Me, Et, or i-Pr.

[00243] In one particular embodiment, with respect to the compound of formulae I-IIc, R^{1d} is Me, Et, Ph, or benzyl.

[00244] In one particular embodiment, with respect to the compound of formulae I-IIc, one of R^{6a}, R^*, and R^{6c} is independently Me, Et, or CH_2OH; and the other two are H.

[00245] In one particular embodiment, with respect to the compound of formulae I-IIc, two of R^{6a}, R^*, and R^{6c} are independently Me, Et, or CH_2OH; and the other is H.

[00246] In one particular embodiment, with respect to the compound of formulae I-IIc, R^{6a} is Me or CH_2OH.

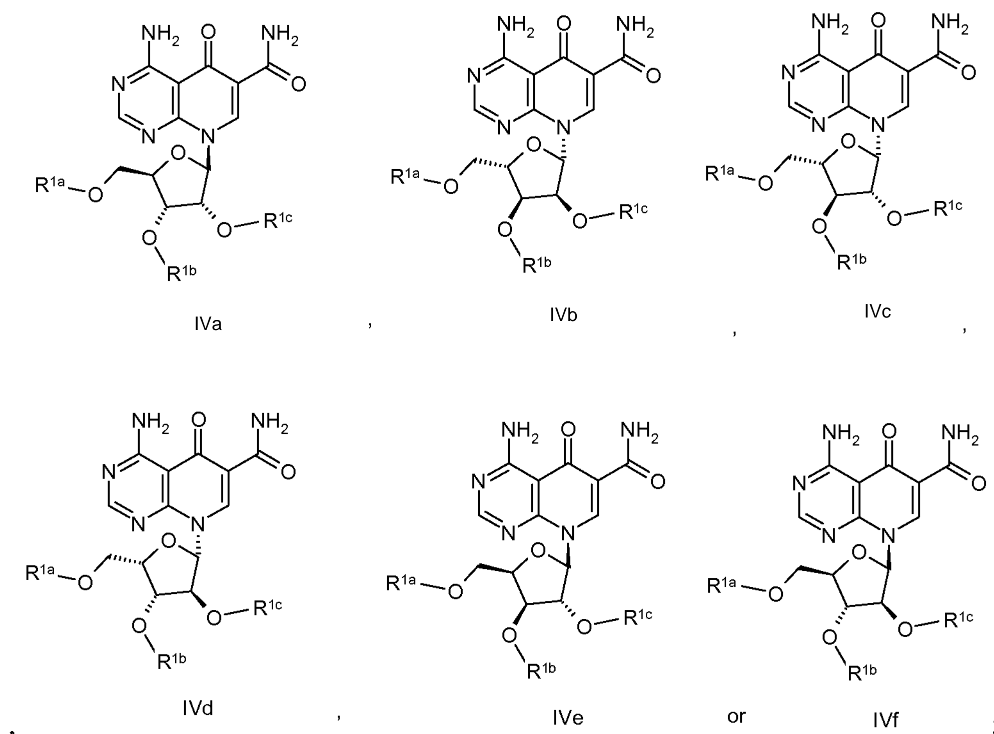
[00247] In one particular embodiment, with respect to the compound of formulae I-IIc, R^{6c} is Me.

[00248] In one particular embodiment, with respect to the compound of formulae I-IIc, R^7 or R^8 is Me.

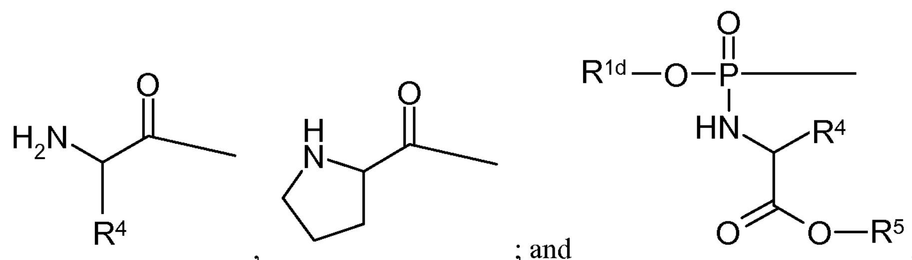
[00249] In one particular embodiment, with respect to the compound of formulae I-IIc,R^7 is H or SMe.

[00250] In one particular embodiment, with respect to the compound of formulae I-IIc, R^8 is H.

[00251] In one particular embodiment, with respect to the compound of formula I, the compound is according to formulae IVa, IVb, IVc, IVd, IVe, or IVf:



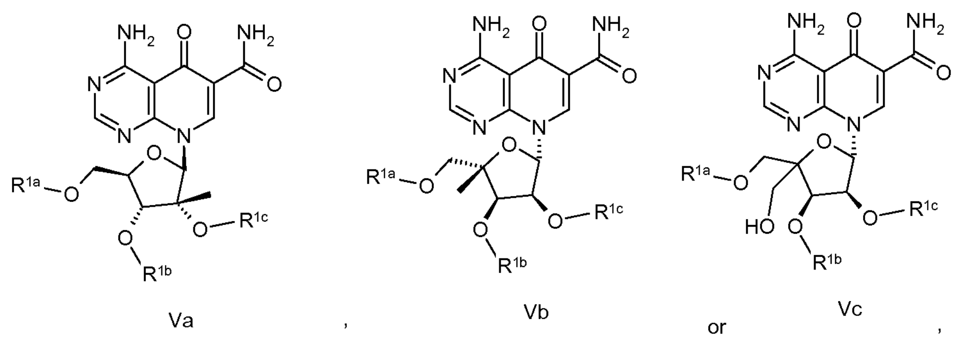
and wherein each R^{1a}, R^{1b}, and R^{1c} is independently selected from H,



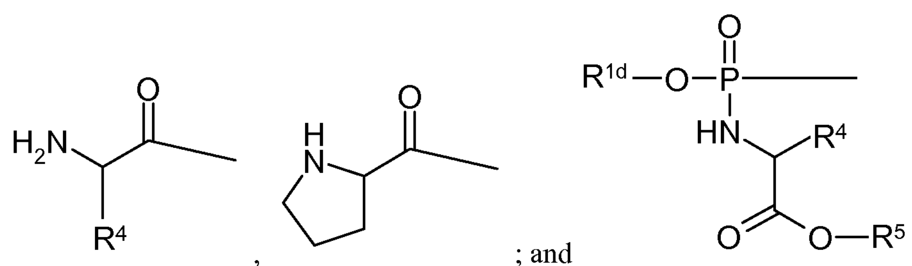
wherein R^{1d} is alkyl, aryl, or heteroaryl; R^4 is H, substituted or unstubstituted alkyl, or substituted or unsubstituted aryl; R^5 is H, or substituted or unstubstituted alkyl;

provided that at least one of R^{1a}, R^{1b}, and R^{1c} is other than H.

[00252] In one particular embodiment, with respect to the compound of formula I, the compound is according to formulae Va, Vb, or Vc:



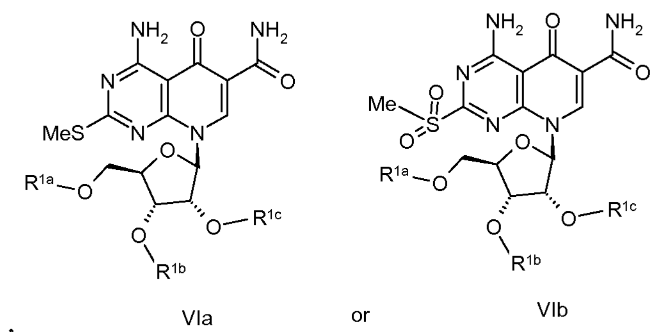
and wherein each R^{1a}, R^{1b}, and R^{1c} is independently selected from H,



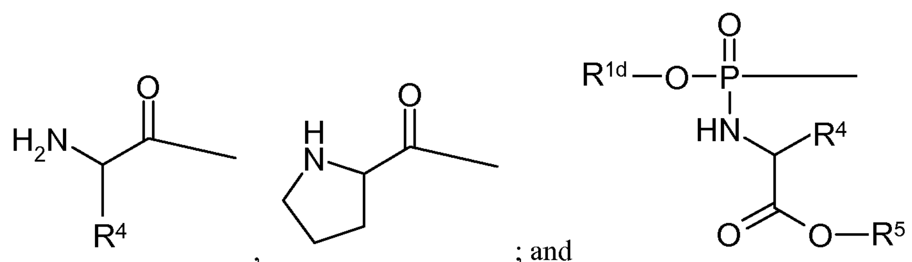
wherein R^{1d} is alkyl, aryl, or heteroaryl; R^4 is H, substituted or unstubstituted alkyl, or substituted or unsubstituted aryl; R^5 is H, or substituted or unstubstituted alkyl;

provided that at least one of R^{1a}, R^{1b}, and R^{1c} is other than H.

[00253] In one particular embodiment, with respect to the compound of formula I, the compound is according to formulae Via or VIb:



and wherein each R^{1a}, R^{1b}, and R^{1c} is independently selected from H,



wherein R^{1d} is alkyl, aryl, or heteroaryl; R^4 is H, substituted or unstubstituted alkyl, or substituted or unsubstituted aryl; R^5 is H, or substituted or unstubstituted alkyl;

provided that at least one of R^{1a}, R^{1b}, and R^{1c} is other than H.

[00254] A further aspect of invention provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a pharmaceutically effective amount of a compound of formulae I-VIb.

[00255] In one embodiment, with respect to the pharmaceutical composition, the carrier is a parenteral carrier.

[00256] In one embodiment, with respect to the pharmaceutical composition, the carrier is an oral carrier.

[00257] In one embodiment, with respect to the pharmaceutical composition, the carrier is a topical carrier.

[00258] Yet another aspect of the invention provides a method for treatment, prophylaxis, prevention or amelioration of conditions in a mammal, where inhibition of Akt and / or its pathways are indicated as the molecular target or cause of such conditions resulting in illness, disease, ailment etc. such as, but not limited to, cancer, macular degeneration, Huntington's disease, ataxia, HIV infection, diabetic retinopathy, diabetis mellitus, hypovolemia, septic shock, wound healing, ulcerative dermatitis, auto-immune disease, rheumatoid arthritis and other Akt-related conditions, which comprises administering to the mammal an effective disease-treating or condition-treating amount of a compound according to formula I-VIb or a pharmaceutical composition thereof.

[00259] In one embodiment, the disease or condition is an oncologic, neurologic, metabolic, dermatologic, immunologic, rheumatological, cardiovascular, respiratory disorders, musculo-skeletal, gastro-intestinal, nephrology, urologic, reproductive, ophthalmologic, otorhinolaryngology, hematological diseases and infectious diseases.

[00260] In one embodiment, the disease or condition is for example, cancer and/or tumor of the anus, bile duct, bladder, bone, bone marrow, bowel (including colon and rectum), breast, eye, gall bladder, kidney, mouth, larynx, esophagus, stomach, testis, cervix, head, neck, ovary, lung, mesothelioma, neuroendocrine, penis, skin, spinal cord, thyroid, vagina, vulva, uterus, liver, muscle, pancreas, prostate, blood cells (including lymphocytes and other immune system cells), or brain.

[00261] A further ascpect of the invention provides a method where inhibition of Akt and / or its pathways are indicated as molecular target or cause of such conditions resulting in illness, disease, ailment etc. such as, but not limited to, cancer, macular degeneration, Huntington's disease, ataxia, HIV infection, diabetic retinopathy, type I diabetis mellitus, hypovolemia, septic shock, wound healing disorders, ulcerative dermatitis, auto-immune disease, rheumatoid arthritis and other Akt-related conditions in any mammalian cell, said method comprising contacting the cell with an effective amount of a compound according to formula I-VIb or a pharmaceutical composition thereof.

[00262] In one embodiment, cell constitutively expresses an Akt protein or said cell expresses elevated, increased, amplified levels of an Akt protein be it natural, aberrant or mutant.

[00263] In another embodiment, the cell is a tumor or cancer cell.

[00264] In another embodiment, the cell is a mammalian (or human) cell.

[00265] A further ascpect of the invention provides a method of treating a disorder in a person or animal, wherein said disorder is associated with constitutive, abnormal, aberrant, mutant or elevated, increased, amplified or up-regulated expression of an Akt protein in a cell, said method comprising administering an effective amount of a compound according to formula I-VIb or a pharmaceutical composition thereof.

[00266] In one embodiment, the disorder is characterized by abnormal cell proliferation, cell survival, cell migration, cell invasion, cell metastasis, cell resistance and/or cell differentiation.

[00267] A further ascpect of the invention provides a compound according to formulae I-VIb or a pharmaceutical composition thereof.

[00268] A further ascpect of the invention provides a compound according to formulae I-VIb or a pharmaceutically acceptable salt or solvate thereof, for use as a pharmaceutical in the treatment or prevention of a disease or condition selected from: cancer and/or tumor of the anus, bile duct, bladder, bone, bone marrow, bowel (including colon and rectum), breast, eye, gall bladder, kidney, mouth, larynx, esophagus, stomach, testis, cervix, head, neck, ovary, lung, mesothelioma, neuroendocrine, penis, skin, spinal cord, thyroid, vagina, vulva, uterus, liver, muscle, pancreas, prostate, blood cells (including lymphocytes and other immune system cells), or brain.

[00269] A further ascpect of the invention provides a compound according to formulae I-VIb or a pharmaceutically acceptable salt or solvate thereof, to treat an oncological condition. In one embodiment, the disease or condition is cancer. In a particular embodiment the cancer is selected from: brain cancer (gliomas), glioblastomas, Bannayan-Zonana syndrome, Cowden disease, Lhermitte-Duclos disease, breast cancer, inflammatory breast cancer, Wilm's tumor, Ewing's sarcoma, Rhabdomyosarcoma, ependymoma, medulloblastoma, colon cancer, head and neck cancer, kidney cancer, lung cancer, liver cancer, melanoma, ovarian cancer, pancreatic cancer, prostate cancer, sarcoma, osteosarcoma, giant cell tumor of bone, thyroid cancer,Lymphoblastic T cell leukemia, Chronic myelogenous leukemia, Chronic lymphocytic leukemia, Hairy-cell leukemia, acute lymphoblastic leukemia, acute myelogenous leukemia, Chronic neutrophilic leukemia, Acute lymphoblastic T cell leukemia, Plasmacytoma, Immunoblastic large cell leukemia, Mantle cell leukemia, Multiple myeloma Megakaryoblastic leukemia, multiple myeloma, acute megakaryocyte leukemia, promyelocytic leukemia, Erythroleukemia,malignant lymphoma, hodgkins lymphoma, non-hodgkins lymphoma, lymphoblastic T cell lymphoma, Burkitt's lymphoma, follicular lymphoma, neuroblastoma, bladder cancer, urothelial cancer, vulval cancer, cervical cancer, endometrial cancer, renal cancer, mesothelioma, esophageal cancer, salivary gland cancer, hepatocellular cancer, gastric cancer, nasopharangeal cancer, buccal cancer, cancer of the mouth, GIST (gastrointestinal stromal tumor) and testicular cancer.

[00270] A further ascpect of the invention provides a compound according to formulae I-VIb or a pharmaceutically acceptable salt or solvate thereof, to treat viral infection. In one embodiment, the viral infection is due to HCV, HIV, or HCMV.

[00271] A further ascpect of the invention provides a compound according to formulae I-VIb or a pharmaceutically acceptable salt or solvate thereof, to treat conditions described herein and the route of

administration of the compound is enteral, parenteral, intravenous, intramuscular, oral, subcutaneous, topical, or intranasal.

[00272] A further ascpect of the invention provides a combination of compound according to formulae I-VIb or a pharmaceutically acceptable salt or solvate thereof and another pharmacologically active agent.

[00273] In one embodiment, the pharmacologically active agent is another anti-cancer agent.

[00274] In another embodiment, the pharmacologically active agent is altretamine, bleomycin, bortczomib (VELCADE), busulphan, calcium folinate, capecitabine, carboplatin, carmutstine, chlorambucil, cisplatin, cladribinc, crisantaspase, cyclophosphamide, cytarabine, dacarbazine, dactinomycin daunorubicin, docetaxel, doxorubicin, epirubicin, etoposide, fludarabine, fluorouracil, gefitinib (IRESSA), gemcitabine, hydroxyurea, idarubicin, ifosfamidc, imatinib (GLEEVEC), irinotecan, liposomal doxorubicin, lomistinie, melphalan, mercaptopunrine, methotrexate, titomycin, mitoxantrone, oxaliplatin, paclitaxel, pentostatin, procarbazine, raltitrexed, streptozocin, tegafur-uracil, temozolomide, thiotepa, tioguaninc/thioguanine, topotecan, treosulfan, vinblastine, vincricstine, vindesine, vinorclbine, melphalan, alcmtuzumab, cetuximab (ERBITUX), gemtuzumab, iodine 131 tositunmomab, rituximab, or trastuzamab (HERCEPTIN).

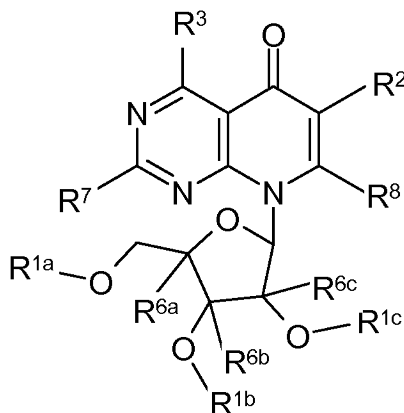
[00275] In another embodiment, the pharmacologically active agent is a mitotic inhibitor, an alkylating agent, an antimetabolite, a DNA intercalator, a topoisomerase inhibitor, an antiangiogenic agent, or an antiestrogen.

[00276] In yet another aspect, the invention provides pharmaceutical formulations comprising the novel pyrido[2,3-d]pyrimidine compounds. In particular, the invention relates to pharmaceutical formulations of 4-amino-8-[3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-5-oxopyrido[2,3-d]pyrimidine-6-carboxamide.

[00277]

[00278] In another aspect, the present invention provides a pharmaceutical formulation comprising

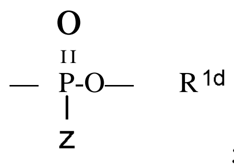
a) a compound according to formula I:



I

wherein

each R^{1a}, R^{1b}, and R^{1c} is independently selected from H, an amino acid, a dipeptide, a tripeptide, and



;

R^{1d} is alkyl, aryl, or heteroaryl; Z is an amino acid, a dipeptide, or a tripeptide;

each R^2 and R^3 is independently selected from H, hydroxy, amino, alkyl, alkoxy, and C(0)-NH $_2$;

each R^{6a}, R^{6b}, R^{6c}, and R^8 is independently selected from H, alkyl, or hydroxyalkyl; or the group –OR^{1b} is absent;

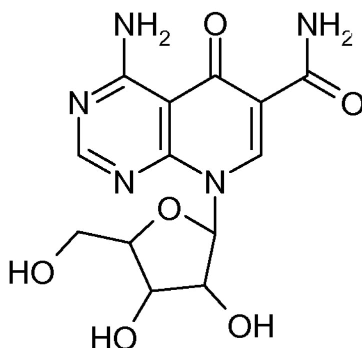
R^8 is selected from H, alkyl, hydroxy, alkoxy, or thioalkoxy;

or a pharmaceutically acceptable salt, solvate or prodrug thereof; and stereoisomers, isotopic variants and tautomers thereof; and

b) a pharmaceutically acceptable carrier.

[00279] In one embodiment, with respect to the pharmaceutical formulation of comprising compound of formula I, each of R^{1a}, R^{1b}, R^{1c}, R^{6a}, R^f , R^{6c}, R^7 and R^8 is H.

[00280] In one embodiment, with respect to the pharmaceutical formulation of comprising compound of formula I, the compound is according to formula III:



III

or a pharmaceutically acceptable salt, solvate or prodrug thereof; and stereoisomers, isotopic variants and tautomers thereof.

[00281] In one embodiment, with respect to the pharmaceutical formulation of comprising compound of formula I or III, the pharmaceutical carrier comprises a mixture of saline, phosphoric acid, and sodium hydroxide.

[00282] In one embodiment, with respect to the pharmaceutical formulation of comprising compound of formula I or III, the pharmaceutical carrier comprises a mixture of normal saline, 30% phosphoric acid, and 20% sodium hydroxide.

[00283] In one embodiment, with respect to the pharmaceutical formulation of comprising compound of formula I or III, the pharmaceutical carrier comprises a mixture of normal saline (0.9 vol), 30% phosphoric acid (0.1 vol), and 20% sodium hydroxide (0.025 vol).

[00284] In one embodiment, with respect to the pharmaceutical formulation of comprising compound of formula I or III, the pharmaceutical carrier comprises a mixture of normal saline (0.8 vol), 30% phosphoric acid (0.1 vol), and 20% sodium hydroxide (0.05 vol).

[00285] In one embodiment, with respect to the pharmaceutical formulation of comprising compound of formula I or III, the pharmaceutical carrier comprises a mixture of normal saline (3.8 vol), 30% phosphoric acid (0.1 vol), and 20% sodium hydroxide (0.025 vol).

[00286] In one embodiment, with respect to the pharmaceutical formulation of comprising compound of formula I or III, the pharmaceutical carrier comprises a mixture of water (9 vol), phosphoric acid (1 vol).

[00287] In one embodiment, with respect to the pharmaceutical formulation of comprising compound of formula I or III, the pharmaceutical carrier comprises a mixture of water (0.9 vol), Na_3P0_4 (0.9 vol), phosphoric acid (0.2 vol).

[00288] In one embodiment, with respect to the pharmaceutical formulation of comprising compound of formula I or III, the pharmaceutical carrier comprises a mixture of 45% HP-β-cyclodextrine, phosphoric acid, and sodium hydroxide.

[00289] In one embodiment, with respect to the pharmaceutical formulation of comprising compound of formula I or III, the pharmaceutical carrier comprises a mixture of 45% HP-β-cyclodextrine, 30% phosphoric acid, and 20% sodium hydroxide.

[00290] In one embodiment, with respect to the pharmaceutical formulation of comprising compound of formula I or III, the pharmaceutical carrier comprises a mixture of 45% HP-β-cyclodextrine (0.85 vol), 30% phosphoric acid (0.1 vol), and 20% sodium hydroxide (0.05 vol).

[00291] In one embodiment, with respect to the pharmaceutical formulation of comprising compound of formula I or III, the pharmaceutical carrier comprises a mixture of 45% HP-β-cyclodextrine (0.90 vol), 30% phosphoric acid (0.05 vol), and 20% sodium hydroxide (0.05 vol).

[00292] In one embodiment, with respect to the pharmaceutical formulation of compound of formula I or III, the pharmaceutical carrier comprises 20% to 40% Captisol®. In another embodiment, the pharmaceutical carrier comprises 20% Captisol®. In another embodiment, the pharmaceutical carrier comprises 30% Captisol®. In another embodiment, the pharmaceutical carrier comprises 40% Captisol®.

[00293] In one embodiment, with respect to the pharmaceutical formulation of compound of formula I or III, the pharmaceutical carrier comprises 20% to 40% Captisol® and normal saline.

[00294] Captisol®. In another embodiment, the pharmaceutical carrier comprises 40% Captisol®.

[00295] In one embodiment, with respect to the pharmaceutical formulation of compound of formula I or III, the pharmaceutical carrier comprises 20% to 40% Captisol® and sodium chloride vehicle.

[00296] Captisol®. In another embodiment, the pharmaceutical carrier comprises 40% Captisol®.

[00297] In one embodiment, with respect to the pharmaceutical formulation of compound of formula I or III, the pharmaceutical carrier comprises 20% to 40% Captisol® and 0.01-5% sodium chloride vehicle.

[00298] In one embodiment, with respect to the pharmaceutical formulation of compound of formula I or III, the pharmaceutical carrier comprises 20% to 40% Captisol® and about 1% sodium chloride vehicle. In a specific embodiment the sodium chloride concentration in the vehicle is 0.9%.

[00299] In one embodiment, with respect to the pharmaceutical formulation of compound of formula I or III, the concentration of the compound is 1-100 mg per mL of the carrier. In another embodiment, the concentration is 1-50 mg/mL. In yet another embodiment, the concentration is 1-20 mg/mL. In yet another embodiment, the concentration is 1-10 mg/mL. In yet another embodiment, the concentration is 5-10 mg/mL. In one specific embodiment, the concentration is 5 mg/mL. In another specific embodiment, the concentration is 10 mg/mL.

[00300] In one embodiment, with respect to the pharmaceutical formulation of comprising compound of formula I or III, the pharmaceutical carrier comprises a mixture of 40% Captisol®, 30% phosphoric acid, and 20% sodium hydroxide.

[00301] In one embodiment, with respect to the pharmaceutical formulation of comprising compound of formula I or III, the pharmaceutical carrier comprises a mixture of 40% Captisol® (1.75 vol), 30% phosphoric acid (0.1 vol), and 20% sodium hydroxide (0.15 vol).

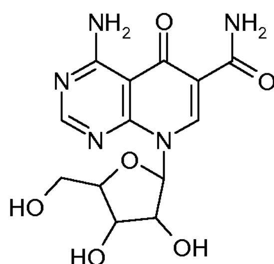
[00302] In one embodiment, with respect to the pharmaceutical formulation of comprising compound of formula I or III, the pharmaceutical carrier comprises a mixture of 30% Captisol®, and normal saline.

[00303] In one embodiment, with respect to the pharmaceutical formulation of comprising compound of formula I or III, the compound concentration varies from 1 mg to 50 mg per mL of the formulation.

[00304] In one embodiment, with respect to the pharmaceutical formulation of comprising compound of formula I or III, the pharmaceutical carrier is any one of carriers or solvents listed in Table 1-6.

[00305] In another aspect, the invention provides preparation of novel pyrido[2,3-d]pyrimidine compounds. In particular, the invention relates to manufacturing methods for preparation of 4-amino-8-[3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-5-oxopyrido[2,3-d]pyrimidine-6-carboxamide.

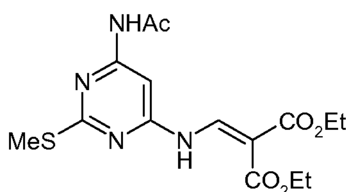
[00306] In another aspect, the present invention provides a process for preparing a compound according to formula III:



III ;

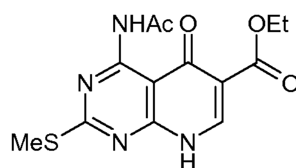
or a pharmaceutically acceptable salt, solvate, stereoisomer, polymorph or isotopic variant thereof comprising the steps of:

Al) heating diethyl 2-((6-acetamido-2-(methylthio)pyrimidin-4-ylamino)methylenemalonate of formula L2:



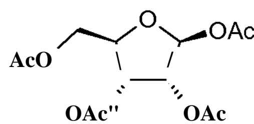
L2 ;

or an isomer thereof; to form the dihydropyrido[2,3-d]pyrimidine compound of formula L3:



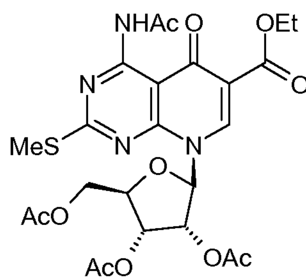
L3 ;

A2) reacting the dihydropyrido[2,3-d]pyrimidine compound of formula L3 with a ribofuranose compound of formula L3':



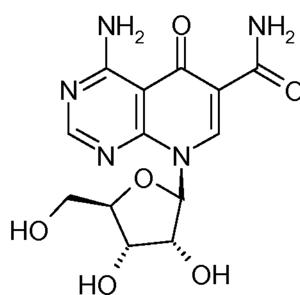
L3' ;

or an isomer thereof; to form the dihydropyrido[2,3-d]pyrimidine compound of formula L4:



L4 ; and

A3) deprotecting the dihydropyrido[2,3-d]pyrimidine compound of formula L4; and followed by reacting the intermediate deprotected compound with ammonia to form 4-amino-8-[3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-5-oxopyrido[2,3-d]pyrimidine-6-carboxamide or a compound of formula LD- 101:



LD-101 ;

or a pharmaceutically acceptable salt, solvate, stereoisomer, polymorph or isotopic variant thereof.

[00307] In one embodiment, with respect to the process for preparing the compound of formula III, the step Al) occurs in the presence of a heat transfer fluid. In one embodiment, the step Al) occurs in a high boiling solvent.

[00308] In one particular embodiment, with respect to the process for preparing the compound of formula III, the heat transfer fluid is Dowtherm A.

[00309] In one embodiment, with respect to the process for preparing the compound of formula III, the step Al) occurs at about 200 to about 300 °C, about 225 to about 275 °C, about 240 to about 260 °C, or about 240 to about 245 °C.

[00310] In one embodiment, with respect to the process for preparing the compound of formula III, the heating in the step Al) is carried out for about 0.25 to 3 hrs.

[00311] In one embodiment, with respect to the process for preparing the compound of formula III, the heating in the step Al) is carried out for about 2 hr or about 20 min.

[00312] In one embodiment, with respect to the process for preparing the compound of formula III, the step Al) further comprises a step of acetylation.

[00313] In one embodiment, with respect to the process for preparing the compound of formula III, the step Al) further comprises a step of heating the product with acetic anhydride. In another embodiment ther reaction can be carried out by heating the product with acetyl chloride.

[00314] In one embodiment, the heating is carried out for about 1 to about 2 hr.

[00315] In one embodiment, with respect to the process for preparing the compound of formula III, the step Al) further comprises a step of heating the product with acetic anhydride and the heating is carried out at about 100 to about 120 °C. In another embodiment, the heating is carried out at about 150 to about 250 °C. In particular embodiment, the heating is carried out at about 175 to about 225 °C. In a more particular embodiment, the heating is carried out at about 175 to about 200 °C. In a further particular embodiment, the heating is carried out at about 185 to about 195 °C.

[00316] In one embodiment, with respect to the process for preparing the compound of formula III, the step A2) occurs under reduced pressure.

[00317] In one embodiment, with respect to the process for preparing the compound of formula III, the step A2) occurs under 5-15. In a particular embodiment, the reaction occurs at 8-10 mbar of pressure.

[00318] In one embodiment, with respect to the process for preparing the compound of formula III, the step A2) is carried out for about 1-5 hrs.

[00319] In one embodiment, with respect to the process for preparing the compound of formula III, the step A2) is carried out for about 2-3 hrs.

[00320] In one embodiment, with respect to the process for preparing the compound of formula III, the deprotection in step A3) occurs in the presence of Raney Ni.

[00321] In one embodiment, with respect to the process for preparing the compound of formula III, the deprotection in step A3) occurs in a solvent selected from the group consisting of methanol, ethanol, or isopropyl alcohol. In one particular embodiment, the deprotection in step A3) occurs in EtOH.

[00322] In one embodiment, with respect to the process for preparing the compound of formula III, the deprotection in step A3) occurs at the reflux temperature of the solvent.

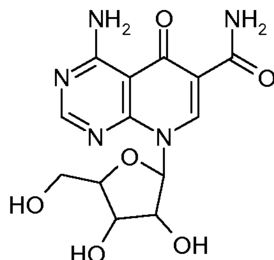
[00323] In one embodiment, with respect to the process for preparing the compound of formula III, the amidation in step A3) occurs in the presence of ammonia in methanol. In one particular embodiment, the amidation in step A3) occurs in the presence of 7M ammonia in methanol.

[00324] In one embodiment, with respect to the process for preparing the compound of formula III, the amidation in step A3) occurs for 10 to 30 hrs. In one particular embodiment, the amidation occurs for about 15 to about 25 hrs. In a more particular embodiment, the amidation occurs for about 15 to about 20 hrs.

[00325] In one embodiment, with respect to the process for preparing the compound of formula III, the amidation in step A3) further comprises a step of purification of the product like LD-101. In one embodiment, the purification is carried out by heating a suspension of the product in a mixture of methanol, water and DMF. In one particular embodiment, the suspension is heated to 40-60 or about 50 °C.

[00326] In one embodiment, with respect to the process for preparing the compound of formula III, the process is utilized to prepare any of the stereo isomers of the compound of formula III.

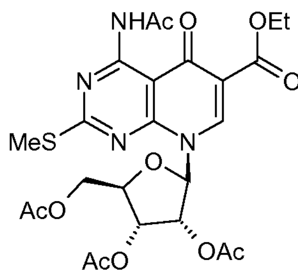
[00327] In another aspect, the present invention provides a process for preparing a compound according to formula III:



III ;

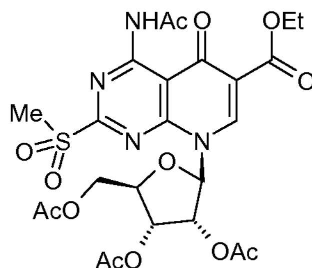
or a pharmaceutically acceptable salt, solvate, stereoisomer, polymorph or isotopic variant thereof comprising the steps of:

Bl) oxidizing the 2-methylthio dihydropyrido[2,3-d]pyrimidine compound of formula L4:



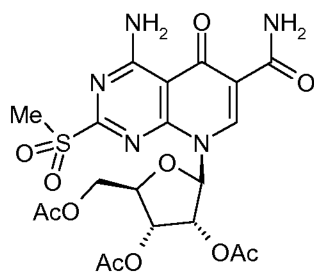
L4

to the corresponding methylsulfone compound L5:



L5

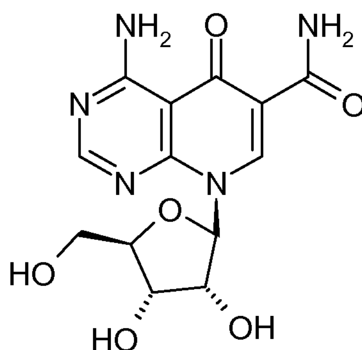
B2) converting the 2-methylsulfonyl dihydropyrido[2,3-d]pyrimidine compound of formula L5 to the carboxamide of formula L6:



;

or an isomer thereof;

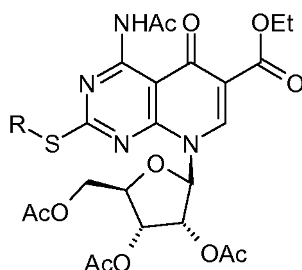
B3) reducing the carboxamide of formula L6 to form 4-amino-8-[3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-5-oxopyrido[2,3-d]pyrimidine-6-carboxamide or a compound of formula LD-101:



;

or a pharmaceutically acceptable salt, solvate, stereoisomer, polymorph or isotopic variant thereof.

[00328] In one embodiment, with respect to the process for preparing the compound of formula III, the starting methylthio compound of formula L4 may be substituted with the corresponding alkylthio compound. In one embodiment, the alkylthio compound may be ethylthio, or isopropylthio compound of formula L4':



L4', R = alkyl like Et, Me, i-Pr etc.

[00329] In one embodiment, with respect to the process for preparing the compound of formula III, the oxidation in step Bl) occurs in the presence of a conventional oxidation agent.

[00330] In one embodiment, with respect to the process for preparing the compound of formula III, the oxidation step Bl) occurs in the presence of

[00331] In one embodiment, with respect to the process for preparing the compound of formula III, the amidation in step B2) occurs in the presence of ammonia. In one particular embodiment, the amidation in step B2) occurs in the presence of ammonia in methanol.

[00332] In one embodiment, with respect to the process for preparing the compound of formula III, the amidation in step B2) occurs in the presence of 7M ammonia in methanol.

[00333] In one embodiment, with respect to the process for preparing the compound of formula III, the amidation in step B2) occurs for 10-30, 15-25, or 15-20 hrs.

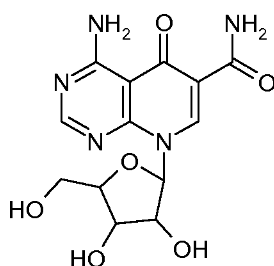
[00334] In one embodiment, with respect to the process for preparing the compound of formula III, the reduction in step B3) occurs in the presence of a borohydride reagent.

[00335] In one embodiment, with respect to the process for preparing the compound of formula III, the reduction in step B3) occurs in the presence of a sodium borohydride reagent.

[00336] In one embodiment, with respect to the process for preparing the compound of formula III, the reduction or the removal of the alkyl sulfone group in step B3) occurs in a solvent selected from the group consisting of methanol, ethanol, or isopropyl alcohol.

[00337] In one embodiment, with respect to the process for preparing the compound of formula III, the reduction in step B3) occurs in EtOH.

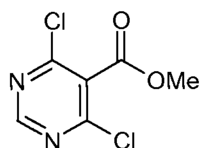
[00338] In another aspect, the present invention provides a process for preparing a compound according to formula III:



III ;

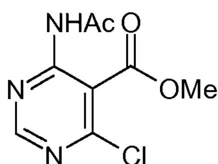
or a pharmaceutically acceptable salt, solvate, stereoisomer, polymorph or isotopic variant thereof comprising the steps of:

CI) converting the 4,6-dichloropyrimidine compound formula (1):



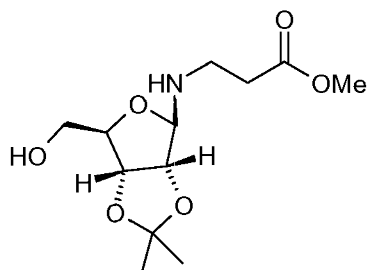
(1)

to the corresponding 4-amino-6-chloropyrimidine compound and then protecting the amino group to form the 4-acetylamino-6-chloropyrimidine compound of formula (2) :



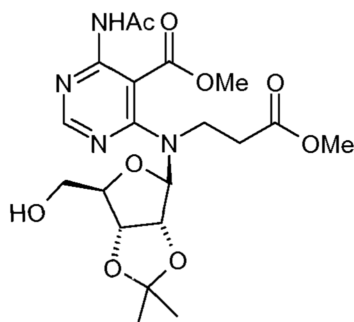
(2)

C2) reacting the 4-acetylamino-6-chloropyrimidine compound (2) with b-D-ribofuranosylamine (3)



(3)

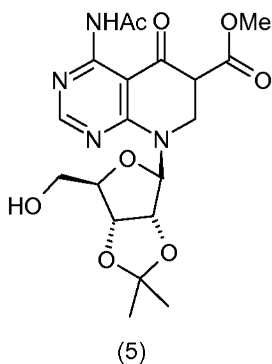
to form the coupled compound of formula (4):



(4) ;

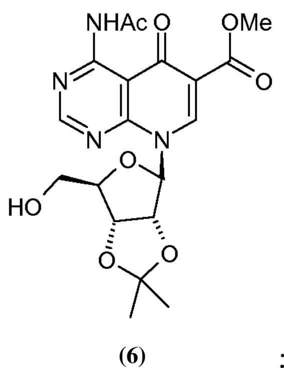
or an isomer thereof;

C3) cyclizing the compound of formula of (4) to form the tetrahydropyrido[2,3-d]pyrimidine of formula (5):



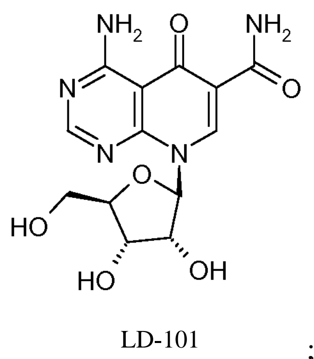
(5) ;

C4) converting the tetrahydropyrido[2,3-d]pyrimidine of formula (5) to form the dihydropyrido[2,3-d]pyrimidine of formula (6):



(6) ;

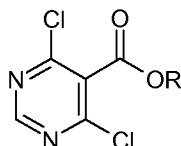
C5) converting the dihydro compound of formula (6) to 4-amino-8-[3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-5-oxopyrido[2,3-d]pyrimidine-6-carboxamide or a compound of formula LD-101:



LD-101 ;

or a pharmaceutically acceptable salt, solvate, stereoisomer, polymorph or isotopic variant thereof.

[00339] In one embodiment, with respect to the process for preparing the compound of formula III, the starting methyl ester compound of formula **(1)** may be substituted with the corresponding alkyl ester compound. In one embodiment, the alkyl ester compound may be methyl, ethyl, or isopropyl ester compound of formula **(1):**



(1), R = alkyl, like Me, Et, i-Pr etc.

[00340] In one embodiment, the starting material **(1)** may be the corresponding bromo-chloro or dibromo compound. For example, the starting material may be **4-6**-dibromopyrimidin-**5**-carboxylic acid alkyl ester.

[00341] In one embodiment, with respect to the process for preparing the compound of formula III, in step CI) the conversion of **4**-chloro to **4**-amino occurs in the presence of ammonia.

[00342] In one embodiment, with respect to the process for preparing the compound of formula III, in step CI) the conversion of **4**-chloro to **4**-amino occurs in the presence of ammonia in MeOH.

[00343] In one embodiment, with respect to the process for preparing the compound of formula III, in step CI) the protection of **4**-amino to **4**-acetylamino occurs in the presence of acetic anhydride.

[00344] In one embodiment, the **4**-amino group may be protected with any other conventional protecting group.

[00345] In one embodiment, with respect to the process for preparing the compound of formula III, the coupling in step C2) occurs in the presence of a base. In one embodiment, the reaction occurs in the presence of an amine.

[00346] In one embodiment, with respect to the process for preparing the compound of formula III, the coupling in step C2) occurs in the presence of trialkylamine.

[00347] In one embodiment, with respect to the process for preparing the compound of formula III, the coupling in step C2) occurs in the presence of di-i-propyl-ethylamine.

[00348] In one embodiment, with respect to the process for preparing the compound of formula III, the coupling in step C2) occurs in the presence of di-i-propyl-ethylamine and DMF.

[00349] In one embodiment, with respect to the process for preparing the compound of formula III, the cyclization in step C3) occurs in the presence of an alkoxide.

[00350] In one embodiment, with respect to the process for preparing the compound of formula III, the cyclization in step C3) occurs in the presence of sodium or potassium alkoxide.

[00351] In one embodiment, with respect to the process for preparing the compound of formula III, the cyclization in step C3) occurs in the presence of Na-O-t-Bu.

[00352] In one embodiment, with respect to the process for preparing the compound of formula III, the cyclization in step C3) occurs in an alcoholic solvent.

[00353] In one embodiment, with respect to the process for preparing the compound of formula III, the cyclization in step C3) occurs in a solvent selected from the group consisting of methanol, ethanol, or isopropyl alcohol.

[00354] In one embodiment, with respect to the process for preparing the compound of formula III, the cyclization in step C3) occurs in EtOH.

[00355] In one embodiment, with respect to the process for preparing the compound of formula III, the conversion in step C4) occurs in presence of bromine.

[00356] In one embodiment, with respect to the process for preparing the compound of formula III, the conversion in step C4) comprises bromination with bromine followed by elimination

[00357] In one embodiment, with respect to the process for preparing the compound of formula III, the conversion in step C4) comprises bromination with bromine followed by elimination in the presence of a base.

[00358] In one embodiment, with respect to the process for preparing the compound of formula III, the conversion in step C4) comprises bromination with bromine followed by elimination in the presence of trialkylamine.

[00359] In one embodiment, with respect to the process for preparing the compound of formula III, the conversion in step C4) comprises bromination with bromine followed by elimination in the presence of triethylamine.

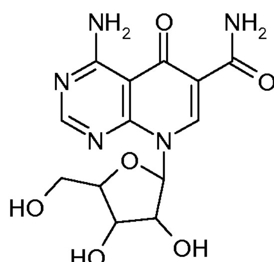
[00360] In one embodiment, with respect to the process for preparing the compound of formula III, the conversion in step C5) comprises amidation followed by the deprotection.

[00361] In one embodiment, with respect to the process for preparing the compound of formula III, the conversion in step C5) comprises amidation with ammonia in methanol followed by the deprotection.

[00362] In one embodiment, with respect to the process for preparing the compound of formula III, the deprotection occurs in the presence of an acid.

[00363] In one embodiment, with respect to the process for preparing the compound of formula III, the deprotection occurs in the presence of trifluoroacetic acid.

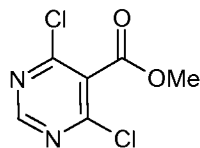
[00364] In another aspect, the present invention provides a process for preparing a compound according to formula III:



III ;

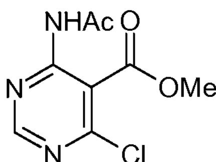
or a phannaceutically acceptable salt, solvate, stereoisomer, polymoiph or isotopic variant thereof comprising the steps of:

Dl) converting the 4,6-dichloropyrimidine compound formula (1):



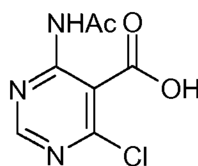
(1)

to the corresponding 4-amino-6-chloropyrimidine compound and then protecting the amino group to form the 4-acetylamino-6-chloropyrimidine compound of formula (2) :



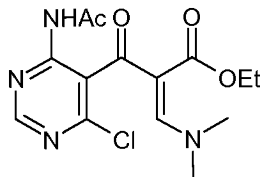
(2)

D2) hydrolyzing the methyl ester with a base to form the corresponding acid (3')



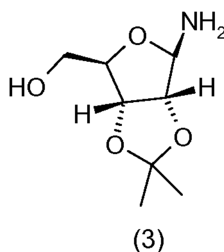
(3') ;

D3) coupling the acid (3) with Me_2N-CH=CH-C0 $_2$Et to form the intennediate 4-acetylamino-6-chloropyrimidine compound (3")



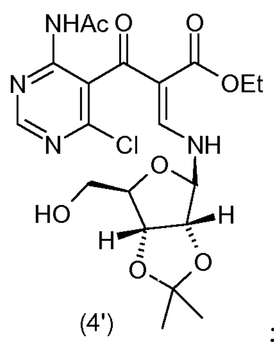
(3") ;

D4) reacting the 4-acetylamino-6-chloropyrimidine compound (3") with b-D-ribofuranosylamine (3)



(3)

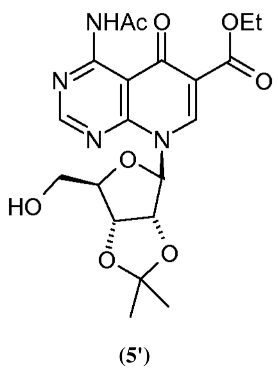
to form the coupled compound of formula (4'):



(4') ;

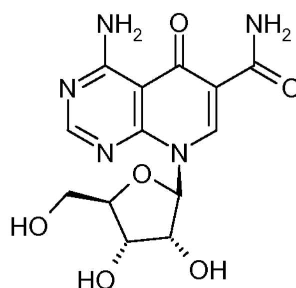
or an isomer thereof;

D5) cyclizing the compound of formula of (4') to form the tetrahydropyrido[2,3-d]pyrimidine of formula (5'):



(5') ;

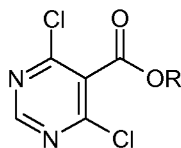
D6) converting the dihydro compound of formula (5') to 4-amino-8-[3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-5-oxopyrido[2,3-d]pyrimidine-6-carboxamide or a compound of formula LD- 10 1:



LD-101 ;

or a pharmaceutically acceptable salt, solvate, stereoisomer, polymorph or isotopic variant thereof.

[00365] In one embodiment, with respect to the process for preparing the compound of formula III, the starting methyl ester compound of formula (1) may be substituted with the corresponding alkyl ester compound. In one embodiment, the alkyl ester compound may be methyl, ethyl, or isopropyl ester compound of formula (1):



(1), R = alkyl, like Me, Et, i-Pretc.

[00366] In one embodiment, the starting material (1) may be the corresponding bromo-chloro or dibromo compound. For example, the starting material may be 4-6-dibromopyrimidin-5-carboxylic acid alkyl ester.

[00367] In one embodiment, with respect to the process for preparing the compound of formula III, in step Dl) the conversion of 4-chloro to 4-amino occurs in the presence of ammonia.

[00368] In one embodiment, with respect to the process for preparing the compound of formula III, in step Dl) the conversion of 4-chloro to 4-amino occurs in the presence of ammonia in MeOH.

[00369] In one embodiment, with respect to the process for preparing the compound of formula III, in step Dl) the protection of 4-amino to 4-acetylamino occurs in the presence of acetic anhydride or acetyl chloride. In one embodiment, the 4-amino group may be protected with any other conventional protecting group.

[00370] In one embodiment, with respect to the process for preparing the compound of formula III, in step D2) the hydrolysis of 5-ester to 5-acid occurs in the presence of a base.

[00371] In one embodiment, with respect to the process for preparing the compound of formula III, in step D2) the hydrolysis of 5-ester to 5-acid occurs in the presence of LiOH.

[00372] In one embodiment, with respect to the process for preparing the compound of formula III, in step D2) the hydrolysis of 5-ester to 5-acid occurs in a solvent.

[00373] In one embodiment, with respect to the process for preparing the compound of formula III, in step D2) the hydrolysis of 5-ester to 5-acid occurs in MeOH/THF.

[00374] In one embodiment, with respect to the process for preparing the compound of formula III, in step D3) the coupling comprises an initial formation of acid chloride.

[00375] In one embodiment, the acid chloride is formed by reacting the acid of formula (3') with thionyl chloride.

[00376] In one embodiment, the acid chloride is reacted with $Me_2N\text{-}CH{=}CH\text{-}C0_2Et$.

[00377] In one embodiment, the acid chloride is reacted with $Me_2N\text{-}CH{=}CH\text{-}C0_2Et$ in the presence of a solvent.

[00378] In one embodiment, with respect to the process for preparing the compound of formula III, in step D4, the reaction of compound of formula (3") with ribofuranosylamine (3) to form compound of formular (4').

[00379] In one embodiment, ribofuranosylamine is D- ribofuranosylamine.

[00380] In one embodiment, with respect to the process for preparing the compound of formula III, in step D5) the cyclization of compound of formular (4') occurs in the presence of a base to form compound of formular (5').

[00381] In one embodiment, with respect to the process for preparing the compound of formula III, in step D5) the cyclization occurs in the presence of K_2C0_3.

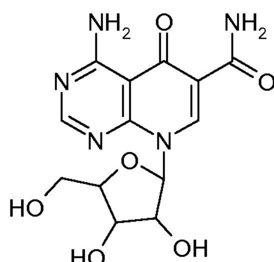
[00382] In one embodiment, with respect to the process for preparing the compound of formula III, the conversion in step D6) comprises amidation followed by the deprotection.

[00383] In one embodiment, with respect to the process for preparing the compound of formula III, the conversion in step D6) comprises amidation with ammonia in methanol followed by the deprotection.

[00384] In one embodiment, with respect to the process for preparing the compound of formula III, the deprotection occurs in the presence of an acid.

[00385] In one embodiment, with respect to the process for preparing the compound of formula III, the deprotection occurs in the presence of trifluoroacetic acid.

[00386] In another aspect, the present invention provides an analytical method useful to analyze a compound according to formula III:



III ;

or a pharmaceutically acceptable salt, solvate, stereoisomer, polymorph or isotopic variant thereof; comprising the steps of

El) preparing a sample of compound III;

E2) loading the sample on a HPLC column;

E3) eluting the HPLC column with a solvent system made of a buffer;

E5) processing the elute outcome with a detector; and

E6) obtain a chromatography trace.

[00387] In one embodiment, with respect to the analytical method, the sample is prepared by dissolving the compound of formula III in a solvent.

[00388] In one embodiment, with respect to the analytical method, the sample is prepared by dissolving the compound of formula III in a mixture of dilute HC1 and methanol.

[00389] In one embodiment, with respect to the analytical method, the sample is prepared by dissolving the compound of formula III in 10 mM HC1 and methanol (60:40).

[00390] In one embodiment, with respect to the analytical method, the sample is prepared by dissolving 0.5 to 1 mg of the compound of formula III in about 1 mL of HC1 (about 10 mM) and methanol (60:40) mixture.

[00391] In one embodiment, with respect to the analytical method, the HPLC column is a column stable over pH values of 2 t ol2.

[00392] In one embodiment, with respect to the analytical method, the HPLC column is a C18 column.

[00393] In one embodiment, with respect to the analytical method, the HPLC column is a Gemini-NX C18 column.

[00394] In one embodiment, with respect to the analytical method, the solvent buffer system comprises a gradient system of two components:

i) a mixture of dilute ammonium carbonate and dilute ammonium bicarbonate; and

ii) methanol.

[00395] In one embodiment, with respect to the analytical method, the solvent buffer system comprises a gradient system made of a mixture of dilute ammonium carbonate and dilute ammonium bicarbonate (1:1); and methanol.

[00396] In one embodiment, with respect to the analytical method, the solvent buffer system comprises a gradient system made of a mixture of dilute ammonium carbonate and dilute ammonium bicarbonate (1:1, 10 mM); and methanol.

[00397] In one embodiment, with respect to the analytical method, the HPLC column is eluted with the buffer system at a rate of about 1.2 mL/min.

[00398] In one embodiment, with respect to the analytical method, the detector is a UV detector.

[00399] In yet another aspect, the present invention provides a method for preventing, treating or ameliorating in a mammal a disease or condition associated with the elevated or constitutively active expression of an Akt protein, which comprises administering to the mammal an effective disease-treating

or condition-treating amount of a compound according to formula I-VIb or a pharmaceutical composition thereof in combination with radiation therapy.

[00400] In yet another aspect, the present invention provides, a method for preventing, treating or ameliorating in a mammal a disease or condition associated with the elevated or constitutively active expression of an Akt protein, which comprises administering to the mammal an effective disease-treating or condition-treating amount of a compound according to formula I-VIb or a pharmaceutical composition thereof in combination with a second pharmaceutical agent.

[00401] In one embodiment, with respect to the combination, the second pharmaceutical agent is selected from an estrogen receptor modulator, an androgen receptor modulator, a retinoid receptor modulator, a cytotoxiccytostatic agent, an antiproliferative agent, a prenyl-protein transferase inhibitor, an HMG-CoA reductase inhibitor, an HIV protease inhibitor, a reverse transcriptase inhibitor, an angiogenesis inhibitor, PPAR-γ agonists, PPAR-δ agonists, an inhibitor of inherent multidrug resistance, an anti-emetic agent, an agent useful in the treatment of anemia, an agent useful in the treatment of neutropenia, an immunologic-enhancing drug, an inhibitor of cell proliferation and survival signaling, and an agent that interferes with a cell cycle checkpoint.

[00402] In one embodiment, with respect to the combination, the second pharmaceutical agent is paclitaxel or trastuzumab.

[00403] In one embodiment, with respect to the combination, the second pharmaceutical agent is a COX-2 inhibitor.

[00404] In one embodiment, with respect to the combination, the disease or condition is an oncological disorder.

[00405] In one embodiment, with respect to the combination, the disease or condition is cancer and/or tumor of the anus, bile duct, bladder, bone, bone marrow, bowel (including colon and rectum), breast, eye, gall bladder, kidney, mouth, larynx, esophagus, stomach, testis, cervix, head, neck, ovary, lung, mesothelioma, neuroendocrine, penis, skin, spinal cord, thyroid, vagina, vulva, uterus, liver, muscle, pancreas, prostate, blood cells (including lymphocytes and other immune system cells), or brain.

[00406] In one embodiment, with respect to the combination, the disease or condition is cancer selected from: brain cancer (gliomas), glioblastomas, Bannayan-Zonana syndrome, Cowden disease, Lhermitte-Duclos disease, breast cancer, inflammatory breast cancer, Wilm's tumor, Ewing's sarcoma, Rhabdomyosarcoma, ependymoma, medulloblastoma, colon cancer, head and neck cancer, kidney cancer, lung cancer, liver cancer, melanoma, ovarian cancer, pancreatic cancer, prostate cancer, sarcoma, osteosarcoma, giant cell tumor of bone, thyroid cancer,Lymphoblastic T cell leukemia, Chronic myelogenous leukemia, Chronic lymphocytic leukemia, Hairy-cell leukemia, acute lymphoblastic leukemia, acute myelogenous leukemia, Chronic neutrophilic leukemia, Acute lymphoblastic T cell leukemia, Plasmacytoma, Immunoblastic large cell leukemia, Mantle cell leukemia, Multiple myeloma Megakaryoblastic leukemia, multiple myeloma, acute megakaryocyte leukemia, promyelocytic leukemia, Erythroleukemia,malignant lymphoma, hodgkins lymphoma, non-hodgkins lymphoma, lymphoblastic T cell lymphoma, Burkitt's lymphoma, follicular lymphoma, neuroblastoma, bladder cancer, urothelial cancer, vulval cancer, cervical cancer, endometrial cancer, renal cancer, mesothelioma, esophageal cancer,

salivary gland cancer, hepatocellular cancer, gastric cancer, nasopharangeal cancer, buccal cancer, cancer of the mouth, GIST (gastrointestinal stromal tumor) and testicular cancer.

[00407] In one embodiment, with respect to the combination, the disease or condition is a viral infection.

[00408] In one embodiment, with respect to the combination, the viral infection is due to HCV, HIV, or HCMV.

[00409] In yet another aspect, the present invention provides, a method for preventing, treating or ameliorating in a mammal a disease or condition associated with mantle cell lymphoma, which comprises administering to the mammal an effective disease-treating or condition-treating amount of a compound according to formula I-VIb or a pharmaceutical composition thereof in combination with a second pharmaceutical agent. In one embodiment the compound is LD-101 or compound according to formula III. In another embodiment, the second pharmaceutical agent is Velcade®.

[00410] In yet another aspect, the present invention provides, a method for preventing, treating or ameliorating in a mammal a disease or condition associated with multiple myeloma, which comprises administering to the mammal an effective disease-treating or condition-treating amount of a compound according to formula I-VIb or a pharmaceutical composition thereof in combination with a second pharmaceutical agent. In one embodiment the compound is LD-101 or compound according to formula III. In another embodiment, the second pharmaceutical agent is Velcade®.

[00411] In yet another aspect, the present invention provides, a method for preventing, treating or ameliorating in a mammal a disease or condition associated with prostate cancer, which comprises administering to the mammal an effective disease-treating or condition-treating amount of a compound according to formula I-VIb or a pharmaceutical composition thereof in combination with a second pharmaceutical agent. In one embodiment the compound is LD-101 or compound according to formula III. In another embodiment, the second pharmaceutical agent is Rapamycin.

[00412] In yet another aspect, the present invention provides, a method for preventing, treating or ameliorating in a mammal a disease or condition associated with breast cancer, which comprises administering to the mammal an effective disease-treating or condition-treating amount of a compound according to formula I-VIb or a pharmaceutical composition thereof in combination with a second pharmaceutical agent. In one embodiment the compound is LD-101 or compound according to formula III. In another embodiment, the second pharmaceutical agent is RAD00 1.

[00413] In yet another aspect, the present invention provides, a method for preventing, treating or ameliorating in a mammal a disease or condition associated with ovarian cancer, which comprises administering to the mammal an effective disease-treating or condition-treating amount of a compound according to formula I-VIb or a pharmaceutical composition thereof in combination with a second pharmaceutical agent. In one embodiment the compound is LD-101 or compound according to formula III. In another embodiment, the second pharmaceutical agent is Rapamycin.

[00414] In yet another aspect, the present invention provides, a method for preventing, treating or ameliorating in a mammal a disease or condition associated with resistant ovarian cancer (CI 3), which comprises administering to the mammal an effective disease-treating or condition-treating amount of a

compound according to formula I-VIb or a pharmaceutical composition thereof in combination with a second pharmaceutical agent. In one embodiment the compound is LD- 101 or compound according to formula III. In another embodiment, the second pharmaceutical agent is Cisplatin. In another embodiment, the second agent is CDDP. In a yet another embodiment, the second agent is Taxol®.

[00415] In yet another aspect, the present invention provides, a method for preventing, treating or ameliorating in a mammal a disease or condition associated with Tumor Growth in Lung Cancer Cell H661, which comprises administering to the mammal an effective disease-treating or condition-treating amount of a compound according to formula I-VIb or a pharmaceutical composition thereof in combination with a second pharmaceutical agent. In one embodiment the compound is LD- 101 or compound according to formula III. In another embodiment, the second pharmaceutical agent is CDDP. In another embodiment, the second agent is Etoposide. In a yet another embodiment, the second agent is Rapamycin.

[00416] Additional embodiments within the scope of the present invention are set forth in non-limiting fashion elsewhere herein and in the examples. It should be understood that these examples are for illustrative purposes only and are not to be construed as limiting this invention in any manner.

[00417] In certain aspects, the present invention provides prodrugs and derivatives of the compounds according to the formulae above. Prodrugs are derivatives of the compounds of the invention, which have metabolically cleavable groups and become by solvolysis or under physiological conditions the compounds of the invention, which are pharmaceutically active, *in vivo.* Such examples include, but are not limited to, choline ester derivatives and the like, N-alkylmorpholinyl esters and the like.

[00418] Certain compounds of this invention have activity in both their acid and acid derivative forms, but the acid sensitive form often offers advantages of solubility, tissue compatibility, or delayed release in the mammalian organism (see, Bundgard, H., Design of Prodrugs, pp. 7-9, 21-24, Elsevier, Amsterdam 1985). Prodrugs include acid derivatives well know to practitioners of the art, such as, for example, esters prepared by reaction of the parent acid with a suitable alcohol, or amides prepared by reaction of the parent acid compound with a substituted or unsubstituted amine, or acid anhydrides, or mixed anhydrides. Simple aliphatic or aromatic esters, amides and anhydrides derived from acidic groups pendant on the compounds of this invention are preferred prodrugs. In some cases it is desirable to prepare double ester type prodrugs such as (acyloxy)alkyl esters or ((alkoxycarbonyl)oxy)alkylesters. Preferred are the C_1 to C_8 or C_1-C_6alkyl, C_2-C_8 alkenyl, aryl, substituted aryl, and arylalkyl esters of the compounds of the invention.

PHARMACEUTICAL COMPOSITIONS

[00419] When employed as pharmaceuticals, the compounds of this invention are typically administered in the form of a pharmaceutical composition. Such compositions can be prepared in a manner well known in the pharmaceutical art and comprise at least one active compound. In certain embodiments, the pharmaceutical composition may comprise a compound of the invention in combination with one or more compounds or compositions of like therapeutic utility and effect.

[00420] Generally, the compounds of this invention are administered in a pharmaceutically effective amount. The amount of the compound actually administered will typically be determined by a physician, in the light of the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound administered, the age, weight, and response of the individual patient, the severity of the patient's symptoms, and the like.

[00421] The pharmaceutical compositions of this invention can be administered by a variety of routes including oral, sublingual, rectal, transdermal, subcutaneous, intravenous, intramuscular, intranasal and direct intra-tumoral injection. Depending on the intended route of delivery, the compounds of this invention are preferably formulated as either injectable or oral compositions or as salves, as lotions or as patches all for transdermal administration.

[00422] The compositions for oral administration can take the form of bulk liquid solutions or suspensions, or bulk powders. More commonly, however, the compositions are presented in unit dosage forms to facilitate accurate dosing. The term 'unit dosage forms' refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient. Typical unit dosage forms include prefilled, premeasured ampules or syringes of the liquid compositions or pills, gels, tablets, caplets, capsules or the like in the case of solid compositions. In such compositions, the furansulfonic acid compound is usually a minor component (from about 0.1 to about 50% by weight or preferably from about 1 to about 40% by weight) with the remainder being various vehicles or carriers and processing aids helpful for forming the desired dosing form.

[00423] Liquid forms suitable for oral administration may include a suitable aqueous or nonaqueous vehicle with buffers, suspending and dispensing agents, colorants, flavors and the like. Solid forms may include, for example, any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring.

[00424] Injectable compositions are typically based upon injectable sterile saline or phosphate-buffered saline or other injectable carriers known in the art. As before, the active compound in such compositions is typically a minor component, often being from about 0.05 to 10% by weight with the remainder being the injectable carrier and the like.

[00425] Transdermal compositions are typically formulated as a topical ointment or lotion or cream containing the active ingredient(s), generally in an amount ranging from about 0.01 to about 20% by weight, preferably from about 0.1 to about 20% by weight, preferably from about 0.1 to about 10% by weight, and more preferably from about 0.5 to about 15% by weight. When formulated as a ointment, the active ingredients will typically be combined with either a paraffmic or a water-miscible ointment base. Alternatively, the active ingredients may be formulated in a cream with, for example an oil-in-water cream base. Such transdermal formulations are well-known in the art and generally include additional

ingredients to enhance the dermal penetration of stability of the active ingredients or the formulation. All such known transdermal formulations and ingredients are included within the scope of this invention.

[00426] The compounds of this invention can also be administered by a transdermal device. Accordingly, transdermal administration can be accomplished using a patch either of the reservoir or porous membrane type, or of a solid matrix variety.

[00427] The above-described components for orally administrable, injectable or topically administrable compositions are merely representative. Other materials as well as processing techniques and the like are set forth in Part 8 of Remington's The Science and Practice of Pharmacy. 21st edition, 2005, Publisher: Lippincott Williams & Wilkins, which is incorporated herein by reference.

[00428] The compounds of this invention can also be administered in sustained release forms or from sustained release drug delivery systems. A description of representative sustained release materials can be found in Remington's Pharmaceutical Sciences.

[00429] The following formulation examples illustrate representative pharmaceutical compositions that may be prepared in accordance with this invention. The present invention, however, is not limited to the following pharmaceutical compositions.

Formulation 1 - Tablets

[00430] A compound of the invention may be admixed as a dry powder with a dry gelatin binder in an approximate 1:2 weight ratio. A minor amount of magnesium stearate is added as a lubricant. The mixture is formed into 240-270 mg tablets (80-90 mg of active compound per tablet) in a tablet press.

Formulation 2 - Capsules

[00431] A compound of the invention may be admixed as a dry powder with a starch diluent in an approximate 1:1 weight ratio. The mixture is filled into 250 mg capsules (125 mg of active compound per capsule).

Formulation 3 - Liquid

[00432] A compound of the invention (125 mg) may be admixed with sucrose (1.75 g) and xanthan gum (4 mg) and the resultant mixture may be blended, passed through a No. 10 mesh U.S. sieve, and then mixed with a previously made solution of microcrystalline cellulose and sodium carboxymethyl cellulose (11:89, 50 mg) in water. Sodium benzoate (10 mg), flavor, and color are diluted with water and added with stirring. Sufficient water may then be added to produce a total volume of 5 mL.

Formulation 4 - Caplets

[00433] A compound of the invention may be admixed as a dry powder with a dry gelatin binder in an approximate 1:2 weight ratio. A minor amount of magnesium stearate is added as a lubricant. The mixture is formed into 450-900 mg tablets (150-300 mg of active compound) in a tablet press.

Formulation 5 - Injection

[00434] A compound of the invention may be dissolved or suspended in a buffered sterile saline injectable aqueous medium to a concentration of approximately 5 mg/mL.

Formulation 6 - Topical

[00435] Stearyl alcohol (250 g) and a white petrolatum (250 g) may be melted at about 75°C and then a mixture of a compound of the invention (50 g) methylparaben (0.25 g), propylparaben (0.15 g),

sodium lauryl sulfate (10 g), and propylene glycol (120 g) dissolved in water (about 370 g) is added and the resulting mixture is stirred until it congeals.

Formulation and Solubility of Compound of Invention

[00436] The following examples describe various formulations prepared or can be prepared which are suitable for intravenous administration of compound of formula I.

[00437] The exemplary compound used in the following studies was LD-101, a compound of formula III.

REAGENTS & EXCIPIENTS

[00438] Table I lists the reagents and excipients used during LD-101 formulation development.

Table I. Reagents and Excipients

Reagent/ Excipient	Comments
Water	In house, Milli-Q System
85% Phosphoric Acid	Spectrum Chemicals
Citric Acid	Spectrum Chemicals
Boric Acid	Spectrum Chemicals
Sodium Bicarbonate	Spectrum Chemicals, EMD
Ascorbic Acid	Spectrum Chemicals, USP Grade
Glycine	JT Baker, USP Grade
L-(+)-Histidine	JT Baker
Tris (base)	JT Baker, ACS Reagent Grade
Sodium Chloride	Spectrum Chemicals, USP Grade
0.9% Sodium Chloride	Hospira, Ricca Chemicals
Hydrochloric Acid (2 N, 6 N)	VWR, JT Baker, EMD
Sodium Hydroxide (1 N, 6 N, 10 N)	VWR, Spectrum Chemicals, JT Baker
Diethanolamine	Spectrum Chemicals
Glacial Acetic Acid	Spectrum Chemicals, USP Grade
Poloxamer 188 (Lutrol F68)	BASF, NF Grade
Polyvinyl Pyrrolidone (Kollidon K12)	BASF, USP Grade
Polyvinyl Pyrrolidone (Kollidon K30)	BASF, USP Grade
Hydroxypropyl-β-Cyclodextrin (HPβCD)	Cargill
Sulfobutyl Ether Cyclodextrin (Captisol)	Cydex
Polysorbate 20	Spectrum, NF Grade
Polysorbate 80	Spectrum Chemicals, NF Grade
Solutol HS15	BASF
Ethanol	Spectrum Chemicals, USP Grade
Glycerin	Fisher Scientific, USP Grade
Polyethylene Glycol 300 (PEG300)	Spectrum Chemicals, NF Grade
Polyethylene Glycol 400 (PEG400)	Spectrum Chemicals, NF Grade
Propylene Glycol	Spectrum Chemicals
Dimethyl Acetamide (DMA)	Burdick & Jackson, HPLC Grade
N-Methyl-2-Pyrrolidone (NMP)	ISP Technologies
Benzyl Alcohol	EMD
2-Pyrrolidone (Soluphor P)	BASF
Albumin (from Bovine Serum)	Sigma Aldrich
Dimethylsulfoxide (DMSO)	Spectrum Chemicals

Solubility Screen Results

[00439] Table II lists LD-101 solubility screen results.

Table II. LD-101 Solubility Screen Results

Excipient	VAL-1674 Visual Solubility Range
Glacial Acetic Acid	21 – 23 mg/mL
5% Albumin (bovine) in Water	4 – 5 mg/mL
3% 2-Pyrrolidone in PEG400	< 16 mg/mL
6% 2-Pyrrolidone in PEG400	< 16 mg/mL
40% HPBCD in 9% Sodium Chloride[1]	= 5 mg/mL
40% HPBCD in Water[1]	< 5 mg/mL
9% Sodium Chloride[1]	< 5 mg/mL
40% HPBCD in 2% Sodium Chloride[1]	= 10 mg/mL
40% HPBCD in 0.9% Sodium Chloride[1]	7.5 mg/mL – 10 mg/mL[2]
40% Captisol in 2% Sodium Chloride[1]	7.5 mg/mL – 10 mg/mL[2]
40% Captisol in 0.9% Sodium Chloride[1]	7.5 mg/mL – 10 mg/mL[2]

[1] Performed on 2-mL scale, no pH adjustment

[2] At 10 mg/mL, VAL-1674 appears to dissolve on heating but precipitate forms on cooling

Formulation Screen Results

[00440] Table III lists LD-101 formulation screen results.

Table III. LD-101 Formulation Screen Results

Formulation Vehicle	[VAL-1674]	Comments / Observations
50% Glacial Acetic Acid in Water	5.3 mg/mL	• pH = 1.43 • approx. 2 days physical stability (visual)
25% Glacial Acetic Acid in Water	2.6 mg/mL	• pH = 1.93 • approx. 2 days physical stability (visual)
50% Glacial Acetic Acid, 0.1% Diethanolamine in Water	10.4 mg/mL	• pH = 1.83 • approx. 2 hours physical stability (visual)
50% Glacial Acetic Acid, 1% Diethanolamine in Water	4.9 mg/mL	• pH = 2.25 • approx. 1 day physical stability (visual)
20% Glacial Acetic Acid, 0.4% Diethanolamine in Water	5.1 mg/mL	• pH = 2.65 • approx. 2.5 hours physical stability (visual)
25% Glacial Acetic Acid, 0.375% Diethanolamine in Water	5.0 mg/mL	• pH = 2.49 • crystal formation after approx. 1 day[1]
25% Glacial Acetic Acid, 1.5% Diethanolamine in Water	5.1 mg/mL	• pH = 3.01 • crystal formation after approx. 1 day[1]
29% Polyvinyl Pyrrolidone K30, 20% Glacial Acetic Acid, 1% Diethanolamine in Water	5.0 mg/mL	• pH = 3.17 • approx. 5 hours physical stability (visual) • extremely viscous
30% Polyethylene Glycol 400, 18% Polyvinyl Pyrrolidone K30, 2% 2-Pyrrolidone in Water	5.0 mg/mL	• = 5 hours physical stability (visual)
40% HPβCD, 0.9% Sodium Chloride in Water[2]	5.1 mg/mL	• = 2.5 hours physical stability (visual) • = 3 days physical stability (visual)
40% HPβCD in 2% Sodium Chloride[2]	7.5 mg/mL	• = 1 day physical stability (visual)
40% HPβCD in 2% Sodium Chloride[2]	10.0 mg/mL	• = 1 day physical stability (visual)
40% HPβCD in 0.9% Sodium Chloride[2]	7.5 mg/mL	• = 1 day physical stability (visual)
40% Captisol in 2% Sodium Chloride[2]	7.5 mg/mL	• = 1 day physical stability (visual)
40% Captisol, 0.9% Sodium Chloride in Water[2]	5.2 mg/mL	• = 1 day physical stability (visual)
40% Captisol in 0.9% Sodium Chloride[2]	7.5 mg/mL	• = 1 day physical stability (visual)

[1] By visual comparison, crystal formation is more extensive in formulation containing 1.5% diethanolamine (pH 3.17) compared to formulation containing 0.375% diethanolamine (pH 2.49)

[2] No pH adjustment

FORMULATION STABILITY

[00441] Of the screened formulation matrices, 20%, 30%, and 40% Captisol in 0.9% Sodium Chloride were selected as the vehicles for LD-101 formulations.
Initially, formulations were prepared at 5 mg/mL and 7.5 mg/mL LD-101 on a 10-mL scale in 40% Captisol in 0.9% Sodium Chloride vehicle for stability storage at 5°C, 25°C, and 40°C, while a prototype formulation at 10 mg/mL LD-101 was prepared on a 5-mL scale for stability storage at 40°C (Part A). Based on solubility screening observations in which precipitation of 10 mg/mL LD-101 out of several cyclodextrin vehicles occurred during cooling, physical stability was assumed to be optimized at elevated temperatures. Visual observations were recorded over the course of 7 days, and LD-101 potency was analyzed at t = 0, t = 1 day, and t = 7 days.

[00442] Subsequently, additional formulations were prepared at 5 mg/mL LD-101 on a 10-mL scale in 20% and 30% Captisol in 0.9% Sodium Chloride vehicles for stability storage at 25°C and 40°C (Part B). Visual observations were recorded over the course of up to 24 hours.

Sections V.A through V.C describe the prototype formulation preparation methods and stability setup (Part A), the analytical methods, and the stability results (Part A), respectively. Sections V.D and V.E describe the prototype formulation preparation methods and stability setup (Part B), and the stability results (Part B), respectively. Section V.F provides a discussion of results.

A. Prototype Formulation Preparation & Stability Setup, Part A

The vehicle for all formulations, 40% (w/w) Captisol in 0.9% Aqueous Sodium Chloride, was prepared by dissolving 12.00 g of Captisol in 18.04 g of 0.9% aqueous sodium chloride (total formulation weight = 30.04 g).

[00443] Formulations were prepared by dissolving LD-101 (accurately weighed) in vehicle (delivered by Class A volumetric pipette). A heat gun was used (approx. temperature 50 - 80°C; approx. 2 - 5 minutes mixing time) while vortex-mixing each formulation until a clear solution was obtained. The 5 mg/mL and 7.5 mg/mL formulations were allowed to equilibrate to room temperature prior to filtering into a clean & dry, clear glass vial through a 0.2 μηι, 25 mm nylon syringe filter. The 10 mg/mL formulation was not allowed to cool before filtering into a clean & dry, clear glass vial through a 0.2 μηι, 25 mm nylon syringe filter. The actual weights and final concentrations are summarized in Table IV.

[00444] After removing approximately 0.5 mL for t = 0 analysis, formulations were transferred into clean & dry, clear glass vials and stored in environmental chambers set to 5°C/ ambient RH, 25°C/60%RH, and 40°C/75%RH as described in Table V. The 10 mg/mL formulation was not allowed to cool before storage at 40°C. Formulations were monitored on stability for 1 to 7 days (see Table V). (LD-101 is LD-101)

Table IV. Formulation Preparation, Part A

Target [VAL-1674], mg/mL	Actual Wt. VAL-1674, mg	Volume Vehicle, mL	[VAL-1674], mg/mL	Lot Number
5.0	49.9	10	5.0	1194-1-53-1
7.5	74.9	10	7.5	1194-1-54-1
10.0	49.7	5	9.9	1194-1-54-2

Table V. Stability Setup, Part A

Lot Number	Storage Conditions	Length of Stability Monitoring
1194-1-53-1	5°C/ ambient RH, 25°C/60%RH, 40°C/75%RH	7 days
1194-1-54-1	5°C/ ambient RH, 25°C/60%RH, 40°C/75%RH	7 days
1194-1-54-2	40°C/75%RH	1 day

B. Analytical Methods

[00445] The potency of prototype formulations was analyzed by spectrophotometry using a detection wavelength of 300 nm. A single-point calibration curve was generated from 30

µg/mL LD-101 standard solutions at each time point, while a standard agreement specification of 96 - 104% was applied to demonstrate system suitability. The standard and sample preparation procedures are described below.

[00446] Standard stock solutions were prepared by accurately weighing approximately 15 mg of LD-101 into a 10-mL volumetric flask, dissolving & diluting to volume in dimethylsulfoxide (DMSO), and mixing by repeated inversion. Working standard solutions were prepared by volumetrically transferring 1.0 mL of standard stock solution into a 50-mL volumetric flask, diluting to volume with DMSO, and mixing by repeated inversion. For each working calibration standard, a duplicate standard solution was prepared as a system suitability check.

[00447] At each time point, prototype formulations were removed from their respective storage conditions and allowed to equilibrate to room temperature prior to preparation for analysis.

[00448] After vortex-mixing, approximately 0.5 mL of each formulation was filtered through a 0.45 µηι, 4 mm nylon syringe filter, and 30 or 60 µL of filtrate was transferred into a tared volumetric flask as described in Table VI, for a final target concentration of approximately 30 µg/mL. Flasks were diluted to volume with DMSO and mixed by repeated inversion.

Table VI. Preparation of Formulation Samples for Analysis

Lot Number	Volume Transferred in Dilution, µL	Volumetric Flask Size, mL
1194-1-53-1	60	10
1194-1-54-1	40	10
1194-1-54-2	60	20

C. Prototype Stability Results, Part A

[00449] Tables VII and VIII summarize the visual observation and potency results for LD-101 prototype formulations on stability.

Table VII. LD-101 Prototype Formulation Stability Results, Part A: Visual Observations -

Lot Number	Target [VAL-1674], mg/mL	Storage Condition	Appearance								
			t = 0	t = 30 min	t = 1 hour	t = 3 hours	t = 5 hours	t = 19 hours	t = 1 day	t = 2 days	t = 7 days
1194-1-53-1	5.0	5¾	deaf	NT	NT	?vT	Ciea:	Clear	Clear	Clear	Ppt
		25°C		NT	NT	NT	Clear	Clear	Clear	CSear	Clear
		4S°C		NT	NT	NT	Clear	C-ear	dear	dear	Ppt
liS4-i-54-i	7.5	5*C	Clear	NT	NT	NT	Clear	Ppt	*Ppt.*	Ppt.	Ppt
		25•C		NT	NT	NT	Clear	Cisar	Sear	Ppt.	Ppt
		4S°C		NT	NT	NT	Clear	Clear	Clear	Ppt.	Ppt
1194-1-54-2	10.0	49¾	Clear	Clear	Clear	*Ppt.*	Ppt.	Ppt	Ppt	ST	XT

NT = Not Teste*; Ppt. = precipitate or crystals visible

Table VIII. LD-101 Prototype Formulation Stability Results, Part A : Potency

Lot Number	Target [VAL-1674], mg/mL	Storage Condition	[VAL-1674] Result, t = 0, mg/mL	VAL-1674 Potency Relative to t = 0	
				t = 1 day	t = 7 days
1194-1-53-1	5.0	5°C	5.0	99%	97%
		25°C		95%	97%
		40°C		103%	96%
1194-1-54-1	7.5	5°C	7.8	98%	Not Tested
		25°C		103%	Not Tested
		40°C		101%	Not Tested
1194-1-54-2	10.0	40°C	10.1	83%	Not Tested

Prototype Stability Setup, Part B

[00450] The 30% (w/w) Captisol in 0.9% Aqueous Sodium Chloride vehicle was prepared by dissolving approximately 3.6 g of Captisol in approximately 8.4 g of 0.9% aqueous sodium chloride (total formulation weight ~ 12.0 g). The 20% Captisol in 0.9% Aqueous Sodium Chloride vehicle was prepared by dissolving approximately 2.4 g of Captisol in approximately 9.6 g of aqueous sodium chloride (total formulation weight ~ 12.0 g).

Prototype formulations were prepared by dissolving LD-101 (accurately weighed) in vehicle (delivered by Class A volumetric pipette). A heat gun was used (approx. temperature 50 - 80°C; approx. 2 - 5 minutes mixing time) while vortex-mixing each formulation until a clear solution was obtained. Formulations were not allowed to cool before filtering into clean & dry, clear glass vials through a 0.2 μιη, 25 mm nylon syringe filters. The actual weights and final concentrations are summarized in Table IX. Formulations were stored in environmental chambers set to 25°C/60%RH and 40°C/75%RH as described in Table X, and monitored visually for up to 24 hours (see Table X).

Table IX. Prototype Formulation Preparation, Part B

Target [VAL-1674], mg/mL	Actual Wt. VAL-1674, mg	Vehicle Description	Volume Vehicle, mL	[VAL-1674], mg/mL	Lot Number
5.0	50.5	30% Captisol in 0.9% Sodium Chloride	10	5.1	1194-1-74-1
5.0	51.0	20% Captisol in 0.9% Sodium Chloride	10	5.1	1194-1-76-2

Table X. Stability Setup, Part B

Lot Number	Storage Conditions	Length of Stability Monitoring
1194-1-74-1	25°C/60%RH, 40°C/75%RH	24 hours
1194-1-76-2	25°C/60%RH, 40°C/75%RH	1.5 hours

E. Prototype Stability Results, Part B

[00451] Table XI summarizes the visual observation results for LD-101 prototypes on stability

Table XI. LD-101 Prototype Formulation Stability Results, Part B: Visual Observations

Lot Number	Target [VAL-1674], mg/mL	Storage Condition	Appearance					
			t = 0	t = 0.5 hours	t = 1 hour	t = 1.5 hours	t = 2 hours	t = 24 hours
1194-1-74-1	5.0	25°C	Clear	Clear	Clear	Clear	Clear	Clear
		40°C		Clear	Clear	Clear	Clear	Clear
1194-1-76-2	5.0	25°C	Clear	Ppt.	Ppt.	Ppt.	NT	NT
		40°C		Clear	Clear	Clear	Ppt.	NT

NT = Not Tested, Ppt- precipitate or crystals visible

[00452] The results from LD-101 stability evaluation (Part A) demonstrate that 10 mg/mL LD-101 formulations in 40% Captisol in 0.9% Sodium Chloride vehicle appear stable for up to 1 hour at 40°C, 7.5 mg/mL; LD-101 formulations in 40% Captisol in 0.9% Sodium Chloride vehicle appear stable for up to 1 day at 25°C, and 40°C, and 5 mg/mL; LD-101 formulations in 40% Captisol in 0.9% Sodium Chloride vehicle appear stable for up to 2 days at 5°C, 25°C, and 40°C. Results from LD- 101 stability evaluation (Part B) demonstrate that 5 mg/mL LD-101 formulations in 20% Captisol in 0.9% Sodium Chloride vehicle appear stable for less that 30 minutes at 25°C and up to 1.5 hours at 40°C, while 5 mg/mL LD-101 formulations in 30% Captisol in 0.9% Sodium Chloride vehicle appear stable for up to 24 hours at 25°C and 40°C. Compounding of 5 mg/mL LD-101 in 30% Captisol in 0.9% Sodium Chloride vehicle was performed on a 25-mL scale.

FORMULATION EXAMPLE 1

[00453] 20 mg/mL of Compound of Invention in NS; maintains clear solution at pH of 2.8 for 6 hours.

Contents:

20 mg of Compound of Invention in 1 mL (20 mg/mL)

- 90% NS : 10% Acid (v/v)
- 0.9 mL (900 uL) of NS:0.1 mL (100 uL) of H_3P0_4 + 25 microL ofNaOH = 1 mL

Solvents stock preparation:

i) NS = Normal Saline = 0.9% NaCl in sterile water

ii) 30% H_3PQ_4 = add 7.34 mL of water to 4 mL of 85% phosphoric acid = 7.94 mL of water in 11.34 mL ofsolution = 30% H_3PO_4

iii) 20% NaOH = 20 gm of NaOH pellets in 100 ml of water OR 5 gm in 25 mL

Procedure:

Step 1: Select a plain (transparent) glass bottle container that could contain at least 3 mL volume of liquid. Bottle must be clean and dry.

Step 2: Weigh between 20 to 20.5 mg of new batch of compound of invention in Step 1 container

Step 3: Add 0.1 mL of 30% H_3PQ_4 to Step 1 container

Step 4: Mix the contents by putting the bottle containing Steps 2 & 3 in an ultrasonic machine for two minutes to get a clear solution

Step 5: Add 0.1 mL of NS slowly

Step 6: Mix the contents by putting the bottle containing Steps 2 - 5 in an ultrasonic machine for one minute, maintains clear solution

Step 7: Add 0.75 mL of NS slowly, then physically shake gently to mix - maintains clear solution

Step 8: Add 0.025 mL (25 microL) of 20% NaOH - until it maintains clear solution.

FORMULATION EXAMPLE 2

[00454] 5 mg/mL of Compound of Invention; maintains clear solution at pH of 3.3 for 6 hours.

Contents:

- 20 mg of Compound of Invention in 4 mL (5 mg/mL)
- 98% NS : 2% acid (v/v)
- 3.80 mL (3800 uL) of NS:0.1 mL (100 uL) of H_3PO_4:0.025 mL (25 uL) of NaOH ~ 4 mL

Solvents stock preparation:

i) NS = Normal Saline = 0.9% NaCl in sterile water

ii) 30% H_3PQ_4 = add 7.34 mL of water to 4 mL of 85% phosphoric acid = 7.94 mL of water in 11.34 mL ofsolution = 30% H_3PO_4

iii) 5% NaOH = 5 gm of NaOH pellets in 100 ml of water OR 1.25 gm in 25 mL

Procedure:

Step 1: Select a plain (transparent) glass bottle container that could contain at least 3 mL volume of liquid. Bottle must be clean and dry.

Step 2: Weigh between 20 to 20.5 mg of new batch of compound of invention in Step 1 container

Step 3: Add 0.1 mL of **30% ¾ PC>4to** Step 1 container

Step 4: Mix the contents by putting the bottle containing Steps 2 & 3 in an ultrasonic machine for two minutes to get a clear solution

Step 5: Add 0.1 mL ofNS slowly

Step 6: Mix the contents by putting the bottle containing Steps 2 - 5 in an ultrasonic machine for one minute, maintains clear solution

Step 7: Add 3.8 mL of NS slowly, then physically shake gently to mix - maintains clear solution

Step 8: Add 0.025 mL (25 microL) of 5% NaOH - it maintains clear solution.

FORMULATION EXAMPLE 3

[00455] Formulation (20 mg/mL of Compound of Invention)

Content:

- 90% Water : 10% Phosphoric acid
- 1.8 mL Water : 0.2 mL Phosphoric acid (2 mL)
- 40 mg of Compound of Invention

Procedure:

Step 1: Select a plain (transparent) glass bottle container that could contain at least 3 mL volume of liquid. Bottle must be clean and dry.

Step 2: Weigh between 40 to 40.5 mg of compound of invention in Step 1 container

Step 3: Add 0.2 mL of 85% H_3P0_4

Step 4: Add 0.2 mL of H_20

Step 5: Mix the contents by putting the bottle containing Steps 2 - 4 in an ultrasonic machine for two minutes to get a clear solution OR (in the absence of ultrasonic mixing machine) go to Step 6

Step 6: Physically shake the bottle and its contents vigorously for two minutes until a clear solution is achieved

Step 7: Add 0.8 mL of H_20 , then physically shake gently to mix - maintains clear solution

Step 8: Add 0.8 mL of H_20 , then physically shake gently to mix - maintains clear solution

FORMULATION EXAMPLE 4

[00456] Formulation (10 mg/mL of Compound of Invention); pH = 5.11

Content:

- 45% Water : 45% Na_3P0_4 : 10% Phosphoric acid
- 0.9 mL Water : 0.9 mL Na_3P0_4 : 0.2 mL Phosphoric acid (2 mL)
- 20 mg of Compound of Invention

Procedure:

Step 1: Select a plain (transparent) glass bottle container that could contain at least 3 mL volume of liquid. Bottle must be clean and dry.

Step 2: Weigh between 20 to 20.5 mg of compound of invention in Step 1 container

Step 3: Add 0.2 mL of 85% H_3P0_4

Step 4: Add 0.2 mL of H_20

Step 5: Mix the contents by putting the bottle containing Steps 2 - 4 in an ultrasonic machine for two minutes to get a clear solution OR (in the absence of ultrasonic mixing machine) go to Step 6

Step 6: Physically shake the bottle and its contents vigorously for two minutes until a clear solution is achieved

Step 7: Add 0.7 mL of H_20, then physically shake gently to mix - maintains clear solution

Step 8: Add 0.9 mL of Na_3P0_4, then physically shake gently to mix - maintains clear solution

FORMULATION EXAMPLE 5

[00457] 10 mg/mL of LD-101 in CD; maintains clear solution at pH of 4.2 for 20 min

Content:

- 10mg ofLD-101 in 1 mL* = 10 mg/mL
- 85% (CD) : 10% (H_3P0_4) : 5% (NaOH) = (v/v)
- 0.8 mL CD (850 microL) : 0.05 mL (50 microL) NaOH : 0.1 mL (100 microL) H_3P0_4 = 1 mL*

Solvents stock preparation:

i) 45% HP-β-Cyclodextrine (CD) = 45 gm CD in 100 mL of water OR 11.25 gm in 25 mL

ii) 30% H_3PO_4 = add 7.34 mL of water to 4 mL of 85% phosphoric acid = 7.94 mL of water in 11.34 mL ofsolution = 30% H_3PO_4

iii) 20% NaOH = 20 gm of NaOH pellets in 100 ml of water OR 5 gm in 25 mL

Procedure:

Step 1: Select a plain (transparent) glass bottle container that could contain at least 3 mL volume of liquid. Bottle must be clean and dry.

Step 2: Weigh between 10 to 10.5 mg of LD-101 in Step 1 container

Step 3: Add 0.1 mL (100 microL) of 30% H_3P0_4

Step 4: Mix the contents by putting the bottle containing Steps 2 & 3 in an ultrasonic machine for two minutes to get a clear solution

Step 5: Add 0.85 mL (850 microL) of 45% HP-β-CD

Step 6: Mix the contents by putting the bottle containing Steps 2 - 5 in an ultrasonic machine for one hour (this will get all LD-101 into CD pockets); still maintains clear solution

Step 7: Add 0.05 mL (50 μL) of 20% NaOH, shake gently to mix - maintains clear solution

FORMULATION EXAMPLE 6

[00458] 20 mg/mL of Compound of Invention in CD; maintains clear solution at pH of 4.2 for 15 min

Content:

- 20 mg of Compound of Invention in 1 mL = 20 mg/mL
- 90% (CD):5% (NaOH):5% (H_3P0_4) = (v/v)

- 0.90 mL CD (900 microL):0.05 mL (50 micoL) H_3PO_4:0.05 mL (50 microL) NaOH = 1 mL

Solvents stock preparation:

iv) 45% HP-β-Cyclodextrine (CD) = 45 gm CD in 100 mL of water OR 11.25 gm in 25 mL

v) 85% H_3PO_4 = commercially available in that concentration

vi) 20% NaOH = 20 gm of NaOH pellets in 100 ml of water OR 5 gm in 25 mL

Procedure:

Step 1: Select a plain (transparent) glass bottle container that could contain at least 3 mL volume of liquid. Bottle must be clean and dry.

Step 2: Weigh between 20 to 20.5 mg of compound of invention in Step 1 container

Step 3: Add 0.05 mL (50 microL) of 85% H_3PO_4

Step 4: Add 0.2 mL (200 microL) of 45% HP-β-CD

Step 5: Mix the contents by putting the bottle containing Steps 2 - 4 in an ultrasonic machine for two minutes to get a clear solution

Step 6: Add 0.7 mL (700 microL) of 45% HP-β-CD

Step 7: Mix the contents by putting the bottle containing Steps 2 - 5 in an ultrasonic machine for one hour (this will get all compound of invention into CD pockets); still maintains clear solution

Step 8: Add 0.05 mL (50 microL) of 20% NaOH, shake gently to mix - maintains clear solution

FORMULATION EXAMPLE 7

[00459] 10 mg/mL of Compound of Invention in Captisol®; maintains clear solution at pH of 3.91 for 4 hrs

Contents:

- 20 mg of Compound of Invention in 2 mL = 10 mg/mL
- 87.5% (40% Captisol®) : 7.5% (20% NaOH) : 5% (30% H_3PO_4) = (v/v)
- 1.750 mL (1750 microL) Captisol® : 0.15 mL (150 microL) NaOH : 0.1 mL (100 microL) H_3PO_4 = 2 mL

Solvents stock preparation:

i) 40% Captisol® = 400 mg Captisol® (Cydex brand) in 1 mL of water OR 800 mg in 2 mL

ii) 30% H3PO4 = add 7.34 mL of water to 4 mL of 85% phosphoric acid = 7.94 mL of water in 11.34 mL ofsolution = 30% H_3PO_4

iii) 20% NaOH = 20 gm of NaOH pellets in 100 ml of water OR 5 gm in 25 mL

Procedure:

Step 1: Select a plain (transparent) glass bottle container that could contain at least 3 mL volume of liquid. Bottle must be clean and dry.

Step 2: Weigh between 20 to 20.5 mg of compound of invention in Step 1 container

Step 3: Add 0.1 mL (100 microL) of 30% H_3PO_4

Step 4: Add 0.2 mL (200 microL) of 40% Captisol®

Step 5: Mix the contents by putting the bottle containing Steps 2, 3 and 4 in an ultrasonic machine for two minutes to get a clear solution

Step 6: Add 1.55 mL (1550 microL) of 40% Captisol® - maintains clear solution.

Step 7: Put in an ultrasonic machine for as long as possible but minimum of one hour (this will get all compound of invention into Captisol' s pockets) - maintains clear solution for 24 hours. Now prepare animals.

Step 8: Add 0.15 mL (150 µL) of 20% NaOH, mix gently - maintains clear solution at pH of 3.9 1 for 4 hours.

FORMULATION EXAMPLE 8

[00460] 20 mg/mL of Compound of Invention in Captisol®; maintains clear solution at pH of 3.90 for 6 hrs

Contents:

- 40 mg of Compound of Invention in 2 mL = 20 mg/mL
- 87.5% (40% Captisol®) : 7.5% (20% NaOH) : 5% (30% H_3P0_4) = (v/v)
- 1.750 mL Captisol® (1750 microL) : 0.15 mL (150 microL) NaOH : 0.1 mL (100 microL) H_3P0_4 = 2 mL

Solvents stock preparation:

iv) 40% Captisol® = 400 mg Captisol® (Cydex brand) in 1 mL of water OR 800 mg in 2 mL

v) 30% H_3PO_4 = add 7.34 mL of water to 4 mL of 85% phosphoric acid = 7.94 mL of water in 11.34 mL ofsolution = 30% H_3PO_4

vi) 20% NaOH = 20 gm of NaOH pellets in 100 ml of water OR 5 gm in 25 mL

Procedure:

Step 1: Select a plain (transparent) glass bottle container that could contain at least 3 mL volume of liquid. Bottle must be clean and dry.

Step 2: Weigh between 40 to 4 1 mg of compound of invention in Step 1 container

Step 3: Add 0.1 mL (100 microL) of 30% H_3P0_4

Step 4: Add 0.2 mL (200 microL) of 40% Captisol®

Step 5: Mix the contents by putting the bottle containing Steps 2, 3 and 4 in an ultrasonic machine for two minutes to get a clear solution

Step 6: Add 1.55 mL (1550 microL) of 40% Captisol® - maintains clear solution.

Step 7: Put in an ultrasonic machine for as long as possible but minimum of two hours (this will get all compound of invention into Captisol's pockets) - maintains clear solution for 24 hours. Now prepare animals.

Step 8: Add 0.15 mL (150 µL) of 20% NaOH, mix gently - maintains clear solution at pH of 3.90 for 6 hours.

FORMULATION EXAMPLE 9

[00461] 5 mg/mL of Compound of Invention in 30% Captisol®; maintains clear solution at RT for 24 Hours

Contents:

10 mg of Compound of Invention in 2 mL of 0.9% NS containing 30% Captisol®

pH SOLUBILITY PROFILE

[00462] The exemplary compound used in the following studies was LD- 101, a compound of formula III.

[00463] The pH solubility profile was determined by adding each buffer solution incrementally to active pharmaceutical ingredient (API), targeting a concentration range of 1 to 10 mg/mL. Vortex-mixing and sonication in warm water were used to dissolve, and visual observations were used to determine solubility range. The results are provided in Table 1.

[00464] Table 1. pH Solubility Profile

Buffer Solution	Visual Solubility Range
50 mM Phosphoric Acid, pH 1	1.1 – 1.3 mg/mL
50 mM Phosphoric Acid, pH 2	< 1.4 mg/mL
50 mM Citric Acid, pH 3	< 1.0 mg/mL
50 mM Citric Acid, pH 4	< 1.2 mg/mL
50 mM Citric Acid, pH 5	< 0.9 mg/mL
50 mM Citric Acid, pH 6	< 1.0 mg/mL
50 mM Phosphoric Acid, pH 7	< 0.9 mg/mL
50 mM Phosphoric Acid, pH 8	< 0.8 mg/mL
50 mM Boric Acid, pH 9	3.0 – 4.5 mg/mL

SOLUBILITY OF EXEMPLARY COMPOUND OF INVENTION IN ORGANIC SOLVENTS, COMPLEXING AGENTS, AND AQUEOUS SURFACTANTS

[00465] The exemplary compound used in the following studies was LD- 101, a compound of formula III.

[00466] The solubility in various organic solvents, complexing agents, and aqueous surfactants was determined by adding each excipient incrementally to active pharmaceutical ingredient, targeting a concentration range of 1 to 100 mg/mL. Vortex-mixing, sonication, and heating were used to dissolve, and visual observations were used to determine solubility range. The results are provided in Table 2.

[00467] Table 2. Solubility Screen Results

Excipient	Visual Solubility Range

Excipient	Visual Solubility Range
Ethanol	< 1.1 mg/mL
Glycerin	< 0.8 mg/mL
Polyethylene Glycol 300	< 1.0 mg/mL
Polyethylene Glycol 400	< 1.4 mg/mL
Propylene Glycol	< 0.8 mg/mL
Dimethylacetamide	12 - 29 mg/mL
N-methyl Pyrrolidone	42 - 52 mg/mL
Benzyl Alcohol	< 1.2 mg/mL
40% Hydroxypropyl -P-cyclodextrin (aq.)	< 1.3 mg/mL
20% Hydroxypropyl -P-cyclodextrin (aq.)	5.5 - 7.0 mg/mL [1]
1% Poloxamer 188 (aq.)	< 1.2 mg/mL
1% Polyvinyl Pyrrolidone K12 (aq.)	< 0.8 mg/mL
1% Polyvinyl Pyrrolidone K30 (aq.)	< 1.2 mg/mL
100 mM Tris, pH 9 (aq.)	< 0.9 mg/mL
100 mM Tris, pH 10.5 (aq.)	< 1.2 mg/mL

Process requires pH modification

[00468] The solubility in various organic solvents, complexing agents, and aqueous surfactants was determined by adding each excipient incrementally to active pharmaceutical ingredient, targeting a concentration range of 1 to 100 mg/mL. Vortex-mixing, sonication but without heating to dissolve. Visual observations were used to determine solubility range. The results are provided in Tables 3-6.

[00469] **Table 3. Solubility Screen Results (without heating)**

S/N	Vehicle	Result
1	H_2O	Suspension
2	Normal Saline (NS)	Suspension
3	pH 3.5 Citrate buffer	Suspension
4	20% Captisol	Suspension
5	10% DMAC+90%(45% HP-β-Cyclodextrine)	Hazy
6	H_2O:45% β-CD (v/v)	Milky
7	10% NMP+90% PEG 200	Hazy
8	DMAc:PEG 400:H_20 (1:2:2) v/v	Clear @ 5mg/mL Hazy @ 10 mg/mL
9	20% Ethanol+20% PEG 400	Suspension

10	Hydrochloric Acid	Clear but pH = 1
11	Acetic Acid:NS (v/v)	Hazy
12	Trifluoroacetic acid:NS (v/v)	Clear but pH = 1
13	5%(70% H_3PO_4) + 95% Normal Saline	Clear but pH = 2.8
14	5%(70% H_3PO_4) :50% NS:45% Buffer* *Buffer = PBS, phosphate, bicarbonate, citrate	Hazy at pH 4
15	Citric acid 1M	Clear Solution - pH ~ 1

[00470] Table 4. Solubility Screen Results

Entry	Weight (mg)	Solvent composition (ml)	Observation	Observation after 15 h	note
1	5.6	TFA 0.25 + water 0.25	clear	clear	
2	5.0	1M HCl 0.5	clear	Some solid	
3	5.0	pH 1 HCl 0.5	solid	-	
4	4.9	Acetic acid 0.25 + water 0.25	milky	solid	
5	5.3	10% K2CO3 0.5	solid	-	
6	4.9	Acetone 0.5	milky	solid	
7	61	methanol	solid	-	
8	5.3	85% Phos. Acid 0.25 + water 0.25	clear	clear	
9	5.3	Ethylene glycol	solid	-	

[00471] Table 5. Solubility Screen Results

Entry	Weight (mg)	Solvent composition (ml)	Observation	Observation after 15 h	note
A1	12.2	DMSO 0.2 + water 0.8	milky	solid	
A2	10.2	DMSO 0.2 + water 0.1	solid	-	
A3	9.7	Phos. Acid 0.3 +water 0.6	clear	clear	
A4	9.4	Phos. Acid 0.25 +water 1.5	clear		
A5	21.3	Phos. Acid 0.2 +water 1.8 (1:9)	clear	clear	
A6	21.4	Phos. Acid 0.2 +water 0.6 +NaHCO3 to pH = 0.8	Clear solid	solid	
A7	21.4	Phos. Acid 0.1+water 1.9 (1:19)	clear	solid	
A8	40.6	Phos. Acid 0.1+water 1.9 (20mg/ml)	clear	solid	

[00472] Table 6. Solubility Screen Results

Entry	Weight (mg)	Solvent composition (ml)	Observation	Observation after 15 h	note
B1	25.9	Phos. Acid 0.1 + water 1.9	Clear (5 minutes)		
B2	42.8	Phos. Acid 0.133 + water 1.87	clear	-	
B3	21.5	Phos. Acid 0.3 +water 0.6	clear	clear	
B4	20.4	Phos. Acid 0.1 +water 1.9	clear	Few solid	
B5	3.2	5.8mg beta-CD + water 0.6	solid		

[00473] Included in the instant invention is the free form of compounds of Formula I, as well as the pharmaceutically acceptable salts and stereoisomers thereof. Some of the isolated specific compounds exemplified herein are the protonated salts of amine compounds. The term 'free form' refers to the amine compounds in non-salt form. The encompassed pharmaceutically acceptable salts not only include the isolated salts exemplified for the specific compounds described herein, but also all the typical pharmaceutically acceptable salts of the free form of compounds of Formula I. The free form of the specific salt compounds described may be isolated using techniques known in the art. For example, the free form may be regenerated by treating the salt with a suitable dilute aqueous base solution such as dilute aqueous NaOH, potassium carbonate, ammonia and sodium bicarbonate. The free forms may differ from their respective salt forms somewhat in certain physical properties, such as solubility in polar solvents, but the acid and base salts are otherwise pharmaceutically equivalent to their respective free forms for purposes of the invention.

[00474] The pharmaceutically acceptable salts of the instant compounds can be synthesized from the compounds of this invention which contain a basic or acidic moiety by conventional chemical methods. Generally, the salts of the basic compounds are prepared either by ion exchange chromatography or by reacting the free base with stoichiometric amounts or with an excess of the desired salt-forming inorganic or organic acid in a suitable solvent or various combinations of solvents. Similarly, the salts of the acidic compounds are formed by reactions with the appropriate inorganic or organic base.

[00475] Thus, pharmaceutically acceptable salts of the compounds of this invention include the conventional non-toxic salts of the compounds of this invention as formed by reacting a basic instant compound with an inorganic or organic acid. For example, conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like, as well as salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxy-benzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, trifluoroacetic (TFA) and the like.

[00476] When the compound of the present invention is acidic, suitable 'pharmaceutically acceptable salts' refers to salts prepared form pharmaceutically acceptable non-toxic bases including inorganic bases and organic bases. Salts derived from inorganic bases include aluminum, ammonium, calcium, copper,

ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc and the like. Particularly preferred are the ammonium, calcium, magnesium, potassium and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary and tertiary amines, substituted amities including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as arginine, betaine caffeine, choline, N,N'-dibenzylethylenediamine, diethylamin, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine tripropylamine, tromethamine and the like.

[00477] The preparation of the pharmaceutically acceptable salts described above and other typical pharmaceutically acceptable salts is more fully described by Berg et al., "Pharmaceutical Salts," J. Pharm. Sci., 1977:66:1-19.

[00478] It will also be noted that the compounds of the present invention are potentially internal salts or zwitterions, since under physiological conditions a deprotonated acidic moiety in the compound, such as a carboxyl group, may be anionic, and this electronic charge might then be balanced off internally against the cationic charge of a protonated or alkylated basic moiety, such as a quaternary nitrogen atom.

METHODS OF TREATMENT AND UTILITY

[00479] The compounds of the instant invention are inhibitors of the activities of Akt and are thus useful in the treatment of cancer, in particular cancers associated with irregularities in the activity of Akt and its downstream molecular targets and cellular effectors. Such cancers include, but are not limited to, ovarian, pancreatic, breast and prostate cancer, as well as cancers (including glioblastoma) where the tumor suppressor PTEN is mutated (Cheng et al., Proc. Natl. Acad. Sci. (1992) 89:9267-9271; Cheng et al., Proc. Natl. Acad. Sci. (1996) 93:3636-3641; Bellacosa et al., Int. J. Cancer (1995) 64:280-285; Nakatani et al., J. Biol. Chem. (1999) 274:21528-21532; Graff, Expert. Opin. Ther. Targets (2002) 6(1): 103-1 13; and Yamada andAraki, J. Cell Science. (2001) 114:2375-2382; Mischel and Cloughesy, Brain Pathol. (2003) 13(1):52-61).

[00480] The compounds, compositions and methods provided herein are particularly deemed useful for the treatment of cancer including solid tumors such as skin, breast, brain, cervical carcinomas, testicular carcinomas, etc. More particularly, cancers that may be treated by the compounds, compositions and methods of the invention include, but are not limited to: Cardiac: sarcoma (angiosarcoma, fibrosarcoma, rhabdomyosarcoma, liposarcoma), myxoma, rhabdomyoma, fibroma, lipoma and teratoma; Lung: bronchogenic carcinoma (squamous cell, undifferentiated small cell, undifferentiated large cell, adenocarcinoma), alveolar (bronchiolar) carcinoma, bronchial adenoma, sarcoma, lymphoma, chondromatous hamartoma, mesothelioma; Gastrointestinal: esophagus (squamous cell carcinoma, adenocarcinoma, leiomyosarcoma, lymphoma), stomach (carcinoma, lymphoma, leiomyosarcoma), pancreas (ductal adenocarcinoma, insulinoma, glucagonoma, gastrinoma, carcinoid tumors, vipoma), small bowel (adenocarcinoma, lymphoma, carcinoid tumors, Karposi's sarcoma, leiomyoma, hemangioma, lipoma, neurofibroma, fibroma), large bowel (adenocarcinoma, tubular adenoma, villous

adenoma, hamartoma, leiomyoma); Genitourinary tract: kidney (adenocarcinoma, Wilm's tumor [nephroblastoma], lymphoma, leukemia), bladder and urethra (squamous cell carcinoma, transitional cell carcinoma, adenocarcinoma), prostate (adenocarcinoma, sarcoma), testis (seminoma, teratoma, embryonal carcinoma, teratocarcinoma, choriocarcinoma, sarcoma, interstitial cell carcinoma, fibroma, fibroadenoma, adenomatoid tumors, lipoma); Liver: hepatoma (hepatocellular carcinoma), cholangiocarcinoma, hepatoblastoma, angiosarcoma, hepatocellular adenoma, hemangioma; Bone: osteogenic sarcoma (osteosarcoma), fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, malignant lymphoma (reticulum cell sarcoma), multiple myeloma, malignant giant cell tumor chordoma, osteochronfroma (osteocartilaginous exostoses), benign chondroma, chondroblastoma, chondromyxofibroma, osteoid osteoma and giant cell tumors; Nervous system: skull (osteoma, hemangioma, granuloma, xanthoma, osteitis deformans), meninges (meningioma, meningiosarcoma, gliomatosis), brain (astrocytoma, medulloblastoma, glioma, ependymoma, germinoma [pinealoma], glioblastoma multiform, oligodendroglioma, schwannoma, retinoblastoma, congenital tumors), spinal cord neurofibroma, meningioma, glioma, sarcoma); Gynecological: uterus (endometrial carcinoma), cervix (cervical carcinoma, pre-tumor cervical dysplasia), ovaries (ovarian carcinoma [serous cystadenocarcinoma, mucinous cystadenocarcinoma, unclassified carcinoma], granulosa-thecal cell tumors, Sertoli-Leydig cell tumors, dysgerminoma, malignant teratoma), vulva (squamous cell carcinoma, intraepithelial carcinoma, adenocarcinoma, fibrosarcoma, melanoma), vagina (clear cell carcinoma, squamous cell carcinoma, botryoid sarcoma (embryonal rhabdomyosarcoma), fallopian tubes (carcinoma); Hematologic; blood (myeloid leukemia [acute and chronic], acute lymphoblastic leukemia, chronic lymphocytic leukemia, myeloproliferative diseases, multiple myeloma, myelodysplastic syndrome), Hodgkin's disease, non-Hodgkin's lymphoma [malignant lymphoma]; Skin: malignant melanoma, basal cell carcinoma, squamous cell carcinoma, Karposi's sarcoma, moles dysplastic nevi, lipoma, angioma, dermatofibroma, keloids, psoriasis; and Adrenal glands: neuroblastoma. Thus, the term 'cancerous cell' as provided herein, includes a cell afflicted by any one of the above-identified conditions.

[00481] Akt signaling regulates multiple critical steps in angiogenesis. Shiojima and Walsh, Circ. Res. (2002) 90: 1243-1250. The utility of angiogenesis inhibitors in the treatment of cancer is known in the literature, see J. Rak et al. Cancer Research, 55:4575-4580, 1995 and Dredge et al., Expert Opin. Biol. Ther. (2002) 2(8):953-966, for example. The role of angiogenesis in cancer has been shown in numerous types of cancer and tissues: breast carcinoma (G. Gasparini and A. L. Harris, J. Clin. Oncol., 1995, 13: 765-782; M. Toi et al., Japan. J. Cancer Res., 1994, 85: 1045-1049); bladder carcinomas (A. J. Dickinson et al., Br. J. Urol., 1994, 74:762-766); colon carcinomas (L. M. Ellis at al., Surgery, 1996; 120(5):871-878); and oral cavity tumors (J. K. Williams et al., Am. J. Surg., 1994, 168:373-380). Other cancers include, advanced tumors, hairy cell leukemia, melanoma, advanced head and neck, metastatic renal cell, non-Hodgkin's lymphoma, metastatic breast, breast adenocarcinoma, advanced melanoma, pancreatic, gastric, glioblastoma, lung, ovarian, non-small cell lung, prostate, small cell lung, renal cell carcinoma, various solid tumors, multiple myeloma, metastatic prostate, malignant glioma, renal carrier, lymphoma, refractory metastatic disease, refractory multiple myeloma, cervical cancer, Kaposi's sarcoma, recurrent anaplastic glioma, and metastatic colon cancer (Dredge et al., Expert Opin. Biol. Ther. (2002) 2(8):953-

966). Thus, the Akt inhibitors disclosed in the instant application; are also useful in the treatment of these angiogenesis related cancers.

[00482] Tumors which have undergone neovascularization show an increased potential for metastasis. In fact, angiogenesis is essential for tumor growth and metastasis. (S. P. Cunningham, et al., Can, Research, 61: 3206-3211 (2001)). The Akt inhibitors disclosed in the present application are therefore useful to prevent or decrease or eradicate tumor cell spread, invasiveness and metastasis.

[00483] Further included within the scope of the invention is a method of treating or preventing a disease in which angiogenesis is implicated, which is comprised of administering to a mammal in need of such treatment a therapeutically effective amount of a compound of the present invention. Ocular neovascular diseases are an example of conditions where much of the resulting tissue damage can be attributed to aberrant infiltration of blood vessels in the eye (see WO 00/30651, published 2 Jun. 2000). The undesirable infiltration can be triggered by ischemic retinopathy, such as that resulting from diabetic retinopathy, retinopathy of prematurity, retinal vein occlusions, etc., or by degenerative diseases, such as the choroidal neovascularization observed in age-related macular degeneration. Inhibiting the growth of blood vessels by administration of the present compounds would therefore prevent the infiltration of blood vessels and prevent or treat diseases where angiogenesis is implicated, such as ocular diseases like retinal vascularization, diabetic retinopathy, age-related macular degeneration, and the like.

[00484] Further included within the scope of the invention is a method of treating or preventing a non-malignant disease in which angiogenesis is implicated, including but not limited to: ocular diseases (such as, retinal vascularization, diabetic retinopathy and age-related macular degeneration), atherosclerosis, arthritis, psoriasis, obesity and Alzheimer's disease (Dredge et al., Expert Opin. Biol. Ther. (2002) 2(8):953-966). In another embodiment, a method of treating or preventing a disease in which angiogenesis is implicated includes: ocular diseases (such as, retinal vascularization, diabetic retinopathy and age-related macular degeneration), atherosclerosis, arthritis and psoriasis.

[00485] Further included within the scope of the invention is a method of treating hyperproliferative disorders such as restenosis, inflammation, autoimmune diseases and allergy/asthma.

[00486] Further included within the scope of the invention is a method of treating hyperinsulinism.

[00487] The compounds of the invention are also useful in preparing a medicament that is useful in treating the diseases described above, in particular cancer.

[00488] In an embodiment of the invention, the instant compound is a selective, specific, potent and pan-isoform inhibitor of Akt. the inhibitory efficacy is non-dependent on the PH domain's order of amino acid sequence or amino acid cahin length (number and or quantity) or amount.

[00489] In a further embodiment, the instant compound is selected from the group consisting of a selective inhibitor of Aktl, a selective inhibitor of Akt2, a selective inhibitor of Akt3, a selective inhibitor of naturally occurring somatic mutant Akt (Aktl -el 7k), a selective inhibitor of mutant Akt (Aktl-e40k), a selective inhibitor of constitutively active Akt, a selective inhibitor of any other isoforms of Akt, and a selective inhibitor of any combination thereof or all of the Akt isoforms and mutants.

[00490] In another embodiment, the instant compound is a potent, specific and selective inhibitor of all three Akt isoforms, regardless of any modifications, mutation, rearrangement of amino acid sequence

on the PH-domain chain, the chain order, amount of amino acids present and or the length of amino acid chain. This is why this compound of instant invention is effective against naturally occurring somatic mutant AKT1-E17K (glutamic acid substitution for lysine at position 17) and mutant AKT1-E40K (ditto at position number 40)..

[00491] The present invention is further directed to a method of inhibiting Akt activity which comprises administering to a mammal in need thereof a pharmaceutically effective amount of the instant compound.

[00492] The present invention is further directed to a method of treating Mantle Cell Lymphoma which comprises administering to a mammal in need thereof a pharmaceutically effective amount of the instant compound. As shown in Fig. 6, LD-101 achieves greater apoptosis in Mantle Cell Lymphoma than Velcade®. The experiments were performed following the methods described in the art (Dennison JB et al (Blood December 16, 2010 vol. 116 no. 255622-5630; Gold MR; Blood September 1, 2006vol. 108 no. 5 1668-1676).

[00493] The present invention is further directed to a method of treating multiple myeloma which comprises administering to a mammal in need thereof a pharmaceutically effective amount of the instant compound. As shown in Fig. 7, LD-101 achieves greater apoptosis in Multiple Myeloma than Velcade®. The experiments were performed following the methods described in the art (Pene F et al.' Nat. 2002, vol. 21, no. 43, pp. 6587-6597).

[00494] The present invention is further directed to a method of treating prostate cancer, which comprises administering to a mammal in need thereof a pharmaceutically effective amount of the instant compound. As shown in Fig. 8, LD-101 achieves greater inhibition of cell growth in prostate cancer than Rapamycin, and even Greater Inhibition in Combination with Rapamycin. The experiments were performed following the methods described in the art (Festuccia C. et al. Prostate. 2008 Jun 15;68(9):965-74).

[00495] The present invention is further directed to a method of treating breast cancer, which comprises administering to a mammal in need thereof a pharmaceutically effective amount of the instant compound. As shown in Fig. 9, LD- 101 achieves greater inhibition of cell growth in breast cancer than RADOOOl, and even Greater Inhibition in Combination with RADOOOl. The experiments were performed following the methods described in the art (Mayo LD et al., PNAS September 25, 2001vol. 98 no. 20 11598-1 1603).

[00496] The present invention is further directed to a method of treating ovarian cancer, which comprises administering to a mammal in need thereof a pharmaceutically effective amount of the instant compound. As shown in Fig. 10, LD-101 achieves greater inhibition of cell growth in ovarian cancer than Rapamycin. The experiments were performed following the methods described in the art (Holland WS. Et al. JCO Vol 26, No 15S (May 20, Supplement), 2008: 16083).

[00497] The present invention is further directed to a method of treating Resistant Ovarian Cancer (CI 3), which comprises administering to a mammal in need thereof a pharmaceutically effective amount of the instant compound. As shown in Fig. 11, LD- 101 achieves greater inhibition of cell Survival in Resistant Ovarian Cancer (CI 3) than Cisplatin, and even Greater Inhibitionin Combination with Cisplatin.

The experiments were performed following the methods described in the art (Zhonghua Zhong Liu Za Zhi. 201 1 Feb;33(2):97-100; Frazer M et al., Cancer Res November 1, 2003 *63;* 708 1; Lee S et all., Gyn Onc.; (04-2005),97[l], 26-34; Altomare DA, et al., Oncogene (2004) 23, 5853-5857).

[00498] The present invention is further directed to a method of treating Resistant Ovarian Cancer (CI 3), which comprises administering to a mammal in need thereof a pharmaceutically effective amount of the instant compound. As shown in Fig. 12, LD-101 achieves greater inhibition of cell growth in Resistant Ovarian Cancer (CI 3) than CDDP, and even Greater Inhibition in Combination with CDDP in Nude Mouse Xenografts. The experiments were performed following the methods described in the art (Zhonghua Zhong Liu Za Zhi. 201 1 Feb;33(2):97-100; Frazer M et al., Cancer Res November 1, 2003 *63;* 7081; Lee S et all., Gyn One; (04-2005),97[l], 26-34; Altomare DA, et al., Oncogene (2004) 23, 5853-5857).

[00499] The present invention is further directed to a method of treating Resistant Ovarian Cancer (CI 3), which comprises administering to a mammal in need thereof a pharmaceutically effective amount of the instant compound. As shown in Fig. 13 (10 µM concentration, for example when Taxol is + and LD- 101 is +, then both are present in 10 µM concentration; when Taxol is -, then there is no Taxol), LD- 10 1 in Combination with Taxol® Achieves Greater Apoptosis in Resistant Ovarian Cancer than either Alone. The experiments were performed following the methods described in the art (Kim SH et al., Ann NY Acad Sci. 2007 Jan; 1095: 82-9).

[00500] The present invention is further directed to a method of treating Resistant Ovarian Cancer (CI 3), which comprises administering to a mammal in need thereof a pharmaceutically effective amount of the instant compound. As shown in Fig. 17, LD- 101 Overcomes CDDP Resistance in Ovarian Cancer. The experiments were performed following the methods described in the art (Yang X., et al. Cancer Res March 15, 2006 66; 3126).

[00501] The present invention is further directed to a method of treating lung cancer, which comprises administering to a mammal in need thereof a pharmaceutically effective amount of the instant compound. As shown in Fig. 2 1, LD- 101 achieves greater inhibition of Tumor Growth in Lung Cancer Cell H66 1 than CDDP, and even Greater Inhibition in Combination with CDDP. The experiments were performed following the methods described in the art (Nie Zeng-Rong Cancer Res 1995;55:4760-4764).

[00502] The present invention is further directed to a method of treating lung cancer, which comprises administering to a mammal in need thereof a pharmaceutically effective amount of the instant compound. As shown in Fig. 22, LD- 101 Achieves Greater Inhibition of Tumor Growth in Lung Cancer Cell H66 1 than Etoposide®, and even Greater Inhibition in Combination with Etoposide®. The experiments were performed following the methods described in the art (Nie Zeng-Rong Cancer Res 1995;55:4760-4764).

[00503] The present invention is further directed to a method of treating lung cancer, which comprises administering to a mammal in need thereof a pharmaceutically effective amount of the instant compound. As shown in Fig. 23, LD-101 Achieves Greater Inhibition of Tumor Growth in Lung Cancer Cell H661 than than Rapamycin, and even Greater Inhibition in Combination with Rapamycin. The experiments

were performed following the methods described in the art (Nie Zeng-Rong Cancer Res 1995;55:4760-4764).

[00504] All patents, publications and pending patent applications identified are hereby incorporated by reference.

[00505] As described herein, the present invention is directed to a method of treating cancers originating from and tumors of breast, bone, lung, prostate, ovary, uterus, kidney, pancreas, neuroendocrine, upper GI and hematologic malignancies such as lymphomas, multiple myeloma, and mantle cell, which comprises administering to a mammal in need thereof a pharmaceutically effective amount of the instant compound. The Fig. 24 shows the data that show the pharmacodynamic (and thus the pharmacology) action (Effectiveness) of LD- 101 in cancer cells (Cell Lines named by numbers and alphabets) from humans, planted in animals. Thus, LD-101 is efficacious in both animal and human cancers of various origins as depicted by the study.

[00506] In summary, this studies show that LD- 101 is useful in the treatment of cancers originating from and tumors of breast, bone, lung, prostate, ovary, uterus, kidney, pancreas, neuroendocrine, upper GI and hematologic malignancies such as lymphomas, multiple myeloma, and mantle cell.

[00507] The compounds of this invention may be administered to mammals, including humans, either alone or, in combination with pharmaceutically acceptable carriers, excipients or diluents, in a pharmaceutical composition, according to standard pharmaceutical practice. The compounds can be administered orally or parenterally, including the intravenous, intramuscular, intraperitoneal, directly into the tumor mass, percutaneously, subcutaneous, intra-thecal, intra-arterial, sublingual, rectal and topical routes of administration.

[00508] The pharmaceutical compositions containing the active ingredient may be in a form suitable for oral use, for example, as tablets, caplets, gels, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs or spray. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, microcrystalline cellulose, sodium crosscarmellose, corn starch, or alginic acid; binding agents, for example starch, gelatin, polyvinyl-pyrrolidone or acacia, and lubricating agents, for example, magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to mask the unpleasant taste of the drug or delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a water soluble taste masking material such as hydroxypropylmethyl-cellulose or hydroxypropylcellulose, or a time delay material such as ethyl cellulose, cellulose acetate buryrate may be employed.

[00509] Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water soluble carrier such as polyethyleneglycol or an oil medium, for example, peanut oil, liquid paraffin, or olive oil.

[00510] Aqueous suspensions contain the active material in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethyl-cellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethylene-oxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose, saccharin or aspartame.

[00511] Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as butylated hydroxyanisol or alpha-tocopherol.

[00512] Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

[00513] The pharmaceutical compositions of the invention may also be in the form of an oil-in-water emulsion. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring phosphatides, for example soy bean lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening, flavoring agents, preservatives and antioxidants.

[00514] Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative, flavoring and coloring agents and antioxidants.

[00515] The pharmaceutical compositions may be in the form of sterile injectable aqueous solutions. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution.

[00516] The sterile injectable preparation may also be a sterile injectable oil-in-water microemulsion where the active ingredient is dissolved in the oily phase. For example, the active ingredient may be first dissolved in a mixture of soybean oil and lecithin. The oil solution then introduced into a water and glycerol mixture and processed to form a microemulsion.

[00517] The injectable solutions or microemulsions may be introduced into a patient's blood-stream by local bolus injection. Alternatively, it may be advantageous to administer the solution or microemulsion in such a way as to maintain a constant circulating concentration of the instant compound. In order to maintain such a constant concentration, a continuous intravenous delivery device may be utilized. An example of such a device is the Deltec CADD-PLUS™ model 5400 intravenous pump.

[00518] The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension for intramuscular and subcutaneous administration. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butane diol. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

[00519] The compounds of the invention may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials include cocoa butter, glycerinated gelatin, hydrogenated vegetable oils, mixtures of polyethylene glycols of various molecular weights and fatty acid esters of polyethylene glycol.

[00520] For topical use, creams, ointments, jellies, solutions or suspensions, etc., containing a compound of the invention are employed. (For purposes of this application, topical application shall include mouth washes and gargles.)

[00521] The compounds for the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles and delivery devices, or via transdermal routes, using those forms of transdermal skin patches well known to those of ordinary skill in the art. To be administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen. Compounds of the present invention may also be delivered as a suppository employing bases such as cocoa butter, glycerinated gelatin, hydrogenated vegetable oils, mixtures of polyethylene glycols of various molecular weights and fatty acid esters of polyethylene glycol.

[00522] When a composition according to this invention is administered into a human subject, the daily dosage will normally be determined by the prescribing physician with the dosage generally varying

according to the age, weight, and response of the individual patient, as well as the severity of the patient's symptoms.

[00523] In an embodiment, a suitable amount of compound of the invention, is administered to a mammal undergoing treatment for cancer. Administration occurs in an amount of inhibitor of between about 0.1 mg/kg of body weight to about 60 mg/kg of body weight per day, or between 0.5 mg/kg of body weight to about 40 mg/kg of body weight per day. Another therapeutic dosage that comprises the instant composition includes from about 0.01 mg to about 1000 mg of inhibitor of Akt. In another embodiment, the dosage comprises from about 1 mg to about 1000 mg of inhibitor of Akt.

[00524] The instant compounds are also useful in combination with known therapeutic agents and anti-cancer agents. For example, instant compounds are useful in combination with known anti-cancer agents. Combinations of the presently disclosed compounds with other anti-cancer or chemotherapeutic agents are within the scope of the invention. Examples of such agents can be found in Cancer Principles and Practice of Oncology by V. T. Devita and S. Hellman (editors), 6th edition (Feb. 15, 2001), Lippincott Williams & Wilkins Publishers. 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. Such anti-cancer agents include the following: estrogen receptor modulators, androgen receptor modulators, retinoid receptor modulators, cytotoxic/cytostatic agents, antiproliferative agents, prenyl-protein transferase inhibitors, HMG-CoA reductase inhibitors and other angiogenesis inhibitors, inhibitors of cell proliferation and survival signaling, and agents that interfere with cell cycle checkpoints. The instant compounds are particularly useful when co-administered with radiation therapy, immunotherapy, radioimmunotherapy, targeted therapeutics, cellular therapy, genetherapy and surgical treatment, either before or during or after surgical removal of tumor mass called de-bulking.

[00525] In an embodiment, the instant compounds are also useful in combination with known anti-cancer agents including the following; estrogen receptor modulators, androgen receptor modulators, retinoid receptor modulators, cytotoxic agents, antiproliferative agents, prenyl-protein transferase inhibitors, HMG-CoA reductase inhibitors, HIV protease inhibitors, reverse transcriptase inhibitors, and other angiogenesis inhibitors.

[00526] 'Estrogen receptor modulators' refers to compounds that interfere with or inhibit the binding of estrogen to the receptor, regardless of mechanism. Examples of estrogen receptor modulators include, but are not limited to, tamoxifen, raloxifene, idoxifene, LY353381, LY1 17081, torernifene, fulvestrant, 4-[7-(2,2-dimethyl- 1-oxopropoxy-4-methyl-2-[4-[2-(l -piperidi nyl)ethoxy]phenyl]-2H- 1-benzopyran-3-yl]-phenyl-2,2-dimethyl propanoate, 4,4'-dihydroxybenzophenone-2,4-dinitrophenyl-hydrazone, and SH646.

[00527] 'Androgen receptor modulators' refers to compounds which interfere or inhibit the binding of androgens to the receptor, regardless of mechanism. Examples of androgen receptor modulators include finasteride and other 5a-reductase inhibitors, flutamide, flutamide, bicalutamide, liarozole, and abiraterone acetate:

[00528] 'Retinoid receptor modulators' refers to compounds which interfere or inhibit the binding of retinoids to the receptor, regardless of mechanism. Examples of such retinoid receptor modulators include

bexarotene, tretinoin, 13-cis-retinoic acid, 9-cis-retinoic acid, a-difluoromethylornithine, ILX23-7553, trans-N-(4'-hydroxyphenyl) retinamide, and N-4-carboxyphenyl retinamide.

[00529] 'Cytotoxic/cytostatic agents' refer to compounds which cause cell death or inhibit cell proliferation primarily by interfering directly with the cell's functioning or inhibit or interfere with cell myosis, including alkylating agents, tumor necrosis factors, intercalators, hypoxia activatable compounds, microtubule inhibitors/microtubule-stabilizing agents, inhibitors of mitotic kinesins, inhibitors of kinases involved in mitotic progression, inhibitors of kinases involved in growth factor and cytokine signal transduction pathways, antimetabolites, biological response modifiers, hormonal/anti-hormonal therapeutic agents, haematopoietic growth factors, monoclonal antibody targeted therapeutic agents, topoisomerase inhibitors, proteosome inhibitors and ubiquitin ligase inhibitors.

[00530] Examples of cytotoxic/cytostatic agents include, but are not limited to, sertenef, cachectin, ifosfamide, tasonermin, lonidamine, carboplatin, altretamine, prednimustine, dibromodulcitol, ranimustine, fotemustine, nedaplatin, oxaliplatin, temozolomide, heptaplatin, estramustine, improsulfan tosilate, trofosfamide, nimustine, dibrospidium chloride, pumitepa, lobaplatin, satraplatin, profiromycin, cisplatin, irofulven, dexifosfamide, cis-aminedichloro(2-methyl-pyridine)platinum, benzylguanine, glufosfamide, GPX100, (trans, trans, trans)-bis-mu-(hexane-l,6-diamine)-mu-[diamine-platinum(II)] bis[diamine(chloro)platinum (II)]tetrachloride, diarizidinylspermine arsenic trioxide, 1-(1 1-dodecylamino-10-hydroxyundecyl)-3,7-dimethylxanthine, zorubicin, idarubicin, daunorubicin, bisantrene, mitoxantrone, pirarubicin, pinafide, valrubicin, amrubicin, antineoplaston, 3'-deamino-3'-morpholino-13-deoxo- 10-hydroxycarminomycin , annamycin, galarubicin, elinafide, MEN10755, 4-demethoxy-3-deamino-3-aziridinyl-4-methylsulphonyl-daunoru bicin (see WO 00/50032), Raf kinase inhibitors (such as Bay43-9006) and mTOR inhibitors (such as Wyeth's CCI-779).

[00531] An example of a hypoxia activatable compound is tirapazamine.

[00532] Examples of proteosome inhibitors include but are not limited to lactacystin and MLN-341 (Velcade).

[00533] Examples of microtubule inhibitors/microtubule-stabilising agents include paclitaxel, vindesine sulfate, 3',4'-didehydro-4'-deoxy-8'-norvincaleukoblastine, docetaxol, rhizoxin, dolastatin, mivobulin isethionate, auristatin, cemadotin, RPR1 09881, BMS 184476, vinflunine, cryptophycin, 2,3,4,5, 6-pentafluoro-N-(3-fluoro-4-methoxyphenyl)benzene sulfonamide, anhydrovinblastine, N,N-dimethyl-L-valyl-L-valyl-N-methyl-L-valyl-L-prolyl-L-proline-t-butylamide, TDX258, the epothilones (see for example, U.S. Patent Nos. 6,284,78 1 and 6,288,237) and BMS 188797. In an embodiment the epothilones are not included in the microtubule inhibitors/microtubule-stabilizing agents.

[00534] Some examples of topoisomerase inhibitors are topotecan, hycaptamine, irinotecan, rubitecan, 6-ethoxypropionyl-3',4'-0-exo-benzylidene-chartreusin, 9-methoxy-N,N-dimethyl-5-nitropyrazolo[3,4,5-kl]acridine-2-(6H) propanamine, l-amino-9-ethyl-5-fluoro-2,3-dihydro-9-hydroxy-4-methyl-lH,l 2H-benzo[de]pyrano[3',4':b,7]-indolizino[l,2b]quinoline- 10,13(9H,15H)dione, lurtotecan, 7-[2-(N-isopropylamino)ethyl]-20S)camptothecin, BNP1350, BNPI1 100, BN80915, BN80942, etoposide phosphate, teniposide, sobuzoxane, 2'-dimethylamino-2'-deoxy-etoposide, GL331, N-[2-(dimethylamino)ethyl]-9-hydroxy-5,6-dimethyl-6H-pyrido[4,3-b]carbazole- 1-carboxamide, asulacrine,

(5a,5aB,8aa,9b)-9-[2-[N-[2-(dimethylamino)ethyl]-N-methylami no]ethyl]-5-[4-hydro0xy-3,5-dimethoxyphenyl]-5,5a,6,8,8a,9-h exohydrofuro(3',4':6,7)naphtho(2,3-d)-l,3-dioxol-6-one, 2,3-(methylenedioxy)-5-methyl-7-hydroxy-8-methoxybenzo[c]-ph enanthridinium, 6,9-bis[(2-aminoethyl)amino]benzo[g]isoquinoline-5, 10-dione, 5-(3-aminopropylamino)-7, 10-dihydroxy-2-(2-hydroxyethylamino methyl)-6H-pyrazolo[4,5,l-de]acridin-6-one, N-[l-[2-(diethylamino)ethylamino]-7-methoxy-9-oxo-9H-thioxan then-4-ylmethyl]formamide, N-(2-(dimethylamino)ethyl)acridine-4-carboxamide, 6-[[2-(dimethylamino)ethyl]amino]-3-hydroxy-7H-indeno[2,l-c] quinolin-7-one, and dimesna.

[00535] Examples of inhibitors of mitotic kinesins, and in particular the human mitotic kinesin KSP, are described in PCT Publications WO 01/30768,WO 01/98278, and WO 2003/049678, and in pending U.S. Ser. Nos. 10/497,413 (filed June 2, 2004), and 11/410,341 (filed April 24, 2006). In an embodiment inhibitors of mitotic kinesins include, but are not limited to inhibitors of KSP, inhibitors of MKLP1, inhibitors of CENP-E, inhibitors of MCAK and inhibitors of Rab6-KIFL.

[00536] 'Inhibitors of kinases involved in mitotic progression' include, hut are not limited to, inhibitors of aurora kinase, inhibitors of Polo-like kinases (P1K; in particular inhibitors of PLK-1), inhibitors of bub- 1 and inhibitors of bub-Rl.

[00537] 'Antiproliferative agents' includes antisense RNA and DNA oligonucleotides such as G3 139, ODN698, RVASKRAS, GEM231, and ΓNX3001, and antimetabolites such as enocitabine, carmofur, tegafur, pentostatin, doxifluridine, trimetrexate, fludarabine, capecitabine, galocitabine, cytarabine ocfosfate, fosteabine sodium hydrate, raltitrexed, paltitrexid, emitefur, tiazofurin, decitabine, nolatrexed, pemetrexed, nelzarabine, 2'-deoxy-2'-methylidenecytidine, 2'-fluoromethylene-27-deoxycytidine, N-[5-(2,3-dihydro-benzofuryl)sulfonyl]-N'-3,4-dichlorophenyl)urea, N6-[4-deoxy-4-[N2-[2(E),4(E)-tetradecadienoyl]glycylamino]-L -glycero-B-L-manno-heptopyranosyl]adenine, aplidine, ecteinascidin, troxacitabine, 4-[2-amino-4-oxo-4,6,7,8-tetrahydro-3H-pyrimidino[5,4-b][l,4]thiazin-6-yl-(S)-ethyl]-2,5-thienoyl-L-glutamic acid, aminopterin, 5-fluorouracil, alanosine, 1l-acetyl-8-(carbamoyloxymethyl)-4-formyl-6-methoxy-14-oxa-l ,1l-diazatetracyclo(7. 4.1.0.0)-tetradeca-2,4,6-trien-9-yl acetic acid ester, swainsonine, lometrexol, dexrazoxane, methioninase, 2'-cyano-2'-deoxy-N4-palmitoyl-l-B-D-arabino furanosyl cytosine, 3-aminopyridine-2-carboxaldehyde thiosemicarbazone and trastuzumab.

[00538] Examples of monoclonal antibody targeted therapeutic agents include those therapeutic agents which have cytotoxic agents or radioisotopes attached to a cancer cell specific or target cell specific monoclonal antibody. Examples include Bexxar.

[00539] 'HMG-CoA reductase inhibitors' refers to inhibitors of 3-hydroxy-3-methylglutaryl-CoA reductase. Examples of HMG-CoA reductase inhibitors that may be used include but are not limited to lovastatin (MEVACOR®; see U.S. Patent Nos. 4,231,938, 4,294,926 and 4,319,039), simvastatin (ZOCOR®; see U.S. Patent Nos. 4,444,784, 4,820,850 and 4,916,239), pravastatin (PRAVACHOL®; see U.S. Patent Nos. 4,346,227, 4,537,859, 4,410,629, 5,030,447 and 5,180,589), fluvastatin (LESCOL®; see U.S. Patent Nos. 5,354,772, 4,941,165, 4,929,437, 5,189,164, 5,1 18,853, 5,290,946 and 5,356,896), atorvastatin (LIPITOR®; see U.S. Patent Nos. 5,273,995, 4,681,893, 5,489,691 and 5,342,952) and cerivastatin (also known as rivastatin and BAYCHOL®; see U.S. Patent No. 5,177,080). The structural

formulas of these and additional HMG-CoA reductase inhibitors that may be used in the instant methods are described at page 87 of M. Yalpani, 'Cholesterol Lowering Drugs', Chemistry & Industry, pp. 85-89 (Feb. 5, 1996) and U.S. Patent Nos. 4,782,084 and 4,885,3 14. The term HMG-CoA reductase inhibitor as used herein includes all pharmaceutically acceptable lactone and open-acid forms (i.e., where the lactone ring is opened to form the free acid) as well as salt and ester forms of compounds which have HMG-CoA reductase inhibitory activity, and therefor the use of such salts, esters, open-acid and lactone forms is included within the scope of this invention.

[00540] 'Prenyl-protein transferase inhibitor' refers to a compound which inhibits any one or any combination of the prenyl-protein transferase enzymes, including farnesyl-protein transferase (FPTase), geranylgeranyl-protein transferase type I (GGPTase-I), and geranylgeranyl-protein transferase type-II (GGPTase-II, also called Rab GGPTase).

[00541] Examples of prenyl-protein transferase inhibitors can be found in the following publications and patents: WO 96/30343, WO 97/18813, WO 97/21701, WO 97/23478, WO 97/38665, WO 98/28980, WO 98/291 19, WO 95/32987, U.S. Patent No. 5,420,245, U.S. Patent No. 5,523,430, U.S. Patent No. 5,532,359, U.S. Patent No. 5,510,510, U.S. Patent No. 5,589,485, U.S. Patent No. 5,602,098, European Patent Publ. 0 618 221, European Patent Publ. 0 675 112, European Patent Publ. 0 604 181, European Patent Publ. 0 696 593, WO 94/19357, WO 95/08542, WO 95/11917, WO 95/12612, WO 95/12572, WO 95/10514, U.S. Patent No. 5,661,152, WO 95/10515, WO 95/10516, WO 95/24612, WO 95/34535, WO 95/25086, WO 96/05529, WO 96/06138, WO 96/06193, WO 96/16443, WO 96/21701, WO 96/21456, WO 96/22278, WO 96/2461 1, WO 96/24612, WO 96/05168, WO 96/05169, WO 96/00736, U.S. Pat. No. 5,571,792, WO 96/17861, WO 96/33159, WO 96/34850, WO 96/34851, WO 96/30017, WO 96/30018, WO 96/30362, WO 96/30363, WO 96/31 111, WO 96/31477, WO 96/31478, WO 96/31501, WO 97/00252, WO 97/03047, WO 97/03050, WO 97/04785, WO 97/02920, WO 97/17070, WO 97/23478, WO 97/26246, WO 97/30053, WO 97/44350, WO 98/02436, and U.S. Patent No. 5,532,359. For an example of the role of a prenyl-protein transferase inhibitor on angiogenesis see European J. of Cancer, Vol. 35, No. 9, pp. 1394-1401 (1999).

[00542] 'Angiogenesis inhibitors' refers to compounds that inhibit the formation of new blood vessels, regardless of mechanism. Examples of angiogenesis inhibitors include, but are not limited to, tyrosine kinase inhibitors, such as inhibitors of the tyrosine kinase receptors Fit- 1 (VEGFR1) and Flk-l/KDR (VEGFR2), inhibitors of epidermal-derived, fibroblast-derived, or platelet derived growth factors, MMP (matrix metalloprotease) inhibitors, integrin blockers, interferon-a, interleukin-12, pentosan polysulfate, cyclooxygenase inhibitors, including nonsteroidal anti-inflammatories (NSAIDs) like aspirin and ibuprofen as well as selective cyclooxy-genase-2 inhibitors like celecoxib and rofecoxib (PNAS, Vol. 89, p. 7384 (1992); JNCI, Vol. 69, p. 475 (1982); Arch. Opthalmol., Vol. 108, p. 573 (1990); Anat. Rec, Vol. 238, p. 68 (1994); FEBS Letters, Vol. 372, p. 83 (1995); Clin, Orthop. Vol. 313, p. 76 (1995); J. Mol. Endocrinol., Vol. 16, p. 107 (1996); Jpn. J. Pharmacol., Vol. 75, p. 105 (1997); Cancer Res., Vol. 57, p. 1625 (1997); Cell, Vol. 93, p. 705 (1998); Intl. J. Mol. Med., Vol. 2, p. 715 (1998); J. Biol. Chem., Vol. 274, p. 9 116 (1999)), steroidal anti-inflammatories (such as corticosteroids, mineralocorticoids, dexamethasone, prednisone, prednisolone, methylpred, betamethasone), carboxyamidotriazole,

combretastatin A-4, squalamine, 6-0-chloroacetyl-carbonyl)-fumagillol, thalidomide, angiostatin, troponin-1, angiotensin II antagonists (see Fernandez et al., J. Lab. Clin. Med. 105:141-145 (1985)), and antibodies to VEGF (see, Nature Biotechnology, Vol. 17, pp. 963-968 (October 1999); Kim et al., Nature, 362, 841-844 (1993); WO 00/44777; and WO 00/61 186).

[00543] Other therapeutic agents that modulate or inhibit angiogenesis and may also be used in combination with the compounds of the instant invention include agents that modulate or inhibit the coagulation and fibrinolysis systems (see review in Clin. Chem. La. Med. 38:679-692 (2000)). Examples of such agents that modulate or inhibit the coagulation and fibrinolysis pathways include, but are not limited to, heparin (see Thromb. Haemost. 80: 10-23 (1998)), low molecular weight heparins and carboxypeptidase U inhibitors (also known as inhibitors of active thrombin activatable fibrinolysis inhibitor [TAFIa]) (see Thrombosis Res. 101:329-354 (2001)). TAFIa inhibitors have been described in U.S. Ser. Nos. 60/310,927 (filed Aug. 8, 2001) and 60/349,925 (filed Jan. 18, 2002).

[00544] 'Agents that interfere with cell cycle checkpoints' refer to compounds that inhibit protein kinases that transduce cell cycle checkpoint signals, thereby sensitizing the cancer cell to DNA damaging agents. Such agents include inhibitors of ATR, ATM, the Chkl and Chk2 kinases and cdk and cdc kinase inhibitors and are specifically exemplified by 7-hydroxystaurosporin, flavopiridol, CYC202 (Cyclacel) and BMS-387032.

[00545] 'Inhibitors of cell proliferation and survival signalling pathway' refer to compounds that inhibit signal transduction cascades downstream of cell surface receptors. Such agents include inhibitors of serine/threonine kinases (including but not limited to inhibitors of Akt such as described in WO 02/083064, WO 02/083139, WO 02/083140 and WO 02/083138), inhibitors of Raf kinase (for example BAY-43-9006), inhibitors of MEK (for example CI-1040 and PD-098059), inhibitors of mTOR (for example Wyeth CCI-779), and inhibitors of PI3K (for example LY294002).

[00546] As described above, the combinations with NSAID's are directed to the use of NSAID's which are potent COX-2 inhibiting agents. For purposes of this specification an NSAID is potent if it possesses an IC_{50} for the inhibition of COX-2 of 1 μM or less as measured by cell or microsomal assays.

[00547] The invention also encompasses combinations with NSAID's which are selective COX-2 inhibitors. For purposes of this specification NSAID's which are selective inhibitors of COX-2 are defined as those which possess a specificity for inhibiting COX-2 over COX-1 of at least 100 fold as measured by the ratio of IC_{50} for COX-2 over IC50 for COX-1 evaluated by cell or microsomal assays. Such compounds include, but are not limited to those disclosed in U.S. Patent No. 5,474,995, U.S. Patent No. 5,861,419, U.S. Patent No. 6,001,843, U.S. Patent No. 6,020,343, U.S. Patent No. 5,409,944, U.S. Patent No. 5,436,265, U.S. Patent No. 5,536,752, U.S. Patent No. 5,550,142, U.S. Patent No. 5,604,260, U.S. Patent No. 5,698,584, U.S. Patent No. 5,710,140, WO 94/15932, U.S. Patent No. 5,344,991, U.S. Patent No. 5,134,142, U.S. Patent No. 5,380,738, U.S. Patent No. 5,393,790, U.S. Patent No. 5,466,823, U.S. Patent No. 5,633,272 and U.S. Patent No. 5,932,598, all of which are hereby incorporated by reference.

[00548] Inhibitors of COX-2 that are particularly useful in the instant method of treatment are: 3-phenyl-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone; and 5-chloro-3-(4-methylsulfonyl)phenyl-2-(2-methyl-5-pyridinyl) pyridine; or a pharmaceutically acceptable salt thereof.

[00549] Compounds that have been described as specific inhibitors of COX-2 and are therefore useful in the present invention include, but are not limited to, the following: parecoxib, BEXTRA® and CELEBREX® or a pharmaceutically acceptable salt thereof.

[00550] Other examples of angiogenesis inhibitors include, but are not limited to, endostatin, ukrain, ranpirnase, IM862, 5-methoxy-4-[2-methyl-3-(3-methyl-2-butenyl)oxiranyl]-l-oxas piro[2,5]oct-6-yl(chloroacetyl)carbamate, acetyldinanaline, 5-amino- 1-[[3,5-dichloro-4-(4-chlorobenzoyl)phenyl]methyl]-l H-l,2,3-triazole-4-carboxamide, CM101, squalamine, combretastatin, RP14610, NX31838, sulfated mannopentaose phosphate, 7,7-(carbonyl-bis[imino-N-methyl-4,2-pyrrolocarbonylimino[N- methyl-4,2-pyrrole]-carbonylimino]-bis-(l,3-naphthalene disulfonate), and 3-[(2,4-dimethylpyrrol-5-yl)methylene]-2-indolinone (SU54 16).

[00551] As used above, 'integrin blockers' refers to compounds which selectively antagonize, inhibit or counteract binding of a physiological ligand to the αvβ3 integrin, to compounds which selectively antagonize, inhibit or counteract binding of a physiological ligand to the αvβ5 integrin, to compounds which antagonize, inhibit or counteract binding of a physiological ligand to both the αvβ3 integrin and the αvβ5 integrin, and to compounds which antagonize, inhibit (or counteract the activity of the particular integrin(s) expressed on capillary endothelial cells. The term also refers to antagonists of the αvβ6, αvβ8, αï βï, α2β1, α5β1, α6βï and α6β4 integrins. The term also refers to antagonists of any combination of αvβ3, αvβ5, αvβ6, αvβ8, αï βï, α2β1, α5β1, α6βï and α6β4 integrins.

[00552] Some specific examples of tyrosine kinase inhibitors include N-(trifluoromethylphenyl)-5-methylisoxazol-4-carboxamide, 3-[(2,4-dimethylpyrrol-5-yl)methylidenyl)indolin-2-one, 17-(allylamino)-17-demethoxygeldanamycin, 4-(3-chloro-4-fluorophenylamino)-7-methoxy-6-[3-(4-morpholin yl)propoxyl]quinazoline, N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinami ne, BIBX1382, 2,3,9,10,1 1,1 2-hexahydro- 10-(hydroxymethyl)- 10-hydroxy-9-met hyl-9, 12-epoxy- 1H-diindolo [1,2,3-fg:3',2',l'-kl]pyrrol o[3,4-i][l,6]benzodiazocin-l-one, SH268, genistein, STI571, CEP2563, 4-(3-chlorophenylamino)-5,6-dimethyl-7H-pyrrolo[2,3-d]pyrimi dinemethane sulfonate, 4-(3-bromo-4-hydroxyphenyl)amino-6,7-dimethoxyquinazoline, 4-(4'-hydroxyphenyl)amino-6,7-dimethoxyquinazoline, SU6668, STI571A, N-4-chlorophenyl-4-(4-pyridylmethyl)- 1-phthalazinamine, and EMD121974.

[00553] Combinations with compounds other than anti-cancer compounds are also encompassed in the instant methods. For example, combinations of the instantly claimed compounds with PPAR-γ (i.e., PPAR-gamma) agonists and PPAR-δ (i.e., PPAR-delta) agonists are useful in the treatment of certain malignancies. PPAR-γ and PPAR-δ are the nuclear peroxisome proliferator-activated receptors γ and δ. The expression of PPAR-γ on endothelial cells and its involvement in angiogenesis has been reported in the literature (see J. Cardiovasc. Pharmacol. 1998; 31:909-913; J. Biol. Chem. 1999; 274:91 16-9121; Invest. Ophthalmol. Vis. Sci. 2000; 41:2309-2317). More recently, PPAR-γ agonists have been shown to inhibit the angiogenic response to VEGF in vitro; both troglitazone and rosiglitazone maleate inhibit the development of retinal neovascularization in mice. (Arch. Ophthamol. 2001; 119:709-717). Examples of PPAR-γ agonists and PPAR-γ/α agonists include, but are not limited to, thiazolidinediones (such as DRF2725, CS-01 1, troglitazone, rosiglitazone, and pioglitazone), fenofibrate, gemfibrozil, clofibrate, GW2570, SB2 19994, AR-H039242, JTT-501, MCC-555, GW2331, GW409544, NN2344, KRP297,

NP0110, DRF4158, NN622, GI262570, PNU182716, DRF552926, 2-[(5,7-dipropyl-3-trifluoromethyl-1,2-benzisoxazol-6-yl)oxy]-2-methylpropionic acid (disclosed in U.S. Ser. No. 09/782,856), and 2(R)-7-(3-(2-chloro-4-(4-fluorophenoxy)phenoxy)propoxy)-2-et hylchromane-2-carboxylic acid (disclosed in U.S. Ser. No. 60/235,708 and 60/244,697).

[00554] Another embodiment of the instant invention is the use of the presently disclosed compounds in combination with gene therapy for the treatment of cancer. For an overview of genetic strategies to treating cancer see Hall et al (Am. J. Hum. Genet. 61:785-789, 1997) and Kufe et al (Cancer Medicine, 5th Ed, pp 876-889, B C Decker, Hamilton 2000). Gene therapy can be used to deliver any tumor suppressing gene. Examples of such genes include, but are not limited to, p53, which can be delivered via recombinant virus-mediated gene transfer (see U.S. Pat. No. 6,069,134, for example), a uPA/uPAR antagonist ('Adenovirus-Mediated Delivery of a uPA/uPAR Antagonist Suppresses Angiogenesis-Dependent Tumor Growth and Dissemination in Mice,' Gene Therapy, August 1998; 5(8): 1105- 13), and interferon gamma (J. Immunol. 2000; 164:217-222).

[00555] The compounds of the instant invention may also be administered in combination with an inhibitor of inherent multidrug resistance (MDR), in particular MDR associated with high levels of expression of transporter proteins. Such MDR inhibitors include inhibitors of p-glycoprotein (P-gp), such as LY335979, XR9576, OC144093, R101922, VX853 and PSC833 (valspodar).

[00556] A compound of the present invention may be employed in conjunction with anti-emetic agents to treat nausea or emesis, including acute, delayed, late-phase, and anticipatory emesis, which may result from the use of a compound of the present invention, alone or with radiation therapy. For the prevention or treatment of emesis, a compound of the present invention may be used in conjunction with other anti-emetic agents, especially neurokinin- 1 receptor antagonists, 5HT3 receptor antagonists, such as ondansetron, granisetron, tropisetron, and zatisetron, GABAB receptor agonists, such as baclofen, a corticosteroid such as Decadron (dexamethasone), Kenalog, Aristocort, Nasalide, Preferid, Benecorten or others such as disclosed in U.S. Patent Nos. 2,789,1 18, 2,990,401, 3,048,581, 3,126,375, 3,929,768, 3,996,359, 3,928,326 and 3,749,712, an antidopaminergic, such as the phenothiazines (for example prochlorperazine, fluphenazine, thioridazine and mesoridazine), metoclopramide or dronabinol. In another embodiment, conjunctive therapy with an anti-emesis agent selected from a neurokinin- 1 receptor antagonist, a 5HT3 receptor antagonist and a corticosteroid is disclosed for the treatment or prevention of emesis that may result upon administration of the instant compounds.

[00557] Neurokinin- 1 receptor antagonists of use in conjunction with the compounds of the present invention are fully described, for example, in U.S. Patent Nos. 5,162,339, 5,232,929, 5,242,930, 5,373,003, 5,387,595, 5,459,270, 5,494,926, 5,496,833, 5,637,699, 5,719,147; European Patent Publication Nos. EP 0 360 390, 0 394 989, 0 428 434, 0 429 366, 0 430 771, 0 436 3 34, 0 443 132, 0 482 539, 0 498 069, 0 499 313, 0 512 901, 0 512 902, 0 514 273, 0 514 274, 0 514 275, 0 514 276, 0 515 681, 0 517 589, 0 520 555, 0 522 808, 0 528 495, 0 532 456, 0 533 280, 0 536 817, 0 545 478, 0 558 156, 0 577 394, 0 585 913, 0 590 152, 0 599 538, 0 610 793, 0 634 402, 0 686 629, 0 693 489, 0 694 535, 0 699 655, 0 699 674, 0 707 006, 0 708 101, 0 709 375, 0 709 376, 0 714 891, 0 723 959, 0 733 632 and 0 776 893; PCT International Patent Publication Nos. WO 90/05525, 90/05729, 91/09844, 91/18899, 92/01688,

92/06079, 92/12151, 92/15585, 92/17449, 92/20661, 92/20676, 92/21677, 92/22569, 93/00330, 93/00331, 93/01159, 93/01 165, 93/01169, 93/01 170, 93/06099, 93/091 16, 93/10073, 93/14084, 93/141 13, 93/18023, 93/19064, 93/21 155, 93/21181, 93/23380, 93/24465, 94/00440, 94/01402, 94/02461, 94/02595, 94/03429, 94/03445, 94/04494, 94/04496, 94/05625 94/07843, 94/08997, 94/10165, 94/10167, 94/10168, 94/10170, 94/1 1368, 94/13639, 94/13663, 94/14767, 94/15903, 94/19320, 94/19323, 94/20500, 94/26735, 94/26740, 94/29309, 95/02595 95/04040, 95/04042, 95/06645, 95/07886, 95/07908, 95/08549, 95/1 1880, 95/14017, 95/1531 1, 95/16679, 95/17382, 95/18124, 95/18129, 95/19344, 95/20575, 95/21819, 95/22525, 95/23798, 95/26338, 95/28418, 95/30674, 95/30687, 95/33744, 96/05181, 96/05193, 96/05203, 96/06094, 96/07649, 96/10562, 96/16939, 96/18643, 96/20197, 96/21661, 96/29304, 96/29317, 96/29326, 96/29328, 96/31214, 96/32385, 96/37489, 97/01553, 97/01554, 97/03066, 97/08144, 97/14671, 97/17362, 97/18206, 97/19084, 97/19942 and 97/21702; and in British Patent Publication Nos. 2 266 529, 2 268 931, 2 269 170, 2 269 590, 2 271 774, 2 292 144, 2 293 168, 2 293 169, and 2 302 689. The preparation of such compounds is fully described in the aforementioned patents and publications, all of which are incorporated herein by reference.

[00558] In an embodiment, the neurokinin- 1 receptor antagonist for use in conjunction with the compounds of the present invention is selected from: 2-(R)-(l-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluorophenyl)-4-(3-(5-oxo-lH,4H-l,2,4-triazolo)methyl)morpholine, or a pharmaceutically acceptable salt thereof, which is described in U.S. Patent No. 5,719,147.

[00559] A compound of the instant invention may also be administered with an agent useful in the treatment of anemia. Such an anemia treatment agent is, for example, a continuous eythropoiesis receptor activator (such as epoetin alfa).

[00560] A compound of the instant invention may also be administered with an agent useful in the treatment of neutropenia. Such a neutropenia treatment agent is, for example, a hermatopoietic growth factor which regulates the production and function of neutrophils such as a human granulocyte colony stimulating factor, (G-CSF). Examples of a G-CSF include filgrastim.

[00561] A compound of the instant invention may also be administered with an immunologic-enhancing drug, such as levamisole, isoprinosine and Zadaxin.

[00562] Thus, the scope of the instant invention encompasses the use of the instantly claimed compounds in combination with a second compound selected from: an estrogen receptor modulator, an androgen receptor modulator, a retinoid receptor modulator, a cytotoxic/cytostatic agent, an antiproliferative agent, a prenyl-protein transferase inhibitor, an HMG-CoA reductase inhibitor, an HIV protease inhibitor, a reverse transcriptase inhibitor, an angiogenesis inhibitor, PPAR-γ agonists, PPAR-δ agonists, an inhibitor of inherent multidrug resistance, an anti-emetic agent, an agent useful in the treatment of anemia, an agent useful in the treatment of neutropenia, an immunologic-enhancing drug, an inhibitor of cell proliferation and survival signaling, and an agent that interferes with a cell cycle checkpoint.

[00563] The term 'administration' and variants thereof (e.g., 'administering' a compound) in reference to a compound of the invention means introducing the compound or a prodrug of the compound into the

system of the animal in need of treatment. When a compound of the invention or prodrug thereof is provided in combination with one or more other active agents (e.g., a cytotoxic agent, etc.), 'administration' and its variants are each understood to include concurrent and sequential introduction of the compound or prodrug thereof and other agents.

[00564] As used herein, the term 'composition' is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

[00565] The term 'therapeutically effective amount' as used herein means that amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician.

[00566] The term 'treating cancer' or 'treatment of cancer' refers to administration to a mammal afflicted with a cancerous condition and refers to an effect that alleviates the cancerous condition by killing the cancerous cells, but also to an effect that results in the inhibition of growth and/or metastasis of the cancer.

[00567] In an embodiment, the angiogenesis inhibitor to be used as the second compound is selected from a tyrosine kinase inhibitor, an inhibitor of epidermal-derived growth factor, an inhibitor of fibroblast-derived growth factor, an inhibitor of platelet derived growth factor, an MMP (matrix metalloprotease) inhibitor, an integrin blocker, interferon-a, interleukin-12, pentosan polysulfate, a cyclooxygenase inhibitor, carboxyamidotriazole, combretastatin A-4, squalamine, 6-O-chloroacetyl-carbonyl)-fumagillol, thalidomide, angiostatin, troponin- 1, or an antibody to VEGF. In an embodiment, the estrogen receptor modulator is tamoxifen or raloxifene.

[00568] Also included in the scope of the claims is a method of treating cancer that comprises administering a therapeutically effective amount of a compound of the invention in combination with radiation therapy and/or in combination with a second compound selected from: an estrogen receptor modulator, an androgen receptor modulator, a retinoid receptor modulator, a cytotoxiccytostatic agent, an antiproliferative agent, a prenyl-protein transferase inhibitor, an HMG-CoA reductase inhibitor, an HIV protease inhibitor, a reverse transcriptase inhibitor, an angiogenesis inhibitor, PPAR-γ agonists, PPAR-δ agonists, an inhibitor of inherent multidrug resistance, an anti-emetic agent, an agent useful in the treatment of anemia, an agent useful in the treatment of neutropenia, an immunologic-enhancing drug, an inhibitor of cell proliferation and survival signaling, and an agent that interferes with a cell cycle checkpoint.

[00569] And yet another embodiment of the invention is a method of treating cancer that comprises administering a therapeutically effective amount of a compound of instant invention in combination with paclitaxel or trastuzumab.

[00570] The invention further encompasses a method of treating or preventing cancer that comprises administering a therapeutically effective amount of a compound of instant invention in combination with a COX-2 inhibitor.

[00571] The instant invention also includes a pharmaceutical composition useful for treating or preventing cancer that comprises a therapeutically effective amount of a compound of the invention and a

second compound selected from: an estrogen receptor modulator, an androgen receptor modulator, a retinoid receptor modulator, a cytotoxic/cytostatic agent, an antiproliferative agent, a prenyl-protein transferase inhibitor, an HMG-CoA reductase inhibitor, an HIV protease inhibitor, a reverse transcriptase inhibitor, an angiogenesis inhibitor, a PPAR-γ agonist, a PPAR-δ agonist, an inhibitor of cell proliferation and survival signaling, and an agent that interferes with a cell cycle checkpoint.

[00572] All patents, publications and pending patent applications identified are hereby incorporated by reference.

[00573] Abbreviations used in the description of the chemistry and in the Examples that follow are: AEBSF (p-aminoethylbenzenesulfonyl fluoride); BSA (bovine serum albumin); BuLi (n-Butyl lithium); CDCI3 (chloroform-d); Cul (copper iodide); CUSO4 (copper sulfate); DCE (dichloroethane); DCM (dichloromethane); DEAD (diethyl azodicarboxylate); DMF (N,N-dimethylformamide); DMSO (dimethyl sulfoxide); DTT (dithiothreitol); EDTA (ethylene-diamine-tetra-acetic acid); EGTA (ethylene-glycol-tetra-acetic acid); EtOAc (ethyl acetate); EtOH (ethanol); HOAc (acetic acid); HPLC (high-performance liquid chromatography); HRMS (high resolution mass spectrum); LCMS (liquid chromatograph-mass spectrometer); LHMDS (lithium bis(trimethylsilyl)amide); LRMS (low resolution mass spectrum); MeOH (methanol); MP-B(CN)H_3 (Macroporous cyanoborohydride); $NaHC0_3$ (sodium bicarbonate); Na_2S0_4 (sodium sulfate); Na(OAc)sBH (sodium triacetoxyborohydride); NH_4OAc (ammonium acetate); NBS (N-bromosuccinamide); NMR (nuclear magnetic resonance); PBS (phosphate buffered saline); PCR (polymerase chain reaction); Pd(dppf) ([l,l'-bis(diphenylphosphino)ferrocene]palladium); Pd(Ph3)4 (palladium(O) tetrakis-triphenylphosphine); POCI3 (phosphorous oxychloride); PS-DIEA (polystyrene diisopropylethylamine); TBAF (tetrabutylammonium fluoride); THF (tetrahydrofuran); TFA (trifluoroacteic acid); and $TMSCH_2N_2$ (trimethylsilyldiazomethane).

[00574] The compounds of this invention may be prepared by employing reactions as shown in the following section (General Synthetic Procedure, Specific (Novel) Synthesis), in addition to other standard manipulations that are known in the literature or exemplified in the experimental procedures. The illustrative Reaction Schemes below, therefore, are not limited by the compounds listed or by any particular substituents employed for illustrative purposes. Substituent numbering as shown in the General Synthetic Procedure does not necessarily correlate to that used in the claims and often, for clarity, a single substituent is shown attached to the compound where multiple substituents are optionally allowed under the definitions of the compound of invention hereinabove.

[00575] Reactions used to generate the compounds of this invention are prepared by employing reactions as shown in the General Synthetic Procedure (next section below), in addition to other standard manipulations such as ester hydrolysis, cleavage of protecting groups, etc., as may be known in the literature or exemplified in the experimental procedures.

GENERAL SYNTHETIC PROCEDURES

[00576] The compounds of this invention can be prepared from readily available starting materials using the following general methods and procedures. *See, e.g.,* Synthetic Scheme, below. It will be appreciated that where typical or preferred process conditions *(i.e.,* reaction temperatures, times, mole

ratios of reactants, solvents, pressures, etc.) are given, other process conditions can also be used unless otherwise stated. Optimum reaction conditions may vary with the particular reactants or solvent used, but such conditions can be determined by one skilled in the art by routine optimization procedures.

[00577] Additionally, as will be apparent to those skilled in the art, conventional protecting groups may be necessary to prevent certain functional groups from undergoing undesired reactions. The choice of a suitable protecting group for a particular functional group as well as suitable conditions for protection and deprotection are well known in the art. For example, numerous protecting groups, and their introduction and removal, are described in T. W. Greene and P. G. M. Wuts, *Protecting Groups in Organic Synthesis,* Second Edition, Wiley, New York, 1991, and references cited therein.

[00578] The compounds of this invention, for example, may be prepared by the reaction of a chloro derivative with an appropriately substituted amine and the product isolated and purified by known standard procedures. Such procedures include (but are not limited to) recrystallization, column chromatography or HPLC. The following schemes are presented with details as to the preparation of representative fused heterocyclics that have been listed hereinabove. The compounds of the invention may be prepared from known or commercially available starting materials and reagents by one skilled in the art of organic synthesis.

[00579] The compounds of the present invention may be prepared by a variety of processes well known for the preparation of compounds of this type, for example reaction schemes,and general procedures as described below.

[00580] The syntheses of representative compounds of this invention are carried out in accordance with the methods set forth above and using the appropriate reagents, starting materials, and purification methods known to those skilled in the art. All starting materials in the following general syntheses may be commercially available or obtained by conventional methods known to those skilled in the art.

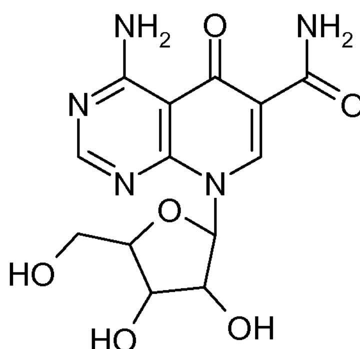
[00581] In this specification, especially in 'Representative Synthetic Methods', the following abbreviations can be used:

BEP	2-bromo- 1-ethylpyridinium tetrafluoroborate
BOP	benzotriazol- 1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate
CDI	2-chloro- 1,3-dimethylimidazolinium chloride
DCC	dicyclohexylcarbodiimide
DCM	dichloromethane
DME	1,2-dimethoxyethane, dimethoxyethane
DMF	N,N-dimethylformamide
DMSO	dimethyl sulfoxide
EDC	l-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrogen chloride
EtOAc	ethyl acetate
EtOH	ethanol
HOBt	1-hydroxybenzotriazole
MeOH	methanol
NMP	N-methyl-2-pyrroliidone

THF	tetrahydrofuran
TFA	trifluoroacetic acid
uM	μM
uL	μL

Synthesis of Intermediates

4-Amino-6-carboxamido-5-oxo-8-(b-D-ribofuranosyl)pyrido [2,3-d] pyrimidine (III)



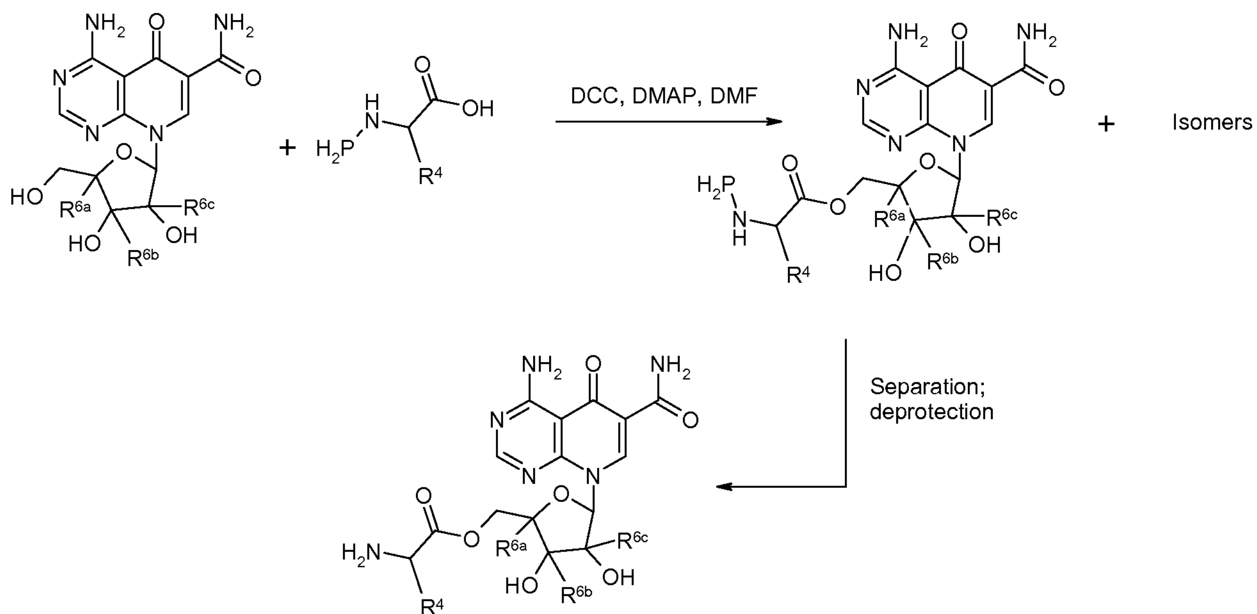
III

[00582] The general preparation method (but not the specific methods) may be apparent to those skilled in the art or could be put together from various reaction methods as described in scientific literatures.

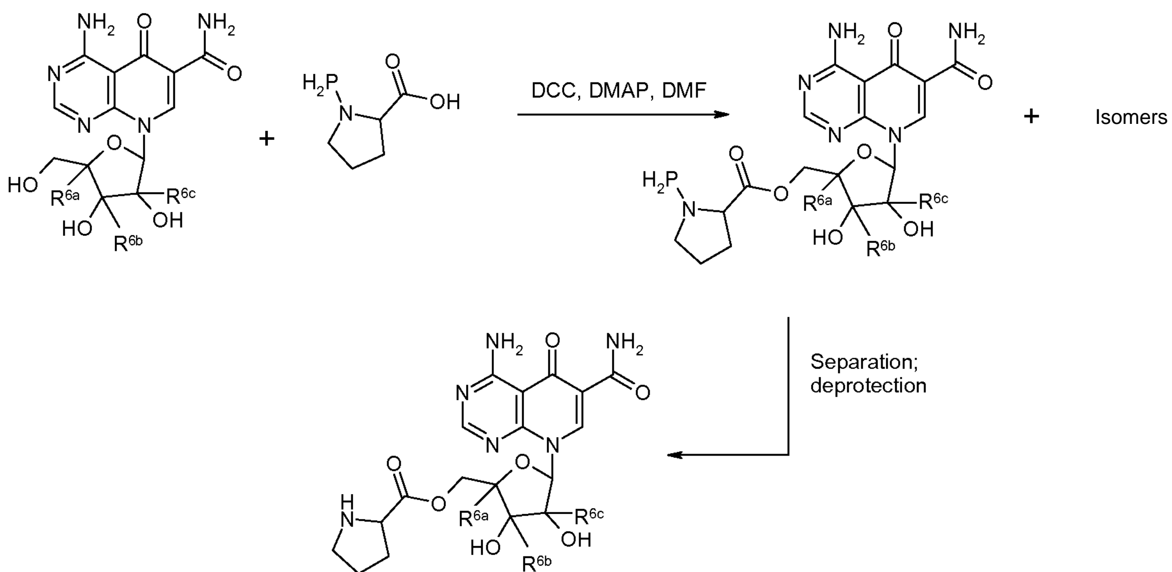
Specific Synthetic Methods for Preparing Compounds of the Invention

[00583] The compounds of the invention may be prepared following the synthetic schemes shown below:

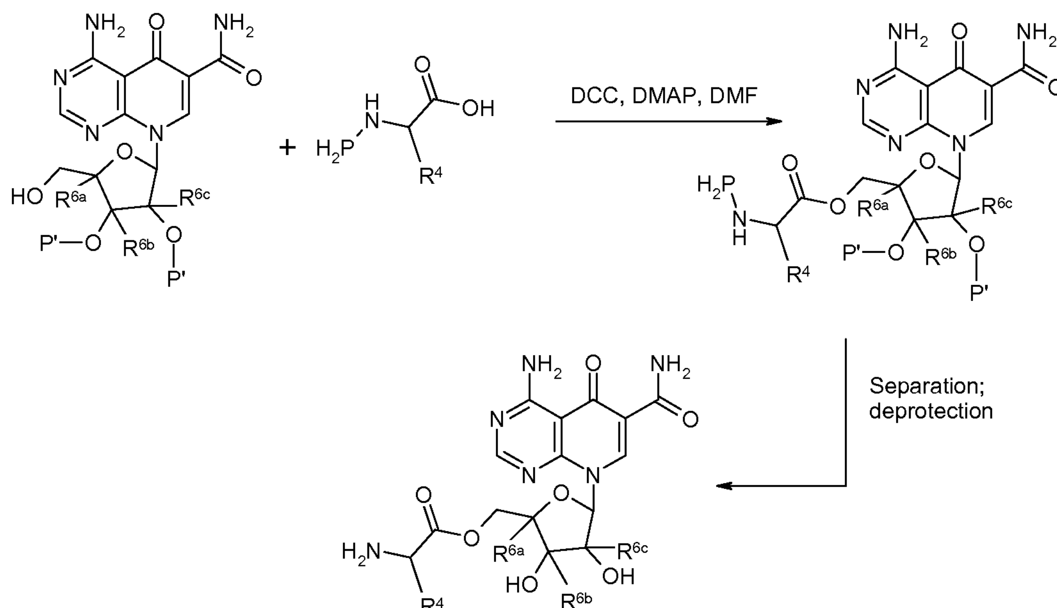
Scheme 1



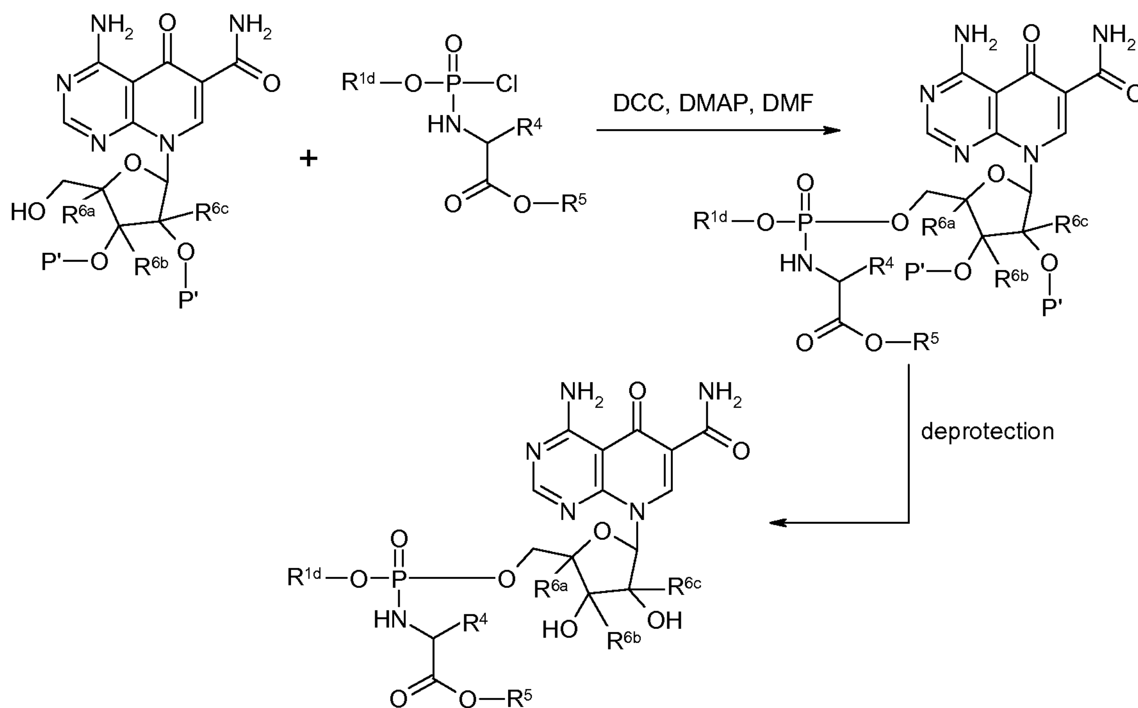
Scheme 2



Scheme 3



Scheme 4



wherein P and P' are protecting groups and R^{1d}, R^4, R^5, R^{6a}, R^{6b}, and R^{7c} are as described herein.

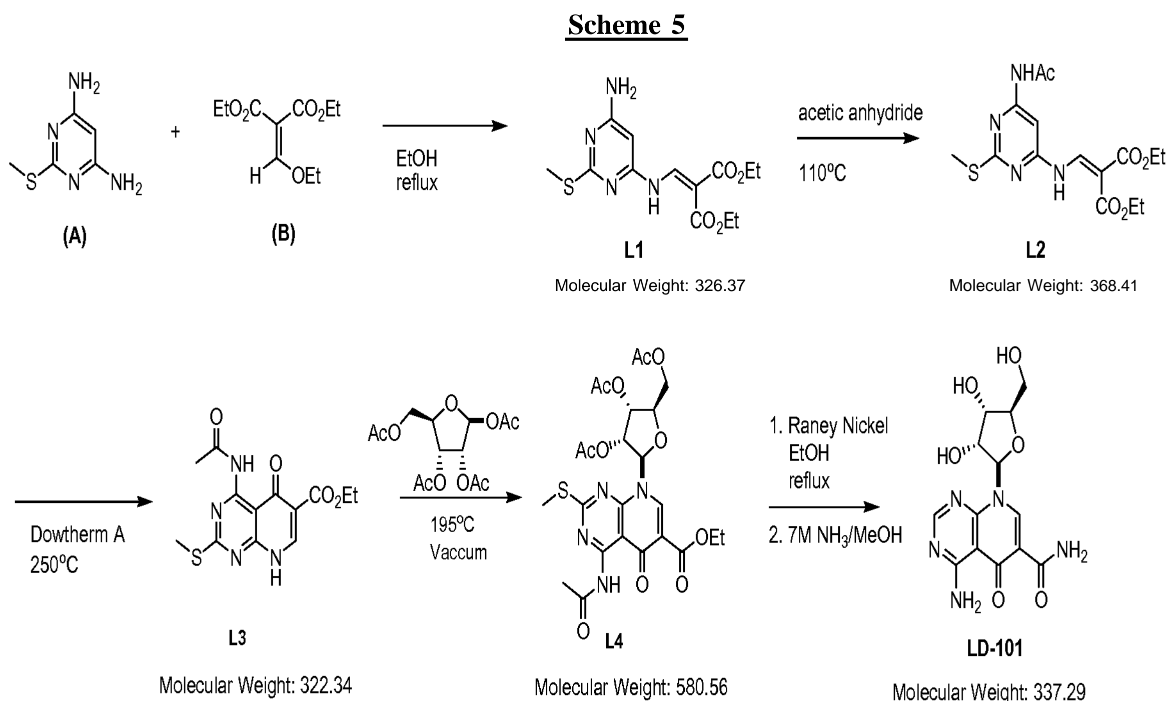
SPECIFIC SYNTHESIS AND MANUFACTURING PROCEDURES FOR REPRESENTATIVE COMPOUND OF INVENTION

[00584] The present invention provides a large scale synthesis of compound of invention. Compound LD- 101, a compound of formula III, is selected as an exemplary compound. The representative synthetic methods used or can be used to prepare LD-101 or analogs are described in the following examples.

SYNTHETIC EXAMPLE 1

[00585] The compound LD- 101 is prepared using the synthetic pathway shown in the Scheme 5.

Scheme 5



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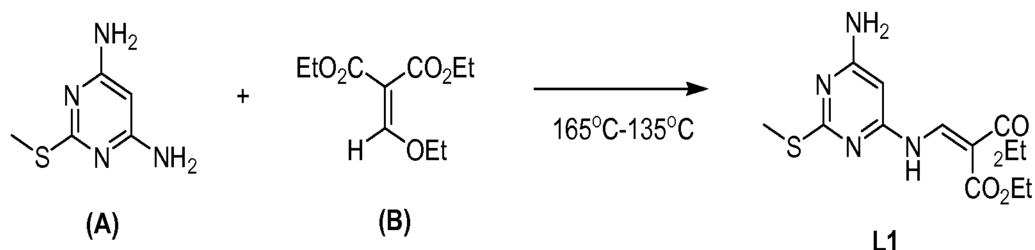
Step 1: Synthesis of LI

(Diethyl-2((6-amino-2-(methylthio)pyrimidin-4-ylamino)methylenemalonate)



[00586] A 2-Liter round bottom flask equipped with a reflux condenser was charged with 2-(methylthio)pyrimidine-4,6-diamine (67.5 g, 432 mmol) and diethylethoxy methylene malonate (93.4 g, 430 mmol) and ethanol (540 mL) and the reaction was heated to between 78°C and 82°C for 10 hours after which time solid had begun to form. The reaction was complete by TLC (ETOAc/Hexane). The reaction was cooled to 30-35°C and stirred for one hour. The reaction mixture was filtered and the filter cake washed with ethanol and dried under vacuum to give the product as an off-white solid (85 g, 60% yield). The product obtained was subsequently characterized by LC/MS and ^{1}HNMR.

MS: 327.0 (M+H)

NMR: Consistent with assigned structure

Step 1: Alternate Synthesis of LI

[00587] A pressure vial was charged with 2-(methylthio)pyrimidine-4,6-diamine (5.0 g, 32.05 mmol) and diethylethoxy methylene malonate (6.93 g, 32.05 mmol) and the reaction heated to 165 °C for 30 minutes. The reaction melted as soon as the temperature reached 140° C and after 10 minutes a solid

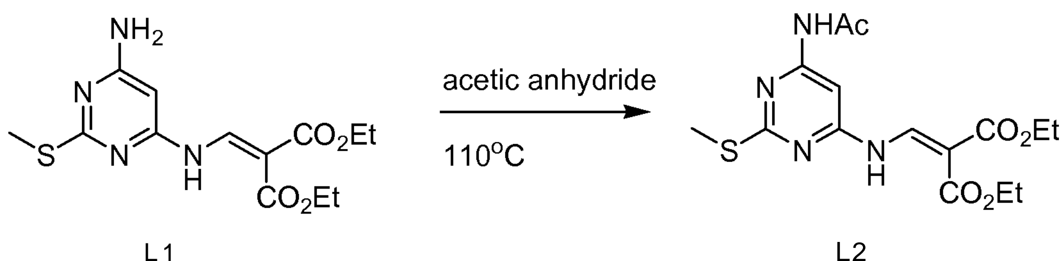
formed. The reaction temperature was lowered to 135° C and stirred for 1 hour. The reaction was cooled and hot ethanol (200 mL) was added and the solid filtered and dried to give the product as off white solid (7.5 g, 72 %). The product obtained was characterized by LC/MS and ^{1}HNMR.

MS: 326.9 (M+H)

NMR: Consistent with assigned structure.

Step 2: Synthesis of L2

(Diethyl 2-((6-acetamido-2-(methylthio)pyrimidin-4-ylamino)methylenemalonate)



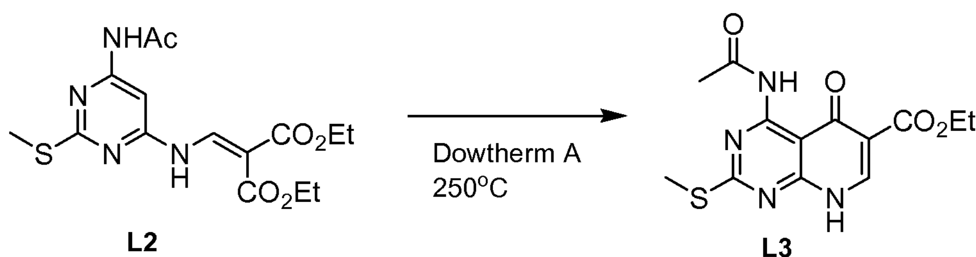
[00588] A 2-Liter round bottom flask equipped with a reflux condenser was charged with **LI** (89.0 g, 273 mmol) and acetic anhydride (1.25 L) and the reaction was stirred between 110 and 115°C for 16 hours. TLC (ETOAc/Hexane) indicated disappearance of LI. The reaction mixture was cooled to 30-35°C and diethyl ether was slowly added to afford precipitation of the product. The reaction mixture was filtered and the filter cake washed with diethyl ether and dried under vacuum to give the product as a light yellow solid (76.5 g, 76% yield). The product obtained was subsequently characterized by LC/MS and ^{1}HNMR.

MS: 369.0 (M+H)

NMR: Consistent with assigned structure

Step 3: Synthesis of L3

(Ethyl 4-acetamido-2-(methylthio)-5-oxo-5,8-dihydropyrido [2,3-rf] pyrimidine-6-carboxylate)



[00589] Intermediate **L3** was prepared as above. The product may be contaminated with some deacetylated compound. Thus, the mixture was further heated with acetic anhydride to reprotect the deacetylated product.

[00590] A 2-Liter round bottom flask equipped with a reflux condenser was charged with **L2** (76.0 g, 206 mmol) and Dowtherm A (1.14 L) and the reaction heated between 240-245°C for 2 hours and monitored by TLC (ETOAc/Hexane). The reaction was allowed to cool to 30-35°C and solid precipitated out. The precipitate was filtered and washed with ether. The mixture of the product and deacetylated product were heated in acetic anhydride at 110°C for 2 hours. The product precipitated upon cooling which was filtered, washed with a minimum amount of diethyl ether to remove excess acetic anhydride and dried under vacuum to give the product as light yellow solid (46.0 g, 69% yield). The product obtained was subsequently characterized by LC/MS and ^{1}HNMR.

MS: 323.0 (M+H)

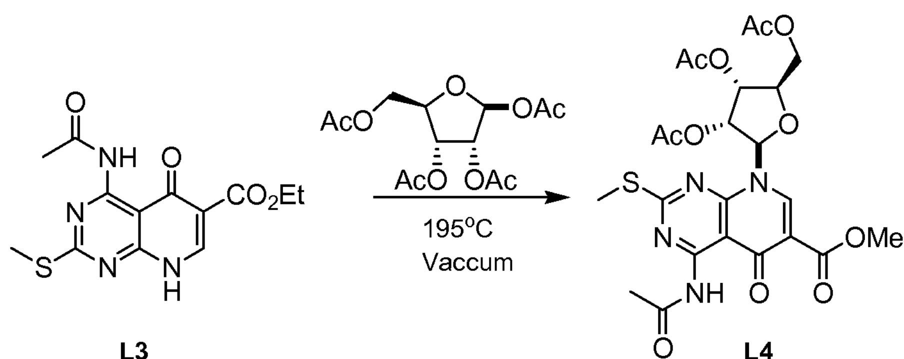
NMR: Consistent with assigned structure

Step 3: Alterenate Synthesis of L3

[00591] A round bottom flask was charged with **L2** (5.2 g, 14.13 mmol) and Dowtherm A (75 mL) and the reaction heated at 250°C for 20 minutes. Since the reaction was not complete the reaction was allowed stir for another 20 minutes and deacetylation of cyclized product was noticed. The reaction was allowed to cool and the product precipitated out. The precipitate was filtered and washed with ether. The mixture of the product and deacetylated product were heated in acetic anhydride at 110°C for 2 hours. The product precipitated on cooling which was filtered, washed with a minimum amount of diethyl ether and dried to give the product as light yellow solid (2.5 g, 55%). The product obtained was characterized by LC/MS and ^{1}HNMR.

Step 4: Synthesis of L4

(4-Acetamido-6-carbethoxy-2-methylthio-5-oxo-8-(2,3,5-tri-0-acetyl -P-D-ribofuranosyl)-pyrido[2,3-d]pyrimidine)

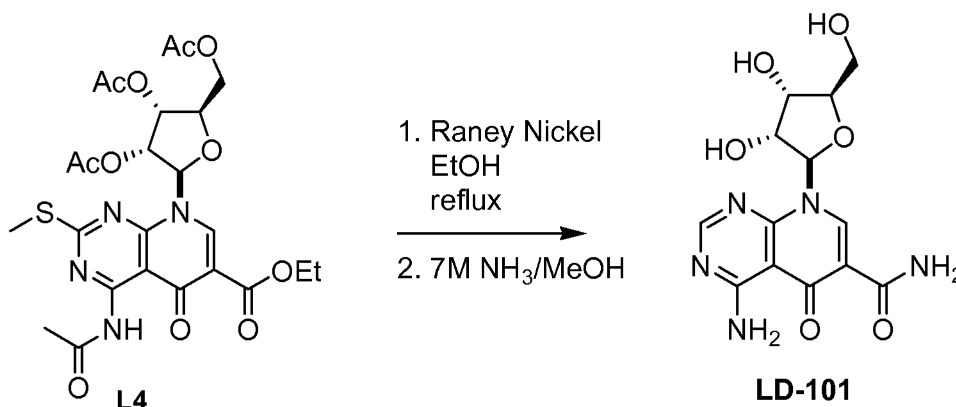


[00592] A 1-Liter round bottom flask equipped with a vacuum adapter was charged with **L3** (46 g, 143 mmol) and tetra-0-acetyl -3-D-ribofuranose (122.6 g, 385 mmol) was heated to 185-195°C under 8-10 mbar of pressure for 2.5 hours and then cooled to 30-35°C. The melt was passed through a column of silica gel purified (eluting with an isocratic mixture of 2:1 EtOAC:Hexane) to give the product as a light yellow solid (44 g, 53%) after evaporation and drying.

MS: 581.0 (M+H)

NMR: Consistent with assigned structure

Step 5: Synthesis of LD-101, a compound of formula III (4-Amino-8-[3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-5-oxopyrido[2, 3-d]pyrimidine-6-carboxamide)



[00593] A 2-Liter round bottom flask equipped with a reflux condenser was charged with **L4** (44 g, 75.8 mmol) and ethanol (1.1 L). Raney Ni (88g, weighed wet) was added to the vessel and the mixture was heated to reflux. After every two hours more 22 additional grams of Raney Ni (weighed wet, a total of 176 g) was added and refluxed continued. The reaction was monitored by TLC (EtOAc/Hexane). After completion, the reaction was filtered over a celite bed and washed with hot ethanol (50-60°C). The solvent was removed under vacuum and the residue was treated with 7M ammonia in methanol (700 mL) overnight (-16 hours). The reaction is monitored by LC/MS for completion and can be verified by ^{1}HNMR. The reaction mixture was cooled to 0-5°C and the precipitated product was filtered and washed with cold methanol. 10.4 g of an off-white solid was obtained which -97% pure by HPLC. For further purification, the solid was suspended in a mixture of Methanol (1 L) and water (150 mL). DMF (50 mL) was added and the suspension was heated to 50°C with stirring for 1 hour. The solid was collected by filtration, washed with cold MeOH followed by diethyl ether to obtain LD-101 as a white solid (7.5 g, 29%).

MS 338 (M+H).

Step 5: Additional Synthesis of LD-101, a compound of formula III

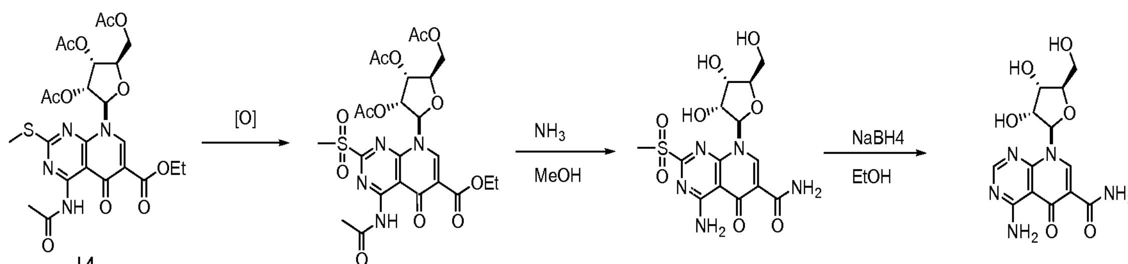
[00594] A round bottom flask was charged with **L4** (6.2 g, 10.68 mmol) and ethanol (150 mL) and Raney Ni (activated by washing with water and ethanol) (12g, weighed wet) and heated to reflux. After that every two hours more 2 additional grams of Raney Ni was added and refluxed. The reaction went to completion in 10 hours by TLC. The reaction was filtered over a celite bed and washed with hot ethanol. The solvent was removed and the residue was treated with 7M ammonia in methanol (100 mL) overnight in a sealed vessel. The product precipitated out which was filtered and washed with methanol. The mother liquor was then concentrated under vacuum at which point additional product precipitated out which was

collected. The collected solid was dried under vacuum to give 1.17 g as white solid. An additional 0.38 grams of LD-101 was collected as described above to give a total of 1.55 grams of LD-101.

SPECIFIC SYNTHETIC EXAMPLE 2

[00595] The compound LD- 101 is prepared using the synthetic pathway shown in the Scheme 6.

Scheme 6

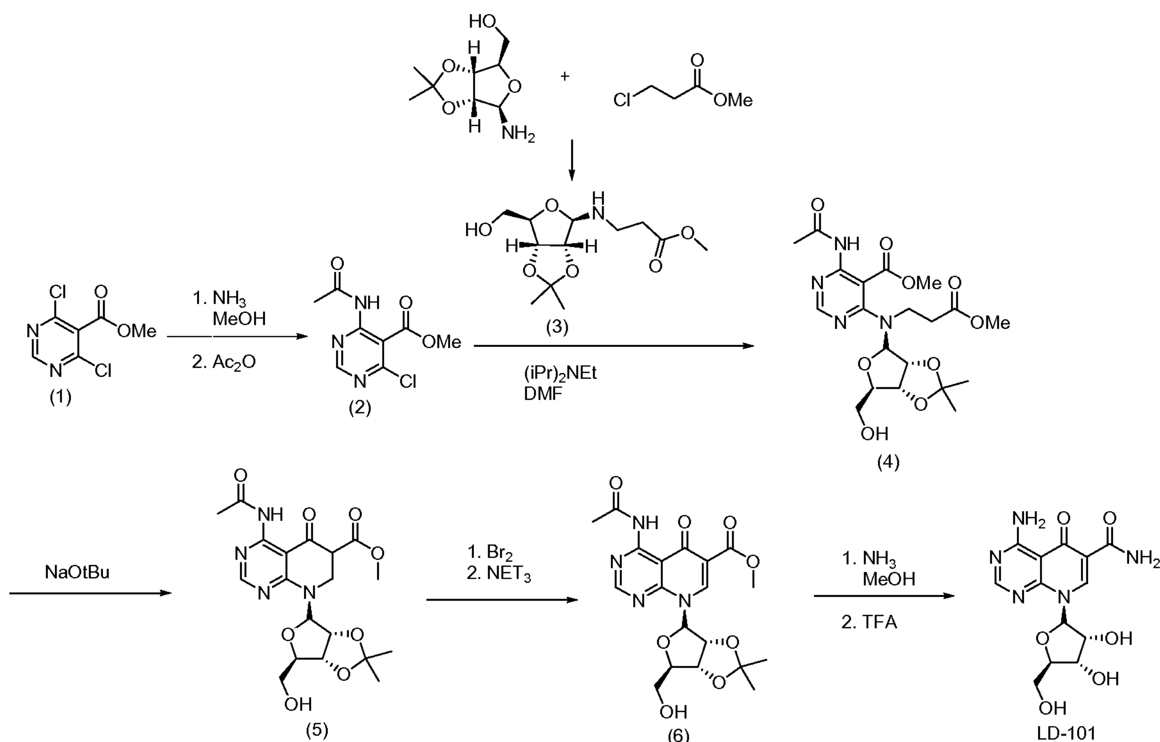


[00596] The compound LD- 101 is or can be prepared using the synthetic pathway depicted in Scheme 6. The oxidation is carried out by conventional method and the amidation using ammonia in MeOH. The reduction is or can be carried out using a borohydride reagent and following the literature procedures (Seto et al. Biorganic and Medicinal Chemistry Letters, 15, (2007) 5083-5089; Uehling et al. David Edward et al, PCT Int. Appl., 2006068826, 29 Jun 2006 ; or Griffin et al. U.S. Pat. Appl. Publ., 2005261354, 24 Nov 2005).

SYNTHETIC EXAMPLE 3

[00597] The compound LD- 101 is prepared using the synthetic pathway shown in the Scheme 7.

Scheme 7

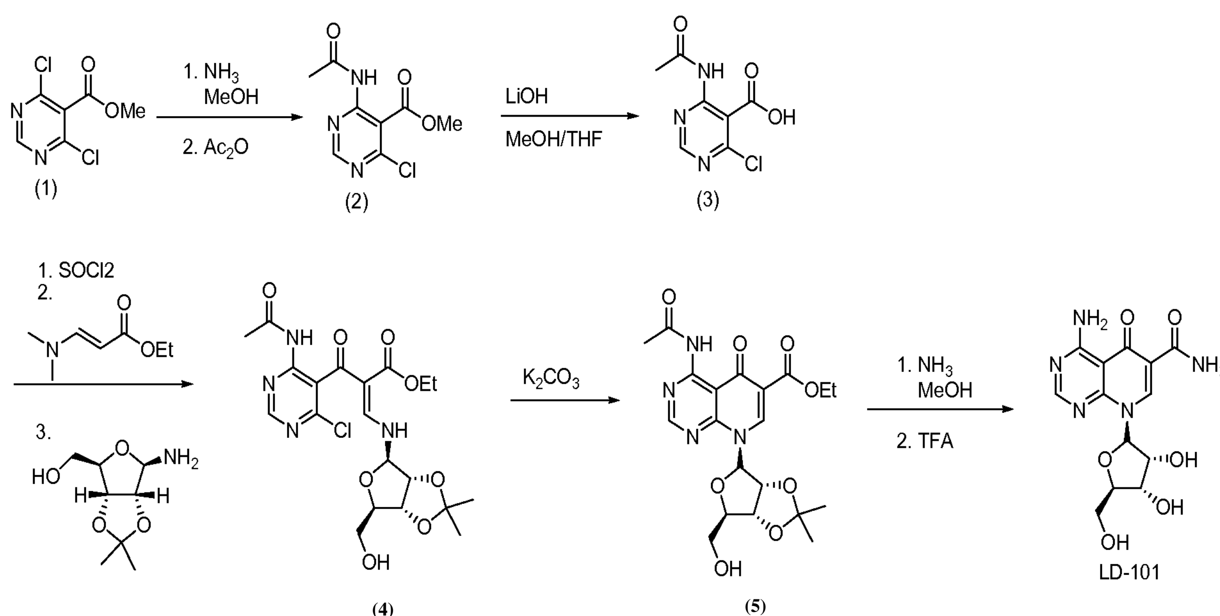


[00598] The compound LD- 101 is or can be prepared using the synthetic pathway depicted in Scheme 7. The substitution chloro with amino can be achieved by using literature methods. In particular, following the procedure described by Lee et al (Biorganic and medicinal Chemistry letters. 11 (2001) 2419-2422). The coupling of ribofuranosylamine (3) with the 6-chloropyrimidine (2) can be performed in the presence of trialkylamine and DMF. The Dieckmann condensation to form the compound of formula 5 followed by halogenations and dehydrohalogenation can be carried out using literature methods, including the method by Player et al (W0200805513 A2).

SYNTHETIC EXAMPLE 4

[00599] The compound LD- 101 is prepared using the synthetic pathway shown in the Scheme 8.

Scheme 8



[00600] The compound LD- 101 is or can be prepared using the synthetic pathway depicted in Scheme 8. The substitution chloro with amino can be achieved by using literature methods. In particular, following the procedure described by Lee et al (Biorganic and medicinal Chemistry letters. 11 (2001) 2419-2422). The hydrolysys of the ester compound (2) to the acid (3) can be carried out in the presence of a base, for example, LiOH. The coversion of the intermediate acid (3) to the cyclized compound (4) can be achieved by following the literature methods (for example, Chen et al WO 2009/089263). The cyclizataion of the intermediate (4) to the pyriopyrimidine compound of formula (5) can be carried out in the presence of a base, like Na_2C03 or K_2C03. The final coversion of the cyclized compound (5) to LD-101 can be carried out via amination with ammonia in MeOH followed by the deprotection with an acid like TFA.

ASSAYS

MATERIALS AND METHODS

Cell Lines, Compounds and Plasmids.

[00601] All cell lines used in this study are either purchased from ATCC or described previously (19-21). The compounds under test herein are prepared in accordance with the invention. HA-tagged Aktl, AKT2 and AKT3 expression plasmids have been described previously (21). The wild-type human AKT1 construct is created by RT-PCR using MCF10A RNA as a template. The PCR products are cloned to *BamH\-EcoKl* sites of pCMV-Myc-Tag2 vector (Stratagene). The AKT1 primers used for PCR are: forward 5'-ATGAGCGACGTGGCTATTGTGAAGG-3 ' and reverse 5'-CTCGCCCCCGTTGGCGTACTCC-3'. AKT1-E17K plasmid was obtained by converting G to A at nucleotide 49 of wild-type AKT1 using QuikChange Site-Directed Mutagenesis Kit (Stratagene). GFP-Akt and GFP-PH domain expression plasmids are created by ligation of Akt and Akt-PH cDNAs into pEGFP-Cl vector (Clontech).

Cloning of full-length human (FL) AKT1.

[00602] Full-length human AKT1 gene was amplified by PCR from a plasmid containing myristylated-AKTl-ER (gift from Robert T. Abraham, Duke University under MTA, described in Klippel et al. in Molecular and Cellular Biology 1998 Volume 18 p. 5699) using the 5' primer: SEQ. ID NO: 2, 5' TATATAGGATCCATGAGCGACGTGGC 3' and the 3' primer: SEQ. ID NO: 3, AAATTTCTCGAGTCAGGCCGTGCTGCTGG 3'. The 5' primer included a BamHI site and the 3' primer included an Xhol site for cloning purposes. The resultant PCR product was subcloned in pcDNA3 as a BamHI/XhoI fragment. A mutation in the sequence (IGC) coding for a Cysteine.sup.25 was converted to the wild-type AKT1 sequence (CGC) coding for an Arginine.sup.25 by site-directed mutagenesis using the QuikChange.RTM. Site Directed Mutagenesis Kit (Stratagene). The AKT1 mutagenic primer: SEQ. ID NO: 4, 5' ACCTGGCGGCCACGCTACTTCCTCC and selection primer: SEQ. ID NO: 5, 5' CTCGAGCATGCAACTAGAGGGCC (designed to destroy an Xbal site in the multiple cloning site of pcDNA3) were used according to manufacturer's suggestions. For expression/purification purposes, AKT1 was isolated as a BamHI/XhoI fragment and cloned into the BamHI/XhoI sites of pFastbacHTb (Invitrogen).

Expression of FL Human AKT1:

[00603] Expression was done using the BAC-to-BAC Baculovirus Expression System from Invitrogen (catalog #10359-016). Briefly 1) the cDNA was transferred from the FastBac vector into bacmid DNA, 2) the bacmid DNA was isolated and used to transfect Sf9 insect cells, 3) the virus was produced in Sf9 cells, 4) T. ni cells were infected with this virus and sent for purification.

Purification of FL Human AKT 1:

[00604] For the purification of full-length AKT1, 130 g sf9 cells (batch # 41646W02) were resuspended in lysis buffer (buffer A, 1 L, pH 7.5) containing 25 mM HEPES, 100 mM NaCl, and 20 mM imidazole. The cell lysis was carried out by Avestin (2 passes at 15K-20K psi). Cell debris was removed by centrifuging at 16K rpm for 1 hour and the supernatant was batch bound to 10 ml Nickel Sepharose HP beads at 4 C for over night. The beads were then transferred to column and the bound material was eluted

with buffer B (25 mM HEPES, 100 mM NaCl, 300 mM imidazole, pH 7.5). AKT eluting fractions were pooled and diluted 3 fold using buffer C (25 mM HEPES, 5 mM DTT; pH 7.5). The sample was filtered and chromatographed over a 10 mL Q-HP column pre-equilibrated with buffer C at 2 mL/min.

[00605] The Q-HP column was washed with 3 column volume (CV) of buffer C, then step eluted with 5 CV 10% D, 5 CV 20% D, 5 CV 30% D, 5 CV 50% D and 5 CV of 100% D; where buffer D is 25 mM HEPES, 1000 mM NaCl, 5 mM DTT; pH 7.5. 5 mL fractions collected. AKT containing fractions were pooled and concentrated to 5 ml. The protein was next loaded to a 120 ml Superdex 75 sizing column that was pre-equilibrated with 25 mM HEPES, 200 mM NaCl, 5 mM DTT; pH 7.5. 2.5 mL fractions were collected.

[00606] AKT 1 eluting fractions were pooled, aliquoted (1 ml) and stored at -80 C. Mass spec and SDS-PAGE analysis were used to confirm purity and identity of the purified full-length AKT1.

[00607] Full length AKT2 and full length AKT3 were cloned, expressed and purified in a similar fashion.

AKT Enzyme Assay

[00608] Compounds of the present invention are tested for AKT 1, 2, and 3 protein serine kinase inhibitory activity in substrate phosphorylation assays. This assay examines the ability of small molecule organic compounds to inhibit the serine phosphorylation of a peptide substrate. The substrate phosphorylation assays use the catalytic domains of AKT 1, 2, or 3. AKT 1, 2 and 3 are also commercially available from Upstate USA, Inc. The method measures the ability of the isolated enzyme to catalyze the transfer of the gamma-phosphate from ATP onto the serine residue of a biotinylated synthetic peptide SEQ. ID NO: 1 (Biotin-ahx-ARKRERAYSFGHHA-amide). Substrate phosphorylation is detected by the following procedure.

[00609] Assays are performed in 384 well U-bottom white plates. 10 nM activated AKT enzyme is incubated for 40 minutes at room temperature in an assay volume of 20 ul containing 50 mM MOPS, pH 7.5, 20 mM MgCl.sub.2, 4 uM ATP, 8 uM peptide, 0.04 uCi [g-.sup.33P] ATP/well, 1 mM CHAPS, 2 mM DTT, and 1 ul of test compound in 100% DMSO. The reaction is stopped by the addition of 50 ul SPA bead mix (Dulbecco's PBS without Mg.sup.2+ and Ca.sup.2+, 0.1% Triton X-100, 5 mM EDTA, 50 uM ATP, 2.5 mg/ml Streptavidin-coated SPA beads.) The plate is sealed, the beads are allowed to settle overnight, and then the plate is counted in a Packard Topcount Microplate Scintillation Counter (Packard Instrument Co., Meriden, Conn.).

[00610] The data for dose responses are plotted as % Control calculated with the data reduction formula 100*(U1-C2)/(C1-C2) versus concentration of compound where U is the unknown value, CI is the average control value obtained for DMSO, and C2 is the average control value obtained for 0.1M EDTA. Data are fitted to the curve described by: y=((Vmax*x)/(K+x)) where Vmax is the upper asymptote and K is the IC50.

Screening for Inhibition of Akt-transformed Cell Growth.

[00611] AKT2 transformed NIH *3T3* cells or LXSN vector-transfected NIH3T3 control cells (19) are plated into 96-well tissue culture plates. Following treatment with 5 μM of each compound, cell growth is

detected with a CellTier 96 One Solution Cell Proliferation kit (Promega). Compounds that inhibit growth in AKT2-transformed but not LXSN-transfected NIH3T3 cells are considered as candidates of Akt inhibitors and are subjected to further analysis.

[00612] Compounds of the invention are or can be tested for activity against AKT1, AKT2, and AKT3 in one or more of the above assays.

***In vitro* Protein Kinase and Apoptosis Assays.**

[00613] *In vitro* kinase assays are performed as previously described (20, 21). Apoptosis is detected with Annexin V (BD Biosciences), which is performed according to manufacture's instruction. Recombinant Akt and PDK1 are purchased from Upstate Biotechnology Inc.

API-1 (or LD-101) and Akt Protein Binding Assay.

[00614] The assay for the binding of the compounds of the invention to Akt may be performed essentially as previously described in Journal of Biological Chemistry, 2010, 285, p8383-8394. The publication is incorporated by reference in its entirety.

Anti-tumor Activity in the Nude Mouse Tumor Xenograft Model.

[00615] Tumor cells are harvested, resuspended in PBS, and injected s.c. into the right and left flanks (2×10^6 cells/flank) of 8-week old female nude mice as reported previously (21). When tumors reached about 100 mm^3, animals are randomized and dosed i.p. with vehicle or drug daily. Control animals receive DMSO (20%) and treated animals are injected i.p. with the compound under test (10 mg/kg/day) in 20% DMSO.

API-1 (or LD101- a representative pyridopyrimidine compound) does not inhibit upstream activators of Akt.

[00616] As described in US2009/0028855, API- 1 (or LD 10 1- a representative pyridopyrimidine compound) does not inhibit upstream activators of Akt. The US patent application publication is incorporated by reference in its entirety.

API-1 (or LD101- a representative pyridopyrimidine compound) is selective for the Akt over the AGC family kinase such as PKA, PKC and SGK, and other signaling transduction molecules ERK, JNK, p38, and STAT3

[00617] As described in US2009/0028855, API- 1 (or LD 10 1- a representative pyridopyrimidine compound) is selective for the Akt over the AGC kinase members PKA, PKC and SGK, and other signaling molecules ERK, JNK, p38, and STAT3. The US patent application publication is incorporated by reference in its entirety.

API-1 (or LD101- a representative pyridopyrimidine compound) inhibits constitutively active Akt, including naturally occurring somatic mutant AKT1-E17K and AKT1-E40K, and its downstream targets / effector molecules / cellular response.

[00618] As described in US2009/0028855, API- 1 (or LD 10 1- a representative pyridopyrimidine compound) inhibits constitutively active Akt, including naturally occurring mutant AKT1-E17K and AKT1-E40K, and its downstream targets. The US patent application publication is incorporated by reference in its entirety.

API-1 (or LD101- a representative pyridopyrimidine compound) suppresses cell growth and induces apoptosis selectively in Akt-overexpressing/activating human cancer cell lines

[00619] As described in US2009/0028855, API- 1 (or LD 10 1- a representative pyridopyrimidine compound) suppresses cell growth and induces apoptosis selectively in Akt-overexpressing/activating human cancer cell lines. The US patent application publication is incorporated by reference in its entirety.

API-1 (or LD101- a representative pyridopyrimidine compound) inhibits the growth in nude mice of tumors with hyperactivated Akt

[00620] As described in US2009/0028855, API- 1 (or LD 10 1- a representative pyridopyrimidine compound) inhibits the growth in nude mice of tumors with hyperactivated Akt. The US patent application publication is incorporated by reference in its entirety.

API-1 (or LD101- a representative pyridopyrimidine compound) directly binds to Akt protein and inhibits Akt membrane translocation.

[00621] As described in Journal of Biological Chemistry, 2010, 285, p8383-8394, API-1 (or LD101- a representative pyridopyrimidine compound) directly binds to Akt protein and inhibits Akt membrane translocation. The publication is incorporated by reference in its entirety.

[00622] In this application, we show that *in vitro,* API- 1 inhibits neither Akt kinase activity nor the phosphorylation of Akt S473 and T308 by rictor mTOR or PDK2 or PDK1. However, <u>in intact cells</u>, (cell culture or in vivo) immunofluorescence and subcellular fractionation experiments demonstrate that API- 1 inhibits IGF 1-stimulated Akt recruitment to the plasma membrane and subsequent phosphorylation of Akt on Ser473 and Thr308. Surface plasmon resonance (SPR) demonstrates that API-1, binds to non-phosphorylated (inactive) Akt on the PH-domain. However, API-1 does not bind already phosphorylated (active) Akt. This means that API- 1 potently, selectively and specifically prevents activation (phosphorylation) of Akt and thereby inhibiting its oncogenic activities. Furthermore, the binding of API-1, to Akt-derived pleckstrin homology (PH) domain as demonstrated by SPR was also confirmed by isothermal calorimetry (ITC) in another high tech experiment aimed at completely elucidating the structural activity relationship between API- 1 and Akt. Consistent with these data, nuclear magnetic resonance (NMR) spectroscopy shows that API- 1 binds to the PH domain engaging amino acid residues in a non-amino acid-specific interaction in the vicinity of the PIP3 binding pocket. Thus, SPR, NMR, as well as biochemical studies and other high tech experiments indicate that API- 1 inhibits Akt function by

binding to the PH domain of Akt, blocking its recruitment (translocation) to the plasma membrane and subsequent inhibition of its phosphorylation (activation). Collectively, these findings indicate API-1 inhibition of Akt is through binding to Akt-PH domain and by blocking Akt membrane translocation, resulting in subsequent blockade of Akt phosphorylation, inhibition Akt activation and its downstream targets and effector molecules.

Analytical Method for Analysis of Compound of the Invention

Analysis of API-1 (or LD101- a representative pyridopyrimidine compound) by Reversed-Phase HPLC

[00623] This method is used to determine the purity of API-1 samples using reversed-phase HPLC. Results are reported as area percentages. Solutions of API-1 prepared at a concentration of 0.5mg/ml in dilute hydrochloric acid and methanol.

Standard Preparation:

[00624] Weigh approximately 5mg of standard is weighed into a 10ml graduated flask. Add 4ml methanol and 4ml 10mM hydrochloric acid. Use heat and sonication to complete dissolution. Allowed to come to room temperature and make up to the mark using 10mM hydrochloric acid. The standard is used to determine the retention time of API- 1.

Sample Preparation:

[00625] Weigh approximately 5mg of test sample into a 10ml graduated flask. Add 4ml methanol and 4ml 10mM hydrochloric acid. Use heat and sonication to complete dissolution. Allowed to come to room temperature and make up to the mark using 10mM hydrochloric acid. Solutions are stable under refrigeration for 48 hours.

Reagent Blank: Methanol and 10mM hydrochloric acid are mixed 1:1 for use as a reagent blank.

Injection: 5ul by Autosampler.

If this results in a peak greater than 1.5AUFS, a smaller injection volume should be used.

Pump Conditions:

Flow rate: 1.2ml/min

Eluant: A= 10mM Ammonium carbonate/Ammonium bicarbonate (1:1).

B=Methanol

Gradient Table:

Time	%A	%B
Pre-run	90	10
1.00	90	10
18.00	10	90
22.00	10	90
22.50	90	10
26.00	90	10

Column:

Manufacturer:: Phenomenex (Phone (310) 212-0555)

Phase: Gemini-NX C-18 150x4.6mm, 5um (P/N: 00F-4454-E0)

Temperature: Ambient

Detection: UV at 272nm, 2.0AUFS. Data collection for 22 minutes.

Interpretation:

[00626] Examine the chromatograms of the samples and the reagent blank. Eliminate any peaks occurring in the blank from the sample chromatograms. The main component peak (API-1) should be between 500 and 1500mAUFS. If it is outside this range the injection volume should be changed appropriately and the method repeated. Identify the peak corresponding to API-using the retention times determined by running standards.

[00627] The Area Percent Purity is determined using the following equation:

[00628] % Area= (Area API-1) x 100% /(Corrected Total Area)

Method Development

Overview:

[00629] A new method for the Purity Determination of API- 1 was needed for an upcoming process development campaign. The standard HPLC method in place uses a trifluoroacetic acid eluant system. Under these pH conditions, API- 1 is likely to be ionized and consequently retention times will be short. This can cause problems with resolution as any related impurities are liable to be similar in polarity and thus poorly resolved.

Chromatography Development:

[00630] The column selected for this project was a Gemini-NX C18 column (Phenomenex). This column is stable over a wide range of pH (2-12), allowing the use of a basic buffer systems which would needed to suppress the ionization of API- 1 (This phase is available in a variety of formats making it suitable for preparative HPLC and LCMS. Initial experiments were performed using a test mix comprising of API-1 and its two precursors L3 and L4. For the initial method development runs, flow rate was set at lml/min. Scouting gradients of 10- 90% or 20-90% over 10 minutes were used, with a 1 minute hold before and after the gradient. The initial run with an unbuffered system (water/acetonitrile gradient, Run 1) shows poor peak shape for several of the components. This is due to there being no control of analyte ionization. (Note: L3 and L4 solutions tend to degrade on standing, however this is useful in method development as it shows other possible product impurities).

[00631] Ammonium Carbonate/Bicarbonate was selected as a as a buffer system. This controls the pH, providing a mildly alkaline environment. These buffers also have the advantage of being volatile which would be useful if preparative HPLC or LCMS was needed to isolate or identify impurities in the future. Three different buffer systems were evaluated: lOmM ammonium bicarbonate (runs 2-3), lOmM

ammonium carbonate (run 4) and lOmM ammonium carbonate + lOmM ammonia (run 5). These systems all gave good separation of API- 1 from the other components, however they did show poor retention and peak shape, with some peak splitting (see run 8).

[00632] The poor peak shape of L5 under these conditions suggested that a different organic modifier might offer improved chromatography, and methanol was evaluated. This gave an immediate improvement in peak shapes and retention (run 18). Ammonium carbonate buffers were screened again with methanol as modifier (runs 18-24). No great differences in selectivity were noted across this pH range, so a buffer of 5mM ammonium carbonate + 5mM ammonium bicarbonate was selected.

[00633] The relatively high viscosity of aqueous methanol eluants can lead to higher system pressure. A flow rate of 1.2 ml/min was selected to keep the system pressure below 2000psi. The gradient time was extended to 17 minutes to provide greater retention and resolution. A typical run of test mix and API- 1 sample are shown in Figures 1, 2, 3 and 4.

Detection Development:

[00634] UV absorbance was selected for use in this method, and no other techniques were evaluated. The detection wavelength was optimized by collecting spectra on-the-fly using a photodiode array detector. The best wavelength under the above conditions was determined to be 272nm. The UV Spectrum is shown in Figure 5.

Sample Preparation Development.

[00635] Compound of invention has been shown in the lab to have poor solubility in common solvents. It was suggested that methanol/water combinations might be used. A 0.5-1.0mg/ml solution in methanol/water (2:1) can be formed using heat almost to boiling and sonication; however this solution is only stable at room temperature for about an hour before it forms a precipitate. As the molecule is basic, it is likely that it would be more soluble in dilute acidic solutions. A mixture of lOmM hydrochloric acid and methanol (60:40) was shown to give solutions of 0.5-1.0mg/ml under mild heating with a heat gun. These solutions were stable in the refrigerator for greater than 64 hours, with no precipitation. The amount of acid in the sample is neutralized by the buffer in the eluant, and has no effect on the chromatography.

Method Validation

Overview:

[00636] The HPLC method for determining the purity of API-1 was validated for repeatability, linearity and sample stability. The method was shown to be suitable for transfer to a manufacturing environment.

Repeatability:

[00637] API-1 retention time repeatability was assessed using six consecutive replicate injections. The percent RSD was found to be 0.15%

[00638] API-1 Retention Time, Injection to injection (n=6)

[00639] Table 7

Run	**Retention Time**
1	7.67
2	7.68
3	7.67
4	7.65
5	7.68
6	7.68
Average	7.67
RSD	0.01
%RSD	0.15

[00640] API-1 peak area repeatability was assessed using six consecutive replicate injections. The percent RSD was found to be 0.52%

[00641] API-1 peak area, Injection to injection (n=6)

[00642] Table 8

Run	**Peak Area**
1	126.60
2	127.10
3	127.30
4	127.70
5	128.10
6	128.40
Average	127.53
RSD	0.67
%RSD	0.52

Linearity:

[00643] Compound of invention peak area linearity was assessed in the range 0.366 to 0.610 mg/ml. This represents about 80-120% of the assay level. The %RSD was found to be 2.0%.

[00644] Table 9

Sample Conc.(mg/ml)	Area	Mean	Response Factor
0.366	93.9	93.85	256.42
0.366	93.8		
0.488	126.8	126.85	259.94
0.488	126.9		
0.610	162.7	162.65	266.64
0.610	162.6		
		RSD	5.19
		%RSD	2.00

Sample Stability:

[00645] As the sample is prepared in a dilute acid, stability was assessed by storing a sample for 65hrs in a refrigerator. The sample was then reanalyzed. No significant changes were seen in the sample.

[00646] Table 10

Sample Time	Retention Time	Peak Area	Area% Assay
0 hours	7.51	147.4	98.11
65 hours	7.67	146.6	98.07

[00647] A new method has been developed for determining the purity of API- 1. The method has been shown to be repeatable and linear in the assay range, and suitable for transfer to a cGMP manufacturing facility. This method would be suitable for use as a weight percentage (external standard) method if a suitable reference standard were available.

[00648] All patents, patent applications, provisional applications, and publications referred to or cited herein are incorporated by reference in their entirety, including all figures and tables, to the extent they are not inconsistent with the explicit teachings of this specification. From the foregoing description, various modifications and changes in the compositions and methods of this invention will occur to those skilled in

the art. All such modifications coming within the scope of the appended claims are intended to be included therein.

[00649] All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

[00650] REFERENCES

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U.S. Patent No. 4,608,392

U.S. Patent No. 4,820,508

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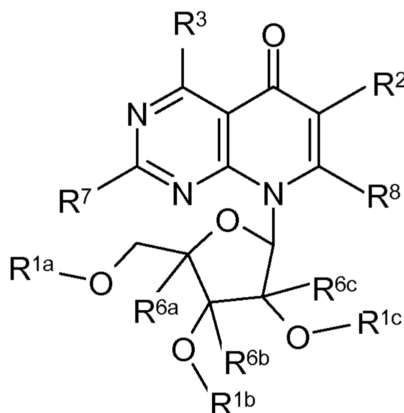
[00651] At least some of the chemical names of compounds of the invention as given and set forth in this application, may have been generated on an automated basis by use of a commercially available chemical naming software program, and have not been independently verified. Representative programs performing this function include the Lexichem naming tool sold by Open Eye Software, Inc. and the Autonom Software tool sold by MDL, Inc. In the instance where the indicated chemical name and the depicted structure differ, the depicted structure will control.

[00652] Chemical structures shown herein were prepared using ISIS®/DRAW. Any open valency appearing on a carbon, oxygen or nitrogen atom in the structures herein indicates the presence of a hydrogen atom. Where a chiral center exists in a structure but no specific stereochemistry is shown for the chiral center, both enantiomers associated with the chiral structure are encompassed by the structure.

WHAT IS CLAIMED IS:

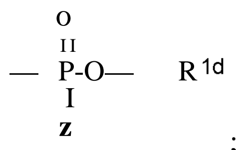
1. A compound according to formula I:



I

wherein

each R^{1a}, R^{1b}, and R^{1c} is independently selected from H, an amino acid, a dipeptide, a tripeptide, and



;

R^{1d} is alkyl, aryl, or heteroaryl; Z is an amino acid, a dipeptide, or a tripeptide;

each R^2 and R^3 is independently selected from H, hydroxy, amino, alkyl, alkoxy, and C(0)-NH $_2$;

each R^{6a}, R^{6b}, R^{6c}, and R^8 is independently selected from H, alkyl, or hydroxyalkyl; or the group -OR^{1b} is absent;

R^7 is selected from H, alkyl, hydroxy, alkoxy, SMe, S(0)Me, or S(0)2Me;

R^8 is selected from H, alkyl, hydroxy, alkoxy, or thioalkoxy;

or a pharmaceutically acceptable salt, solvate or prodrug thereof; and stereoisomers, isotopic variants and tautomers thereof;

provided that at least one of R^{1a}, R^{1b}, and R^{1c} is other than H.

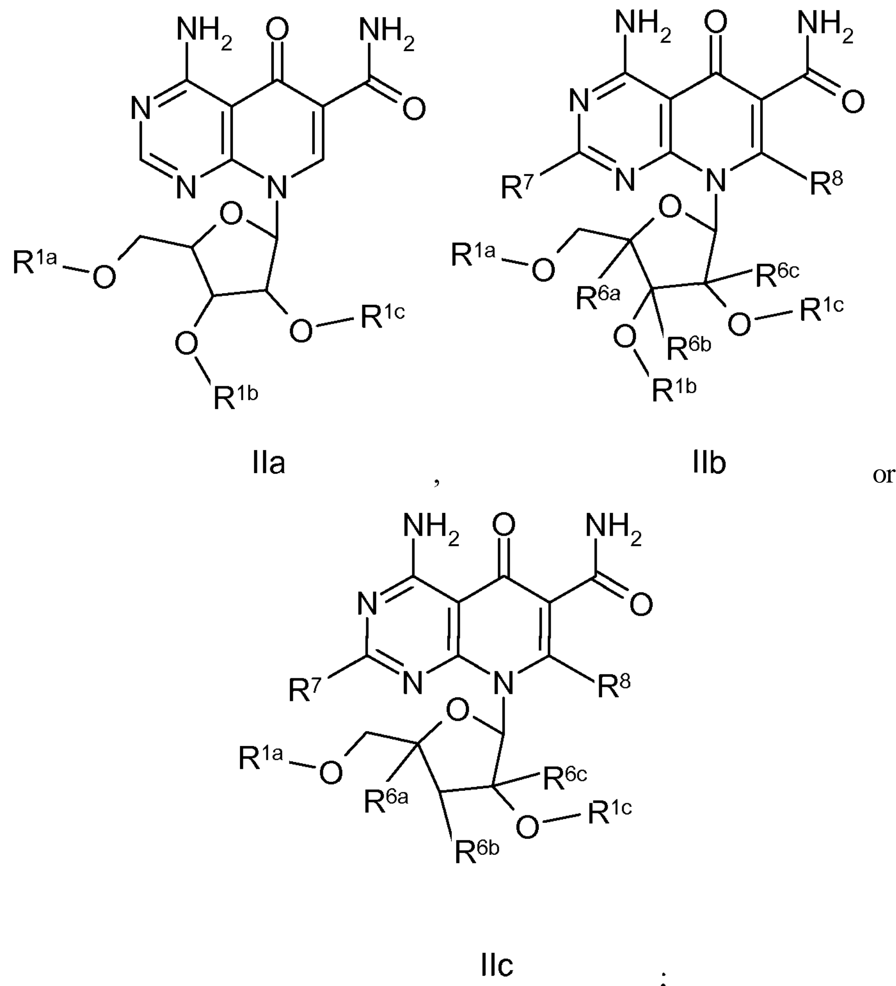
2. The compound according to claim 1, wherein each R^{6a}, R*, R^{6c}, R^7, and R^8 is H.

3. The compound according to claim 1, wherein at least one of R^{6a}, R*, R^{6c}, R^7, and R^8 is other than H.

4. The compound according to any one of claims 1-3, wherein R^2 is C(0)NH $_2$.

5. The compound according to any one of claims 1-3, wherein R^3 is NH_2.

6. The compound according to claim 1, wherein the compound is according to formula Ila, lib, or lie:



and wherein R^{1a}, R^{1b}, R^{1c}, R^{6a}, R^{6b}, R^{6c}, R^{7}, and R^{8} are as in claim 1.

7. The compound according to any one of claims 1-6, wherein at least one of R^{1a}, R^{1b}, and R^{1c} is an amino acid.

8. The compound according to claim 7, wherein the amino acid is an L-amino acid.

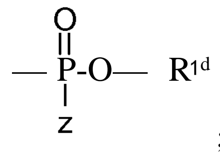
9. The compound according to claim 7, wherein the amino acid is a D-amino acid.

10. The compound according to any one of claims 1-6, wherein at least one of R^{1a}, R^{1b}, and R^{1c} is selected from -D-isoleucyl; -L-isoleucyl; -D-valy; -L-valyl ; -glycyl; -D-phenylalanyl; -L-phenylalanyl; - D-leucyl; -L-leucyl; -L-aspartyl; -D-alpha-aspartyl; -L-alpha-aspartyl; -D-beta-aspartyl; -L-beta- aspartyl; and -L-prolyl.

11. The compound according to any one of claims 1-6, wherein at least one of R^{1a}, R^{1b}, and R^{1c} is a dipeptide.

12. The compound according to any one of claims 1-6, wherein at least one of R^{1a}, R^{1b}, and R^{1c} is a tripeptide.

13. The compound according to any one of claims 1-6, wherein at least one of R^{1a}, R^{1b}, and R^{1c} is



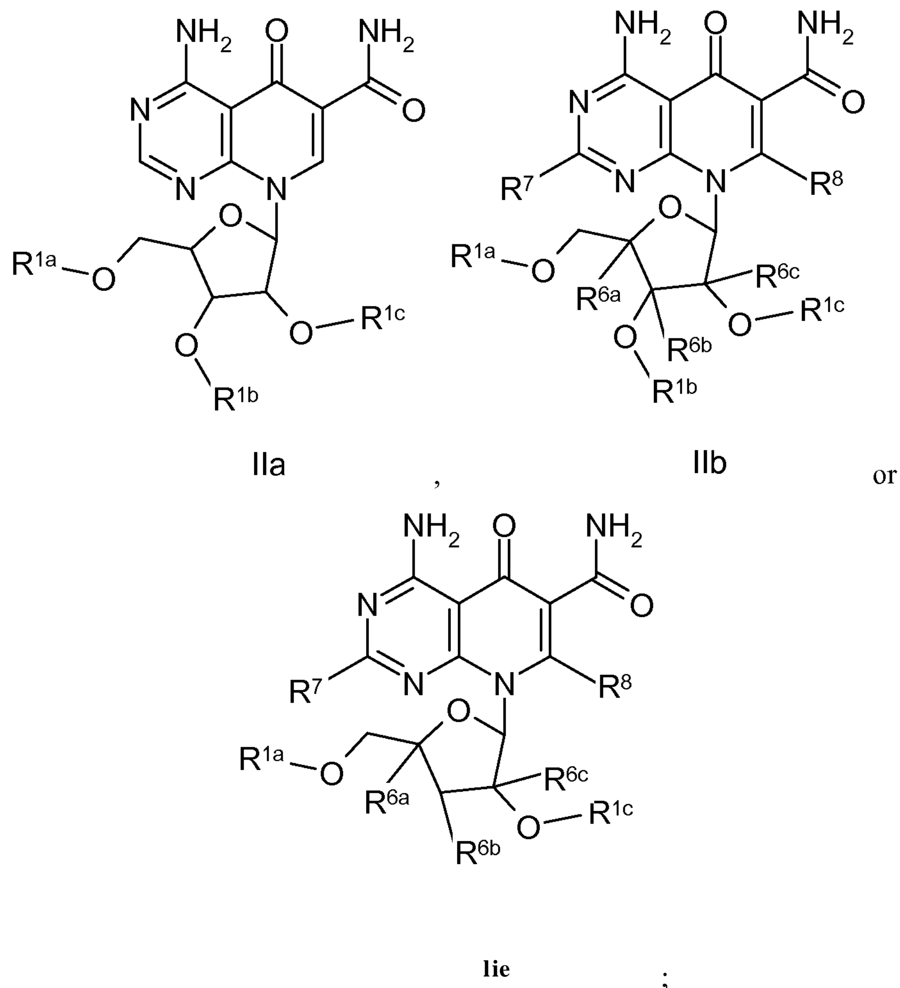
and wherein Z and R^{1d} are as in claim 1.

14. The compound according to claim 13, wherein Z is an amino acid.

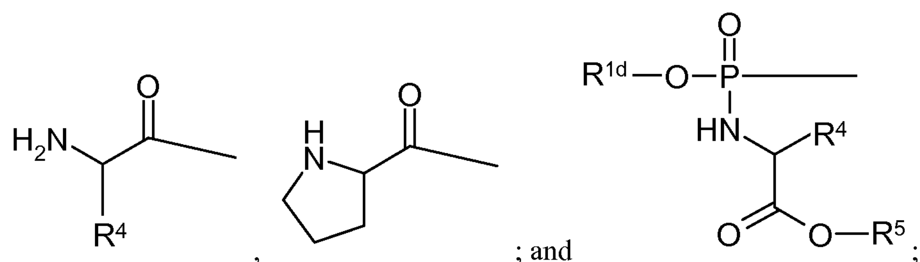
15. The compound according to claim 13, wherein R^{1d} is benzyl.

16. The compound according to any one of claims 1-6, wherein at least one ofR^{1a}, R^{1b}, and R^{1c} is selected from -D-isoleucyl phosphoramidate; -L-isoleucyl phosphoramidate; -D-valyl phosphoramidate; -L-valyl phosphoramidate; -glycyl phosphoramidate; -D-phenylalanyl phosphoramidate; -L-phenylalanyl phosphoramidate; 5'-0-L- leucyl phosphoramidate; 5'-0-L-aspartyl phosphoramidate; -D-alpha-aspartyl phosphoramidate; -L-alpha-aspartyl phosphoramidate; D-beta-aspartyl phosphoramidate; -L-beta- aspartyl phosphoramidate; and -L-prolyl phosphoramidate.

17. A compound according to claim 1, wherein the compound is according to formula Ila, lib, or lie:



and wherein each R^{1a}, R^{1b}, and R^{1c} is independently selected from H,



wherein R^{1d} is alkyl, aryl, or heteroaryl; R^4 is H, substituted or unstubstituted alkyl, or substituted or unsubstituted aryl; R^5 is H, or substituted or unstubstituted alkyl; and R^{6a}, R^f , R^{6c}, R^7, and R^8 are as in claim 1;

provided that at least one of R^{1a}, R^{1b}, and R^{1c} is other than H;

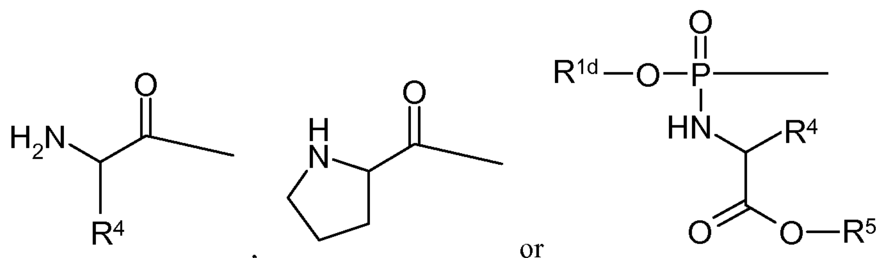
and at least one of R^{6a}, R^f , R^{6c}, R^7, and R^8 is other than H.

18. The compound according to claim 17, wherein each R^{1b}, and R^{1c} is H.

19. The compound according to claim 17, wherein each R^{1a}, and R^{1b} is H.

20. The compound according to claim 17, wherein each R^{1a}, and R^{1c} is H.

21. The compound according to any one of claims 17-20, wherein R^{1a} is



and each R^{1b} and R^{1c} is H.

22. The compound according to any one of claims 17-21, wherein R^4 is a standard amino acid side chain.

23. The compound according to any one of claims 17-21, wherein R^4 is H.

24. The compound according to any one of claims 17-21, wherein R^4 is substituted or unstubstituted alkyl.

25. The compound according to any one of claims 17-21, wherein R^4 is alkyl, substituted with hydroxyl, amino, carboxy, SH, SMe, phenyl, hydroxyphenyl, amido, imidazolyl, indolyl, or -NH-C(=NH)-NH_2.

26. The compound according to any one of claims 17-21, wherein R^4 is Me, Et, i-Pr, n-Bu, i-Bu, sec-Bu, hydroxymethyl, hydroxyethyl, aminopropyl, carboxymethyl, carboxyethyl, amidomethyl, amidoethyl, thiomethyl, methylthioethyl, benzyl, (4-hydroxyphenyl)methyl, (3-indolyl)methyl, or imidazomethyl.

27. The compound according to any one of claims 17-21, wherein R^4 is -$(CH_2)_3$-NH-C(=NH)-NH_2.

28. The compound according to any one of claims 17-27, wherein R^5 is H, Me, Et, or i-Pr.

29. The compound according to any one of claims 17-28, wherein R^{1d} is Me, Et, Ph, or benzyl.

30. The compound according to any one of claims 1, and 3-28, wherein one of R^{6a}, R^{6b}, and R^{6c} is independently Me, Et, or CH_2OH; and the other two are H.

31. The compound according to any one of claims 1, and 3-28, wherein two of R^{6a}, R*, and R^{6c} are independently Me, Et, or CH_2OH; and the other is H.

32. The compound according to any one of claims 1, and 3-28, wherein R^{6a} is Me or CH_2OH.

33. The compound according to any one of claims 1, and 3-28, wherein R^{6c} is Me.

34. The compound according to any one of claims 1, and 3-33, wherein R^7 or R^8 is Me.

35. The compound according to any one of claims 1, and 3-33, wherein R^7 is H or SMe.

36. The compound according to any one of claims 1, and 3-33, wherein R^8 is H.

37. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a pharmaceutically effective amount of a compound of any of claims 1-36.

38. The pharmaceutical composition of claim 37, wherein the carrier is a parenteral carrier.

39. The pharmaceutical composition of claim 37, wherein the carrier is an oral carrier.

40. The pharmaceutical composition of claim 37, wherein the carrier is a topical carrier.

41. A method for preventing, treating or ameliorating in a mammal a disease or condition associated with the elevated or constitutively active expression of an Akt protein, which comprises administering to the mammal an effective disease-treating or condition-treating amount of a compound according to any of claims 1-36 or a pharmaceutical composition according to any of claims 37-40.

42. The method of claim 41, wherein the disease or condition is an oncological disorder.

43. The method of claim 42, wherein the disease or condition is cancer and/or tumor of the anus, bile duct, bladder, bone, bone marrow, bowel (including colon and rectum), breast, eye, gall bladder, kidney, mouth, larynx, esophagus, stomach, testis, cervix, head, neck, ovary, lung, mesothelioma, neuroendocrine, penis, skin, spinal cord, thyroid, vagina, vulva, uterus, liver, muscle, pancreas, prostate, blood cells (including lymphocytes and other immune system cells), or brain.

44. The method of claim 42, wherein the disease or condition is cancer selected from: brain cancer (gliomas), glioblastomas, Bannayan-Zonana syndrome, Cowden disease, Lhermitte-Duclos disease, breast cancer, inflammatory breast cancer, Wilm's tumor, Ewing's sarcoma, Rhabdomyosarcoma, ependymoma, medulloblastoma, colon cancer, head and neck cancer, kidney cancer, lung cancer, liver cancer, melanoma, ovarian cancer, pancreatic cancer, prostate cancer, sarcoma, osteosarcoma, giant cell tumor of bone, thyroid cancer,Lymphoblastic T cell leukemia, Chronic myelogenous leukemia, Chronic lymphocytic leukemia, Hairy-cell leukemia, acute lymphoblastic leukemia, acute myelogenous leukemia, Chronic neutrophilic leukemia, Acute lymphoblastic T cell leukemia, Plasmacytoma, Immunoblastic large cell leukemia, Mantle cell leukemia, Multiple myeloma Megakaryoblastic leukemia, multiple myeloma, acute megakaryocyte leukemia, promyelocytic leukemia, Erythroleukemia,malignant lymphoma, hodgkins lymphoma, non-

hodgkins lymphoma, lymphoblastic T cell lymphoma, Burkitt's lymphoma, follicular lymphoma, neuroblastoma, bladder cancer, urothelial cancer, vulval cancer, cervical cancer, endometrial cancer, renal cancer, mesothelioma, esophageal cancer, salivary gland cancer, hepatocellular cancer, gastric cancer, nasopharangeal cancer, buccal cancer, cancer of the mouth, GIST (gastrointestinal stromal tumor) and testicular cancer.

45. The method of claim 41, wherein the disease or condition is a viral infection.

46. The method according to claim 45, wherein the viral infection is due to HCV, HIV, or HCMV.

47. The method according to claim 41, wherein the route of administration of said compound is enteral, parenteral, intravenous, intramuscular, oral, subcutaneous, topical, or intranasal.

48. A method for inhibiting the Akt/PKB pathway in a cell, said method comprising contacting the cell with an effective amount of a compound according to any of claims 1-36 or a pharmaceutical composition according to any of claims 37-40.

49. The method according to claim 44, wherein said cell constitutively expresses an Akt protein or said cell expresses elevated levels of an Akt protein.

50. The method according to claim 44, wherein said cell is a tumor or cancer cell

5 1. The method according to claim 44, wherein said cell is a human cell.

52. A method of treating a disorder in a person or animal, wherein said disorder is associated with constitutive, abnormal, or elevated expression of an Akt protein in a cell, said method comprising administering an effective amount of a compound according to any of claims 1-36 or a pharmaceutical composition according to any of claims 37-40.

53. The method according to claim 48, wherein said disorder is characterized by abnormal cell proliferation, cell survival, cell migration, and/or cell differentiation.

54. A compound according to any one of claims 1-36, or a pharmaceutically acceptable salt or solvate thereof, for use as a pharmaceutical.

55. A compound according to any one of claims 1-36, or a pharmaceutically acceptable salt or solvate thereof, for use as a pharmaceutical in the treatment or prevention of a disease or condition selected from: cancer and/or tumor of the anus, bile duct, bladder, bone, bone marrow, bowel (including colon and rectum), breast, eye, gall bladder, kidney, mouth, larynx, esophagus, stomach, testis, cervix, head, neck, ovary, lung, mesothelioma, neuroendocrine, penis, skin, spinal cord, thyroid, vagina, vulva, uterus, liver, muscle, pancreas, prostate, blood cells (including lymphocytes and other immune system cells), or brain.

56. A combination of a compound as defined in any one of Claims 1-36, and another pharmacologically active agent.

57. The combination of claim 52, wherein the said pharmacologically active agent is another anti-cancer agent.

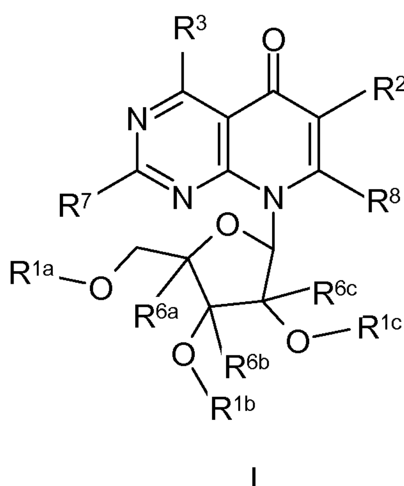
58. The combination of claim 52, wherein the said pharmacologically active agent is altretamine, bleomycin, bortczomib (VELCADE), busulphan, calcium folinate, capecitabine, carboplatin, carmutstine, chlorambucil, cisplatin, cladribinc, crisantaspase, cyclophosphamide, cytarabine,

dacarbazine, dactinomycin daunorubicin, docetaxel, doxorubicin, epirubicin, etoposide, fludarabine, fluorouracil, gefitinib (IRESSA), gemcitabine, hydroxyurea, idarubicin, ifosfamidc, imatinib (GLEEVEC), irinotecan, liposomal doxorubicin, lomistinie, melphalan, mercaptopunrine, methotrexate, titomycin, mitoxantrone, oxaliplatin, paclitaxel, pentostatin, procarbazine, raltitrexed, streptozocin, tegafur-uracil, temozolomide, thiotepa, tioguaninc/thioguanine, topotecan, treosulfan, vi nblastine, vincricstine, vindesine, vinorclbine, melphalan, alcmtuzumab, cetuximab (ERBITUX), gemtuzumab, iodine 131 tositunmomab, rituximab, or trastuzamab (HERCEPTIN).

59. The combination of claim 52, wherein the said pharmacologically active agent is a mitotic inhibitor, an alkylating agent, an antimetabolite, a DNA intercalator, a topoisomerase inhibitor, an antiangiogenic agent, or an antiestrogen.

60. A pharmaceutical formulation comprising

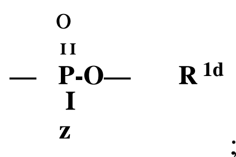
a) a compound according to formula I:



I

wherein

each R^{1a}, R^{1b}, and R^{1c} is independently selected from H, an amino acid, a dipeptide, a tripeptide, and



;

R^{1d} is alkyl, aryl, or heteroaryl; Z is an amino acid, a dipeptide, or a tripeptide;

each R^2 and R^3 is independently selected from H, hydroxy, amino, alkyl, alkoxy, and C(0)-NH_2;

each R^{6a}, R^{6b}, R^{6c}, and R^8 is independently selected from H, alkyl, or hydroxyalkyl; or the group -OR^{1b} is absent;

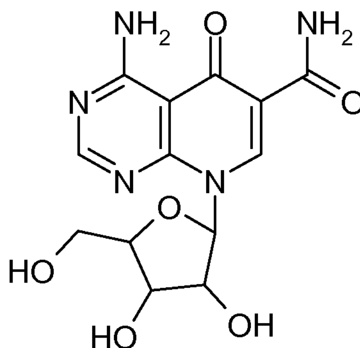
R^8 is selected from H, alkyl, hydroxy, alkoxy, or thioalkoxy;

or a pharmaceutically acceptable salt, solvate or prodrug thereof; and stereoisomers, isotopic variants and tautomers thereof; and

b) a pharmaceutically acceptable carrier.

61. The pharmaceutical formulation according to claim 56, wherein each of R^{1a}, R^{1b}, R^{1c}, R^{6a}, R^{6b}, R^{6c}, R^7 and R^8 is H.

62. The pharmaceutical formulation according to claim 56, wherein the compound is according to formula III:



III

or a pharmaceutically acceptable salt, solvate or prodrug thereof; and stereoisomers, isotopic variants and tautomers thereof.

63. The pharmaceutical formulation according to any one of claims 56-58, wherein the pharmaceutical carrier comprises a mixture of saline, phosphoric acid, and sodium hydroxide.

64. The pharmaceutical formulation according to any one of claims 56-58, wherein the pharmaceutical carrier comprises a mixture of normal saline, 30% phosphoric acid, and 20% sodium hydroxide.

65. The pharmaceutical formulation according to any one of claims 56-58, wherein the pharmaceutical carrier comprises a mixture of normal saline (0.9 vol), 30% phosphoric acid (0.1 vol), and 20% sodium hydroxide (0.025 vol).

66. The pharmaceutical formulation according to any one of claims 56-58, wherein the pharmaceutical carrier comprises a mixture of normal saline (0.8 vol), 30% phosphoric acid (0. 1 vol), and 20% sodium hydroxide (0.05 vol).

67. The pharmaceutical formulation according to any one of claims 56-58, wherein the pharmaceutical carrier comprises a mixture of normal saline (3.8 vol), 30% phosphoric acid (0.1 vol), and 20% sodium hydroxide (0.025 vol).

68. The pharmaceutical formulation according to any one of claims 56-58, wherein the pharmaceutical carrier comprises a mixture of water (9 vol), phosphoric acid (1 vol).

69. The pharmaceutical formulation according to any one of claims 56-58, wherein the pharmaceutical carrier comprises a mixture of water (0.9 vol), Na_3P0_4 (0.9 vol), phosphoric acid (0.2 vol).

70. The pharmaceutical formulation according to any one of claims 56-58, wherein the pharmaceutical carrier comprises a mixture of 45% HP-β-cyclodextrine, phosphoric acid, and sodium hydroxide.

71. The pharmaceutical formulation according to any one of claims 56-58, wherein the pharmaceutical carrier comprises a mixture of 45% HP-β-cyclodextrine, 30% phosphoric acid, and 20% sodium hydroxide.

72. The pharmaceutical formulation according to any one of claims 56-58, wherein the pharmaceutical carrier comprises a mixture of 45% HP-β-cyclodextrine (0.85 vol), 30% phosphoric acid (0. 1 vol), and 20% sodium hydroxide (0.05 vol).

73. The pharmaceutical formulation according to any one of claims 56-58, wherein the pharmaceutical carrier comprises a mixture of 45% HP-β-cyclodextrine (0.90 vol), 30% phosphoric acid (0.05 vol), and 20% sodium hydroxide (0.05 vol).

74. The pharmaceutical formulation according to any one of claims 56-58, wherein the pharmaceutical carrier comprises a mixture of 40% Captisol®, 30% phosphoric acid, and 20% sodium hydroxide.

75. The pharmaceutical formulation according to any one of claims 56-58, wherein the pharmaceutical carrier comprises a mixture of 40% Captisol® (1.75 vol), 30% phosphoric acid (0.1 vol), and 20% sodium hydroxide (0.15 vol).

76. The pharmaceutical formulation according to any one of claims 56-58, wherein the pharmaceutical carrier comprises 20% -40% Captisol®.

77. The pharmaceutical formulation according to any one of claims 56-58, wherein the pharmaceutical carrier comprises a mixture of 20% -40% Captisol®, and normal saline.

78. The pharmaceutical formulation according to any one of claims 56-58, wherein the pharmaceutical carrier comprises a mixture of 20% -40% Captisol®, and 0.9% sodium chloride vehicle.

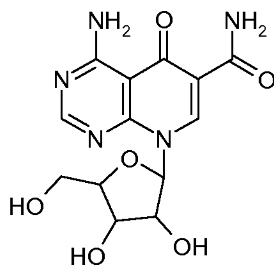
79. The pharmaceutical formulation according to any one of claims 76-78, wherein the compound concentration is 5-100 mg of compound per mL of the carrier.

80. The pharmaceutical formulation according to any one of claims 76-78, wherein the compound concentration is 5-10 mg of compound per mL of the carrier.

81. The pharmaceutical formulation according to any one of claims 56-58, wherein the pharmaceutical carrier comprises a mixture of 20% Captisol® and normal saline, a mixture of 30% Captisol® and normal saline, or a mixture of 40% Captisol® and normal saline.

82. The pharmaceutical formulation according to any one of claims 56-73, wherein the compound concentration varies from 1 mg to 50 mg per mL of the formulation.

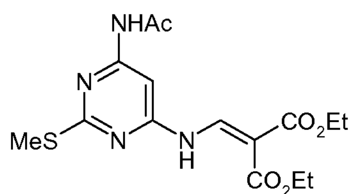
83. A process for preparing a compound according to formula III:



III ;

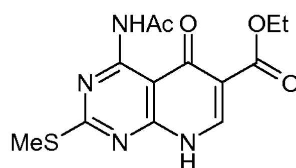
or a pharmaceutically acceptable salt, solvate, stereoisomer, polymorph or isotopic variant thereof comprising the steps of:

Al) heating diethyl 2-((6-acetamido-2-(methylthio)pyrimidin-4-ylamino)methylenemalonate of formula L2:



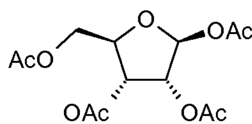
L2 ;

or an isomer thereof; to form the dihydropyrido[2,3-d]pyrimidine compound of formula L3:



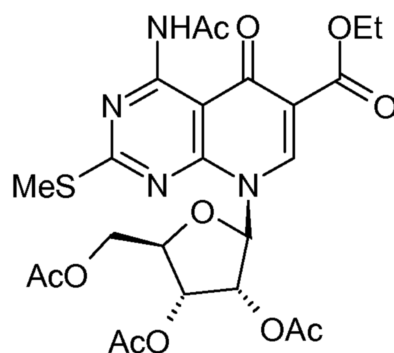
L3 ;

A2) reacting the dihydropyrido[2,3-d]pyrimidine compound of formula L3 with a ribofuranose compound of formula L3':



L3' ;

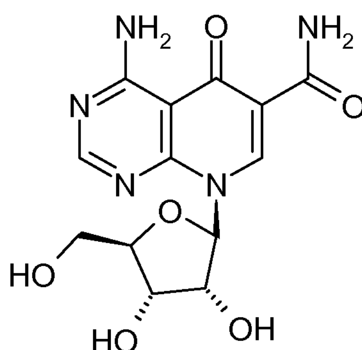
or an isomer thereof; to form the dihydropyrido[2,3-d]pyrimidine compound of formula L4:



L4

; and

A3) deprotecting the dihydropyrido[2,3-d]pyrimidine compound of formula L4; and followed by reacting the intermediate deprotected compound with ammonia to form 4-amino-8-[3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-5-oxopyrido[2,3-d]pyrimidine-6-carboxamide or a compound of formula LD- 101:



LD-1 01

;

or a pharmaceutically acceptable salt, solvate, stereoisomer, polymorph or isotopic variant thereof.

84. The process according to claim 74, wherein the step Al) occurs in the presence of a heat transfer fluid.

85. The process according to claim 75, wherein the heat transfer fluid is Dowtherm A.

86. The process according to claim 74, wherein the step Al) occurs at about 200 to about 300 °C, about 225 to about 275 °C, about 240 to about 260 °C, or about 240 to about 245 °C.

87. The process according to claim 74, wherein in the step Al) the heating is carried out for about 0.25 to 3 hrs.

88. The process according to claim 74, wherein in the step Al) the heating is carried out for about 2 hr or about 20 min.

89. The process according to claim 74, wherein the step Al) further comprises a step of acetylation.

90. The process according to claim 74, wherein the step Al) further comprises a step of heating the product with acetic anhydride.

91. The process according to claim 81, the heating is carried out for about 1 to about 2 hr.

92. The process according to claim 81, the heating is carried out at about 100 to about 120 °C.

93. The process according to claim 74, wherein the step A2) occurs at about 150 to about 250 °C, about 175 to about 225 °C, about 175 to about 200 °C, or about 185 to about 195 °C.

94. The process according to claim 74, wherein the step A2) occurs under reduced pressure.

95. The process according to claim 74, wherein the step A2) occurs under 5-15, or 8-10 mbar pressure.

96. The process according to claim 74, wherein the step A2) is carried out for about 1-5 hrs.

97. The process according to claim 74, wherein the step A2) is carried out for about 2-3 hrs.

98. The process according to claim 74, wherein the deprotection in step A3) occurs in the presence of Raney Ni.

99. The process according to claim 74, wherein the deprotection in step A3) occurs in a solvent selected from the group consisting of methanol, ethanol, or isopropyl alcohol.

100. The process according to claim 74, wherein the deprotection in step A3) occurs in EtOH.

101. The process according to claim 74, wherein the deprotection in step A3) occurs at the reflux temperature of the solvent.

102. The process according to claim 74, wherein the amidation in step A3) occurs in the presence of ammonia in methanol.

103. The process according to claim 74, wherein the amidation in step A3) occurs in the presence of 7M ammonia in methanol.

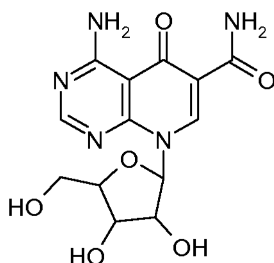
104. The process according to claim 74, wherein the amidation in step A3) occurs for 10-30, 15-25, or 15-20 hrs.

105. The process according to claim 74, wherein the amidation in step A3) further comprises a step of purification of the LD-101.

106. The process according to claim 96, wherein the purification is carried out by heating a suspension of the product in a mixture of methanol, water and DMF.

107. The process according to claim 97, wherein the heating is carried out at 40-60, or about 50 °C.

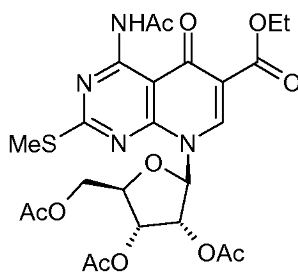
108. A process for preparing a compound according to formula III:



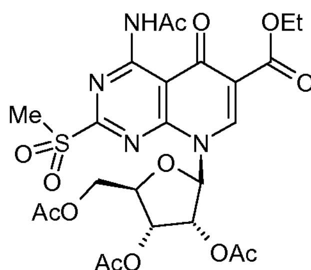
III ;

or a pharmaceutically acceptable salt, solvate, stereoisomer, polymorph or isotopic variant thereof comprising the steps of:

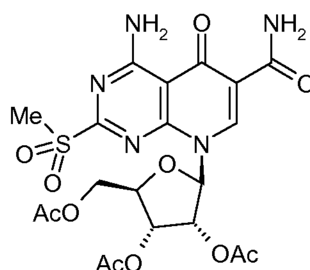
Bl) oxidizing the 2-methylthio dihydropyrido[2,3-d]pyrimidine compound of formula L4:



to the corresponding methylsulfone compound L5:



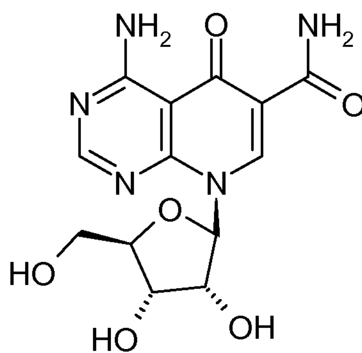
B2) converting the 2-methylsulfonyl dihydropyrido[2,3-d]pyrimidine compound of formula L5 to the carboxamide of formula L6:



;

or an isomer thereof;

B3) reducing the carboxamide of formula L6 to form 4-amino-8-[3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-5-oxopyrido[2,3-d]pyrimidine-6-carboxamide or a compound of formula LD-101:



LD-1 0 1 ;

or a pharmaceutically acceptable salt, solvate, stereoisomer, polymorph or isotopic variant thereof.

109. The process according to claim 103, wherein the oxidation in step Bl) occurs in the presence of a conventional oxidation agent.

110. The process according to claim 103, wherein the oxidation in step Bl) occurs in the presence of

111. The process according to claim 103, wherein the amidation in step B2) occurs in the presence of ammonia in methanol.

112. The process according to claim 103, wherein the amidation in step B2) occurs in the presence of 7M ammonia in methanol.

113. The process according to claim 103, wherein the amidation in step B2) occurs for 10-30, 15-25, or 15-20 hrs.

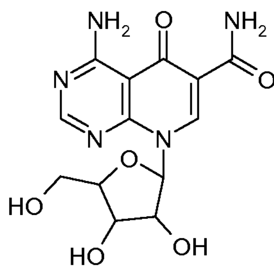
114. The process according to claim 103, wherein the reduction in step B3) occurs in the presence of a borohydride reagent.

115. The process according to claim 103, wherein the reduction in step B3) occurs in the presence of a sodium borohydride reagent.

116. The process according to claim 103, wherein the reduction in step B3) occurs in a solvent selected from the group consisting of methanol, ethanol, or isopropyl alcohol.

117. The process according to claim 103, wherein the reduction in step B3) occurs in EtOH.

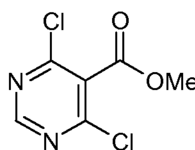
118. A process for preparing a compound according to formula III:



III ;

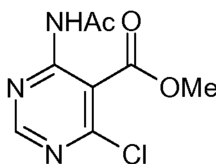
or a pharmaceutically acceptable salt, solvate, stereoisomer, polymorph or isotopic variant thereof comprising the steps of:

CI) converting the 4,6-dichloropyrimidine compound formula (1):



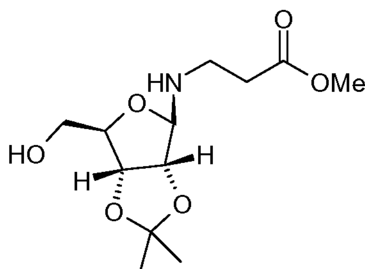
(1)

to the corresponding 4-amino-6-chloropyrimidine compound and then protecting the amino group to form the 4-acetylamino-6-chloropyrimidine compound of formula (2) :



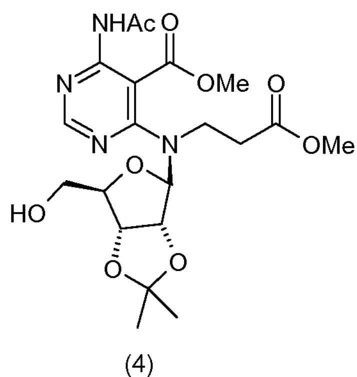
(2)

C2) reacting the 4-acetylamino-6-chloropyrimidine compound (2) with b-D-ribofuranosylamine (3)



(3)

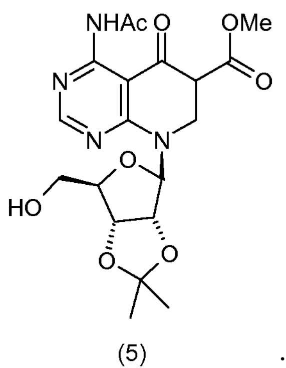
to form the coupled compound of formula (4):



(4) ;

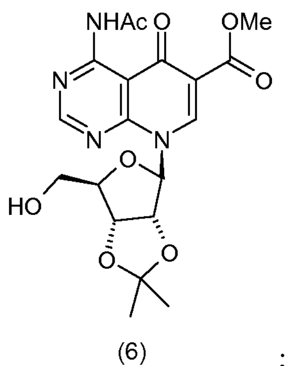
or an isomer thereof;

C3) cyclizing the compound of formula of (4) to form the tetrahydropyrido[2,3-d]pyrimidine of formula (5):



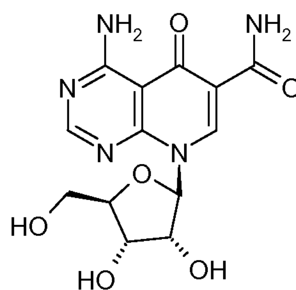
(5) ;

C4) converting the tetrahydropyrido[2,3-d]pyrimidine of formula (5) to form the dihydropyrido[2,3-d]pyrimidine of formula (6):



(6) ;

C5) converting the dihydro compound of formula (6) to 4-amino-8-[3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-5-oxopyrido[2,3-d]pyrimidine-6-carboxamide or a compound of formula LD-101:



LD-101 ;

or a pharmaceutically acceptable salt, solvate, stereoisomer, polymorph or isotopic variant thereof.

119. The process according to claim 113, wherein in step CI) the conversion of 4-chloro to 4-amino occurs in the presence of ammonia.

120. The process according to claim 113, wherein in step CI) the conversion of 4-chloro to 4-amino occurs in the presence of ammonia in MeOH.

121. The process according to claim 113, wherein in step CI) the protection of 4-amino to 4-acetylamino occurs in the presence of acetic anhydride.

122. The process according to claim 113, wherein the coupling in step C2) occurs in the presence of an amine.

123. The process according to claim 113, wherein the coupling in step C2) occurs in the presence of trialkylamine.

124. The process according to claim 113, wherein the coupling in step C2) occurs in the presence of di-i-propyl-ethylamine.

125. The process according to claim 113, wherein the coupling in step C2) occurs in the presence of di-i-propyl-ethylamine and DMF.

126. The process according to claim 113, wherein the cyclization in step C3) occurs in the presence of an alkoxide.

127. The process according to claim 113, wherein the cyclization in step C3) occurs in the presence of sodium or potassium alkoxide.

128. The process according to claim 113, wherein the cyclization in step C3) occurs in the presence of Na-O-t-Bu.

129. The process according to claim 113, wherein the cyclization in step C3) occurs in an alcoholic solvent.

130. The process according to claim 113, wherein the cyclization in step C3) occurs in a solvent selected from the group consisting of methanol, ethanol, or isopropyl alcohol.

131. The process according to claim 113, wherein the cyclization in step C3) occurs in EtOH.

132. The process according to claim 113, wherein the conversion in step C4) occurs in presence of bromine.

133. The process according to claim 113, wherein the conversion in step C4) comprises bromination with bromine followed by elimination.

134. The process according to claim 113, wherein the conversion in step C4) comprises bromination with bromine followed by elimination in the presence of a base.

135. The process according to claim 113, wherein the conversion in step C4) comprises bromination with bromine followed by elimination in the presence of trialkylamine.

136. The process according to claim 113, wherein the conversion in step C4) comprises bromination with bromine followed by elimination in the presence of triethylamine.

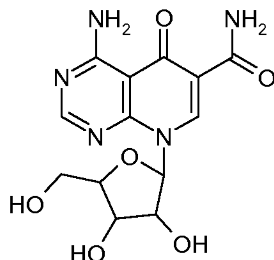
137. The process according to claim 113, wherein the conversion in step C5) comprises amidation followed by the deprotection.

138. The process according to claim 113, wherein the conversion in step C5) comprises amidation with ammonia in methanol followed by the deprotection.

139. The process according the claim 133, wherein the deprotection occurs in the presence of an acid.

140. The process according the claim 133, wherein the deprotection occurs in the presence of trifluoroacetic acid.

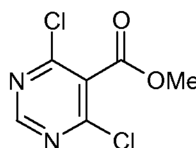
141. A process for preparing a compound according to formula III:



III ;

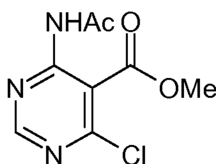
or a pharmaceutically acceptable salt, solvate, stereoisomer, polymorph or isotopic variant thereof comprising the steps of:

Dl) converting the 4,6-dichloropyrimidine compound formula (1):



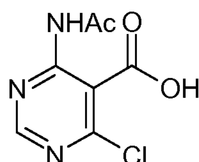
(1)

to the corresponding 4-amino-6-chloropyrimidine compound and then protecting the amino group to form the 4-acetylamino-6-chloropyrimidine compound of formula (2) :



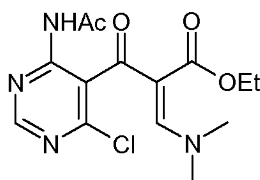
(2)

D2) hydrolyzing the methyl ester with a base to form the corresponding acid (3')



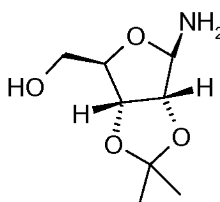
(3') ;

D3) coupling the acid (3) with Me_2N-CH=CH-C0 $_2$Et to form the intermediate 4-acetylamino-6-chloropyrimidine compound (3")



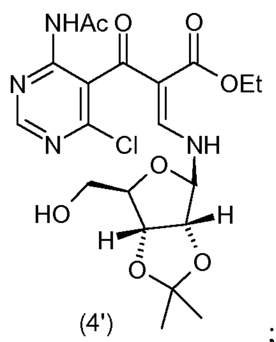
(3") ;

D4) reacting the 4-acetylamino-6-chloropyrimidine compound (3") with b-D-ribofuranosylamine (3)



(3)

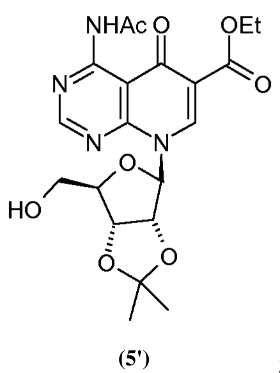
to form the coupled compound of formula (4'):



;

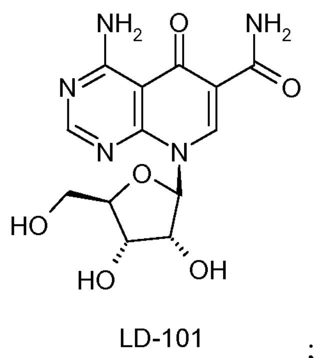
or an isomer thereof;

D5) cyclizing the compound of formula of (4') to form the tetrahydropyrido[2,3-d]pyrimidine of formula (5'):



;

D6) converting the dihydro compound of formula (5') to 4-amino-8-[3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-5-oxopyrido[2,3-d]pyrimidine-6-carboxamide or a compound of formula LD-101:



;

or a pharmaceutically acceptable salt, solvate, stereoisomer, polymorph or isotopic variant thereof.

142. The process according to claim 136, wherein in step Dl) the conversion of 4-chloro to 4-amino occurs in the presence of ammonia.

143. The process according to claim 136, wherein in step Dl) the conversion of 4-chloro to 4-amino occurs in the presence of ammonia in MeOH.

144. The process according to claim 136, wherein in step Dl) the protection of 4-amino to 4-acetylamino occurs in the presence of acetic anhydride.

145. The process according to claim 136, wherein in step D2) the hydrolysis of 5-ester to 5-acid occurs in the presence of a base.

146. The process according to claim 136, wherein in step D2) the hydrolysis of 5-ester to 5-acid occurs in the presence of LiOH.

147. The process according to claim 136, wherein in step D2) the hydrolysis of 5-ester to 5-acid occurs in a solvent.

148. The process according to claim 136, wherein in step D2) the hydrolysis of 5-ester to 5-acid occurs in MeOH/THF.

149. The process according to claim 136, wherein in step D3) the coupling comprises an initial formation of acid chloride.

150. The process according to claim 144, wherein the acid chloride is formed by reacting the acid of formula (3') with thionyl chloride.

151. The process according to claim 144, wherein the acid chloride is reacted with Me_2N-CH=CH-$C0_2Et$.

152. The process according to claim 144, wherein the acid chloride is reacted with Me_2N-CH=CH-$C0_2Et$ in the presence of a solvent.

153. The process according to claim 136, wherein in step D4) the reaction of the compound of formula (3") with the ribofuranosylamine occurs in the presence of a catalyst or solvent.

154. The process according to claim 136, wherein in step D5) the cyclization occurs in the presence of a base.

155. The process according to claim 136, wherein in step D5) the cyclization occurs in the presence of K_2CO_3.

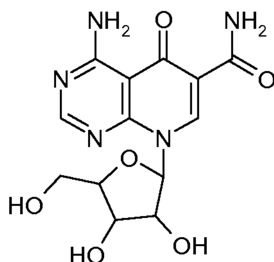
156. The process according to claim 136, wherein the conversion in step D6) comprises amidation followed by the deprotection.

157. The process according to claim 136, wherein the conversion in step D6) comprises amidation with ammonia in methanol followed by the deprotection.

158. The process according the claim 152, wherein the deprotection occurs in the presence of an acid.

159. The process according the claim 152, wherein the deprotection occurs in the presence of trifluoroacetic acid.

160. An analytical method useful to analyze a compound according to formula III:



III ;

or a pharmaceutically acceptable salt, solvate, stereoisomer, polymorph or isotopic variant thereof; comprising the steps of

El) preparing a sample of compound III;

E2) loading the sample on a HPLC column;

E3) eluting the HPLC column with a solvent system made of a buffer;

E5) processing the elute outcome with a detector; and

E6) obtain a chromatography trace.

161. The analytical method according to claim 155, wherein the sample is prepared by dissolving the compound of formula III in a solvent.

162. The analytical method according to claim 155, wherein the sample is prepared by dissolving the compound of formula III in a mixture of dilute HC1 and methanol.

163. The analytical method according to claim 155, wherein the sample is prepared by dissolving the compound of formula III in 10 mM HC1 and methanol (60:40).

164. The analytical method according to claim 155, wherein the sample is prepared by dissolving 0.5 to 1 mg of the compound of formula III in about 1 mL of HC1 (about 10 mM) and methanol (60:40) mixture.

165. The analytical method according to claim 155, wherein the HPLC column is a column stable over pH values of 2 t ol2.

166. The analytical method according to claim 155, wherein the HPLC column is a C18 column.

167. The analytical method according to claim 155, wherein the HPLC column is a Gemini-NX C 18 column.

168. The analytical method according to claim 155, wherein the solvent buffer system comprises a gradient system of two components:

iii) a mixture of dilute ammonium carbonate and dilute ammonium bicarbonate; and

iv) methanol.

169. The analytical method according to claim 155, wherein the solvent buffer system comprises a gradient system made of a mixture of dilute ammonium carbonate and dilute ammonium bicarbonate (1:1); and methanol.

170. The analytical method according to claim 155, wherein the solvent buffer system comprises a gradient system made of a mixture of dilute ammonium carbonate and dilute ammonium bicarbonate (1:1, 10 mM); and methanol.

171. The analytical method according to claim 155, wherein the HPLC column is eluted with the buffer system at a rate of about 1.2 mL/min.

172. The analytical method according to claim 155, wherein the detector is a UV detector.

173. A method for preventing, treating or ameliorating in a mammal a disease or condition associated with the elevated or constitutively active expression of an Akt protein, which comprises administering to the mammal an effective disease-treating or condition-treating amount of a compound according to any of claims 1-36 or a pharmaceutical composition according to any of claims 37-40 in combination with radiation therapy.

174. A method for preventing, treating or ameliorating in a mammal a disease or condition associated with the elevated or constitutively active expression of an Akt protein, which comprises administering to the mammal an effective disease-treating or condition-treating amount of a compound according to any of claims 1-36 or a pharmaceutical composition according to any of claims 37-40 in combination with a second pharmaceutical agent.

175. The method of claim 169, wherein the second pharmaceutical agent is selected from an estrogen receptor modulator, an androgen receptor modulator, a retinoid receptor modulator, a cytotoxiccytostatic agent, an antiproliferative agent, a prenyl-protein transferase inhibitor, an HMG-CoA reductase inhibitor, an HIV protease inhibitor, a reverse transcriptase inhibitor, an angiogenesis inhibitor, PPAR-γ agonists, PPAR-δ agonists, an inhibitor of inherent multidrug resistance, an anti-emetic agent, an agent useful in the treatment of anemia, an agent useful in the treatment of neutropenia, an immunologic-enhancing drug, an inhibitor of cell proliferation and survival signaling, and an agent that interferes with a cell cycle checkpoint.

176. The method of claim 169, wherein the second pharmaceutical agent is paclitaxel or trastuzumab.

177. The method of claim 169, wherein the second pharmaceutical agent is a COX-2 inhibitor.

178. The method of any one of claims 168-172, wherein the disease or condition is an oncological disorder.

179. The method of any one of claims 168-172, wherein the disease or condition is cancer and/or tumor of the anus, bile duct, bladder, bone, bone marrow, bowel (including colon and rectum), breast, eye, gall bladder, kidney, mouth, larynx, esophagus, stomach, testis, cervix, head, neck, ovary, lung, mesothelioma, neuroendocrine, penis, skin, spinal cord, thyroid, vagina, vulva, uterus, liver, muscle, pancreas, prostate, blood cells (including lymphocytes and other immune system cells), or brain.

180. The method of any one of claims 168-172, wherein the disease or condition is cancer selected from: brain cancer (gliomas), glioblastomas, Bannayan-Zonana syndrome, Cowden disease, Lhermitte-Duclos disease, breast cancer, inflammatory breast cancer, Wilm's tumor, Ewing's sarcoma, Rhabdomyosarcoma, ependymoma, medulloblastoma, colon cancer, head and neck

cancer, kidney cancer, lung cancer, liver cancer, melanoma, ovarian cancer, pancreatic cancer, prostate cancer, sarcoma, osteosarcoma, giant cell tumor of bone, thyroid cancer,Lymphoblastic T cell leukemia, Chronic myelogenous leukemia, Chronic lymphocytic leukemia, Hairy-cell leukemia, acute lymphoblastic leukemia, acute myelogenous leukemia, Chronic neutrophilic leukemia, Acute lymphoblastic T cell leukemia, Plasmacytoma, Immunoblastic large cell leukemia, Mantle cell leukemia, Multiple myeloma Megakaryoblastic leukemia, multiple myeloma, acute megakaryocyte leukemia, promyelocytic leukemia, Erythroleukemia,malignant lymphoma, hodgkins lymphoma, non-hodgkins lymphoma, lymphoblastic T cell lymphoma, Burkitt's lymphoma, follicular lymphoma, neuroblastoma, bladder cancer, urothelial cancer, vulval cancer, cervical cancer, endometrial cancer, renal cancer, mesothelioma, esophageal cancer, salivary gland cancer, hepatocellular cancer, gastric cancer, nasopharangeal cancer, buccal cancer, cancer of the mouth, GIST (gastrointestinal stromal tumor) and testicular cancer.

181. The method of any one of claims 168-175, wherein the disease or condition is a viral infection.

182. The method according to claim 176, wherein the viral infection is due to HCV, HIV, or HCMV.

183. A method for preventing, treating or ameliorating in a mammal a disease or condition associated with mantle cell lymphoma, which comprises administering to the mammal an effective disease-treating or condition-treating amount of a compound according to formula I-Vlb or a pharmaceutical composition thereof in combination with a second pharmaceutical agent.

184. A method for preventing, treating or ameliorating in a mammal a disease or condition associated with multiple myeloma, which comprises administering to the mammal an effective disease-treating or condition-treating amount of a compound according to formula I-Vlb or a pharmaceutical composition thereof in combination with a second pharmaceutical agent.

185. The method according to either of claims 183-1 84, wherein the compound is according to formula III or the compound is LD- 101.

186. The method according to any one of claims 183- 186, wherein the second pharmaceutical agent is Velcade®.

187. A method for preventing, treating or ameliorating in a mammal a disease or condition associated with prostate cancer, breast cancer, ovarian cancer or resistant ovarian cancer (CI 3), which comprises administering to the mammal an effective disease-treating or condition-treating amount of a compound according to formula I-VIb or a pharmaceutical composition thereof in combination with a second pharmaceutical agent.

188. The method according to claim 187, wherein the compound is according to formula III or the compound is LD- 101.

189. The method according to any one of claims 187- 188, wherein the second pharmaceutical agent is Rapamycin, RADOOl, Cisplatin, CDDP, or Taxol®.

190. A method for preventing, treating or ameliorating in a mammal a disease or condition associated with lung cancer, which comprises administering to the mammal an effective disease-treating or condition-treating amount of a compound according to formula I-VIb or a pharmaceutical composition thereof in combination with a second pharmaceutical agent.

191. The method according to claim 190, wherein the compound is according to formula III or the compound is LD- 101.

192. The method according to any one of claims 190-191, wherein the second pharmaceutical agent is CDDP, Etoposide®, or Rapamycin.

FIGURE 1

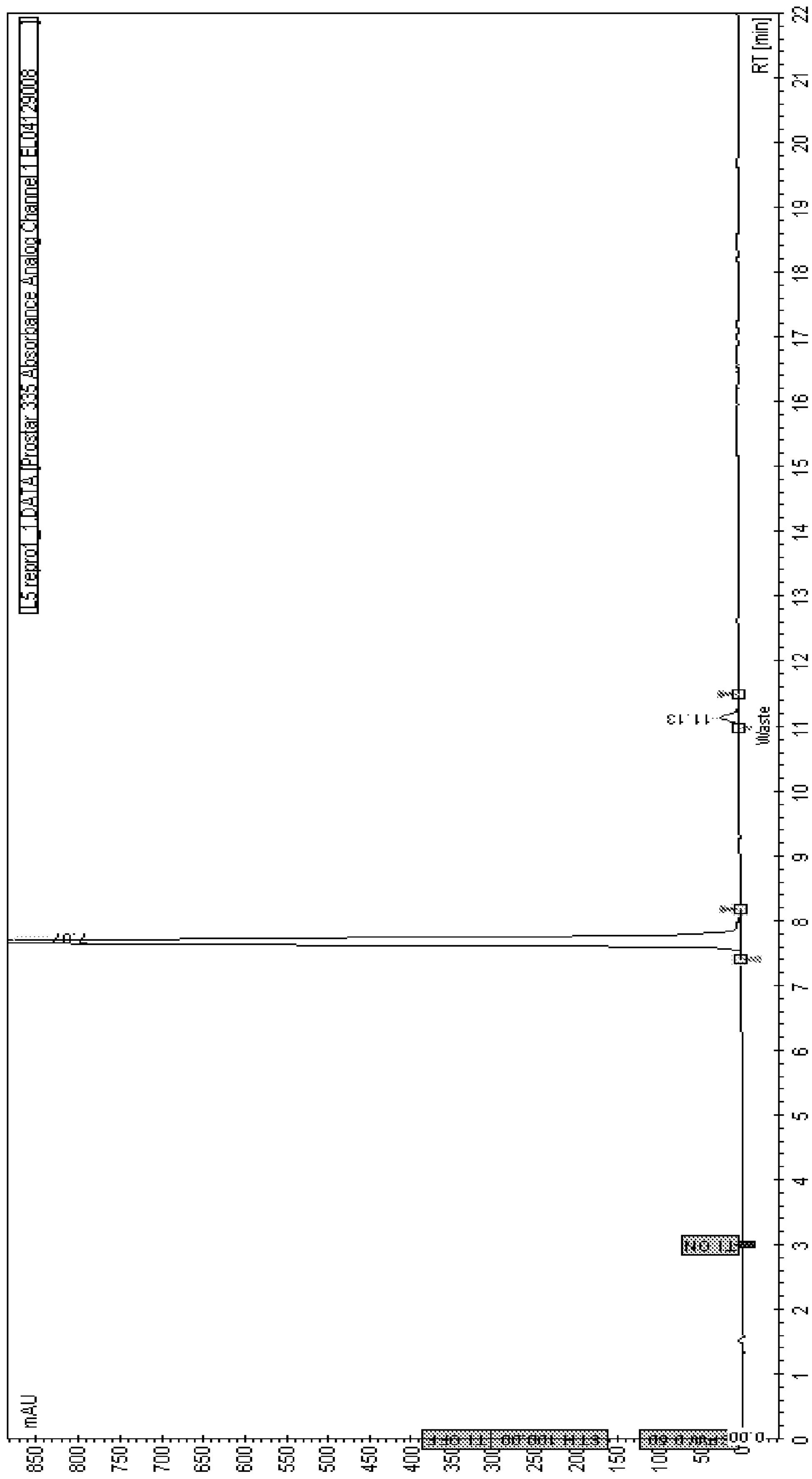


FIGURE 2

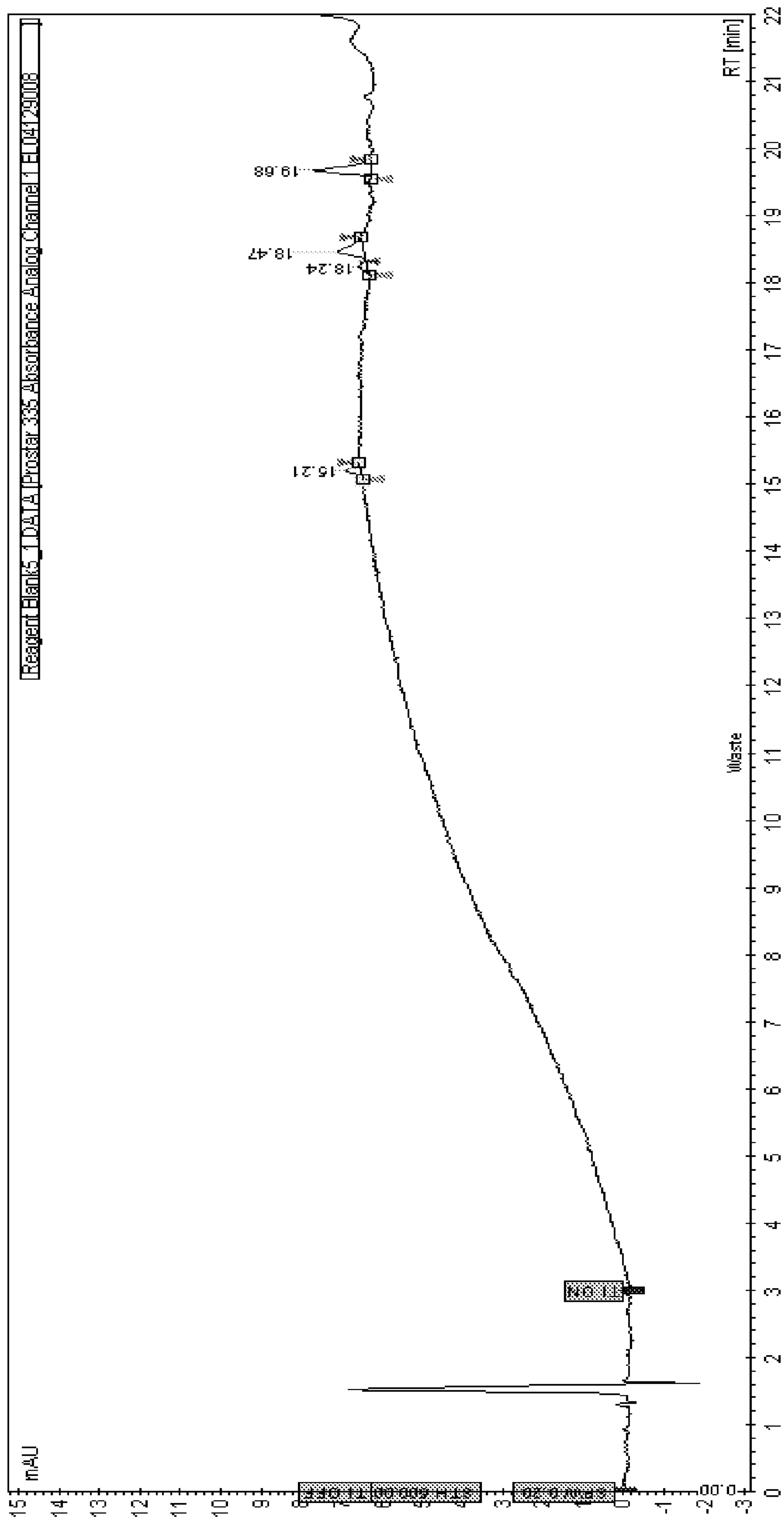


FIGURE 3

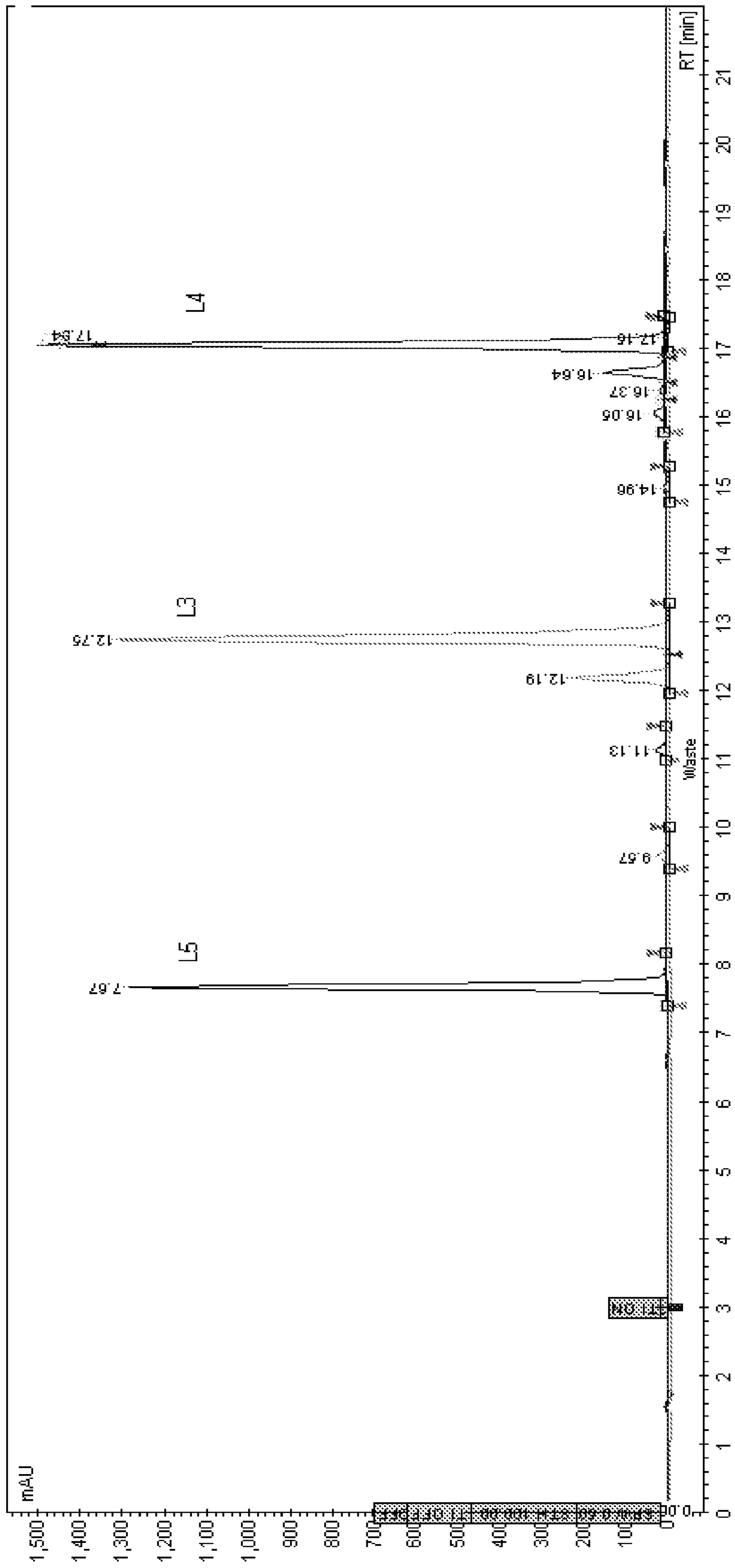


FIGURE 4

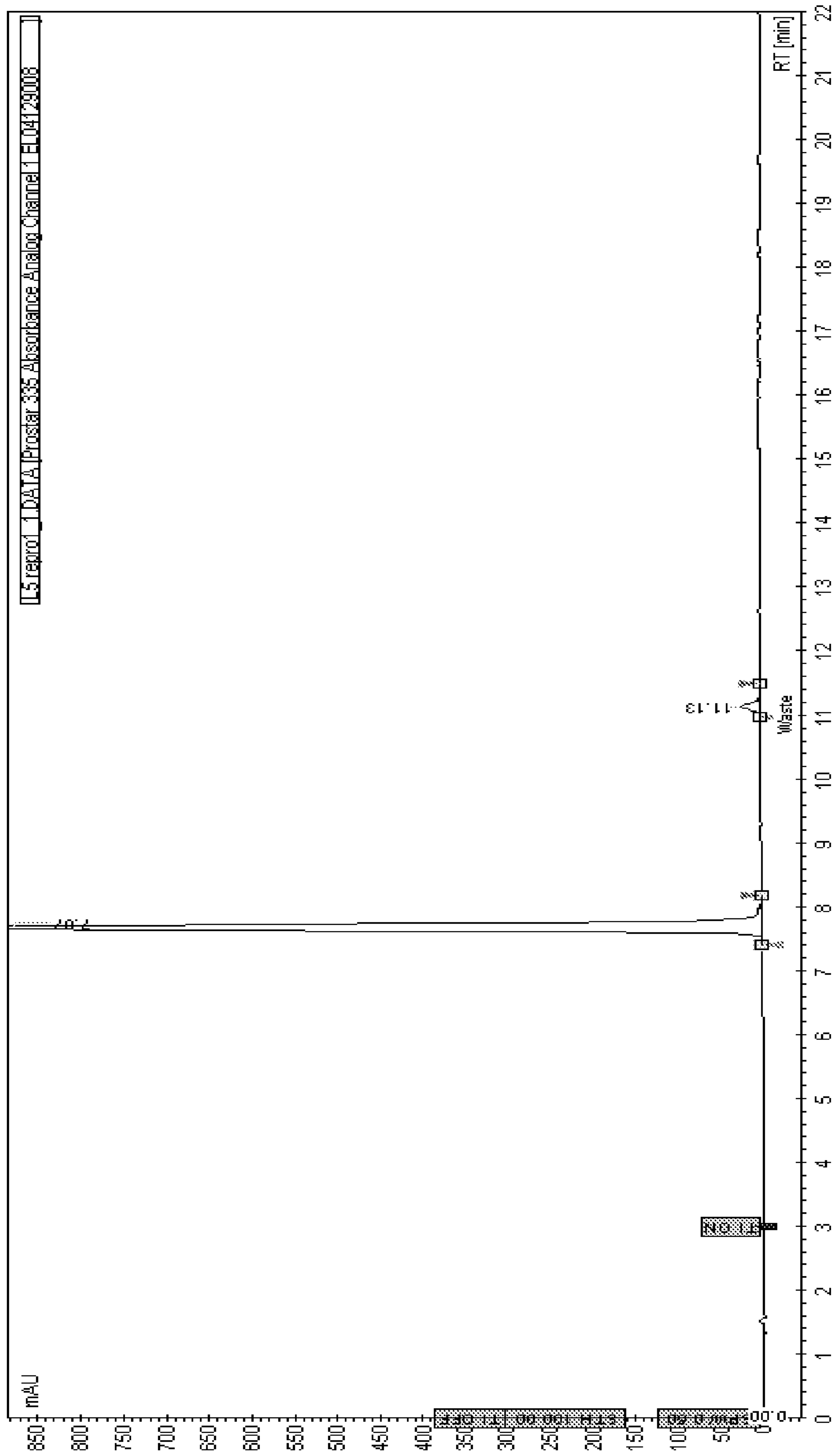


FIGURE 5

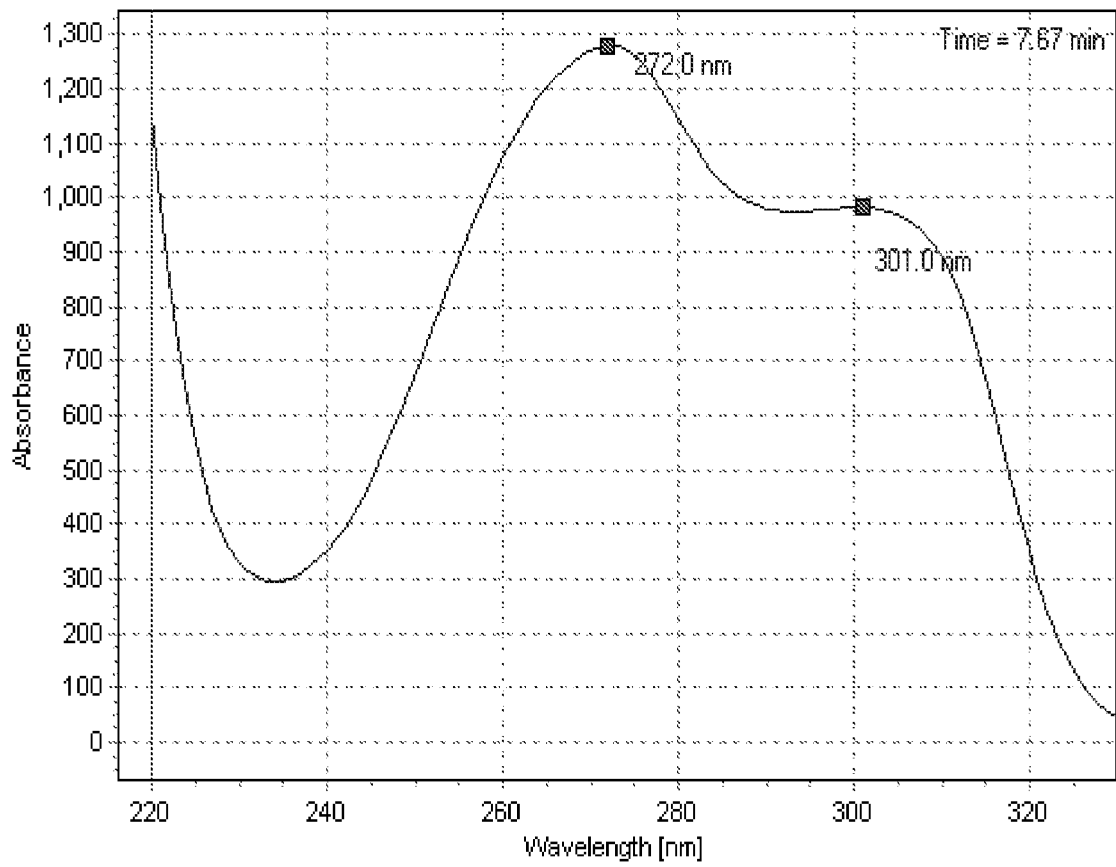


FIGURE 6

LD-101 Achieves Greater Apoptosis in Mantle Cell Lymphoma than Velcade®

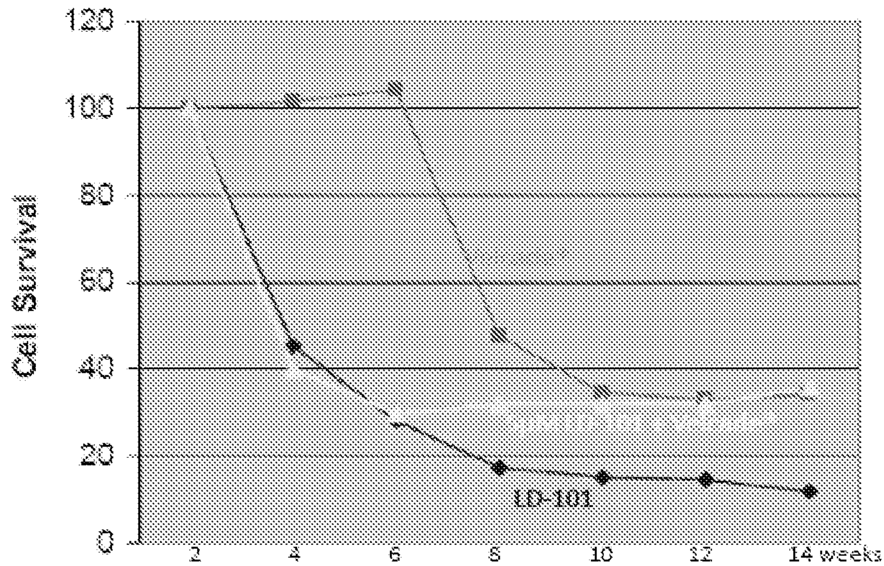


FIGURE 7

LD-101 Achieves Greater Apoptosis in Multiple Myeloma than Velcade®, and even Greater Apoptosis in Combination with Velcade®

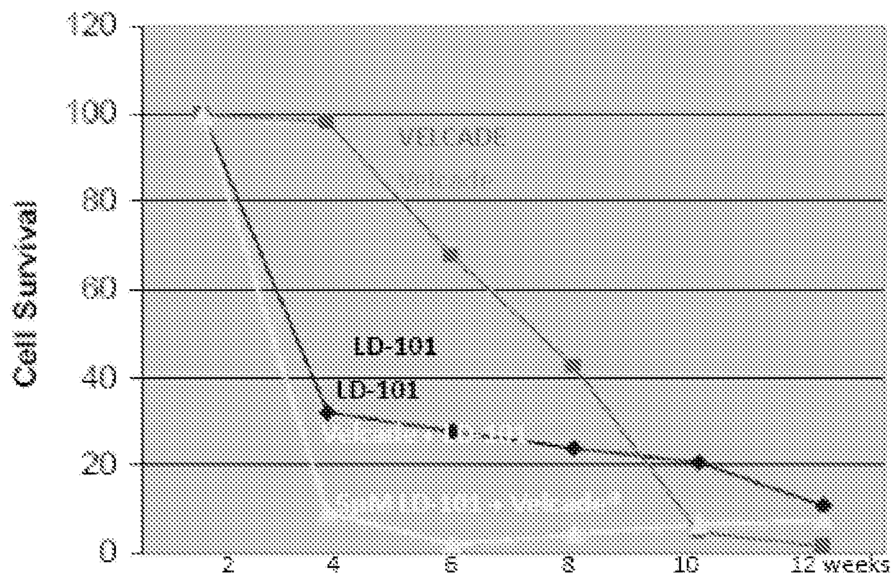


FIGURE 8

LD-101 Achieves Greater Inhibition of Cell Growth in Prostate Cancer than Rapamycin, and even Greater Inhibition in Combination with Rapamycin

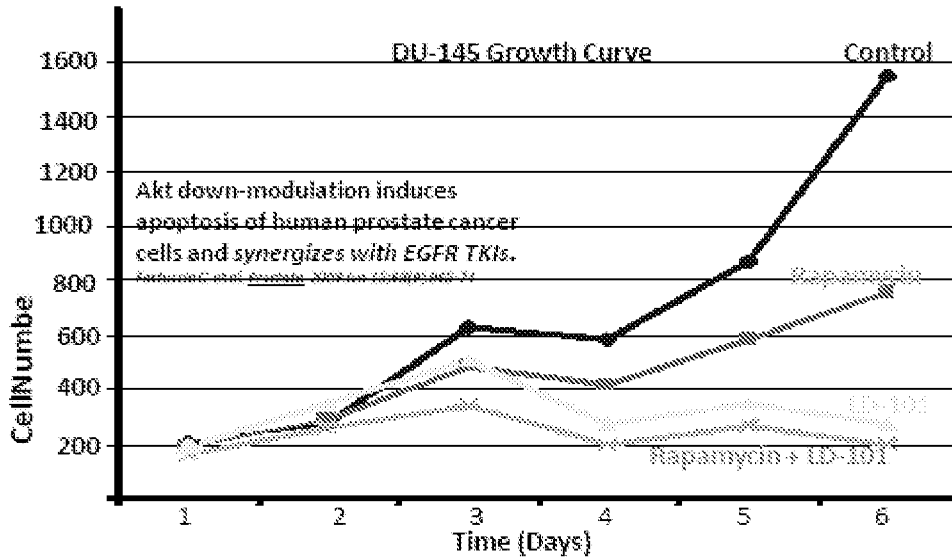


FIGURE 9

LD-101 Achieves Greater Inhibition of Cell Growth in Breast Cancer than RAD001, and even Greater Inhibition in Combination with RAD001

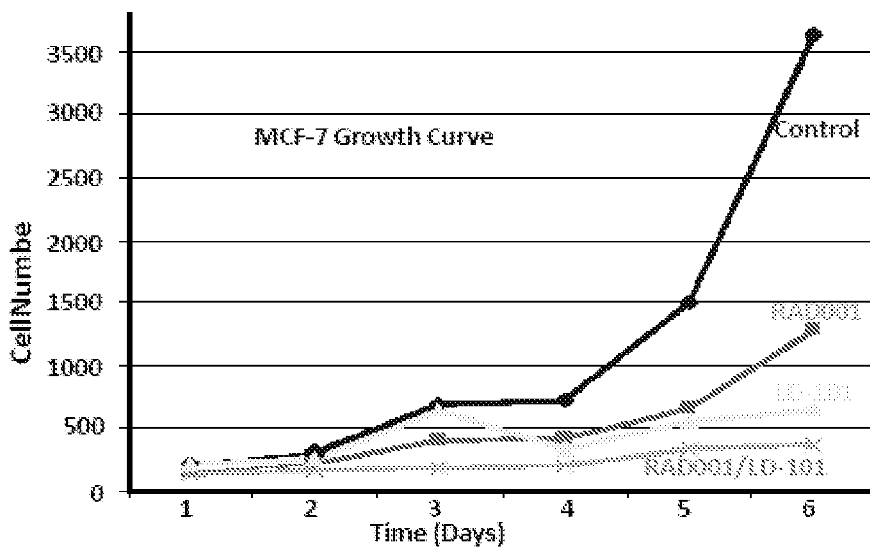


FIGURE 10

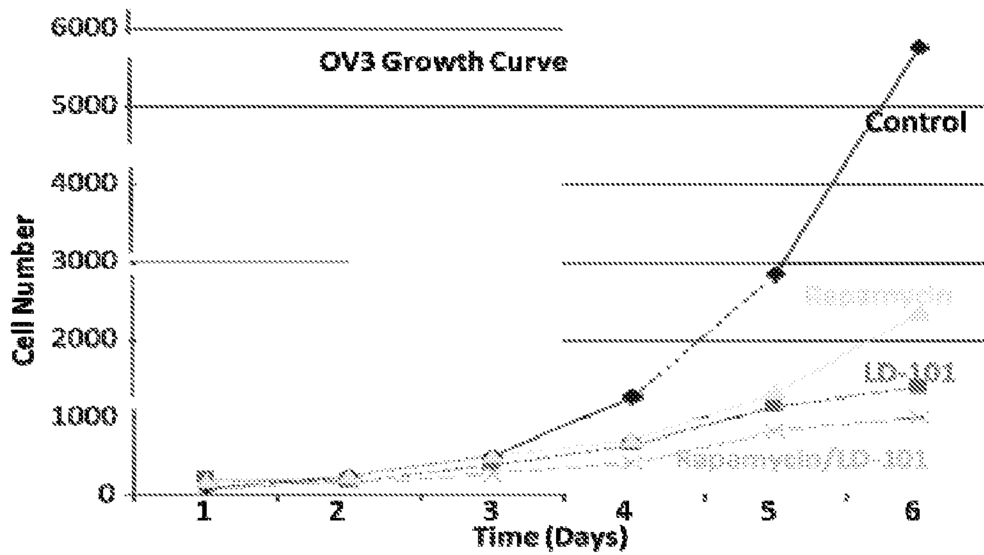


FIGURE 11

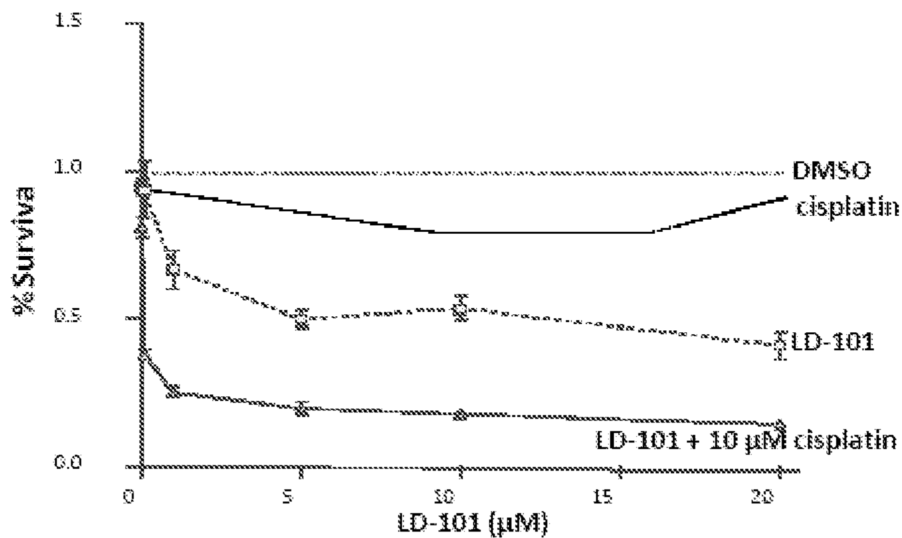


FIGURE 12

LD-101 Achieves Greater Inhibition of Cell Growth in Resistant Ovarian Cancer (C13) than CDDP, and even Greater Inhibition in Combination with CDDP in Nude Mouse Xenografts

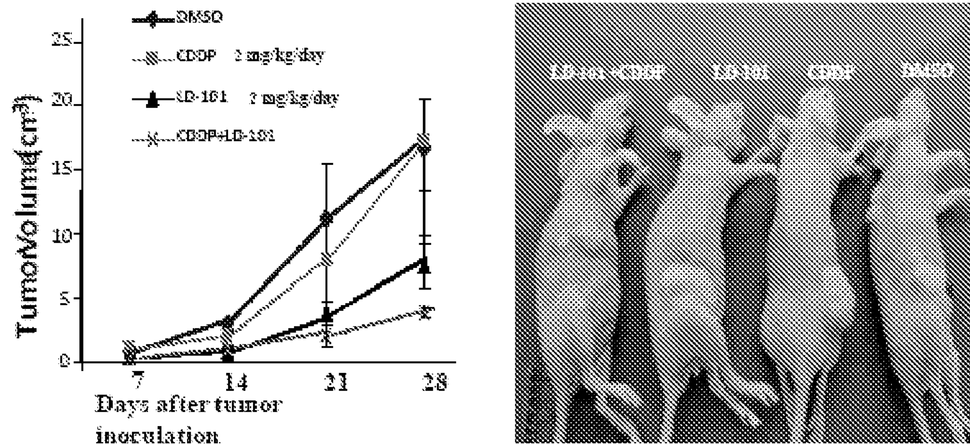
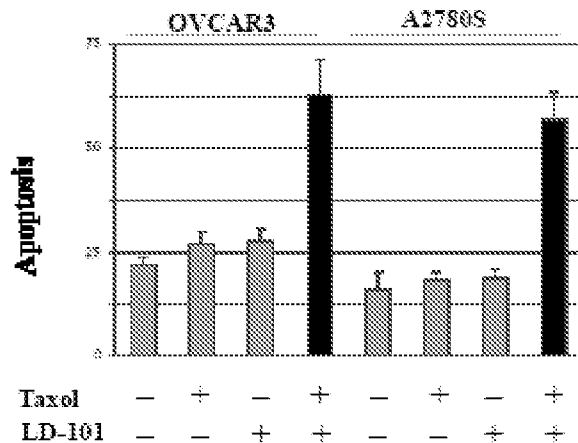


FIGURE 13

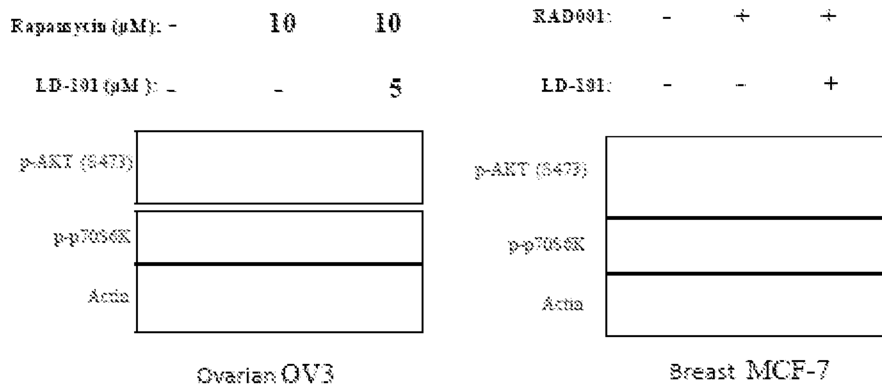
LD-101 in Combination with Taxol® Achieves Greater Apoptosis in Resistant Ovarian Cancer than either Alone



*+ means compound is present in 10 μM concentration; - means compound is absent.

FIGURE 14

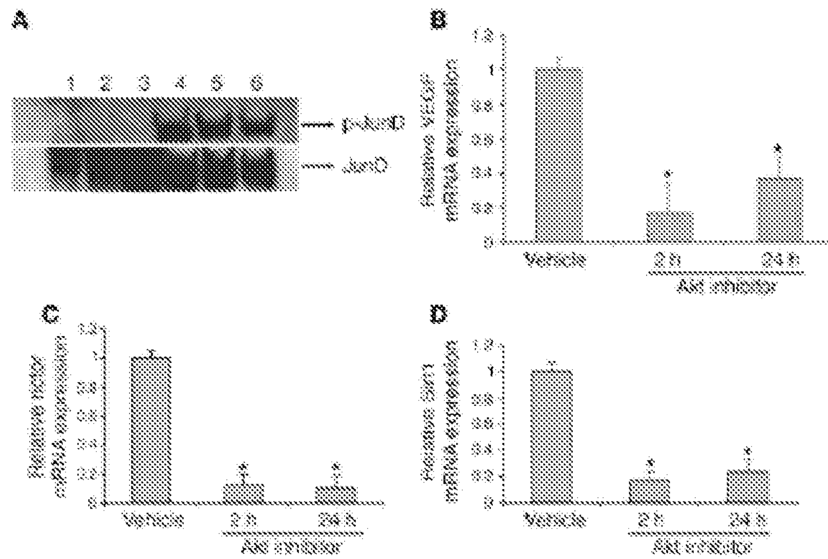
LD-101 Overcomes and Inhibits Rapamycin and RAD001 Feedback Activation of Akt



Also see, Shi-Yong Sun et al. Cancer Research. 2005 (65)(7052-7058)

FIGURE 15

Inhibition of Akt Downregulates VEGF, mTor Rictor and Sirt1



Govindarajan B. et al: J. Clin. Invest. 117(3): 719-729 (2007)

FIGURE 16

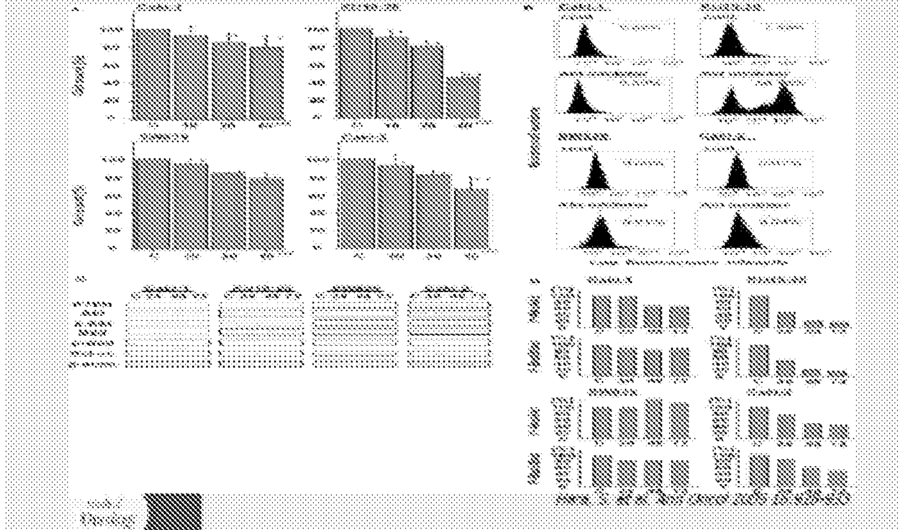


FIGURE 17

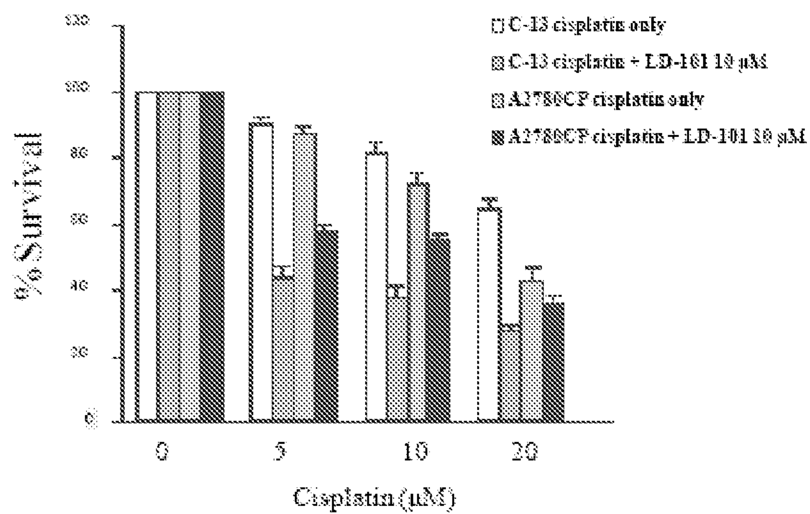
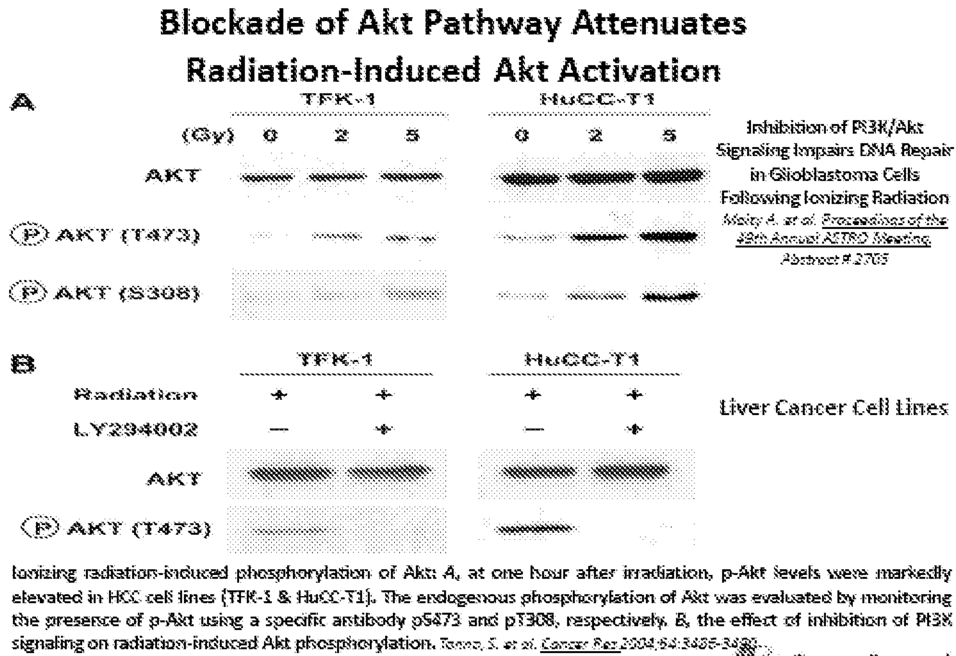
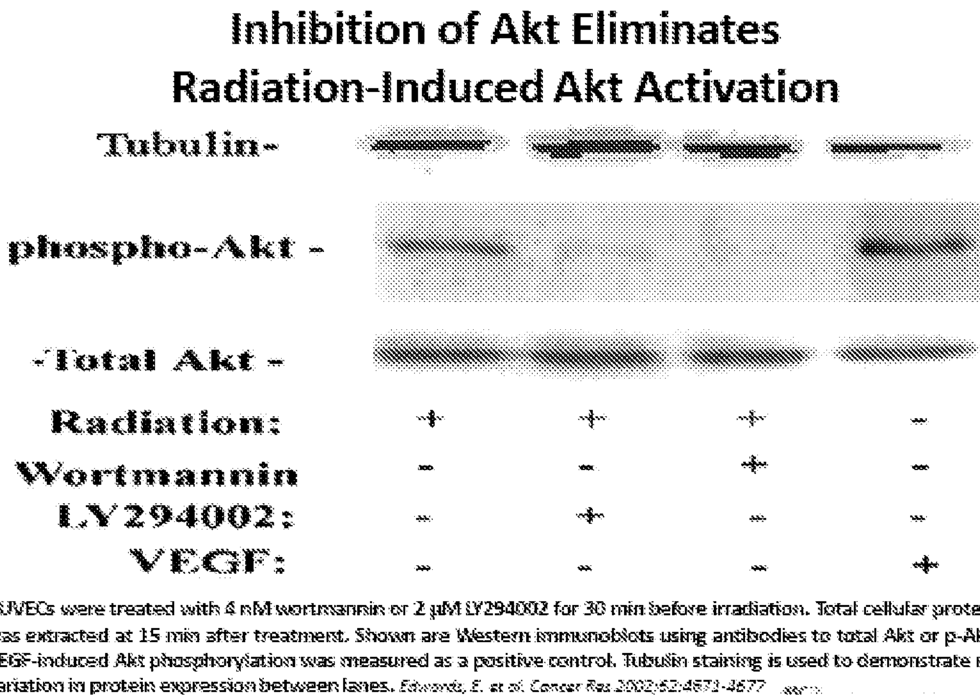


FIGURE 18



Ionizing radiation-induced phosphorylation of Akt: A, at one hour after irradiation, p-Akt levels were markedly elevated in HCC cell lines (TFK-1 & HuCC-T1). The endogenous phosphorylation of Akt was evaluated by monitoring the presence of p-Akt using a specific antibody pS473 and pT308, respectively. B, the effect of inhibition of PI3K signaling on radiation-induced Akt phosphorylation.

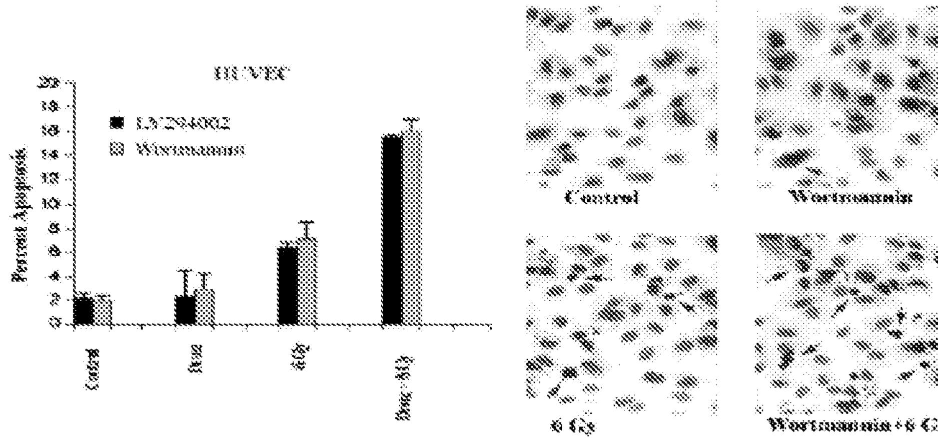
FIGURE 19



HUVECs were treated with 4 nM wortmannin or 2 μM LY294002 for 30 min before irradiation. Total cellular protein was extracted at 15 min after treatment. Shown are Western immunoblots using antibodies to total Akt or p-Akt. VEGF-induced Akt phosphorylation was measured as a positive control. Tubulin staining is used to demonstrate no variation in protein expression between lanes.

FIGURE 20

Inhibition of Akt Pathway Potentiates/Sensitizes Radiation-Induced Apoptosis



HUVECs were treated with either 2 µM LY 294002 or 4 nM Wortmannin, incubated for 30 min, and treated with radiation (6 Gy). After a 24-h incubation period, cells were fixed and stained. Four high-powered fields (x400) were observed and counted for each experimental group. Shown is the percentage of apoptotic cells for each experimental group. Photographs show representative HUVECs treated with radiation, LY294002, or LY294002 before irradiation. *Arrows*, apoptotic nuclei. *Bans, SD. Edwards, E. et al. Cancer Res 2002;62:4671-4677.*

FIGURE 21

LD-101 Achieves Greater Inhibition of Tumor Growth in Lung Cancer Cell H661 than CDDP, and even Greater Inhibition in Combination with CDDP

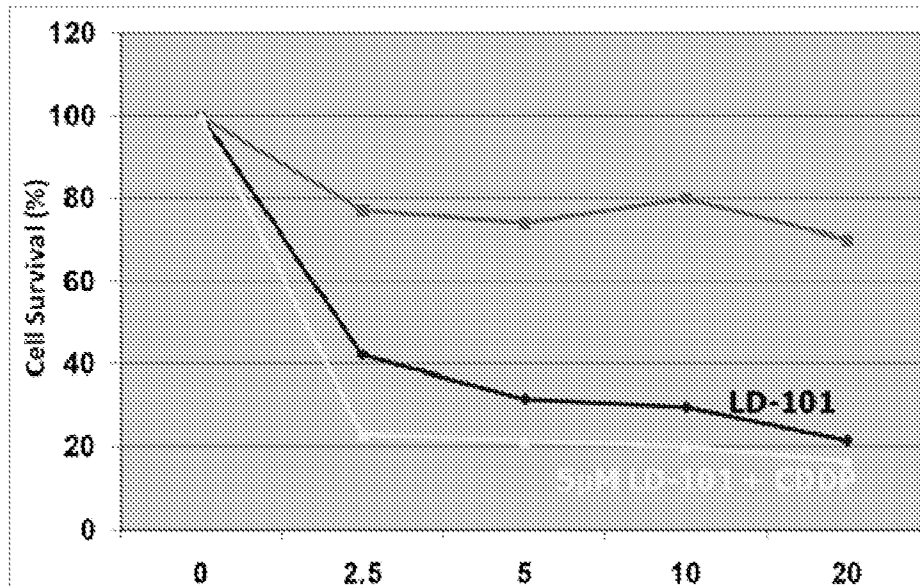


FIGURE 22

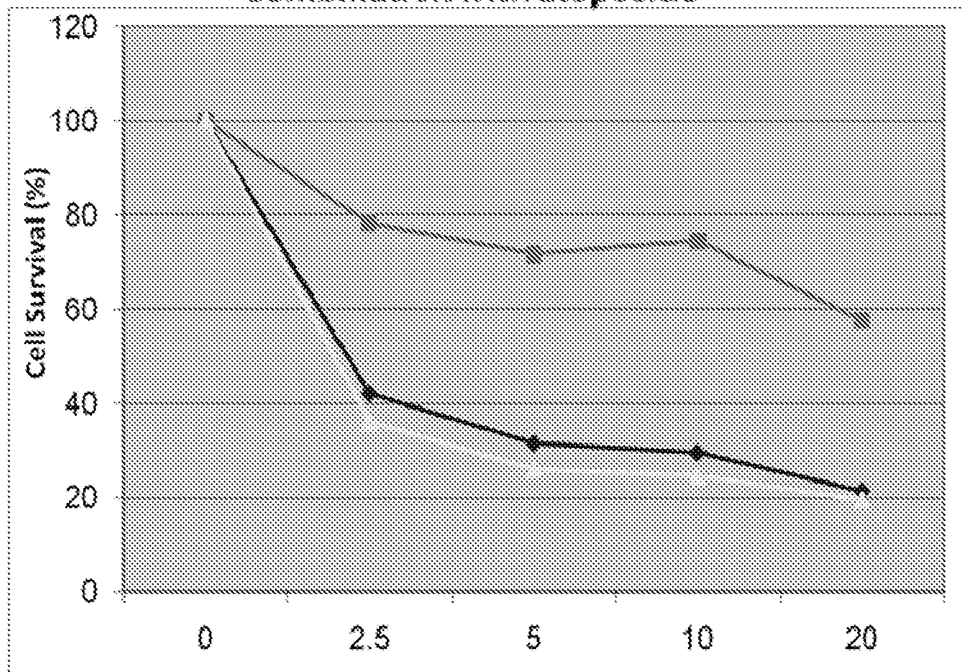


FIGURE 23

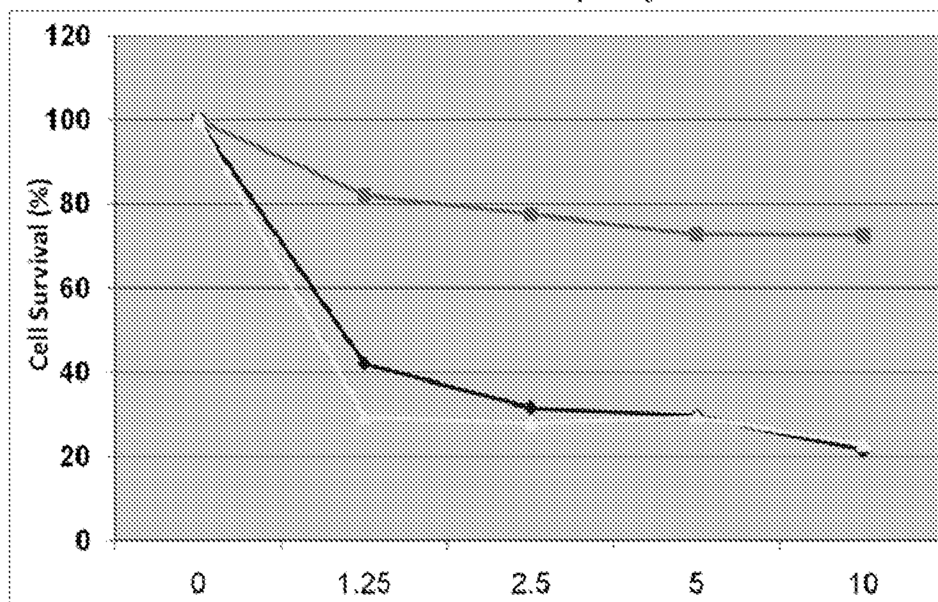


FIGURE 24