AZAINDOLES USEFUL AS INHIBITORS OF ROCK AND OTHER PROTEIN KINASES

TECHNICAL FIELD OF INVENTION

[0001] The present invention relates to compounds useful as inhibitors of protein kinases. The invention also provides pharmaceutically acceptable compositions comprising the compounds of the invention and methods of using the compositions in the treatment of various disorders.

BACKGROUND OF THE INVENTION

[0002] The search for new therapeutic agents has been greatly aided in recent years by a better understanding of the structure of enzymes and other biomolecules associated with diseases. One important class of enzymes that has been the subject of extensive study is protein kinases.

[0003] Protein kinases constitute a large family of structurally related enzymes that are responsible for the control of a variety of signal transduction processes within the cell. (See, Hardie, G. and Hanks, S. *The Protein Kinase Facts Book, I and II,* Academic Press, San Diego, CA: 1995). Protein kinases are thought to have evolved from a common ancestral gene due to the conservation of their structure and catalytic function. Almost all kinases contain a similar 250-300 amino acid catalytic domain. The kinases may be categorized into families by the substrates they phosphorylate (e.g., protein-tyrosine, protein-serine/threonine, lipids, etc.). Sequence motifs have been identified that generally correspond to each of these kinase families (See, for example, Hanks, S.K., Hunter, T., *FASEB J.* **1995**, *9*, 576-596; Knighton *et al.*,

Science **1991**, *253*, 407-414; Hiles *et al., Cell* **1992**, *70*, 419-429; Kunz *et al., Cell* **1993**, *73*, 585-596; Garcia-Bustos *et al., EMBO J.* **1994**, *13*, 2352-2361).

[0004] Many diseases are associated with abnormal cellular responses triggered by protein kinase-mediated events. These diseases include autoimmune diseases, inflammatory diseases, bone diseases, metabolic diseases, neurological and neurodegenerative diseases, cancer, cardiovascular diseases, allergies and asthma, Alzheimer's disease and hormone-related diseases. Accordingly, there has been a substantial effort in medicinal chemistry to find protein kinase inhibitors that are effective as therapeutic agents.

[0005] One kinase family of interest is Rho-associated coiled-coil forming protein serine/threonine kinase (ROCK), which is believed to be an effector of Ras-related small GTPase Rho. The ROCK family includes p160ROCK (ROCK-1) (Ishizaki *et al., EMBO J.* **1996**, *15*, 1885-1893) and ROKα/Rho-kinase/ROCK-II (Leung *et al., J. Biol. Chem.* **1995**, *270*, 29051-29054; Matsui *et al., EMBO J.* **1996**, *15*, 2208-2216; Nakagawa *et al., FEBS Lett.* **1996**, *392*, 189-193), protein kinase PKN (Amano *et al., Science* **1996**, *271*, 648-650; Watanabe *et al., Science* **1996**, *271*, 645-648), and citron and citron kinase (Madaule *et al. Nature*, **1998**, *394*, 491-494; Madaule *et al., FEBS Lett.* **1995**, *377*, 243-248). The ROCK family of kinases have been shown to be involved in a variety of functions including Rho-induced formation of actin stress fibers and focal adhesions (Leung *et al., Mol. Cell Biol.* **1996**, *16*, 5313-5327; Amano *et al., Science,* **1997**, *275*, 1308-1311; Ishizaki *et al., FEBS Lett.* **1997**, *404*, 118-124) and in downregulation of myosin phosphatase (Kimura *et al., Science,* **1996**, *273*, 245-248), platelet activation (Klages *et al., J. Cell. Biol.*, **1999**, *144*, 745-754), aortic smooth muscle contraction by various stimuli (Fu *et al., FEBS Lett.*, **1998**, *440*, 183-187), thrombin-induced responses of aortic smooth muscle cells (Seasholtz *et al., Cir. Res.*, **1999**, *84*, 1186-1193), hypertrophy of cardiomyocytes (Kuwahara *et al., FEBS Lett.*, **1999**, *452*, 314-318), bronchial smooth muscle contraction (Yoshii *et al., Am. J. Respir. Cell Mol. Biol.*, **1999**, *20*, 1190-1200), smooth muscle contraction and cytoskeletal reorganization of non-muscle cells (Fukata *et al., Trends in Pharm. Sci* **2001**, *22*, 32-39), activation of volume-regulated anion channels (Nilius *et al., J. Physiol.*, **1999**, *516*, 67-74), neurite retraction (Hirose *et al., J. Cell. Biol.*, **1998**, *141*, 1625-1636), neutrophil chemotaxis (Niggli, *FEBS Lett.*, **1999**, *445*, 69-72), wound

healing (Nobes and Hall, *J. Cell. Biol.*, **1999**, *144*, 1235-1244), tumor invasion (Itoh *et al., Nat. Med.*, **1999**, *5*, 221-225) and cell transformation (Sahai *et al., Curr. Biol.*, **1999**, *9*, 136-145). More specifically, ROCK has been implicated in various diseases and disorders including hypertension (Satoh *et al., J. Clin. Invest.* **1994**, *94*, 1397-1403; Mukai *et al., FASEB J.* **2001**, *15*, 1062-1064; Uehata *et al., Nature* **1997**, *389*, 990-994; Masumoto *et al., Hypertension*, **2001**, *38*, 1307-1310), cerebral vasospasm (Sato *et al., Circ. Res.* **2000**, *87*, 195-200; Miyagi *et al., J. Neurosurg.* **2000**, *93*, 471-476; Tachibana *et al., Acta Neurochir (Wien)* **1999**, *141*, 13-19), coronary vasospasm (Shimokawa *et al., Jpn. Cir. J.* **2000**, *64*, 1-12; Kandabashi *et al., Circulation* **2000**, *101*, 1319-1323; Katsumata *et al., Circulation* **1997**, *96*, 4357-4363; Shimokawa *et al., Cardiovasc. Res.* **2001**, *51*, 169-177; Utsunomiya *et al., J. Pharmacol.* **2001**, *134*, 1724-1730; Masumoto *et al., Circulation* **2002**, *105*, 1545-1547), bronchial asthma (Chiba *et al., Comp. Biochem. Physiol. C Pharmacol. Toxicol. Endocrinol.* **1995**, *11*, 351-357; Chiba *et al., Br. J. Pharmacol.* **1999**, *127*, 597-600; Chiba *et al., Br. J. Pharmacol.* **2001**, *133*, 886-890; Iizuka *et al., Eur. J. Pharmacol.* **2000**, *406*, 273-279), preterm labor (Niro *et al., Biochem. Biophys. Res. Commun.* **1997**, *230*, 356-359; Tahara *et al., Endocrinology* **2002**, *143*, 920-929; Kupittayanant *et al., Pflugers Arch.* **2001**, *443*, 112-114), erectile dysfunction (Chitaley *et al., Nat. Med.* **2001**, *7*, 119-122; Mills *et al., J. Appl. Physiol.* **2001**, *91*, 1269-1273), glaucoma (Honjo *et al., Arch. Ophthalmol.* **2001**, 1171-1178; Rao *et al., Invest. Ophthalmol. Vis. Sci.* **2001**, *42*, 1029-1037), vascular smooth muscle cell proliferation (Shimokawa *et al., Cardiovasc. Res.* **2001**, *51*, 169-177; Morishige *et al., Arterioscler. Thromb. Vasc. Biol.* **2001**, *21*, 548-554; Eto *et al., Am. J. Physiol. Heart Circ. Physiol.* **2000**, *278*, H1744-H1750; Sawada *et al., Circulation* **2000**, *101*, 2030-2023; Shibata *et al., Circulation* **2001**, *103*, 284-289), myocardial hypertrophy (Hoshijima *et al., J. Biol. Chem.* **1998**, *273*, 7725-77230; Sah *et al., J. Biol. Chem.* **1996**, *271*, 31185-31190; Kuwahara *et al., FEBS Lett.* **1999**, *452*, 314-318; Yanazume *et al., J. Biol. Chem.* **2002**, *277*, 8618-8625), malignoma (Itoh *et al., Nat. Med.* **1999**, *5*, 221-225; Genda *et al., Hepatology* **1999**, *30*, 1027-1036; Somlyo *et al., Biochem. Biophys. Res. Commun.* **2000**, *269*, 652-659), ischemia/reperfusion-induced injury (Ikeda *et al., J. of Surgical Res.* **2003**, *109*, 155-160; Miznuma *et al. Transplantation* **2003**, *75*, 579-586), endothelial dysfunction (Hernandez-Perera *et al., Circ. Res.* **2000**, *87*, 616-622;

Laufs *et al., J. Biol. Chem.* **1998**, *273*, 24266-24271; Eto *et al., Circ. Res.* **2001**, *89*, 583-590), Crohn's Disease and colitis (Segain *et al. Gastroenterology* **2003**, *124(5),* 1180-1187), neurite outgrowth (Fournier *et al. J. Neurosci.* **2003**, *23*, 1416-1423), Raynaud's Disease (Shimokawa *et al. J. Cardiovasc. Pharmacol.* **2002**, *39*, 319-327), angina (Utsunomiya *et al. Br. J. Pharmacol.* **2001**, *134*, 1724-1730; Masumoto *et al, Circulation* **2002**, *105*, 1545-1547; Shimokawa *et al, J. Cardiovasc. Pharmacol.,* **2002**, *40*, 751-761; Satoh *et al., Jpn. J. Pharmacol.*, **2001**, *87*, 34-40), Alzheimer's disease (Zhou *et al., Science* **2003**, *302*, 1215-1218), benign prostatic hyperplasia (Rees *et al., J. Urology,* **2003**, *170*, 2517-2522) and atherosclerosis (Retzer *et al. FEBS Lett.* **2000**, *466*, 70-74; Ishibashi *et al. Biochim. Biophys. Acta* **2002**, *1590*, 123-130). Accordingly, the development of inhibitors of ROCK kinase would be useful as therapeutic agents for the treatment of disorders implicated in the ROCK kinase pathway.

[0006] ERK2 (extracellular signal regulated kinase) is a member of the mammalian mitogen-activated protein (MAP)1 kinase family. (MAP)1 kinases are serine/threonine kinases that mediate intracellular signal transduction pathways (Cobb and Goldsmith, *J Biol. Chem.*, **1995**, *270*, 14843; Davis, *Mol. Reprod. Dev.* **1995**, *42*, 459) and are activated by mitogens and growth factors (Bokemeyer *et al.. Kidney Int.* **1996**, *49*, 1187). Members of the MAP kinase family share sequence similarity and conserved structural domains, and, in addition to ERK2, include the JNK (Jun N-terminal kinase), and p38 kinases. JNKs and p38 kinases are activated in response to the pro-inflammatory cytokines TNF-alpha and interleukin-1, and by cellular stress such as heat shock, hyperosmolarity, ultraviolet radiation, lipopolysaccharides and inhibitors of protein synthesis (Derijard *et al., Cell* **1994**, *76*, 1025; Han *et al., Science* **1994,** *265*, 808; Raingeaud *et al., J Biol. Chem.* **1995**, *270*, 7420; Shapiro and Dinarello, *Proc. Natl. Acad. Sci. USA* **1995**, *92*, 12230). In contrast, ERKs are activated by mitogens and growth factors (Bokemeyer *et al., Kidney Int.* **1996**, *49*, 1187).

[0007] ERK2 is a widely distributed protein kinase that achieves maximum activity when both Thr183 and Tyr185 are phosphorylated by the upstream MAP kinase kinase, MEK1 (Anderson et al., *Nature* **1990**, *343*, 651; Crews *et al., Science* **1992**, *258*, 478). Upon activation, ERK2 phosphorylates many regulatory proteins,

including the protein kinases Rsk90 (Bjorbaek *et al., J. Biol. Chem.* **1995**, *270*, 18848) and MAPKAP2 (Rouse *et al., Cell* **1994,** *78*, 1027), and transcription factors such as ATF2 (Raingeaud *et al., Mol. Cell Biol.* **1996**, *16*, 1247), Elk-1 (Raingeaud *et al., Mol. Cell Biol.* **1996**, *16*, 1247), c-Fos (Chen *et al., Proc. Natl. Acad. Sci. USA* **1993**, *90*, 10952), and c-Myc (Oliver *et al., Proc. Soc. Exp. Biol. Med.* **1995,** *210*, 162). ERK2 is also a downstream target of the Ras/Raf dependent pathways (Moodie *et al., Science* **1993**, *260*, 1658) and may help relay the signals from these potentially oncogenic proteins. ERK2 has been shown to play a role in the negative growth control of breast cancer cells (Frey and Mulder, *Cancer Res.* **1993**, *57*, 628) and hyperexpression of ERK2 in human breast cancer has been reported (Sivaraman *et al., J Clin. Invest.* **1997**, *99*, 1478). Activated ERK2 has also been implicated in the proliferation of endothelin-stimulated airway smooth muscle cells, suggesting a role for this kinase in asthma (Whelchel *et al., Am. J. Respir. Cell Mol. Biol.* **1997**, *16*, 589).

[0008] Glycogen synthase kinase-3 (GSK-3) is a serine/threonine protein kinase comprised of α and β isoforms that are each encoded by distinct genes [Coghlan *et al., Chemistry & Biology* **2000**, *7*, 793-803; and Kim and Kimmel, *Curr. Opinion Genetics Dev.*, **2000** *10*, 508-514]. GSK-3 has been implicated in various diseases including diabetes, Alzheimer's disease, CNS disorders such as manic depressive disorder and neurodegenerative diseases, and cardiomyocyte hypertrophy [PCT Application Nos.: WO 99/65897 and WO 00/38675; and Haq *et al., J. Cell Biol.* **2000**, *151*, 117-130]. These diseases are associated with the abnormal operation of certain cell signaling pathways in which GSK-3 plays a role. GSK-3 has been found to phosphorylate and modulate the activity of a number of regulatory proteins. These proteins include glycogen synthase, which is the rate limiting enzyme necessary for glycogen synthesis, the microtubule associated protein Tau, the gene transcription factor β-catenin, the translation initiation factor e1F2B, as well as ATP citrate lyase, axin, heat shock factor-1, c-*Jun*, c-*myc*, c-*myb*, CREB, and CEPBα. These diverse protein targets implicate GSK-3 in many aspects of cellular metabolism, proliferation, differentiation, and development.

[0009] In a GSK-3 mediated pathway that is relevant for the treatment of type II diabetes, insulin-induced signaling leads to cellular glucose uptake and glycogen

synthesis. Along this pathway, GSK-3 is a negative regulator of the insulin-induced signal. Normally, the presence of insulin causes inhibition of GSK-3 mediated phosphorylation and deactivation of glycogen synthase. The inhibition of GSK-3 leads to increased glycogen synthesis and glucose uptake [Klein *et al., PNAS* **1996**, *93*, 8455-8459; Cross *et al., Biochem. J.* **1994**, *303*, 21-26); Cohen, *Biochem. Soc. Trans.* **1993**, *21*, 555-567; and Massillon *et al., Biochem J.* **1994**, *299*, 123-128]. However, in a diabetic patient, where the insulin response is impaired, glycogen synthesis and glucose uptake fail to increase despite the presence of relatively high blood levels of insulin. This leads to abnormally high blood levels of glucose with acute and long- term effects that may ultimately result in cardiovascular disease, renal failure and blindness. In such patients, the normal insulin-induced inhibition of GSK-3 fails to occur. It has also been reported that in patients with type II diabetes, GSK-3 is overexpressed [see, PCT Application: WO 00/38675]. Therapeutic inhibitors of GSK-3 are therefore potentially useful for treating diabetic patients suffering from an impaired response to insulin.

[0010] GSK-3 activity is also associated with Alzheimer's disease. This disease is characterized by the well-known β-amyloid peptide and the formation of intracellular neurofibrillary tangles. Aβ peptides are derived from the amyloid precursor protein (APP) by sequential proteolysis, catalysed by the aspartyl protease BACE2, followed by presenilin-dependent γ-secretase cleavage. It has been demonstrated that antibodies against β-amyloid plaques can slow cognitive decline in patients with Alzheimer's disease (Hock *et al., Neuron*, **2003**, *38*, 547-554), and thus other β-amyloid-lowering strategies (e.g., the development of agents capable of inhibiting β-amyloid peptide) would be useful in the treatment of Alzherimer's disease and other psychotic and neurodegenerative disorders. Additionally, the neurofibrillary tangles contain hyperphosphorylated Tau protein, in which Tau is phosphorylated on abnormal sites, and thus agents capble of inhibiting the hyperphosphorylation of Tau protein would be useful in the treatment of Alzherimer's disease and other psychotic and neurodegenerative disorders.

[0011] GSK-3 is known to phosphorylate these abnormal sites in cell and animal models. Furthermore, inhibition of GSK-3 has been shown to prevent

hyperphosphorylation of Tau in cells [Lovestone *et al.*, *Current Biology* **1994**, *4*, 1077-86; and Brownlees *et al.*, *Neuroreport* **1997**, *8*, 3251-55]. Therefore, GSK-3 activity promotes generation of the neurofibrillary tangles and the progression of Alzheimer's disease. It has also been shown that GSK-3 facilitates APP processing and that a GSK-3 inhibitor (lithium) inhibits of the generation of Aβ peptides through the inhibition of GSK-3 (Phiel *et al. Nature* **2003**, *423*, 435-439). Thus, the development of inhibitors of GSK-3 would be useful for the reduction of the formation of amyloid plaques and neurofibrillry tangles, the pathological hallmarks of Alzheimer's Disease, and would also be useful for the treament of other psychotic and neurodegenerative disorders.

[0012] Another substrate of GSK-3 is β-catenin, which is degradated after phosphorylation by GSK-3. Reduced levels of β-catenin have been reported in schizophrenic patients and have also been associated with other diseases related to increase in neuronal cell death [Zhong *et al.*, *Nature* **1998**, *395*, 698-702; Takashima *et al.*, *PNAS* **1993**, *90*, 7789-93; and Pei *et al.*, *J. Neuropathol. Exp* **1997**, ***56***, 70-78].

[0013] GSK-3 activity is also associated with stroke [Wang *et al.*, *Brain Res* **2000**, *859*, 381-5; Sasaki *et al.*, *Neurol Res* **2001**, *23*, 588-92; Hashimoto *et al.*, *J. Biol. Chem* **2002**, *277*, 32985-32991].

[0014] The AGC sub-family of kinases phosphorylate their substrates at serine and threonine residues and participate in a variety of well-known signaling processes, including, but not limited to cyclic AMP signaling, the response to insulin, apoptosis protection, diacylglycerol signaling, and control of protein translation (Peterson *et al.*, *Curr. Biol.* **1999**, *9*, R521). This sub-family includes PKA, PKB (c-Akt), PKC, PRK1, PRK2, $p70^{S6K}$, and PDK.

[0015] AKT (also known as PKB or Rac-PK beta), a serine/threonine protein kinase, has been shown to be overexpressed in several types of cancer and is a mediator of normal cell functions [(Khwaja, A., *Nature* **1999**, *401*, 33-34); (Yuan, Z.Q., *et al., Oncogene* **2000**, *19*, 2324-2330); (Namikawa, K., *et al., J Neurosci.* **2000**, *20*, 2875-2886,)]. AKT comprises an N-terminal pleckstrin homology (PH) domain, a kinase domain and a C-terminal "tail" region. Three isoforms of human AKT kinase (AKT-1, -2 and -3) have been reported so far [(Cheng, J.Q., *Proc. Natl. Acad. Sci. USA* **1992**, *89*, 9267-9271); (Brodbeck, D. *et al.*, *J. Biol. Chem.* **1999**, *274*,

9133-9136)]. The PH domain binds 3-phosphoinositides, which are synthesized by phosphatidyl inositol 3-kinase (PI3K) upon stimulation by growth factors such as platelet derived growth factor (PDGF), nerve growth factor (NGF) and insulin-like growth factor (IGF-1) [(Kulik *et al.*, *Mol. Cell. Biol.*, **1997**, *17*, 1595-1606,); (Hemmings, B.A., *Science*, **1997**, *275*, 628-630)]. Lipid binding to the PH domain promotes translocation of AKT to the plasma membrane and facilitates phosphorylation by another PH-domain-containing protein kinases, PDK1 at Thr308, Thr309, and Thr305 for the AKT isoforms 1, 2 and 3, respectively. A second, as of yet unknown, kinase is required for the phosphorylation of Ser473, Ser474 or Ser472 in the C-terminal tails of AKT-1, -2 and -3 respectively, in order to yield a fully activated AKT enzyme.

[0016] Once localized to the membrane, AKT mediates several functions within the cell including the metabolic effects of insulin (Calera, M.R. *et al.*, *J. Biol. Chem.* **1998**, *273*, 7201-7204) induction of differentiation and/or proliferation, protein synthesis and stress responses (Alessi, D.R. *et al.*, *Curr. Opin. Genet. Dev.* **1998**, *8*, 55-62,).

[0017] Manifestations of altered AKT regulation appear in both injury and disease, the most important role being in cancer. The first account of AKT was in association with human ovarian carcinomas where expression of AKT was found to be amplified in 15% of cases (Cheng, J.Q. *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **1992**, *89*, 9267-9271). It has also been found to be overexpressed in 12% of pancreatic cancers (Cheng, J. Q. *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **1996**, *93*, 3636-3641). It was demonstrated that AKT-2 was over-expressed in 12% of ovarian carcinomas and that amplification of AKT was especially frequent in 50% of undifferentiated tumours, suggesting that AKT may also be associated with tumour aggressiveness (Bellacosa, *et al.*, *Int. J. Cancer* **1995**, *64*, 280-285).

[0018] PKA (also known as cAMP-dependent protein kinase) has been shown to regulate many vital functions including energy metabolism, gene transcription, proliferation, differentiation, reproductive function, secretion, neuronal activity, memory, contractility and motility (Beebe, S.J., *Semin. Cancer Biol.* **1994**, *5*, 285-294). PKA is a tetrameric holoenzyme, which contains two catalytic subunits bound to a homo-dimeric regulatory subunit (which acts to inhibit the catalytic sub-units).

On binding of cAMP (enzyme activation), the catalytic subunits dissociate from the regulatory subunits to yield the active serine/threonine kinase (McKnight, G.S. *et al.*, *Recent Prog. Horm. Res.* **1988**, *44*, pp. 307). Three isoforms of the catalytic subunit (C-α, C-β and C-γ) have been reported to date (Beebe, S.J. *et al., J. Biol. Chem.* **1992**, *267*, 25505-25512) with the C-α subunit being the most extensively studied, primarily because of its elevated expression in primary and metastatic melanomas (Becker, D. *et al., Oncogene* **1990**, *5*, 1133). To date, strategies to modulate the activity of the C-α subunit involve the use of antibodies, molecules that block PKA activity by targeting regulatory dimers and antisense oligonucleotides expression.

[0019] The ribosomal protein kinases $p70^{S6K}$-1 and -2 are also members of the AGC sub-family of protein kinases and catalyze the phosphorylation and subsequent activation of the ribosomal protein S6, which has been implicated in the translational up-regulation of mRNAs coding for the components of the protein synthetic apparatus. These mRNAs contain an oligopyrimidine tract at their 5' transcriptional start site, termed a 5'TOP, which has been shown to be essential for their regulation at the translational level (Volarevic, S. *et al., Prog. Nucleic Acid Res. Mol. Biol.* **2001**, *65*, 101-186). $p70^{S6K}$ dependent S6 phosphorylation is stimulated in response to a variety of hormones and growth factors primarily via the PI3K pathway (Coffer, P.J. *et al., Biochem. Biophys. Res. Commun*, **1994** *198*, 780-786), which may be under the regulation of mTOR, since rapamycin acts to inhibit $p70^{S6K}$ activity and blocks protein synthesis, specifically as a result of a down-regulation of translation of these mRNA's encoding ribosomal proteins (Kuo, C.J. *et al., Nature* **1992,** *358*, 70-73).

[0020] *In vitro* PDK1 catalyses the phosphorylation of Thr252 in the activation loop of the p70 catalytic domain, which is indispensable for p70 activity (Alessi, D.R., *Curr. Biol.*, **1998**, *8*, 69-81). The use of rapamycin and gene deletion studies of dp70S6K from Drosophila and $p70^{S6K}1$ from mouse have established the central role p70 plays in both cell growth and proliferation signaling.

[0021] The 3-phosphoinositide-dependent protein kinase-1 (PDK1) plays a key role in regulating the activity of a number of kinases belonging to the AGC subfamily of protein kinases (Alessi, D. *et al., Biochem. Soc. Trans* **2001**, *29*, 1). These include isoforms of protein kinase B (PKB, also known as AKT), p70 ribosomal S6 kinase (S6K) (Avruch, J. *et al., Prog. Mol. Subcell. Biol.* **2001**, *26*, 115), and p90 ribosomal

S6 kinase (Frödin, M. *et al., EMBO J.* **2000**, *19*, 2924-2934). PDK1 mediated signaling is activated in response to insulin and growth factors and as a consequence of attachment of the cell to the extracellular matrix (integrin signaling). Once activated these enzymes mediate many diverse cellular events by phosphorylating key regulatory proteins that play important roles controlling processes such as cell survival, growth, proliferation and glucose regulation [(Lawlor, M.A. *et al., J. Cell Sci.* **2001**, *114*, 2903-2910), (Lawlor, M.A. *et al., EMBO J.* **2002**, *21*, 3728-3738)]. PDK1 is a 556 amino acid protein, with an N-terminal catalytic domain and a C-terminal pleckstrin homology (PH) domain, which activates its substrates by phosphorylating these kinases at their activation loop (Belham, C. *et al., Curr. Biol.* **1999**, *9*, R93-R96). Many human cancers including prostate and NSCL have elevated PDK1 signaling pathway function resulting from a number of distinct genetic events such as PTEN mutations or over-expression of certain key regulatory proteins [(Graff, J.R., *Expert Opin. Ther. Targets* **2002**, *6*, 103-113), (Brognard, J., *et al., Cancer Res.* **2001**, *61*, 3986-3997)]. Inhibition of PDK1 as a potential mechanism to treat cancer was demonstrated by transfection of a PTEN negative human cancer cell line (U87MG) with antisense oligonucleotides directed against PDK1. The resulting decrease in PDK1 protein levels led to a reduction in cellular proliferation and survival (Flynn, P., *et al., Curr. Biol.* **2000**, *10*, 1439-1442). Consequently the design of ATP binding site inhibitors of PDK1 offers, amongst other treatments, an attractive target for cancer chemotherapy.

[0022] The diverse range of cancer cell genotypes has been attributed to the manifestation of the following six essential alterations in cell physiology: self-sufficiency in growth signaling, evasion of apoptosis, insensitivity to growth-inhibitory signaling, limitless replicative potential, sustained angiogenesis, and tissue invasion leading to metastasis (Hanahan, D. *et al., Cell* **2000**, *100*, 57-70). PDK1 is a critical mediator of the PI3K signalling pathway, which regulates a multitude of cellular function including growth, proliferation and survival. Consequently, inhibition of this pathway could affect four or more of the six defining requirements for cancer progression. As such it is anticipated that a PDK1 inhibitor will have an effect on the growth of a very wide range of human cancers.

[0023] Specifically, increased levels of PI3K pathway activity has been directly associated with the development of a number of human cancers, progression to an aggressive refractory state (acquired resistance to chemotherapies) and poor prognosis. This increased activity has been attributed to a series of key events including decreased activity of negative pathway regulators such as the phosphatase PTEN, activating mutations of positive pathway regulators such as Ras, and overexpression of components of the pathway itself such as PKB, examples include: brain (gliomas), breast, colon, head and neck, kidney, lung, liver, melanoma, ovarian, pancreatic, prostate, sarcoma, thyroid [(Teng, D.H. *et al., Cancer Res.*, **1997** *57*, 5221-5225), (Brognard, J. *et al., Cancer Res.*, **2001**, *61*, 3986-3997), (Cheng, J.Q. *et al., Proc. Natl. Acad. Sci.* **1996**, *93*, 3636-3641), (*Int. J. Cancer* **1995**, *64*, 280), (Graff, J.R., *Expert Opin. Ther. Targets* **2002,** *6*, 103-113), (*Am. J. Pathol.* **2001**, *159*, 431)]. Additionally, decreased pathway function through gene knockout, gene knockdown, dominant negative studies, and small molecule inhibitors of the pathway have been demonstrated to reverse many of the cancer phenotypes *in vitro* (some studies have also demonstrated a similar effect *in vivo*) such as block proliferation, reduce viability and sensitize cancer cells to known chemotherapies in a series of cell lines, representing the following cancers: pancreatic [(Cheng, J.Q. *et al., Proc. Natl. Acad. Sci.* **1996**, *93*, 3636-3641), (*Neoplasia* **2001**, *3*, 278)], lung [(Brognard, J. *et al., Cancer Res.* **2001**, *61*, 3986-3997), (*Neoplasia* **2001**, *3*, 278)], ovarian [(Hayakawa, J. *et al., Cancer Res.* **2000**, *60*, 5988-5994), (*Neoplasia* **2001**, *3*, 278)], breast (*Mol. Cancer Ther.* **2002**, *1*, 707), colon [(*Neoplasia* **2001**, *3*, 278), (Arico, S. *et al., J. Biol. Chem.* **2002**, *277*, 27613-27621)], cervical (*Neoplasia* **2001**, *3*, 278), prostate [(*Endocrinology* **2001**, *142*, 4795), (Thakkar, H. *et al. J. Biol. Chem.* **2001**, *276*, 38361-38369), (Chen, X. *et al., Oncogene* **2001**, *20*, 6073-6083)] and brain (glioblastomas) [(Flynn, P. *et al., Curr. Biol.* **2000**, *10*, 1439-1442)].

[0024] The Tec family of non-receptor tyrosine kinases plays a central role in signaling through antigen-receptors such as the TCR, BCR and Fcγ receptors (reviewed in Miller A, et al. Current Opinion in Immunology 14;331-340 (2002). Tec family kinases are essential for T cell activation. Three members of the Tec family, Itk, Rlk and Tec, are activated downstream of antigen receptor engagement in T cells and transmit signals to downstream effectors, including PLC-γ. Deletion of Itk in

mice results in reduced T cell receptor (TCR)-induced proliferation and secretion of the cytokines IL-2, IL-4, IL-5, IL-10 and IFN-γ (Schaeffer *et al*, Science 284; 638-641 (1999)), Fowell *et al*, Immunity 11;399-409 (1999), Schaeffer *et al* Nature Immunology 2,12; 1183-1188 (2001))). The immunological symptoms of allergic asthma are attenuated in Itk-/- mice. Lung inflammation, eosinophil infiltration and mucous production are drastically reduced in Itk-/- mice in response to challenge with the allergen OVA (Mueller *et al*, Journal of Immunology 170: 5056-5063 (2003)). Itk has also been implicated in atopic dermatitis. This gene has been reported to be more highly expressed in peripheral blood T cells from patients with moderate and/or severe atopic dermatitis than in controls or patients with mild atopic dermatitis (Matsumoto *et al*, International archives of Allergy and Immunology 129; 327-340 (2002)).

[0025] Splenocytes from Rlk-/- mice secrete half the IL-2 produced by wild type animals in response to TCR engagement (Schaeffer *et al*, Science 284; 638-641 (1999)), while combined deletion of Itk and Rlk in mice leads to a profound inhibition of TCR-induced responses including proliferation and production of the cytokines IL-2, IL-4, IL-5 and IFN-γ (Schaeffer *et al* Nature Immunology 2,12; 1183-1188 (2001)), Schaeffer *et al*, Science 284; 638-641 (1999)). Intracellular signaling following TCR engagement is effected in Itk/Rlk deficient T cells; inositol triphosphate production, calcium mobilization, MAP kinase activation, and activation of the transcription factors NFAT and AP-1 are all reduced (Schaeffer *et al*, Science 284; 638-641 (1999), Schaeffer *et al* Nature Immunology 2,12; 1183-1188 (2001)).

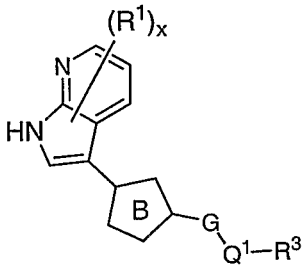
[0026] Tec family kinases are also essential for B cell development and activation. Patients with mutations in Btk have a profound block in B cell development, resulting in the almost complete absence of B lymphocytes and plasma cells, severely reduced Ig levels and a profound inhibition of humoral response to recall antigens (reviewed in Vihinen et al Frontiers in Bioscience 5:d917-928). Mice deficient in Btk also have a reduced number of peripheral B cells and greatly decreased levels of IgM and IgG3. Btk deletion in mice has a profound effect on B cell proliferation induced by anti-IgM, and inhibits immune responses to thymus-independent type II antigens (Ellmeier et al, J Exp Med 192:1611-1623 (2000)).

[0027] Tec kinases also play a role in mast cell activation through the high-affinity IgE receptor (FcεRI). Itk and Btk are expressed in mast cells and are activated by FcεRI cross-linking (Kawakami *et al*, Journal of Immunology; 3556-3562 (1995)). Btk deficient murine mast cells have reduced degranulation and decreased production of proinflammatory cytokines following FcεRI cross-linking (Kawakami *et al.* Journal of leukocyte biology 65:286-290). Btk deficiency also results in a decrease of macrophage effector functions (Mukhopadhyay et al, Journal of Immunology; 168, 2914-2921 (2002)).

[0028] Accordingly, there is a great need to develop inhibitors of ROCK, ERK, GSK, and members of the AGC sub-family of protein kinases (e.g., PKA, PDK, $p70^{S6K}$-1 and –2, and PKB) that would be useful in treating various diseases or conditions associated with ROCK, ERK or GSK activation, or activation of the AGC sub-family of protein kinases (e.g., PKA, PDK, $p70^{S6K}$-1 and –2, and PKB), particularly given the inadequate treatments currently available for the majority of these disorders. It would also be desirable to develop compounds that are useful as inhibitors of Tec family (e.g.,Tec, Btk, Itk/Emt/Tsk, Bmx, Txk/Rlk) protein kinases, particularly given the inadequate treatments currently available for the majority of the disorders implicated in their activation.

SUMMARY OF THE INVENTION

[0029] It has now been found that compounds of this invention, and pharmaceutically acceptable compositions thereof, are effective as inhibitors of ROCK, ERK, GSK, and members of the AGC sub-family of protein kinases (e.g., PKA, PDK, $p70^{S6K}$-1 and –2, and PKB). These compounds have the general formula **I:**



I

or a pharmaceutically acceptable derivative thereof, wherein ring B, R^1, R^2, R^3, x, G, and Q^1 are as defined below.

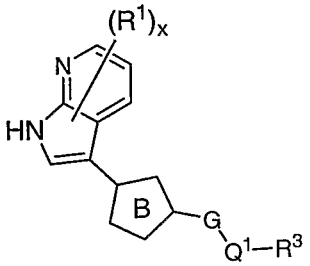
[0030] These compounds, and pharmaceutically acceptable compositions thereof, are useful for treating or lessening the severity of a variety of disorders, including allergic disorders such as asthma and atopic dermatitis, autoimmune diseases such as SLE lupus and psoriasis, conditions associated with organ transplantation, proliferative disorders such as cancer, inflammatory diseases, destructive bone disorders, hypertension, angina pectoris, cerebrovascular contraction, asthma, peripheral circulation disorder, premature birth, arteriosclerosis, spasm, retinopathy, erectile dysfunction (ED), Alzheimer's Disease, reperfusion/ischemia induced injury (e.g., stroke), and AIDS, to name a few.

[0031] The compounds provided by this invention are also useful for the study of kinases in biological and pathological phenomena; the study of intracellular signal transduction pathways mediated by such kinases, and the comparative evaluation of new kinase inhibitors.

DETAILED DESCRIPTION OF THE INVENTION

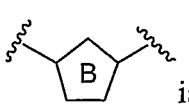
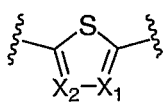
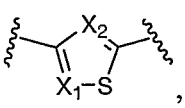
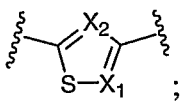
[0032] *I. General Description of Compounds of the Invention:*

[0033] The present invention relates to a compound of formula **I**:



I

or a pharmaceutically acceptable salt thereof, wherein:

wherein  is  ,  , or  ;

x is 0, 1, 2, or 3;

R^1 is halogen, -CN, $-NO_2$, or $-V_mR'$;

G is $-NR^2$ or C=O;

R^2 is $-U_nR'$;

X^1 and X^2 are each independently CR^4 or N;

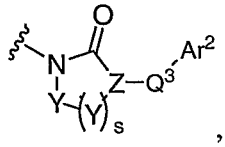
each occurrence of R^4 is independently halogen, -CN, $-NO_2$, or $-V_mR$;

each occurrence of U or V is independently an optionally substituted C_{1-6} alkylidene chain, wherein up to two methylene units of the chain are optionally and independently replaced by –NR-, -S-, -O-, -CS-, $-CO_2-$, -OCO-, -CO-, -COCO-, -CONR-, -NRCO-, $-NRCO_2-$, $-SO_2NR-$, $-NRSO_2-$, -CONRNR-, -NRCONR-, -OCONR-, -NRNR-, $-NRSO_2NR-$, -SO-, $-SO_2-$, -PO-, $-PO_2-$, or -POR-;

m and n are each independently 0 or 1;

each occurrence of R is independently hydrogen or an optionally substituted C_{1-6} aliphatic group; and each occurrence of R' is independently hydrogen or an optionally substituted C_{1-6} aliphatic group, a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-12 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring system having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; or R and R', two occurrences of R, or two occurrences of R', are taken together with the atom(s) to which they are bound to form an optionally substituted 3-12 membered saturated, partially unsaturated, or fully unsaturated monocyclic or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

Q^1 is –CO-, $-SO_2-$, $-NR^2$, $-NR^2CO-$, $-CONR^2-$, $-SO_2NR^2-$, or is a bond;

R^3 is Q^2-Ar^1, or when G is $-NR^2$, R^2 and Q^1-R^3, taken together with the nitrogen atom, form the cyclic group: , where s is 1 or 2, Z is CH or N; each occurrence of Y is independently, as valency and stability permit, -CO-, -CS-, $-SO_2-$, -O-, -S-, $-NR^5-$, or $-C(R^5)_2-$, and R^5 is U_nR';

Q^2 and Q^3 are each independently a bond or a C_{1-6} alkylidene chain, wherein up to two methylene units of the chain are each optionally and independently replaced by –NR'-, -S-, -O-, -CS-, $-CO_2-$, -OCO-, -CO-, -COCO-, -CONR'-, -NR'CO-, $-NR'CO_2-$, $-SO_2NR'-$, $-NR'SO_2-$, -CONR'NR'-, -NR'CONR'-, -OCONR'-, -

NR'NR'-, -NR'SO_2NR'-, -SO-, -SO_2-, -PO-, -PO_2-, or –POR'-; and wherein any carbon atom in the one or more methylene units is optionally substituted with one or two occurrences of R^6, wherein each occurrence of R^6 is independently halogen, -CN, -NO_2, or -U_nR', or two occurrences of R^6, or R' and R^6, taken together with the atoms to which they are bound, form an optionally substituted 3-6-membered cycloalkyl, heterocyclyl, aryl or heteroaryl ring; and

Ar^1 and Ar^2 are each independently a C_{1-6} aliphatic, a 3-8 membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-12 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring system having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; wherein Ar^1 and Ar^2 are each optionally substituted with 0-5 independent occurrences of TR^7; wherein T is a bond or is a C_1-C_6 alkylidene chain wherein up to two methylene units of T are optionally and independently replaced by –NR-, -S-, -O-, -CS-, -CO_2-, -OCO-, -CO-, -COCO-, -CONR-, -NRCO-, -$NRCO_2$-, -SO_2NR-, -$NRSO_2$-, -CONRNR-, -NRCONR-, -OCONR-, -NRNR-, -$NRSO_2$NR-, -SO-, -SO_2-, -PO-, -PO_2-, or -POR-; and each occurrence of R^7 is independently -R', halogen, -NO_2, -CN or =O.

[0034] In other embodiments, the compound is as described above, wherein

Q^1 is –CO-, -SO_2-, -NR^2, -NR^2CO-, -$CONR^2$-, –SO_2NR^2-; and

Ar^1 and Ar^2 are each independently a 5-8 membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-12 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring system having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; wherein Ar^1 and Ar^2 are each optionally substituted with 0-5 independent occurrences of TR^7; wherein T is a bond or is a C_1-C_6 alkylidene chain wherein up to two methylene units of T are optionally and independently replaced by –NR-, -S-, -O-, -CS-, -CO_2-, -OCO-, -CO-, -COCO-, -CONR-, -NRCO-, -$NRCO_2$-, -SO_2NR-, -$NRSO_2$-, -CONRNR-, -NRCONR-, -OCONR-, -NRNR-, -$NRSO_2$NR-, -SO-, -SO_2-, -PO-, -PO_2-, or -POR-; and each occurrence of R^7 is independently -R', halogen, -NO_2 or -CN.

[0035] *2. Compounds and Definitions:*

[0036] Compounds of this invention include those described generally above, and are further illustrated by the classes, subclasses, and species disclosed herein. As used herein, the following definitions shall apply unless otherwise indicated. For purposes of this invention, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 75th Ed. Additionally, general principles of organic chemistry are described in "Organic Chemistry", Thomas Sorrell, University Science Books, Sausalito: 1999, and "March's Advanced Organic Chemistry", 5th Ed., Ed.: Smith, M.B. and March, J., John Wiley & Sons, New York: 2001, the entire contents of which are hereby incorporated by reference.

[0037] As described herein, compounds of the invention may optionally be substituted with one or more substituents, such as are illustrated generally above, or as exemplified by particular classes, subclasses, and species of the invention. It will be appreciated that the phrase "optionally substituted" is used interchangeably with the phrase "substituted or unsubstituted." In general, the term "substituted", whether preceded by the term "optionally" or not, refers to the replacement of hydrogen radicals in a given structure with the radical of a specified substituent. Unless otherwise indicated, an optionally substituted group may have a substituent at each substitutable position of the group, and when more than one position in any given structure may be substituted with more than one substituent selected from a specified group, the substituent may be either the same or different at every position. Combinations of substituents envisioned by this invention are preferably those that result in the formation of stable or chemically feasible compounds. The term "stable", as used herein, refers to compounds that are not substantially altered when subjected to conditions to allow for their production, detection, and preferably their recovery, purification, and use for one or more of the purposes disclosed herein. In some embodiments, a stable compound or chemically feasible compound is one that is not substantially altered when kept at a temperature of 40°C or less, in the absence of moisture or other chemically reactive conditions, for at least a week.

[0038] The term "aliphatic" or "aliphatic group", as used herein, means a straight-chain (i.e., unbranched) or branched, substituted or unsubstituted hydrocarbon chain

that is completely saturated or that contains one or more units of unsaturation, or a monocyclic hydrocarbon or bicyclic hydrocarbon that is completely saturated or that contains one or more units of unsaturation, but which is not aromatic (also referred to herein as "carbocycle" "cycloaliphatic" or "cycloalkyl"), that has a single point of attachment to the rest of the molecule. Unless otherwise specified, aliphatic groups contain 1-20 aliphatic carbon atoms. In some embodiments, aliphatic groups contain 1-10 aliphatic carbon atoms. In other embodiments, aliphatic groups contain 1-8 aliphatic carbon atoms. In still other embodiments, aliphatic groups contain 1-6 aliphatic carbon atoms, and in yet other embodiments aliphatic groups contain 1-4 aliphatic carbon atoms. In some embodiments, "cycloaliphatic" (or "carbocycle" or "cycloalkyl") refers to a monocyclic C_3-C_8 hydrocarbon or bicyclic C_8-C_{12} hydrocarbon that is completely saturated or that contains one or more units of unsaturation, but which is not aromatic, that has a single point of attachment to the rest of the molecule wherein any individual ring in said bicyclic ring system has 3-7 members. Suitable aliphatic groups include, but are not limited to, linear or branched, substituted or unsubstituted alkyl, alkenyl, alkynyl groups and hybrids thereof such as (cycloalkyl)alkyl, (cycloalkenyl)alkyl or (cycloalkyl)alkenyl.

[0039] The term "heteroaliphatic", as used herein, means aliphatic groups wherein one or two carbon atoms are independently replaced by one or more of oxygen, sulfur, nitrogen, phosphorus, or silicon. Heteroaliphatic groups may be substituted or unsubstituted, branched or unbranched, cyclic or acyclic, and include "heterocycle", "heterocyclyl", "heterocycloaliphatic", or "heterocyclic" groups.

[0040] The term "heterocycle", "heterocyclyl", "heterocycloaliphatic", or "heterocyclic" as used herein means non-aromatic, monocyclic, bicyclic, or tricyclic ring systems in which one or more ring members are an independently selected heteroatom. In some embodiments, the "heterocycle", "heterocyclyl", "heterocycloaliphatic", or "heterocyclic" group has three to fourteen ring members in which one or more ring members is a heteroatom independently selected from oxygen, sulfur, nitrogen, or phosphorus, and each ring in the system contains 3 to 7 ring members.

[0041] The term "heteroatom" means one or more of oxygen, sulfur, nitrogen, phosphorus, or silicon (including, any oxidized form of nitrogen, sulfur, phosphorus,

or silicon; the quaternized form of any basic nitrogen or; a substitutable nitrogen of a heterocyclic ring, for example N (as in 3,4-dihydro-2*H*-pyrrolyl), NH (as in pyrrolidinyl) or NR^+ (as in N-substituted pyrrolidinyl)).

[0042] The term "unsaturated", as used herein, means that a moiety has one or more units of unsaturation.

[0043] The term "alkoxy", or "thioalkyl", as used herein, refers to an alkyl group, as previously defined, attached to the principal carbon chain through an oxygen ("alkoxy") or sulfur ("thioalkyl") atom.

[0044] The terms "haloalkyl", "haloalkenyl" and "haloalkoxy" means alkyl, alkenyl or alkoxy, as the case may be, substituted with one or more halogen atoms. The term "halogen" means F, Cl, Br, or I.

[0045] The term "aryl" used alone or as part of a larger moiety as in "aralkyl", "aralkoxy", or "aryloxyalkyl", refers to monocyclic, bicyclic, and tricyclic ring systems having a total of five to fourteen ring members, wherein at least one ring in the system is aromatic and wherein each ring in the system contains 3 to 7 ring members. The term "aryl" may be used interchangeably with the term "aryl ring". The term "aryl" also refers to heteroaryl ring systems as defined hereinbelow.

[0046] The term "heteroaryl", used alone or as part of a larger moiety as in "heteroaralkyl" or "heteroarylalkoxy", refers to monocyclic, bicyclic, and tricyclic ring systems having a total of five to fourteen ring members, wherein at least one ring in the system is aromatic, at least one ring in the system contains one or more heteroatoms, and wherein each ring in the system contains 3 to 7 ring members. The term "heteroaryl" may be used interchangeably with the term "heteroaryl ring" or the term "heteroaromatic".

[0047] An aryl (including aralkyl, aralkoxy, aryloxyalkyl and the like) or heteroaryl (including heteroaralkyl and heteroarylalkoxy and the like) group may contain one or more substituents and thus may be "optionally substituted". Unless otherwise defined above and herein, suitable substituents on the unsaturated carbon atom of an aryl or heteroaryl group are generally selected from halogen; -R°; -OR°; -SR°; phenyl (Ph) optionally substituted with R°; -O(Ph) optionally substituted with R°; $-(CH_2)_{1-2}$(Ph), optionally substituted with R°; -CH=CH(Ph), optionally substituted with R°; $-NO_2$; -CN; $-N(R°)_2$; -NR°C(O)R°; -NR°C(S)R°; $-NR°C(O)N(R°)_2$; -

$NR°C(S)N(R°)_2$; $-NR°CO_2R°$; $-NR°NR°C(O)R°$; $-NR°NR°C(O)N(R°)_2$; $-NR°NR°CO_2R°$; $-C(O)C(O)R°$; $-C(O)CH_2C(O)R°$; $-CO_2R°$; $-C(O)R°$; $-C(S)R°$; $-C(O)N(R°)_2$; $-C(S)N(R°)_2$; $-OC(O)N(R°)_2$; $-OC(O)R°$; $-C(O)N(OR°)\ R°$; $-C(NOR°)\ R°$; $-S(O)_2R°$; $-S(O)_3R°$; $-SO_2N(R°)_2$; $-S(O)R°$; $-NR°SO_2N(R°)_2$; $-NR°SO_2R°$; $-N(OR°)R°$; $-C(=NH)-N(R°)_2$; $-P(O)_2R°$; $-PO(R°)_2$; $-OPO(R°)_2$; $-(CH_2)_{0-2}NHC(O)R°$; phenyl (Ph) optionally substituted with $R°$; -O(Ph) optionally substituted with $R°$; $-(CH_2)_{1-2}(Ph)$, optionally substituted with $R°$; or -CH=CH(Ph), optionally substituted with $R°$; wherein each independent occurrence of $R°$ is selected from hydrogen, optionally substituted C_{1-6} aliphatic, an unsubstituted 5-6 membered heteroaryl or heterocyclic ring, phenyl, -O(Ph), or $-CH_2(Ph)$, or, notwithstanding the definition above, two independent occurrences of $R°$, on the same substituent or different substituents, taken together with the atom(s) to which each $R°$ group is bound, to form an optionally substituted 3-12 membered saturated, partially unsaturated, or fully unsaturated monocyclic or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0048] . Optional substituents on the aliphatic group of $R°$ are selected from NH_2, $NH(C_{1-4}aliphatic)$, $N(C_{1-4}aliphatic)_2$, halogen, $C_{1-4}aliphatic$, OH, $O(C_{1-4}aliphatic)$, NO_2, CN, CO_2H, $CO_2(C_{1-4}aliphatic)$, $O(haloC_{1-4}\ aliphatic)$, or $haloC_{1-4}aliphatic$, wherein each of the foregoing $C_{1-4}aliphatic$ groups of $R°$ is unsubstituted.

[0049] An aliphatic or heteroaliphatic group, or a non-aromatic heterocyclic ring may contain one or more substituents and thus may be "optionally substituted". Unless otherwise defined above and herein, suitable substituents on the saturated carbon of an aliphatic or heteroaliphatic group, or of a non-aromatic heterocyclic ring are selected from those listed above for the unsaturated carbon of an aryl or heteroaryl group and additionally include the following: =O, =S, $=NNHR^*$, $=NN(R^*)_2$, $=NNHC(O)R^*$, $=NNHCO_2(alkyl)$, $=NNHSO_2(alkyl)$, or $=NR^*$, where each R^* is independently selected from hydrogen or an optionally substituted C_{1-6} aliphatic group.

[0050] Unless otherwise defined above and herein, optional substituents on the nitrogen of a non-aromatic heterocyclic ring are generally selected from $-R^+$, $-N(R^+)_2$, $-C(O)R^+$, $-CO_2R^+$, $-C(O)C(O)R^+$, $-C(O)CH_2C(O)R^+$, $-SO_2R^+$, $-SO_2N(R^+)_2$,

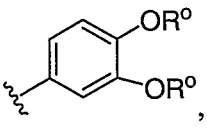
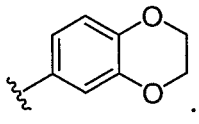
$-C(=S)N(R^{+1})_2$, $-C(=NH)-N(R^+)_2$, or $-NR^+SO_2R^+$; wherein R^+ is hydrogen, an optionally substituted C_{1-6} aliphatic, optionally substituted phenyl, optionally substituted -O(Ph), optionally substituted $-CH_2(Ph)$, optionally substituted $-(CH_2)_{1-2}(Ph)$; optionally substituted -CH=CH(Ph); or an unsubstituted 5-6 membered heteroaryl or heterocyclic ring having one to four heteroatoms independently selected from oxygen, nitrogen, or sulfur, or, notwithstanding the definition above, two independent occurrences of R^+, on the same substituent or different substituents, taken together with the atom(s) to which each R^+ group is bound, form an optionally substituted 3-12 membered saturated, partially unsaturated, or fully unsaturated monocyclic or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0051] Optional substituents on the aliphatic group or the phenyl ring of R^+ are selected from $-NH_2$, $-NH(C_{1-4}$ aliphatic), $-N(C_{1-4}$ aliphatic$)_2$, halogen, C_{1-4} aliphatic, -OH, $-O(C_{1-4}$ aliphatic), $-NO_2$, -CN, $-CO_2H$, $-CO_2(C_{1-4}$ aliphatic), -O(halo C_{1-4} aliphatic), or halo(C_{1-4} aliphatic), wherein each of the foregoing C_{1-4}aliphatic groups of R^+ is unsubstituted.

[0052] The term "alkylidene chain" refers to a straight or branched carbon chain that may be fully saturated or have one or more units of unsaturation and has two points of attachment to the rest of the molecule.

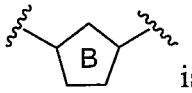
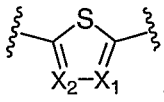
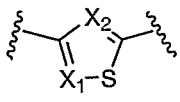
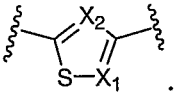
[0053] As detailed above, in some embodiments, two independent occurrences of R^o (or R^+, R, R' or any other variable similarly defined herein), are taken together with the atom(s) to which they are bound to form an optionally substituted 3-12 membered saturated, partially unsaturated, or fully unsaturated monocyclic or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

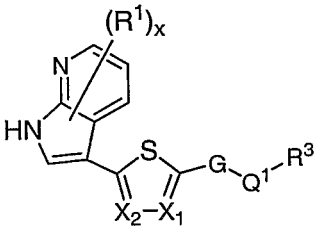
[0054] Exemplary rings that are formed when two independent occurrences of R^o (or R^+, R, R' or any other variable similarly defined herein), are taken together with the atom(s) to which each variable is bound include, but are not limited to the following: a) two independent occurrences of R^o (or R^+, R, R' or any other variable similarly defined herein) that are bound to the same atom and are taken together with that atom to form a ring, for example, $N(R^o)_2$, where both occurrences of R^o are taken together with the nitrogen atom to form a piperidin-1-yl, piperazin-1-yl, or morpholin-4-yl group; and b) two independent occurrences of R^o (or R^+, R, R' or any other

variable similarly defined herein) that are bound to different atoms and are taken together with both of those atoms to form a ring, for example where a phenyl group is substituted with two occurrences of OR^o , these two occurrences of R^o are taken together with the oxygen atoms to which they are bound to form a fused 6-membered oxygen containing ring: . It will be appreciated that a variety of other rings can be formed when two independent occurrences of R^o (or R^+, R, R' or any other variable similarly defined herein) are taken together with the atom(s) to which each variable is bound and that the examples detailed above are not intended to be limiting.

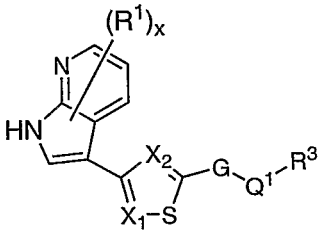
[0055] Unless otherwise stated, structures depicted herein are also meant to include all isomeric (e.g., enantiomeric, diastereomeric, and geometric (or conformational)) forms of the structure; for example, the R and S configurations for each asymmetric center, (Z) and (E) double bond isomers, and (Z) and (E) conformational isomers. Therefore, single stereochemical isomers as well as enantiomeric, diastereomeric, and geometric (or conformational) mixtures of the present compounds are within the scope of the invention. Unless otherwise stated, all tautomeric forms of the compounds of the invention are within the scope of the invention. Additionally, unless otherwise stated, structures depicted herein are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures except for the replacement of hydrogen by deuterium or tritium, or the replacement of a carbon by a ^{13}C- or ^{14}C-enriched carbon are within the scope of this invention. Such compounds are useful, for example, as analytical tools or probes in biological assays.

[0056] *3. Description of Exemplary Compounds:*

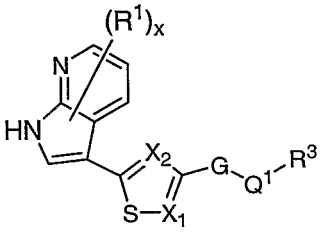
[0057] As described generally above for compounds of formula **I**,  is  ,  , or  . Thus, in certain embodiments, compounds of formulae **I-A, I-B,** or **I-C** are provided:



I-A

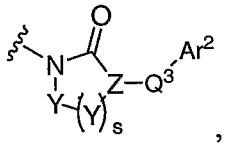


I-B



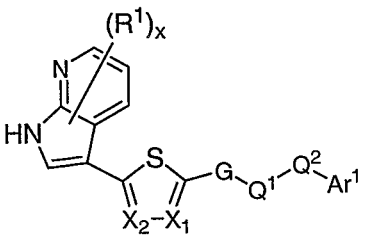
I-C

[0058] As also described generally above for compounds of formula **I**, R^3 is Q^2-Ar^1, or R^2 and Q^1-R^3, taken together with the nitrogen atom, form the cyclic group:

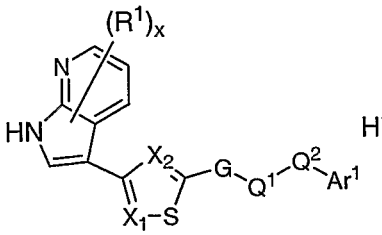
 , where s is 1 or 2, Z is CH or N, each occurrence of Y is independently, as valency and stability permit, -CO-, -CS-, -SO_2-, -O-, -S-, -NR^5-, or -$C(R^5)_2$-, and R^5 is U_nR'.

[0059] In some embodiments, wherein the compound has the formula **I-B**, G is -NR^2 and Q^1 is -CO- or G is C=O and Q^1 is -NR^2-. In further embodiments, G is -NR^2 and Q^1 is -CO-. In yet further embodiments, X_1 is CR^4 and X_2 is CR^4 or N.

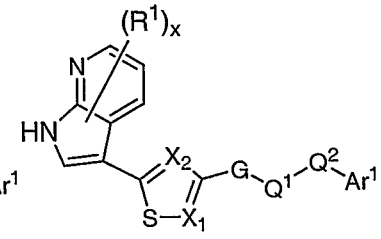
[0060] Accordingly, in one embodiment, R^3 is Q^2-Ar^1 and compounds of formulae **I-A-i, I-B-i,** and **I-C-i** are provided.



I-A-i

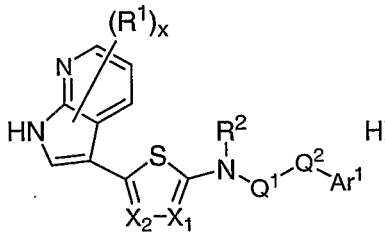


I-B-i

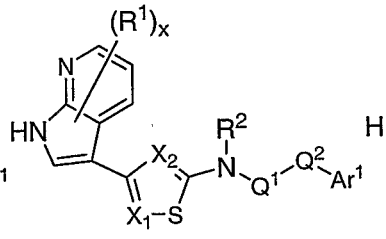


I-C-i

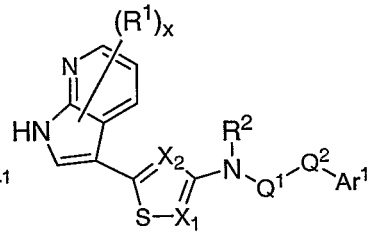
[0061] In some embodiments, G is NR^2, R^3 is Q^2-Ar^1, and compounds of formulae **I-A-i-a**, **I-B-i-a**, and **I-C-i-a** are provided:



I-A-i-a

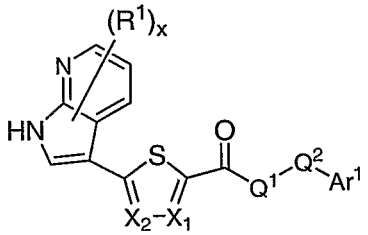


I-B-i-a

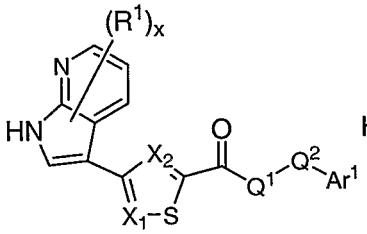


I-C-i-a

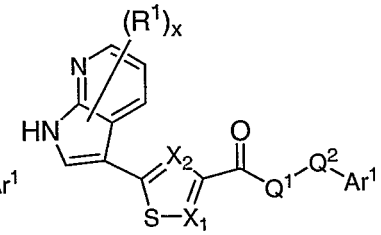
[0062] In other embodiments, G is C=O, R^3 is Q^2-Ar^1, and compounds of formulae **I-A-i-b**, **I-B-i-b**, and **I-C-i-b** are provided:



I-A-i-b



I-B-i-b



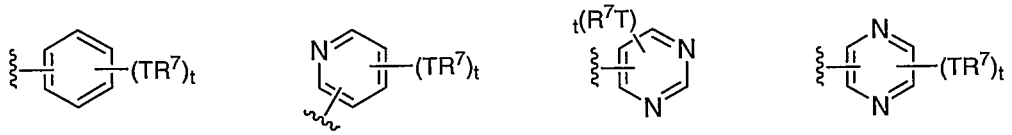
I-C-i-b

[0063] In general, for compounds of formula **I**, and subsets thereof, R^2 is U_nR'. In certain embodiments, R^2 is hydrogen, or is U_nR', where n is 1, and U is a C_{1-6} alkylidene chain wherein one or two methylene units are optionally and independently replaced by –O-, -NR-, -S-, or –CO-. In other embodiments, U is $–CH_2$-, $-CH_2CH_2$-, $–CH_2CH_2CH_2$-, $-CH_2CH_2CH_2CH_2$-, $-CH_2O$-, $-CH_2S$-, $–CH_2NR$-, $-CH_2CH_2O$-, $-CH_2CH_2S$-, $–CH_2CH_2NR$-, $-CH_2CH_2CH_2O$-, $-CH_2CH_2CH_2S$-, $-CH_2CH_2CH_2NR$-, $-CH_2CH_2CH_2CH_2O$-, $-CH_2CH_2CH_2CH_2S$-, $-CH_2CH_2CH_2CH_2NR$-, $-CH_2CH_2OCH_2CH_2$-, $-(CH_2)_4NHCH_2$-, $-(CH_2)_3NHCH_2CH_2$-, or $-CH_2CH_2NHCH_2CH_2$-, and exemplary R' groups are hydrogen, C_1-C_4alkyl, an optionally substituted group selected from tetrahydropyranyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, pyridinyl, imidazolyl, phenyl, or cyclohexyl, or R and R', taken together with the nitrogen atom to which they are bound, form an optionally substituted 5- or 6-membered saturated, partially unsaturated, or unsaturated heterocyclyl ring.

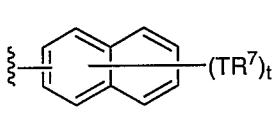
[0064] As described generally above, for compounds of formula **I**, and subsets thereof, Q^1 is –CO-, -SO_2-, -NR^2, -NR^2CO-, -$CONR^2$-, or –SO_2NR^2-. In some embodiments, Q^1 is –CO-, -$CONR^2$-, -NR^2-, -SO_2-, or –SO_2NR^2-. In other embodiments, Q^1 is –CO-, -NR^2-, or –$CONR^2$-.

[0065] For compounds of general formula **I**, and subsets thereof, Q^2 is a bond or a C_{1-6} alkylidene chain, wherein up to two methylene units of the chain are each optionally and independently replaced by –NR'-, -S-, -O-, -CS-, -CO_2-, -OCO-, -CO-, -COCO-, -CONR'-, -NR'CO-, -NR'CO_2-, -SO_2NR'-, -NR'SO_2-, -CONR'NR'-, -NR'CONR'-, -OCONR'-, -NR'NR'-, -NR'SO_2NR'-, -SO-, -SO_2-, -PO-, -PO_2-, or –POR'-; and wherein any carbon atom in the one or more methylene units is optionally substituted with one or two occurrences of R^6, wherein each occurrence of R^6 is independently halogen, CN, NO_2, or U_nR', or two occurrences of R^6, or R' and R^6, taken together with the atoms to which they are bound, form an optionally substituted 3-6-membered cycloalkyl, heterocyclyl, aryl or heteroaryl ring. In some embodiments, Q^2 is a direct bond, or is -$(CHR^6)_q$-, -$(CHR^6)_q$O-, -$(CHR^6)_q$S-, -$(CHR^6)_q$S(O)$_2$-, -$(CHR^6)_q$S(O)- , -$(CHR^6)_q$NR-, or –$(CHR^6)_q$C(O)-, wherein q is 0, 1, 2, or 3. In certain other embodiments, R^6 is R', -N(R)(R'), -$(CH_2)_{1-4}$N(R)(R'), -$(CH_2)_{1-4}C(CH_3)_2$N(R)(R'), -OR', -$(CH_2)_{1-4}$OR', -$NR(CH_2)_{1-4}$N(R)(R'), -$NR(CH_2)_{1-4}SO_2$R', -$NR(CH_2)_{1-4}$COOR', or -$NR(CH_2)_{1-4}$COR', or two occurrences of R^6, taken together with the atoms to which they are bound, form an optionally substituted 3-6-membered saturated, partially unsaturated, or fully unsaturated ring. Examples of such R^6 groups include, but are not limited to -CH_2OH, -CH_2CH_2OH, -OH, -OMe, -OEt, -NH_2, -NH(Me), -NH(Et), -N(Me)(Me), -CH_2NH_2, -$CH_2CH_2NH_2$, -$NHCO_2$*t*-butyl, phenyl, cyclopentyl, methyl, ethyl, isopropyl, cyclopropyl, -$NH(CH_2)_3NH_2$, -$NH(CH_2)_2NH_2$, -$NH(CH_2)_2$NHEt, -NHCH$_2$pyridyl, -NHSO_2phenyl, -NHCOCH_2C(O)O*t*-butyl, -NHCOCH_2NH_3, -$CH_2C(CH_3)_2NH_2$, -NHCH_2-imidazol-4-yl.

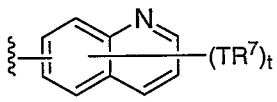
[0066] In certain exemplary embodiments, Ar^1 groups are:



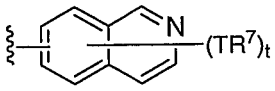
a **b** **c** **d**



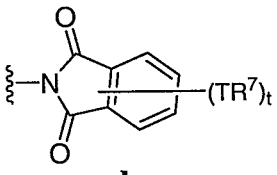
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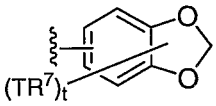
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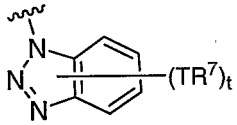
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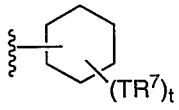
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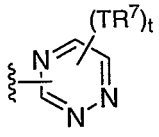
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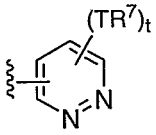
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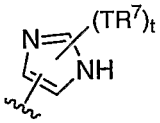
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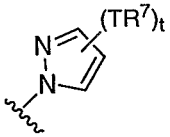
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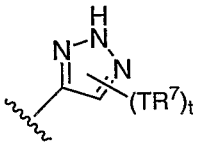
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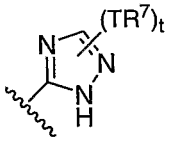
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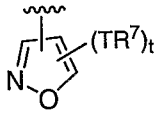
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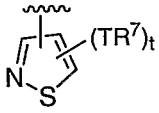
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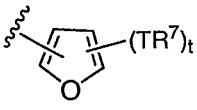
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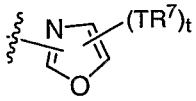
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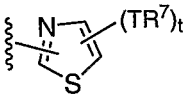
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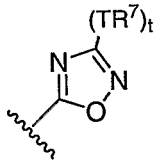
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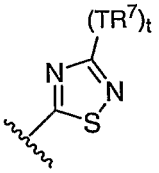
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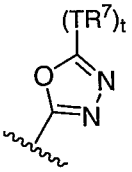
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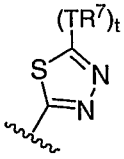
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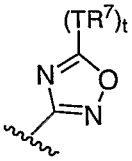
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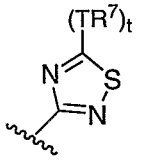
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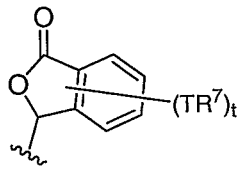
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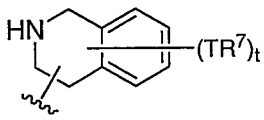
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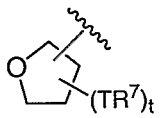
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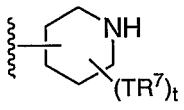
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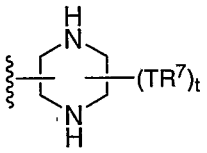
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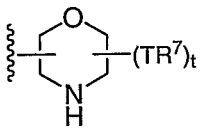
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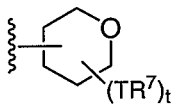
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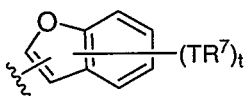
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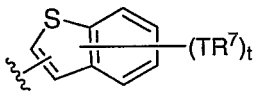
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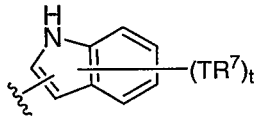
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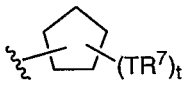
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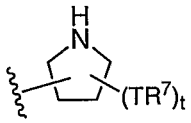
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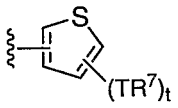
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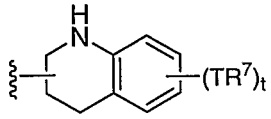
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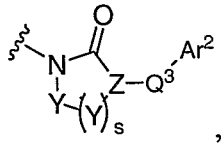


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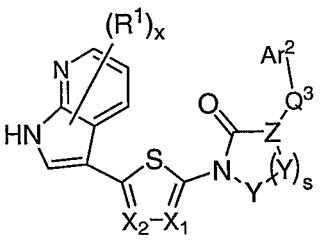
wherein t is 0, 1, 2, 3, 4, or 5, and wherein any Ar^1 is bonded to Q^2 through any substitutable nitrogen or carbon atom, and wherein one or more hydrogen atoms on any substitutable nitrogen or carbon atom is substituted with one or more independent occurrences of TR^7, wherein TR^7 is defined generally above.

[0067] In other embodiments, Ar^1 is **a, b, e, f, g, h, i, j, k, r, cc, dd, ff, jj, ll**, or **pp**. As described generally above, Ar^1 is optionally substituted with 0-5 independent occurrences of TR^7; wherein T is a bond or is a C_1-C_6 alkylidene chain wherein up to

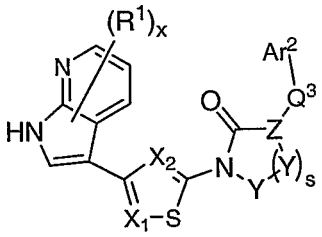
two methylene units of T are optionally replaced by –NR-, -S-, -O-, -CS-, -CO_2-, -OCO-, -CO-, -COCO-, -CONR-, -NRCO-, -$NRCO_2$-, -SO_2NR-, -$NRSO_2$-, -CONRNR-, -NRCONR-, -OCONR-, -NRNR-, -$NRSO_2NR$-, -SO-, -SO_2-, -PO-, -PO_2-, or -POR-; and each occurrence of R^7 is independently R', halogen, NO_2, or CN. In certain embodiments, T is a bond or is an optionally substituted C_{1-6} alkylidene chain wherein one or two methylene units are optionally and independently replaced by –O-, -NR-, -S-, -SO-, -SO_2-, –COO-, -CO-, -OSO_2-, -$NRSO_2$, -CONR-, or -SO_2NR-, and R^7 is R' or halogen. In other embodiments, each occurrence of TR^7 is independently -C_{1-3}alkyl, -OR', -SR', -CF_3, -OCF_3, -SCF_3, -F, -Cl, I, -Br, -COOR', -COR', -$O(CH_2)_4N(R)(R')$, -$O(CH_2)_3N(R)(R')$, -$O(CH_2)_2N(R)(R')$, -$O(CH_2)N(R)(R')$, -$O(CH_2)_4CON(R)(R')$, -$O(CH_2)_3CON(R)(R')$, -$O(CH_2)_2CON(R)(R')$, -$O(CH_2)CON(R)(R')$, -CON(R)(R'), -$(CH_2)_4OR'$, -$(CH_2)_3OR'$, -$(CH_2)_2OR'$, -CH_2OR', optionally substituted phenyl or benzyl, -N(R)(R'), -$(CH_2)_4N(R)(R')$, -$(CH_2)_3N(R)(R')$, -$(CH_2)_2N(R)(R')$, -$(CH_2)N(R)(R')$, -$SO_2N(R)(R')$, -$NRSO_2R'$, -CON(R)(R'), -$NRSO_2(CH_2)_{1-4}N(R)(R')$, -$CONR(CH_2)_{1-4}N(R)(R')$, -$COO(CH_2)_{1-4}N(R)(R')$,or –$OSO_2R'$, where, as defined generally above, each occurrence of R is independently hydrogen or an optionally substituted C_{1-6} aliphatic group; and each occurrence of R' is independently hydrogen or an optionally substituted C_{1-6} aliphatic group, a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-12 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring system having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; or R and R', two occurrences of R, or two occurrences of R', are taken together with the atom(s) to which they are bound to form an optionally substituted 3-12 membered saturated, partially unsaturated, or fully unsaturated monocyclic or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0068] In another embodiment, R^3 is Q^2-Ar^1, or R^2 and Q^1-R^3, taken together with the nitrogen atom, form the cyclic group: , where Z is CH or N, s is 1 or 2, each occurrence of Y is independently, as valency and stability permit, -CO-, -

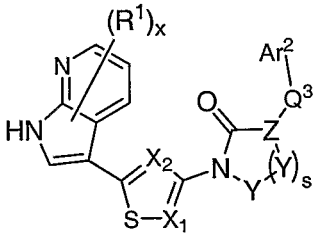
CS-, $-SO_2-$, -O-, -S-, $-NR^5-$, or $-C(R^5)_2-$, and R^5 is U_nR', and compounds of formulae **I-A-ii, I-B-ii,** and **I-C-ii** are provided:



I-A-ii



I-B-ii



I-C-ii

[0069] For compounds of formula **I-A-ii, I-B-ii,** and **I-C-ii**, Q^3 is a bond or a C_{1-6} alkylidene chain, wherein up to two methylene units of the chain are each optionally and independently replaced by –NR'-, -S-, -O-, -CS-, $-CO_2-$, -OCO-, -CO-, -COCO-, -CONR'-, -NR'CO-, $-NR'CO_2-$, $-SO_2NR'-$, $-NR'SO_2-$, -CONR'NR'-, -NR'CONR'-, -OCONR'-, -NR'NR'-, $-NR'SO_2NR'-$, -SO-, $-SO_2-$, -PO-, $-PO_2-$, or –POR'-; and wherein any carbon atom in the one or more methylene units is optionally substituted with one or two occurrences of R^6, wherein each occurrence of R^6 is independently halogen, CN, NO_2, or U_nR', or two occurrences of R^6, or R' and R^6, taken together with the atoms to which they are bound, form an optionally substituted 3-6-membered cycloalkyl, heterocyclyl, aryl or heteroaryl ring. In some embodiments, Q^2 is a direct bond, or is $-(CHR^6)_q-$, $-(CHR^6)_qO-$, $-(CHR^6)_qS-$, $-(CHR^6)_qS(O)_2-$, $-(CHR^6)_qS(O)-$, $-(CHR^6)_qNR-$, or $–(CHR^6)_qC(O)-$, wherein q is 0, 1, 2, or 3. In certain other embodiments, R^6 is R', -N(R)(R'), $-(CH_2)_{1-4}N(R)(R')$, $-(CH_2)_{1-4}C(CH_3)_2N(R)(R')$, $-(CH_2)_{1-4}CH(CH_3)$ N(R)(R'), -OR', $-(CH_2)_{1-4}OR'$, $-NR(CH_2)_{1-4}N(R)(R')$, $-NR(CH_2)_{1-4}SO_2R'$, $-NR(CH_2)_{1-4}COOR'$, or $-NR(CH_2)_{1-4}COR'$, or two occurrences of R^6, taken together with the atoms to which they are bound, form an optionally substituted 3-6-membered saturated, partially unsaturated, or fully unsaturated ring. Examples of such R^6 groups include, but are not limited to $-CH_2OH$, $-CH_2CH_2OH$, -OH, -OMe, -OEt, $-NH_2$, -NH(Me), -NH(Et), -N(Me)(Me), $-CH_2NH_2$, $-CH_2CH_2NH_2$, $-NHCO_2t$-butyl, phenyl, cyclopentyl, methyl, ethyl, isopropyl, cyclopropyl, $-NH(CH_2)_3NH_2$, $-NH(CH_2)_2NH_2$, $-NH(CH_2)_2NHEt$, $-NHCH_2$pyridyl, $-NHSO_2$phenyl, -

$NHCOCH_2C(O)Ot$-butyl, $-NHCOCH_2NH_3$, $-CH_2C(CH_3)_2NH_2$, $-NHCH_2$-imidazol-4-yl.

[0070] For compounds of general formula **I-A-ii, I-B-ii,** and **I-C-ii**, exemplary Ar^2 groups are the same as those described for Ar^1 (**a-qq**) groups in **[0066]**.

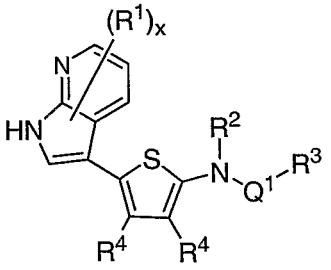
[0071] In more preferred embodiments, Ar^2 is **a, b, e, f, g, h, i, j, k, n, r, cc, dd, ff, jj, ll**, or **pp**.

[0072] As described generally above, Ar^1 is optionally substituted with 0-5 independent occurrences of $-TR^7$; wherein T is a bond or is a C_1-C_6 alkylidene chain wherein up to two methylene units of T are optionally replaced by –NR-, -S-, -O-, -CS-, $-CO_2-$, -OCO-, -CO-, -COCO-, -CONR-, -NRCO-, $-NRCO_2-$, $-SO_2NR-$, $-NRSO_2-$, -CONRNR-, -NRCONR-, -OCONR-, -NRNR-, $-NRSO_2NR-$, -SO-, $-SO_2-$, -PO-, $-PO_2-$, or -POR-; and each occurrence of R^7 is independently R', halogen, $-NO_2$, or -CN. In certain embodiments, T is a bond or is an optionally substituted C_{1-6} alkylidene chain wherein one or two methylene units are optionally and independently replaced by –O-, -NR-, -S-, -SO-, $-SO_2-$,–COO-, -CO-, $-OSO_2-$, $-NRSO_2$, -CONR-, or $-SO_2NR-$, and R^7 is R' or halogen. In other embodiments, each occurrence of TR^7 is independently $-C_{1-3}$alkyl, -OR', -SR', $-CF_3$, $-OCF_3$, $-SCF_3$, -F, -Cl, -I, -Br, -COOR', -COR', $-O(CH_2)_4N(R)(R')$, $-O(CH_2)_3N(R)(R')$, $-O(CH_2)_2N(R)(R')$, $-O(CH_2)N(R)(R')$, $-O(CH_2)_4CON(R)(R')$, $-O(CH_2)_3CON(R)(R')$, $-O(CH_2)_2CON(R)(R')$, $-O(CH_2)CON(R)(R')$, -C(O)N(R)(R'), $-(CH_2)_4OR'$, $-(CH_2)_3OR'$, $-(CH_2)_2OR'$, $-CH_2OR'$, optionally substituted phenyl or benzyl, -N(R)(R'), $-(CH_2)_4N(R)(R')$, $-(CH_2)_3N(R)(R')$, $-(CH_2)_2N(R)(R')$, $-(CH_2)N(R)(R')$, $-SO_2N(R)(R')$, $-NRSO_2R'$, -CON(R)(R'), $-NRSO_2(CH_2)_{1-4}N(R)(R')$, $-CONR(CH_2)_{1-4}N(R)(R')$, $-COO(CH_2)_{1-4}N(R)(R')$,or $-OSO_2R'$, where, as defined generally above, each occurrence of R is independently hydrogen or an optionally substituted C_{1-6} aliphatic group; and each occurrence of R' is independently hydrogen or an optionally substituted C_{1-6} aliphatic group, a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-12 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring system having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; or R and R', two occurrences of R, or two occurrences of R', are taken together with the atom(s) to which they are bound to form an optionally

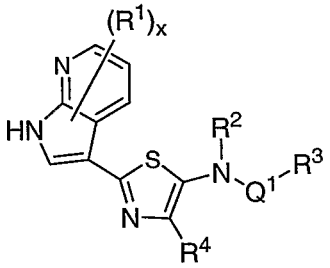
substituted 3-12 membered saturated, partially unsaturated, or fully unsaturated monocyclic or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0073] In certain embodiments, for compounds of formula **I-b**, R^5 is hydrogen, $-(CH_2)_3OR'$, $-(CH_2)_2OR'$, $-(CH_2)OR'$, $-(CH_2)_3N(R')_2$, $-(CH_2)_2N(R')_2$, $-(CH_2)N(R')_2$, or $-C_{1-4}$aliphatic.

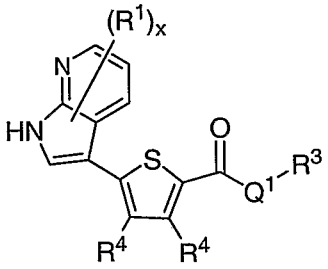
[0074] As described generally above, for compounds of formula **I, I-A-i, I-B-i, I-C-i, I-A-i-a, I-B-i-a, I-C-i-a, I-A-i-b, I-B-i-b,** and **I-B-i-c,** X^1 and X^2 are each independently CR^4 or N, and thus compounds of formulae **II-A, II-B, III-A, III-B, IV-A, IV-B, V-A, V-B, VI-A, VI-B, VII-A, VII-B, VIII-A, VIII-B, IX-A, IX-B, X-A, X-B, XI-A, XI-B, XII-A, XII-B, XIII-A,** and **XIII-B** are provided:



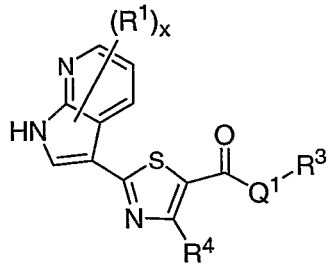
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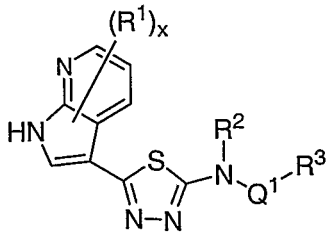
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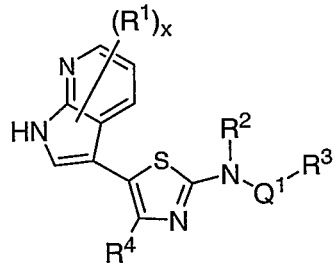
II-B



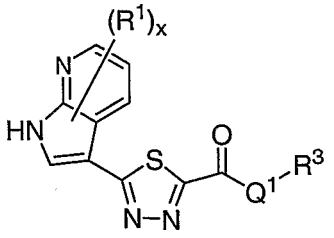
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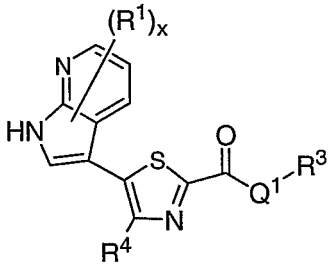
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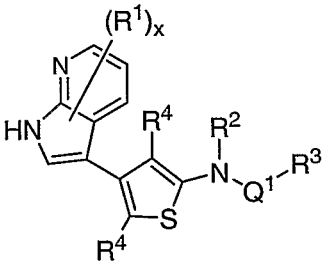
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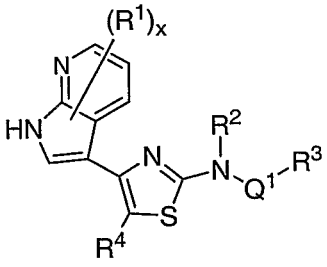
IV-B



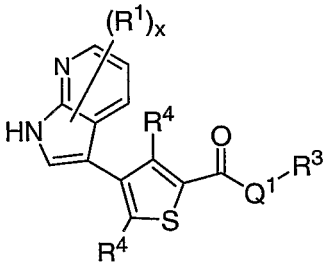
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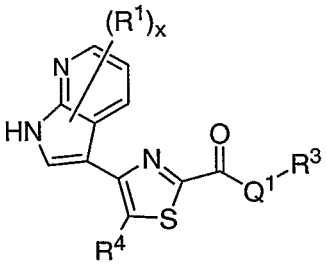
VI-A



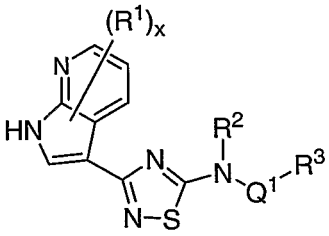
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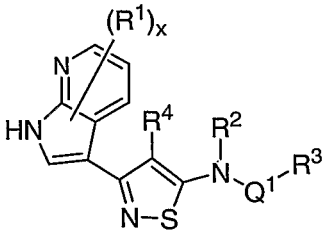
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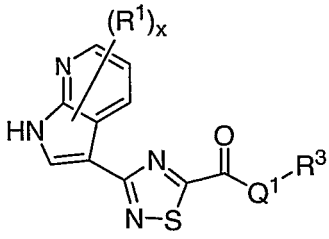
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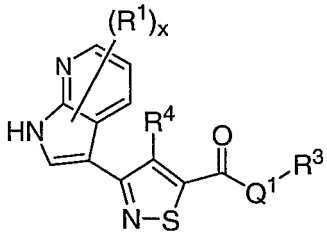
VIII-A



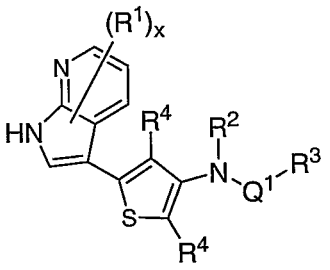
IX-A



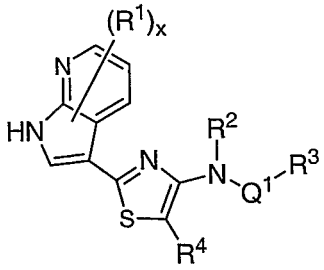
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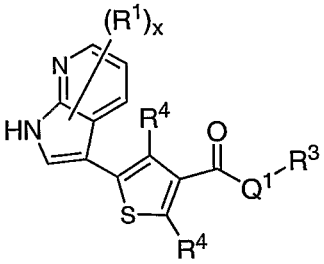
IX-B



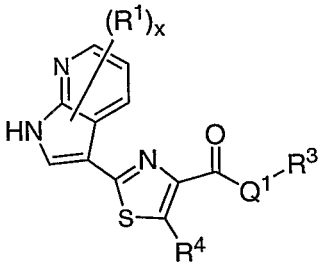
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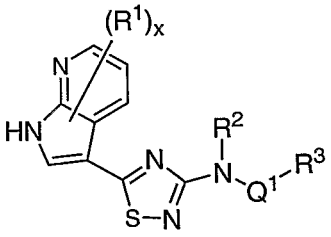
XI-A



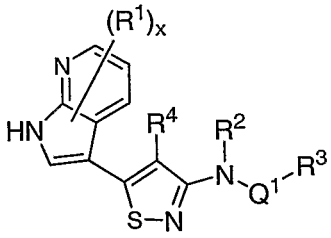
X-B



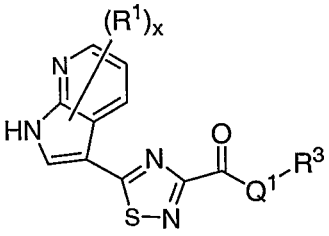
XI-B



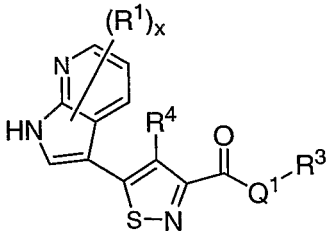
XII-A



XIII-A



XII-B

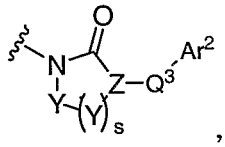


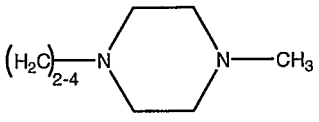
XIII-B

[0075] In general, for compounds of formula **I**, and subsets thereof, x is 0, 1, 2, or 3, and each occurrence of R^1 is independently halogen, -CN, $-NO_2$, or $-V_mR'$. In certain embodiments, x is 0, 1, or 2, and R^1 groups, when present, are each independently hydrogen, halogen, optionally substituted C_1-C_4aliphatic, -OH, -OR', -SR', or $-N(R')_2$. In other embodiments, R^1 groups are each independently hydrogen, halogen, $-CH_3$, $-CH_2CH_3$, -OH, $-OCH_3$, $-SCH_3$, $-NH_2$, $-N(CH_3)_2$, $-N(CH_2CH_3)_2$, -

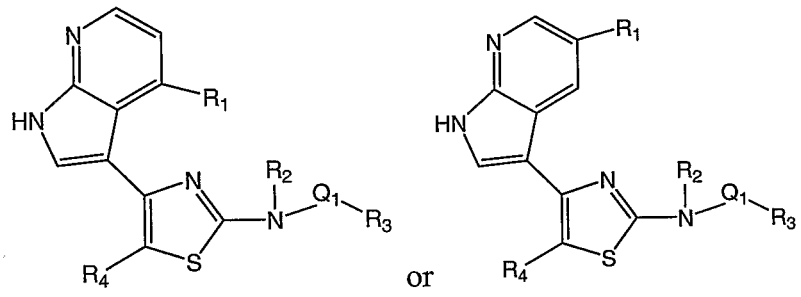
$NH(CH_2)_2NHCH_3$, -NH(cyclopropyl), -$NH(CH_2)$cyclopropyl, or -$NH(CH_2)_2N(CH_3)_2$. In other embodiments, R^1 groups are not an optionally substituted phenyl. In other embodiments, R^1 groups are not heterocyclic, heteroaryl, cycloaliphatic or aryl.

[0076] As described generally above, the thiadiazole, thiazole, thiophene, and isothiazole rings are each optionally substituted with zero, one or two occurrences of R^4, as valency permits, wherein each occurrence of R^4 is independently halogen, -CN, $-NO_2$, or $-V_mR$. In some embodiments, R^4 groups are each independently hydrogen, C_{1-6}aliphatic, -CN, -COR, -COOR, $CON(R)_2$, or halogen. In other embodiments, R^4 groups are each hydrogen.

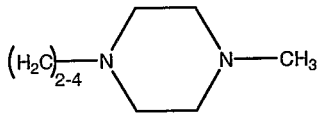
[0077] It will also be appreciated that for compounds of formulae **II-A, II-B, III-A, III-B, IV-A, IV-B, V-A, V-B, VI-A, VI-B, VII-A, VII-B, VIII-A, VIII-B, IX-A, IX-B, X-A, X-B, XI-A, XI-B, XII-A, XII-B, XIII-A,** and **XIII-B,** in some embodiments R^3 is Q^2-Ar^1, wherein Q^2 and Ar^1 are described generally and in subsets above and herein. In other exemplary embodiments, for each of the above-described classes and subclasses of compounds, R^2 and Q^1-R^3, taken together with the nitrogen atom, form the cyclic group: , where Z is CH or N, s is 1 or 2, each occurrence of Y is independently, as valency and stability permit, -CO-, -CS-, $-SO_2$-, -O-, -S-, $-NR^5$-, or $-C(R^5)_2$-, and R^5 is $-U_nR'$, wherein Q^3, Ar^2, and R^5 are described generally above and in classes and subclasses above and herein.

[0078] For compounds of formula **VII-B**, in some embodiments, Q^1 is -CO-. In further embodiments, R^2 is H, $-C_{1-4}$ aliphatic, -cyclopropyl or . In further embodiments, R^2 is H. In other embodiments for compounds of formula **VII-B**, R^4 is H or $-C_{1-4}$ aliphatic. In further embodiments, R^4 is H.

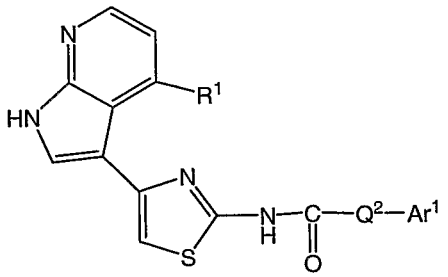
[0079] In further embodiments, x is 1 and said compound has a formula selected from formulae VII-B-i or VII-B-ii:



VII-B-i or **VII-B-ii**

In certain embodiments of **VII-B-i** or **V-B-ii**, R^1 is H, halogen, OH or CH_3. In some embodiments of **VII-B-i**, R^1 is H or F. In some embodiments of **VII-B-ii**, R^1 is Br. In some embodiments of **VII-B-i** or **V-B-ii**, Q^1 is -CO-, R^1 is H, halogen, OH or CH_3, R^2 is H, -C_{1-4} aliphatic, -cyclopropyl or  and R^4 is H or -C_{1-4} aliphatic. R^1 is H or F, R^2 is H and R^4 is H or -C_{1-4} aliphatic.

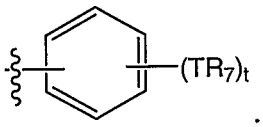
[0080] In further embodiments, R^1 is H or F, R^2 is H and R^4 is H, and the compound has a structure of formula **V-B-iii**:



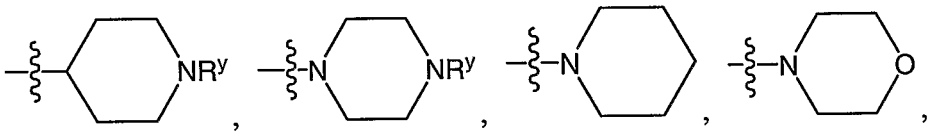
VII-B-iii.

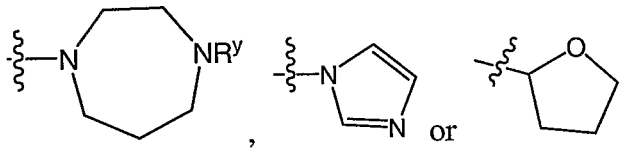
[0081] In further embodiments, for compounds having a structure of formula **V-B-iii**, Q^2 is -$(CHR^6)_q$-, -$(CHR^6)_q$O-, -$(CHR^6)_q$S-, -$(CHR^6)_q$S(O)$_2$-, -$(CHR^6)_q$S(O)- , -$(CHR^6)_q$NR-, or –$(CHR^6)_q$C(O)-, wherein q is 0, 1, 2, or 3, and each R^6 is R', -N(R)(R'), -$(CH_2)_{1-4}$N(R)(R'), -$(CH_2)_{1-4}$C$(CH_3)_2$N(R)(R'), -$(CH_2)_{1-4}$CH(CH_3)N(R)(R'), -OR', -$(CH_2)_{1-4}$OR', -NR$(CH_2)_{1-4}$N(R)(R'), -NR$(CH_2)_{1-4}SO_2$R', -NR$(CH_2)_{1-4}$COOR', or -NR$(CH_2)_{1-4}$COR', or two occurrences of R^6, taken together with the atoms to which they are bound, form an optionally substituted 3-6-membered saturated, partially unsaturated, or fully unsaturated ring. In further embodiments, Q^2 is -$(CHR^6)_q$-, q is 1 or 2, and R^6 is R', -N(R)(R'), -$(CH_2)_{1-4}$N(R)(R'), -OR', -$(CH_2)_{1-4}$

$_4$OR' or -NR$(CH_2)_{1-4}SO_2$R'. In yet further embodiments, Q^2 is -$(CHR^6)_q$-, q is 1 or 2, and each R^6 is H. In still further embodiments, Q^2 is -$(CHR^6)_q$-, q is 1, and R^6 is H. In other embodiments of **V-B-iii**, Ar^1 is selected from rings **a** - **qq** as described in paragraph [0067] above, wherein t is 0, 1, 2, 3, 4, or 5, and wherein any Ar^1 is bonded to Q^2 through any substitutable nitrogen or carbon atom, and wherein one or more hydrogen atoms on any substitutable nitrogen or carbon atom is substituted with one or more independent occurrences of TR^7. In further embodiments, Ar^1 is



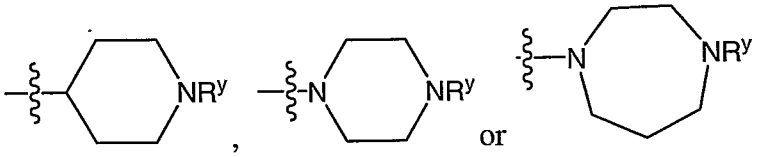
. In still further embodiments, t is 0, 1 or 2, and each TR^7 is independently selected from halogen, -CN, -R', -O$(CH_2)_{0-5}$R', -NRR', -O$SO_2(CH_2)_{0-4}$R', -NR$SO_2(CH_2)_{0-5}$R', -NRSO_2NR$(CH_2)_{0-5}$R', -SO_2NR$(CH_2)_{0-5}$R', -CONRR', -COR', -COOR', -NRCOR' or -$SO_2(CH_2)_{0-5}$R'. In yet further embodiments, TR^7 is selected from -F, -Cl, -CN, -NH_2, -CH_3, - CH_2CH_3, -$CH(CH_3)_2$, -OH, -OCH_3, -NR"SO_2R", -NR"SO_2N(R")$_2$, -$COOC(CH_3)_3$, -OSO_2CH_3, -OH, -SO_2N(R")$_2$, -SO_2NHR', -SO_2R", -pyrollidinone, tetrahydrofuran or -D-$(CH_2)_p$-Z, wherein R" is a H or a C_{1-4} alkyl, D is -SO_2-, -SO_2NH-, -NHSO_2- or -O-, p is 0-3, and Z is selected from:





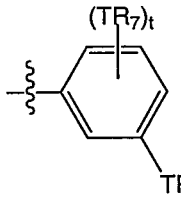
or

, wherein R^y is H or C_{1-3} alkyl, and wherein one or more carbon atoms of Z is optionally substituted with =O. In further embodiments, t is 1 or 2, one TR^7 is -D-$(CH_2)_p$-Z, D is -O-, p is 2 or 3, Z is



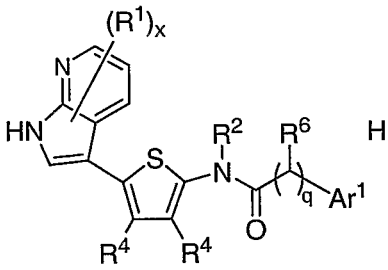
or

, and R^y is H or CH_3, and wherein one or more carbon atoms of Z is optionally substituted with =O. In yet further embodiments, t is 1 or 2, and one TR^7 is -NR"SO_2R", NHSO_2R", OR", F or Cl.

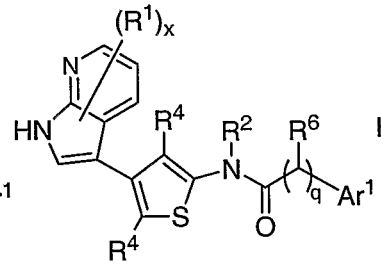


[0082] In another embodiment of Ar^1, Ar^1 is and t is 0 or 1.

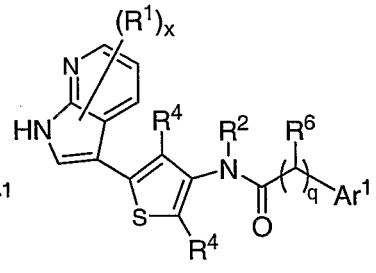
[0083] It will be appreciated that for compounds as described above, certain additional compounds are of special interest. For example, in certain exemplary embodiments, thiophene compounds are provided where G is NR^2, Q^1 is -CO-, Q^2 is CHR^6, q is 1 2, or 3, and compounds have one of formulae **XIV-A, XV-A,** or **XVI-A:**



XIV-A

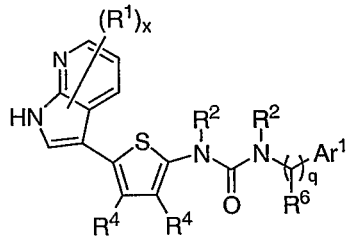


XV-A

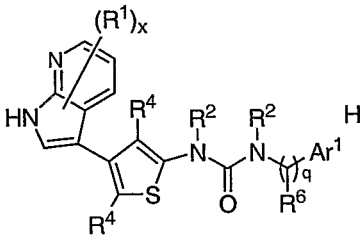


XVI-A

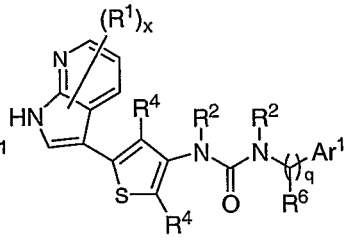
[0084] In other embodiments, thiophene compounds are provided where G is NR^2, Q^1 is $-CONR^2-$, Q^2 is CHR^6, q is 1 2, or 3, and compounds have one of formulae **XIV-B, XV-B,** or **XVI-B:**



XIV-B

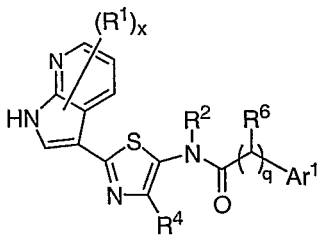


XV-B

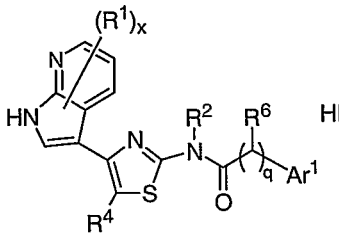


XVI-B

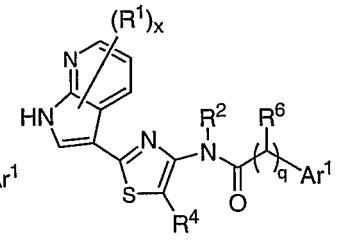
[0085] In other embodiments, thiazole compounds are provided where G is NR^2, Q^1 is –CO-, Q^2 is CHR^6, q is 1, 2 or 3, and compounds have one of formulae **XVII-A, XVIII-A,** or **XIX-A:**



XVII-A

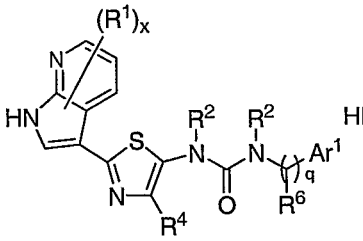


XVIII-A

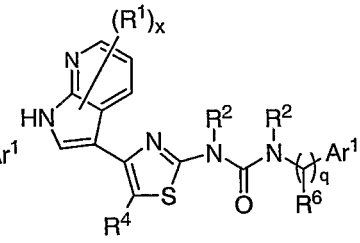


XIX-A

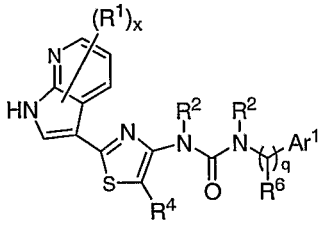
[0086] In other embodiments, thiazole compounds are provided where G is NR^2, Q^1 is $-CONR^2-$, Q^2 is CHR^6, q is 1, 2 or 3, and compounds have one of formulae **XVII-B, XVIII-B,** or **XIX-B:**



XVII-B



XVIII-B



XIX-B

[0087] In certain embodiments, for compounds of formulae **XIV-A, XIV-B, XV-A, XV-B, XVI-A, XVI-B, XVII-A, XVII-B, XVIII-A, XVIII-B, XIX-A** or **XIX-A,** compound variables are selected from one of more of the following groups:

a) each occurrence of R^1 is independently hydrogen, halogen, optionally substituted C_1-C_4aliphatic, -OR', -SR', or $-N(R')_2$;

b) each occurrence of R^1 is independently hydrogen, halogen, $-CH_3$, $-CH_2CH_3$, -OH, $-OCH_3$, $-SCH_3$, $-NH_2$, $-N(CH_3)_2$, $-N(CH_2CH_3)_2$, $-NH(CH_2)_2NHCH_3$, -NH(cyclopropyl), $-NH(CH_2)$cyclopropyl, or $-NH(CH_2)_2N(CH_3)_2$;

c) R^2 is hydrogen, or is U_nR', where n is 1, and U is $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH_2CH_2CH_2CH_2-$, $-CH_2O-$, $-CH_2S-$, $-CH_2NR-$, $-CH_2CH_2O-$, $-CH_2CH_2S-$, $-CH_2CH_2NR-$, $-CH_2CH_2CH_2O-$, $-CH_2CH_2CH_2S-$, $-CH_2CH_2CH_2NR-$, $-CH_2CH_2CH_2CH_2O-$, $-CH_2CH_2CH_2CH_2S-$, $-CH_2CH_2CH_2CH_2NR-$, $-CH_2CH_2OCH_2CH_2-$, $-(CH_2)_4NHCH_2-$, $-(CH_2)_3NHCH_2CH_2-$, or $-CH_2CH_2NHCH_2CH_2-$, wherein R' groups are hydrogen, C_1-C_4alkyl, an optionally substituted group selected from tetrahydropyranyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, pyridinyl, imidazolyl, phenyl, or cyclohexyl, or R and R', taken together with the nitrogen atom to which they are bound, form an optionally substituted 5- or 6-membered saturated, partially unsaturated, or unsaturated heterocyclyl ring;

d) each occurrence of R^4 is independently hydrogen, C_{1-6}aliphatic, CN, COR, COOR, $CON(R)_2$, or halogen;

e) q is 1, 2, or 3;

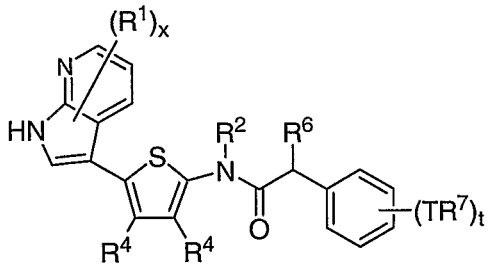
f) R^6 is R', -N(R)(R'), -$(CH_2)_{1-4}$N(R)(R'), -$(CH_2)_{1-4}C(CH_3)_2$N(R)(R'), -$(CH_2)_{1-4}$CH(CH_3) N(R)(R') -OR', -$(CH_2)_{1-4}$OR', -NR$(CH_2)_{1-4}$N(R)(R'), -NR$(CH_2)_{1-4}SO_2$R', -NR$(CH_2)_{1-4}$COOR', or -NR$(CH_2)_{1-4}$COR', or two occurrences of R^6, taken together with the atoms to which they are bound, form an optionally substituted 3-6-membered saturated, partially unsaturated, or fully unsaturated ring;

g) R^6 is -CH_2OH, -CH_2CH_2OH, -OH, -OMe, -OEt, -NH_2, -NH(Me), -NH(Et), -N(Me)(Me), -CH_2NH_2, -$CH_2CH_2NH_2$, -NHCO_2*t*-butyl, phenyl, cyclopentyl, methyl, ethyl, isopropyl, cyclopropyl, -NH$(CH_2)_3NH_2$, -NH$(CH_2)_2NH_2$, -NH$(CH_2)_2$NHEt, -NHCH_2pyridyl, -NHSO_2phenyl, -NHCOCH_2COO*t*-butyl, -NHCOCH_2NH_3, -$CH_2C(CH_3)_2NH_2$, -NHCH_2-imidazol-4-yl;

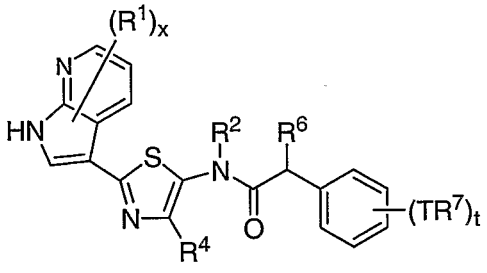
h) Ar^1 is ring **a, b, e, f, g, h, i, j, k, r, cc, dd, ff, jj, ll**, or **pp**, wherein t is 0, 1, 2, or 3, and T is a bond or is an optionally substituted C_{1-6} alkylidene chain wherein one or two methylene units are optionally and independently replaced by –O-, -NR-, -S-, -SO-, -SO_2-,–COO-, -CO-, -OSO_2-, -$NRSO_2$, -CONR-, or -SO_2NR-, and R^7 is R' or halogen; or

i) Ar^1 is ring **a, b, e, f, g, h, i, j, k, r, cc, dd, ff, jj, ll**, or **pp**, wherein t is 0, 1, 2, or 3, and each occurrence of TR^7 is independently -C_{1-3}alkyl, -OR', -SR', -CF_3, -OCF_3, -SCF_3, -F, -Cl, I, -Br, -COOR', -COR', -O$(CH_2)_4$N(R)(R'), -O$(CH_2)_3$N(R)(R'), -O$(CH_2)_2$N(R)(R'), -O(CH_2)N(R)(R'), -O$(CH_2)_4$CON(R)(R'), -O$(CH_2)_3$CON(R)(R'), -O$(CH_2)_2$CON(R)(R'), -O(CH_2)CON(R)(R'), -CON(R)(R'), -$(CH_2)_4$OR', -$(CH_2)_3$OR', -$(CH_2)_2$OR', -CH_2OR', optionally substituted phenyl or benzyl, -N(R)(R'), -$(CH_2)_4$N(R)(R'), -$(CH_2)_3$N(R)(R'), -$(CH_2)_2$N(R)(R'), -(CH_2)N(R)(R'), -SO_2N(R)(R'), -$NRSO_2$R', -CON(R)(R'), -$NRSO_2(CH_2)_{1-4}$N(R)(R'), -CONR$(CH_2)_{1-4}$N(R)(R'), -COO$(CH_2)_{1-4}$N(R)(R'),or –OSO_2R'.

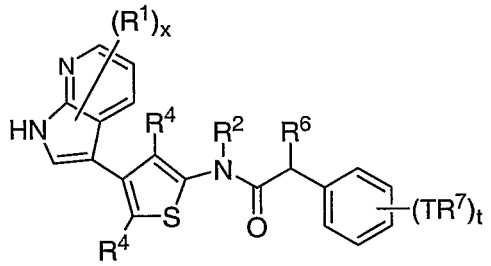
[0088] In other embodiments, for certain of the thiophene and thiazole compounds of formulae **XIV-A** through **XIX-A**, q is 1, and Ar^1 is optionally substituted phenyl and compounds of formulae **XIV-C** through **XIX-C** are provided:



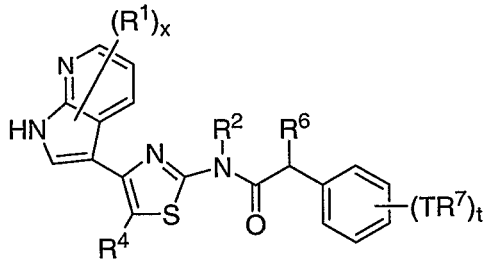
XIV-C



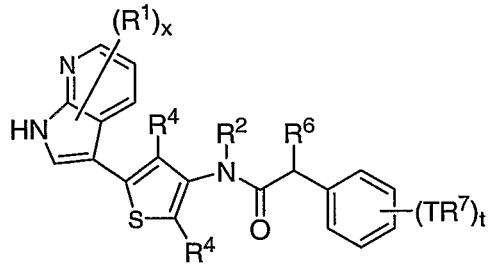
XV-C



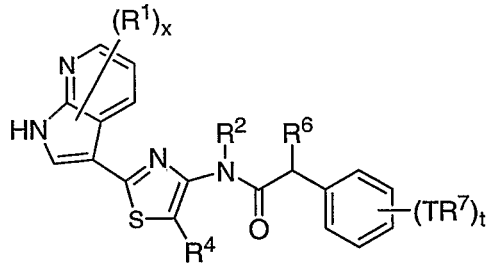
XVI-C



XVII-C



XVIII-C



XIX-C

wherein R^1, R^Z, R^2, R^4, R^6, T, R^7 and t are as defined generally and in classes and subclasses above and herein.

[0089] In preferred embodiments, for compounds of formulae **XIV-C** through **XIX-C**:

each occurrence of R^1 is hydrogen;

R^2 is hydrogen, or is U_nR', where n is 1, and U is $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH_2CH_2CH_2CH_2-$, $-CH_2O-$, $-CH_2S-$, $-CH_2NR-$, $-CH_2CH_2O-$, $-CH_2CH_2S-$, $-CH_2CH_2NR-$, $-CH_2CH_2CH_2O-$, $-CH_2CH_2CH_2S-$, $-CH_2CH_2CH_2NR-$, $-CH_2CH_2CH_2CH_2O-$, $-CH_2CH_2CH_2CH_2S-$, $-CH_2CH_2CH_2CH_2NR-$, $-CH_2CH_2OCH_2CH_2-$, $-(CH_2)_4NHCH_2-$, $-(CH_2)_3NHCH_2CH_2-$, or $-CH_2CH_2NHCH_2CH_2-$, wherein R' groups are hydrogen, C_1-C_4alkyl, an optionally substituted group selected

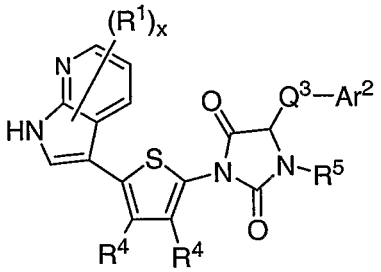
from tetrahydropyranyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, pyridinyl, imidazolyl, phenyl, or cyclohexyl, or R and R', taken together with the nitrogen atom to which they are bound, form an optionally substituted 5- or 6-membered saturated, partially unsaturated, or unsaturated heterocyclyl ring;

each occurrence of R^4 is independently hydrogen, C_{1-6}aliphatic, CN, COR, COOR, $CON(R)_2$, or halogen;

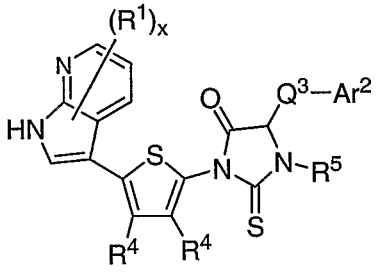
R^6 is -R', -N(R)(R'), $-(CH_2)_{1-4}N(R)(R')$, $-(CH_2)_{1-4}C(CH_3)_2N(R)(R')$, $-(CH_2)_{1-4}CH(CH_3)$ N(R)(R'), -OR', $-(CH_2)_{1-4}OR'$, $-NR(CH_2)_{1-4}N(R)(R')$, $-NR(CH_2)_{1-4}SO_2R'$, $-NR(CH_2)_{1-4}COOR'$, or $-NR(CH_2)_{1-4}COR'$; and

t is 0, 1, 2, or 3, and each occurrence of TR^7 is independently $-C_{1-3}$alkyl, -OR', -SR', $-CF_3$, $-OCF_3$, $-SCF_3$, -F, -Cl, -I, -Br, -COOR', -COR', $-O(CH_2)_4N(R)(R')$, $-O(CH_2)_3N(R)(R')$, $-O(CH_2)_2N(R)(R')$, $-O(CH_2)N(R)(R')$, $-O(CH_2)_4CON(R)(R')$, $-O(CH_2)_3CON(R)(R')$, $-O(CH_2)_2CON(R)(R')$, $-O(CH_2)CON(R)(R')$, -CON(R)(R'), $-(CH_2)_4OR'$, $-(CH_2)_3OR'$, $-(CH_2)_2OR'$, $-CH_2OR'$, optionally substituted phenyl or benzyl, -N(R)(R'), $-(CH_2)_4N(R)(R')$, $-(CH_2)_3N(R)(R')$, $-(CH_2)_2N(R)(R')$, $-(CH_2)N(R)(R')$, $-SO_2N(R)(R')$, $-NRSO_2R'$, -CON(R)(R'), $-NRSO_2(CH_2)_{1-4}N(R)(R')$, $-CONR(CH_2)_{1-4}N(R)(R')$, $-COO(CH_2)_{1-4}N(R)(R')$,or $-OSO_2R'$.

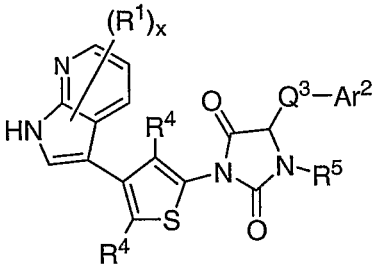
[0090] Other subsets include those compounds where G is NR^2, and R^2 and Q^1-R^3, taken together with the atoms to which they are bound form a 5-membered cyclic group, and compounds have one of formulae **XX** through **XXVIII:**



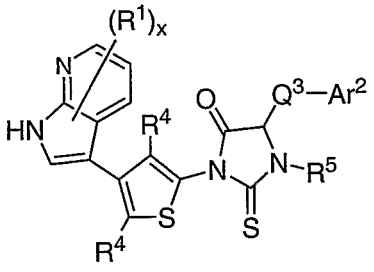
XX



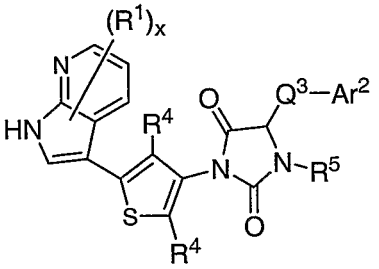
XXI



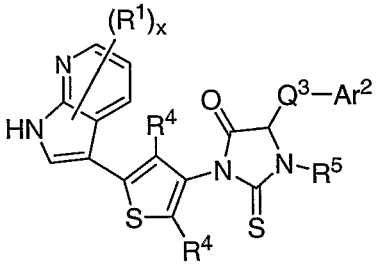
XXII



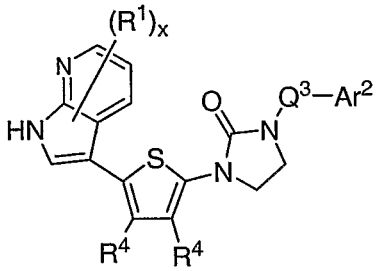
XXIII



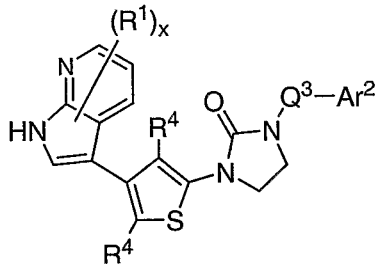
XXIV



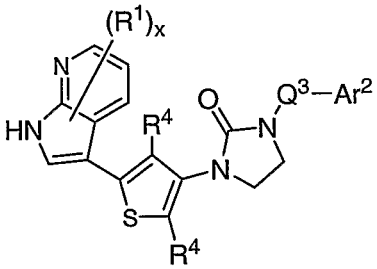
XXV



XXVI

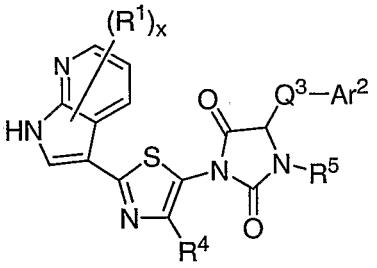


XXVII

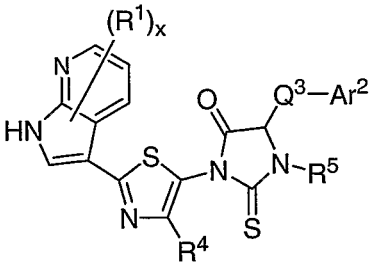


XXVIII

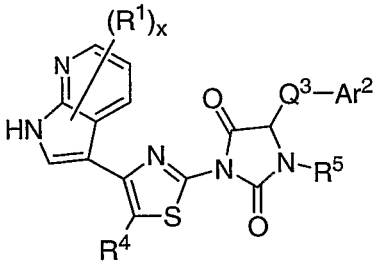
[0091] In other embodiments, thiazole compounds are provided where G is NR^2, and R^2 and Q^1-R^3, taken together with the atoms to which they are bound form a 5-membered cyclic group, and compounds have one of formulae **XXIX** through **XXXVII:**



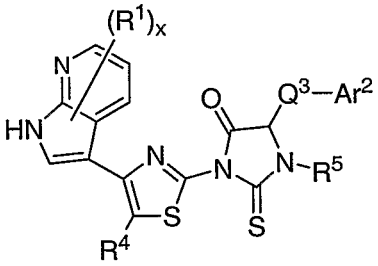
XXIX



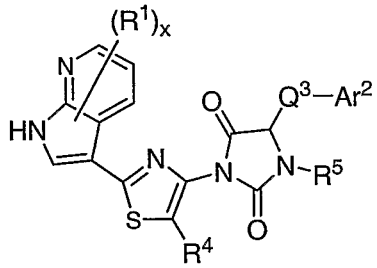
XXX



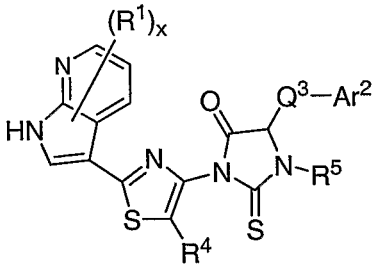
XXXI



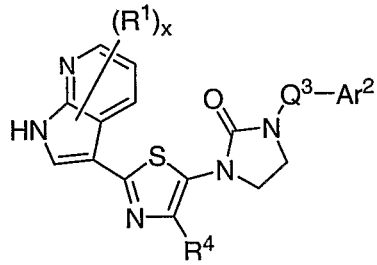
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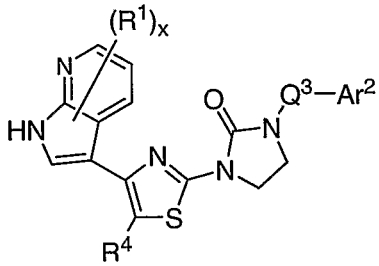
XXXIII



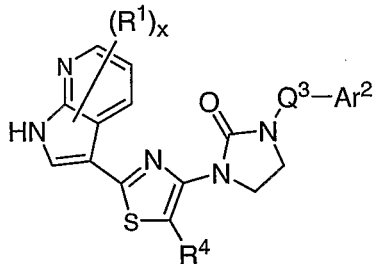
XXXIV



XXXV

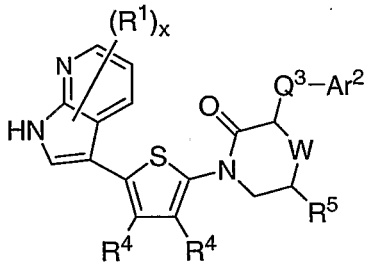


XXXVI

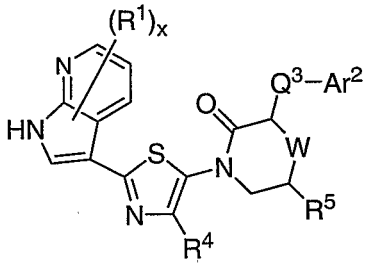


XXXVII

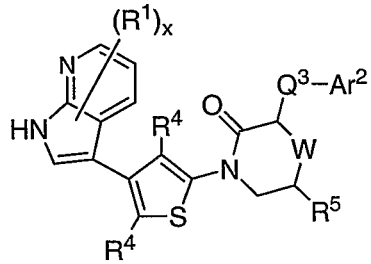
[0092] In still other embodiments, thiophene and thiazole compounds are provided where G is NR^2, and R^2 and Q^1-R^3, taken together with the atoms to which they are bound form a 6-membered cyclic group, and compounds have one of formulae **XXXVIII** through **XLIII:**



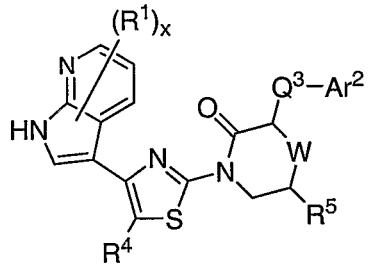
XXXVIII



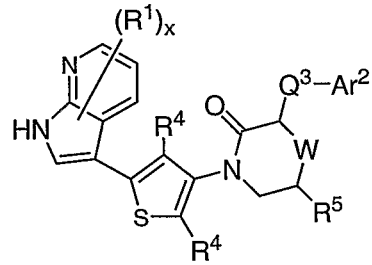
XXXIX



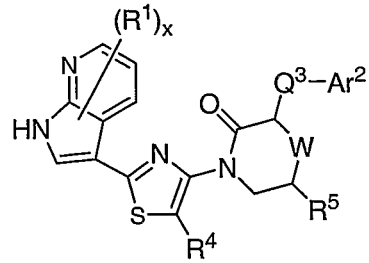
XL



XLI



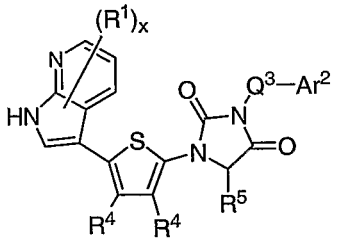
XLII



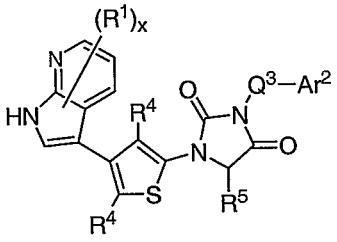
XLIII

wherein W is O, NR^5, or CHR^5.

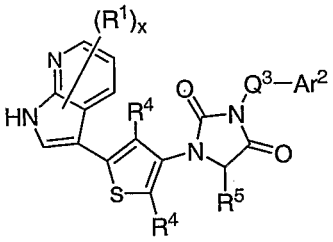
[0093] In yet other embodiments, thiophene and thiazole compounds are provided where G is NR^2, and R^2 and Q^1-R^3, taken together with the atoms to which they are bound form a 5- or 6-membered cyclic group, and compounds have one of formulae **XLIV** through **LXI:**



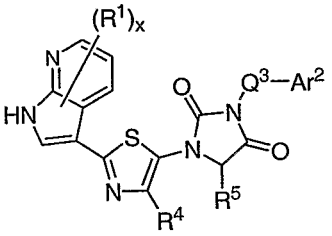
XLIV



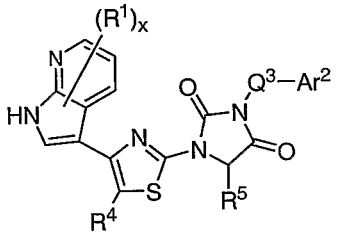
XLV



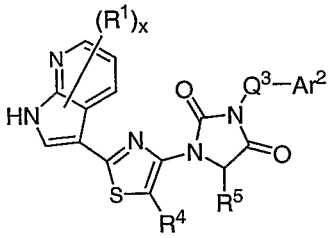
XLVI



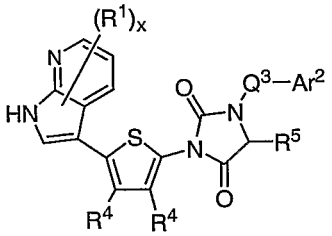
XLVII



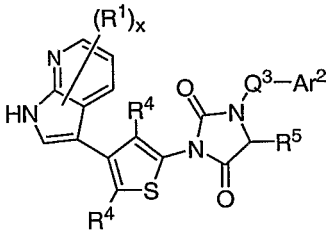
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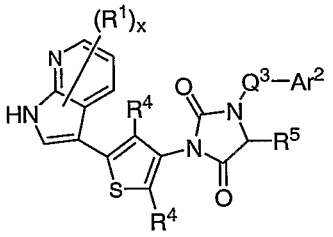
XLIX



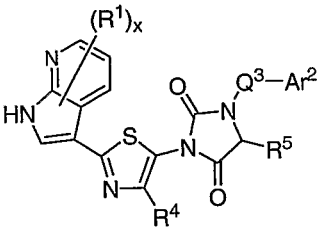
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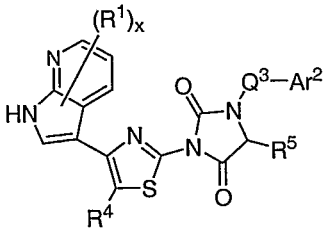
LI



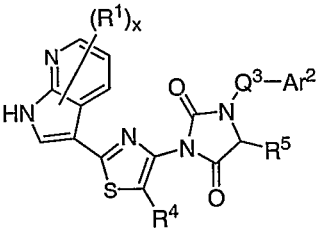
LII



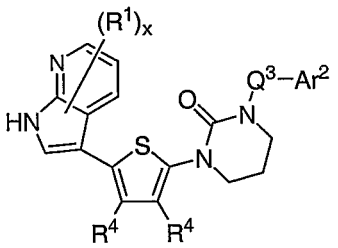
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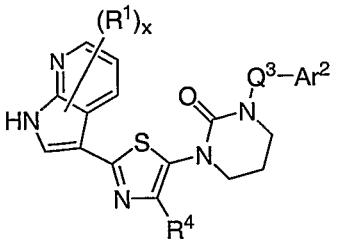
LIV



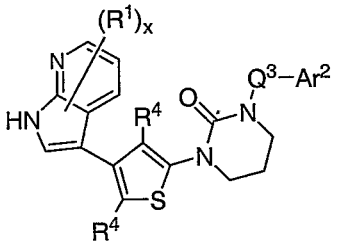
LV



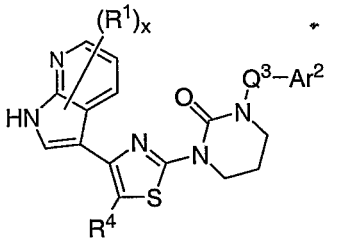
LVI



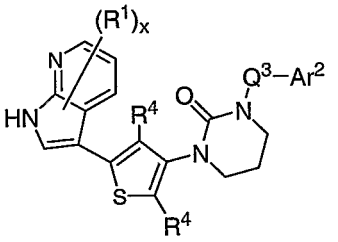
LVII



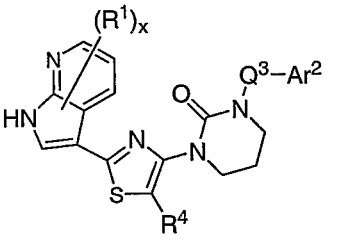
LVIII



LIX



LX



LXI

[0094] In certain embodiments, for compounds of formulae **XX** through **LXI** compound variables are selected from one of more of the following groups:

a) each occurrence of R^1 is hydrogen, halogen, optionally substituted -C_1-C_4aliphatic, -OR', -SR', or -N(R')$_2$;

b) each occurrence of -R^4 is independently hydrogen, C_{1-6}aliphatic, -CN, -COR, -COOR, -CON(R)$_2$, or halogen;

c) R^5 is hydrogen, -$(CH_2)_3$OR', -$(CH_2)_2$OR', -(CH_2)OR', -$(CH_2)_3$N(R')$_2$, -$(CH_2)_2$N(R')$_2$, -(CH_2)N(R')$_2$, or C_{1-4}aliphatic;

d) Q^3 is a direct bond, or is -$(CHR^6)_q$-, -$(CHR^6)_q$O-, -$(CHR^6)_q$S-, -$(CHR^6)_q$S(O)$_2$-, -$(CHR^6)_q$S(O)- , -$(CHR^6)_q$NR-, or –$(CHR^6)_q$C(O)-, wherein q is 0, 1, 2, or 3; and

e) Ar^2 is ring **a, b, e, f, g, h, i, j, k, n, r, cc, dd, ff, jj, ll**, or **pp**, wherein t is 0, 1, 2, or 3, and T is a bond or is an optionally substituted C_1-C_6 alkylidene chain wherein one or two methylene units are optionally and independently replaced by –O-, -NR-, -S-, -SO_2-,–COO-, -CO-, -OSO_2-, -$NRSO_2$, -CONR-, or -SO_2NR-, and R^7 is R' or halogen.

[0095] In certain other embodiments, for compounds of formulae **XX** through **LXI** compound variables are selected from one of more of the following groups:

a) each occurrence of R^1 is independently hydrogen, halogen, $-CH_3$, $-CH_2CH_3$, -OH, $-OCH_3$, $-SCH_3$, $-NH_2$, $-N(CH_3)_2$, $-N(CH_2CH_3)_2$, $NH(CH_2)_2NHCH_3$, NH(cyclopropyl), $NH(CH_2)$cyclopropyl, or $NH(CH_2)_2N(CH_3)_2$;

b) each occurrence of R^4 is independently hydrogen, C_{1-6}aliphatic, -CN, -COR, -COOR, $-CON(R)_2$, or halogen;

c) R^5 is hydrogen, $-(CH_2)_3OR'$, $-(CH_2)_2OR'$, $-(CH_2)OR'$, $-(CH_2)_3N(R')_2$, $-(CH_2)_2N(R')_2$, $-(CH_2)N(R')_2$, or C_{1-4}aliphatic;

d) Q^3 is a direct bond, or is $-(CHR^6)_q-$, $-(CHR^6)_qO-$, $-(CHR^6)_qS-$, $-(CHR^6)_qS(O)_2-$, $-(CHR^6)_qS(O)-$, $-(CHR^6)_qNR-$, or $-(CHR^6)_qC(O)-$, wherein q is 0, 1, 2, or 3; and

e) Ar^2 is ring **a, b, e, f, g, h, i, j, k, n, r, cc, dd, ff, jj, ll**, or **pp**, wherein t is 0, 1, 2, or 3, and each occurrence of $-TR^7$ is independently $-C_{1-3}$alkyl, -OR', -SR', $-CF_3$, $-OCF_3$, $-SCF_3$, -F, -Cl, -I, -Br, -COOR', -COR', $-O(CH_2)_4N(R)(R')$, $-O(CH_2)_3N(R)(R')$, $-O(CH_2)_2N(R)(R')$, $-O(CH_2)N(R)(R')$, $-O(CH_2)_4CON(R)(R')$, $-O(CH_2)_3CON(R)(R')$, $-O(CH_2)_2CON(R)(R')$, $-O(CH_2)CON(R)(R')$, $-CON(R)(R')$, $-(CH_2)_4OR'$, $-(CH_2)_3OR'$, $-(CH_2)_2OR'$, $-CH_2OR'$, optionally substituted phenyl or benzyl, $-N(R)(R')$, $-(CH_2)_4N(R)(R')$, $-(CH_2)_3N(R)(R')$, $-(CH_2)_2N(R)(R')$, $-(CH_2)N(R)(R')$, $-SO_2N(R)(R')$, $-NRSO_2R'$, $-CON(R)(R')$, $-NRSO_2(CH_2)_{1-4}N(R)(R')$, $-CONR(CH_2)_{1-4}N(R)(R')$, $-COO(CH_2)_{1-4}N(R)(R')$,or $-OSO_2R'$.

[0096] In other embodiments, for the thiophene and thiazole compounds of formulae **XX-LIX** as described above, Ar^2 is optionally substituted phenyl.

[0097] In still other embodiments, for the thiophene and thiazole compounds of formulae **XX-LIX**:

Ar^2 is optionally substituted phenyl;

each occurrence of R^1 is hydrogen;

each occurrence of R^4 is independently hydrogen, C_{1-6}aliphatic, -CN, -COR, -COOR, $-CON(R)_2$, or halogen.

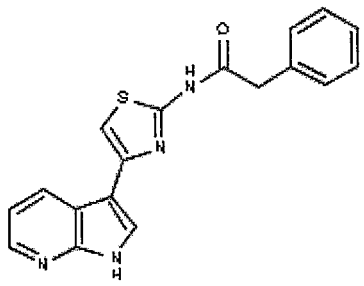
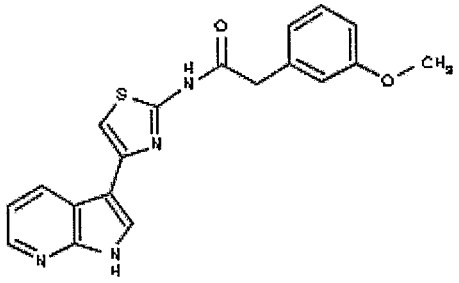
[0098] In another embodiment of the invention, Ar^1 is a C_{1-6} optionally substituted aliphatic. In further embodiments, Ar^1 is a C_{1-3} optionally substituted alkyl and Q^2 is $-(CHR^6)_q-$, $-(CHR^6)_qO-$, $-(CHR^6)_qS-$, $-(CHR^6)_qS(O)_2-$, $-(CHR^6)_qS(O)-$, $-(CHR^6)_qNR-$, or $-(CHR^6)_qC(O)-$, wherein q is 0, 1, 2, or 3, and each R^6 is R', $-N(R)(R')$, $-(CH_2)_{1-4}N(R)(R')$, $-(CH_2)_{1-4}C(CH_3)_2N(R)(R')$, $-(CH_2)_{1-4}CH(CH_3)N(R)(R')$, -OR', $-(CH_2)_{1-}$

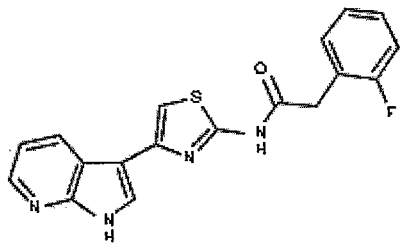
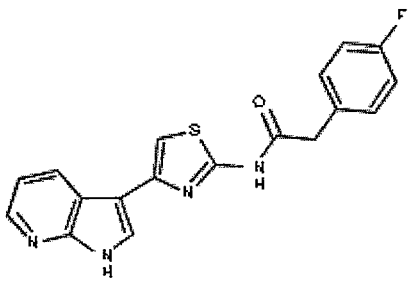
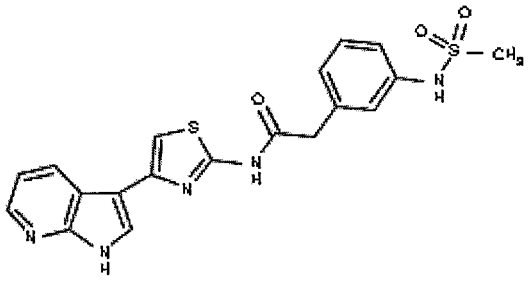
$_4$OR', -NR(CH_2)$_{1-4}$N(R)(R'), -NR(CH_2)$_{1-4}$$SO_2$R', -NR($CH_2$)$_{1-4}$COOR', or -NR($CH_2$)$_{1-4}$COR'. In further embodiments, Q^2-Ar^1 is -CH_2CN.

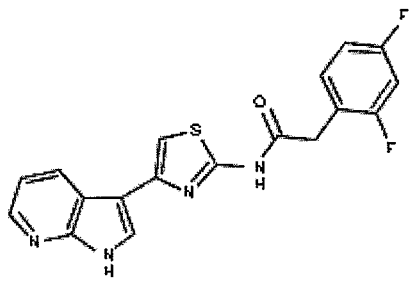
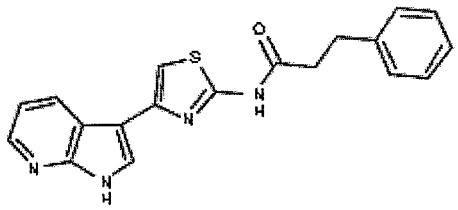
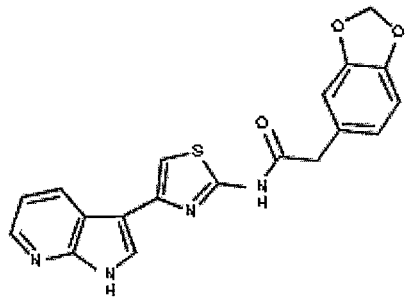
[0099] In still other embodiments, X_1 is CR^4, X_2 is CR^4 or N, G is -NR^2- or -CO- and Q^1 is a bond for compounds of formula **I-B**. In further embodiments, Q^2 is a bond.

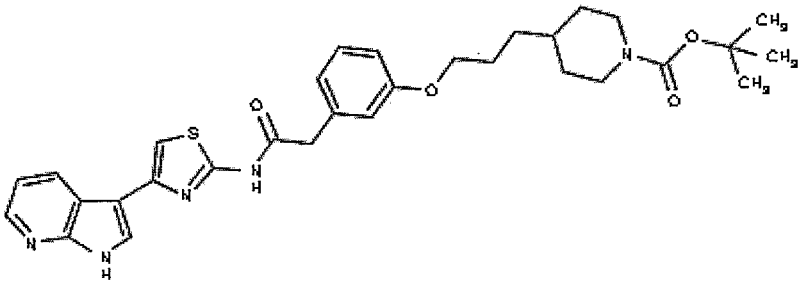
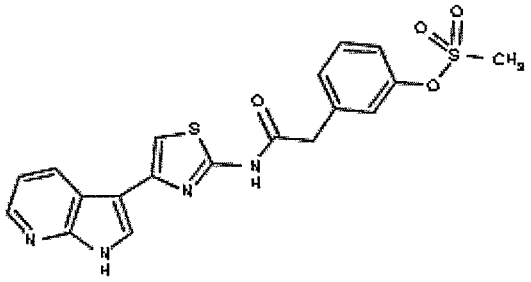
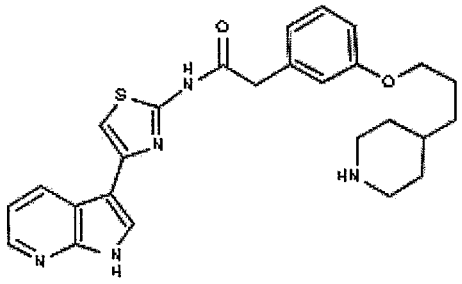
[00100] Representative examples of compounds of formula **I** are set forth below in Tables 1 and 2 below.

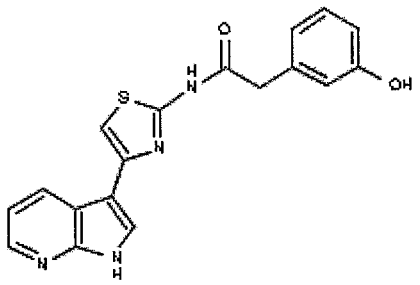
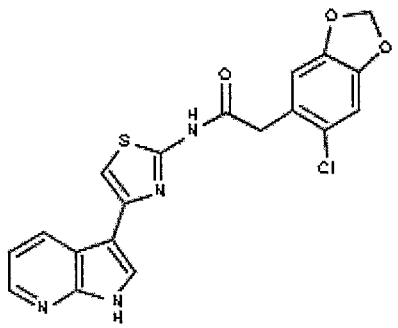
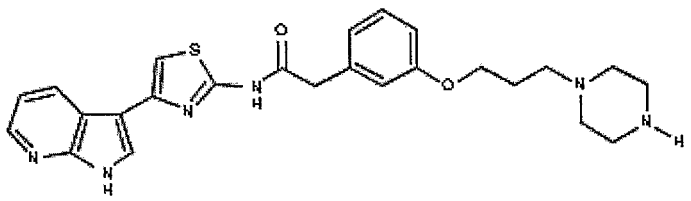
[00101] Table 1. Examples of Compounds of Formula **I**:

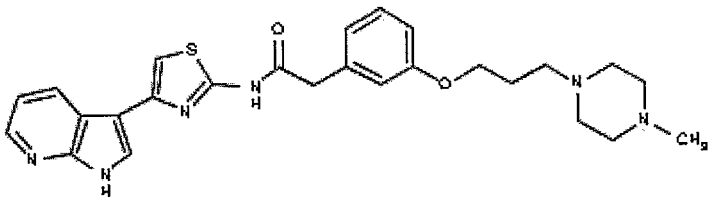
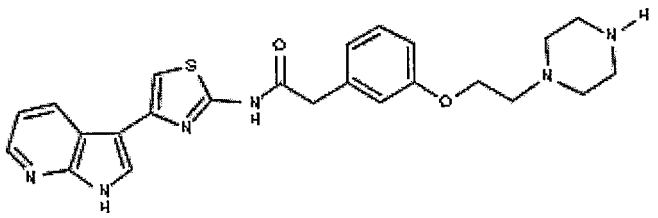
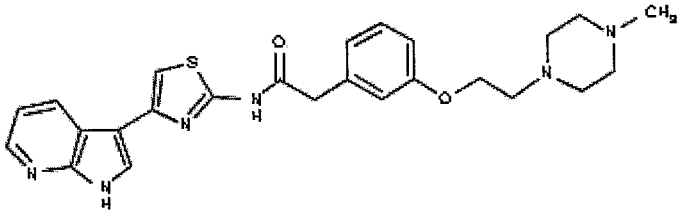
Compound	Cmpd #
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	I-2

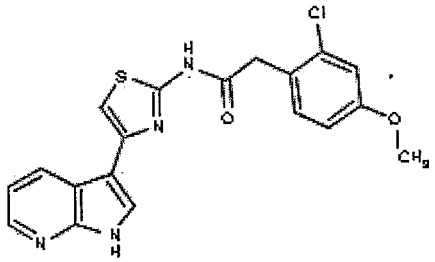
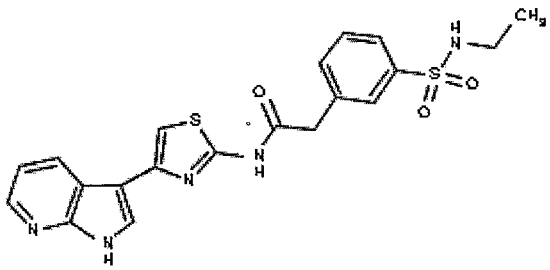
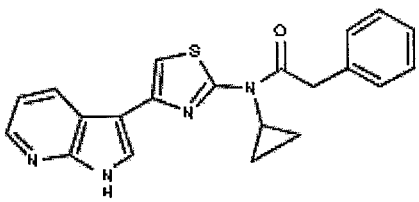
Compound	Cmpd #
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	I-4
	I-5

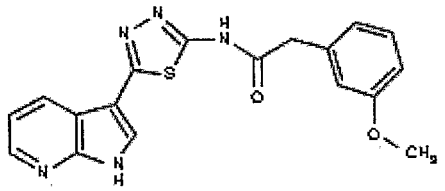
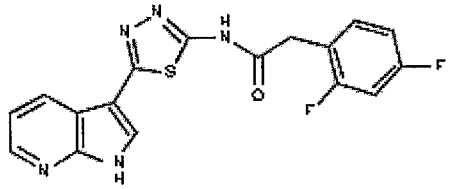
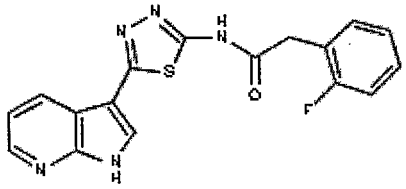
Compound	Cmpd #
	I-6
	I-7
	I-8

Compound	Cmpd #
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	I-10
	I-11

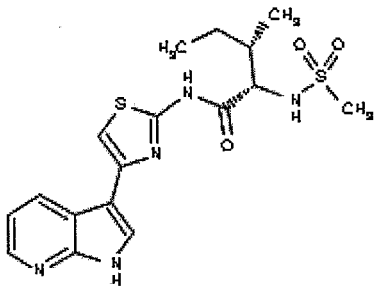
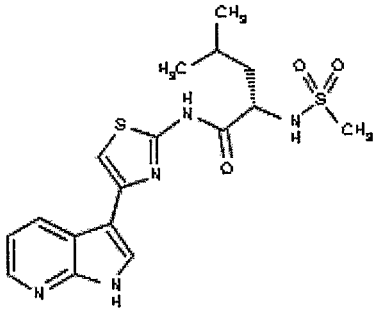
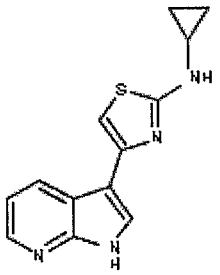
Compound	Cmpd #
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	I-13
	I-14

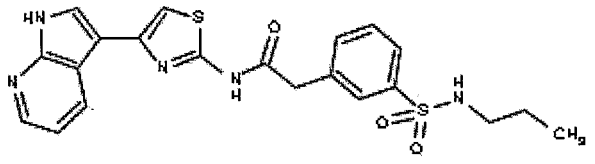
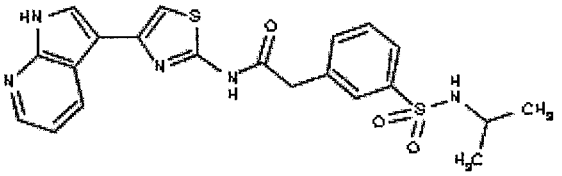
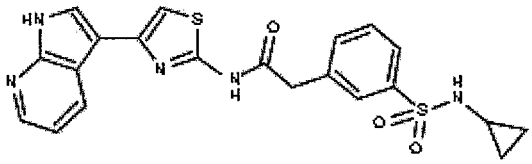
Compound	Cmpd #
	I-15
	I-16
	I-17

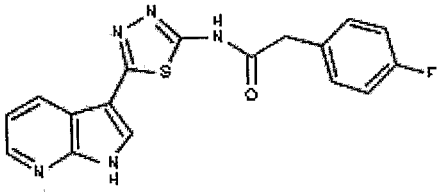
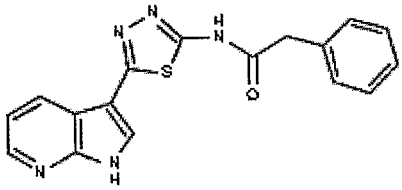
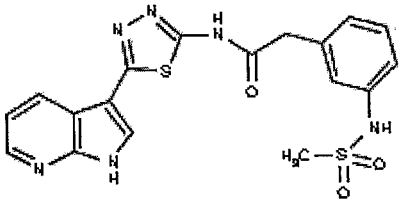
Compound	Cmpd #
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	I-19
	I-20

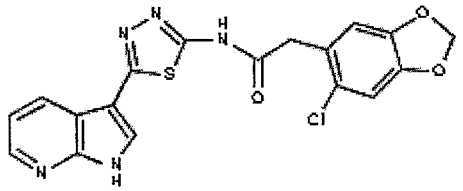
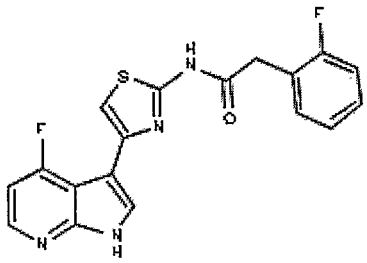
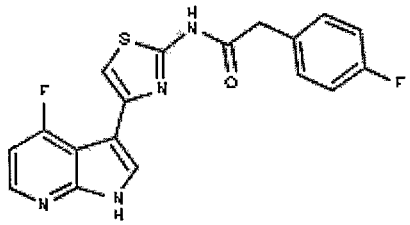
Compound	Cmpd #
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	I-22
	I-23

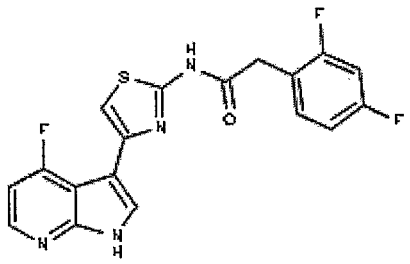
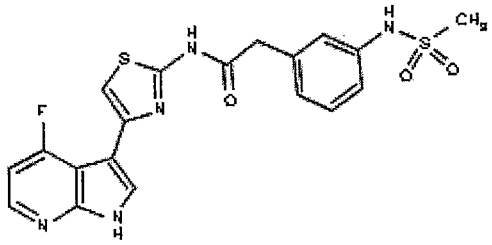
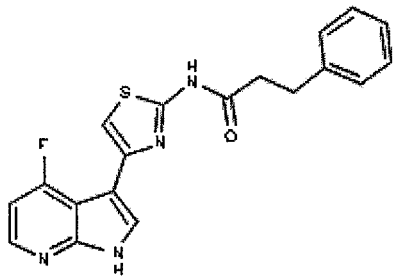
[00102] Table 2. Examples of Compounds of Formula **I**:

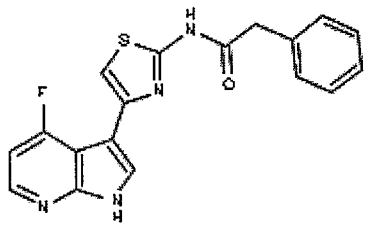
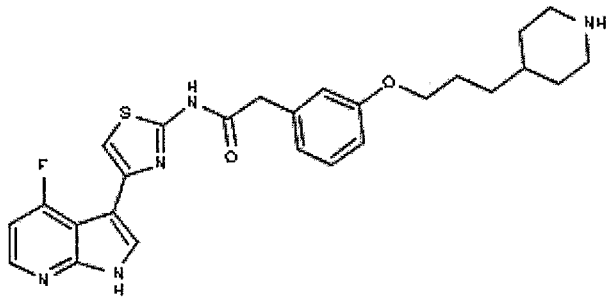
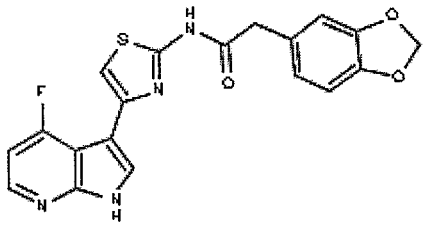
Compound	Cmpd #
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	II-2
	II-3

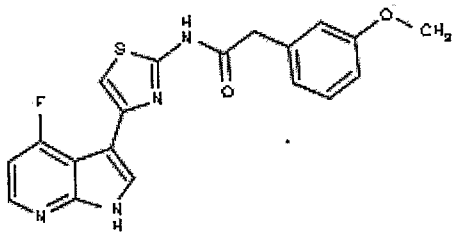
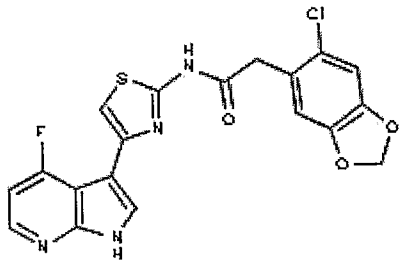
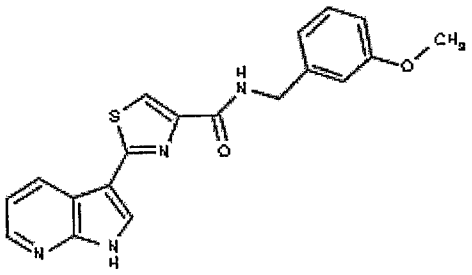
Compound	Cmpd #
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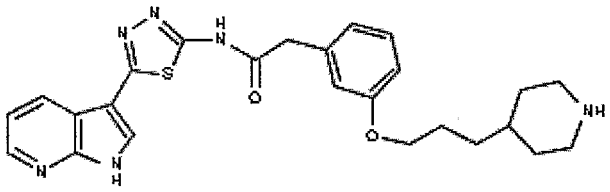
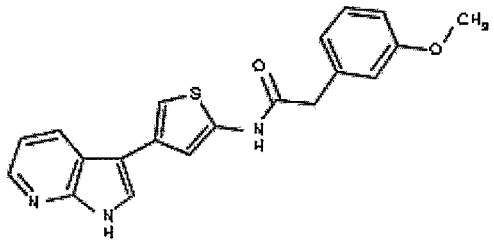
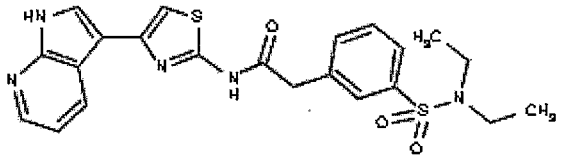
Compound	Cmpd #
	II-7
	II-8
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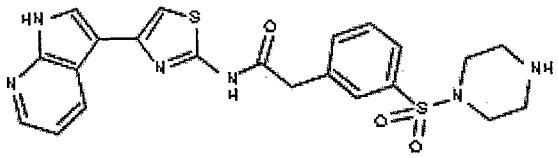
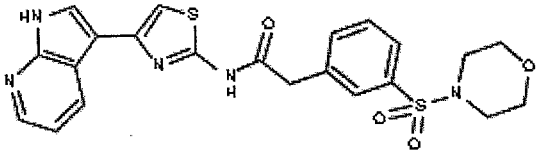
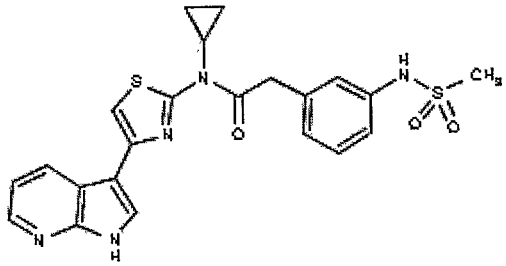
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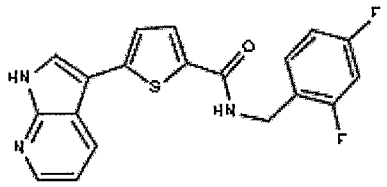
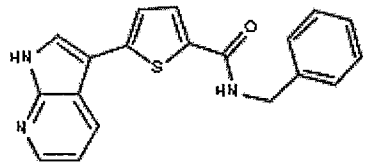
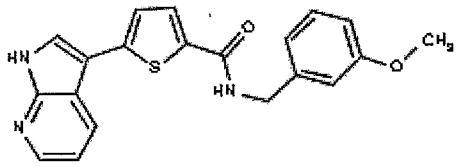
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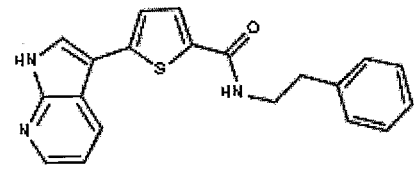
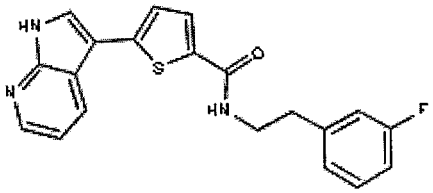
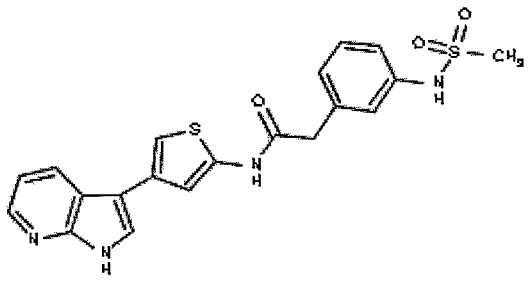
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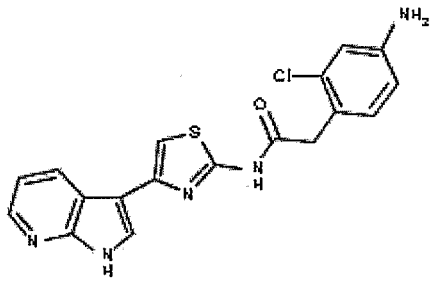
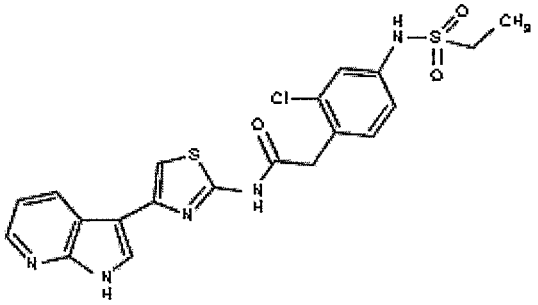
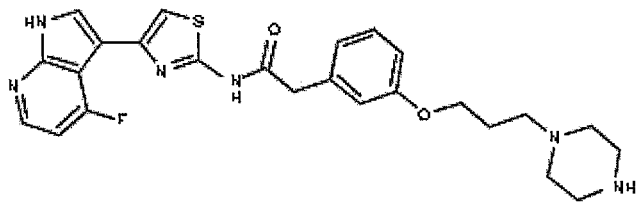
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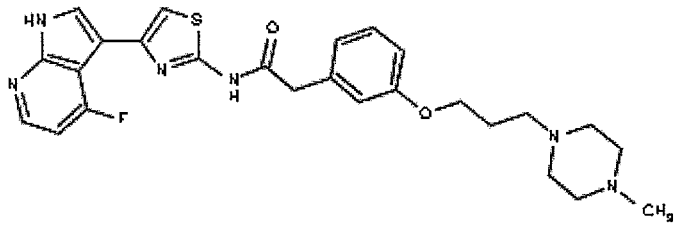
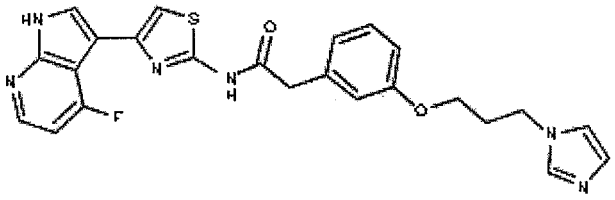
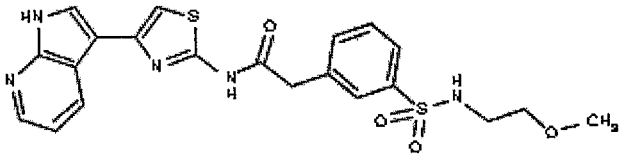
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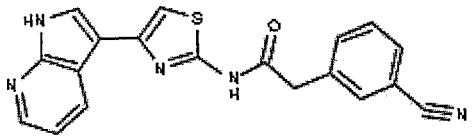
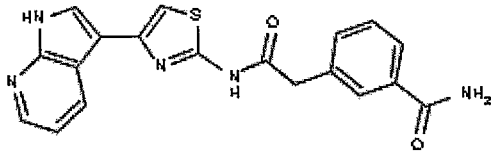
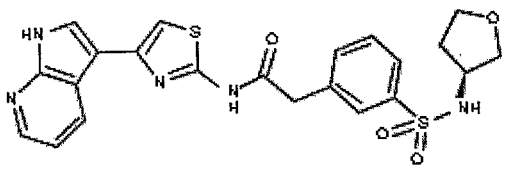
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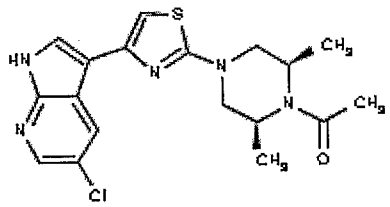
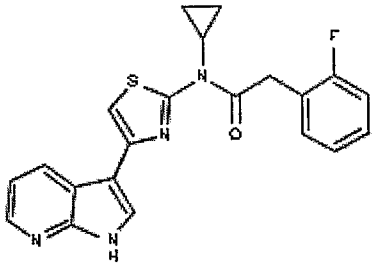
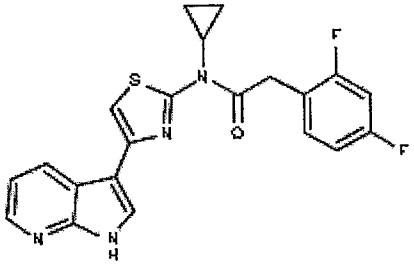
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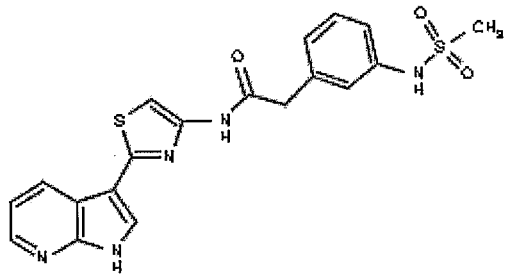
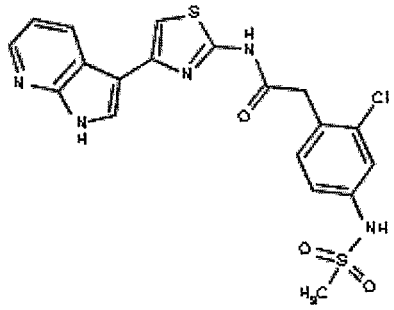
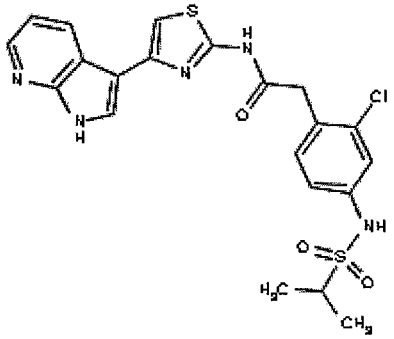
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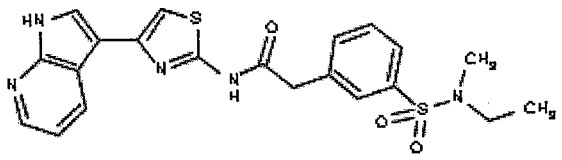
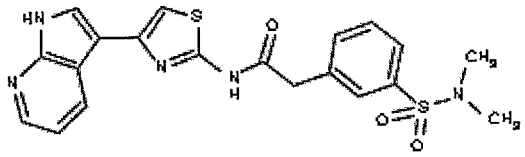
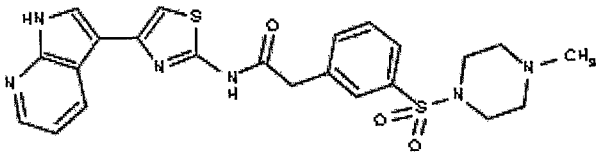
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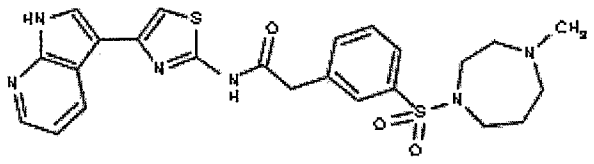
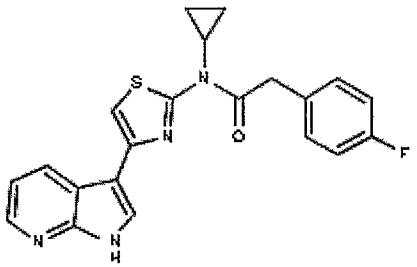
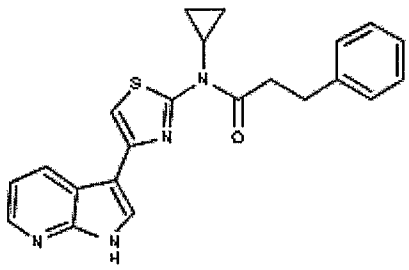
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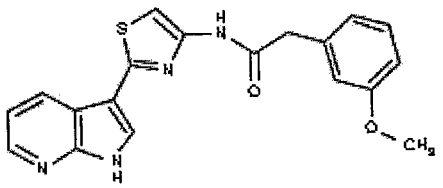
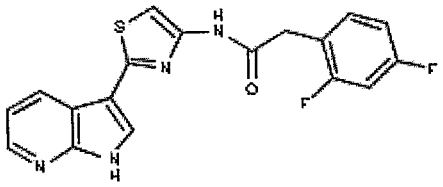
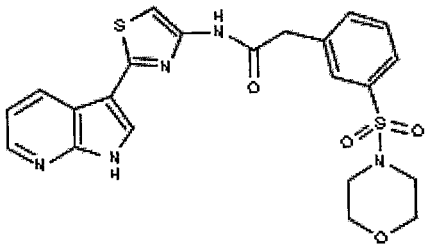
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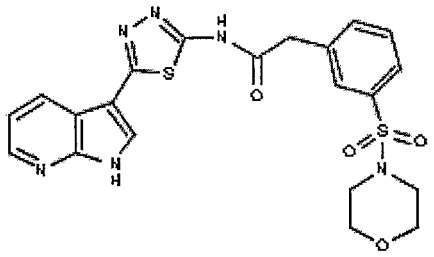
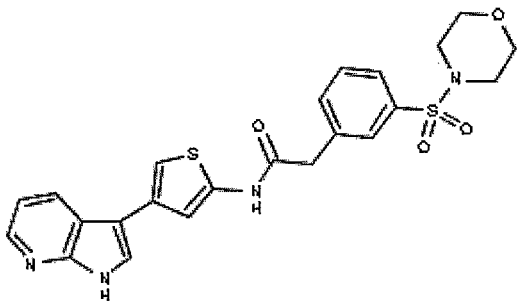
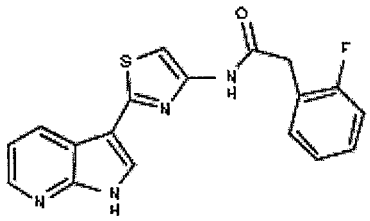
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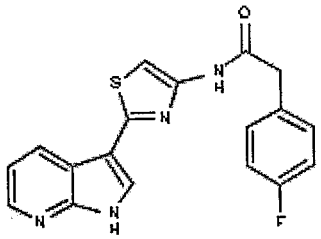
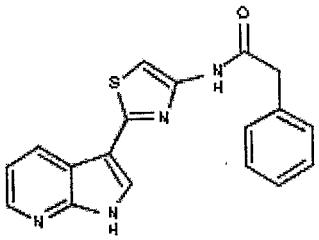
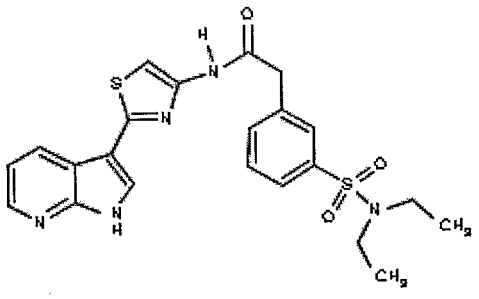
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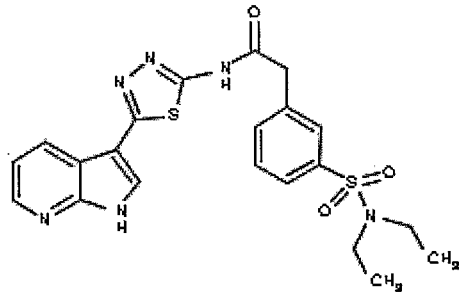
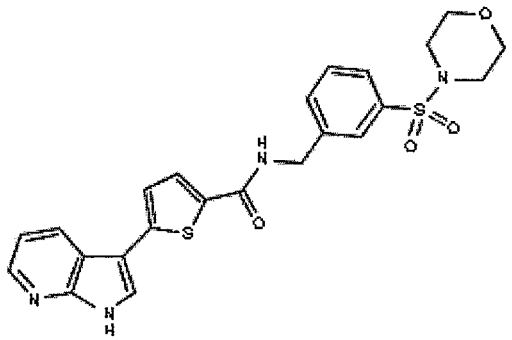
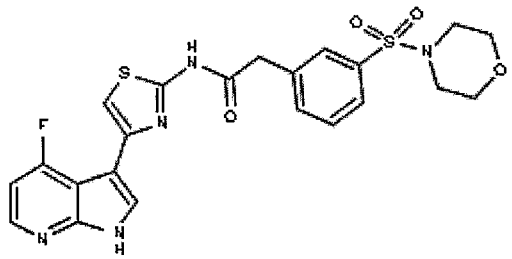
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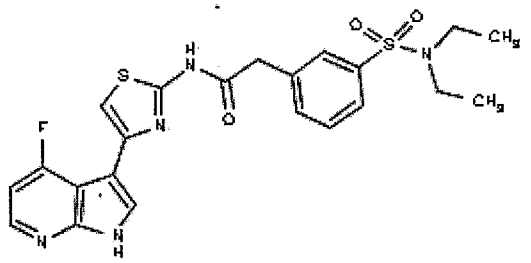
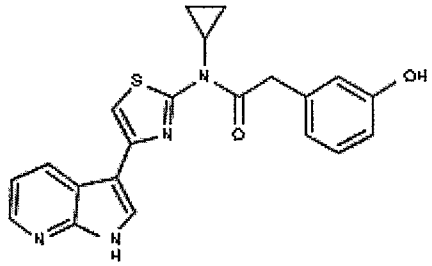
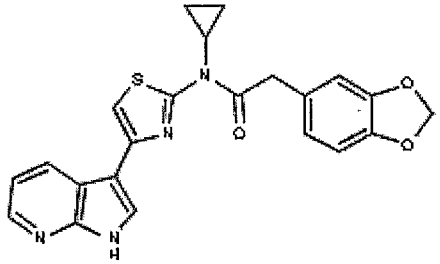
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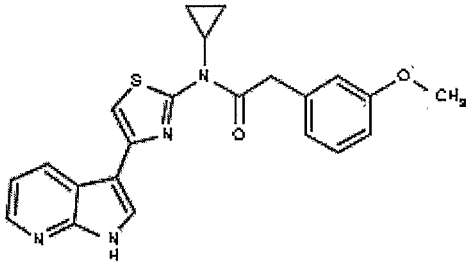
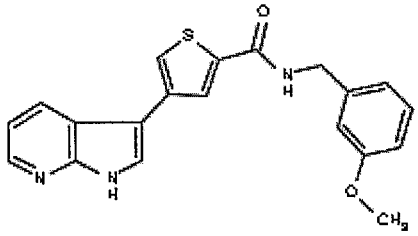
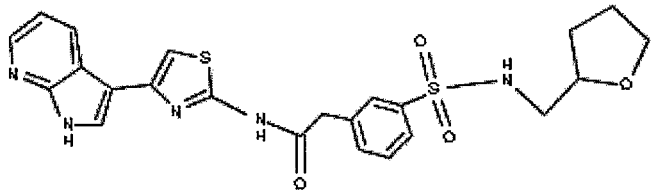
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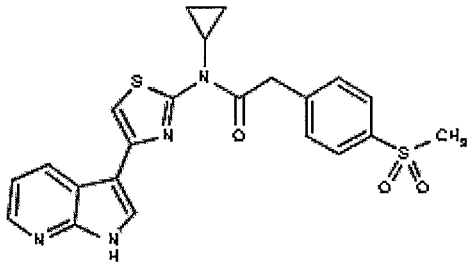
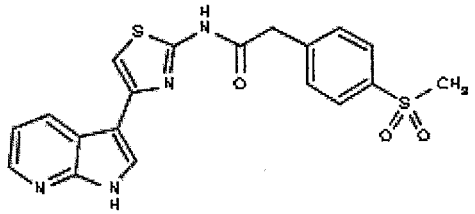
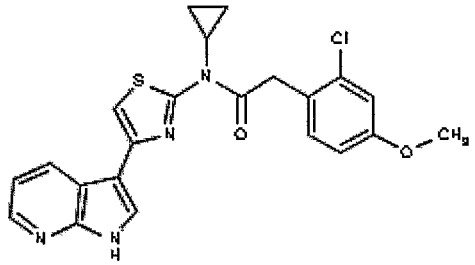
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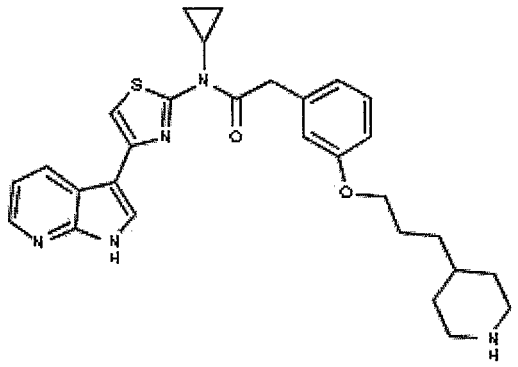
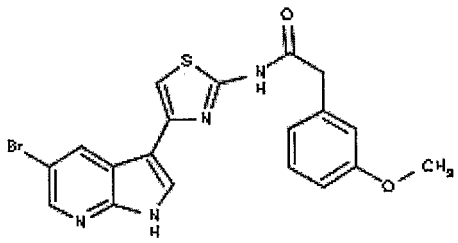
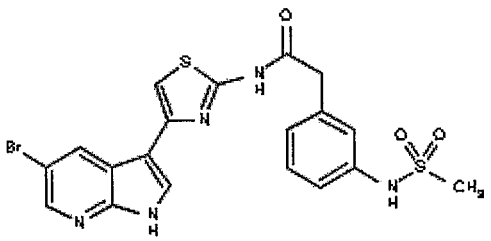
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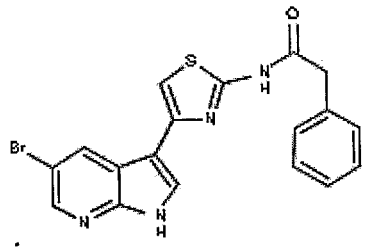
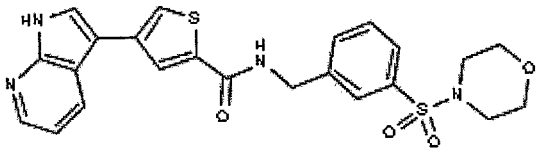
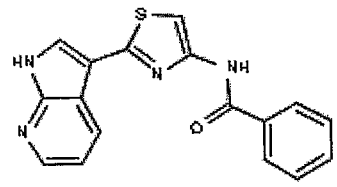
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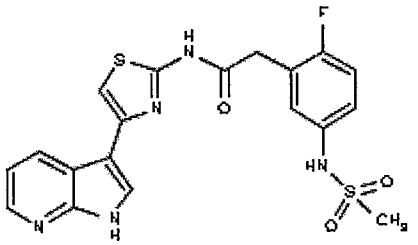
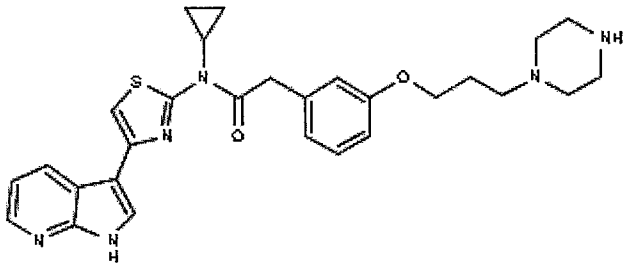
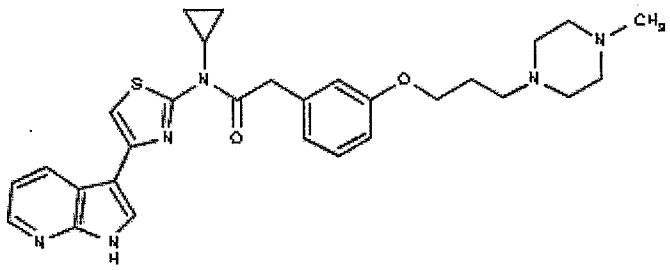
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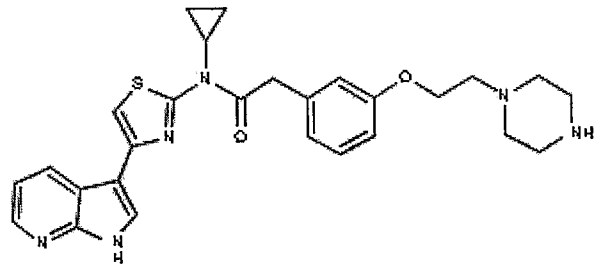
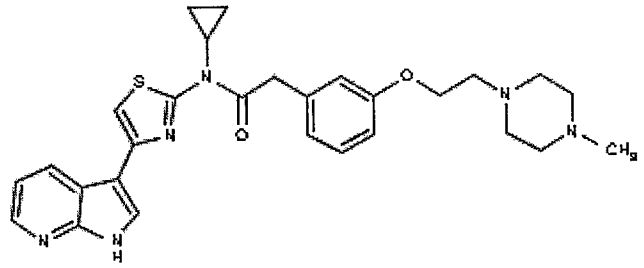
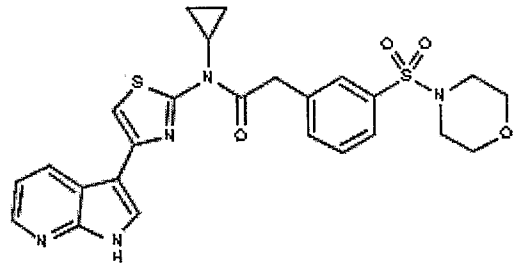
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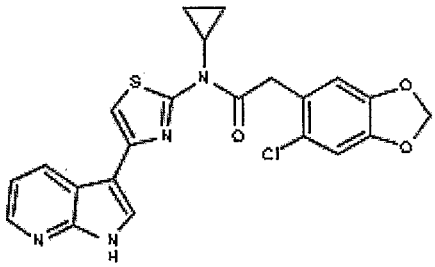
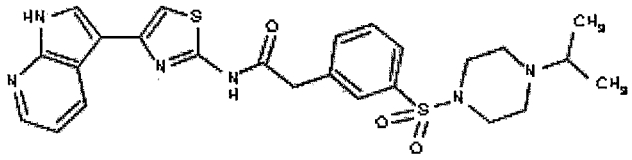
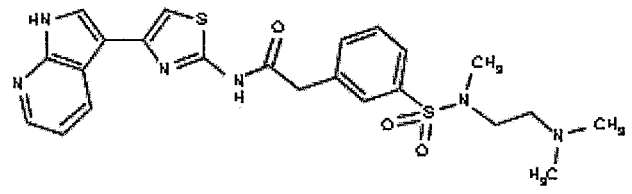
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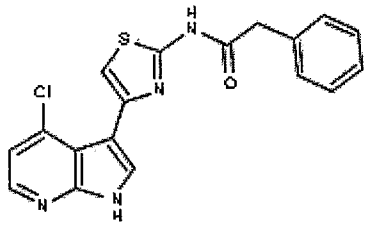
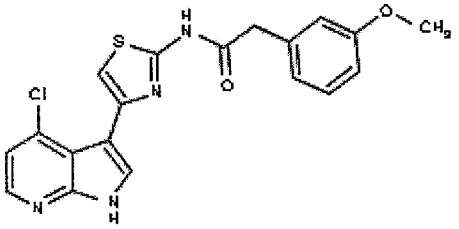
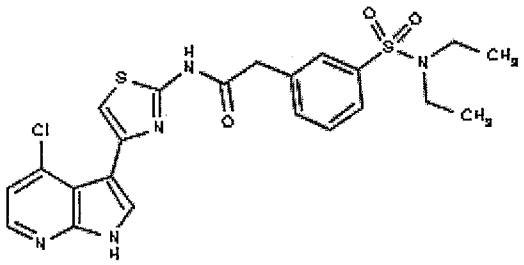
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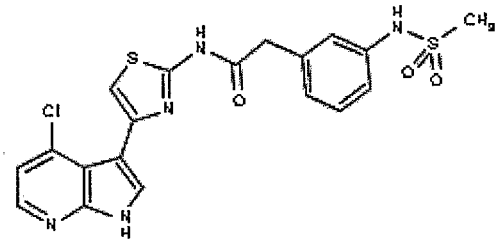
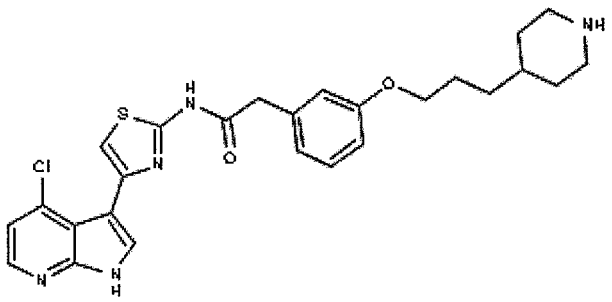
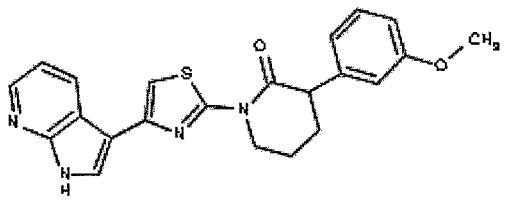
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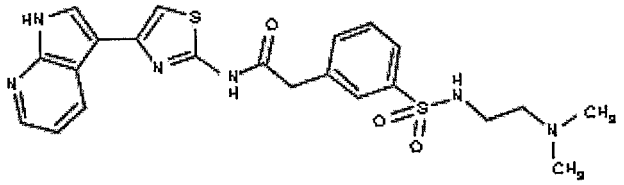
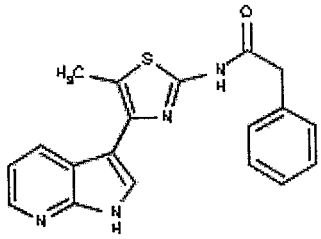
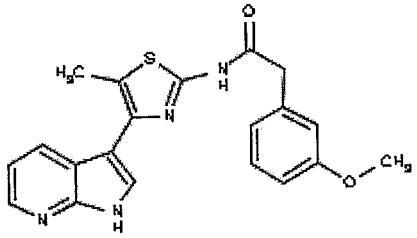
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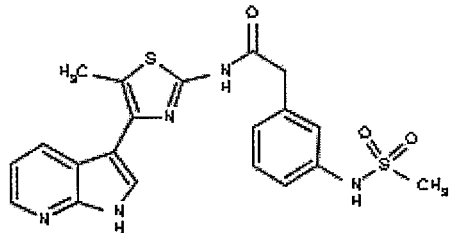
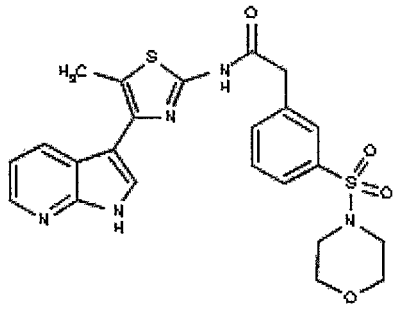
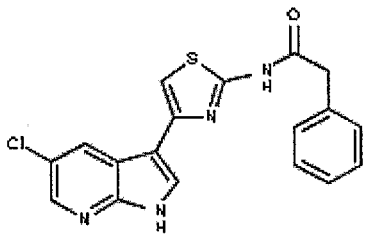
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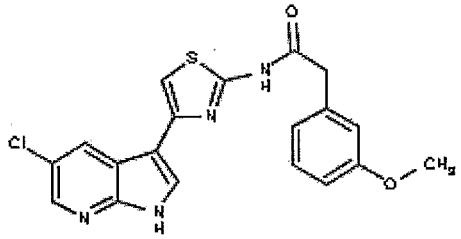
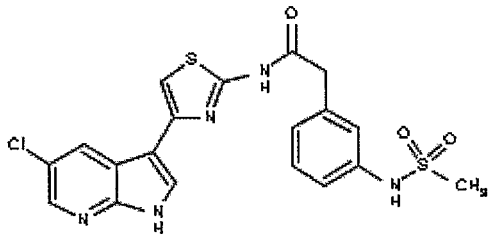
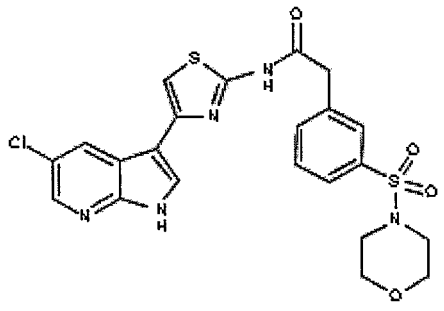
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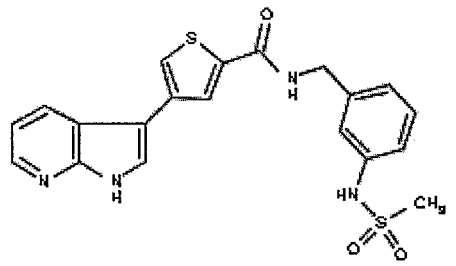
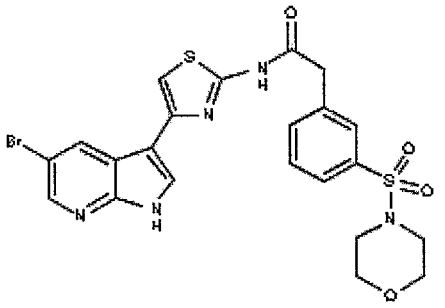
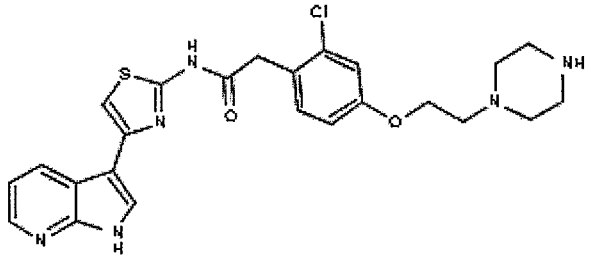
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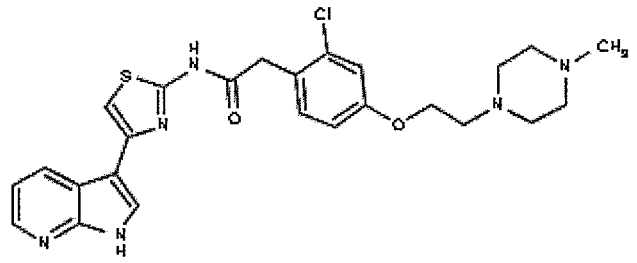
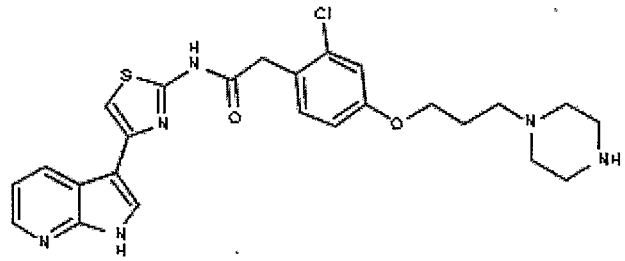
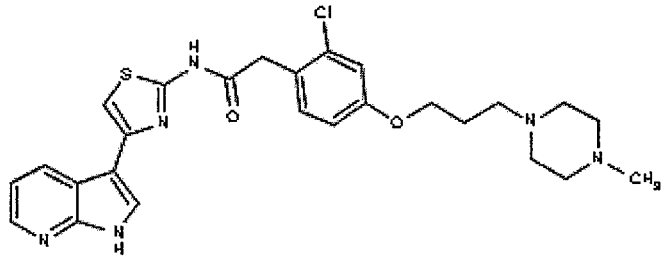
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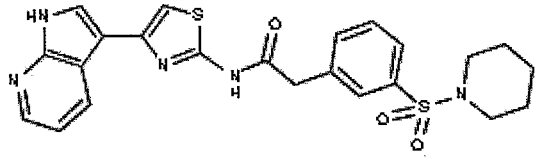
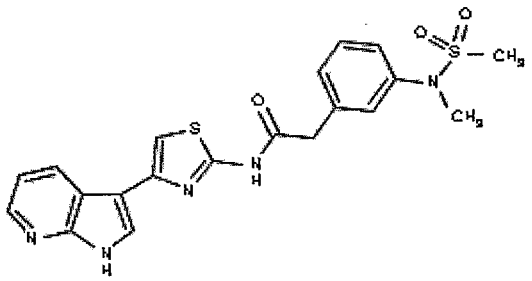
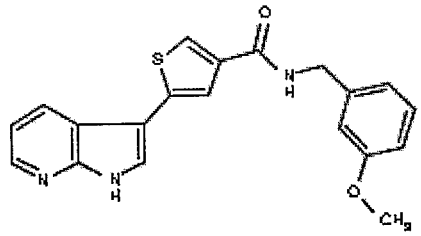
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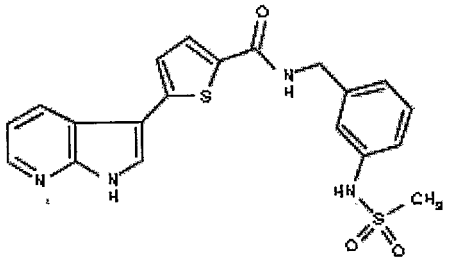
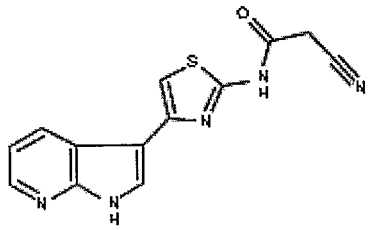
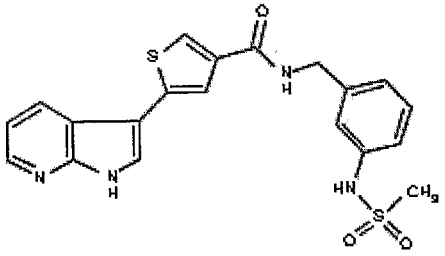
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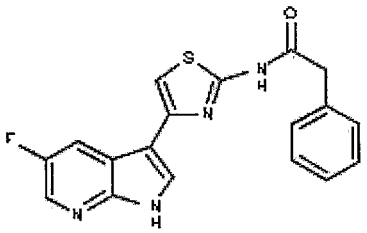
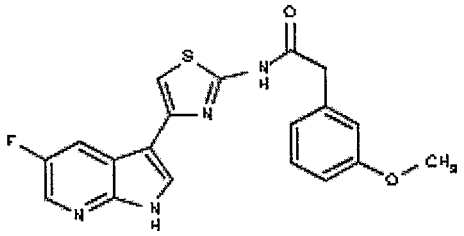
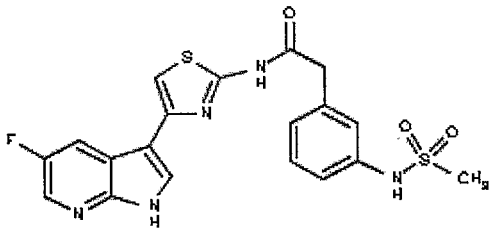
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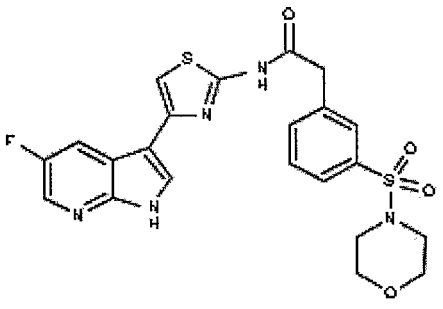
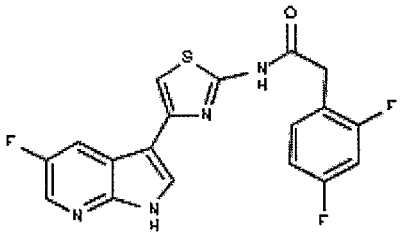
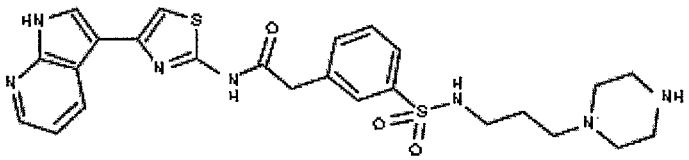
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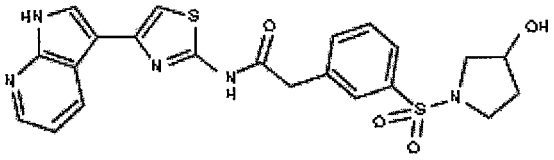
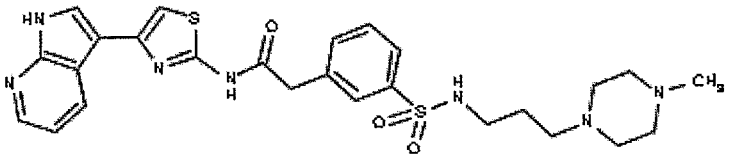
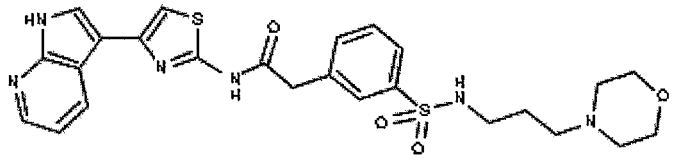
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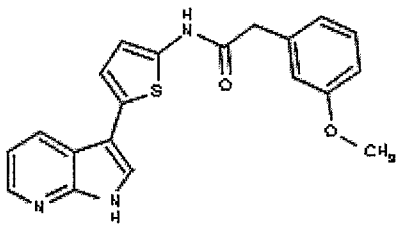
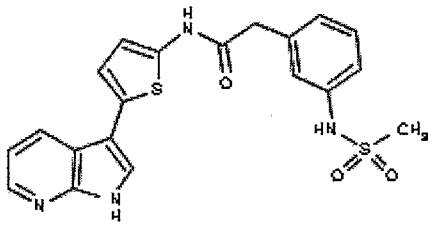
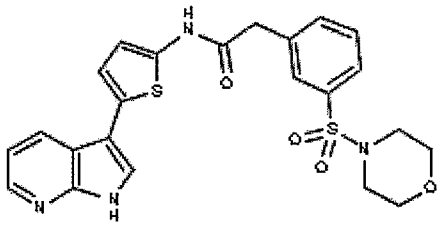
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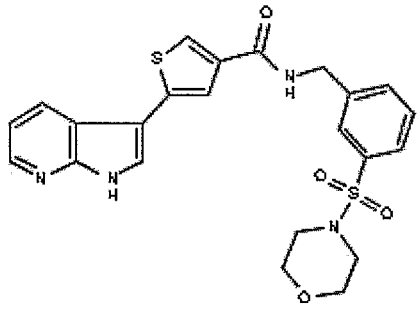
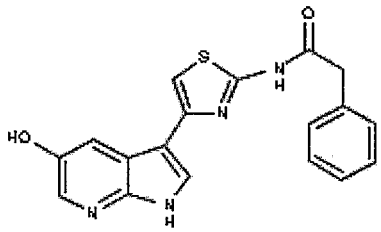
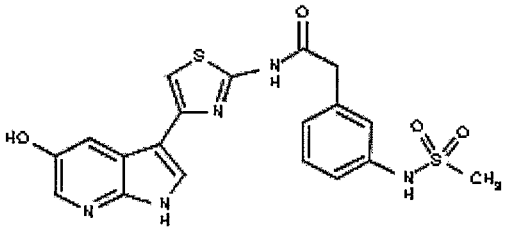
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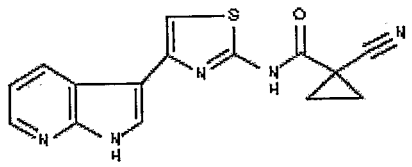
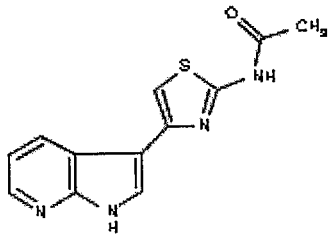
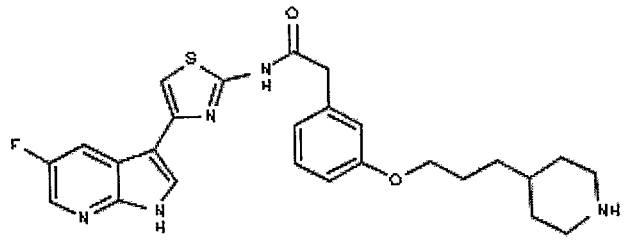
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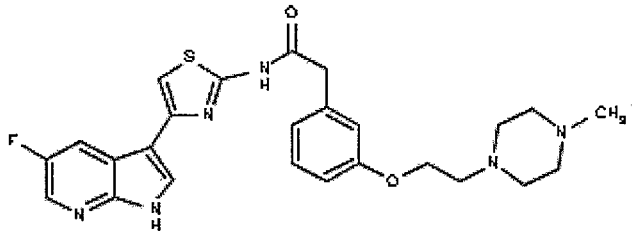
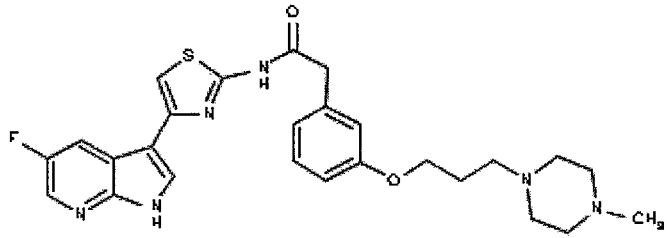
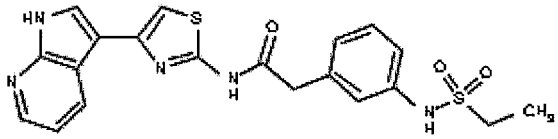
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	II-123

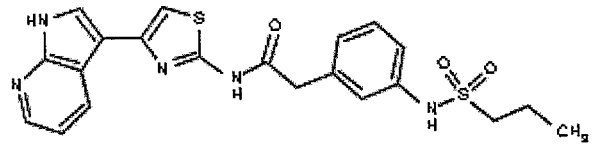
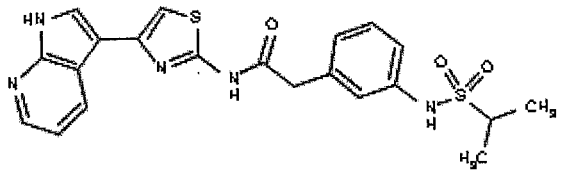
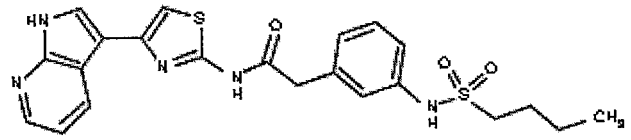
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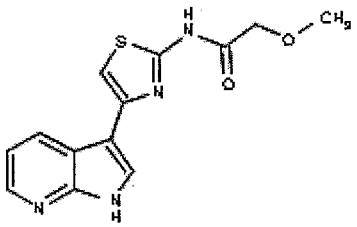
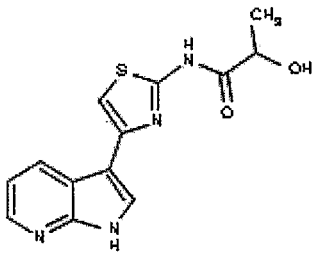
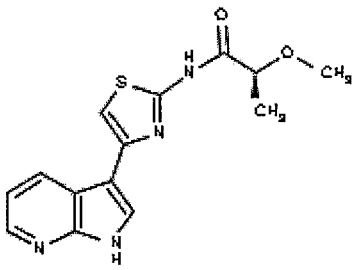
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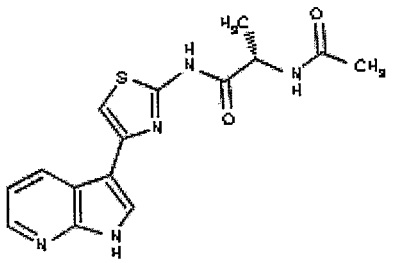
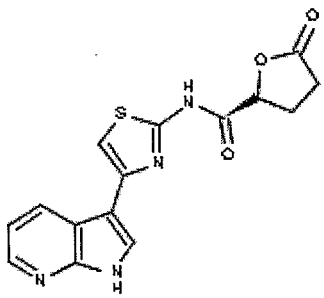
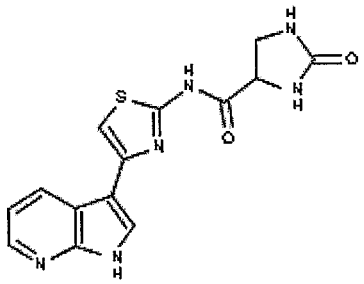
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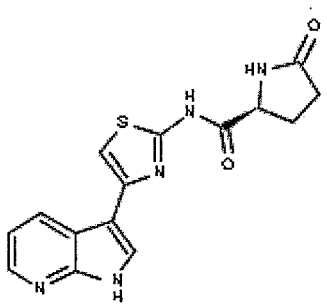
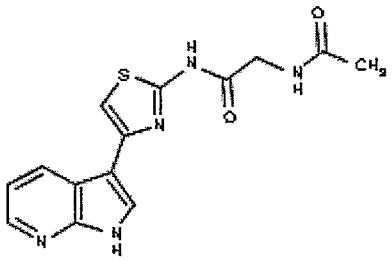
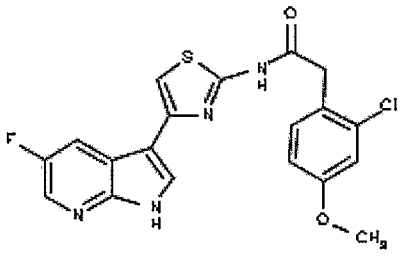
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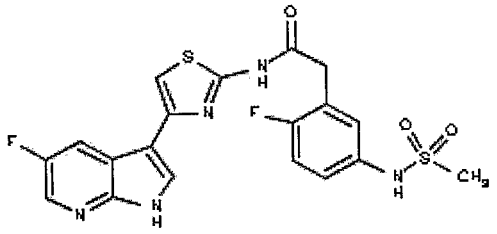
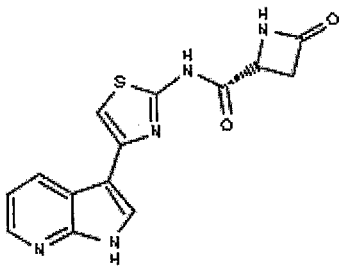
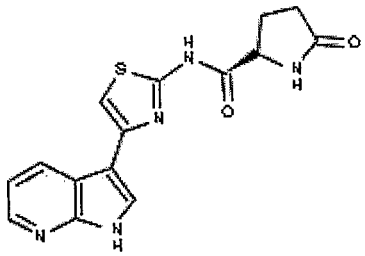
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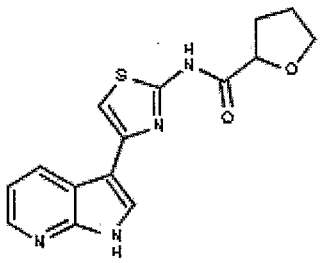
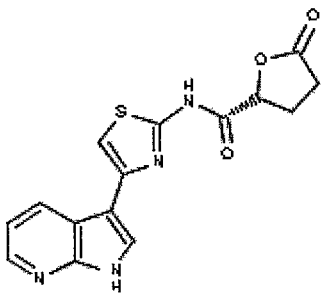
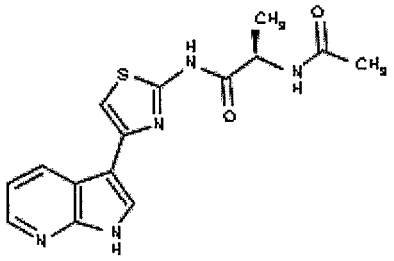
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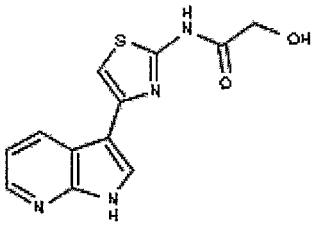
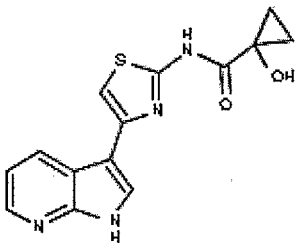
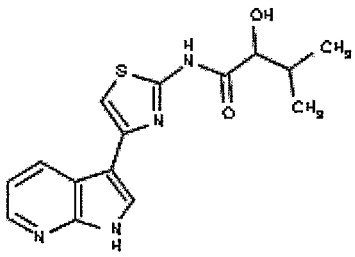
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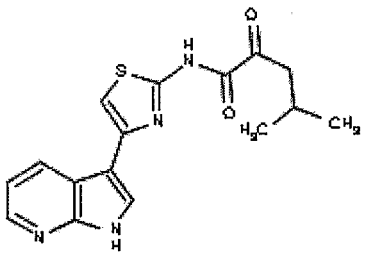
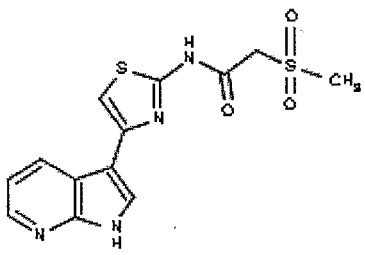
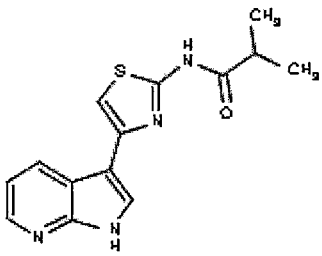
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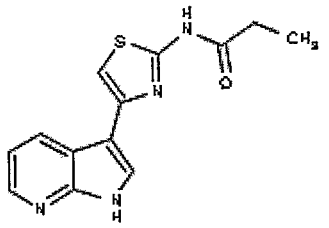
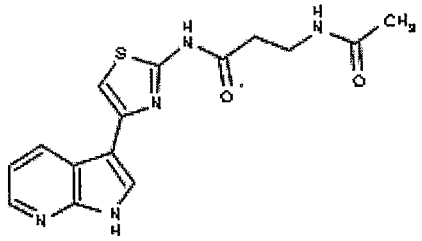
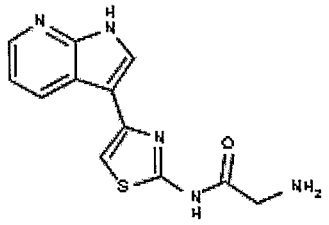
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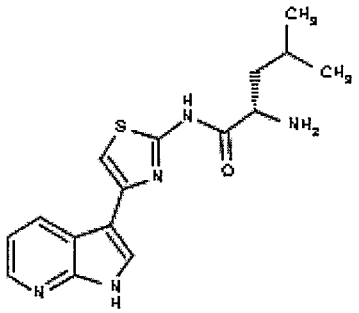
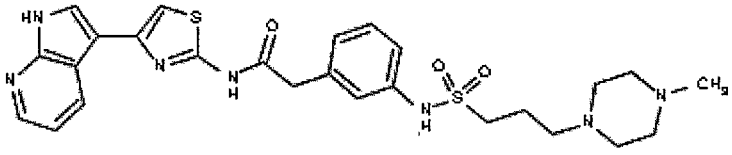
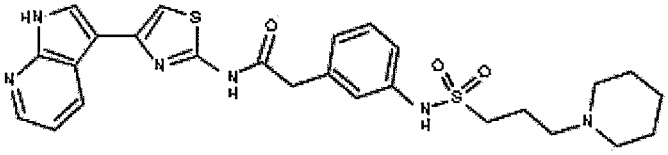
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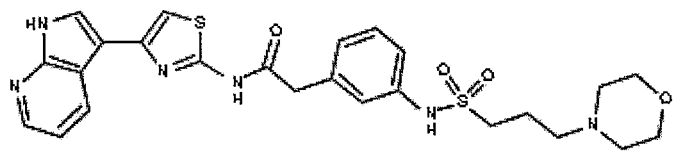
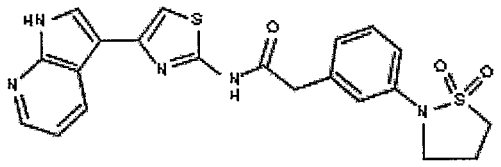
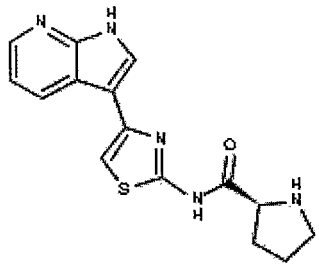
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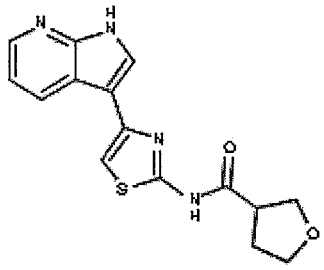
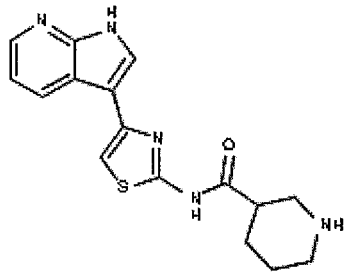
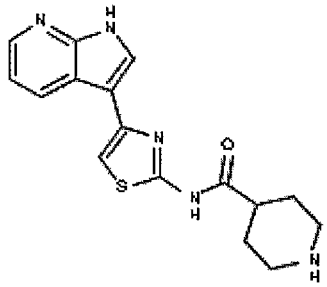
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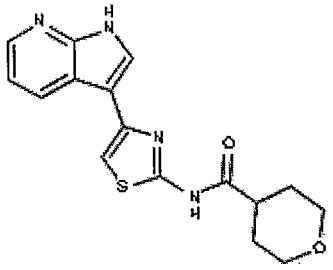
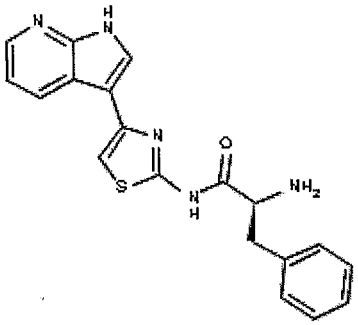
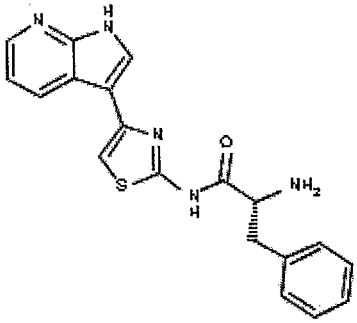
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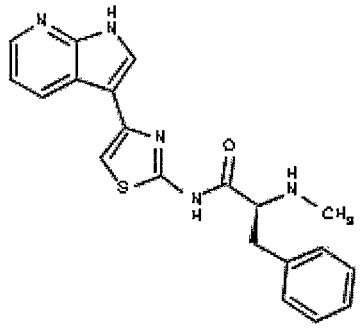
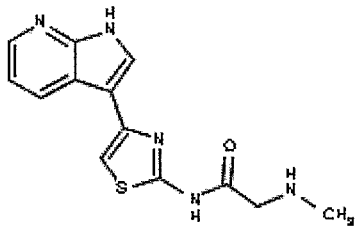
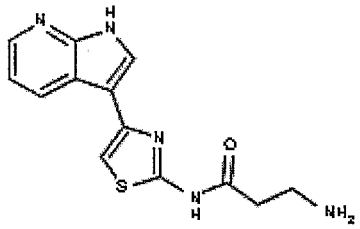
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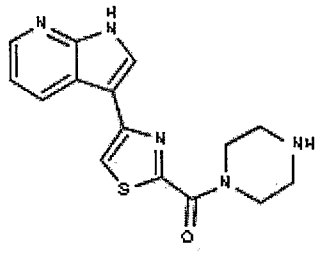
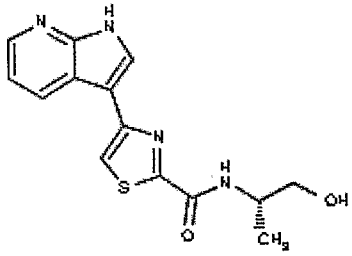
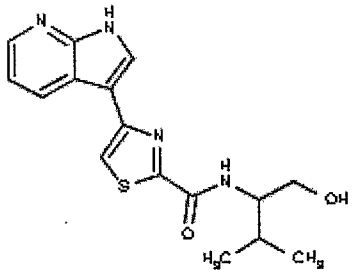
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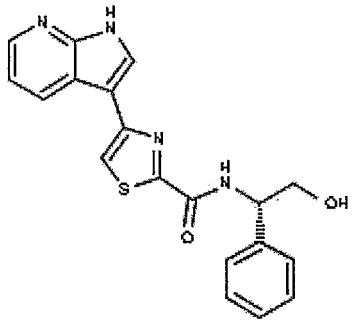
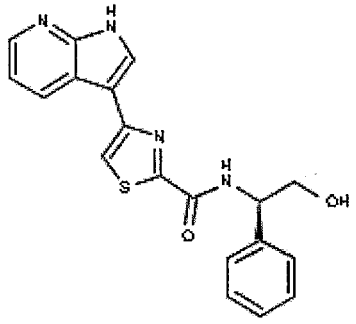
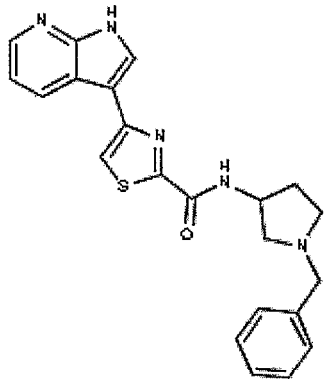
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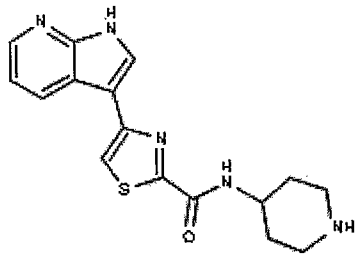
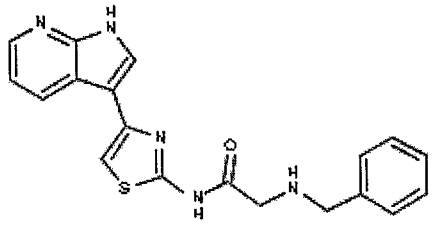
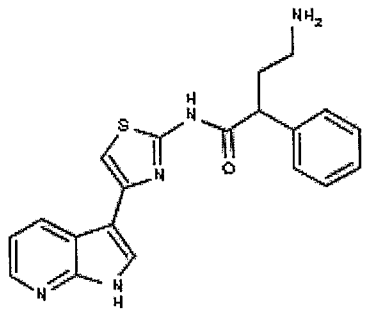
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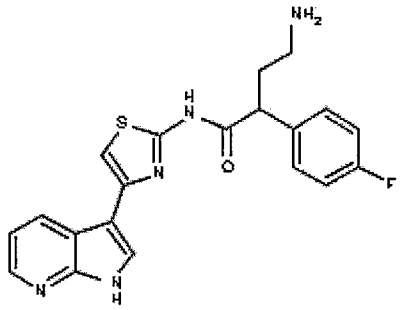
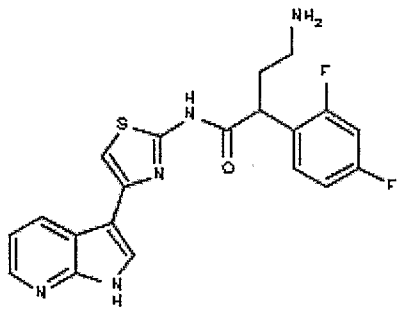
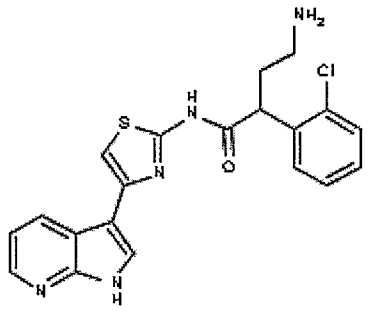
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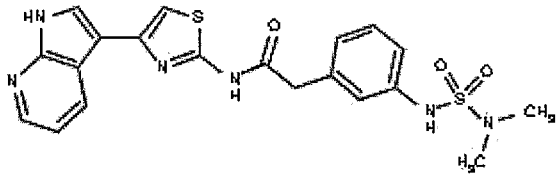
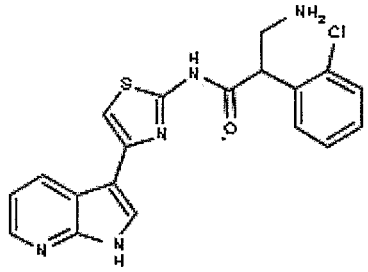
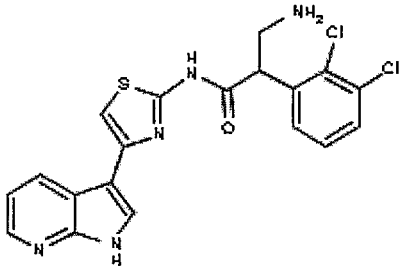
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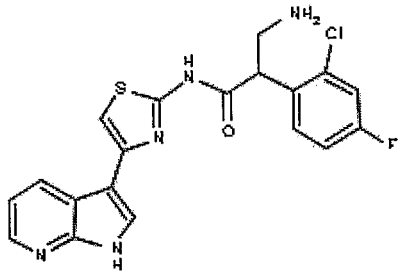
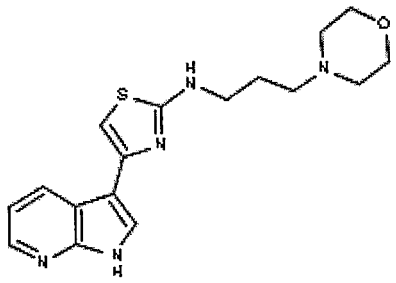
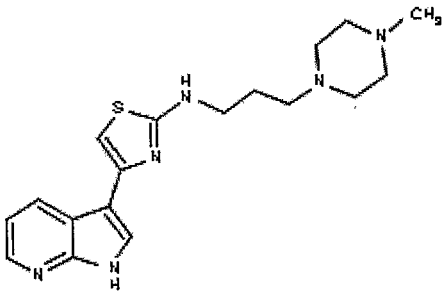
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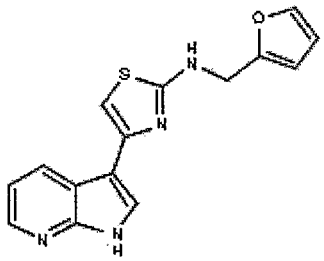
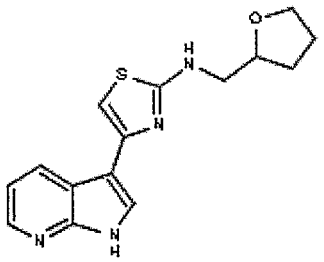
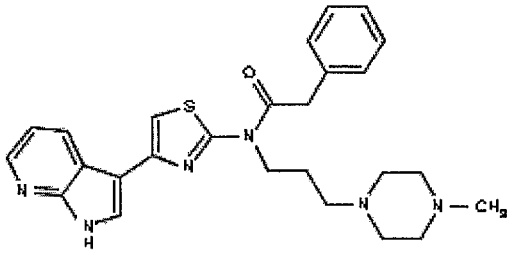
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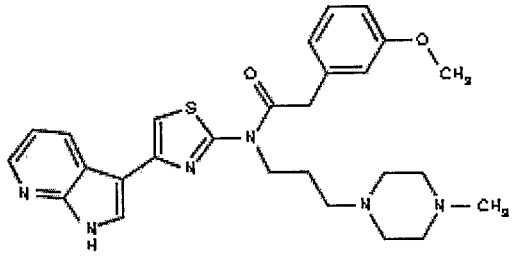
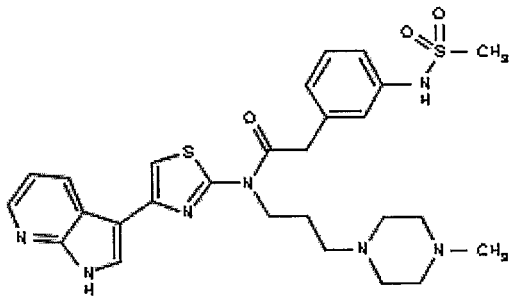
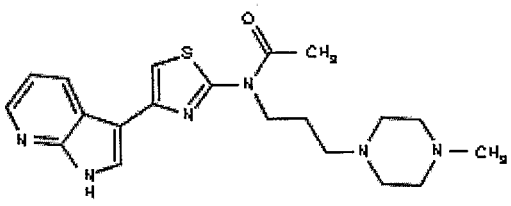
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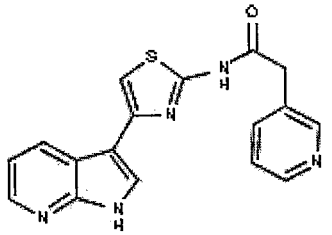
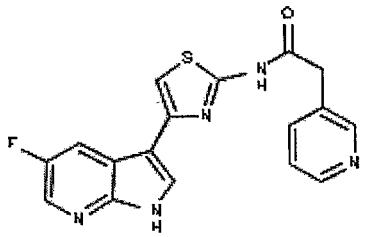
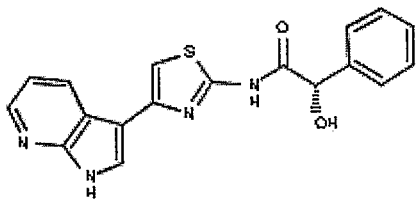
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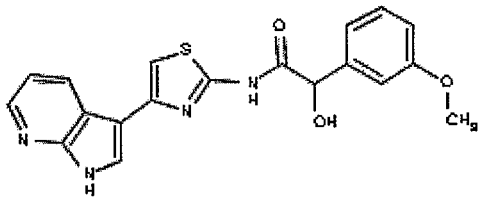
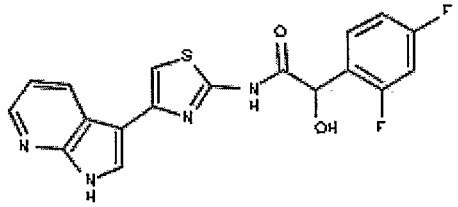
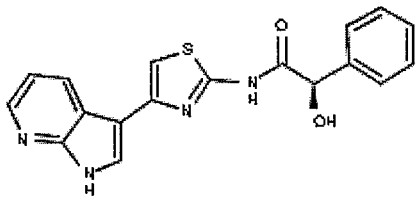
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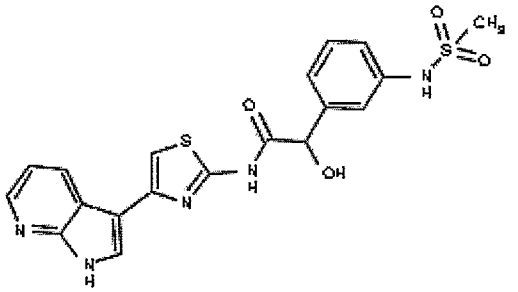
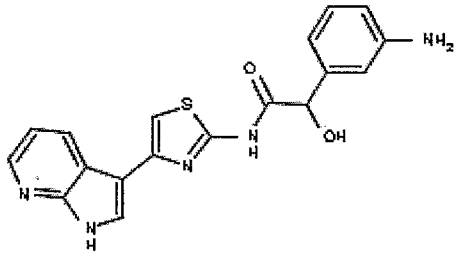
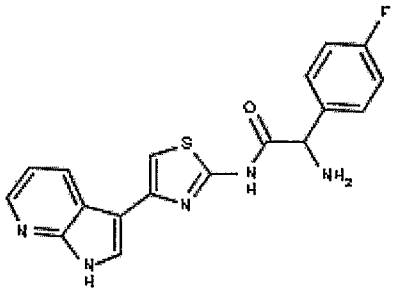
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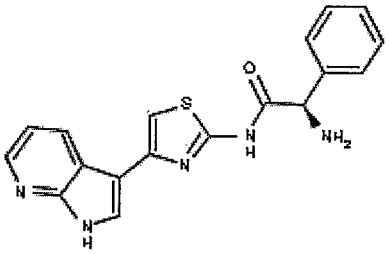
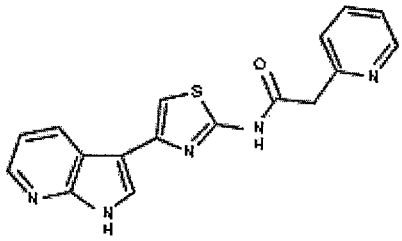
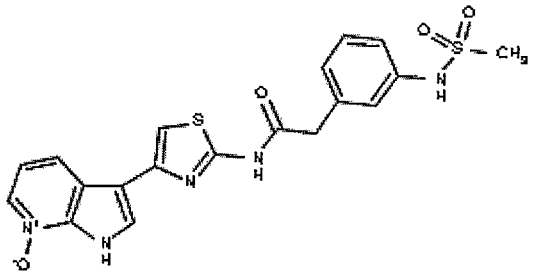
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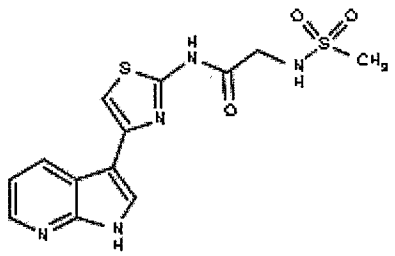
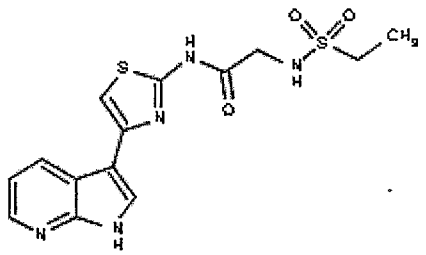
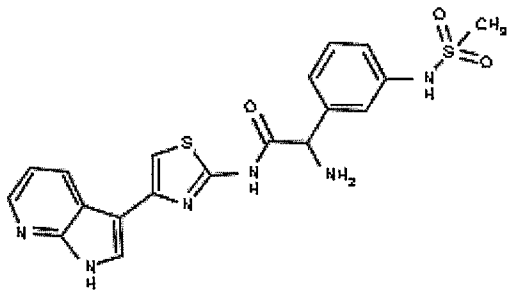
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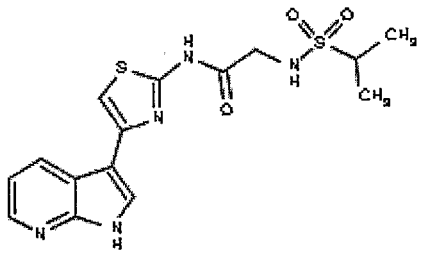
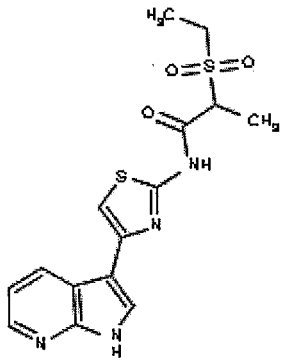
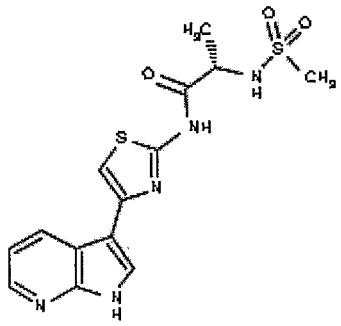
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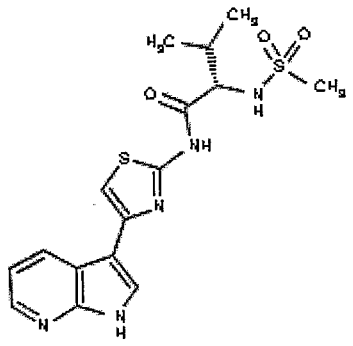
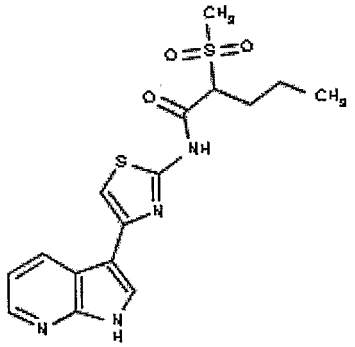
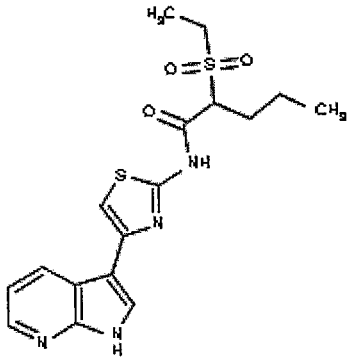
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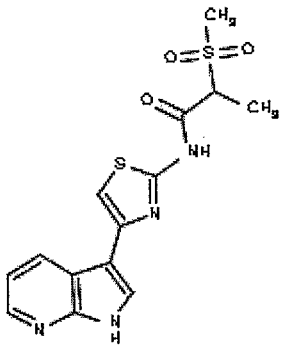
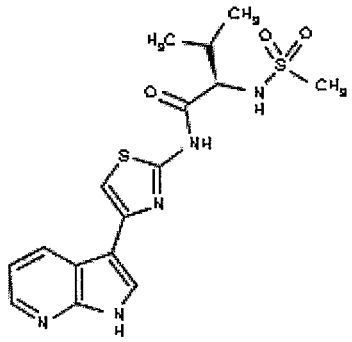
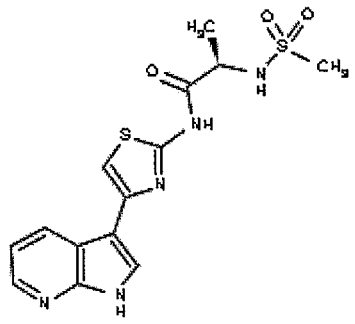
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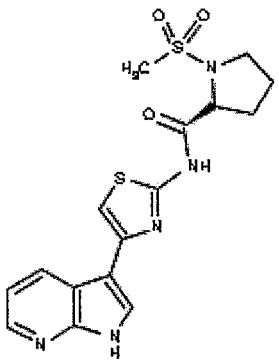
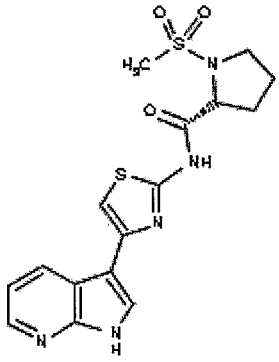
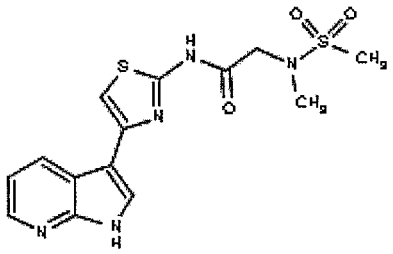
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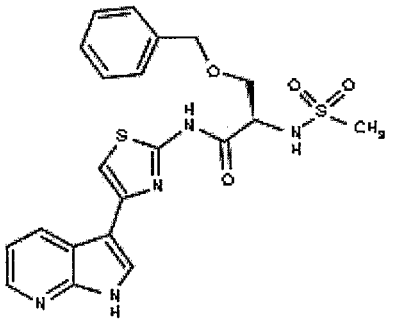
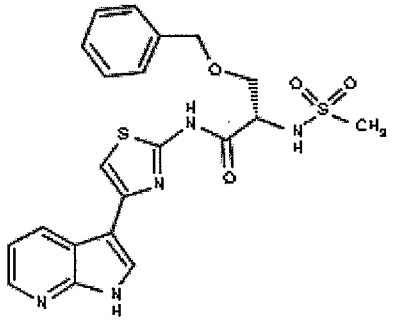
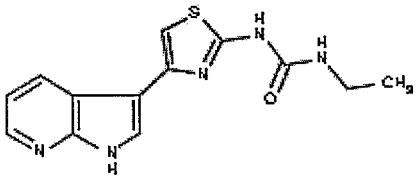
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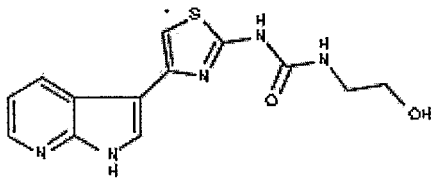
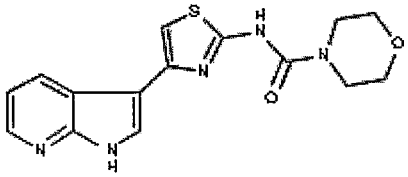
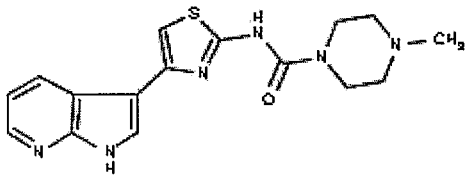
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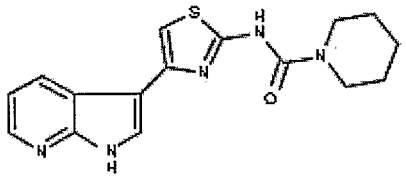
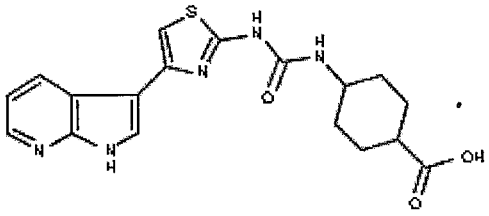
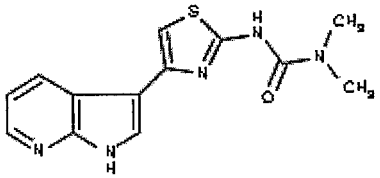
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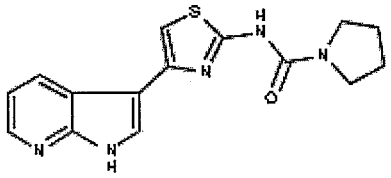
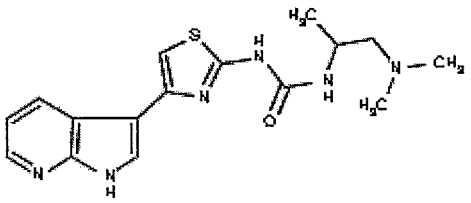
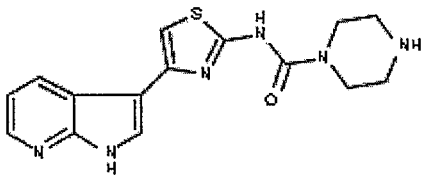
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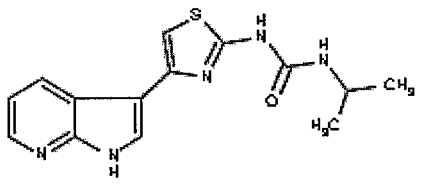
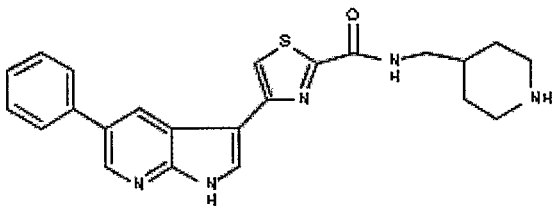
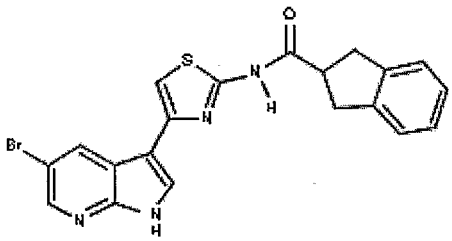
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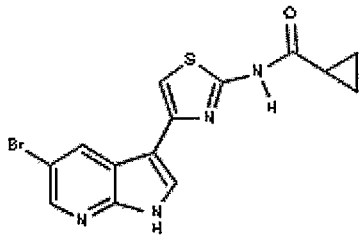
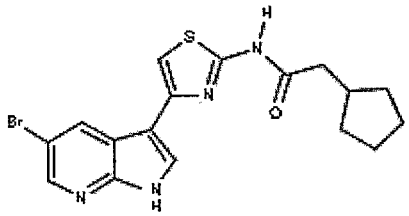
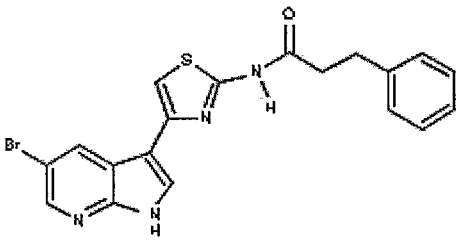
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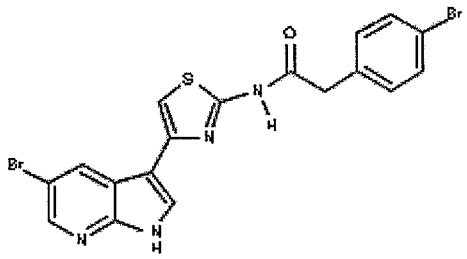
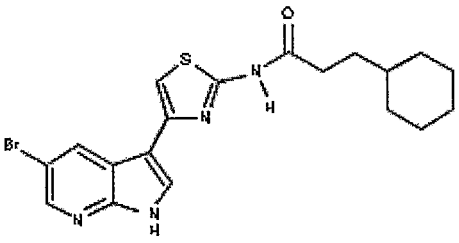
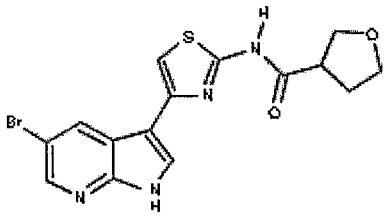
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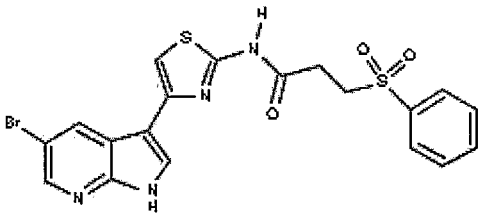
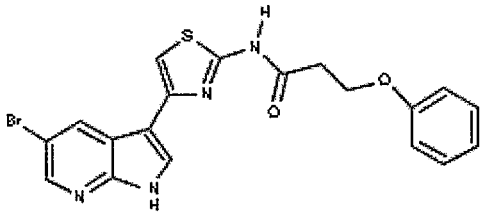
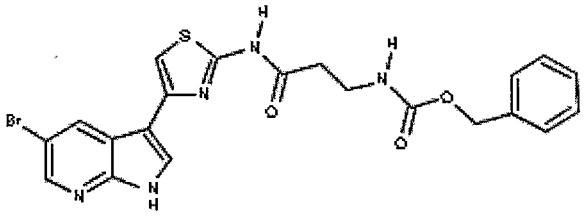
Compound	Cmpd #
	II-238
	II-239
	II-240

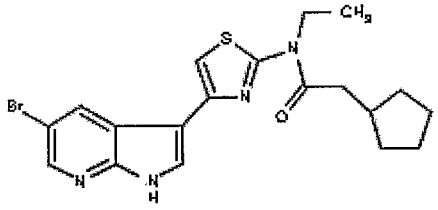
Compound	Cmpd #
	II-241
	II-242
	II-243

Compound	Cmpd #
	II-244
	II-245
	II-246

Compound	Cmpd #
	II-247
	II-248
	II-249

Compound	Cmpd #
	II-250
	II-251
	II-252

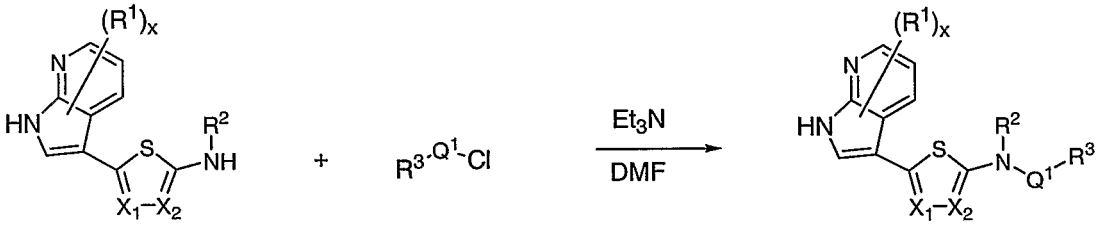
Compound	Cmpd #
	II-253
	II-254
	II-255

Compound	Cmpd #
	II-256

[00103] *4. General Synthetic Methodology:*

[00104] The compounds of this invention may be prepared in general by methods known to those skilled in the art for analogous compounds, as illustrated by the general schemes below, and the preparative examples that follow.

[00105] **Scheme 1** below shows a general method for preparing compounds of formula **I-A**.



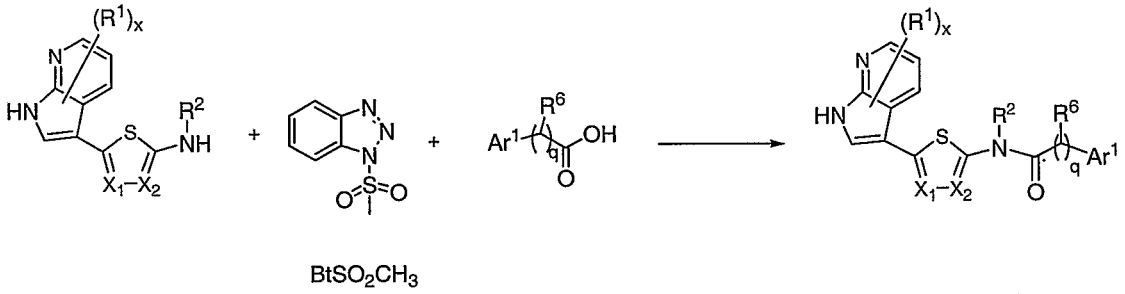
1 **2** **Formula I-A**

Scheme 1

[00106] Specifically, as shown in **Scheme 1**, the intermediate amine **1** is reacted with a desired acid chloride **2** in the presence of dimethylformamide (DMF) and triethylamine (Et_3N) to yield desired compounds of formula **I-A** as described generally and in classes, subclasses and species herein.

[00107] In certain embodiments, for compounds of formula **I-A**, Q^1 is CO, and R^3 is Q^2—Ar^1, wherein Q^2 is $(CHR^6)_q$, wherein R^6 and q are defined generally and in classes, subclasses and species herein. Scheme 2 below depicts a general procedure

for the preparation of compounds of formula **I'-A**, where Q^1 is CO, and R^3 is Q^2—Ar^1, wherein Q^2 is $(CHR^6)_q$:



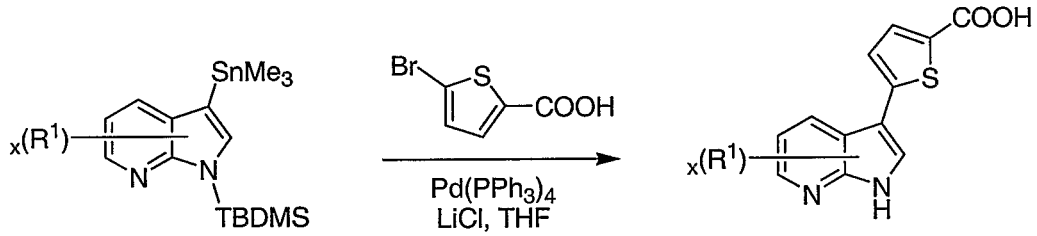
$BtSO_2CH_3$

1 **3** **4** **I'-A**

Scheme 2

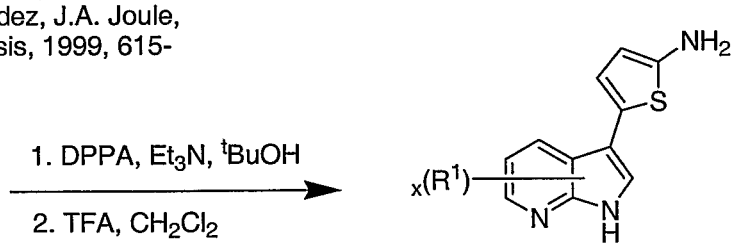
[00108] Specifically, as shown in **Scheme 2**, the intermediate amine **1** is reacted with $BtSO_2CH_3$ **3** and a desired acid **4** in the presence of the presence of triethylamine (Et_3N) to yield desired compounds of formula **I'-A** as described generally and in classes, subclasses and species herein.

[00109] **Scheme 3** below shows a general method for preparing intermediate compounds of formula **1-a**.



$Pd(PPh_3)_4$
LiCl, THF

M. Alvarez, D. Fernandez, J.A. Joule, Synthesis, 1999, 615-620

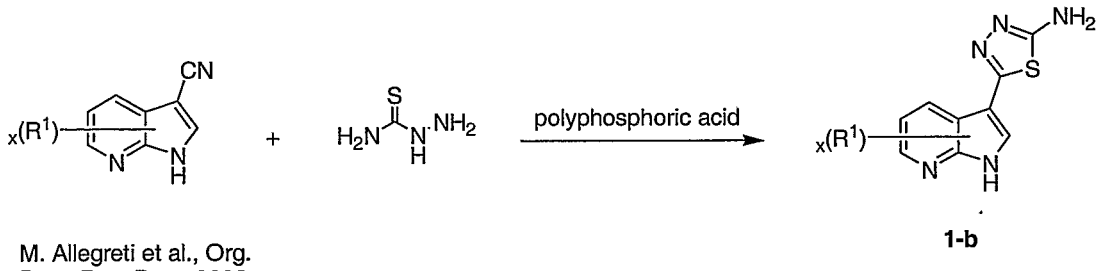


1. DPPA, Et_3N, ^tBuOH
2. TFA, CH_2Cl_2

1-a

Scheme 3

[00110] **Scheme 4** below shows a general method for preparing intermediate compounds of formula **1-b**.

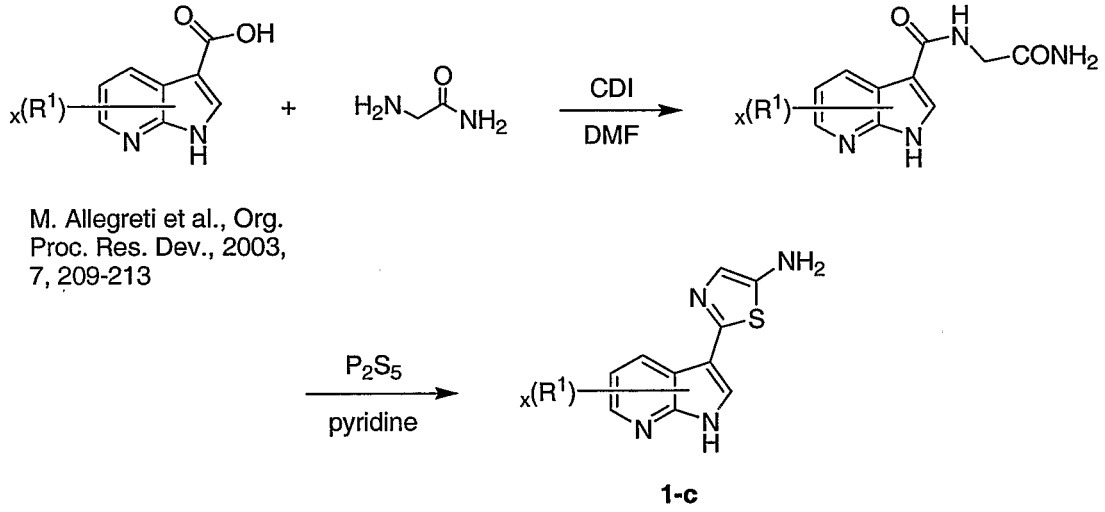


M. Allegreti et al., Org. Proc. Res. Dev., 2003, 7, 209-213

1-b

Scheme 4

[00111] **Scheme 5** below shows a general method for preparing intermediate compounds of formula **1-c**.

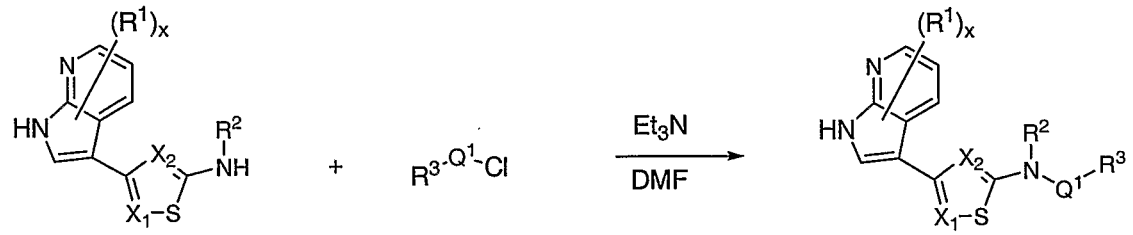


M. Allegreti et al., Org. Proc. Res. Dev., 2003, 7, 209-213

1-c

Scheme 5

[00112] **Scheme 6** below shows a general method for preparing compounds of formula **I-B**.

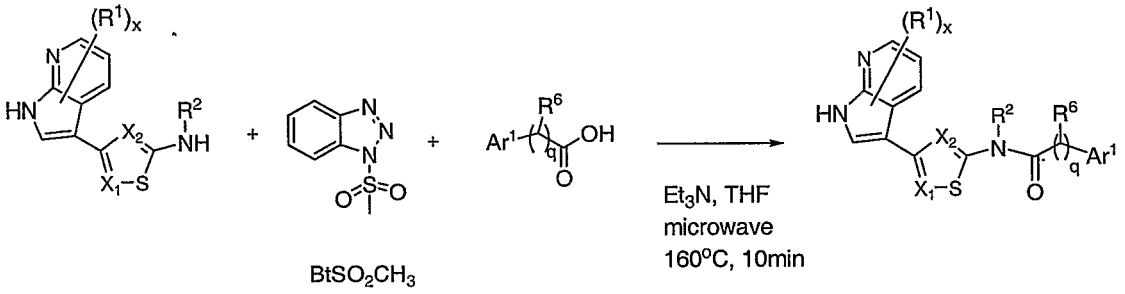


5 **2** **Formula I-B**

Scheme 6

[00113] Specifically, as shown in **Scheme 6**, the intermediate amine **5** is reacted with a desired acid chloride **2** in the presence of dimethylformamide (DMF) and triethylamine (Et_3N) to yield desired compounds of formula **I-B** as described generally and in classes, subclasses and species herein.

[00114] In certain embodiments, for compounds of formula **I-B**, Q^1 is CO, and R^3 is Q^2—Ar^1, wherein Q^2 is $(CHR^6)_q$, wherein R^6 and q are defined generally and in classes, subclasses and species herein. Scheme 4 below depicts a general procedure for the preparation of compounds where Q^1 is CO, and R^3 is Q^2—Ar^1, wherein Q^2 is $(CHR^6)_q$:

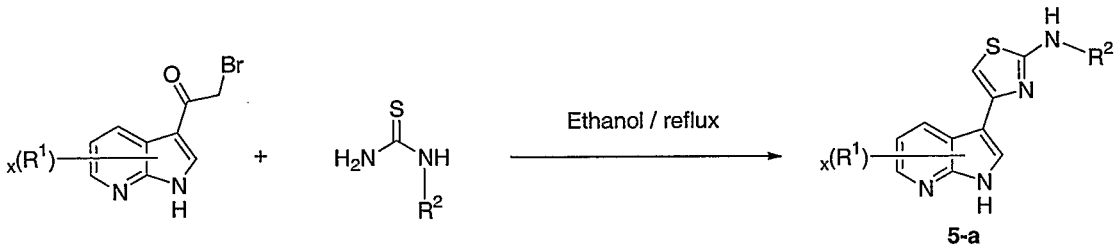


5 **3** **4** **I'-B**

Scheme 7

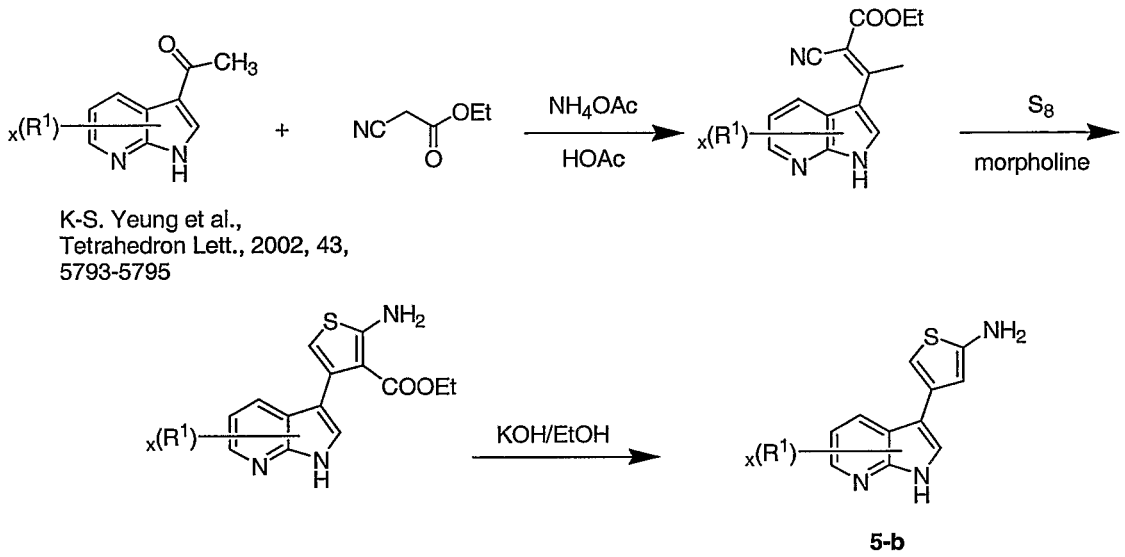
[00115] Specifically, as shown in **Scheme 7**, the intermediate amine **5** is reacted with $BtSO_2CH_3$ **3** and a desired acid **4** in the presence of the presence of triethylamine (Et_3N) to yield desired compounds of formula **I'-B** as described generally and in classes, subclasses and species herein.

[00116] **Scheme 8** below shows a general method for preparing intermediate compounds of formula **5-a**.



Scheme 8

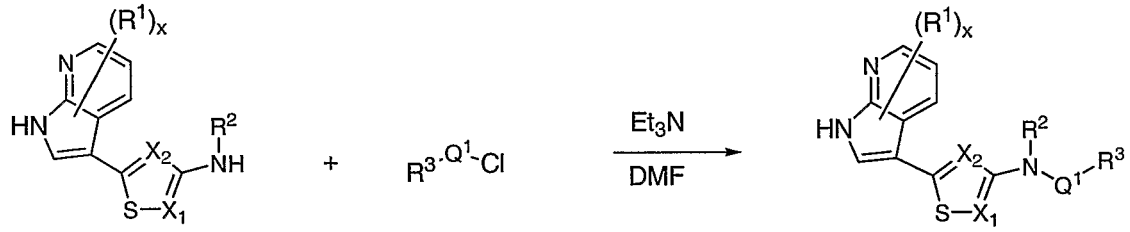
[00117] **Scheme 9** below shows a general method for preparing intermediate compounds of formula **5-b**.



K-S. Yeung et al.,
Tetrahedron Lett., 2002, 43,
5793-5795

Scheme 9

[00118] **Scheme 10** below shows a general method for preparing compounds of formula **I-C**.

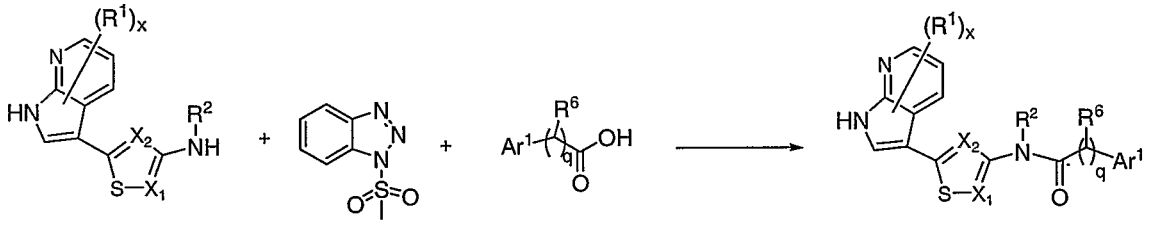


6 **2** **Formula I-C**

Scheme 10

[00119] Specifically, as shown in **Scheme 10**, the intermediate amine **6** is reacted with a desired acid chloride **2** in the presence of dimethylformamide (DMF) and triethylamine (Et_3N) to yield desired compounds of formula **I-C** as described generally and in classes, subclasses and species herein.

[00120] In certain embodiments, for compounds of formula **I-C**, Q^1 is CO, and R^3 is Q^2—Ar^1, wherein Q^2 is $(CHR^6)_q$, wherein R^6 and q are defined generally and in classes, subclasses and species herein. Scheme 6 below depicts a general procedure for the preparation of compounds where Q^1 is CO, and R^3 is Q^2—Ar^1, wherein Q^2 is $(CHR^6)_q$:



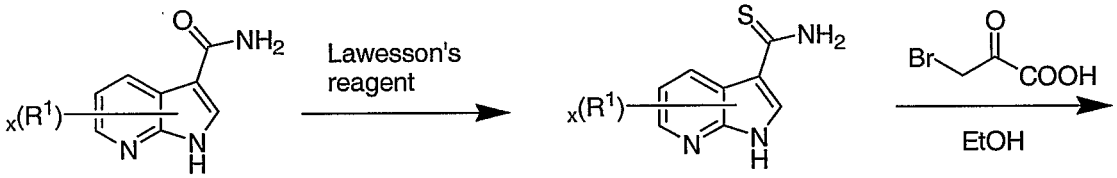
$BtSO_2CH_3$

6 **3** **4** **I'-C**

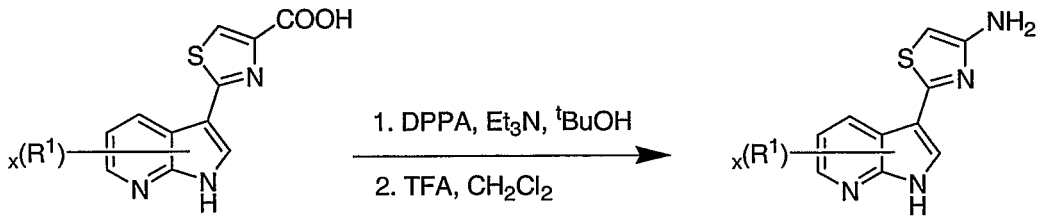
Scheme 11

[00121] Specifically, as shown in **Scheme 11**, the intermediate amine **6** is reacted with $BtSO_2CH_3$ **3** and a desired acid **4** in the presence of the presence of triethylamine (Et_3N) to yield desired compounds of formula **I'-C** as described generally and in classes, subclasses and species herein.

[00122] **Scheme 12** below shows a general method for preparing intermediate compounds of formula **6-a**.



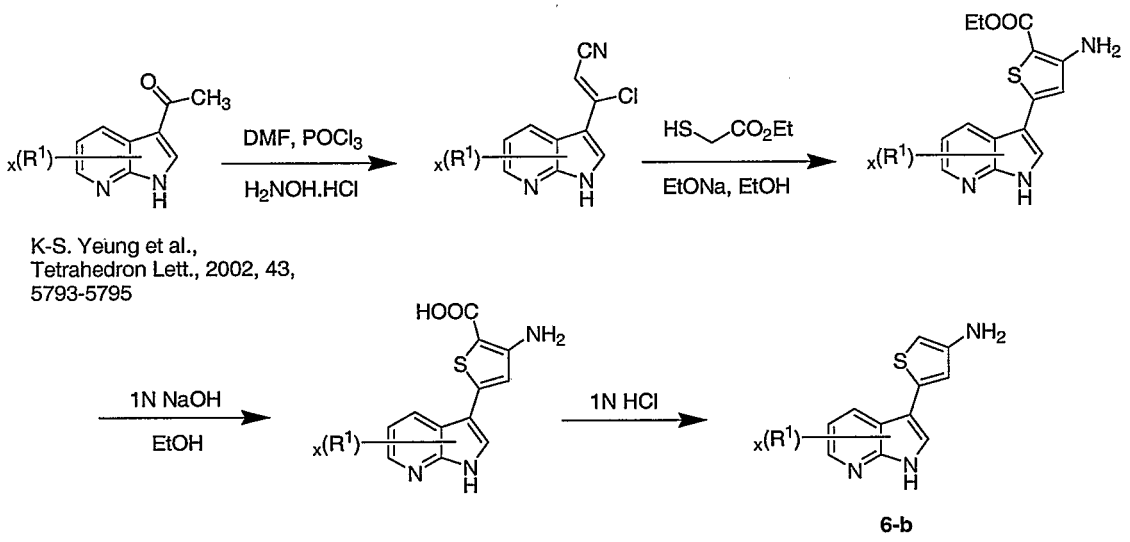
S.W. Schneller and J-K. Luo, J. Org. Chem., 1980, 45, 4045-4048



6-a

Scheme 12

[00123] **Scheme 13** below shows a general method for preparing intermediate compounds of formula **6-b**.



K-S. Yeung et al., Tetrahedron Lett., 2002, 43, 5793-5795

Scheme 13

[00124] Although certain exemplary embodiments are depicted and described above and herein, it will be appreciated that compounds of the invention can be prepared according to the methods described generally above using appropriate starting materials by methods generally available to one of ordinary skill in the art. Additional embodiments are exemplified in more detail herein.

[00125] *5. Uses, Formulation and Administration*

[00126] *Pharmaceutically acceptable compositions*

[00127] As discussed above, the present invention provides compounds that are inhibitors of protein kinases, and thus the present compounds are useful for the treatment of diseases, disorders, and conditions including, but not limited to a proliferative disorder, a cardiac disorder, a neurodegenerative disorder, psychotic disorders, an autoimmune disorder, a condition associated with organ transplant, an inflammatory disorder, an immunologically mediated disorder, a viral disease, or a bone disorder. In preferred embodiments, the compounds are useful for the treatment of allergy, asthma, diabetes, Alzheimer's disease, Huntington's disease, Parkinson's disease, AIDS-associated dementia, amyotrophic lateral sclerosis (AML, Lou Gehrig's disease), multiple sclerosis (MS), schizophrenia, cardiomyocyte hypertrophy, reperfusion/ischemia (e.g., stroke), baldness, cancer, hepatomegaly, cardiovascular disease including cardiomegaly, cystic fibrosis, viral disease, autoimmune diseases, atherosclerosis, restenosis, psoriasis, inflammation,

hypertension, angina pectoris, cerebrovascular contraction, peripheral circulation disorder, premature birth, arteriosclerosis, vasospasm (cerebral vasospasm, coronary vasospasm), retinopathy, erectile dysfunction (ED), AIDS, osteoporosis, Crohn's Disease and colitis, neurite outgrowth, and Raynaud's Disease. In other embodiments, the compounds are useful for the treatment of hypertension, cerebral vasospasm, coronary vasospasm, bronchial asthma, preterm labor, erectile dysfunction, glaucoma, vascular smooth muscle cell proliferation, myocardial hypertrophy, malignoma, ischemia/reperfusion-induced injury, endothelial dysfunction, Crohn's Disease and colitis, neurite outgrowth, Raynaud's Disease, angina, Alzheimer's disease, benign prostatic hyperplasia, or atherosclerosis.

[00128] In still other embodiments, the disease, condition, or disorder is atherosclerosis, hypertension, erectile dysfunction (ED), reperfusion/ischemia (e.g., stroke), or vasospasm (cerebral vasospasm and coronary vasospasm).

[00129] Accordingly, in another aspect of the present invention, pharmaceutically acceptable compositions are provided, wherein these compositions comprise any of the compounds as described herein, and optionally comprise a pharmaceutically acceptable carrier, adjuvant or vehicle. In certain embodiments, these compositions optionally further comprise one or more additional therapeutic agents.

[00130] It will also be appreciated that certain of the compounds of present invention can exist in free form for treatment, or where appropriate, as a pharmaceutically acceptable derivative thereof. According to the present invention, a pharmaceutically acceptable derivative includes, but is not limited to, pharmaceutically acceptable prodrugs, salts, esters, salts of such esters, or any other adduct or derivative which upon administration to a patient in need is capable of providing, directly or indirectly, a compound as otherwise described herein, or a metabolite or residue thereof.

[00131] As used herein, the term "pharmaceutically acceptable salt" refers to those salts which are, within the scope of sound medical judgement, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. A "pharmaceutically acceptable salt" means any non-toxic salt or salt of an ester of a compound of this invention that, upon administration to a

recipient, is capable of providing, either directly or indirectly, a compound of this invention or an inhibitorily active metabolite or residue thereof. As used herein, the term "inhibitorily active metabolite or residue thereof" means that a metabolite or residue thereof is also an inhibitor of a ROCK, ERK, or GSK kinase, or members of the AGC sub-family of protein kinases (e.g., PKA, PDK, $p70^{S6K}$-1 and –2, and PKB).

[00132] Pharmaceutically acceptable salts are well known in the art. For example, S. M. Berge *et al.,* describe pharmaceutically acceptable salts in detail in *J. Pharmaceutical Sciences*, **1977**, *66*, 1-19, incorporated herein by reference. Pharmaceutically acceptable salts of the compounds of this invention include those derived from suitable inorganic and organic acids and bases. Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid or by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p-toluenesulfonate, undecanoate, valerate salts, and the like. Salts derived from appropriate bases include alkali metal, alkaline earth metal, ammonium and $N^+(C_{1-4}alkyl)_4$ salts. This invention also envisions the quaternization of any basic nitrogen-containing groups of the compounds disclosed herein. Water or oil-soluble or dispersable products may be obtained by such quaternization. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations

formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, loweralkyl sulfonate and aryl sulfonate.

[00133] As described above, the pharmaceutically acceptable compositions of the present invention additionally comprise a pharmaceutically acceptable carrier, adjuvant, or vehicle, which, as used herein, includes any and all solvents, diluents, or other liquid vehicle, dispersion or suspension aids, surface active agents, isotonic agents, thickening or emulsifying agents, preservatives, solid binders, lubricants and the like, as suited to the particular dosage form desired. Remington's Pharmaceutical Sciences, Sixteenth Edition, E. W. Martin (Mack Publishing Co., Easton, Pa., 1980) discloses various carriers used in formulating pharmaceutically acceptable compositions and known techniques for the preparation thereof. Except insofar as any conventional carrier medium is incompatible with the compounds of the invention, such as by producing any undesirable biological effect or otherwise interacting in a deleterious manner with any other component(s) of the pharmaceutically acceptable composition, its use is contemplated to be within the scope of this invention. Some examples of materials which can serve as pharmaceutically acceptable carriers include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, or potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, wool fat, sugars such as lactose, glucose and sucrose; starches such as corn starch and potato starch; cellulose and its derivatives such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients such as cocoa butter and suppository waxes; oils such as peanut oil, cottonseed oil; safflower oil; sesame oil; olive oil; corn oil and soybean oil; glycols; such a propylene glycol or polyethylene glycol; esters such as ethyl oleate and ethyl laurate; agar; buffering agents such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol, and phosphate buffer solutions, as well as other non-toxic compatible lubricants such as sodium lauryl sulfate and

magnesium stearate, as well as coloring agents, releasing agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the composition, according to the judgment of the formulator.

[00134] *Uses of Compounds and Pharmaceutically acceptable compositions*

[00135] In yet another aspect, a method for the treatment or lessening the severity of a proliferative disorder, a cardiac disorder, a neurodegenerative disorder, a psychotic disorder, an autoimmune disorder, a condition associated with organ transplant, an inflammatory disorder, an immunologically mediated disorder, a viral disease, or a bone disorder is provided comprising administering an effective amount of a compound, or a pharmaceutically acceptable composition comprising a compound to a subject in need thereof. In certain embodiments of the present invention an "effective amount" of the compound or pharmaceutically acceptable composition is that amount effective for treating or lessening the severity of a proliferative disorder, a cardiac disorder, a neurodegenerative disorder, a psychotic disorder, an autoimmune disorder, a condition associated with organ transplant, an inflammatory disorder, an immunologically mediated disorder, a viral disease, or a bone disorder. The compounds and compositions, according to the method of the present invention, may be administered using any amount and any route of administration effective for treating or lessening the severity of a proliferative disorder, a cardiac disorder, a neurodegenerative disorder, an autoimmune disorder, a condition associated with organ transplant, an inflammatory disorder, an immunologically mediated disorder, a viral disease, or a bone disorder. The exact amount required will vary from subject to subject, depending on the species, age, and general condition of the subject, the severity of the infection, the particular agent, its mode of administration, and the like. The compounds of the invention are preferably formulated in dosage unit form for ease of administration and uniformity of dosage. The expression "dosage unit form" as used herein refers to a physically discrete unit of agent appropriate for the patient to be treated. It will be understood, however, that the total daily usage of the compounds and compositions of the present invention will be decided by the attending physician within the scope of sound medical judgment. The specific effective dose level for any particular patient or organism will depend

upon a variety of factors including the disorder being treated and the severity of the disorder; the activity of the specific compound employed; the specific composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed, and like factors well known in the medical arts. The term "patient", as used herein, means an animal, preferably a mammal, and most preferably a human.

[00136] The pharmaceutically acceptable compositions of this invention can be administered to humans and other animals orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, or drops), bucally, as an oral or nasal spray, or the like, depending on the severity of the infection being treated. In certain embodiments, the compounds of the invention may be administered orally or parenterally at dosage levels of about 0.01 mg/kg to about 50 mg/kg and preferably from about 1 mg/kg to about 25 mg/kg, of subject body weight per day, one or more times a day, to obtain the desired therapeutic effect.

[00137] Liquid dosage forms for oral administration include, but are not limited to, pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

[00138] Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution, suspension or emulsion in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-

butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, U.S.P. and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables.

[00139] The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium prior to use.

[00140] In order to prolong the effect of a compound of the present invention, it is often desirable to slow the absorption of the compound from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the compound then depends upon its rate of dissolution that, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered compound form is accomplished by dissolving or suspending the compound in an oil vehicle. Injectable depot forms are made by forming microencapsule matrices of the compound in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of compound to polymer and the nature of the particular polymer employed, the rate of compound release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the compound in liposomes or microemulsions that are compatible with body tissues.

[00141] Compositions for rectal or vaginal administration are preferably suppositories which can be prepared by mixing the compounds of this invention with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active compound.

[00142] Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is mixed

with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidinone, sucrose, and acacia, c) humectants such as glycerol, d) disintegrating agents such as agar--agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, e) solution retarding agents such as paraffin, f) absorption accelerators such as quaternary ammonium compounds, g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite clay, and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents.

[00143] Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polethylene glycols and the like.

[00144] The active compounds can also be in micro-encapsulated form with one or more excipients as noted above. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings, release controlling coatings and other coatings well known in the pharmaceutical formulating art. In such solid dosage forms the active compound may be admixed with at least one inert diluent such as sucrose, lactose or starch. Such dosage forms may also comprise, as is normal practice, additional substances other than inert diluents, e.g., tableting lubricants and other tableting aids such a magnesium stearate

and microcrystalline cellulose. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes.

[00145] Dosage forms for topical or transdermal administration of a compound of this invention include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants or patches. The active component is admixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives or buffers as may be required. Ophthalmic formulation, ear drops, and eye drops are also contemplated as being within the scope of this invention. Additionally, the present invention contemplates the use of transdermal patches, which have the added advantage of providing controlled delivery of a compound to the body. Such dosage forms can be made by dissolving or dispensing the compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate can be controlled by either providing a rate controlling membrane or by dispersing the compound in a polymer matrix or gel.

[00146] As described generally above, the compounds of the invention are useful as inhibitors of protein kinases. In one embodiment, the compounds and compositions of the invention are inhibitors of one or more of ROCK, ERK, or GSK kinase, or members of the AGC sub-family of protein kinases (e.g., PKA, PDK, $p70^{S6K}$-1 and –2, and PKB), and thus, without wishing to be bound by any particular theory, the compounds and compositions are particularly useful for treating or lessening the severity of a disease, condition, or disorder where activation of one or more of ROCK, ERK, or GSK kinase, or members of the AGC sub-family of protein kinases (e.g., PKA, PDK, $p70^{S6K}$-1 and –2, and PKB) is implicated in the disease, condition, or disorder. When activation of ROCK, ERK, or GSK kinase, or members of the AGC sub-family of protein kinases (e.g., PKA, PDK, $p70^{S6K}$-1 and –2, and PKB) is implicated in a particular disease, condition, or disorder, the disease, condition, or disorder may also be referred to as "ROCK, ERK, GSK, AGC (e.g., PKA, PDK, $p70^{S6K}$-1 and –2, and PKB) -mediated disease" or disease symptom.

Accordingly, in another aspect, the present invention provides a method for treating or lessening the severity of a disease, condition, or disorder where activation or one or more of ROCK, ERK, or GSK kinase, or members of the AGC sub-family of protein kinases (e.g., PKA, PDK, $p70^{S6K}$-1 and –2, and PKB) is implicated in the disease state.

[00147] The activity of a compound utilized in this invention as an inhibitor of ROCK, ERK, or GSK kinase, or members of the AGC sub-family of protein kinases (e.g., PKA, PDK, $p70^{S6K}$-1 and –2, and PKB), may be assayed *in vitro, in vivo* or in a cell line. *In vitro* assays include assays that determine inhibition of either the phosphorylation activity or ATPase activity of activated ROCK, ERK, or GSK kinase, or members of the AGC sub-family of protein kinases (e.g., PKA, PDK, $p70^{S6K}$-1 and –2, and PKB). Alternate *in vitro* assays quantitate the ability of the inhibitor to bind to ROCK, ERK, or GSK kinase, or members of the AGC sub-family of protein kinases (e.g., PKA, PDK, $p70^{S6K}$-1 and –2, and PKB). Inhibitor binding may be measured by radiolabelling the inhibitor prior to binding, isolating the inhibitor/ ROCK, inhibitor/ERK, inhibitor/GSK kinase, or inhibitor/AGC (e.g., PKA, PDK, $p70^{S6K}$-1 and –2, and PKB) complex and determining the amount of radiolabel bound. Alternatively, inhibitor binding may be determined by running a competition experiment where new inhibitors are incubated with ROCK, ERK, or GSK kinase, or members of the AGC sub-family of protein kinases (e.g., PKA, PDK, $p70^{S6K}$-1 and – 2, and PKB) bound to known radioligands.

[00148] The term "measurably inhibit", as used herein means a measurable change in ROCK, ERK, or GSK kinase, or members of the AGC sub-family of protein kinases (e.g., PKA, PDK, $p70^{S6K}$-1 and –2, and PKB) activity between a sample comprising said composition and a ROCK, ERK, or GSK kinase, or members of the AGC sub-family of protein kinases (e.g., PKA, PDK, $p70^{S6K}$-1 and –2, and PKB) kinase and an equivalent sample comprising ROCK, ERK, or GSK kinase, or members of the AGC sub-family of protein kinases (e.g., PKA, PDK, $p70^{S6K}$-1 and – 2, and PKB) kinase in the absence of said composition.

[00149] The terms "AKT-mediated disease" or "AKT-mediated condition", as used herein, mean any disease or other deleterious condition in which AKT is known to play a role. The terms "AKT-mediated disease" or "AKT-mediated condition"

also mean those diseases or conditions that are alleviated by treatment with a AKT inhibitor. AKT-mediated diseases or conditions include, but are not limited to, proliferative disorders, cancer, and neurodegenerative disorders. The association of AKT, also known as protein kinase B, with various diseases has been described [Khwaja, A. *Nature* **1999**, *401,* 33-34; Yuan, Z.Q. *et al., Oncogene* **2000**, *19,* 2324-2330; Namikawa, K. *et al., The Journal of Neuroscience* **2000,** *20*, 2875-2886].

[00150] The term "PDK1-mediated condition" or "disease", as used herein, means any disease or other deleterious condition in which PDK1 is known to play a role. The term "PDK1-mediated condition" or "disease" also means those diseases or conditions that are alleviated by treatment with a PDK1 inhibitor. PDK1-mediated diseases or conditions include, but are not limited to, proliferative disorders, and cancer. Preferably, said cancer is selected from pancreatic, prostate, or ovarian cancer.

[00151] The term "PKA-mediated condition" or "disease", as used herein, means any disease or other deleterious condition in which PKA is known to play a role. The term "PKA-mediated condition" or "disease" also means those diseases or conditions that are alleviated by treatment with a PKA inhibitor. PKA-mediated diseases or conditions include, but are not limited to, proliferative disorders and cancer.

[00152] The term "$p70^{S6K}$-mediated condition" or "disease", as used herein, means any disease or other deleterious condition in which $p70^{S6K}$ is known to play a role. The term "p70S6K-mediated condition" or "disease" also means those diseases or conditions that are alleviated by treatment with a $p70^{S6K}$ inhibitor. $p70^{S6K}$-mediated diseases or conditions include, but are not limited to, proliferative disorders, such as cancer and tuberous sclerosis.

[00153] The terms "ERK-mediated disease" or "ERK-mediated condition", as used herein mean any disease or other deleterious condition in which ERK is known to play a role. The terms "ERK-2-mediated disease" or "ERK-2-mediated condition" also mean those diseases or conditions that are alleviated by treatment with an ERK-2 inhibitor. Such conditions include, without limitation, cancer, stroke, diabetes, hepatomegaly, cardiovascular disease including cardiomegaly, Alzheimer's disease, cystic fibrosis, viral disease, autoimmune diseases, atherosclerosis, restenosis, psoriasis, allergic disorders including asthma, inflammation, neurological disorders,

and hormone-related diseases. The term "cancer" includes, but is not limited to the following cancers: breast, ovary, cervix, prostate, testis, genitourinary tract, esophagus, larynx, glioblastoma, neuroblastoma, stomach, skin, keratoacanthoma, lung, epidermoid carcinoma, large cell carcinoma, small cell carcinoma, lung adenocarcinoma, bone, colon, adenoma, pancreas, adenocarcinoma, thyroid, follicular carcinoma, undifferentiated carcinoma, papillary carcinoma, seminoma, melanoma, sarcoma, bladder carcinoma, liver carcinoma and biliary passages, kidney carcinoma, myeloid disorders, lymphoid disorders, Hodgkin's, hairy cells, buccal cavity and pharynx (oral), lip, tongue, mouth, pharynx, small intestine, colon-rectum, large intestine, rectum, brain and central nervous system, and leukemia. ERK-2 protein kinase and its implication in various diseases has been described [Bokemeyer *et al.*, *Kidney Int.* **1996**, *49*, 1187; Anderson *et al.*, *Nature* **1990**, *343*, 651; Crews *et al.*, *Science* **1992**, *258*, 478; Bjorbaek *et al.*, *J. Biol. Chem.* **1995**, *270*, 18848; Rouse *et al.*, *Cell* **1994**, *78*, 1027; Raingeaud *et al.*, *Mol. Cell Biol.* **1996**, *16*, 1247; Chen *et al.*, *Proc. Natl. Acad. Sci. USA* **1993**, *90*, 10952; Oliver *et al.*, *Proc. Soc. Exp. Biol. Med.* **1995**, *210*, 162; Moodie *et al.*, *Science* **1993**, *260*, 1658; Frey and Mulder, *Cancer Res.* **1997**, *57*, 628; Sivaraman *et al.*, *J Clin. Invest.* **1997**, *99*, 1478; Whelchel *et al.*, *Am. J. Respir. Cell Mol. Biol.* **1997**, *16*, 589].

[00154] The term "GSK-3-mediated disease" as used herein, means any disease or other deleterious condition or disease in which GSK-3 is known to play a role. Such diseases or conditions include, without limitation, autoimmune diseases, inflammatory diseases, metabolic, neurological and neurodegenerative diseases (e.g., Alzheimer's disease, Huntington's disease, Parkinson's disease and basal ganglia movement disorders, chorea, dystonia, Wilson Disease, Pick Disease, frontal lobe degeneration, progessive supranuclear palsy (PSP), Creutzfeldt-Jakob Disease, taupathology and corticobasal degeneration (CBD)), psychotic disorders (e.g., schizophrenia, AIDS-associated dementia, depression, bipolar disorder, and anxiety disorders), cardiovascular diseases, allergy, asthma, diabetes, amyotrophic lateral sclerosis (AML, Lou Gehrig's disease), multiple sclerosis (MS), cardiomyocyte hypertrophy, reperfusion/ischemia, stroke, and baldness.

[00155] The term "ROCK-mediated condition" or "disease", as used herein, means any disease or other deleterious condition in which ROCK is known to play a role.

The term "ROCK-mediated condition" or "disease" also means those diseases or conditions that are alleviated by treatment with a ROCK inhibitor. Such conditions include, without limitation, hypertension, angina, angina pectoris, cerebrovascular contraction, asthma, peripheral circulation disorder, premature birth, cancer, erectile dysfunction, arteriosclerosis, spasm (cerebral vasospasm and coronary vasospasm), retinopathy (e.g., glaucoma), inflammatory disorders, autoimmune disorders, AIDS, osteoporosis, myocardial hypertrophy, ischemia/reperfusion-induced injury, endothelial dysfunction, Alzheimer's disease, or benign prostatic hyperplasia. In other embodiments, such conditions in which ROCK is known to play a role include, without limitation, hypertension, cerebral vasospasm, coronary vasospasm, bronchial asthma, preterm labor, erectile dysfunction, glaucoma, vascular smooth muscle cell proliferation, myocardial hypertrophy, malignoma, ischemia/reperfusion-induced injury, endothelial dysfunction, Crohn's Disease and colitis, neurite outgrowth, Raynaud's Disease, angina, Alzheimer's disease, benign prostatic hyperplasia, or atherosclerosis.

[00156] In other embodiments, the invention relates to a method of enhancing glycogen synthesis and/or lowering blood levels of glucose in a patient in need thereof, comprising administering to said patient a therapeutically effective amount of a composition comprising a compound of formula **I**. This method is especially useful for diabetic patients.

[00157] In yet another embodiment, the invention relates to a method of inhibiting the production of hyperphosphorylated Tau protein in a patient in need thereof, comprising administering to said patient a therapeutically effective amount of a composition comprising a compound of formula **I**. This method is especially useful in halting or slowing the progression of Alzheimer's disease.

[00158] In still another embodiments, the invention relates to a method of inhibiting the phosphorylation of β-catenin in a patient in need thereof, comprising administering to said patient a therapeutically effective amount of a composition comprising a compound of formula **I**. This method is especially useful for treating schizophrenia.

[00159] The term "Tec family tyrosine kinases-mediated condition", as used herein means any disease or other deleterious condition in which Tec family kinases are

known to play a role. Such conditions include, without limitation, autoimmune, inflammatory, proliferative, and hyperproliferative diseases and immunologically-mediated diseases including rejection of transplanted organs or tissues and Acquired Immunodeficiency Syndrome (AIDS).

[00160] For example, Tec family tyrosine kinases-mediated conditions include diseases of the respiratory tract including, without limitation, reversible obstructive airways diseases including asthma, such as bronchial, allergic, intrinsic, extrinsic and dust asthma, particularly chronic or inveterate asthma (e.g. late asthma airways hyper-responsiveness) and bronchitis. Additionally, Tec family tyrosine kinases diseases include, without limitation, those conditions characterised by inflammation of the nasal mucus membrane, including acute rhinitis, allergic, atrophic thinitis and chronic rhinitis including rhinitis caseosa, hypertrophic rhinitis, rhinitis purulenta, rhinitis sicca and rhinitis medicamentosa; membranous rhinitis including croupous, fibrinous and pseudomembranous rhinitis and scrofoulous rhinitis, seasonal rhinitis including rhinitis nervosa (hay fever) and vasomotor rhinitis, sarcoidosis, farmer's lung and related diseases, fibroid lung and idiopathic interstitial pneumonia.

[00161] Tec family tyrosine kinases-mediated conditions also include diseases of the bone and joints including, without limitation, (pannus formation in) rheumatoid arthritis, seronegative spondyloarthropathis (including ankylosing spondylitis, psoriatic arthritis and Reiter's disease), Behcet's disease, Sjogren's syndrome, and systernic sclerosis.

[00162] Tec family kinases-mediated conditions also include diseases and disorders of the skin, including, without limitation, psoriasis, systemic sclerosis, atopical dermatitis, contact dermatitis and other eczematous dermatitis, seborrhoetic dermatitis, Lichen planus, Pemphigus, bullous Pemphigus, epidermolysis bullosa, urticaria, angiodermas, vasculitides, erythemas, cutaneous eosinophilias, uveitis, Alopecia, areata and vernal conjunctivitis.

[00163] Tec family tyrosine kinases-mediated conditions also include diseases and disorders of the gastrointestinal tract, including, without limitation, Coeliac disease, proctitis, eosinophilic gastro-enteritis, mastocytosis, pancreatitis, Crohn's disease, ulcerative colitis, food-related allergies which have effects remote from the gut, e.g. migraine, rhinitis and eczema.

[00164] Tec family tyrosine kinases-mediated conditions also include those diseases and disorders of other tissues and systemic disease, including, without limitation, multiple sclerosis, atherosclerosis, acquired immunodeficiency syndrome (AIDS), lupus erythematosus, systemic lupus, erythematosus, Hashimoto's thyroiditis, myasthenia gravis, type I diabetes, nephrotic syndrome, eosinophilia fascitis, hyper IgE syndrome, lepromatous leprosy, sezary syndrome and idiopathic thrombocytopenia purpura, restenosis following angioplasty, tumours (for example leukemia, lymphomas), artherosclerosis, and systemic lupus erythematosus.

[00165] Tec family tyrosine kinases-mediated conditions also include allograft rejection including, without limitation, acute and chronic allograft rejection following for example transplantation of kidney, heart, liver, lung, bone marrow, skin and cornea; and chronic graft versus host disease.

[00166] It will also be appreciated that the compounds and pharmaceutically acceptable compositions of the present invention can be employed in combination therapies, that is, the compounds and pharmaceutically acceptable compositions can be administered concurrently with, prior to, or subsequent to, one or more other desired therapeutics or medical procedures. The particular combination of therapies (therapeutics or procedures) to employ in a combination regimen will take into account compatibility of the desired therapeutics and/or procedures and the desired therapeutic effect to be achieved. It will also be appreciated that the therapies employed may achieve a desired effect for the same disorder (for example, an inventive compound may be administered concurrently with another agent used to treat the same disorder), or they may achieve different effects (e.g., control of any adverse effects). As used herein, additional therapeutic agents that are normally administered to treat or prevent a particular disease, or condition, are known as "appropriate for the disease, or condition, being treated".

[00167] For example, chemotherapeutic agents or other anti-proliferative agents may be combined with the compounds of this invention to treat proliferative diseases and cancer. Examples of known chemotherapeutic agents include, but are not limited to, For example, other therapies or anticancer agents that may be used in combination with the inventive anticancer agents of the present invention include surgery, radiotherapy (in but a few examples, gamma.-radiation, neutron beam radiotherapy,

electron beam radiotherapy, proton therapy, brachytherapy, and systemic radioactive isotopes, to name a few), endocrine therapy, biologic response modifiers (interferons, interleukins, and tumor necrosis factor (TNF) to name a few), hyperthermia and cryotherapy, agents to attenuate any adverse effects (e.g., antiemetics), and other approved chemotherapeutic drugs, including, but not limited to, alkylating drugs (mechlorethamine, chlorambucil, Cyclophosphamide, Melphalan, Ifosfamide), antimetabolites (Methotrexate), purine antagonists and pyrimidine antagonists (6-Mercaptopurine, 5-Fluorouracil, Cytarabile, Gemcitabine), spindle poisons (Vinblastine, Vincristine, Vinorelbine, Paclitaxel), podophyllotoxins (Etoposide, Irinotecan, Topotecan), antibiotics (Doxorubicin, Bleomycin, Mitomycin), nitrosoureas (Carmustine, Lomustine), inorganic ions (Cisplatin, Carboplatin), enzymes (Asparaginase), and hormones (Tamoxifen, Leuprolide, Flutamide, and Megestrol), Gleevec™, adriamycin, dexamethasone, and cyclophosphamide. For a more comprehensive discussion of updated cancer therapies see, http://www.nci.nih.gov/, a list of the FDA approved oncology drugs at http://www.fda.gov/cder/cancer/druglistframe.htm, and The Merck Manual, Seventeenth Ed. 1999, the entire contents of which are hereby incorporated by reference.

[00168] Other examples of agents the inhibitors of this invention may also be combined with include, without limitation: treatments for Alzheimer's Disease such as Aricept® and Excelon®; treatments for Parkinson's Disease such as L-DOPA/carbidopa, entacapone, ropinrole, pramipexole, bromocriptine, pergolide, trihexephendyl, and amantadine; agents for treating Multiple Sclerosis (MS) such as beta interferon (e.g., Avonex® and Rebif®), Copaxone®, and mitoxantrone; treatments for asthma such as albuterol and Singulair®; agents for treating schizophrenia such as zyprexa, risperdal, seroquel, and haloperidol; anti-inflammatory agents such as corticosteroids, TNF blockers, IL-1 RA, azathioprine, cyclophosphamide, and sulfasalazine; immunomodulatory and immunosuppressive agents such as cyclosporin, tacrolimus, rapamycin, mycophenolate mofetil, interferons, corticosteroids, cyclophosphamide, azathioprine, and sulfasalazine; neurotrophic factors such as acetylcholinesterase inhibitors, MAO inhibitors, interferons, anti-convulsants, ion channel blockers, riluzole, and anti-Parkinsonian agents; agents for

treating cardiovascular disease such as beta-blockers, ACE inhibitors, diuretics, nitrates, calcium channel blockers, and statins; agents for treating liver disease such as corticosteroids, cholestyramine, interferons, and anti-viral agents; agents for treating blood disorders such as corticosteroids, anti-leukemic agents, and growth factors; and agents for treating immunodeficiency disorders such as gamma globulin.

[00169] The amount of additional therapeutic agent present in the compositions of this invention will be no more than the amount that would normally be administered in a composition comprising that therapeutic agent as the only active agent. Preferably the amount of additional therapeutic agent in the presently disclosed compositions will range from about 50% to 100% of the amount normally present in a composition comprising that agent as the only therapeutically active agent.

[00170] The compounds of this invention or pharmaceutically acceptable compositions thereof may also be incorporated into compositions for coating implantable medical devices, such as prostheses, artificial valves, vascular grafts, stents and catheters. Accordingly, the present invention, in another aspect, includes a composition for coating an implantable device comprising a compound of the present invention as described generally above, and in classes and subclasses herein, and a carrier suitable for coating said implantable device. In still another aspect, the present invention includes an implantable device coated with a composition comprising a compound of the present invention as described generally above, and in classes and subclasses herein, and a carrier suitable for coating said implantable device.

[00171] Vascular stents, for example, have been used to overcome restenosis (re-narrowing of the vessel wall after injury). However, patients using stents or other implantable devices risk clot formation or platelet activation. These unwanted effects may be prevented or mitigated by pre-coating the device with a pharmaceutically acceptable composition comprising a kinase inhibitor. Suitable coatings and the general preparation of coated implantable devices are described in US Patents 6,099,562; 5,886,026; and 5,304,121. The coatings are typically biocompatible polymeric materials such as a hydrogel polymer, polymethyldisiloxane, polycaprolactone, polyethylene glycol, polylactic acid, ethylene vinyl acetate, and mixtures thereof. The coatings may optionally be further covered by a suitable

topcoat of fluorosilicone, polysaccarides, polyethylene glycol, phospholipids or combinations thereof to impart controlled release characteristics in the composition.

[00172] Another aspect of the invention relates to inhibiting ROCK, ERK, GSK, or AGC (e.g., PKA, PDK, $p70^{S6K}$-1 and –2, and PKB) activity in a biological sample or a patient, which method comprises administering to the patient, or contacting said biological sample with a compound of formula **I** or a composition comprising said compound. The term "biological sample", as used herein, includes, without limitation, cell cultures or extracts thereof; biopsied material obtained from a mammal or extracts thereof; and blood, saliva, urine, feces, semen, tears, or other body fluids or extracts thereof.

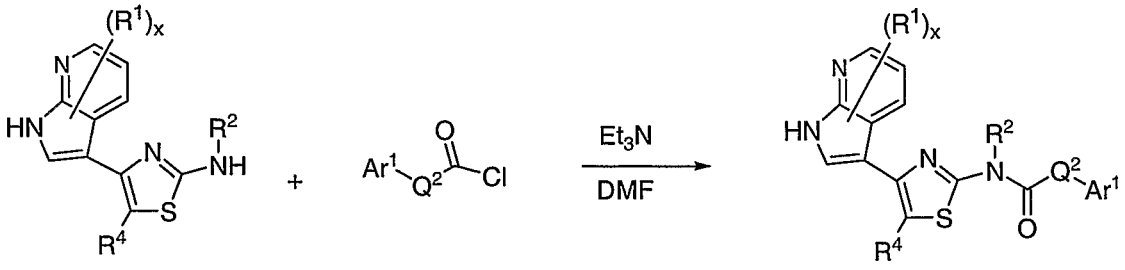
[00173] Inhibition of ROCK, ERK, GSK, or AGC (e.g., PKA, PDK, $p70^{S6K}$-1 and –2, and PKB) kinase activity in a biological sample is useful for a variety of purposes that are known to one of skill in the art. Examples of such purposes include, but are not limited to, blood transfusion, organ-transplantation, biological specimen storage, and biological assays.

EXAMPLES

[00174] GENERAL EXPERIMENTAL PROCEDURES:

[00175] As depicted in Schemes 14, 15, 16, 17, and 18 below, in certain exemplary embodiments, compounds are prepared according to the following general procedures. It will be appreciated that although the general methods depict the synthesis of compounds of general formula **VII**, the following general methods can be applied to all compounds and subclasses and species of each of these compounds, as described herein.

[00176] General Method A: Acylation of amines

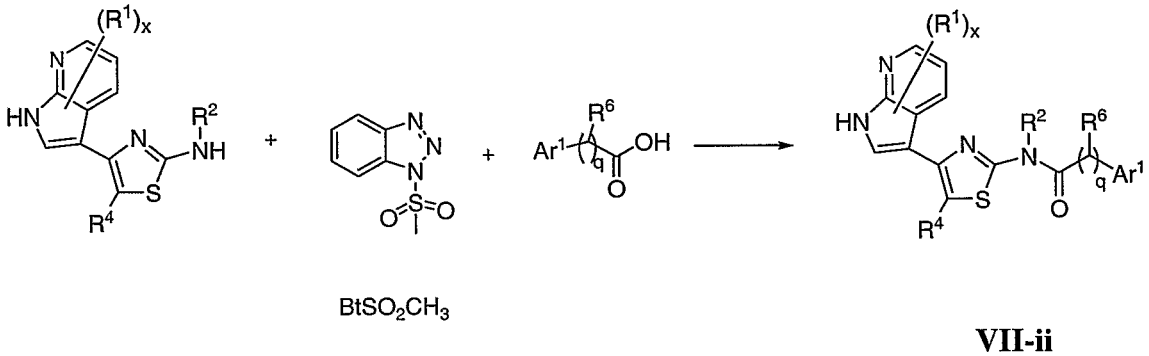


VII-i

Scheme 14

0.25 mmol of amine, and 0.5 mmol of acid chloride were dissolved in 2 mL of anhydrous DMF. 0.75 mmol of Et_3N was then added to the reaction mixture, and the mixture was stirred at RT for overnight. After completion of the reaction, EtOAc was added, the organic layer was washed with H_2O and brine, and was then dried over Na_2SO_4. Removal of the solvent gave a solid, **VII-i,** which was further purified by preparative HPLC.

[00177] General Method B: Acylation of amines



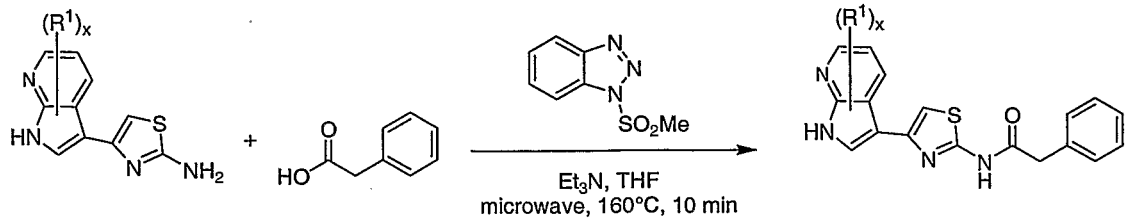
$BtSO_2CH_3$

VII-ii

Scheme 15

A mixture of $BtSO_2CH_3$ (preparation described below) (0.25 mmol), acid (0.25 mmol), and Et_3N (0.35mmol) was refluxed in dry THF for about 20 min. Amine (0.25 mmol) was then added to the reaction mixture, and the mixture was refluxed for 18 h. After the mixture was concentrated, EtOAc (5 mL) was added, and the organic phase was washed with 2 M NaOH and dried over anhydrous $MgSO_4$. Removal of the solvent gave a solid, **VII-ii,** which was purified by preparative HPLC.

[00178] General Method C: Acylation of amines



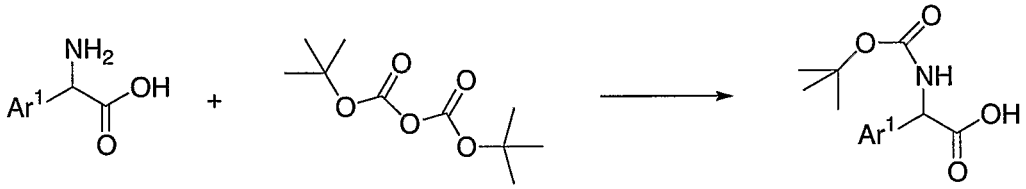
Scheme 16

[00179] Amine (1 mmol), carboxylic acid (1.2 mmol) and Bt-SO_2Me (1.2 mmol) are combined in a microwave reaction vessel. Anhydrous THF (2 mL) is added followed by triethylamine (2 mmol) and the mixture heated by microwave irradiation

at 160°C for 10 minutes. Product is isolated by precipitation following addition of acetonitrile, or by preparative HPLC.

[00180] Standard protection and deprotection of amino and hydroxyl functionalities:

[00181] General Method D: Protection of amino groups



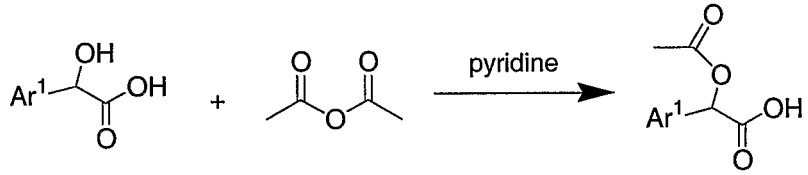
Scheme 17

[00182] 0.25 mmol of amine, 0.25 mmol of Boc anhydride were mixed in 2 mL of anhydrous CH_2Cl_2. To the reaction mixture, 0.75 mmol of Et_3N was added and the mixture was stirred at RT for overnight. The solvent was evaporated to give the Boc protected amine.

[00183] General Method E: Deprotection of Boc-protected amines

[00184] To the Boc protected amine (0.25 mmol) in a vial, 2 mL 4N HCl in dioxane was added and the reaction mixture was stirred at RT for 30 min. The solvent was evaporated to give the free amine product.

[00185] General Method F: Protection of phenols and alcohols



Scheme 18

[00186] Hydroxy acid (2.5 mol) was stirred with acetic anhydride (0.57 mL, 6 mol) in pyridine (5mL) overnight and then evaporated in vacuo. The resulting oil was partitioned between EtOAc and 1N HCl and the resulting organic layer washed successively with 1 N HCl, water and brine, dried over $MgSO_4$, and evaporated to dryness.

[00187] General Method G: Deprotection of acetylated phenols and alcohols

[00188] The acetyl-protected alcohol or phenol (0.25 mmol) was dissolved in EtOH, 0.5 mL 2N NaOH was added and the mixture was stirred at RT for 1h. The

solvent was evaporated and redissolved in DMF/CH_3CN/H_2O, and subjected to preparative HPLC for purification.

[00189] General Method H: Preparation of phenylacetic acids

[00190] Substituted benzaldehyde (5 mmol) and zinc iodide (10 mg) were dissolved or suspended in anhydrous acetonitrile (5 – 10 mL). Trimethylsilyl cyanide (12 mmol) was added dropwise and the mixture stirred at room temperature overnight. The mixture was rotary evaporated and the residue dissolved in glacial acetic acid (2 mL) and concentrated hydrochloric acid (3 mL). Tin (II) chloride dihydrate (12 mmol) was added and the mixture heated to reflux for 1 – 2 hours. To the cooled mixture was added water (20 mL) and the mixture was extracted with methylene chloride (3 x 15 mL). The extracts were washed with water (x 2) and brine and dried over $MgSO_4$. The solution is concentrated and the product precipitated by addition of hexane.

[00191] General Method I: Preparation of α-hydroxyphenylacetic acids

[00192] Substituted benzaldehyde (5 mmol) and zinc iodide (10 mg) were dissoved or suspended in anhydrous acetonitrile (5 – 10 mL). Trimethylsilyl cyanide (12 mmol) was added dropwise and the mixture stirred at room temperature overnight. The mixture was rotary evaporated and the residue dissolved in glacial acetic acid (2 mL) and concentrated hydrochloric acid (3 mL) and the mixture heated to reflux for 1 – 2 hours. To the cooled mixture was added water (20 mL) and the mixture was extracted with methylene chloride (3 x 15 mL). The extracts were washed with water (x 2) and brine and dried over $MgSO_4$. The solution is concentrated and the product precipitated by addition of hexane.

[00193] Although the preparation of certain amines are described below, it will be appreciated that a variety of alternate amines can be prepared as described generally below and can be utilized in the preparation of compounds of the invention.

[00194] EXPERIMENTAL PROCEDURES:

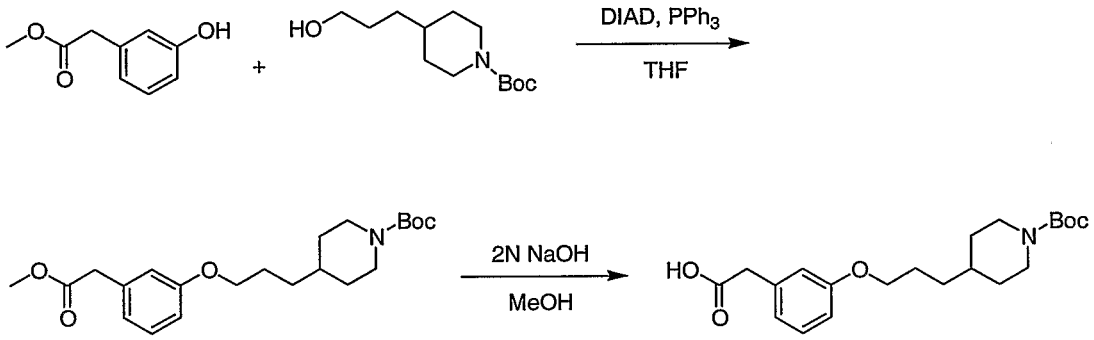
[00195] **Preparation of N-(1-Methanesulfonyl)benzotriazole ($BtSO_2CH_3$):**

[00196] To an ice-cold solution of benzotriazole (11.9g, 0.10 mol) and pyridine (12.0 g, 0.16 mol) in dry toluene (120 mL) was added methylsulfonyl chloride (9.3 mL, 0.12 mol) in toluene (30 mL) dropwise. The mixture was then stirred overnight at room temperature. EtOAc (150 mL) and H_2O (100 mL) were added, the organic layer

was separated, successively washed with water and brine, and dried over anhydrous $MgSO_4$. Removal of solvents in vacuo gave $BtSO_2CH_3$ as a white solid.

[00197] The synthesis of certain exemplary acids is described below. It will be appreciated that a variety of acids can be prepared according to the general methods described below.

[00198] Preparation of 3-(3-(N-Boc-piperidin-4-yl)-propoxy)-phenylacetic acid



Scheme 19

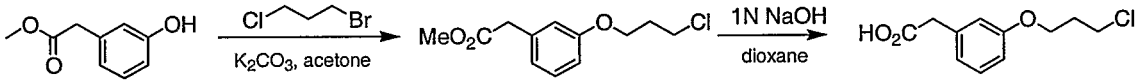
[00199] Methyl 3-hydroxyphenylacetate: 3-Hydroxyphenylacetic acid (75.3 g, 0.5 mol) was dissolved in methanol (900 mL). Concentrated sulfuric acid (2 mL) was added and the mixture refluxed for 5 hours. The solvent was evaporated and the residue dissolved in ethyl acetate (1000 mL) and washed with water (2 x 600 mL) and brine, and dried (MgSO4). Solvent was evaporated to afford methyl 3-hydroxyphenylacetate as an oil (82 g, quantitative yield). ^1H NMR (500 MHz, $CDCl_3$) δ 7.2 (1H, t), 6.9 – 6.75 (3H, m), 5.5 (1H, br), 3.75 (3H, s), 3.63 (2H, s).

[00200] Methyl 3-(3-(N-Boc-piperidin-4-yl)-propoxy)-phenylacetate: To THF solution of 0.409g (2.4 mmol) methyl 3-hydroxyphenylacetate, 0.50 g (20.5 mmol) N-Boc-piperidin-4-yl-propanol and 0.645 g (24.6 mmol) triphenylphosphine was added diisopropyl azodicarboxylate at 0 ^0C slowly, then the ice bath was removed and the reaction mixture was stirred at room temperature overnight. The solvent was removed by rotary evaporation, the residue was dissolved in 2 mL methylene chloride and was loaded on a silica gel column and, the product eluted with 80% hexane and 20% ethyl acetate. Methyl 3-(3-(N-Boc-piperidin-4-yl)-propoxy)-phenylacetate (0.5 g, 62%) was obtained. ^1H NMR (500 MHz, $CDCl_3$) δ 1.1 (m, 2H),

1.4 (m, 2H), 1.46 (s, 9H), 1.66 (d, 2H), 1.7 8(m, 2H), 2.67 (t, 2H), 3.58 (s, 2H), 3.68 (s, 3H), 4.05 (m, 2H), 6.75 (m, 3H), 7.18 (dd, 1H).

[00201] 3-(3-(N-Boc-piperidin-4-yl)-propoxy)-phenylacetic acid: Methyl 3-(3-(N-Boc-piperidin-4-yl)-propoxy)-phenylacetate (0.5 g, 1.3 mmol) was dissolved in methanol, and 2N NaoH (3 mL) added. The reaction was stirred at 60 ^{0}C for 2h, then the solution was adjusted to pH 6.5, the product was extracted into ethyl acetate and the organic phase was dried by $MgSO_4$. Removal of solvent revealed 3-(3-(N-Boc-piperidin-4-yl)-propoxy)-phenylacetic acid (0.30 g). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.02 (m, 2H), 1.25 (m, 2H), 1.55 (m, 2H), 1.65 (m, 2H), 2.57 (m, 2H), 3.33 (m, 1H), 3.75 (s, 2H), 3.95 (m, 2H), 6.63 (m, 3H), 6.98 (m, 1H).

[00202] Preparation of 3-(3-chloro-propoxy)-phenylacetic acid

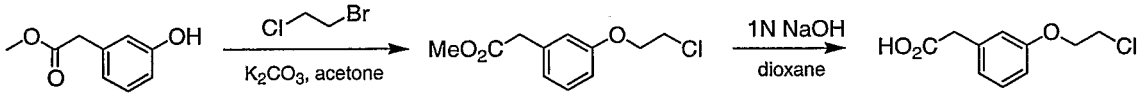


Scheme 20

[00203] Methyl 3-(3-chloro-propoxy)-phenylacetate: Methyl 3-hydroxyphenylacetate (87 g, 0.52 mol) was dissolved in acetone (500 mL). 1-Bromo-3-chloropropane (55 mL, 0.56 mol) was added, followed by potassium carbonate (73 g, 0.53 mol) and acetone (100 mL). The reaction was heated to reflux. After 24 hours, more 1-bromo-3-chloropropane (5 mL, 50 mmol) was added and the reaction refluxed for a further 24 hours. The mixture was cooled, filtered and rotary evaporated. The product was purified by passage over a short column of silica gel (650 g: 135 mm diameter column) eluted with hexane, and 30% ethyl acetate in hexane, to afford methyl 3-(3-chloro-propoxy)-phenylacetate (120g, 95%) as an oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (1H, dd), 6.93 – 6.85 (3H, m), 4.16 (2H, t), 3.79 (2H, t), 3.73 (3H, s), 3.62 (2H, s), 2.28 (2H, m).

[00204] 3-(3-Chloro-propoxy)-phenylacetic acid: Methyl 3-(3-chloro-propoxy)-phenylacetate (12.7 g, 52.3 mmol) was dissolved in dioxane (25 mL) and 1N NaOH (53 mL) was added. The mixture was stirred at room temperature for 45 minutes then acidified by addition of 1N hydrochloric acid (60 mL). A white precipitae formed which was filtered, washed with 1N HCl, water and dried. 3-(3-Chloro-propoxy)-phenylacetic acid (11.7 g, 98 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (1H, dd), 6.93 – 6.85 (3H, m), 4.11 (2H, t), 3.79 (2H, t), 3.70 (2H, s), 2.25 (2H, m).

[00205] Preparation of 3-(2-chloro-ethoxy)-phenylacetic acid



Scheme 21

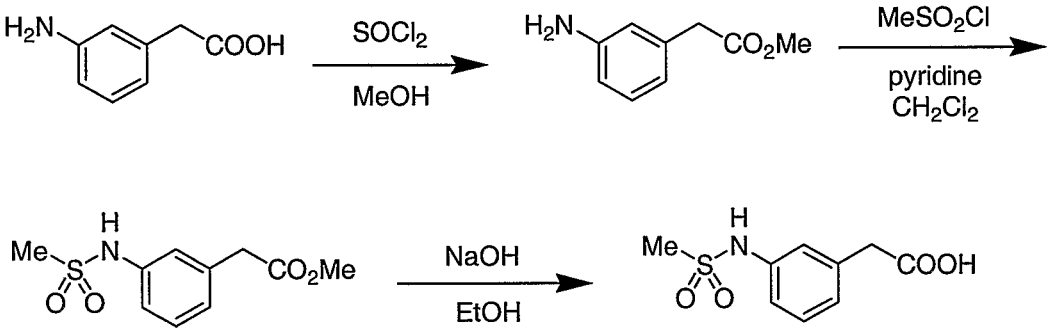
[00206] Methyl 3-(2-chloroethoxy)-phenylacetate: Methyl 3-hydroxyphenylacetate (10.8 g, 65 mmol) was dissolved in acetone (120 mL). 1-Bromo-2-chloroethane (5.5 mL, 66 mmol) was added, followed by potassium carbonate (10.1 g, 73.6 mmol). The reaction was heated to reflux. After 24 hours, more 1-bromo-2-chloroethane (11 mL, 132 mmol) was added and the reaction refluxed for a further 24 hours. The mixture was cooled, filtered and rotary evaporated. The product was purified by passage over a short column of silica gel eluted with hexane, and 30% ethyl acetate in hexane, to afford methyl 3-(3-chloroethoxy)-phenylacetate as an oil.

[00207] 3-(2-Chloroethoxy)-phenylacetic acid: Methyl 3-(2-chloro-ethoxy)-phenylacetate (7.0 g, 32.9 mmol) was dissolved in methanol (40 mL) and 6N NaOH (5.5 mL) was added. The mixture was stirred at room temperature overnight then acidified by addition of 6N hydrochloric acid (5.5 mL). A white precipitae formed which was filtered, washed with 1N HCl, water and dried. 3-(3-Chloroethoxy)-phenylacetic acid (6.5 g, 99 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ3.55 (s, 2H), 3.75 (t, 2H), 4.15 (t, 2H), 6.78 (dd, 1H), 6.80 (d, 1H), 6.84 (dd, 1H), 7.16 (dd, 1H).

[00208] Preparation of 3-Ethoxyphenylacetic acid

[00209] Methyl 3-ethoxyphenylacetate: Methyl 3-hydroxyphenylacetate (6.4 g, 38.5 mmol) was dissolved in acetone (50 mL). Ethyl bromide (3.5 mL, 46.9 mmol) was added, followed by potassium carbonate (6.37 g, 46 mmol). The reaction was heated to reflux. After 24 hours, more ethyl bromide (3.55 mL, 46.9 mmol) was added and the reaction refluxed for a further 24 hours. The mixture was cooled, filtered and rotary evaporated. The product was dissolved in ethyl acetate and the solution washed with saturated sodium bicarbonate (2 x 50 mL) and brine, and dried (MgSO4). Removal of solvent revealed methyl 3-ethoxyphenylacetate as an oil that crystallized upon standing. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (1H, dd), 6.87 (3H, m), 4.08 (2H, q), 3.73 (3H, s), 3.65 (2H, s), 1.45 (3H, t).

[00210] **3-Ethoxyphenylacetic acid**: Methyl 3-ethoxyphenylacetate (7.5 g, 38.6 mmol) was dissolved in ethanol (15 mL) and 1N NaOH (40 mL) was added. The mixture was stirred at room temperature for 30 minutes then acidified by addition of 1N hydrochloric acid (45 mL). A white precipitate formed which was filtered, washed with 1N HCl, water and dried. 3-Ethoxyphenylacetic acid (6.4 g, 92 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20 (1H, dd), 6.8 (3H, m), 4.0 (2H, q), 3.6 (2H, s), 1.4 (3H, t).



Scheme 22

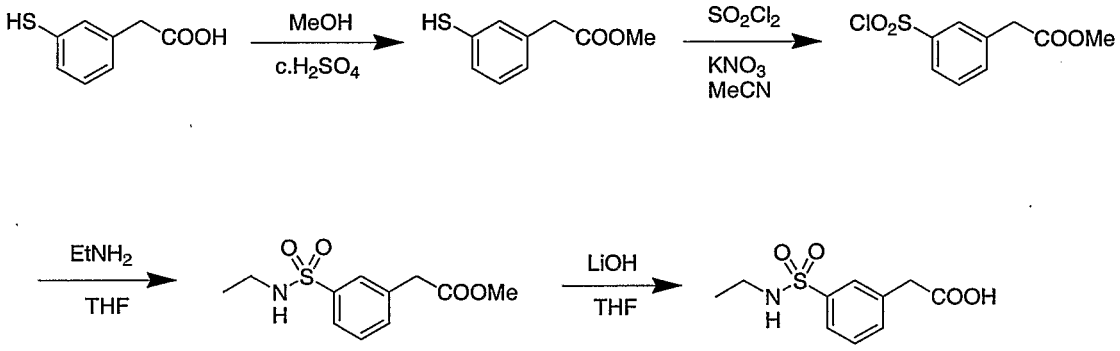
[00211] **Preparation of 3-(Methanesulfonylamino)-phenylacetic acid**

[00212] **Methyl 3-aminophenylacetate**: 3-Aminophenylacetic acid (15.5 g, 0.10 mol) was suspended in methanol (150 mL) and cooled to 0 °C. Thionyl chloride (11.2 mL, 0.15 mol) was added dropwise under stirring. A clear orange solution was obtained, which was stirred for 4 hours, then evaporated. The solid residue was partitioned between ethyl acetate (150 mL) and saturated sodium bicarbonate (150 mL) and the organic phase washed with saturated sodium bicarbonate (100 mL), and brine and dried (Na_2SO_4). Methyl 3-aminophenylacetate was isolated as a brown oil. (14.1g, 83%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.12 (1H, dd), 6.7 – 6.6 (3H, m), 3.71 (3H, s), 3.55 (2H, s).

[00213] **Methyl (3-Methanesulfonylamino-phenyl)-acetate**: Methyl 3-aminophenylacetate (2.26 g, 13.7 mmol) was dissolved in dry methylene chloride (20 mL) and cooled to 0 °C. Pyridine (2.2 mL, 27.2 mmol) was added followed by dropwise addition of methanesulfonyl chloride (1.3 mL, 16.8 mmol). The mixture was stirred at 0 °Ç for 1 hour and at room temperature for 3 hours, then poured into 100 mL of saturated sodium bicarbonate solution. The organic layer was washed with saturated sodium bicarbonate (100 mL), 1N HCl (2 x 100 mL) and brine. Dried over $MgSO_4$. Solvent was evaporated to reveal methyl 3-(methanesulfonyl)phenylacetate.

(3.36 g, 100%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (1H, dd), 7.2 – 7.1 (3H, m), 6.57 (1H, s), 3.72 (3H, s), 3.64 (2H, s), 3.02 (3H, s).

[00214] 3-(Methanesulfonylamino)-phenylacetic acid: Methyl 3-(methanesulfonylamino)-phenylacetate (3.36 g, 13.8 mmol) was dissolved in ethanol (16 mL) and 1N NaOH (30 mL) added. The reaction was stirred for 1 hour, then 1N HCl (50 mL) and water (50 mL) were added. The product was extracted into ethyl acetate (3 x 50 mL) and the combined extracts were washed with water and brine and dried ($MgSO_4$). Removal of solvent afforded 3-(methanesulfonyl)phenylacetic acid (2.90 g, 92%). ^{1}H NMR (500 MHz, DMSO-d6) □ 12.32 (1H, br), 9.69 (1H, br), 7.26 (1H, dd), 7.10 (2H, m), 7.00 (1H, d), 6.57 (1H, s), 3.54 (2H, s), 2.97 (3H, s).



Scheme XX

[00215] Preparation of 2-(3-ethylsulfonamidophenyl)-N-(4-(pyridin-4-yl)thiazol-2-yl) acetamide

[00216] Methyl 2-(3-mercaptophenyl)acetate: 2-(3-mercaptophenyl)acetic acid (1.0 g, 6.0 mmol) was dissolved in dry methanol (40 mL). To this solution 10 drops concentrated sulfuric acid was added and the reaction mixture was heated to reflux for 36 hours. The reaction mixture was then concentrated to about half the volume, diluted with ethyl acetate, and the organic layer washed with saturated sodium bicarbonate solution, then dried over sodium sulfate and concentrated to an oil, 0.55 g, 3.0 mmol, 50 % yield. 1H NMR 500 MHz (CDCl3) 7.05 ppm, 3H, m; 6.88 ppm, 1H, m; 3.53 ppm, 3H, s; 3.38 ppm, 2H, s.

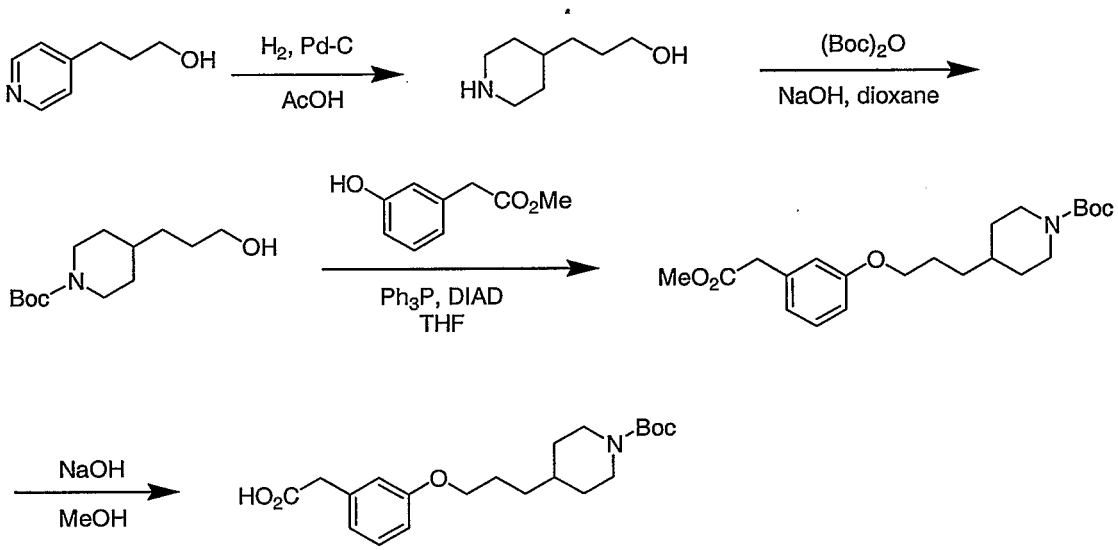
[00217] Methyl 2-(3-chlorosulfonylphenyl)acetate: Methyl 2-(3-mercaptophenyl)acetate (0.55 g, 3.0 mmol) was dissolved in 10 mL acetonitrile and potassium nitrate (0.76 g, 7.5 mmol) was added and the reaction mixture cooled to 0 ° C. To this suspension sulfuryl chloride was added (0.6 mL, 7.5 mmol) at 0 ° C and

the reaction mixture was let warm to room temperature and stirred overnight. A solution of saturated sodium bicarbonate was added followed by ethyl acetate (100 mL each). The organic layer was washed with brine, dried over sodium sulfate and concentrated to an oil 0.59 g, 2.4 mmol, 79% yield. 1H NMR 500 MHz (CDCl3) 7.91 ppm, 2H, m; 7.60 ppm, 1H, d; 7.53 ppm, 1H, t; 3.73 ppm, 2H, s; 3.72 ppm, 3H, s.

[00218] (3-Ethylsulfamoyl-phenyl)-acetic acid methyl ester: Methyl 2-(3-chlorosulfonyl-phenyl)acetate (0.29g, 1.17 mmol) was dissolved in THF (10 mL) and to this solution 1 mL (2mmol) of 2M ethylamine in THF was added. Let stir at room temperature 30 minutes, diluted with ethyl acetate and the organic layer was washed with 10 % citric acid, brine, dried over sodium sulfate and concentrated to an oil. 0.28 g, 1.09 mmol, 93% yield. 1H NMR 500 MHz (CDCl3) 7.72 ppm, 2H, m; 7.41 ppm, 2H, m; 4.32 ppm, 1H, t; 3.68 ppm, 3H, s; 3.67 ppm, 2H, s; 2.98 ppm, 2H, m; 1.07 ppm, 3H, t.

[00219] (3-Ethylsulfamoyl-phenyl)-acetic acid: (3-Ethylsulfamoyl-phenyl)-acetic acid methyl ester (0.28 g, 1.1 mmol) was dissolved in THF and LiOH hydrate (63 mg, 1.5 mmol) in water was added. The reaction mixture was stirred at room temperature for 4 hours and then diluted with ethyl acetate and 10% citric acid. The organic layer was washed with brine, dried over sodium sulfate, and concentrated to a solid. 0.25 g, 1.1 mmol 99% yield. 1H NMR 500 MHz (DMSO) 7.71 ppm, 1H, s; 7.70 ppm, 1H, m; 7.50 ppm, 3H, m; 4.11 ppm, 1H, br s; 3.70 ppm, 2H, s; 2.81 ppm, 2H, m; 0.99 ppm, 3H, t.

[00220] Preparation of 3-(3-(N-Boc-piperidin-4-yl)-propoxy)-phenylacetic acid



Scheme 23

[00221] **3-Piperidin-4-yl-propan-1-ol**: 4-Pyridinepropanol (10.0 g, 73 mmol) was dissolved in glacial acetic acid (50 mL). 10% Palladium on carbon (1.1 g) was added and the mixture hydrogenated under 50 psi hydrogen gas for 6 days. The mixture was filtered through Celite and the solvent removed by rotary evaporation. The crude product 3-piperidin-4-yl-propan-1-ol (acetic acid salt) was used as obtained. ^{1}H NMR (500 MHz, $CDCl_3$) □ 6.3 (br), 3.65 (2H, t), 3.36 (2H, m), 2.79 (2H, dt), 2.01 (3H, s), 1.85 (2H, m), 1.7 – 1.3 (7H, m).

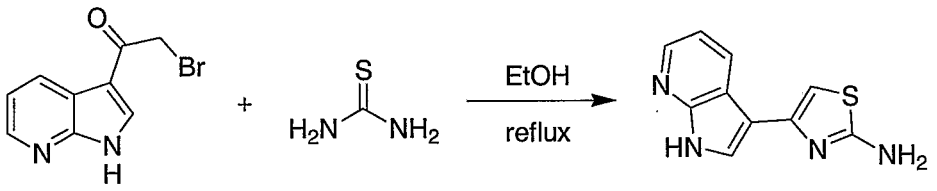
[00222] **3-(N-Boc-Piperidin-4-yl)-propan-1-ol**: The crude 3-piperidin-4-yl-propan-1-ol (73 mmol) was dissolved in dioxane (100 mL) and 3N NaOH (25 mL) was added to give a pH9 solution. Di-tert-butyl dicarbonate (16.0 g, 73 mmol) in dioxane (35 mL) was added dropwise, with simultaneous addition of 3N NaOH to maintain the solution at approximately pH9. After 2 hours no residual amine was visible by TLC (ninhydrin stain) and the reaction was diluted with water (200 mL)and extracted with ethyl acetate (3 x 100 mL). The combined extracts were washed with water and brine and dried ($MgSO_4$). Removal of solvent afforded 20 g crude product which was purified by silica gel chromatography (200 g silica) in a sintered glass funnel (L.M. Harwood, Aldrichimica Acta, 1985, 18, 25) eluted with 500 mL each of hexane, 20%, 40%, 60% and 80% ethyl acetate in hexane. 3-(N-Boc-Piperidin-4-yl)-propan-1-ol was isolated as a clear, colorless oil (14.5 g, 82%). ^{1}H NMR (500 MHz, $CDCl_3$) □ 4.09 (2H, m), 3.66 (2H, t), 2.69 (2H, dt), 1.7-1.5 (4H, m), 1.47 (9H, s), 1.4 - 1.3 (5H, m), 1.12 (2H, m).

[00223] **Methyl 3-(3-(N-Boc-piperidin-4-yl)-propoxy)-phenylacetate**: To a solution of methyl 3-hydroxyphenylacetate (0.409 g, 2.4 mmol), 3-(N-Boc-piperidin-4-yl)-propan-1-ol (0.50 g, 20.5 mmol) and triphenylphosphine (0.645, 24.6 mmol) in THF, was added diisopropyl azodicarboxylate at 0 °C slowly, then the ice bath was removed and the reaction mixture was stirred at room temperature overnight. The solvent was removed and the residue was dissolved in methylene chloride (2 mL) and loaded on a silica gel column. The product was eluted with 20% ethyl acetate in hexane, to afford methyl 3-(3-(N-Boc-piperidin-4-yl)-propoxy)-phenylacetate (0.5 g, 62%). ^{1}H NMR (500 MHz, $CDCl_3$) □1.1 (m, 2H), 1.4 (m, 2H), 1.46 (s, 9H), 1.66 (d, 2H), 1.78 (m, 2H), 2.67 (t, 2H), 3.58 (s, 2H), 3.68 (s, 3H), 4.05 (m, 2H), 6.75 (m, 3H), 7.18 (dd, 1H).

3-(3-(N-Boc-piperidin-4-yl)-propoxy)-phenylacetic acid: Methyl 3-(3-(N-Boc-piperidin-4-yl)-propoxy)-phenylacetate (0.5 g, 1.3 mmol) was dissolved in methanol and 2N NaOH (3 mL) added. The reaction was stirred at 60 °C for 2 hours then the solution was adjusted to pH 6.5. The product was extracted into ethyl acetate, and the organic phase was dried by $MgSO_4$. The solvent was evaporated to afford 3-(3-(N-Boc-piperidin-4-yl)-propoxy)-phenylacetic acid (0.30 g). ^{1}H NMR (500 MHz, $CDCl_3$) □ 1.02 (m, 2H), 1.25 (m, 2H), 1.55 (m, 2H), 1.65 (m, 2H), 2.57 (m, 2H), 3.33 (m, 1H), 3.75 (s, 2H), 3.95 (m, 2H), 6.63 (m, 3H), 6.98 (m, 1H).

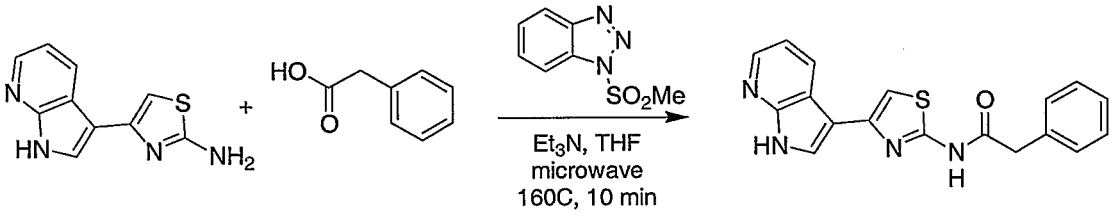
[00224] The synthesis of certain exemplary amines (described generally above in Schemes 1-13) are described more specifically below. It will be appreciated that a variety of alternate amines can be prepared according to methods known in the art and can be utilized in the preparation of compounds of the invention. Additionally, although certain exemplary acids are described in more detail below and in Schemes 14-23, it will be appreciated that a variety of alternate acids can be prepared according to methods known in the art and can be utilized in the preparation of compounds of the invention.

[00225] **4-(1*H*-Pyrrolo[2,3-*b*]pyridin-3-yl)-thiazol-2-ylamine; hydrobromide (A):**



A

[00226] A mixture of 2-Bromo-1-(1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-ethanone (prepared according to Galvez C. et al, *J. Het. Chem.* **21**, 1984, p421-423) (2.2 g, 10.5 mmol) and thiourea (0.8 g, 10.5 mmol) was heated in ethanol (60mL), at reflux for 4 hours. The reaction mixture was cooled to 0°C with and ice-water bath, then the solids were filtered and dried to give 5-pyridin-4-yl-[1,3,4]thiadiazol-2-ylamine as a tan solid. (2.5 g, 83%). ^{1}H NMR DMSO: 12.234 (s,1H), 8.92 (bs,2H), 8.34 (m,2H), 8.10 (s,1H), 7.26 (m, 1H,), 7.08 (s,1H)

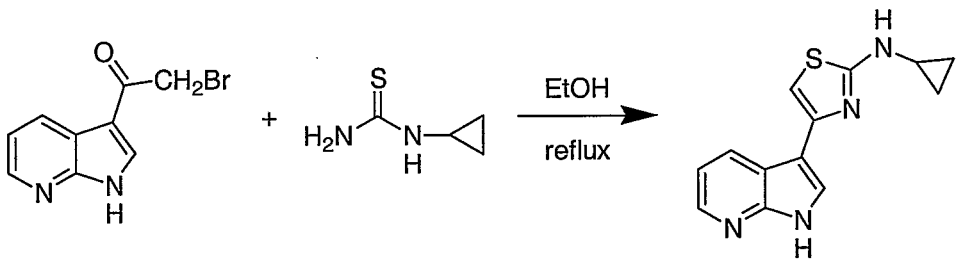


B

Scheme 24

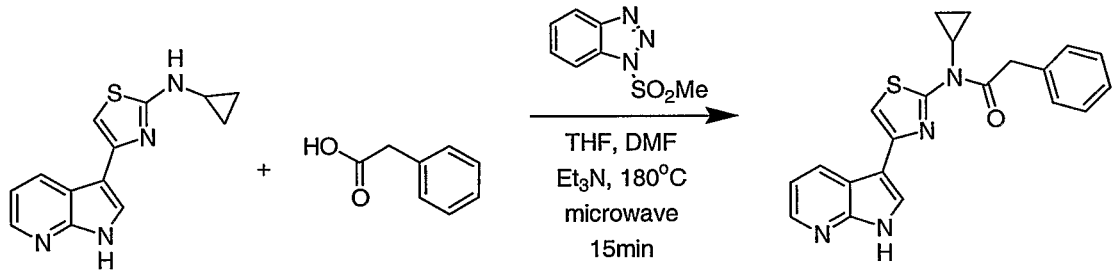
[00227] **2-Phenyl-*N*-[4-(1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-thiazol-2-yl]-acetamide (B):** 4-(1*H*-Pyrrolo[2,3-*b*]pyridin-3-yl)-thiazol-2-ylamine (216 mg, 1.0 mmol), phenylacetic acid (150 mg, 1.10 mmol) and N-(1-methanesulfonyl)benzotriazole (220 mg, 1.10 mmol) were placed in a microwave reaction vessel (Personal Chemistry, Uppsala, Sweden). THF (2 mL) was added followed by triethylamine (0.5 mL, 3.59 mmol) and the mixture heated in the sealed tube at 160 °C for 10 minutes. Upon cooling to room temperature the reaction was concentrated to 1mL, and then acetonitrile was added (4mL) and the product 2-Phenyl-*N*-[4-(1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-thiazol-2-yl]-acetamide precipitated, was filtered, washed with acetonitrile and dried. (150 mg, 45%). ^{1}H NMR (500 MHz, DMSO-d6) □ 12.39 (1H, s), 11.83 (s,1H), 8.50 (1H, d, J=7.91Hz), 8.27 (m,1H), 7.84 (1H, d, J=2.48Hz), 7.36-7.15 (7H, m), 3.81 (2H, s). LC-MS Rt = 2.8 min, $[M+H]^+$ = 335.0, $[M-H]^-$ = 333.1.

[00228] **Cyclopropyl-[4-(1H-pyrrolo[2,3-b]pyridin-3-yl)-thiazol-2-yl]-amine**



[00229] A mixture of 2-Bromo-1-(1H-pyrrolo[2,3-b]pyridin-3-yl)-ethanone (prepared according to Galvez C. et al, J. Het. Chem. 21, 1984, p421-423) (0.90 g, 3.76 mmol) and cyclopropyl-thiourea (prepared according to Marletta, M. et al, J. Med. Chem. 35, 1992, p1137-1144) (0.46 g, 3.96 mmol) was heated in ethanol (20mL), at reflux for 4 hours. The reaction mixture was cooled to 0°C with and ice-water bath, then the solids were filtered and dried to give cyclopropyl-[4-(1H-pyrrolo[2,3-b]pyridin-3-yl)-thiazol-2-yl]-amine as a tan solid (1.2 g, 92%). LC/MS MH+ = 257.02, LC/MS RT: 1.62min. 1H NMR (500MHz, DMSO-d6, ppm) 12.22 (s,1H), 9.20 (bs,1H), 8.42 (d,1H, J=7.82Hz), 8.36 (dd,1H, J=4.81, 1.22Hz), 8.00 (s,1H), 7.25 (m,1H), 6.12 (s,1H), 2.77 (t, 1H,J=4.75), 0.86 (m,2H), 0.71 (m,2H).

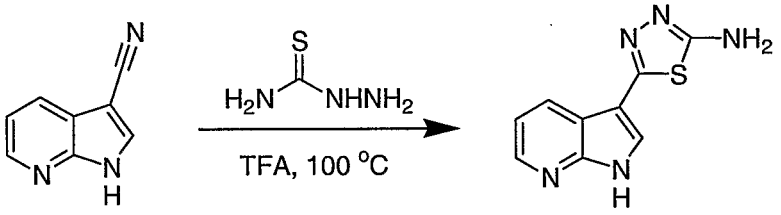
[00230] N-Cyclopropyl-2-phenyl-N-[4-(1H-pyrrolo[2,3-b]pyridin-3-yl)-thiazol-2-yl]-acetamide



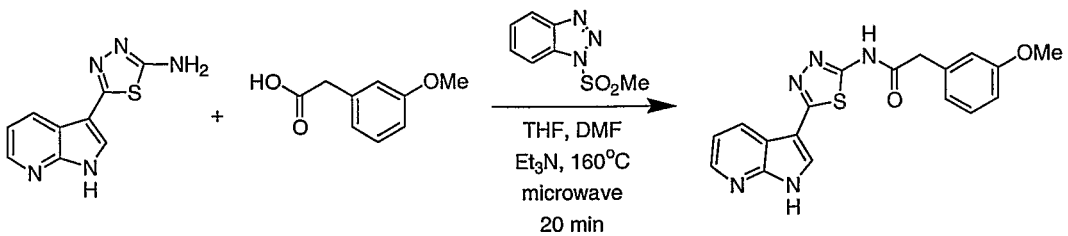
[00231] Cyclopropyl-[4-(1H-pyrrolo[2,3-b]pyridin-3-yl)-thiazol-2-yl]-amine (50 mg, 0.39 mmol), phenylacetic acid (63 mg, 0.47 mmol) and N-(1-methanesulfonyl)benzotriazole (93 mg, 0.47 mmol) were placed in a microwave reaction vessel (Personal Chemistry, Uppsala, Sweden). 5% DMF-THF (4 mL) was added followed by triethylamine (0.163 mL, 1.17 mmol) and the mixture heated in the sealed tube at 180 °C for 15 minutes. Upon cooling to room temperature the reaction was concentrated and then purified by prepartative TLC (thin layer chromatography) and eluted with ethylacetate and hexane (3:1). Extraction of the silica gel with 5%MeOH-EtOAc was carried out to give product (15 mg, 10%). Alternatively, Cyclopropyl-[4-(1H-pyrrolo[2,3-b]pyridin-3-yl)-thiazol-2-yl]-amine (50 mg, 0.39

mmol), phenylacetic acid (63 mg, 0.47 mmol) and fluoro-N,N',N',N'-tetramethylformamidiniun hexafluorophosphate (148 mg, 0.59 mmol) were placed in a microwave reaction vessel (Personal Chemistry, Uppsala, Sweden). 5% DMF-THF (4 mL) was added followed by triethylamine (0.163 mL, 1.17 mmol) and the mixture heated in the sealed tube at 180 °C for 15 minutes. Upon cooling to room temperature the reaction was concentrated and then purified by prepartative TLC (thin layer chromatography) and eluted with ethylacetate and hexane (3:1). Extraction of the silica gel with 5%MeOH-EtOAc was carried out to give product (18 mg, 12%). The material was isolated as an HCl salt. LC/MS MH+ = 375.2, LC/MS RT: 3.39min. 1H NMR (500MHz, DMSO-d6, ppm) 11.92 (s,1H), 8.63 (d,1H, J=7.88Hz), 8.29 (dd,1H, J=4.71, 1.49Hz), 8.96 (d,J=2.58,1H), 7.44 (s,1H), 7.36-7.19 (m,6H), 4.27 (s,2H), 3.29 (t, 1H,J=3.78), 1.33 (m,2H), 1.06 (m,2H).

[00232] 5-(1H-pyrrolo[2,3-*b*]pyridin-3-yl)-1,3,4-thiadiazol-2-amine



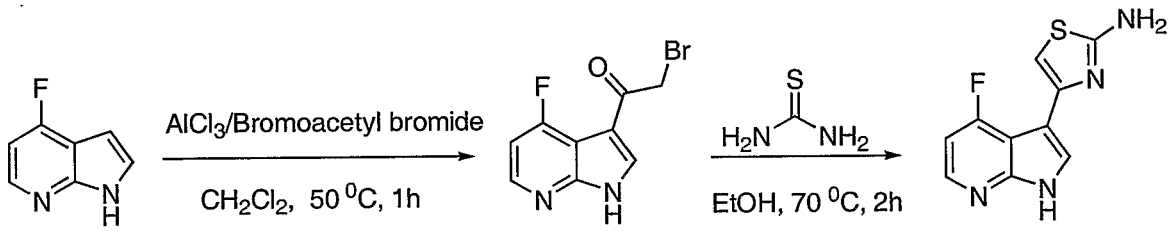
[00233] A mixture of 3-cyano-7-azaindole (prepared as described in Org. Proc. Res. Dev. **2003**, *7*, 209) (1.0 g,7 mmol) and thiosemicarbazide (2.34 g, 21 mmol) in trifluoroacetic acid (25 mL) was heated in a sealed tube at 100^{0}C for 2 hr. The brown solution was cooled to room temperature and poured into ice. The mixture was then basified with c.NH_4OH and the pale brown precipitate formed was filtered on a sintered glass filter. The solid was washed thoroughly with water (3 x 50 mL) and ethyl acetate (3 x 50 mL) and dried under vacuum to afford 5-(1H-pyrrolo[2,3-*b*]pyridin-3-yl)-1,3,4-thiadiazol-2-amine (1.3 g, 85%) as a gray solid.; Mass Spec FIA MS 218 (M+1). ^{1}H NMR (DMSO-d6, 500 MHz) δ 12.11 (s, 1H), 8.43 (dd, 1H), 8.31 (dd, 1H), 7.96 (d,1H), 7.19 (m, 1H), 7.14 (br s, 2H).



[00234] N-(5-(1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-1,3,4-thiadiazol-2-yl)2-(3-methoxyphenyl)-acetamide

[00235] A suspension of 5-(1H-pyrrolo[2,3-*b*]pyridin-3-yl)-1,3,4-thiadiazol-2-amine (0.050 g, 0.23 mmol), 3-methoxyphenylacetic acid (0.038 g, 0.23 mml), triethylamine (0.1 mL) and $BtSO_2CH_3$ (0.055 g, 0.28 mml) in THF (3 mL) and DMF (0.3 mL) was heated in a microwave oven for 20 min. The brown solution was added to water (50 mL) and ethyl acetate (50 mL). Brine (10 ml) was added to separate the layers. The organic phase was separated and washed with water (2 x 50 mL). The organic layer was concentrated to give a solid which was placed in a small Buchner funnel and washed with methanol (2 x 5 mL) and ethyl acetate (2 x 5 mL). The brown solid collected was dried under vacuum to afford the desired product (0.018 g, 21%).

[00236] 4-(4-Fluoro-1H-pyrrolo[2,3-b]pyridin-3-yl)-thiazol-2-ylamine



[00237] 2-Bromo-1-(4-fluoro-1H-pyrrolo[2,3-b]pyridin-3-yl)-ethanone:

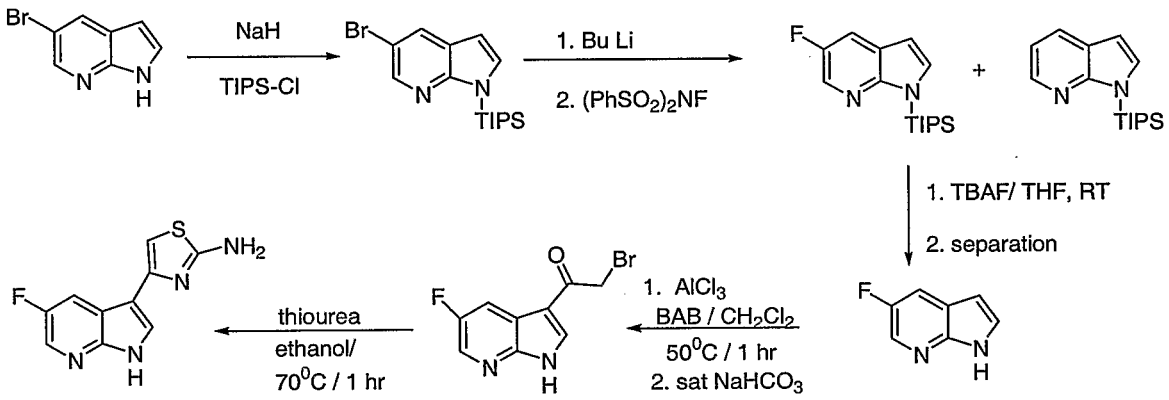
To a solution of 4-fluoro-1*H*-pyrrolo[2,3-*b*]pyridine (2.00 g, 0.0147 mol) (*Org. Lett.*, **2003**, *5*, 5023-5025) in dichloromethane was added aluminum chloride (3.92g, 0.0294mol) in portions, the mixture was stirred at RT for 30 min, then bromoacetyl bromide (4.45g, 0.022 mol) was added dropwise. The reaction mixture was stirred at 50 ^{0}C for 1h, when TLC indicated no starting material. To the reaction mixture was added 150 mL water, and the resulting suspension was heated at 100 ^{0}C for 1h, then filtered to afford the desired product, 90% pure. H NMR, DMSO-d6: 4.72(s, 2H), 7.12(m, 1H), 8.36(m, 1H), 8.67(s, 1H).

[00238] 4-(4-Fluoro-1H-pyrrolo[2,3-b]pyridin-3-yl)-thiazol-2-ylamine

To an ethanol suspension of 2-bromo-1-(4-fluoro-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-ethanone (3.00 g 0.0117 mol) was added thiourea (1.18 g, 0.0234 mol), the reaction mixture was heated at 70 ^{0}C for 1h. The suspension was filtered while still warm and to the filtration cake was added sat. sodium carbonate solution until the aqueous phase pH was around 7.5. The suspension was filtered to afford 1.8 g free base (75%). H

NMR, DMSO-d6: 6.78 (s, 1H), 6.9 (s, br, 2H), 6.98 (m, 1H), 7.71 (s, 1H), 8.25 (m, 1H).

[00239] Preparation of 4-(5-Fluoro-1H-pyrrolo[2,3-b]pyridin-3-yl)-thiazol-2-ylamine



[00240] 5-Bromo-1-(triisopropylsilyl)-1*H*-pyrrolo[2,3-*b*]pyridine:

Sodium hydride (0.63 g, 25.15 mol) was added in small portion to a stirred solution of 5-bromo-7-azaindole (3.3 g, 16.75 mmmol) in THF (50 mL) at room temperature and the resulting suspension was stirred at room temperature for 15 min. Triisopropylsilyl chloride (5.3 mL, 25.15 mmol) was added and the mixture was heated at 80 ^{0}C for 3h. The solvent was evaporated and the residue was dissolved in water (50 mL). The aqueous layer was extracted with EtOAc (3X50 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by Biotage HPFC system (10% EtOAc/Hexane) to afford the desired 5-bromo-1-(triisopropylsilyl)-1*H*-pyrrolo[2,3-*b*]pyridine as a white solid (5.2g, 88%).; Mass Spec 355 (M+1).

[00241] 5-Fluoro-1-(triisopropylsilyl)-1*H*-pyrrolo[2,3-*b*]pyridine:

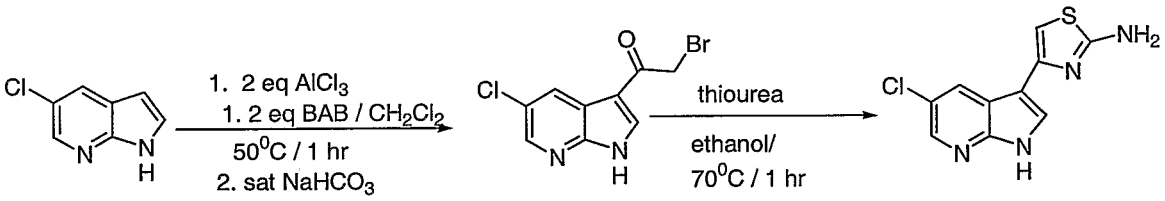
2.5M Butyl lithium (4.4 mL, 10.8 mmol) was added dropwise to a stirred solution of 5-bromo-1-(triisopropylsilyl)-1*H*-pyrrolo[2,3-*b*]pyridine (2.55 g, 7.23 mmol) in THF (65 mL) over 10 min at –78^{0}C under nitrogen in three necked flask. The resulting solution was stirred at –78 ^{0}C for 1h and solid N –fluorobenzenesulfonimide (2.84 g, 9.03 mmol) was added in one portion and stirred at –78 ^{0}C for 2 h. The solvent was evaporated and the crude material was dissolved in water (50 mL) and extracted with EtOAc (3x25 mL). The organic extract was dried and concentrated under reduced pressure to give a residue which was suspended in hexane (5 mL) and filtered. The

filtrate was chromatographed (Biotage HPFC) on silica gel eluting with hexane to give 5-fluoro-1-(triisopropylsilyl)-1*H*-pyrrolo[2,3-*b*]pyridine (1.06 g, 50.2%) as a viscous oil.; Mass Spec.; MS 293 (M+1); ^{1}H NMR(CDCl3,500 MHz) 8.11(d,1H), 7.51(dd,1H), 7.34(d,1H), 6.50(d,1H), 1.84(q,3H), 1.10(d,18H).

[00242] 4-(5-Fluoro-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)thiazol-2-amine: Tetrabutylamonium fluoride, 1M in THF (2 mL), was added to a stirred solution of 5-fluoro-1-(triisopropylsilyl)-1*H*-pyrrolo[2,3-*b*]pyridine (1 g, 3.94 mmol) in THF (10 mL) at room temperature and stirred for 15 min. The solvent was evaporated and the crude product was purified by Biotage HPFC system (40-75% EtOAc/Hexane) to afford 5-fluoro-1*H*-pyrrolo[2,3-*b*]pyridine as a white solid (0.45 g, 84); Mass Spec.; MS 137 (M+1); ^{1}H NMR(DMSO-d6, 500 MHz) δ 11.75(s, 1H), 8.17(t,1H), 7.81(dd,1H), 7.55(t,1H), 6.44(dd,1H).

[00243] 4-(5-Fluoro-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)thiazol-2-amine: Aluminum chloride (0.48 g, 3.6 mmol) was added slowly to a stirred solution of 5-fluoro-1*H*-pyrrolo[2,3-*b*]pyridine (0.164 g,1.2 mmol) in CH_2Cl_2 (5 mL)). Bromoacetyl bromide (0.1 mL, 1.5 mmol) was added and the resulting solution was heated at 50 ^{0}C for 1 h and cooled to room temperature. Water (25 mL) was added, the solution was basified with saturated $NaHCO_3$ and the mixture was extracted with EtOAc (3X25 mL). The organic extracts were dried and concentrated under reduced pressure to give 2-bromo-1-(5-fluoro-1H-pyrrolo[2,3-b]pyridin-3-yl)-ethanone as a pale brown solid. A mixture of 2-bromo-1-(5-fluoro-1H-pyrrolo[2,3-b]pyridin-3-yl)-ethanone (0.28 g) and thiourea (0.13 g) in ethanol (10 mL) were heated at 70 ^{0}C for 1 h. Water (50 mL) was added and the solution was basified with concentrated NH_4OH. The aqueous layer was extracted with EtOAc (3X25 mL). The organic extracts were dried and concentrated under reduced pressure to give 4-(5-fluoro-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)thiazol-2-amine (0.21 g, 75%, 2 steps) as pale brown solid. Mass Spec.; MS 235 (M+1); ^{1}H NMR(DMSO-d6, 500 MHz) δ 11.86(s, 1H), 8.27(d, 1H), 8.22(s,1H), 7.83(d,1H), 6.95(brs,2H), 6.81(s,1H).

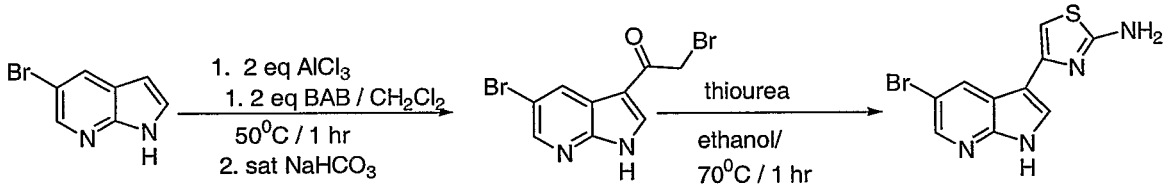
[00244] Preparation of 4-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-yl)-thiazol-2-ylamine



[00245] 4-(5-Chloro-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)thiazol-2-amine:

The title compound was synthesized in 2 steps in a manner similar to that described above using 5-chloro-7-azaindole (0.32 g, 1.17 mmol), $AlCl_3$ (0.47 g, 3.51 mmol), bromoacetylbromide (0.1mL, 1.46 mmol) and thiourea (0.158 g, 2.08 mmol) (0.21 g, 67.5%, 2 steps) as pale brown solid. Mass Spec.; MS 251 (M+1); ^{1}H NMR(DMSO-d6, 500 MHz) δ 11.97(s, 1H), 8.50(d, 1H), 8.22(d,1H), 7.84(d,1H),7.02(brs,2H), 6.83(s,1H).

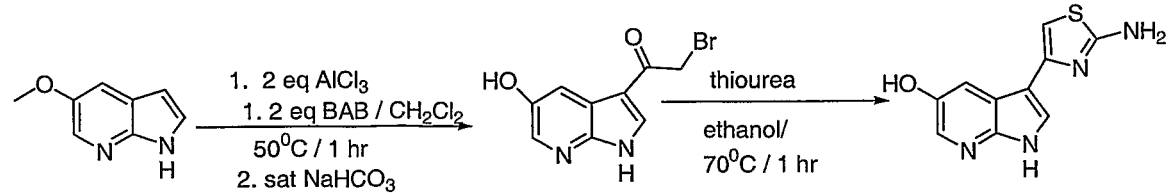
[00246] Preparation of 4-(5-Bromo-1H-pyrrolo[2,3-b]pyridin-3-yl)-thiazol-2-ylamine



[00247] 4-(5-Bromo-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)thiazol-2-amine:

The title compound was synthesized in 2 steps in a manner similar to that described above using 5-bromo-7-azaindole (1.0 g,5.07 mmol), $AlCl_3$ (1.35g,10.15 mmol),bromoacetylbromide (0.41 mL, 6.34 mmol) and thiourea (0.36 g, 4.72 mmol) (0.21 g, 48%, 2 steps) as a brown solid. Mass Spec.; MS 297 (M+1); ^{1}H NMR(DMSO-d6, 500 MHz) δ 8.63(d, 1H), 8.28(d,1H), 7.82(s,1H),6.98(s,2H), 6.82(s,1H).

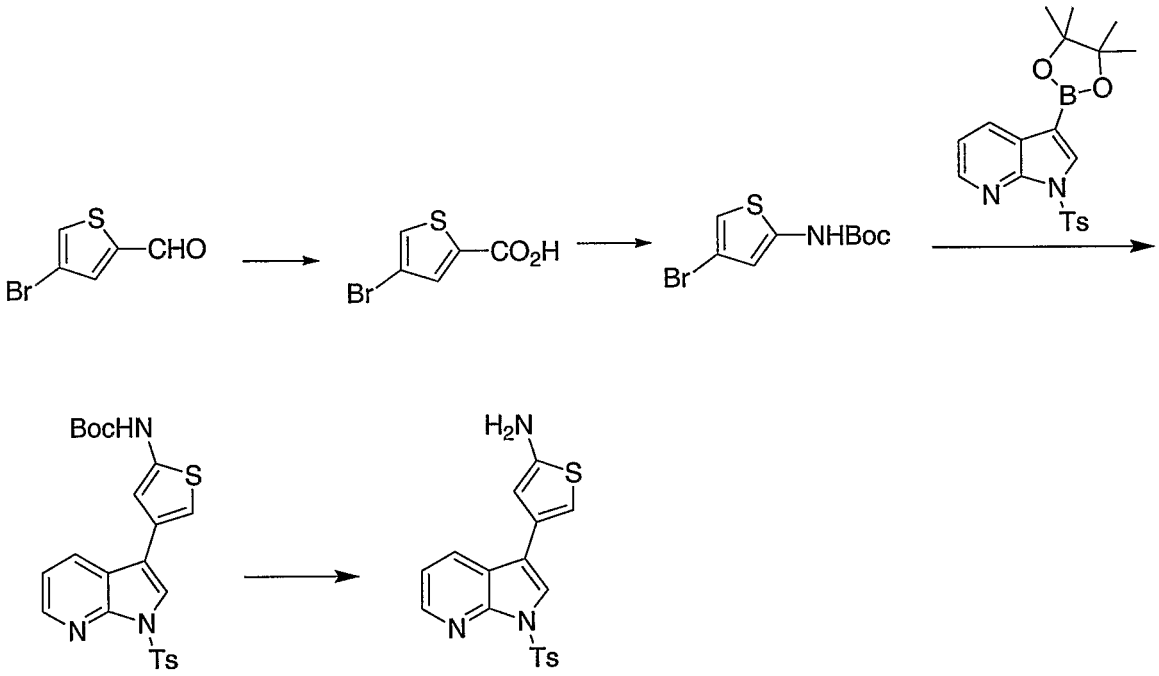
[00248] Preparation of 4-(5-Hydroxy-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)thiazol-2-amine



[00249] 4-(5-Hydroxy-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)thiazol-2-amine:

The title compound was synthesized in 2 steps in a manner similar to that described above using 5-methoxy-7-azaindole (0.37 g,2.48 mmol), $AlCl_3$ (1 g,7.54 mmol), bromoacetylbromide (0.2 mL, 3 mmol) and thiourea (0.14 g,1.88 mmol) (0.21 g, 39 %, 2 steps) as a brown solid. Mass Spec.; MS 233 (M+1); ^{1}H NMR(DMSO-d6, 500 MHz) δ 11.37 (s,1H), 9.10(s,1H), 7.86(d,1H), 7.70(d,1H), 7.61(d,1H), 6.88(s,2H), 6.67(s,1H).

[00250] Preparation of 4-[1-(Toluene-4-sulfonyl)-1H-pyrrolo[2,3-b]pyridin-3-yl]-thiophen-2-ylamine



[00251] 4-Bromothiophene-2-carboxylic acid:

4-Bromothiophene-2-carbaldehyde (1.9 g, 10 mmol) was dissolved in 40 mL of t-BuOH and 4 mL of 2-methyl-2-butene. The reaction mixture was cooled to 0 °C and $NaClO_2$ (1.1 g, 12 mmol) dissolved in 12 mL of 1M NaH_2PO_4 was added. The reaction mixture was let warm to room temperature and stirred for 5 hours. The reaction mixture was concentrated to about half the volume, and poured into 20 mL 1N NaOH and 50 mL Et2O. The aqueous layer was made acidic with 6N HCl and extracted with EtOAc. This organic layer was dried over sodium sulfate and concentrated to obtain the product as a white solid, 1.75 g, 8.5 mmol, 85% yield. ^{1}H NMR 500 MHz (DMSO-d_6) 8.02 (1H, s), 7.78 (1H, s).

[00252] tert-Butyl 4-bromothiophen-2-ylcarbamate:

4-Bromothiophene-2-carboxylic acid (1.75 g, 8.5 mmol) was dissolved in 40 mL of t-BuOH. To this solution diphenylphosphoryl azide (2.8 g, 10.2 mmol) and triethylamine (1.4 mL, 10.1 mmol) were added. The reaction mixture was heated to reflux for 5 hours, cooled room temperature, and diluted with EtOAc. The organic layer was washed with 10% citric acid, saturated sodium bicarbonate and brine, and concentrated to an oil, which was purified by column chromatography on silica (0 to 25% EtOAc/hexanes) to give the product, 1.3 g, 4.7 mmol, 55%. ^{1}H NMR 500 MHz (CDCl3) 6.96 (1H, br s), 6.83 (1H, s), 6.43 (1H, s), 1.54 (9H, s).

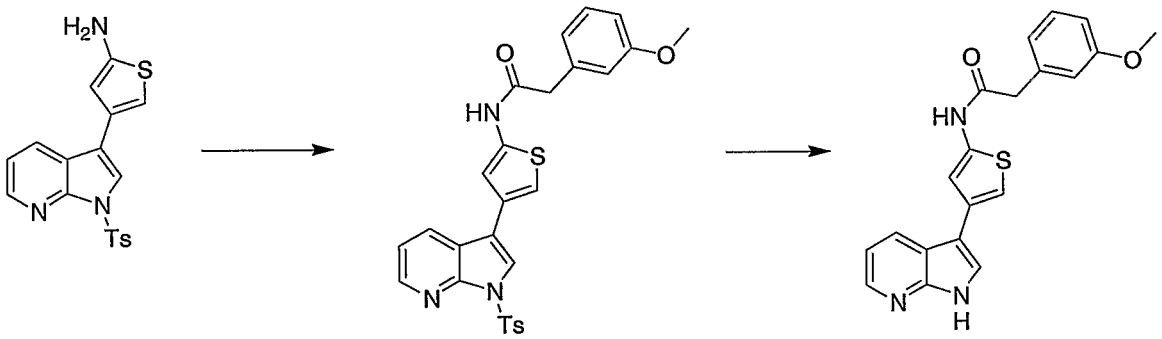
[00253] tert-Butyl 4-(1-tosyl-1H-pyrrolo[2,3-b]pyridin-3-yl)thiophen-2-ylcarbamate:

3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-tosyl-1H-pyrrolo[2,3-b]pyridine (398 mg, 1 mmol), tert-butyl 4-bromothiophen-2-ylcarbamate (190 mg, 0.68 mmol), potassium carbonate (310 mg, 2.25 mmol), and tetrakis(triphenylphosphine) palladium (0) (20 mg) were combined in 4 mL DME, 1 mL water, and heated to 160 °C in the microwave for 10 minutes, followed by 170 °C for 10 minutes. The reaction mixture was diluted with EtOAc and washed with saturated sodium bicarbonate. The organic layer was filtered through celite and concentrated to an oil which was purified by column chromatography on silica (15 to 60 % EtOAc/hexanes) to give the product as a brown foam, 0.12 g, 0.26 mmol, 38% yield. MH+ 470.1.

[00254] 4-[1-(Toluene-4-sulfonyl)-1H-pyrrolo[2,3-b]pyridin-3-yl]-thiophen-2-ylamine:

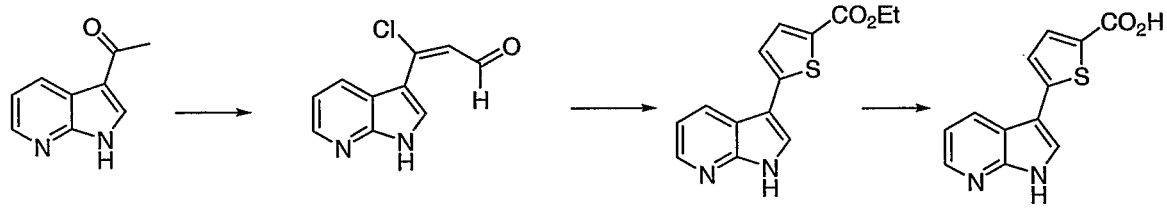
tert-Butyl 4-(1-tosyl-1H-pyrrolo[2,3-b]pyridin-3-yl)thiophen-2-ylcarbamate (120 mg, 0.26 mmol) was dissolved in 2 mL CH_2Cl_2, 2 mL TFA. After 15 minutes the reaction mixture was concentrated to an oil, dissolved in EtOAc, and washed with 0.1 NaOH. The organic layer was dried to a brown oil which was used as obtained.

[00255] Preparation of N-(4-(1H-pyrrolo[2,3-b]pyridin-3-yl)thiophen-2-yl)-2-(3-methoxyphenyl)acetamide



4-[1-(Toluene-4-sulfonyl)-1H-pyrrolo[2,3-b]pyridin-3-yl]-thiophen-2-ylamine was coupled to 3-methoxyphenylacetic acid according to General Method B and the product 2-(3-methoxyphenyl)-N-(4-(1-tosyl-1H-pyrrolo[2,3-b]pyridin-3-yl)thiophen-2-yl)acetamide (70 mg, 0.14 mmol) was dissolved in 6 mL THF and LiOH hydrate (63 mg, 1.5 mmol) was added in 1mL of water. The reaction mixture was heated to 150 °C by microwave irradiation for 15 minutes and then diluted with EtOAc and water and the organic layer dried over sodium sulfate and concentrated to an oil, which was purified by column chromatography on silica (40 to 100% EtOAc/hexanes to give 20 mg of a light brown solid, 0.055 mmol, 39%. 1H NMR 500 MHz (DMSO-d6) 11.80 (1H, s), 11.37 (1H, s) 8.28 (2H, m), 7.78 (1H, s), 7.25 (1H, t), 7.16 (2H, m), 7.07 (1H, s) 6.88 (2H, m), 6.82 (1H, m), 3.78 (3H, s), 3.69 (2H, s). MH+ 364.20.

[00256] Preparation of 5-(1H-pyrrolo[2,3-b]pyridin-3-yl)thiophene-2-carboxylic acid



[00257] (E)-3-chloro-3-(1H-pyrrolo[2,3-b]pyridin-3-yl)acrylaldehyde:

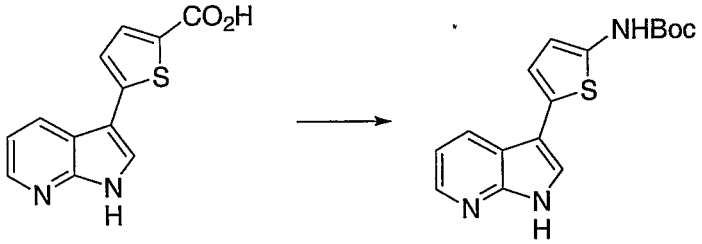
Phosphorous oxychloride (3.7 mL, 40 mmol) was added dropwise to DMF (6.2 mL, 80 mmol) at 0 °C. The reaction mixture was let warm to room temperature and stirred for 15 minutes. 1-(1H-Pyrrolo[2,3-b]pyridin-3-yl)-ethanone was added in DMF (20 mL) and the reaction heated to 60 °C for 4 hours, cooled to 0 °C and 150 mL of saturated NaOAc solution added. The reaction mixture was heated briefly to 50 °C and then extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to an oil which contains impure product. Upon

standing a solid precipitated from the aqueous layer to give 0.9 g of a brown solid, 4.3 mmol, 22% yield.

[00258] Ethyl 5-(1H-pyrrolo[2,3-b]pyridin-3-yl)thiophene-2-carboxylate: (E)-3-chloro-3-(1H-pyrrolo[2,3-b]pyridin-3-yl)acrylaldehyde (0.9 g. 4.3 mmol) was dissolved in EtOH (20 mL) and ethyl 2-mercaptoacetate (0.76 g, 6.3 mmol) and sodium ethoxide (1.0 g, 14.7 mmol) were added. The reaction mixture was heated to reflux for 90 minutes. The reaction mixture was diluted with EtOAc and the organic layer was washed with saturated sodium bicarbonate, dried over sodium sulfate, and concentrated to a solid, which was purified by column chromatography on silica (20 to 100% EtOAc/hexanes) to give the product, 890 mg, 3.3 mmol, 74% yield. 1H NMR 500 MHz (DMSO-d6) 12.19 (1H, br s), 8.32 (2H, m), 8.13 (1H, s), 7.78 (1H, d), 7.48 (1H, d), 7.23 (1H, dd), 4.31 (2H, q), 1.30 (3H, t).

[00259] 5-(1H-pyrrolo[2,3-b]pyridin-3-yl)thiophene-2-carboxylic acid: Ethyl 5-(1H-pyrrolo[2,3-b]pyridin-3-yl)thiophene-2-carboxylate (0.89 g, 3.3 mmol) was partly dissolved in 1,4 dioxane and 10 mL 1N NaOH added. The reaction mixture was heated to 80 °C where it became homogenous. After 2 hours the reaction mixture was cooled to room temperature, diluted with ethyl acetate, and a 10% citric acid solution. A precipitate formed which was filtered off, washed with water and dried to 0.71 g, 2.9 mmol, 88% yield.

[00260] Preparation of tert-butyl 5-(1H-pyrrolo[2,3-b]pyridin-3-yl)thiophen-2-ylcarbamate

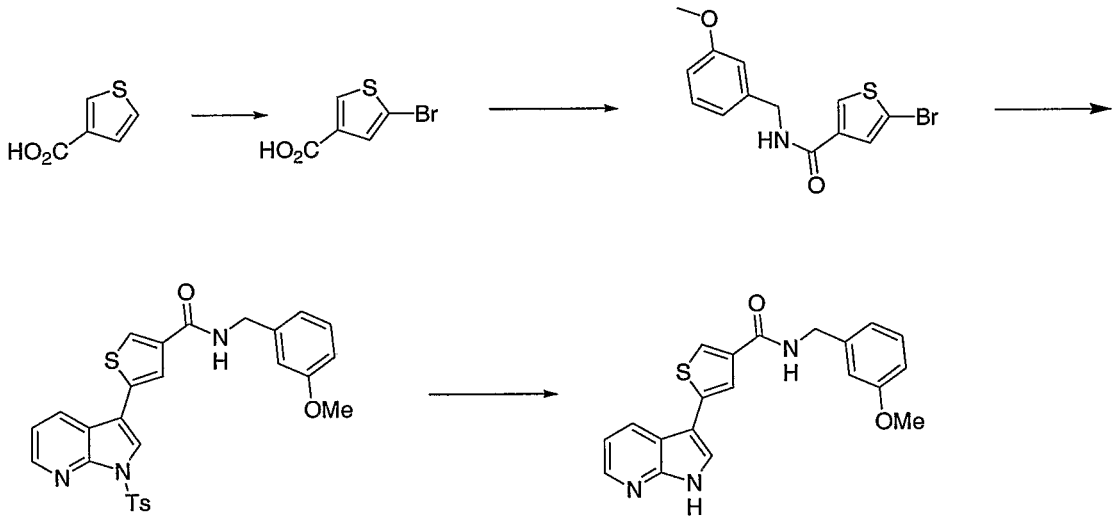


[00261] tert-butyl 5-(1H-pyrrolo[2,3-b]pyridin-3-yl)thiophen-2-ylcarbamate: 5-(1H-pyrrolo[2,3-b]pyridin-3-yl)thiophene-2-carboxylic acid (0.60 g, 2.5 mmol) was dissolved in 20 mL t-BuOH. To this solution diphenylphosphoryl azide (0.81 g, 2.9 mmol) and triethylamine (0.4 mL, 2.9 mmol) were added. The reaction mixture was heated to reflux for 6 hours, then let stand overnight. The reaction mixture was concentrated to a green residue that was dissolved in EtOAc. The organic layer was

washed with saturated sodium bicarbonate and concentrated to an solid, which was purified by column chromatography on silica (20 to 100% EtOAc/hexanes) to give the product as a yellow solid, 0.33 g, 1.05 mmol, 42% yield. MH+ 316.0.

The Boc-amine was deprotected with 4N HCl in dioxane and coupled using the usual method.

[00262] Preparation of N-(3-methoxybenzyl)-5-(1H-pyrrolo[2,3-b]pyridin-3-yl)thiophene-3-carboxamide



[00263] 5-Bromothiophene-3-carboxylic acid:

Thiophene-3-carboxylic acid (0.51 g, 4 mmol) was dissolved in HOAc (5 mL) and Br_2 (0.21 mL, 4 mmol) was added in 1 mL HOAc. The reaction mixture was stirred for 40 minutes, poured into water and a white precipitate formed, which was filtered and dried to 0.70 g grams of product that contains about 30 % 2,5-dibromothiophane-3-carboxylic acid.

[00264] N-(3-Methoxybenzyl)-5-bromothiophene-3-carboxamide:

5-Bromothiophene-3-carboxylic acid (70%) (200 mg, 0.6 mmol of monobromide) was dissolved in DMF with 3-methoxybenzyl amine (0.3 g, 2.2 mmol), EDCI (0.42 g, 2.2 mmol), and HOBt hydrate (0.06g, 0.4 mmol). The reaction mixture was stirred at room temperature for 3 days, diluted with EtOAc and the organic layer washed with 10% citric acid, saturated sodium bicarbonate, and brine. The organic layer was then dried over sodium sulfate and concentrated to an oil, which was purified by column chromatography on silica (10 to 30 5 EtOAc/hexanes) to give the product as a colorless oil, 195 mg, 0.6 mmol, 100%. ^{1}H NMR 500 MHz (CDCl3) 7.81 (1H, s),

7.35 (1H, s), 7.28 (1H, m), 6.93 (1H, m), 6.87 (2H, m), 6.23 (1H, br s), 4.57 (2H, d), 3.84 (3H, s).

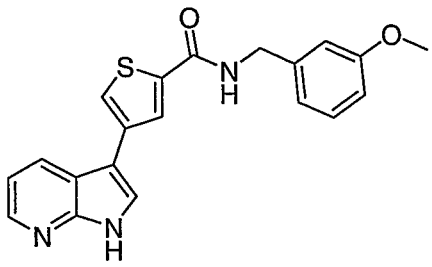
[00265] N-(3-Methoxybenzyl)-5-(1-tosyl-1H-pyrrolo[2,3-b]pyridin-3-yl)thiophene-3-carboxamide:

N-(3-Methoxybenzyl)-5-bromothiophene-3-carboxamide (100 mg, 0.3 mmol), 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-tosyl-1H-pyrrolo[2,3-b]pyridine (122 mg, 0.3 mmol), potassium carbonate (125 mg, 0.9 mmol), and tetrakis(triphenylphosphine) palladium (0) (20 mg) were combined in 4 mL DME, 1 mL water, and heated to 160 °C in the microwave for 10 minutes. The reaction mixture was diluted with EtOAc and water. The organic layer was filtered through celite and concentrated to an oil which was purified by column chromatography on silica (20 to 60 % EtOAc/hexanes) to give the product as a brown oil, 0.07 g, 0.14 mmol, 45% yield. MH+ 518.0

[00266] N-(3-Methoxybenzyl)-5-(1H-pyrrolo[2,3-b]pyridin-3-yl)thiophene-3-carboxamide:

N-(3-Methoxybenzyl)-5-(1-tosyl-1H-pyrrolo[2,3-b]pyridin-3-yl)thiophene-3-carboxamide (70 mg, 0.14 mmol) was dissolved in THF (4 mL) and LiOH hydrate (42 mg, 1 mmol) was added in water (1 mL). The reaction mixture was heated to 150 °C in the microwave for 10 minutes. The reaction mixture was diluted with EtOAc and the organic layer was washed with 10% citric acid, saturated sodium bicarbonate, and then dried over sodium sulfate and concentrated to an oil, which was purified by column chromatography on silica (50 to 100% EtOAc/hexanes) to give the product as a white solid 30 mg, 0.083 mmol, 59%. ^{1}H NMR 500 MHz (DMSO-d6) 12.00 (1H, s), 8.88 (1H, t), 8.32 (2H, m), 8.01 (1H, s), 7.87 (1H, s), 7.83 (1H, s), 7.26 (2H, m), 6.92 (2H, m), 6.93 (2H, m), 6.82 (1H, d), 4.43 (2H, d), 3.70 (3H, s). MH+ 364.10

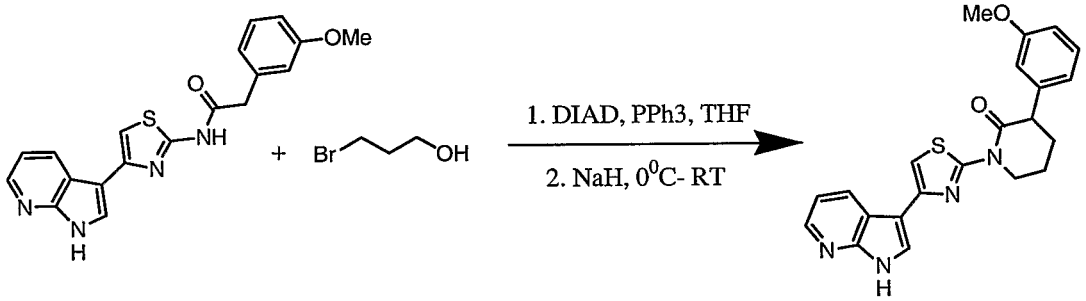
[00267] Preparation of N-(3-Methoxybenzyl)-4-(1H-pyrrolo[2,3-b]pyridin-3-yl)thiophene-2-carboxamide



[00268] N-(3-Methoxybenzyl)-4-(1H-pyrrolo[2,3-b]pyridin-3-yl)thiophene-2-carboxamide:

The above compound was made by the same procedure as N-(3-methoxybenzyl)-5-(1H-pyrrolo[2,3-b]pyridin-3-yl)thiophene-3-carboxamide starting with the regioisomer, 4-bromothiophene-2-carboxylic acid.

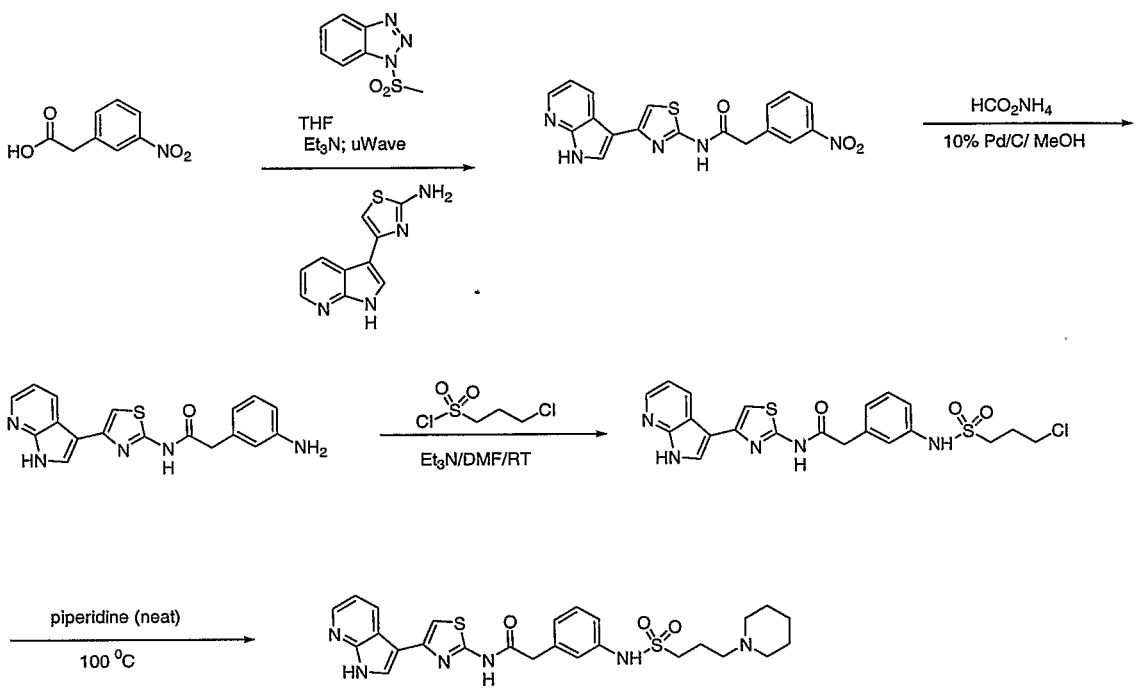
[00269] Preparation of 3-(3-Methoxy-phenyl)-1-[4-(1H-pyrrolo[2,3-b]pyridin-3-yl)-thiazol-2-yl]-piperidin-2-one



[00270] 3-(3-Methoxy-phenyl)-1-[4-(1H-pyrrolo[2,3-b]pyridin-3-yl)-thiazol-2-yl]-piperidin-2-one:

To 2-(3-methoxy-phenyl)-N-[4-(1H-pyrrolo[2,3-b]pyridin-3-yl)-thiazol-2-yl]-acetamide (1 mmol) in THF was added 1.2 mmol of PPh_3, 1.2 mmol of 3-bromopropanol and 1.2 mmol of DIAD and the reaction mixture was stirred at room temperature for 16 h. The reaction mixture was cooled to 0°C and 1.2 mmol of NaH was added and reaction mixture was stirred at 0°C for 30 minutes. MeOH was added to quench reaction and the solvent evaporated. The residue was redissolved in EtOAc and the organic layer was washed with H2O and dried over Na2SO4.. After removal of solvent, the final product was purified by preparative HPLC to afford 3-(3-methoxy-phenyl)-1-[4-(1H-pyrrolo[2,3-b]pyridin-3-yl)-thiazol-2-yl]-piperidin-2-one in 30% yield.

[00271] Preparation of 2-[3-(3-Piperidin-1-yl-propane-1-sulfonylamino)-phenyl]-N-[4-(1H-pyrrolo[2,3-b]pyridin-3-yl)-thiazol-2-yl]-acetamide



[00272] 2-(3-Nitro-phenyl)-N-[4-(1H-pyrrolo[2,3-b]pyridin-3-yl)-thiazol-2-yl]-acetamide:

Prepared from 3-nitrophenyl acetic acid (1g, 5.52 mmol), N-(1-methanesulfonyl)-benzotriazole (1.5eq, 1.6g), 4-(1H-pyrrolo[2,3-b]pyridin-3-yl)-thiazol-2-ylamine and triethylamine (3eq, 2.3ml) in THF (20 mL) by microwave irradiation at 170^{0}C for 10 mins as described above. The reaction mixture was concentrated to dryness and CH3CN added. The desired final product was filtered and washed with ether to give clean 2-(3-nitrophenyl)-N-[4-(1H-pyrrolo[2,3-b]pyridin-3-yl)-thiazol-2-yl]-acetamide (1.4g, 66% yield.)

[00273] 2-(3-Amino-phenyl)-N-[4-(1H-pyrrolo[2,3-b]pyridin-3-yl)-thiazol-2-yl]-acetamide:

2-(3-Nitro-phenyl)-N-[4-(1H-pyrrolo[2,3-b]pyridin-3-yl)-thiazol-2-yl]-acetamide (200mg, 0.5mmol) was taken in DMF- MeOH (5mL) and added to sat. NH4OH (5 ml) and Fe powder (3eq, 83mg). Then the suspension was heated overnight at 100 °C. The brown colored reaction mixture was passed through a celite plug and washed with ethyl acetate. Then the reaction mixture was concentrated to dryness and taken up in ethyl acetate and extracted with water. The organic layer was dried and concentrated to give the desired product as a tan solid (50 mg, 30 % yield).

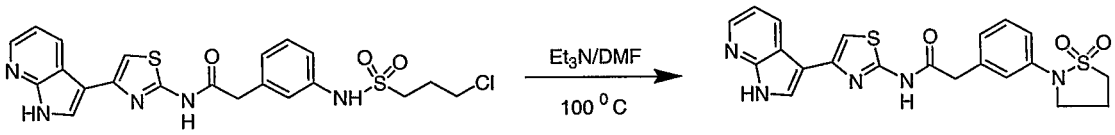
[00274] 2-[3-(3-Chloro-propane-1-sulfonylamino)-phenyl]-N-[4-(1H-pyrrolo[2,3-b]pyridin-3-yl)-thiazol-2-yl]-acetamide:

2-(3-Amino-phenyl)-N-[4-(1H-pyrrolo[2,3-b]pyridin-3-yl)-thiazol-2-yl]-acetamide (100 mg, 0.28 mmol) was dissolved in DMF (5 mL) and 3-chloro-propane-1-sulfonyl chloride (1 eq, 35 □L) was added followed by triethylamine (2 eq, 80 □L). The reaction mixture was stirred at RT for 3 hours and then diluted with EtOAc and extracted with water. The organic layer was dried and concentrated to give brown oil, which was used without further purification.

[00275] 2-[3-(3-Piperidin-1-yl-propane-1-sulfonylamino)-phenyl]-N-[4-(1H-pyrrolo[2,3-b]pyridin-3-yl)-thiazol-2-yl]-acetamide:

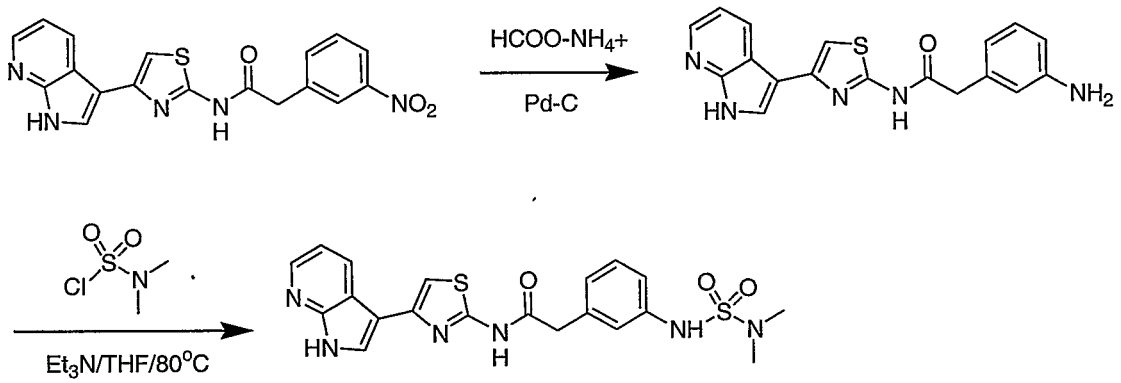
The crude 2-[3-(3-chloro-propane-1-sulfonylamino)-phenyl]-N-[4-(1H-pyrrolo [2,3-b]pyridin-3-yl)-thiazol-2-yl]-acetamide was treated with neat piperidine and heated to 100 °C overnight. The reaction mixture was diluted with DMF and purified by preparative HPLC to give the desired compound.

[00276] Preparation of 2-[3-(1,1-Dioxo-1l6-isothiazolidin-2-yl)-phenyl]-N-[4-(1H-pyrrolo[2,3-b]pyridin-3-yl)-thiazol-2-yl]-acetamide



[00277] 2-[3-(1,1-Dioxo-1l6-isothiazolidin-2-yl)-phenyl]-N-[4-(1H-pyrrolo[2,3-b]pyridin-3-yl)-thiazol-2-yl]-acetamide: 2-[3-(3-Chloro-propane-1-sulfonylamino)-phenyl]-N-[4-(1H-pyrrolo[2,3-b]pyridin-3-yl)-thiazol-2-yl]-acetamide was prepared as described above, then was dissolved in DMF in a refluxing tube and triethylamine added. Heated to 100 °C overnight. The reaction mixture was diluted with DMF and purified by prep HPLC to give the desired compound. (25.0mg, 20% yield).

[00278] Preparation of 2-(3-(N-Dimethylsulfamoyl)-amino-phenyl)-N-[4-(1H-pyrrolo[2,3-b]pyridin-3-yl)-thiazol-2-yl]-acetamide



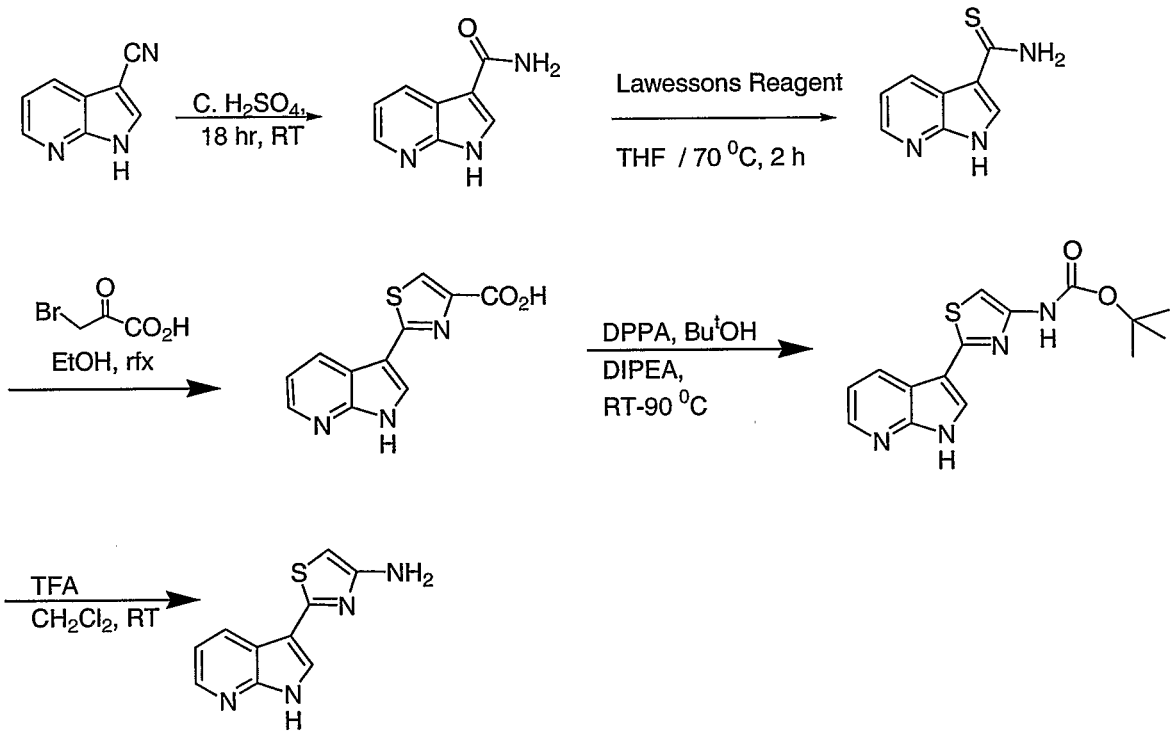
[00279] 2-(3-Amino-phenyl)-N-[4-(1H-pyrrolo[2,3-b]pyridin-3-yl)-thiazol-2-yl]-acetamide:

2-(3-Nitro-phenyl)-N-[4-(1H-pyrrolo[2,3-b]pyridin-3-yl)-thiazol-2-yl]-acetamide (1g, 2.6 mmol) was dissolved in MeOH (100 ml) and added 10% Pd/C (100 mg) followed by ammonium formate (3eq, 500mg). The reaction mixture was refluxed overnight. Then the reaction mixture was filtered and concentrated to give a white solid. The solid was taken up in EtOAc, filtered again, concentrated to give white solid. (500 mg, 55% yield).

[00280] 2-(3-(N-Dimethylsulfamoyl)-amino-phenyl)-N-[4-(1H-pyrrolo[2,3-b]pyridin-3-yl)-thiazol-2-yl]-acetamide:

2-(3-Amino-phenyl)-N-[4-(1H-pyrrolo[2,3-b]pyridin-3-yl)-thiazol-2-yl]-acetamide (100 mg, 0.28 mmol) was dissolved in THF (5 mL) and dimethyl sulfamoyl chloride (3eq, 90 □L) was added, followed by triethylamine (3eq, 120 □L). The reaction mixture was heated to 80 ^{0}C overnight, then was concentrated and taken up in DMF/H2O and purified by preparative HPLC to afford 2-(3-(N-dimethylsulfamoyl)-amino-phenyl)-N-[4-(1H-pyrrolo[2,3-b]pyridin-3-yl)-thiazol-2-yl]-acetamide (24.5mg, 20% yield)

[00281] Preparation of 2-(1H-Pyrrolo[2,3-b]pyridin-3-yl)-thiazol-4-ylamine



[00282] 1*H*-Pyrrolo[2,3-*b*]pyridin-3-carboxylic acid amide:

A solution of 3-cyano-7-azaindole (3 g, 20.98 mmol) in concentrated sulfuric acid (50 mL) was stirred at room temperature for 1 h. The solution was slowly poured into ice and basified with concentrated NH_4OH. The solution was concentrated under reduced pressure to produce brown residue which was extracted with acetone (4x100 mL). The organic extracts were dried and concentrated under reduced pressure to give title compound as a brown solid (3 g,91%).; Mass Spec.; MS 162 (M+1); ^1H NMR (DMSO-d6; 500 MHz) 8.44(dd,1H),8.25(dd,1H), 8.14(s,1H), 7.45(brs,1H), 7.15(dd, 1H), 6.89(brs,1H).

[00283] 1*H*-Pyrrolo[2,3-*b*]pyridin-3-carbothioc acid amide:

A mixture of Lawesson's reagent (11g, 27.93 mmol) and 1*H*-Pyrrolo[2,3-*b*]pyridin-3-caboxylic acid amide (3 g, 18.63 g) in THF (150 mL)was heated at 70 °C for 2 h. The solution was cooled to room temperature and the solvent was removed under reduced pressure to produce a yellow foam. Saturated K_2CO_3 (100 mL) and EtOAc (100mL) were added and stirred for 30 min at room temperature. Organic layer was separated and the aqueous layer was extracted EtOAc (3X25 mL). The combined organic extracts were dried and concentrated to give yellow residue which was triturated with CH_2Cl_2 (50 mL) to produce a solid. The solid was filtered and dried to give title

compound **3** (2.53 g, 77%).; Mass Spec.; MS 178 (M+1); ^{1}H NMR(DMSO-d6,500 MHz) 12.26 (s,1H), 9.05(s,1H), 8.97(d,1H), 8.94(s,1H), 8.26(dd,1H), 8.20(d,1H), 7.19(dd,1H),

[00284] 2-(1*H*-Pyrrolo[2,3-*b*]pyridin-3-yl)-thiazole-4-carboxylic acid:

A mixture of 1H-pyrrolo[2,3-b]pyridine-3-carbothioic acid amide (2.53 g, 14.37 mmol), bromopyruvic acid (2.4 g, 14.37 mmol) in ethanol (50 mL) was refluxed for 2 h. The solution was left at room temperature for 16 h and precipitated solid was filtered to give 2-(1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-thiazole-4-carboxylic acid (3.5 g, 100%) as a yellow solid MS 246 (M+1).

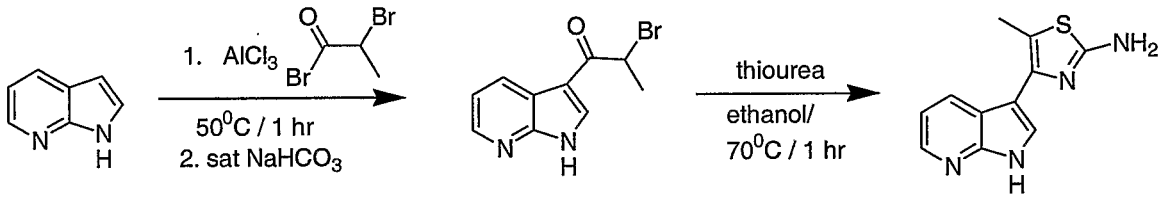
[00285] [2-(1*H*-Pyrrolo[2,3-*b*]pyridin-3-yl)-thiazol-4-yl]-carbamic acid *tert*-butyl ester:

A mixture of 2-(1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-thiazole-4-carboxylic acid (3 g, 12.24 mmol), diphenylphosphoryl azide (4.4 g, 15.91 mmol) and Et_3N (4 mL) in tertiary butanol (100 mL) was refluxed for 2 h and cooled to room temperature and concentrated. The residue was dissolved in EtOAC (10 mL) and insoluble material was filtered. The filtrate was chromatographed on silica gel (Biotage) eluting with EtOAc/hexane to give [2-(1H-pyrrolo[2,3-b]pyridin-3-yl)-thiazol-4-yl]-carbamic acid tert-butyl ester as a off white solid (1.8 g, 46%).; Mass Spec.; MS 317 (M+1); ^{1}H NMR(DMSO-d6,500 MHz) 12.19 (s,1H), 10.15(s,1H), 8.57(dd,1H),8.32(dd,1H), 8.12(d,1H), 7.23(dd,1H), 7.03(s,1H), 1.49(s,9 H).

[00286] 2-(1*H*-Pyrrolo[2,3-*b*]pyridin-3-yl)-thiazol-4-yl amine:

Trifluoroacetic acid (1 mL) was added to a stirred solution of [2-(1H-pyrrolo[2,3-b]pyridin-3-yl)-thiazol-4-yl]-carbamic acid tert-butyl ester (0.1 g, 0.316 mmol) in CH_2Cl_2 (2 mL) and stirred at room temperature for 2 h. The solution was poured into ice/water and basified with saturated $NaHCO_3$ and extracted with EtOAc (3x25 mL). The combined organic extracts were dried and concentrated to afford title compound as a pale green solid (0.058 g, 85%).; Mass Spec.; MS 217 (M+1)

[00287] Preparation of 5-Methyl-4-(1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)thiazol-2-amine



[00288] **5-Methyl-4-(1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)thiazol-2-amine**: The title compound was synthesized in 2 steps in a manner similar to that described for 4-(1H-pyrrolo[2,3-b]pyridin-3-yl)-thiazol-2-ylamine, using 7-azaindole (1.0 g, 8.47 mmol), $AlCl_3$ (3.4 g, 25.41 mmol, 3 eq),2-bromopropionylbromide (1.1 mL, 10.58 mmol) and thiourea (0.57 g, 7.5 mmol) (0.93 g, 41%, 2 steps) as a brown solid. Mass Spec.; MS 231 (M+1); ^{1}H NMR(DMSO-d6, 500 MHz) δ 11.71 (s,1H), 8.36(dd, 1H), 8.21(dd,1H), 7.53(d,1H), 7.06(dd,1H), 6.67(brs,2H),2.31(s,3H).

[00289] It will be appreciated that a variety of compounds can be prepared according to the general methods described above. Tables 3 and 4 includes exemplary data for certain compounds prepared according to the general methods described above. Compound numbers in Tables 1 and 2 correspond to the numbers assigned to compounds in Tables 1 and 2, respectively.

Table 3

Cmpd #	LC/MS (M+1) (obs)	RT (mins)	^{1}H NMR
I-1	335.00	2.80	H1NMR (500MHz, DMSO-d6, ppm) 12.39 (s,1H), 11.83 (s,1H), 8.50 (d,1H, J=7.91Hz), 8.27 (m,1H), 7.84 (d,1H, J=2.48Hz), 7.36-7.15 (m, 7H,), 3.81 (s,2H)
I-2	365.00	2.84	H1NMR (500MHz, DMSO-d6, ppm) 12.37 (s,1H), 11.83 (s,1H), 8.49 (d,1H, J=7.42), 8.27 (dd,1H, J=5.17, 1.4Hz), 7.84 (d,1H, J=2.48), 7.36 (s, 1H,), 7.25 (t,1H, J=7.86Hz), 7.16 (dd,1HJ=7.92,3.26Hz), 6.93 (m,2H), 6.84 (dd,1H, J=8.37,2.3Hz), 3.77 (s,2H), 3.75 (s,3H)
I-3	353.00	2.86	
I-4	353.00	2.93	
I-5	427.90, 428.10, 428.10, 428.10, 428.10, 428.24,	2.43, 2.46, 2.59, 2.59, 2.45, 2.43,	H1NMR (500MHz, DMSO-d6, ppm) 12.41 (s,1H), 11.83 (s,1H), 9.74 (s,1H), 8.50 (dd,1H, J=7.95, 1.43 Hz), 8.28 (dd,1H, J=4.64, 1.52Hz), 7.85 (d,1H,J=2.46), 7.37-7.10, (m,6H), 3.80 (s,2H), 3.00 (s,3H),H1NMR (500MHz, DMSO-d6, ppm) 12.61 (s,1H), 12.50 (s,1H), 9.78 (s,1H), 8.88 (d,1H,

Cmpd #	LC/MS (M+1) (obs)	RT (mins)	^{1}H NMR
	428.20, 428.00, 428.10, 428.10, 428.10, 428.10	2.43, 2.42, 2.72, 2.80, 2.38, 2.38	J=7.83Hz), 8.44 (d,1H, J=4.78Hz), 8.03 (s,1H), 7.51(s,1H), 7.44 (m,1H), 7.30(t,1H, J=7.83Hz), 7.23 (s,1H), 7.12 (m, 2H), 3.82 (s,2H), 3.00 (s,3H), 2.35 (s,3H),H1NMR (500MHz, DMSO-d6, ppm) 12.61 (s,1H), 12.50 (s,1H), 9.78 (s,1H), 8.88 (d,1H, J=7.83Hz), 8.44 (d,1H, J=4.78Hz), 8.03 (s,1H), 7.51(s,1H), 7.44 (m,1H), 7.30(t,1H, J=7.83Hz), 7.23 (s,1H), 7.12 (m, 2H), 3.82 (s,2H), 3.00 (s,3H),H1NMR (500MHz, DMSO-d6, ppm) 12.41 (s,1H), 11.83 (s,1H), 9.74 (s,1H), 8.50 (dD,1H, J=7.95, 1.43 Hz), 8.28 (dd,1H, J=4.64, 1.52Hz), 7.85 (d,1H,J=2.46), 7.37-7.10, (m,6H), 3.80 (s,2H), 3.00 (s,3H),H1NMR (500MHz, DMSO-d6, ppm) 12.41 (s,1H), 8.48 (dd,1H, J=7.95, 1.43 Hz), 8.25 (dd,1H, J=4.64, 1.52Hz), 7.85 (d,1H,J=2.46), 7.20-7.13, (m,2H), 6.94-6.74, (m,3H), 6.52, (d,1H,J=7.48), 3.54 (s,2H), 2.58 (s,3H),H1NMR (500MHz, DMSO-d6, ppm) 12.41 (s,1H), 11.83 (s,1H), 9.74 (s,1H), 8.50 (dd,1H, J=7.91, 1.20 Hz), 8.27 (dd,1H, J=4.61, 1.46Hz), 7.84 (d,1H,J=2.58), 7.37-7.09, (m,6H), 3.79 (s,2H), 3.00 (s,3H),H1NMR (500MHz, DMSO-d6, ppm) 12.61 (s,1H), 12.50 (s,1H), 9.78 (s,1H), 8.88 (d,1H, J=7.83Hz), 8.44 (d,1H, J=4.78Hz), 8.03 (s,1H), 7.51(s,1H), 7.44 (m,1H), 7.30(t,1H, J=7.83Hz), 7.23 (s,1H), 7.12 (m, 2H), 3.82 (s,2H), 3.00 (s,3H),H1NMR (500MHz, DMSO-d6, ppm) 12.61 (s,1H), 12.50 (s,1H), 9.78 (s,1H), 8.88 (d,1H, J=7.83Hz), 8.44 (d,1H, J=4.78Hz), 8.03 (s,1H), 7.51(s,1H), 7.44 (m,1H), 7.30(t,1H, J=7.83Hz), 7.23 (s,1H), 7.12 (m, 2H), 3.82 (s,2H), 3.00 (s,3H), 2.35 (s,3H),H1NMR (500MHz, DMSO-d6, ppm) 12.41 (s,1H), 9.75 (s,1H), 8.48 (dd,1H, J=7.95, 1.43 Hz), 8.25 (dd,1H, J=4.64, 1.52Hz), 7.85 (d,1H,J=2.46), 7.20-7.13, (m,2H), 6.94-6.74, (m,3H), 6.52, (d,1H,J=7.48), 3.80 (s,2H), 3.02 (s,3H),H1NMR (500MHz, DMSO-d6, ppm) 12.61 (s,1H), 12.50 (s,1H), 9.78 (s,1H), 8.88 (d,1H, J=7.83Hz), 8.44 (d,1H, J=4.78Hz), 8.03 (s,1H), 7.51(s,1H), 7.44 (m,1H), 7.30(t,1H, J=7.83Hz), 7.23 (s,1H), 7.12 (m, 2H), 3.82 (s,2H), 3.00 (s,3H),H1NMR (500MHz, DMSO-d6, ppm) 12.43 (s,1H), 12.10 (s,1H), 9.74 (s,1H), 8.66 (m,1H), 8.35 (m,1H), 7.90 (m,1H) 7.51(s,1H), 7.44 (m,1H), 7.30(t,1H, J=7.83Hz), 7.25 (m, 1H), 7.23 (s,1H), 7.16-7.06 (m, 4H), 3.82 (s,2H),

Cmpd #	LC/MS (M+1) (obs)	RT (mins)	^{1}H NMR
			2.30 (s,3H)
I-6	371.00	2.98	
I-7	349.00	3.05	
I-8	379.00	2.77	
I-9	576.00	4.39	
I-10	428.90	2.73	
I-11	476.20	2.17	H1NMR (500MHz, DMSO-d6, ppm) 9.04 (s,1H), 8.85 (d,1H, J=7.75Hz), 8.80 (s, 1H), 8.44 (,1H, J=4.31Hz), 8.02 (d,1H, J=2.03Hz), 7.49 (s, 1H,), 7.42 (dd,1H, J=7.92, 5.22Hz), 7.24 (t,1H, J=7.88Hz), 6.92 (m,2H), 6.84 (m, 1H), 6.64 (bs,1H), 3.96 (t,2H, J=6.36), 3.78 (s,3H), 3.20 (m,2H), 2.79 (m,2H), 2.8 (m,4H), 2.50 (m,1H), 1.40 (m,4H)
I-12	351.00	2.31	
I-13	412.90	2.99	H1NMR (500MHz, DMSO-d6, ppm) 12.59 (s,1H), 12.10 (s,1H), 8.75 (d,1H, J=6.87Hz), 8.27 (dd,1H, J=4.67, 1.44Hz), 8.08 (d,1H, J=2.47), 7.58 (s, 1H,), 7.40 (dd,1H, J=7.94, 4.71Hz), 7.29 (s,1H), 7.26 (s,1H), 6.29 (s,2H), 4.10 (s,1H)
I-14	477.00	1.56	H1NMR (500MHz, DMSO-d6, ppm) 12.42 (s,1H), 12.08 (s,1H), 9.68 (bs,2H), 8.61 (d,1H, J=7.82Hz), 8.33 (dd,1H, J=4.83, 1.38Hz), 7.90 (d,1H, J=2.36Hz), 7.41 (s, 1H), 7.25 (m,2H), 6.96 (m,2H), 6.87 (m,1H,), 6.90 (bs,1H), 4.07 (t, 2H, J=6.0Hz), 3.80 (s,2H), 3.77 (bs, 1H), 3.20-3.60 (m,8H), 2.21 (m,1H)
I-15	491.00	1.67	H1NMR (500MHz, DMSO-d6, ppm) 12.44 (s,1H), 12.28 (s,1H), 8.71 (d,1H, J=7.73Hz), 8.37 (dd,1H, J=4.79, 1.25Hz), 7.94 (d,1H, J=2.42), 7.44 (s, 1H), 7.30 (m,2H), 6.94 (m,2H), 6.86 (m, 1H), 4.08 (t, 2H, J=5.91Hz), 3.79 (s,2H), 3.31-3.75 (m,10H), 2.83 (s,3H), 2.23 (m,2H)
I-16	463.00	1.51	H1NMR (500MHz, DMSO-d6, ppm) 12.45 (s,1H), 12.17 (s,1H), 9.73 (bs,2H), 8.66 (d,1H, J=7.87Hz), 8.34 (dd,1H, J=4.85, 1.45Hz), 7.92 (d,1H, J=2.18Hz), 7.42 (s, 1H), 7.29 (m,2H), 7.01 (m,2H), 6.92 (dd, 1H, J=8.14, 2.19Hz), 6.45 (bs,1H), 4.42 (t, 2H, J=4.68Hz), 3.81 (s,2H), 3.36-3.83 (m,8H)

Cmpd #	LC/MS (M+1) (obs)	RT (mins)	^{1}H NMR
I-17	477.00, 477.00, 477.30, 477.00, 477.10	1.69, 1.87, 1.67, 1.70, 1.60	H1NMR (500MHz, DMSO-d6, ppm) 12.43 (s,1H), 12.09 (s,1H), 8.62 (d,1H, J=7.73Hz), 8.33 (dd,1H, J=4.79, 1.25Hz), 7.90 (d,1H, J=2.42), 7.41 (s, 1H), 7.24-7.31 (m,2H), 7.00 (m,2H), 6.92 (dd, 1H, J=8.27, 2.12Hz), 5.90 (bs,1H), 4.40 (bs, 2H, J=4.68Hz), 3.80 (s,2H), 3.38-3.76 (m,9H), 2.82 (s,3H),DMSO-d6: 12.37(s,1H), 11.87(s,1H), 8.48(d,1H), 8.27(dd,1H), 7.84(d,1H), 7.36(s,1H), 7.25(t,1H), 7.17(dd,1H), 6.95(m,2H), 6.84(dd,1H), 4.09(t,2H), 3.76(s,2H), 3.02(brm,4H), 2.81(t,2H), 2.67& 2.57(dAB, J= 15.3 HZ, 8H), 2.63(s,3H), 2.60-2.80(brm, 4H),H NMR (500 MHz, DMSO-d6) ppm 12.35 (s, 1H), 11.83 (s, 1H), , 8.49 (d, J = 7.9 Hz, 1H), 8.27 (d, J = 6.1 Hz, 1H), 7.85 (d, J = 2.5 Hz, 1H), 7.36 (s, 1H), 7.24 (t, J = 7.9 Hz, 1H), 7.18-7.15 (m, 1H), 6.95-6.90 (m, 2H), 6.84 (dd, J = 8.1, 2.2 Hz, 1H), 4.06 (m, 3H), 3.76 (s, 2H), 3.29 (s, 2H), 3.17 (d, J = 4.9 Hz, 2H), 2H), 2.51-2.49 (m, 10H), 2.31 (s, 3H),H NMR (400 MHz, acetic acid-d4) ppm 12.37 (s, 1H), 11.84 (s, 1H), 8.49 (dd, J = 7.9, 1.4 Hz, 1H), 8.28 (dd, J = 4.6, 1.5 Hz, 1H), 7.85 (d, J = 2.0 Hz, 1H), 7.36 (s, 1H), 7.27-7.24 (m, 1H), 7.18-7.15 (m, 1H), 6.95-6.84 (m, 3H), 4.09 (t, J = 5.5 Hz, 2H), 3.17 (s, 2H), 2.93-2.49 (m, 20H),H NMR (500 MHz, DMSO-d6) ppm 12.39 (s, 1H), 11.85 (s, 1H), 10.36 (m, 1H), 8.50-8.49 (m, 1H), 8.28 (dd, J = 4.6, 1.4 Hz, 1H), 7.85 (d, J = 2.5 Hz, 1H), 7.37 (s, 1H), 7.26 (t, J = 7.8 Hz, 1H), 7.17 (dd, J = 7.9, 4.6 Hz, 1H), 6.94 (m, 2H), 6.87-6.85 (m, 1H), 4.09 (s, 2H), 3.78 (s, 2H), 3.32 (s, 4H), 3.04 (s, 3H), 2.80 (s, 2H), 2.72 (s, 2H), 2.54 (s, 1H)
I-18	399.00, 399.00	3.29, 3.46	H1NMR (500MHz, DMSO-d6, ppm) 12.39 (s,1H), 11.83 (s,1H), 8.50 (d,1H, J=7.89Hz), 8.28 (dd,1H, J=4.62, 1.42Hz), 6.91-7.85 (m,6H), 3.91 (s,2H), 3.78 (s,3H),MeOD8.52 d (2H), 8.23 d (1H), 7.83 s (1H), 7.32 d (1H), 7.20 m (2H), 7.01 s (1H), 6.90 m (1H), 3.92 s (2H), 3.80 s (3H)
I-19	442.10	2.96	H1NMR (500MHz, MeOH-d4, ppm) 8.54 (t,1H, J=6.72), 8.88 (dd,1H, J=4.81Hz, 1.27Hz), 7.75-7.90. (m,4H), 7.51-7.66 (m,2H), 7.20-7.22 (m,1H), 3.95 (s,1H), 3.73 (s,1H), 2.9 (m,2H), 1.07 (t,3H, J=7.24)

Cmpd #	LC/MS (M+1) (obs)	RT (mins)	^{1}H NMR
I-20	375.20	3.39	H1NMR (500MHz, DMSO-d6, ppm) 11.92 (s,1H), 8.63 (d,1H, J=7.88Hz), 8.29 (dd,1H, J=4.71, 1.49Hz), 8.96 (d,J=2.58,1H), 7.44 (s,1H), 7.36-7.19 (m,6H), 4.27 (s,2H), 3.29 (t, 1H,J=3.78), 1.33 (m,2H), 1.06 (m,2H)
I-21	366.00	2.93	DMSO-d6: 12.71(s,1H), 12.29(s,1H), 8.52(d,1H), 8.33(dd,1H), 8.23(d,1H), 7.24(m,2H), 6.92(m,2H), 6.84(dd,1H), 3.81(s,2H), 3.75(s,3H).
I-22	372.00	2.95	DMSO-d6: 12.77(s,1H), 12.30(s,1H), 8.52(d,1H), 8.34(d,1H), 8.23(d,1H), 7.46(m,1H), 7.24(m,2H), 7.08(m,1H), 3.92(s,2H).
I-23	354.00	2.84	DMSO-d6: 12.90(brs,1H), 12.31(brs,1H), 8.51(d,1H), 8.34(d,1H), 8.23(s,1H), 7.42(m,1H), 7.34(m,1H), 7.17-7.26(m,3H), 3.94(s,2H).

Table 4

Cmpd #	LC/MS (M+1) (obs)	RT (mins)	^{1}H NMR
II-1	408.20	2.60	
II-2	408.20	2.60	
II-3	257.02, 257.10	1.62, 1.66	A1919-180A:H1NMR (500MHz, DMSO-d6, ppm) 12.22 (s,1H), 9.20 (bs,1H), 8.42 (d,1H, J=7.82Hz), 8.36 (dd,1H, J=4.81, 1.22Hz), 8.00 (s,1H), 7.25 (m,1H), 6.12 (s,1H), 2.77 (t, 1H,J=4.75), 0.86 (m,2H), 0.71 (m,2H)
II-4	456.30	3.12	
II-5	456.20	3.12	
II-6	454.20	3.05	
II-7	354.00	2.94	DMSO-d6: 12.72(s,1H), 12.30(s,1H),8.52(d,1H), 8.34(dd,1H), 8.23(d,1H), 7.37(m,2H), 7.24(dd,1H), 7.17(t,2H), 3.84(s,2H).
II-8	336.00	2.93	DMSO-d6: 12.73(s,1H), 12.29(s,1H),8.51(dd,1H), 8.33(dd,1H), 8.23(d,1H), 7.34(m,4H), 7.25(m,2H), 3.84(s,2H).
II-9	429.00	2.39	DMSO-d6: 12.75(s,1H), 12.29(s,1H), 9.73(s,1H), 8.52(dd,1H), 8.33(dd,1H), 8.24(d,1H), 7.30(t, 1H), 7.24(m,1H), 7.21(s,1H), 7.10(m,2H), 3.82(s,2H), 2.99(s,3H).
II-10	414.00	3.07	DMSO-d6: 12.71(s,1H), 12.30(s,1H), 8.51(dd,1H), 8.34(dd,1H), 8.23(d,1H), 7.09(s, 1H), 7.05(s,1H), 6.07(s,2H), 3.92(s,2H). 2.99(s,3H).

Cmpd #	LC/MS (M+1) (obs)	RT (mins)	^{1}H NMR
II-11	371.10	3.38	H CD3OD: 3.92(s, 2H), 6.99(m, 1H), 7.1(dd, 1H), 7.15(dd, 1H), 7.25(s, 1H), 7.32(m, 1H), 7.37(dd, 1H), 7.87(s, 1H), 8.25(m, 1)
II-12	371.10	3.48	H CD3OD & CDCl3: 3.8(s, 2H), 6.97(m, 1H), 7.06(dd, 1H), 7.25(s, 1H), 7.35(m, 1H), 7.85(s, 1H), 8.25(m, 1H)
II-13	388.90	3.23	H CD3OD: 3.85(s, 2H), 6.95(m 2H), 7.02(m, 1H), 7.27(s, 1H), 7.39(m, 1H), 7.89(s, 1H),8.25(m, 1H)
II-14	446.20	2.96	H CD3OD: 2.97(s, 3H), 3.8(s, 2H), 7.0(m, 1H), 7.13(dd, 1H), 7.16(dd, 1H), 7.25(s, 1H), 7.32(dd, 1H), 7.87(s, 1H), 8.25(m,1H)
II-15	367.00	3.60	H CD3OD: 2.78(t, 2H), 3.02(t, 2H), 7.02(m, 1H), 7.15(m, 1H), 7.25(m, 5H), 7.84(s, 1H), 8.25(m, 1H)
II-16	353.10	3.34	H DMSOd-6: 3.76(s, 2H),7.0(m, 1H), 7.3(m, 6H), 7.78(s, 1H), 8.25(m, 1H)
II-17	494.40	2.35	H CD3OD: 1.37(m, 2H), 1.49(m, 2H), 1.67(m, 1H),1.83(m, 2H), 1.97(m, 2H),2.95(t, 2H), 3.75(s, 2H), 4.04(t, 2H), 6.82(dd, 1H), 6.95(m, 3H), 6.23(dd, 1H0, 6.25(s, 1H), 7.85(s, 1H), 8.22(m, 1H)
II-18	397.10	3.32	H DMSO d-6: 3.7(s, 2H), 6.0(s, 2H), 6.8(d, 1H), 6.85(d, 1H), 6.9(s, 1H), 7.0(m, 1H), 7.2(s, 1H), 7.77(s, 1H), 8.25(m, 1H)
II-19	383.00	3.38	H CD3OD: 3.77(s, 2H), 3.81(s, 3H), 6.8(dd, 1H), 6.9(dd, 1H), 6.9(s, 1H), 6.97(m, 1H), 7.24(m, 2H), 7.87(s, 1H), 8.25(m, 1H)
II-20	431.10	3.47	H CD3OD: 3.9(s, 2H), 6.0(s, 2H)6.9(m, 3H), 7.25(s, 1H), 7.84(s, 1H), 8.2(m, 1H)
II-21	365.00	3.17	DMSO-d6: 12.31(s,1H), 8.96(t,1H),8.84(dd,1H), 8.34(dd,1H), 8.30(d,1H) 8.13(s,1H), , 7.24(m,2H), 6.92(m,2H), 6.82(dd,1H), 4.51(d,2H), 3.73(s,3H).
II-22	477.00	2.14	DMSO-d6: 12.71(s,1H), 12.31(s,1H), 8.52(d,1H), 8.34(dd,1H), 8.23(d,1H), 7.24(m,2H), 6.90(m,2H), 6.83(dd,1H), 3.95(t,2H), 3.79(s,2H), 3.24(m,2H), 2.82(m,2H), 1.83(m,2H), 1.79(m,2H), 1.75(brm,1H), 1.26-1.40(m,4H).
II-23	364.20	3.20	1H NMR 500 MHz (DMSO-d6) 11.80 ppm, 1H, s; 11.37 ppm, 1H, s; 8.28 ppm, 2H, m; 7.78 ppm, 1H, s; 7.25 PPM, 1H, t; 7.16 ppm, 2H, m; 7.07 ppm, 1H, s; 6.88 ppm, 2H, m; 6.82 ppm, 1H, m; 3.78 ppm, 3H,s 3.69 ppm, 2H, s.

Cmpd #	LC/MS (M+1) (obs)	RT (mins)	^{1}H NMR
II-24	470.30, 470.10	3.16, 3.21	1H NMR 500 MHz (DMSO-d6) 12.45 ppm, 1H, s; 11.82 ppm, 1H, s; 8.60ppm, 1H, m; 8.25 ppm, 1H, m; 7.82 ppm, 2H, m; 7.70 ppm, 1H, m; 7.63 ppm, 1H, m; 7.58 ppm, 1H, m; 7.38 ppm, 1H, s; 7.17 ppm, 1H, m; 3.93 ppm, 2H, s; 3.15 ppm, 4H, m; 1.04 ppm, 6H, m.
II-25	483.30, 483.10	1.83, 1.87	
II-26	484.30, 484.10	2.97, 3.06	1H NMR 500 MHz (DMSO-d6) 12.44 ppm, 1H, br s; 11.80 ppm, 1H, s; 8.47 ppm, 1H, d; 8.26 ppm, 1H, d; 7.83 ppm, 1H, s; 7.78 ppm, 1H, s; 7.70 ppm, 1H, m; 7.62 ppm, 2H, m; 7.36 ppm, 1H, s; 7.17 ppm, 1H, m; 3.97 ppm, 2H, s; 3.60 ppm, 4H, m; 2.88 ppm, 4H, m.
II-27	468.20	281.00	H1NMR (500MHz, DMSO-d6, ppm) 11.92 (s,1H), 9.70, (s,1H), 8.63 (d,1H, J=7.91Hz), 8.28 (dd,1H, J=4.71, 1.49Hz), 7.96 (d,1H, J=2.46), 7.44, (s,1H), 7.31-7.05 (m,5H), 4.25 (s,2H), 3.30, (m,1H), 2.98 (t, 1H,J=3.78), 1.31 (m,2H), 1.05 (m,2H)
II-28	370.00	2.86	
II-29	333.96	2.73	
II-30	364.04	2.73	
II-31	347.97	2.84	
II-32	366.03	2.86	
II-33	427.00	2.76	1H NMR 500 MHz (CDCl3/CD3OD) 8.60 ppm, 1H, d; 8.28 ppm, 1H, m; 7.63 ppm, 1H, s; 7.40 ppm, 1H, m; 7.32 ppm, 1H, m; 7.18 ppm, 3H, m; 6.93 ppm, 2H, m; 3.72 ppm, 2H, s; 3.00 ppm, 3H, s.
II-34	384.00	2.16	CD3CN 12.92 s (1H), 10.86 s (1H), 9.08 d (1H), 8.40 d (1H), 8.07 s (1H), 7.68 s (2H), 7.59 m (1H), 7.32 s (1H), 7.20 d (1H), 6.85 s (1H), 6.71 m (1H), 3.89 s (2H)

Cmpd #	LC/MS (M+1) (obs)	RT (mins)	^{1}H NMR
II-35	476.00, 476.00	2.71, 2.77	CD3CN12.80 s (1H), 10.46 s (1H), 9.02 d (1H), 8.38 d (1H), 8.04 s (1H), 7.76 s (1H), 7.54 m (1H), 7.42 d (1H), 7.36 s (1H), 7.30 s (1H), 7.22 m (1H), 3.99 s (1H),3.15 q (2H), 1.31t (3H),
II-36	495.10	1.92	
II-37	509.10	2.02	
II-38	477.10, 477.10	2.21, 2.44	
II-39	472.00	2.51	
II-40	360.10	2.72	
II-41		2.10	
II-42	484.00	2.47	
II-43	390.00	3.17	9.95 (s, 1H), 8.46 (d, 1H), 8.28 (d, 1H), 7.87 (d, 1H), 6.83 (s, 1H), 4.1-4.8 (s, 2H), 3.92 (m, dH), 3.29 (m, 2H), 2.12 (s, 3H), 1.35 (m, 6H) CD3CN
II-44	393.10	3.32	H1NMR (500MHz, DMSO-d6, ppm) 12.15 (s,1H), 8.74 (d,1H, J=7.87), 8.33 (m,1H), 8.02 (d,1H, J=2.41Hz), 7.49 (s,1H), 7.42-7.17, (m,5H), 4.34 (s,2H), 3.38 (m,1H), 1.36 (m,2H), 1.10 (m,1H)
II-45	411.10	3.46	H1NMR (500MHz, DMSO-d6, ppm) 12.44 (s,1H), 8.89 (d,1H, J=7.87), 8.40 (m,1H), 8.08 (d,1H, J=1,80Hz), 7.55 (s,1H), 7.47 (m,1H), 7.39 (m,1H), 7.25 (m,1H), 7.11 (m,1H), 4.34 (s,2H), 3.40 (m,1H), 1.36 (m,2H), 1.10 (m,1H).
II-46	428.00	2.69	CD3OD: 8.65(d,1H), 8.29(d,1H), 8.00(s,1H), 7.44(s,1H), 7.16-7.32(m,5H), 3.75(s,2H), 2.97(s,3H)
II-47	462.00	2.63	CD3CN9.48 s (1H), 8.35 d (1H), 7.63 s (1H), 7.52 m (1H), 7.42 s (1H), 7.29 m (1H), 7.07 m (1H), 6.94 m (2H), 6.87 m (1H). 3.81 s (3H),3.70s (2H),
II-48	490.00	2.90	CD3CN12.81 s (1H), 10.44 s (1H), 9.05 d (1H), 8.38 d (1H), 8.04 s (1H), 7.70 s (1H), 7.54 m (1H), 7.39 m (2H), 7.30 s (1H), 7.24 m (1H), 3.34 m (1H),1.36 d (6H),
II-49	456.10	2.95	
II-50	442.00, 442.10, 442.08	2.75, 3.11, 2.98	H1NMR (500MHz, DMSO-d6, ppm) 12.90 (s,1H), 12.62 (s,1H), 11.67 (bs,1H), 9.01 (d,1H, J=7.91), 8.49 (d,1H, J=5.31Hz), 8.08 (s,1H), 7.80(s,1H), 7.72-7.52 (m,6H), 4.02 (s,2H), 2.51 (s,3H), 2.50 (s,3H)
II-51	497.00, 497.10	1.86, 1.82	

Cmpd #	LC/MS (M+1) (obs)	RT (mins)	^{1}H NMR
II-52	511.10	1.92	
II-53	393.30	3.38	
II-54	389.10	3.60	H1NMR (500MHz, DMSO-d6, ppm) 11.81 (s,1H), 8.58 (d,1H, J=7.92), 8.26 (m,1H), 7.92 (d,1H, J=2.58Hz), 7.41 (s,1H), 7.30-7.14 (m,6H), 3.25 (m,3H), 2.97 (t,2H, J=7.42Hz),1.23 (m,2H), 0.95 (m,1H)
II-55	365.00	3.13	CDCl3: 10.71(brs,1H), 8.40(d,1H),8.33(m,2H), 7.77(d,1H), 7.51(s,1H), 7.24(t,1H), 7.17(m,1H), 6.86(d,1H), 6.80(m,2H), 3.79(s,3H), 3.69(s,2H).
II-56	371.00	3.30	CD3OD: 8.82(d,1H),8.34(d,1H), 8.08(s,1H), 7.45(s,1H), 7.31-7.42(m,2H),6.95(m,2H), 3.81(s,2H),
II-57	484.00	3.02	CD3OD: 8.95(d,1H),8.36(d,1H), 8.10(s,1H), 7.82(m,1H), 7.55-7.75(m,3H), 7.48(s,1H), 7.35(m,1H), 3.90(s,2H), 3.66(m, 4H), 2.97(m,4H)
II-58	485.00	2.72	DMSO-d6: 12.80(s,1H), 12.20(s,1H), 8.52(dd,1H), 8.33(dd,1H),8.24(d,1H), 7.77(s,1H), 7.70(m,1H), 7.65(m,12H), 7.25(dd,1H), 4.02 (s,1H), 3.62(m, 4H), 2.87(m,4H)
II-59	483.10	2.70	1H NMR 500 MHz (DMSO-d6) 8.25 ppm, 2H, m; 7.71 ppm, 3H, m; 7.63 ppm, 2H, m; 7.14 ppm, 2H, m; 7.05 ppm, 1H, s; 3.88 ppm, 2H, s; 3.60 ppm, 4H, m; 2.88 ppm, 4H, m.
II-60	353.00	3.16	CD3OD: 8.93(d,1H), 8.38(d,1H), 8.12(d,1H),7.16-7.48(m,6H).
II-61	353.00	3.22	DMSO-d6: 12.27(s,1H), 11.13(s,1H), 8.57(d,1H),8.34(d,1H), 8.15(d,1H), 7.36-7.41(m,3H), 7.26(dd,1H), 7.14(t,2H), 3.71(s,2H)
II-62	335.00	3.13	CD3OD: 8.45(d,1H), 8.35(d,1H), 8.08(s,1H),7.47(s,1H), 7.24-7.40(m,5H), 3.75(s,1H)
II-63	470.00	3.38	
II-64	471.00	3.07	
II-65	483.30	2.84	1H NMR 500 MHz (DMSO-d6) 9.07 ppm, 1H, m; 8.30 ppm, 2H, m; 7.99 ppm, 1H, d; 7.79 ppm, 1H, d; 7.70 ppm, 2H, m; 7.63 ppm, 2H, m; 7.42 ppm, 1H, d; 7.20 ppm, 1H, m; 4.57 ppm, 2H, d; 3.61 ppm, 4H, m; 2.84 ppm, 4H, m.

Cmpd #	LC/MS (M+1) (obs)	RT (mins)	^{1}H NMR
II-66	502.00	3.16	H NMR DMSO: 2.88(t, 4H), 3.64(t, 4H), 3.96(s, 2H), 7.03(m, 1H), 7.21(s, 1H), 7.62(m, 2H), 7.68(m 1H), 7.76(d, 1H), 7.81(d, 1H), 8.23(m, 1H)
II-67	488.20	3.56	H NMD DMSO: 1.0(t, 6H), 3.16(q, 4H),3.93(s, 2H), 7.02(m, 1H), 7.20(s, 1H), 7.55(m, 1H), 7.60(m, 1H),7.65(dd, 1H), 7.77(d, 1H), 7.80(d, 1H), 8.24(m, 1H)
II-68	391.10	2.72	H1NMR (500MHz, DMSO-d6, ppm) 11.96 (s,1H), 8.66 (d,1H, J=7.80), 8.29 (m,1H), 7.97 (d,1H, J=2.47Hz), 7.45 (s,1H), 7.22 (m,1H), 7.12 (m,1H), 6.72-6.65 (m,4H), 4.17 (s, 2H), 3.26 (m,1H), 1.33 (m,2H), 1.04 (m, 2H)
II-69	419.10	3.20	H1NMR (500MHz, DMSO-d6, ppm) 11.91 (s,1H), 8.66 (d,1H, J=7.90), 8.29 (m,1H), 7.97 (d,1H, J=2.51Hz), 7.44 (s,1H), 7.20 (m,1H), 7.12 (m,1H), 6.88 (m,2H), 6.76 (m,1H), 5.99 (s,2H), 4.18 (s, 2H), 3.28 (m,1H), 1.33 (m,2H), 1.04 (m, 2H)
II-70	405.10	3.31	
II-71	364.10	2.78	1H NMR 500 MHz (DMSO-d6) 11.82 ppm, 1H, s; 9.04 ppm, 1H, m; 8.35 ppm, 1H, d; 8.25 ppm, 2H, m; 7.93 ppm, 1H, s; 7.79 ppm, 1H, s; 7.23 ppm, 1H, m; 7.14 ppm, 1H, m; 6.88 ppm, 2H, m; 6.83 ppm, 1H, m; 4.46 ppm, 2H, d; 3.73 ppm, 3H, s.
II-72	498.00	2.64	1H-NMR(DMSO) 12.45, s, 1H; 11.85, s, 1H; 8.50, d, 1H; 8.30, m, 1H; 7.85, d, 1H; 7.80, s, 1H; 7.70-7.75, m, 2H; 7.55-7.60, m, 2H; 7.38, s, 1H; 7.18-7.20, m, 1H; 4.00, s, 2H; 3.15, 2.80-2.83, m, 2H; 1.75-1.80, m, 3H; 1.70-1.75, m, 2H; 1.45-1.50, m, 2H
II-73	453.06	2.72	H1NMR (500MHz, DMSO-d6, ppm) 11.92 (s,1H), 8.64 (d,1H, J=7.18Hz), 8.29 (m,1H), 7.96 (d,1H, J=2.51Hz), 7.90 (d,2H, J=8.26Hz), 7.60 (d,2H, J=8.25Hz), 7.45 (s,1H), 7.20 (m,1H), 4.43 (s, 2H), 3.20 (m,3H), 3.18 (m,1H), 1.34 (m,2H), 1.10 (m, 2H)
II-74	413.05	2.32	H1NMR (500MHz, DMSO-d6, ppm) 12.48 (s,1H), 11.89 (s,1H), 8.52 (d,1H, J=7.28Hz), 8.29 (m,1H), 7.92-7.86 (m,3H), 7.62 (d,1H, J=8.22Hz), 7.38 (s,1H), 7.20 (m,1H), 3.96 (s, 2H), 3.20 (m,3H)

Cmpd #	LC/MS (M+1) (obs)	RT (mins)	^{1}H NMR
II-75	439.10	3.60	H1NMR (500MHz, DMSO-d6, ppm) 11.87 (s,1H), 8.61 (d,1H, J=7.31Hz), 8.28 (dd,1H, J=4.62,1.29Hz), 7.95 (d,1H, J=2.52Hz), 7.43 (s,1H), 7.35 (d,1H, J=8.51Hz), 7.19 (m,1H), 7.06 (d,1H, 2.57Hz), 6.92 (m,1H), 4.33 (s, 2H), 3.36 (m,1H), 3.17 (s,3H), 1.36 (m,2H), 1.09 (m, 2H)
II-76	515.10	2.44	
II-77	444.90	3.80	DMSO-d6: 12.35(brs,1H), 12.09(s,1H), 8.74(d,1H),8.32(d,1H), 7.96(s,1H), 7.43(s,1H), 7.25(t,1H), 7.91(m,2H), 6.84(dd,1H), 3.77(s,2H), 3.75(s,3H),.
II-78	507.90	3.32	DMSO-d6: 12.40(s,1H), 12.10(s,1H), 9.73(s,1H), 8.74(d,1H),8.32(d,1H), 7.97(d,1H), 7.43(s,1H), 7.30(t,1H), 7.21(s,1H), 7.10(m,1H), 3.79(s,2H), 2.89(s,3H),
II-79	414.90, 413.00	3.78, 9.60	DMSO-d6: 12.39(s,1H), 12.09(s,1H), 8.74(d,1H),8.33(d,1H), 7.97(d,1H), 7.25-7.43(m,6H), 3.77(s,2H), 3.81(s,2H).,1H NMR (DMSO) 3.81 (2H, s), 7.20-7.49 (6H, m), 7.99 (1H, s), 8.35 (1H, brs), 8.77 (1H, brs), 12.15 (1H, brs), 12.45 (1H, brs).
II-80	483.10	2.67	1H NMR 500 MHz (DMSO-d6) 11.85 ppm, 1H, S; 9.20 PPM, 1H, m; 8.36 ppm, 1H, d; 8.24 ppm, 2H, m; 7.93 ppm, 1H, s; 7.82 ppm, 1H, s; 7.67 ppm, 4H, m; 7.15 ppm, 1H, m; 4.62 ppm, 2H, d; 3.60 ppm, 4H, m; 2.82 ppm, 4H, m.
II-81	321.00	2.43	12.29 (s, 1H), 11.27 (s, 1H), 8.68 (d, 1H), 8.33 (d, 1H), 8.20 (s, 1H), 8.08 (d, 2H), 7.65 (s, 1H), 7.58 (m, 1H), 7.51 (m, 2H), 7.26 (m, 1H) DMSO-d6
II-82	446.00	2.49	CD3OD 8.52 d (1H), 8.23 d (1H), 7.83 s (1H), 7.21 m (5H), 3.89 s (2H), 2.96 s (3H)
II-83	517.20	1.92	H1NMR (500MHz, CDCl3+MeOH-d4, ppm) 9.09 (d,1H, J= 7.85Hz), 8.28 (d,1H, J= 5.59), 7.92 (s,1H), 7.45 (m,1H,), 7.25 (m,3H), 6.9 (m,1H), 6.8 (m, 2H), 4.20 (s,2H), 4.05 (m,2H), 3.30 (m,2H), 3.20 (m,1H), 2.20 (m, 2H), 1.38 (m,2H), 1.07 (m,2H)

Cmpd #	LC/MS (M+1) (obs)	RT (mins)	^{1}H NMR
II-84	531.20	1.96	H1NMR (500MHz, CDCl3+MeOH-d4, ppm) 9.12 (d,1H, J= 7.56Hz), 8.28 (m,1H), 7.93 (s,1H), 7.47 (m,1H,), 7.25 (m,2H), 7.20 (s,1H), 6.95 (m,1H), 6.80 (m, 2H), 4.25 (s,2H), 4.10 (m,2H), 3.35 (m,2H), 3.20 (m,1H), 2.93 (s,3H), 2.25 (m, 2H), 1.41 (m,2H), 1.09 (m,2H)
II-85	503.20	1.96	H1NMR (500MHz, CDCl3+MeOH-d4, ppm) 9.11 (d,1H, J= 7.88Hz), 8.28 (m,1H), 7.92 (s,1H), 7.47 (m,1H,), 7.25 (m,2H), 7.20 (s,1H), 6.95 (m,1H), 6.80 (m, 2H), 4.30 (m,2H), 4.21 (s,2H), 3.60 (m,8H), 3.23 (m,1H), 2.25 (m, 2H), 1.38 (m,2H), 1.07 (m,2H)
II-86	517.20	2.06	H1NMR (500MHz, CDCl3+MeOH-d4, ppm) 9.09 (d,1H, J= 7.92Hz), 8.28 (m,1H), 7.92 (s,1H), 7.47 (m,1H,), 7.25 (m,2H), 7.18 (s,1H), 6.94 (m,1H), 6.87 (s,1H), 6.82 (m, 1H), 4.28 (m,2H), 4.20 (s,2H), 3.50 (m,7H), 3.34 (m, 2H), 3.22 (m,1H), 2.86 (s,3H), 2.25 (m, 2H), 1.38 (m,2H), 1.07 (m,2H)
II-87	524.10	3.41	H1NMR (500MHz, MeOH-d4, ppm) 8.78 (d,1H, J= 7.74Hz), 8.31 (m,1H), 7.95 (s,1H), 7.60 (m,6H,) 4.42 (s,2H), 3.70 (m,4H),3.30 (m,1H), 2.95 (m,4H), 3.20 (m,1H), 2.20 (m, 2H), 1.40 (m,2H), 1.10 (m,2H)
II-88	453.00	3.90	H1NMR (500MHz, MeOH-d4, ppm) 8.99 (d,1H, J= 7.89Hz), 8.31 (m,1H), 7.98 (s,1H), 7.44 (m,2H,) 7.38 (s,1H), 6.80 (m, 5H), 4.26 (s,2H), 3.30 (m,1H),1.34 (m,2H), 1.05 (m,2H)
II-89		1.91	
II-90		1.86	
II-91	369.10	3.45	H NMR CD3OD: 3.8(s, 2H), 7.2(s, 1H), 7.27(m, 1H), 7.35(m, 4H), 7.73(d, 1H), 8.20(d, 1H)
II-92	399.00	3.44	H NMR CD3OD: 3.76(s, 2H), 3.80(s, 3H), 6.85(dd, 1H), 6.97(m 2H), 7.19(m, 2H), 7.26(dd, 1H), 7.7(s, 1H), 8.16(d, 1H)
II-93	504.00	3.66	H NMR CD3OD: 1.15(t, 6H), 3.25(q, 4H), 3.95(s, 2H), 7.2(m, 2H), 7.6(dd, 1H), 7.65(dd, 1H), 7.69(s, 1H), 7.75(dd, 1H),7.85(s, 1H), 8.13(d, 1H)
II-94	462.00	2.90	H NMR DMSOd-6: 3.0(s, 3H), 3,78(s, 2H), 7.1(m, 2H), 7.24(m, 3H), 7.3(dd, 1H), 7.78(s, 1H), 8.25(d, 1H), 9.74(s, br, 1H)
II-95	510.10	2.24	H NMR DMSO: 1.28(m, 2H), 1.38(m, 2H), 1.59(m, 1H), 1.75(m, 2H), 1.80(d, 2H), 2.83(m 2H), 3.25(d, 2H), 3.75(s, 2H), 3.97(t, 2H), 6.85(dd, 1H), 6.9(m, 2H), 7.20(m, 3H), 7.75(s, 1H), 8.20(d, 1H)

Cmpd #	LC/MS (M+1) (obs)	RT (mins)	^{1}H NMR
II-96	405.10	3.65	CD3CN 13.11 s (1H), 9.18 d (1H), 8.39 d (1H), 8.08 s (1H), 7.57 q (1H), 7.35 s (1H), 7.29 m (1H), 6.87 m (3H), 4.57 m (1H), 4.32 m (1H), 3.94 m (1H), 3.80 s (3H), 2.24 m (2H), 2.12 m (2H)
II-97	485.10	1.71	
II-98	349.00	3.11	DMSO-d6: 12.21(brs,1H), 11.99(s,1H), 8.52(dd,1H),8.29(dd,1H), 7.71(d,1H), 7.26-7.36(m,5H), 7.17(dd,1H), 3.78(s,2H), 2.41(s,3H),.
II-99	379.10	2.93	DMSO-d6: 12.19(s,1H), 12.04(s,1H), 8.54(dd,1H),8.31(dd,1H), 7.72(d,1H), 7.19-7.26(m,2H), 6.80-6.85(m,3H), 7.10(m,1H), 3.73(s,3H),3.69(s,2H), 2.41(s,3H).
II-100	442.00	2.88	DMSO-d6: 12.22(s,1H), 11.99(s,1H), 9.73(s,1H), 8.51(d,1H), 8.29(dd,1H), 7.71(d,1H), 7.29(t,1H), 7.08-7.21(m,4H), 3.76(s,2H), 2.99(s,3H), 2.41(s,3H).
II-101	498.00	2.70	DMSO-d6: 12.26(s,1H), 11.99(s,1H),8.51(d,1H),8.29(dd,1H), 7.64-7.76(m,5H), 7.17(dd,1H), 3.96(s,2H), 3.60(m,4H), 2.87(m,4H), 2.41(s,3H).
II-102	369.00	3.74	CDCl3: 11.85(brs,1H), 9.59(brs,1H), 8.15(d,1H),8.11(d,1H), 7.76(s,1H), 7.17-7.26(m,5H), 6.84(s,1H), 3.76(s,2H), .
II-103	399.00	3.75	DMSO-d6: 12.36(s,1H), 12.09(s,1H), 8.61(d,1H),8.26(dd,1H), 7.98(d,1H), 7.43(s,1H), 7.25(t,1H), 6.83-6.96(m,3H), 3.77(s,2H), 3.75(s,3H).
II-104	462.00	3.29	CD3OD: 8.62(s,1H), 8.20(s,1H), 7.88(s,1H), 7.32(t,1H), 7.10-7.25(m,3H), 3.82(s,2H), 2.97(s,3H)
II-105	518.00	3.54	CD3OD: 8.63(d,1H),8.20(d,1H), 7.89(s,1H), 7.81(s,1H), 7.71(m,2H), 7.63(s,1H), 7.22(d,1H), 3.97(s,2H), 3.68(m,4H), 2.97(m,4H)
II-106	427.10	2.79	1H NMR 500MHz (DMSO-d6) 11.86 ppm, 1H, s; 9.74 ppm, 1H, s; 9.10 ppm, 1H, t; 8.37 ppm, 1H,d; 8.26 ppm, 2H, m; 7.92 ppm, 1H, s; 7.81 ppm, 1H, s; 7.28 ppm, 1H, m; 7.13 ppm, 4H, m; 4.46 ppm, 2H, d; 2.98 ppm, 3H, s.
II-107	563.00	3.60	DMSO-d6: 12.46(s,1H), 12.10(s,1H), 8.74(d,1H), 8.32(d,1H), 7.97(d,1H),7.77(s,1H), 7.64-7.71(m,3H), 7.44(s,1H), 3.98(s,2H), 3.61(m,4H), 2.87(m,4H)

Cmpd #	LC/MS (M+1) (obs)	RT (mins)	^{1}H NMR
II-108	497.10	1.54	CD3CN13.6 s (1H), 11.68 s (1H), 10.85 s (1H),8.97 d (1H), 8.35 d (1H), 8.0 s (1H), 7.50 dd (1H), 7.34 d (1H), 7.24 s (1H), 7.07 s (1H), 6.92 m (1H), 4.36 m (2H), 3.93 s (2H), 3.65 s (4H), 3.55 m (6H),
II-109	511.10	1.70	CD3CN13.18 s (1H), 10.90 s (1H),9.03 d (1H), 8.38 d (1H), 8.04 s (1H), 7.53 dd (1H), 7.34 d (1H), 7.28 s (1H), 7.10 s (1H), 6.92 dd (1H), 4.36 m (2H), 3.95 s (2H), 3.55 m (8H), 2.85 s (3H)
II-110	511.10	1.45	CD3CN13.18 s (1H), 10.90 s (2H),9.05 d (1H), 8.40 d (1H), 8.06 s (1H), 7.56 dd (1H), 7.34 d (1H), 7.30 s (1H), 7.05 s (1H), 6.92 dd (1H), 4.11 m (2H), 3.95 s (2H), 3.59 m (8H), 3.33 m (2H), 2.22 m (2H)
II-111	525.10	1.70	CD3CN13.21 s (1H), 11.19 s (1H),9.05 d (1H), 8.40 d (1H), 8.06 s (1H), 7.53 dd (1H), 7.34 d (1H), 7.30 s (1H), 7.05 s (1H), 6.92 dd (1H), 4.11 m (2H), 3.95 s (2H), 3.59 m (8H), 3.33 m (2H),2.86 s (3H), 2.22 m (2H)
II-112	482.10	3.19	
II-113	442.10	2.59	H1NMR (500MHz, dmso-d6, ppm) 8.55 (d,1H, J= 7.85Hz), 8.25 (d,1H, J= 5.59Hz), 7.40-7.10 (m,6H), 3.90(s,2H), 3.30 (s,3H), 2.95 (s, 3H)
II-114	364.10	2.87	1H NMR 500 MHz (DMSO-d6) 12.00 ppm, 1H, s; 8.88 ppm, 1H, t; 8.32 ppm, 2H, m; 8.01 ppm, 1H, s; 7.87 ppm, 1H, s; 7.83 ppm, 1H, s; 7.26 ppm, 2H, m; 6.92 ppm, 2H, m; 6.93 ppm, 2H, m; 6.82 ppm, 1H, d; 4.43 ppm, 2H, d; 3.70 ppm, 3H, s.
II-115	427.10	2.72	1H NMR 500 MHz (DMSO-d6) 12.10 ppm, 1H, s; 9.72 ppm, 1H, s; 8.98 ppm, 1H, t; 8.32 ppm, 2H, m; 7.99 ppm, 1H, s; 7.81 ppm, 1H, s; 7.42 ppm, 1H, s; 7.28 ppm, 1H, m; 7.20 ppm, 2H, m; 7.11 ppm, 2H, m; 4.43 ppm, 2H, d; 2.95 ppm, 3H, s.
II-116	284.00, 284.00	2.00, 1.92	1H NMR 500 MHz (DMSO-d6) 12.50 ppm, 1H, s; 11.84 ppm, 1H, s; 8.50 ppm, 1H, d; 8.29 ppm, 1H, d; 7.78 ppm, 1H, d; 7.42 ppm, 1H, s; 7.15 ppm, 1H, m; 4.08 ppm, 2H, s.,1H NMR 500 MHz (DMSO-d6) 12.53 ppm, 1H, s; 11.81 ppm, 1H, s; 8.47 ppm, 1H, d; 8.28 ppm, 1H, d; 7.83 ppm, 1H, s; 7.40 ppm, 1H, s; 7.15 ppm, 1H, m; 4.05 ppm, 2H, s.

Cmpd #	LC/MS (M+1) (obs)	RT (mins)	^{1}H NMR
II-117	427.10	2.76	1H NMR 500 MHz (DMSO-d6) 9.78 ppm, 1H, s; 8.88 ppm, 1H, t; 8.27 ppm, 2H, m; 8.00 ppm, 1H, s; 7.88 ppm, 1H, s; 7.77 ppm, 1H, s; 7.25 ppm, 1H, m; 7.15 ppm, 2H, m, 7.08 ppm, 2H, m; 4.43 ppm, 2H, d; 2.97 ppm, 3H, s.
II-118	353.00	3.46	CD3OD: 8.33(dd,1H), 8.15(dd,1H), 7.90(s,1H),7.28-7.38(m,4H), 7.28(m,1H), 7.19(s,1H), 3.81(s,2H)..
II-119	383.00	3.49	CD3OD: 8.33(dd,1H), 8.15(s,1H), 7.90(s,1H),7.25(m,1H),7.20(d,1H), 6.94(m,1H), 6.85(m,1H), 3.80(s,3H), 3.78(s,2H).
II-120	446.00	3.03	DMSO-d6: 12.38(s,1H), 12.00(s,1H), 9.73(s,1H), 8.36(dd,1H), 8.26(s,1H),7.97(d,1H), 7.41(s,1H),7.30(t,1H), 7.13(s,1H), 7.10(m,3H),3.78(s,2H), 2.99(s,3H)
II-121	502.00	3.38	CD3OD: 8.34((dd,1H), 8.16(d,1H), 7.91(s,1H),7.81(s,1H), 7.70(m,2H), 7.62(m,1H), 7.21(s,1H),3.97(s,2H), 3.67(m,4H), 2.97(m,4H)
II-122	389.00	3.72	DMSO-d6: 12.42(s,1H), 12.01(s,1H), 8.36(dd,1H), 8.26(s,1H),7.98(d,1H), 7.46(m,1H),7.41(s,1H), 7.23(m, 1H), 7.08(m,1H),3.88(s,2H)3.78(s,2H), 2.99(s,3H)
II-123	540.00	1.54	
II-124	484.10	2.40	
II-125	554.20	2.60	H1NMR (500MHz, MeOH-d4, ppm) 8.88 (d,1H, J= 8.04Hz), 8.34 (d,1H,J=5.34Hz), 7.96 (s,1H), 7.89 (s,1H,) 7.79 (d,1H,J=7.17Hz), 7.64 (d,1HJ=8.00Hz), 7.58 (m,2H), 7.40 (m,1H), 7.32 (s,1H), 3.96 (m,2H), 2.97 (m, 14H), 2.81 (s,3H)
II-126	541.00	1.89	
II-127	364.10	2.75	1H NMR (DMSO-d6) 8.25 ppm, 1H, d;8.18 ppm, 1H, d; 7.76 ppm, 1H, d; 7.25 ppm, 1H, t;7.16 ppm, 1H, m; 7.08 ppm, 1H, d; 6.91 ppm, 2H, m;6.87 ppm, 1H, m; 6.67 ppm, 1H, d; 3.78 ppm, 3H, s; 3.63 ppm, 2H, s.
II-128	427.10	2.69	1H NMR (DMSO-d6) 11.80 ppm, 1H, s;11.33 ppm, 1H, s; 9.70 ppm, 1H, s; 8.27 ppm, 1H, d;8.18 ppm, 1H, d; 7.71 ppm, 1H, s; 7.25 ppm, 1H, t;7.15 ppm, 5H, m; 6.66 ppm, 1H, s; 3.67 ppm, 2H, s;2.98 ppm, 3H, s.

Cmpd #	LC/MS (M+1) (obs)	RT (mins)	^{1}H NMR
II-129			1H NMR (DMSO-d6) 8.24 ppm, 1H, d;8.18 ppm, 1H, d; 7.74 ppm, 1H, s; 7.70 ppm, 2H, m;7.64 ppm, 3H, m; 7.18 ppm, 1H, m; 7.11 ppm, 1H, d;6.69 ppm, 1H, d; 3.87 ppm, 2H, s; 3.60 ppm, 4H, m;2.85 ppm, 4H, m.
II-130	483.10	2.73	1H NMR 500 MHz (DMSO-d6) 12.oo ppm, 1H, s; 9.04 ppm, 1H, t; 8.31 ppm, 2H, m; 8.05 ppm, 1H, s; 7.86 ppm, 1H, d; 7.77 ppm, 1H, s; 7.63 ppm, 4H, m; 7.20 ppm, 1H, m; 4.60 ppm, 2H, d; 3.59 ppm, 4H, m; 2.85 ppm, 4H, m.
II-131	351.00	2.69	CD3OD: 8.33(s,1H), 7.95(s,1H), 7.90(s,1H),7.27-7.38(m,5H), 7.22(s,1H), 3.82(s,2H)..
II-132	444.00	2.50	CD3OD: 8.49(s,1H), 7.95(m,2H), 7.26-7.32(m,3H), 7.30(t,1H), 7.17(m,2H), 3.82(s,2H), 2.96(s,3H)
II-133	310.00	2.31	1HNMR (DMSO) 12.30, s, 1H; 11.89, s, 1H; 8.49, s, 1H; 8.30, d, 1H; 7.91, s, 1H; 7.40, s, 1H; 7.18-7.20, m, 1H; 1.70-1.90, m, 4H
II-134	259.00	1.70	1HNMR (DMSO) 12.12, s, 1H; 11.81, s, 1H; 8.49, d, 1H; 8.26, d, 1H; 7.83, s, 1H; 7.32, s, 1H; 7.15-7.17, m, 1H; 2.16, s, 3H
II-135	494.00	2.57	CD3OD: 8.33(d,1H), 8.15(t,1H), 7.89(s,1H), 7.22(t,1H), 7.19(s,1H), 6.92(m,2H), 6.82(dd,1H), 4.00(t,2H), 3.78(s,1H), 3.33(m,1H), 2.91(m,2H), 1.94(m,2H), 1.80(m,2H), 1.65(brs,1H), 1.47(m,2H), 1.37(m,2H).
II-136	495.00	2.09	CD3OD: 8.35(dd,1H), 8.16(t,1H), 7.91(s,1H), 7.27(t,1H), 7.19(s,1H), 6.99(m,2H), 6.90(dd,1H), 4.29(brm,2H), 3.32-3.50(m,10H), 2.90(s,3H)
II-137	509.00	2.05	CD3OD: 8.32(dd,1H), 8.15(t,1H), 7.90(s,1H), 7.26(t,1H), 7.19(s,1H), 6.99(m,2H), 6.86(dd,1H), 4.12(t,2H), 3.79(s,2H), 3.40-3.55(brm, 8H), 3.25(m,2H), 2.91(s,3H), 2.18(m,2H).
II-138	442.10	2.83	
II-139	456.10	2.78	
II-140	456.10	2.73	
II-141	470.10	3.37	

Cmpd #	LC/MS (M+1) (obs)	RT (mins)	^{1}H NMR
II-142	289.20	1.90	1H NMR 500 MHz (DMSO-d6) 12.1 ppm, 1H, s;11.94 ppm, 1H, s; 8.66 ppm, 1H, d; 8.26 ppm, 1H, d;7.88 ppm, 1H, s;7.42 ppm, 1H, s; 7.22 ppm, 1H, d; 4.14 ppm, 3H; s;3.35 ppm, 2H, s.
II-143	289.10	1.70	
II-144	303.20	2.10	.
II-145	330.20	1.70	
II-146	329.10	2.00	1H NMR 500 MHz (DMSO-d6) 12.60 ppm, 1H, s;11.91 ppm, 1H, s; 8.58 ppm, 1H, d; 8.32 ppm, 1H, d;7.91 ppm, 1H, s; 7.40 ppm, 1H, s; 7.25 ppm, 1H, d;5.20 ppm, 1H, m; 2.52 ppm, 2H, m; 2.49 ppm, 2H, m.
II-147	329.10	1.45	
II-148	328.10	1.69	
II-149	316.10	1.41	1H NMR 500 MHz (DMSO-d6) 12.25 ppm, 1H, s;11.92 ppm, 1H, s; 8.62 ppm, 1H, d; 8.32 ppm, 2H, m;7.88 ppm, 1H, s; 7.40 ppm, 1H, s; 7.25 ppm, 1H, m;4.02 ppm, 2H, s; 1.84 ppm, 3H, s..
II-150	417.00	3.78	DMSO-d6: 12.38(s,1H), 12.01(s,1H), 8.38(dd,1H), 8.26(d,1H), 7.40(s,1H), 7.36(d,1H), 7.04(d,1H), 6.91(dd,1H), 3.91(s,2H), 3.78(s,3H)
II-151	464.00	3.13	DMSO-d6: 12.43(s,1H), 12.01(s,1H), 9.67(s,1H), 8.36(dd,1H), 8.26(s,1H), 7.98(d,1H), 7.42(s,1H), 7.24(d,1H), 7.17(m,2H), 6.91(dd,1H), 3.88(s,2H), 2.97(s,3H)
II-152			
II-153	328.00	1.72	1H NMR 500 MHz (DMSO-d6) 12.38 ppm, 1H, s;11.92 ppm, 1H, s; 8.58 ppm, 1H, d; 8.32 ppm, 1H, s;7.90 ppm, 2H, m; 7.39 ppm, 1H, s; 7.20 ppm, 1H, d;4.38 ppm, 1H, m; 2.41 ppm, 1H, m; 2.20 ppm, 2H, m; 2.08 ppm, 1H, m.
II-154	315.10	2.34	1H NMR 500 MHz (DMSO-d6) 12.02 ppm, 1H, s;11.98 ppm, 1H, s; 8.62 ppm, 1H, d; 8.40 ppm, 1H, s;7.40 ppm, 1H, s; 7.24 ppm, 1H, d; 4.60 ppm, 1H, m;4.03 ppm, 1H, m; 3.86 ppm, 1H, m; 2.24 ppm, 1H, m;1.96 ppm, 3H, m.
II-155	329.00	1.88	1H NMR 500 MHz (DMSO-d6) 12.60 ppm, 1H, s; 11.91 ppm, 1H, s; 8.58 ppm, 1H, d; 8.32 ppm, 1H, d; 7.91 ppm, 1H, s; 7.40 ppm, 1H, s; 7.25 ppm, 1H, d; 5.20 ppm, 1H, m; 2.52 ppm, 4H, m.

Cmpd #	LC/MS (M+1) (obs)	RT (mins)	^{1}H NMR
II-156	330.10	1.70	1H NMR 500 MHz (DMSO-d6) 12.25 ppm, 1H, s; 11.92 ppm, 1H, s; 8.60 ppm, 1H, d; 8.32 ppm, 2H, m; 7.88 ppm, 1H, s; 7.43 ppm, 1H, s; 7.25 ppm, 1H, d; 4.53 ppm, 1H, m; 1.88 ppm, 3H, s; 1.30 ppm, 3H, d.
II-157	275.10	1.60	1H NMR 500 MHz (DMSO-d6) 11.92 ppm, 1H, s;11.76 ppm, 1H, s; 8.58 ppm, 1H, d; 8.29 ppm, 1H, d;7.91 ppm, 1H, s; 7.41 ppm, 1H, s; 7.22 ppm, 1H, d;4.15 ppm, 2H, s.
II-158	301.16	1.89	1H NMR 500 MHz (DMSO-d6) 11.90 ppm, 1H, s;11.32 ppm, 1H, s; 8.65 ppm, 1H, d; 8.29 ppm, 1H, d;7.91 ppm, 1H, s; 7.41 ppm, 1H, s; 7.22 ppm, 1H, d;1.23 ppm, 2H, m; 1.15 ppm, 2H, m.
II-159	317.16	2.15	1H NMR 500 MHz (DMSO-d6) 11.95 ppm, 1H, s;11.60 ppm, 1H, s; 8.61 ppm, 1H, d; 8.32 ppm, 1H, s;7.92 ppm, 2H, m; 7.42 ppm, 1H, s; 7.22 ppm, 1H, d;4.00ppm, 1H, m; 2..05 ppm, 1H, m; 1.04 ppm, 6H, m.
II-160	329.21	2.89	1H NMR 500 MHz (DMSO-d6) 12.60 ppm, 1H, s;11.92 ppm, 1H, s; 8.68 ppm, 1H, d; 8.32 ppm, 1H, d;7.96 ppm, 1H, s; 7.50 ppm, 1H, s; 7.22 ppm, 1H, d;2.84 ppm, 2H, d; 2.04 ppm, 1H, m; 0.99 ppm, 6H, d.
II-161	337.00, 336.90	2.36, 1.70	1H NMR 500 MHz (DMSO-d6) 12.60 ppm, 1H, s;11.95 ppm, 1H, s; 8.58 ppm, 1H, d; 8.32 ppm, 1H, d;7.93 ppm, 1H, s; 7.51 ppm, 1H, s; 7.22 ppm, 1H, d;4.50 ppm, 2H, s; 3.20 ppm, 3H, s.,H NMR (500 MHz, DMSO-d6) 12.62 (s, 1H), 11.86 (s, 1H), 8.49 (d, J = 8.0 Hz, 1H), 8.28 (dd, J = 4.6, 1.5 Hz, 1H), 7.88 (d, J = 2.6 Hz, 1H), 7.47 (s, 1H), 7.18 (dd, J = 7.9, 4.6 Hz, 1H), 4.47 (s, 2H), 3.21 (s, 3H).
II-162	287.10, 287.00	2.78, 8.04	1H NMR 500 MHz (DMSO-d6) 12.08 ppm, 1H, s;11.96 ppm, 1H, s; 8.66 ppm, 1H, d; 8.32 ppm, 1H, d;7.88 ppm, 1H, s; 7.33 ppm, 1H, s; 7.22 ppm, 1H, d;2.78 ppm, 1H, m; 1.16 ppm, 6H, d.,1H NMR (DMSO) 1.13 (6H, d, J = 6.8Hz), 2.71-2.86 (1H, m), 7.11-7.21 (1H, m), 7.38 (1H, s), 7.85 (1H, brs), 8.22-8.30 (1H, m), 8.46-8.52 (1H, m), 11.85 (1H, brs), 12.12 (1H, brs).
II-163	273.10	2.19	1H NMR 500 MHz (DMSO-d6) 12.08 ppm, 1H, s;11.95 ppm, 1H, s; 8.58 ppm, 1H, d; 8.32 ppm, 1H, d;7.88 ppm, 1H, s; 7.38 ppm, 1H, s; 7.22 ppm, 1H, d;2.50 ppm, 2H, q; 1.16 ppm, 3H, t.

Cmpd #	LC/MS (M+1) (obs)	RT (mins)	^{1}H NMR
II-164	330.20	1.65	1H NMR 500 MHz (DMSO-d6) 12.18 ppm, 1H, s;11.95 ppm, 1H, s; 8.58 ppm, 1H, d; 8.32 ppm, 1H, d;8.04 ppm, 1H, s; 7.88 ppm, 1H, s; 7.30 ppm, 1H, s; 7.22 ppm, 1H, d; 3.35ppm, 2H, m; 2.60 ppm, 2H, m;1.90 ppm, 3H, s.
II-165	274.10	0.55	!H NMR 500 MHz (DMSO-d6) 12.60 ppm, 1H, s; 11.92 ppm, 1H, s; 8.54 ppm, 1H, d; 8.32 ppm, 1H, d; 8.28 ppm, 3H, s;7.87 ppm, 1H, s; 7.46 ppm, 1H, s; 7.22 ppm, 1H, d; 3.93 ppm, 2H, s.
II-166	330.10	1.58	1H NMR 500 MHz (DMSO-d6) 12.95 ppm, 1H, s; 11.93 ppm, 1H, s; 8.48 ppm, 1H, d; 8.36 ppm, 3H, s; 8.32 ppm, 1H, s; 7.90 ppm, 1H, s; 7.51 ppm, 1H, s; 7.18 ppm, 1H, m; 4.13 ppm, 1H, m; 1.70 ppm, 3H, m; 0.96 ppm, 6H, d.
II-167	554.20	1.83	
II-168	539.20, 539.10	2.00, 1.92	
II-169	541.20, 541.10	1.90, 1.80	
II-170	339.00	1.27	
II-171	314.10	0.90	1H NMR 500 MHz (DMSO-d6) 12.90 (1H, s); 11.96 (1H, s); 9.50 (1H, s); 8.86 (1H, s); 8.52 (1H, d); 8.32 (1H, d); 7.88 (1H, s); 7.50 (1H, s); 7.22 (1H, m); 4.48 (1H, m); 3.32 (1H, m); 2.45 (1H, m); 2.05 (1H, m); 2.00 (2H, m).
II-172	315.10	2.17	1H NMR 500 MHz (DMSO-d6) 12.25 (1H, s); 11.89 (1H, s); 8.58 (1H, d); 8.30 (1H, d); 7.86 (1H, s); 7.40 (1H, s); 7.18 (1H, m); 3.95 (1H, t); 3.63-3.75 (3H, m); 3.34 (1H, m); 2.14 (2H, m).
II-173	328.10	0.94	1H NMR 500 MHz (DMSO-d6) 12.41 (1H, s); 11.97 (1H, s); 8.62 (2H, br s); 8.53 (1H, d); 8.30 (1H, d); 7.85 (1H, d); 7.40 (1H, s); 7.17 (1H, m); 3.40 (1H, m); 3.11-3.28 (2H, m); 2.88-3.05 (2H, m); 2.11 (1H, m); 1.80 (1H, m); 1.66 (2H, m).

Cmpd #	LC/MS (M+1) (obs)	RT (mins)	^{1}H NMR
II-174	328.10	0.74	1H NMR 500 MHz (DMSO-d6) 12.28 (1H, s); 11.92 (1H, s); 8.61 (1H, br s); 8.51 (1H, d); 8. 33 (1H, br s); 8.28 (1H, d); 7.85 (1H, d); 7.36 (1H, s); 7.17 (1H, m); 3.38 (2H, m); 2.96 (2H, m); 2.83 (1H, m); 2.04 (2H, m); 1.84 (2H, m).
II-175	329.10	2.51	1H NMR 500 MHz (DSMO-d6) 12.16 (1H, s); 11.92 (1H, s); 8,58 (1H, d); 8.32 (1H, d); 7.87 (1H, d); 7.36 (1H, s); 7.23 (1H, m); 3.95 (2H, m); 3.34 (2H, m); 2.80 (1H, m); 1.70 (4H, m).
II-176	364.20	1.73	H NMR (500 MHz, DMSO-d6) 12.73 (s, 1H), 11.91 (s, 1H), 8.48 (d, J = 7.9 Hz, 1H), 8.43 (s, 2H), 8.30 (d, J = 4.6 Hz, 1H), 7.86 (s, 1H), 7.48 (s, 1H), 7.36 (m, 2H), 7.29 (m, 2H), 7.19 (dd, J = 7.9, 4.7 Hz, 1H), 4.34 (s, 1H), 3.26 (m, 1H), 3.11 (m, 1H).
II-177	364.20	1.73	H NMR (500 MHz, DMSO-d6) 12.73 (s, 1H), 11.91 (s, 1H), 8.48 (d, J = 7.9 Hz, 1H), 8.43 (s, 2H), 8.30 (d, J = 4.6 Hz, 1H), 7.86 (s, 1H), 7.48 (s, 1H), 7.36 (m, 2H), 7.29 (m, 2H), 7.19 (dd, J = 7.9, 4.7 Hz, 1H), 4.34 (s, 1H), 3.26 (m, 1H), 3.11 (m, 1H)
II-178	378.20	1.70	H NMR (500 MHz, DMSO-d6) 12.81 (s, 1H), 11.92 (s, 1H), 9.23 (d, J = 24.1 Hz, 2H), 8.47 (d, J = 7.8 Hz, 1H), 8.29 (d, J = 4.5 Hz, 1H), 7.86 (s, 1H), 7.49 (s, 1H), 7.33 (m, 2H), 7.27 (m, 2H), 7.19 (dd, J = 7.9, 4.7 Hz, 1H), 3.97 (m, 1H), 3.27 (m, 2H), 2.59 (s, 3H).
II-179	288.10	0.50	H NMR (500 MHz, DMSO-d6) 12.73 (s, 1H), 11.93 (s, 1H), 8.95 (s, 2H), 8.51 (d, J = 7.4 Hz, 1H), 8.30 (d, J = 3.4 Hz, 1H), 7.89 (s, 1H), 7.48 (s, 1H), 7.20 (dd, J = 7.9, 4.7 Hz, 1H), 4.09 (s, 2H), 2.68 (s, 3H).
II-180	288.10	0.56	H NMR (500 MHz, DMSO-d6) 12.35 (s, 1H), 11.89 (s, 1H), 8.51 (d, J = 7.0 Hz, 1H), 8.29 (d, J = 6.0 Hz, 1H), 7.86 (s, 1H), 7.86 (s, 2H), 7.40 (s, 1H), 7.19 (dd, J = 7.9, 4.7 Hz, 1H), 3.15 (m, 2H), 2.85 (m, 2H).
II-181	314.10	0.67	H NMR (500 MHz, DMSO-d6) 12.05 (s, 1H), 8.99 (s, 1H), 8.44 (d, J = 7.9 Hz, 1H), 8.32 (d, J = 4.4 Hz, 1H), 8.20 (s, 1H), 8.12 (d, J = 2.4 Hz, 1H), 7.21 (dd, J = 7.9, 4.7 Hz, 1H), 4.70 (s, 2H), 3.91 (s, 2H), 3.36 (s, 2H), 3.29 (s, 2H).

Cmpd #	LC/MS (M+1) (obs)	RT (mins)	^{1}H NMR
II-182	303.00	1.68	H NMR (500 MHz, DMSO-d6) 12.03 (s, 1H), 8.63 (d, J = 7.9 Hz, 1H), 8.31 (m, 2H), 8.14 (m, 2H), 7.22 (m, 1H), 4.05 (m, 1H), 3.51 (m, 2H), 2.50 (d, J = 1.6 Hz, 3H).
II-183	331.00	1.92	H NMR (500 MHz, DMSO-d6) 12.07 (s, 1H), 8.62 (d, J = 7.1 Hz, 1H), 8.32 (d, J = 5.9 Hz, 1H), 8.15 (m, 2H), 7.23 (dd, J = 7.9, 4.7 Hz, 1H), 3.79 (m, 1H), 3.62 (m, 2H), 1.99 (m, 1H), 0.95 (dd, J = 14.8, 6.7 Hz, 6H)
II-184	365.10	2.06	H NMR (500 MHz, DMSO-d6) 12.10 (s, 1H), 8.91 (d, J = 8.4 Hz, 1H), 8.66 (d, J = 7.5 Hz, 1H), 8.32 (s, 1H), 8.18 (m, 2H), 7.45 (m, 2H), 7.35 (m, 2H), 7.25 (m, 2H), 5.11 (m, 1H), 3.87 (m, 1H), 3.79 (m, 1H).
II-185	365.10	2.05	H NMR (500 MHz, DMSO-d6) 12.10 (s, 1H), 8.91 (d, J = 8.4 Hz, 1H), 8.66 (d, J = 7.5 Hz, 1H), 8.32 (s, 1H), 8.18 (m, 2H), 7.45 (m, 2H), 7.35 (m, 2H), 7.25 (m, 2H), 5.11 (m, 1H), 3.87 (m, 1H), 3.79 (m, 1H).
II-186	404.00	1.78	H NMR (500 MHz, DMSO-d6) 12.04 (s, 1H), 10.13 (s, 1H), 9.11 (d, J = 6.9 Hz, 1H), 9.00 (m, 1H), 8.63 (m, 1H), 8.31 (m, 1H), 8.18 (s, 1H), 8.12 (d, J = 9.6 Hz, 1H), 7.55 (m, 2H), 7.50 (m, 2H), 1H), 4.60 (m, 2H), 3.22-3.80 (m, 4H), 2.2-2.3 (m, 2H).
II-187	328.10	1.48	
II-188	364.20	1.75	H NMR (500 MHz, DMSO-d6) 12.68 (s, 1H), 11.91 (s, 1H), 9.50 (s, 1H), 8.49 (d, J = 7.3 Hz, 1H), 8.29 (d, J = 4.6 Hz, 1H), 7.88 (d, J = 2.4 Hz, 1H), 7.53 (m, 2H), 7.47 (m, 4H), 7.19 (dd, J = 7.9, 4.7 Hz, 1H), 4.28 (s, 2H), 4.08 (s, 2H)
II-189	378.20	2.67	MeOD-H9.07 d (1H), 8.38 d (1H), 8.03 s (1H), 7.41 m (7H), 3.96 m (1H), 2.98 m (1H), 2.87 m (1H), 2.49 m (1H), 2.23 m (1H)
II-190	394.10	2.98	MeOD-H9.07 d (1H), 8.38 d (1H), 8.03 s (1H), 7.50 m (3H), 7.38 s (1H), 7.15 t (2H), 3.96 t (1H), 2.98 m (1H), 2.87 m (1H), 2.49 m (1H), 2.23 m (1H)
II-191	414.10	3.04	.MeOD-H9.07 d (1H), 8.38 d (1H), 8.03 s (1H), 7.50 m (2H), 7.38 s (1H), 7.05 t (2H), 4.30 t (1H), 3.04 m (1H), 2.98 m (1H), 2.52 m (1H), 2.21 m (1H)
II-192	412.10	3.01	MeOD-H8.99 d (1H), 8.33 d (1H), 7.98 s (1H), 7.48 m (3H), 7.34 m (3H), 4.52 t (1H), 3.06 m (2H), 2.53 m (1H), 2.23 m (1H),
II-193	457.10	2.83	2.5(CH3), 2.7(CH3),3.8(CH2),7.05(H),7.1(H), 7.2(2H), 7.25(H), 7.4(H), 7.89(H),

Cmpd #	LC/MS (M+1) (obs)	RT (mins)	^{1}H NMR
II-194	398.10	1.91	CD3CN (H)13.02 s (1H), 8.97 d (1H), 8.37 d (1H), 8.0 s (1H),7.90 d (1H), 7.55 d (1H), 7.42 m (3H), 7.30 s (1H)4.95 s (2H), 4.90 m (1H), 3.70 q (1H), 4.43 q (1H)
II-195	432.00	2.12	CD3CN (H)12.84 s (1H), 8.93 d (1H), 8.37 d (1H), 7.95 s (1H),7.62 d (1H), 7.42 m (3H), 7.28 s (1H)4.98 q(1H), 4.42 s (2H), 3.70 q (1H), 3.43 q (1H)
II-196	416.10	2.00	CD3CN (H)13.02 s (1H), 8.93 d (1H), 8.35 d (1H), 7.95 s (1H),7.46 d (2H), 7.36 m (1H), 7.24 s (1H)7.15 m (1H),5.45 s (2H), 4.90 q (1H), 3.70 q (1H), 3.37 q (1H)
II-197	344.00	1.30	H NMR (500 MHz, MeOD) ppm 8.63 (dd, J = 8.0, 1.3 Hz, 1H), 8.41 (dd, J = 5.3, 1.3 Hz, 1H), 8.07 (s, 1H), 7.45 (dd, J = 8.0, 5.3 Hz, 1H), 4.02 (s, 2H), 3.82 (s, 2H), 3.58 (t, J = 6.7 Hz, 2H), 3.52 (m, 2H), 3.35-3.26 (m, 6H), 2.24 (m, 2H)
II-198	357.20	1.26	H NMR (500 MHz, MeOD) ppm , 8.61 (d, J = 8.0 Hz, 1H), 8.42 (d, J = 6.5 Hz, 1H), 8.06 (s, 1H), , 7.45 (dd, J = 8.0, 5.2 Hz, 1H), 3.56-3.25(m, 13H), 3.15 (m,2H), 2.95 (s,3H) 2.15 (m,2H)
II-199	297.00	1.82	
II-200	301.10	1.61	
II-201	475.10	1.91	
II-202	505.20	1.90	
II-203	568.10	1.76	
II-204	399.10	1.56	
II-205	336.00	1.30	DMSO-d6: 12.5(brs,1H), 11.81(s,1H), 8.54(d,1H), 8.47-8.49(m,2H), 8.26(dd,1H), 7.84(s,1H), 7.75(d,1H), 7.36(dd,1H), 7.33(s,1H), 7.15(dd,1H), 3.84(s,2H)
II-206	354.00	1.60	CD3OD: 8.98(s,1H), 8.78(d,1H), 8.58(d,1H), 8.33(dd,1H), 8.16(t,1H), 8.04(dd,1H), 7.91(s,1H), 7.22(s,1H), 4.17(s,2H)
II-207	351.10	3.10	MeOD (H)8.56 d (1H), 8.24 d (1H), 7.85 s (1H), 7.53 d (2H),7.37 m (3H), 7.22 m (2H), 5.33 s (1H)
II-208	381.10	3.19	MeOD (H)8.92 d (1H), 8.34 d (1H), 7.98 s (1H), 7.42 m (1H), 7.33 s (1H), 7.28 t (1H), 7.12 m (2H), 6.88 d (1H), 5.31 s (1H) 3.80 s (3H)
II-209	387.10	3.23	MeOD (H)8.55 d (1H), 8.24 d (1H), 7.87 s (1H), 7.57 m (1H), 7.27 s (1H),7.21 m (1H), 7.0 m (2H), 5.58 s (1H)

Cmpd #	LC/MS (M+1) (obs)	RT (mins)	^{1}H NMR
II-210	351.10	2.74	MeOD (H) 8.56 d (1H), 8.24 d (1H), 7.85 s (1H), 7.53 d (2H), 7.37 m (3H), 7.22 m (2H), 5.33 s (1H)
II-211	444.10	3.30	DMSO (H)12.08 s (1H), 11.97 s (1H), 9.80 s (1H),8.62 d (1H), 8.31 d (1H), 7.92 s (1H),7.43 s (2H), 7.35 m (1H), 7.30 m (1H), 7.22 m (1H), 7.16 m (1H), 5.32 s (1H)
II-212	366.10	2.00	DMSO (H)12.17 s (1H), 12.0 s (1H), 8.62 d (1H), 8.32 d (1H), 7.92 s (1H), 7.47 m (4H), 7.23 m (2H), 5.41 s (1H)
II-213	368.10	1.76	DMSO (H)-HCl salt 13.01 s (1H), 12.24 s (1H), 9.10 s (3H), 8.67 d (1H), 8.38 d (1H), 7.95 s (1H), 7.70 m (2H), 7.55 s (1H), 7.38 m (2H), 7.30 m (1H), 5.34 s (1H)
II-214	350.00	1.67	DMSO (H)- HCl salt 13.06 s (1H), 12.40 s (1H), 9.16 s (3H), 8.70 d (1H), 8.39 d (1H), 8.0 s (1H), 7.70 m (2H), 7.59 s (1H), 7.50 m (3H), 7.33 m (1H), 5.36 s (1H)
II-215	336.00	0.26	H1NMR (500MHz, DMSO-d6, ppm) 8.63-8.59 (m,2H), 8.28 (d,1H, J=4.4Hz), 7.93 (m,1H), 7.86 (s,1H), 7.65 (s,1H), 7.57 (d,1H, J=2.8Hz), 7.55 (d,1H, J=2.8Hz), 7.44 (m,1H), 7.17 (s,1H), 3.33 (s,2H)
II-216	444.10	2.40	H NMR (500 MHz, DMSO-d6) ppm , 12.74 (s, 1H), 12.43 (s, 1H), 9.71 (s, 1H), , 8.25-8.23 (m, 2H), 7.85 (s, 1H), 7.46 (s, 1H), 7.31-7.28 (m, 1H), 7.23-7.20 (m, 2H), 7.13-7.09 (m, 2H), 3.80 (s, 2H), 3.00 (s, 3H)
II-217	352.00	1.77	H NMR (500 MHz, DMSO-d6) 12.23 (s, 1H), 11.92 (s, 1H), 8.54 (s, 1H), 8.30 (d, J = 4.5 Hz, 1H), 7.88 (s, 1H), 7.56 (s, 1H), 7.42 (s, 1H), 7.21 (dd, J = 10.3, 2.4 Hz, 1H), 4.02 (d, J = 5.4 Hz, 2H), 3.00 (s, 3H)
II-218	366.00	2.24	H NMR (500 MHz, DMSO-d6) 12.22 (s, 1H), 11.95 (s, 1H), 8.56 (d, J = 9.1 Hz, 1H), 8.30 (s, 1H), 7.89 (s, 1H), 7.56 (t, J = 5.9 Hz, 1H), 7.42 (s, 1H), 7.21 (dd, J = 7.9, 4.7 Hz, 1H), 4.00 (d, J = 5.9 Hz, 2H), 3.08 (q, J = 7.3 Hz, 2H), 1.26 (t, J = 7.3 Hz, 3H).
II-219	443.10	1.40	MeOD 9.28 d (1H), 8.48 d (1H), 8.12 s (1H), 7.66 m (1H), 7.58 s (1H), 7.53 m (2H), 7.40 m (2H), 5.36 s (1H), 3.04 s (3H)

Cmpd #	LC/MS (M+1) (obs)	RT (mins)	^{1}H NMR
II-220	380.10	2.14	H NMR (500 MHz, DMSO-d6) 12.19 (s, 1H), 11.95 (s, 1H), 8.52 (d, J = 6.8 Hz, 1H), 8.29 (dd, J = 4.7, 1.4 Hz, 1H), 7.87 (d, J = 2.6 Hz, 1H), 7.51 (t, J = 6.0 Hz, 1H), 7.41 (s, 1H), 7.19 (dd, J = 7.9, 4.7 Hz, 1H), 4.01 (d, J = 6.1 Hz, 2H), 3.22 (m, 1H), 1.27 (d, J = 6.8 Hz, 3H).
II-221	365.00	2.26	H NMR (500 MHz, DMSO-d6) 12.63 (s, 1H), 11.93 (s, 1H), 8.54 (d, J = 7.9 Hz, 1H), 8.30 (dd, J = 4.7, 1.4 Hz, 1H), 7.90 (d, J = 2.5 Hz, 1H), 7.48 (s, 1H), 7.20 (dd, J = 7.9, 4.7 Hz, 1H), 4.39 (q, J = 7.1 Hz, 1H), 3.25 (m, 2H), 1.60 (d, J = 7.0 Hz, 3H), 1.26 (t, J = 7.4 Hz, 3H).
II-222	366.00	2.24	H NMR (500 MHz, DMSO-d6) 12.23 (s, 1H), 11.95 (s, 1H), 8.57 (d, J = 7.9 Hz, 1H), 8.31 (dd, J = 4.7, 1.4 Hz, 1H), 7.90 (d, J = 2.5 Hz, 1H), 7.67 (d, J = 7.8 Hz, 1H)1H), 7.22 (dd, J = 7.9, 4.7 Hz, 1H), 4.30 (m, 1H), 2.93 (s, 3H), 1.38 (d, J=7.0 Hz, 3H).
II-223	394.00	2.30	H NMR (500 MHz, DMSO-d6) 12.31 (s, 1H), 11.89 (s, 1H), 8.53 (d, J = 6.8 Hz, 1H), 8.29 (dd, J = 4.7, 1.5 Hz, 1H), 7.88 (d, J = 2.6 Hz, 1H), 7.60 (d, J = 9.2 Hz, 1H), 7.42 (s, 1H), 7.19 (dd, J = 7.9, 4.7 Hz, 1H), 4.00 (q, J = 5.4 Hz, 1H), 2.87 (s, 3H), 2.05 (m, 1H), 0.94 (d, J = 6.7 Hz, 6H).
II-224	379.00	2.65	H NMR (500 MHz, DMSO-d6) 12.74 (s, 1H), 11.93 (s, 1H), 8.53 (dd, J = 7.9, 1.1 Hz, 1H), 8.30 (dd, J = 4.7, 1.5 Hz, 1H), 7.90 (d, J = 2.6 Hz, 1H), 7.49 (s, 1H), 7.20 (dd, J = 7.9, 4.7 Hz, 1H), 4.25 (dd, J = 11.3, 3.3 Hz, 1H), 3.08 (s, 3H), 2.13 (m, 1H), 1.96 (m, 1H), 1.34 (m, 2H), 0.94 (t, J = 7.3 Hz, 3H)
II-225	393.00	2.74	H NMR (500 MHz, DMSO-d6) 12.72 (s, 1H), 11.91 (s, 1H), 8.52 (d, J = 6.8 Hz, 1H), 8.29 (dd, J = 4.7, 1.5 Hz, 1H), 7.89 (d, J = 2.6 Hz, 1H), 7.48 (s, 1H), 7.20 (dd, J = 7.9, 4.7 Hz, 1H), 4.32 (dd, J = 11.4, 3.3 Hz, 1H), 3.24 (m, 2H), 2.14 (m, 1H), 1.93 (m, 1H), 1.33 (m, 1H), 1.26 (t, J = 7.4 Hz, 3H), 1.11 (t, J=7.5 Hz)
II-226	351.00	2.06	H NMR (500 MHz, DMSO-d6) 12.65 (s, 1H), 11.95 (s, 1H), 8.55 (d, J = 9.2 Hz, 1H), 8.30 (dd, J = 4.7, 1.5 Hz, 1H), 7.91 (d, J = 2.6 Hz, 1H), 7.49 (s, 1H), 7.21 (dd, J = 7.9, 4.7 Hz, 1H), 4.32 (q, J = 7.0 Hz, 1H), 3.09 (s, 3H), 1.61 (d, J = 7.1 Hz, 3H).

Cmpd #	LC/MS (M+1) (obs)	RT (mins)	^{1}H NMR
II-227	394.00	2.41	H NMR (500 MHz, DMSO-d6) 12.31 (s, 1H), 11.93 (s, 1H), 8.55 (d, J = 7.9 Hz, 1H), 8.30 (dd, J = 4.7, 1.5 Hz, 1H), 7.89 (d, J = 2.5 Hz, 1H), 7.60 (d, J = 9.1 Hz, 1H), 7.43 (s, 1H), 7.21 (dd, J = 7.9, 4.7 Hz, 1H), 4.00 (m, 1H), 2.87 (s, 3H), 2.06 (m, 1H), 0.94 (d, J = 6.7 Hz, 3H).
II-228	366.00	1.92	H NMR (500 MHz, DMSO-d6) 12.23 (s, 1H), 11.92 (s, 1H), 8.55 (d, J = 6.6 Hz, 1H), 8.30 (dd, J = 4.7, 1.5 Hz, 1H), 7.89 (d, J = 2.5 Hz, 1H), 7.67 (d, J = 7.8 Hz, 1H), 7.43 (s, 1H), 7.20 (dd, J = 7.9, 4.7 Hz, 1H), 4.29 (m, 1H), 2.93 (s, 3H), 1.38 (d, J = 7.1 Hz, 3H).
II-229	392.00	2.18	H NMR (500 MHz, DMSO-d6) 12.13 (s, 1H), 11.91 (s, 1H), 8.54 (dd, J = 7.9, 1.2 Hz, 1H), 8.30 (dd, J = 4.7, 1.5 Hz, 1H), 7.89 (d, J = 2.6 Hz, 1H), 7.42 (s, 1H), 7.20 (dd, J = 7.9, 4.7 Hz, 1H), 4.50 (m, 1H), 3.72 (m, 1H), 3.51 (m, 1H), 3.42 (m, 1H), 3.00 (s, 3H), 2.29 (m, 1H), 2H), 1.92 (m, 1H).
II-230	392.00	2.18	
II-231	366.00	2.13	H NMR (500 MHz, DMSO-d6) 12.31 (s, 1H), 11.90 (s, 1H), 8.53 (dd, J = 7.9, 1.2 Hz, 1H), 8.29 (dd, J = 4.7, 1.2 Hz, 1H), 7.87 (d, J = 2.6 Hz, 1H), 7.43 (s, 1H), 7.19 (dd, J = 7.9, 4.7 Hz, 1H), 4.21 (s, 2H), 3.03 (s, 3H), 2.93 (s, 3H).
II-232	472.20	2.89	H NMR (500 MHz, DMSO-d6) 12.35 (s, 1H), 11.84 (s, 1H), 8.50 (dd, J = 7.9, 1.2 Hz, 1H), 8.28 (dd, J = 4.6, 1.4 Hz, 1H), 7.87 (d, J = 2.4 Hz, 1H), 7.80 (d, J = 8.4 Hz, 1H), 7.43 (s, 1H), 7.30 (m, 4H), 7.26 (m, 1H), 7.17 (dd, J = 7.9, 4.6 Hz, 1H), 4.55 (d, J = 2.9 Hz, 2H), 4.51 (m, 1H), 3.73 (dd, J = 6.2, 1.5 Hz, 2H), 2.94 (s, 3H).
II-233	472.00	2.87	H NMR (500 MHz, DMSO-d6) 12.35 (s, 1H), 11.84 (s, 1H), 8.50 (dd, J = 7.9, 1.2 Hz, 1H), 8.28 (dd, J = 4.6, 1.4 Hz, 1H), 7.87 (d, J = 2.4 Hz, 1H), 7.80 (d, J = 8.4 Hz, 1H), 7.43 (s, 1H), 7.30 (m, 4H), 7.26 (m, 1H), 7.17 (dd, J = 7.9, 4.6 Hz, 1H), 4.55 (d, J = 2.9 Hz, 2H), 4.51 (m, 1H), 3.73 (dd, J = 6.2, 1.5 Hz, 2H), 2.94 (s, 3H).
II-234	288.10	1.90	H NMR (500 MHz, DMSO-d6) ppm 14.12 (s, 1H), 12.40 (s, 1H), 9.53 (t, J = 5.5 Hz, 1H), 8.60 (dd, J = 7.9, 1.3 Hz, 1H), 8.46 (dd, J = 4.8, 1.3 Hz,1H), 8.30 (s, 1H), 7.43 (m, 2H), 7.12 (s, 1H), 3.47 (m, 2H), 1.24 (t, J = 7.2 Hz, 3H)

Cmpd #	LC/MS (M+1) (obs)	RT (mins)	^{1}H NMR
II-235	304.10	1.60	H NMR (500 MHz, DMSO-d6) ppm 12.48 (s, 1H), 9.68 (t, J = 5.5 Hz, 1H), 8.60 (dd, J = 8.0, 1.3 Hz, 1H), 8.46 (dd, J = 4.8, 1.2 Hz, 1H), 8.31 (s, 1H), 7.43 (m, 2H), 7.13 (s, 1H), 3.61 (t, J = 5.5 Hz, 2H), 3.51 (q, J = 5.5 Hz, 2H), 2.54 (s, 1H)
II-236	329.70	1.60	H NMR (500 MHz, dmso-d6) ppm 11.54 (s, 1H), 8.49 (d, J = 7.9 Hz, 1H), 8.40 (m, 1H), 7.96 (s, 1H), 7.35-7.32 (m, 2H), 7.04 (s,1H), 3.72 (t, J = 4.6 Hz, 4H), 3.52 (s, 4H), 2.54 (s, 1H), 2.07 (s, 1H)
II-237	343.10	1.30	H NMR (500 MHz, dmso-d6) ppm 14.53 (s, 1H), 9.91-9.87 (m, 1H), 8.54 (dd, J = 7.9, 1.3 Hz, 1H), 8.42 (dd, J = 4.7, 1.3 Hz, 1H), 7.95 (s, 1H), 7.52-7.10 (m, 2H), 7.06 (s, 1H), 4.13 (m, 2H), 3.51-3.41 (m, 4H), 3.27 (s, 2H), 2.90 (s, 3H)
II-238	327.80	1.90	H NMR (500 MHz, dmso-d6) ppm 8.47 (d, J = 8.0 Hz, 1H), 8.39 (d, J = 4.7 Hz, 1H), 7.97 (s, 1H), 7.33 (q, J = 4.2 Hz, 1H), 7.06 (s, 1H), 3.46 (s, 4H), 2.07 (s, 6H)
II-239	386.00	1.60	H NMR (500 MHz, DMSO-d6) ppm 12.35 (s, 1H), 11.90 (s, 1H), 9.53 (d, J = 7.6 Hz, 1H), 8.61 (dd, J = 7.9, 1.3 Hz, 1H), 8.46 (dd, J = 4.8, 1.2 Hz, 1H), 8.29 (s, 1H), 7.45-7.42 (m, 2H), 7.13 (s, 1H), 3.74 (m, 1H), 2.28 (m, 1H), 2.10-1.94 (m, 5H), 1.79 (m, 1H), 1.47 (m, 4H)
II-240	287.80	1.50	H NMR (500 MHz, DMSO-d6) ppm 14.62 (s, 1H), 13.49 (s, 1H), 8.48 (m, 1H), 8.40 (dd, J = 4.6, 1.2 Hz, 1H), 7.95 (s, 1H), 7.62 (s, 1H), 7.33 (dd, J = 7.9, 4.6 Hz, 1H), 7.05 (s, 1H), 3.04 (s, 6H)
II-241	314.10	1.70	H NMR (500 MHz, DMSO-d6) ppm 13.06 (s, 1H), 8.47 (dd, J = 8.0, 1.3 Hz, 1H), 8.40 (dd, J = 4.7, 1.3 Hz, 1H), 8.01 (s, , 7.66 (m, 1H), 7.33 (q, J = 4.2 Hz, 1H), 7.06 (s, 1H), 3.53 (s, 4H), 2.07 (s, 4H)
II-242	345.80	1.40	H NMR (500 MHz, DMSO-d6) ppm 13.83 (s, 1H), 11.58 (s, 1H), 9.61 (d, J = 8.7 Hz, 1H), 9.15 (s, 1H), 8.65 (d, J = 7.9 Hz, 1H), 8.47 (d, J = 4.8 Hz, 1H), 8.27 (s, , 7.45 (dd, J = 7.9, 4.8 Hz, 1H), 7.27 (m, 1H), 7.13 (s, 1H)4.53 (d, J = 8.1Hz, 1H), 3.52 (t, J = 11.0 Hz, 1H), 3.27 (m, 1H), 2.93 (d, J = 4.5 Hz, 3H), 2.83 (d, J = 4.5 Hz, 3H), 1.35 (d, J = 6.7 Hz, 3H)
II-243	329.10	1.20	H NMR (400 MHz, acetic acid-d4) ppm 15.76 (s, 1H), 13.54 (s, 1H), 8.83 (s, 2H), 8.54 (d, J = 8.2 Hz, 1H), 8.40 (d, J = 4.4 Hz, , 8.12 (m, 1H), 7.94 (s, , 7.36 (q, J = 4.2 Hz, 1H), 7.04 (s, , 3.73 (s, 4H), 3.29 (s, 4H)

Cmpd #	LC/MS (M+1) (obs)	RT (mins)	^{1}H NMR
II-244	301.80	2.10	H NMR (400 MHz, acetic acid-d4) □ 13.87 (s, 1H), 12.48 (s, 1H), 11.07 (m, 1H), 9.48 (d, J = 7.4 Hz, 1H), 8.60 (dd, J = 8.0, 1.2 Hz, 1H), 8.47 (dd, J = 4.8, 1.2 Hz, 1H), 8.30 (s, 1H), 8.12 (m, 1H), 7.50 (m, 2H), 7.13 (s, 1H), 6.93 (m, 1H), 4.09 (m, , 2.07 (s, 6H)
II-245	418.50	4.09	1H NMR (DMSO): 1.40 (2H, t), 1.80-1.95 (3H, m), 2.88 (2H, t), 3.22-3.31 (4H, m), 7.39 (1H, t), 7.51 (2H, t), 7.85 (2H, d), 8.15 (1H, s), 8.29 (2H, br s), 8.60 (1H, s), 8.78 (1H, s), 8.99 (1H, t), 12.17 (1H, s).
II-246	439.00	10.13	1H NMR (DMSO) 3.11-3.30 (4H, m), 3.50-3.65 (1H, m), 7.10-7.29 (4H, m), 7.45 (1H, s), 8.00 (1H, s), 8.35 (1H, brs), 8.79 (1H, brs), 12.15 (1H, brs), 12.35 (1H, brs).
II-247	363.00	9.01	1H NMR (DMSO) 0.89-0.96 (4H, m), 1.95-2.05 91H, m), 7.41 (1H, s), 7.98 (1H, s), 8.35 (1H, s), 8.75 (1H, s), 12.11 (1H, brs), 12.44 (1H, s).
II-248	405.00	9.24	1H NMR (DMSO) 1.11-1.28 (2H, m), 1.46-1.83 (6H, m), 2.20-2.30 (1H, m), 2.40-2.50 (2H, m), 7.42 (1H, s), 7.98 91(1H, brs), 8.35 (1H, brs), 8.76 (1H, brs), 12.13 (2H, brs).
II-249	427.00	9.88	1H NMR (DMSO) 2.70-2.85 (2H, m), 2.90-3.00 (2H, m), 7.11-7.34 (5H, m), 7.45 (1H, s), 8.00 (1H, brs), 8.35 91H, brs), 8.75 (1H, brs), 12.10-12.24 92H, m).
II-250	491.00	10.16	1H NMR (DMSO) 3.80 92H, s), 7.29-7.36 (2H, m), 7.45 91H, s), 7.50-7.60 (2H, m), 8.00 91H, brs), 8.33 91H, brs), 8.75 91H, brs), 12.15 91H, brs), 12.49 (1H, brs).
II-251	433.00	10.78	1H NMR (DMSO) 0.79-0.98 (2H, m), 1.05-1.30 (5H, m), 1.47-1.78 (6H, m), 2.41-2.50 (2H, m), 7.40 (1H, s), 7.98 (1H, brs), 8.32 (1H, brs), 8.76 (1H, brs), 12.10 (2H, brs).
II-252	393.00	8.58	1H NMR (DMSO) 2.06-2.19 (2H, m), 3.103.35 (1H, m), 3.69-4.00 (4H, m), 7.45 (1H, s), 8.00 (1H, s), 8.35 (1H, brs), 8.76 (1H, brs), 12.15 (1H, brs), 12.30 (1H, brs).
II-253	491.00	8.97	1H NMR (DMSO) 2.85 (2H, t, J = 7.3Hz), 3.69 (2H, t, J = 7.3Hz), 7.45 (1H, s), 7.64-7.80 (3H, m), 7.90-8.02 (3H, m), 8.34 (1H, brs), 8.75 (1H, brs), 12.10-12.33 (2H, m).

Cmpd #	LC/MS (M+1) (obs)	RT (mins)	^{1}H NMR
II-254	443.00	9.79	1H NMR (DMSO) 2.97 (2H, t, J = 6.0Hz), 4.31 (2H, t, J = 6.0Hz), 6.90-7.00 (3H, m), 7.25-7.34 (2H, m), 7.47 (1H, s), 8.00 (1H, brs), 8.35 (1H, brs), 8.78 (1H, brs), 12.13 (1H, brs), 12.35 (1H, brs).
II-255	500.00	9.43	1H NMR (DMSO) 2.62-2.71 (2H, m), 3.30-3.38 (2H, m), 5.03 (2H, s), 7.25-7.49 (7H, m), 7.99 (1H, brs), 8.35 (1H, brs), 8.76 (1H, brs), 12.10-12.25 (2H, m).
II-256	433.00	5.37	CDCl3 1.08-1.30 (3H, m), 1.42-1.53 (1H, m), 1.55-1.74 (4H. m), 1.94-2.03 (2H, m), 2.39-2.55 (2H, m), 2.68 (2H, d), 4.36-4.43 (2H, m), 7.05 (1H, s), 7.80 (1H, s), 8.40 (1H, s), 8.65 (1H, s), 9.50 (1H, br s)

[00290] BIOLOGICAL TESTING

[00291] Example 1: ROCK INHIBITION ASSAY

[00292] Compounds were screened for their ability to inhibit ROCK I (AA 6-553) activity using a standard coupled enzyme system (Fox et al. (1998) *Protein Sci.* 7, 2249). Reactions were carried out in a solution containing 100 mM HEPES (pH 7.5), 10 mM $MgCl_2$, 25 mM NaCl, 2 mM DTT and 1.5% DMSO. Final substrate concentrations in the assay were 45 μM ATP (Sigma Chemicals, St Louis, MO) and 200 μM peptide (American Peptide, Sunnyvale, CA). Reactions were carried out at 30 °C and 45 nM ROCK I. Final concentrations of the components of the coupled enzyme system were 2.5 mM phosphoenolpyruvate, 350 μM NADH, 30 μg/ml pyruvate kinase and 10 μg/ml lactate dehydrogenase.

[00293] Example 2: ERK INHIBITION ASSAY

[00294] Compounds were assayed for the inhibition of ERK2 by a spectrophotometric coupled-enzyme assay (Fox et al (1998) *Protein Sci* 7, 2249). In this assay, a fixed concentration of activated ERK2 (10 nM) was incubated with various concentrations of the compound in DMSO (2.5 %) for 10 min. at 30°C in 0.1 M HEPES buffer, pH 7.5, containing 10 mM $MgCl_2$, 2.5 mM phosphoenolpyruvate, 200 μM NADH, 150 μg/mL pyruvate kinase, 50 μg/mL lactate dehydrogenase, and 200 μM erktide peptide. The reaction was initiated by the addition of 65 μM ATP.

The rate of decrease of absorbance at 340 nM was monitored. The K_i was determined from the rate data as a function of inhibitor concentration.

[00295] Example 3: GSK INHIBITION ASSAY

[00296] Compounds were screened for their ability to inhibit GSK-3β (AA 1-420) activity using a standard coupled enzyme system (Fox et al. (1998) *Protein Sci.* 7, 2249). Reactions were carried out in a solution containing 100 mM HEPES (pH 7.5), 10 mM $MgCl_2$, 25 mM NaCl, 300 μM NADH, 1 mM DTT and 1.5% DMSO. Final substrate concentrations in the assay were 20 μM ATP (Sigma Chemicals, St Louis, MO) and 300 μM peptide (American Peptide, Sunnyvale, CA). Reactions were carried out at 30 °C and 20 nM GSK-3β. Final concentrations of the components of the coupled enzyme system were 2.5 mM phosphoenolpyruvate, 300 μM NADH, 30 μg/ml pyruvate kinase and 10 μg/ml lactate dehydrogenase.

[00297] An assay stock buffer solution was prepared containing all of the reagents listed above with the exception of ATP and the test compound of interest. The assay stock buffer solution (175 μl) was incubated in a 96 well plate with 5 μl of the test compound of interest at final concentrations spanning 0.002 μM to 30 μM at 30 °C for 10 min. Typically, a 12 point titration was conducted by preparing serial dilutions (from 10 mM compound stocks) with DMSO of the test compounds in daughter plates. The reaction was initiated by the addition of 20 μl of ATP (final concentration 20 μM). Rates of reaction were obtained using a Molecular Devices Spectramax plate reader (Sunnyvale, CA) over 10 min at 30°C. The K_i values were determined from the rate data as a function of inhibitor concentration.

[00298] Example 4: PKA INHIBITION ASSAY

[00299] Compounds were screened for their ability to inhibit PKA using a standard coupled enzyme assay (Fox *et al., Protein Sci,* **1998,** *7,* 2249). Assays were carried out in a mixture of 100 mM HEPES (pH 7.5), 10 mM $MgCl_2$, 25 mM NaCl , 1 mM DTT and 3% DMSO. Final substrate concentrations in the assay were 50 μM ATP (Sigma Chemicals) and 80 μM peptide (Kemptide, American Peptide, Sunnyvale, CA). Assays were carried out at 30 °C and 18 nM PKA. Final concentrations of the components of the coupled enzyme system were 2.5 mM phosphoenolpyruvate, 300 μM NADH, 30 μg/ml pyruvate kinase and 10 μg/ml lactate dehydrogenase.

[00300] An assay stock buffer solution was prepared containing all of the reagents listed above, with the exception of ATP, and the test compound of the present invention. 55 μl of the stock solution was placed in a 96 well plate followed by addition of 2 μl of DMSO stock containing serial dilutions of the test compound of the present invention (typically starting from a final concentration of 5μM). The plate was preincubated for 10 minutes at 30°C and the reaction initiated by addition of 5 μl of ATP (final concentration 50 μM). Initial reaction rates were determined with a Molecular Devices SpectraMax Plus plate reader over a 15 minute time course. IC_{50} and K_i data were calculated from non-linear regression analysis using the Prism software package (GraphPad Prism version 3.0a for Macintosh, GraphPad Software, San Diego California, USA).

[00301] Example 5: Itk INHIBITION ASSAY

[00302] Compounds were screened for their ability to inhibit Itk using a standard coupled enzyme assay (Fox et al., Protein Sci., (1998) 7, 2249). Assays were carried out in a mixture of 20 mM MOPS (pH 7.0), 10mM MgCl2, 0.1% BSA,1mM DTT, 2.5 mM phosphoenolpyruvate, 300 μM NADH, 30 μg/ml pyruvate kinase and 10 μg/ml lactate dehydrogenase. Final substrate concentrations in the assay were 100μM ATP (Sigma Chemicals) and 3μM peptide (Biotinylated SAM68 D332-443). Assays were carried out at 25 °C and in the presence of 100nM Itk.

[00303] An assay stock buffer solution was prepared containing all of the reagents listed above, with the exception of ATP and the test compound of interest. 60 μl of the stock solution was placed in a 96 well plate followed by addition of 2 μl of DMSO stock containing serial dilutions of the test compound (typically starting from a final concentration of 15μM). The plate was preincubated for 10 minutes at 25°C and the reaction initiated by addition of 5 μl of ATP. Initial reaction rates were determined with a Molecular Devices SpectraMax Plus plate reader over a 10 minute time course. IC50 and Ki data were calculated from non-linear regression analysis using the Prism software package (GraphPad Prism version 3.0cx for Macintosh, GraphPad Software, San Diego California, USA).

[00304] Tables 5 and 6 depict enzyme inhibition data (K_i) for certain exemplary compounds. Compound numbers in Tables 5 and 6 correspond to those compounds depicted in Tables 1 and 2, respectively.

[00305] In Tables 5 and 6, "A" represents a K_i of less than 0.5 μM, "B" represents a K_i of between 0.5 and 5.0μM, and "C" represents a K_i greater than 5.0 μM for the indicated enzyme. If more than one value of K_i has been determined, the average K_i is indicated. If no value is indicated, then the K_i was not determined. For ROCK, the term "Enzyme" indicates that an enzyme-linked assay was used; the term "^{33}P" indicates that a radioactive assay was used.

Table 5

Cmpd #	Itk	PKA	ROCK	
			^{33}P	Enzyme
I-1	B	A	A	A
I-2		A		A
I-3		A		A
I-4		A		A
I-5		A	A	A
I-6		A		A
I-7		A		A
I-8		A		A
I-9		B		A
I-10		A		A
I-11		A		A
I-12		A		A
I-13		A		A
I-14		A	A	
I-15		B	A	A
I-16		A	A	A
I-17		A	A	A
I-18		A		A
I-19		A		A
I-20	B	A		A
I-21		A		A
I-22		A		A
I-23		A		A

Table 6

Cmpd #	Itk	PKA	ROCK	
			^{33}P	Enzyme
II-1				
II-2				
II-3		B		B
II-4		A		A
II-5		A		A

Cmpd #	Itk	PKA	ROCK	
			^{33}P	Enzyme
II-6		A		A
II-7		A		A
II-8		A		A
II-9		A		A
II-10		B		A
II-11		A		A
II-12		A		A
II-13		A		A
II-14		B		A
II-15		A		A
II-16		A		A
II-17		B		A
II-18		A		A
II-19		A		A
II-20		A		A
II-21				A
II-22				A
II-23		A		A
II-24		B		A
II-25		A		A
II-26		B		A
II-27		A		A
II-28		A		A
II-29		A		A
II-30		A		A
II-31		A		A
II-32		A		A
II-33		A		A
II-34		A		A
II-35		B		A
II-36		B		A
II-37		B		A
II-38		B		A
II-39		A		A
II-40		A		A
II-41		A		A
II-42		A		A
II-43		B		B
II-44		A		A
II-45		A		A
II-46		A		A
II-47		A		A
II-48		A		A
II-49				

Cmpd #	Itk	PKA	ROCK	
			^{33}P	Enzyme
II-50		A	A	A
II-51		A	A	A
II-52		A		A
II-53	B	A		A
II-54	B	A		A
II-55		A		A
II-56		A		A
II-57		B		A
II-58		B		B
II-59		A		A
II-60		A		A
II-61		A		A
II-62		A		A
II-63		B		A
II-64		B		B
II-65		A		A
II-66		B		A
II-67		B		A
II-68		A		A
II-69		A		A
II-70		A		A
II-71		A		A
II-72		A		A
II-73		B		A
II-74		B		A
II-75		A		A
II-76		B		A
II-77		B		A
II-78		B		A
II-79	B	A	A	A
II-80		B		A
II-81		B		A
II-82		A		A
II-83		B		A
II-84		B		A
II-85		A		A
II-86		B		A
II-87		A		A
II-88		A		A
II-89		B		A
II-90		A		A
II-91		A		A
II-92		A		A
II-93		B		B

Cmpd #	Itk	PKA	ROCK	
			^{33}P	Enzyme
II-94		A		A
II-95		A		A
II-96		A		A
II-97		A		A
II-98		B		A
II-99		B		A
II-100		B		A
II-101		B		B
II-102		A		A
II-103		A		A
II-104		B		A
II-105		B		A
II-106		A		A
II-107		B		A
II-108		B	A	A
II-109		B	A	A
II-110		B	A	A
II-111		B	A	A
II-112		B		A
II-113		A		A
II-114		A	A	A
II-115		A	A	A
II-116		A	A	A
II-117		A	A	A
II-118		A	A	A
II-119		A	A	A
II-120		A	A	A
II-121		B	A	A
II-122		A	A	A
II-123		A	A	A
II-124		A	A	A
II-125		A	A	A
II-126		A	A	A
II-127		A	A	A
II-128		A	A	A
II-129		B	A	A
II-130		B	A	
II-131		A	A	
II-132		B	A	
II-133		A	A	
II-134		B	A	
II-135		A	A	
II-136		B	A	
II-137		B	A	

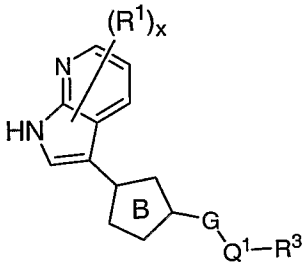
Cmpd #	Itk	PKA	ROCK	
			^{33}P	Enzyme
II-138		A	A	
II-139		A	A	
II-140		A	A	
II-141		A	A	
II-142		B	A	
II-143		B	A	
II-144		B	A	
II-145		B	A	
II-146		B	A	
II-147		A	A	
II-148		A	A	
II-149		B	A	
II-150		A	A	
II-151		A	A	
II-152		A	A	
II-153		B	A	
II-154		A	A	
II-155		A	A	
II-156		B	A	
II-157		B	A	
II-158		A	A	
II-159		A	A	
II-160		A	A	
II-161		A	A	
II-162	B	B	A	
II-163		B	A	
II-164		B	A	
II-165		A	A	
II-166		A	A	
II-167		A	A	
II-168		A	A	
II-169		A	A	
II-170		A	A	
II-171		A	A	
II-172		A	A	
II-173		A	A	
II-174		B	A	
II-175		A	A	
II-176		A	A	
II-177		A	A	
II-178		A	A	
II-179		A	A	
II-180		A	A	
II-181		A	A	

Cmpd #	Itk	PKA	ROCK	
			^{33}P	Enzyme
II-182		B	A	
II-183		B	A	
II-184		A	A	
II-185		B	A	
II-186		B	A	
II-187		A	A	
II-188		A	A	
II-189		A	A	
II-190		A	A	
II-191		A	A	
II-192		A	A	
II-193		A	A	
II-194		A	A	
II-195		A	A	
II-196		A	A	
II-197		B	B	
II-198		B	B	
II-199		B	A	
II-200		B	B	
II-201		A	A	
II-202		A	A	
II-203		A	A	
II-204		B	A	
II-205		A	A	
II-206		A	A	
II-207		A	A	
II-208		A	A	
II-209		A	A	
II-210		A	A	
II-211		A	A	
II-212		A	A	
II-213		A	A	
II-214		A	A	
II-215		A	A	
II-216		B	A	
II-217		A	A	
II-218		A	A	
II-219		A	A	
II-220		A	A	
II-221		A	A	
II-222		A	A	
II-223		A	A	
II-224		B	A	
II-225		B	A	

Cmpd #	Itk	PKA	ROCK	
			^{33}P	Enzyme
II-226		A	A	
II-227		A	A	
II-228		A	A	
II-229		A	A	
II-230		A	A	
II-231		A	A	
II-232		A	A	
II-233		A	A	
II-234		B	B	
II-235		B	B	
II-236		B	B	
II-237		B	B	
II-238		B	B	
II-239		B	A	
II-240		B	B	
II-241		B	B	
II-242		B	B	
II-243		B	B	
II-244		B	A	
II-245	B	B	A	
II-246	B	B	A	
II-247	B	B	A	
II-248	B	A	B	
II-249	B	B	A	
II-250	B	A		
II-251	B	A	B	
II-252	B	B	A	
II-253	B	A	B	
II-254	B	B	A	
II-255	B	B		
II-256	B			

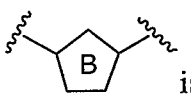
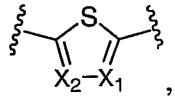
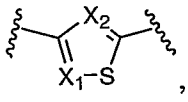
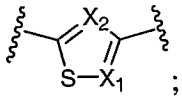
CLAIMS

1. A compound of formula **I**:



I

or a pharmaceutically acceptable salt thereof, wherein:

wherein  is , , or ;

x is 0, 1, 2, or 3;

R^1 is halogen, -CN, $-NO_2$, or $-V_mR'$;

G is $-NR^2$ or C=O;

R^2 is $-U_nR'$;

X^1 and X^2 are each independently CR^4 or N;

each occurrence of R^4 is independently halogen, CN, NO_2, or V_mR;

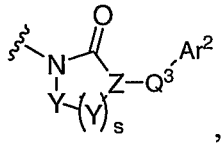
each occurrence of U or V is independently an optionally substituted C_{1-6} alkylidene chain, wherein up to two methylene units of the chain are optionally and independently replaced by –NR-, -S-, -O-, -CS-, $-CO_2-$, -OCO-, -CO-, -COCO-, -CONR-, -NRCO-, $-NRCO_2-$, $-SO_2NR-$, $-NRSO_2-$, -CONRNR-, -NRCONR-, -OCONR-, -NRNR-, $-NRSO_2NR-$, -SO-, $-SO_2-$, -PO-, $-PO_2-$, or -POR-;

m and n are each independently 0 or 1;

each occurrence of R is independently hydrogen or an optionally substituted C_{1-6} aliphatic group; and each occurrence of R' is independently hydrogen or an optionally substituted C_{1-6} aliphatic group, a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-12 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring system having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; or R and R', two occurrences of R, or two occurrences of R', are taken together with the

atom(s) to which they are bound to form an optionally substituted 3-12 membered saturated, partially unsaturated, or fully unsaturated monocyclic or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

Q^1 is –CO-, $-SO_2-$, $-NR^2$, $-NR^2CO-$, $-CONR^2-$, $–SO_2NR^2-$, or is a bond;

R^3 is Q^2-Ar^1, or when G is $-NR^2$, R^2 and Q^1-R^3, taken together with the nitrogen atom, form the cyclic group: , where s is 1 or 2, Z is CH or N; each occurrence of Y is independently, as valency and stability permit, -CO-, -CS-, $-SO_2-$, -O-, -S-, $-NR^5-$, or $-C(R^5)_2-$, and R^5 is U_nR';

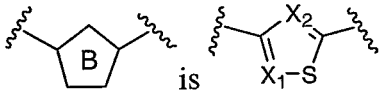
Q^2 and Q^3 are each independently a bond or a C_{1-6} alkylidene chain, wherein up to two methylene units of the chain are each optionally and independently replaced by –NR'-, -S-, -O-, -CS-, $-CO_2-$, -OCO-, -CO-, -COCO-, -CONR'-, -NR'CO-, $-NR'CO_2-$, $-SO_2NR'-$, $-NR'SO_2-$, -CONR'NR'-, -NR'CONR'-, -OCONR'-, -NR'NR'-, $-NR'SO_2NR'-$, -SO-, $-SO_2-$, -PO-, $-PO_2-$, or –POR'-; and wherein any carbon atom in the one or more methylene units is optionally substituted with one or two occurrences of R^6, wherein each occurrence of R^6 is independently halogen, -CN, $-NO_2$, or $-U_nR'$, or two occurrences of R^6, or R' and R^6, taken together with the atoms to which they are bound, form an optionally substituted 3-6-membered cycloalkyl, heterocyclyl, aryl or heteroaryl ring; and

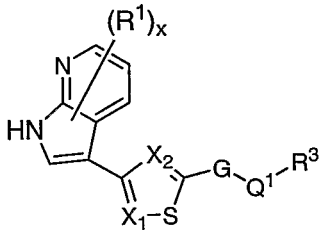
Ar^1 and Ar^2 are each independently a C_{1-6} aliphatic, a 3-8 membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-12 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring system having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; wherein Ar^1 and Ar^2 are each optionally substituted with 0-5 independent occurrences of TR^7; wherein T is a bond or is a C_1-C_6 alkylidene chain wherein up to two methylene units of T are optionally and independently replaced by –NR-, -S-, -O-, -CS-, $-CO_2-$, -OCO-, -CO-, -COCO-, -CONR-, -NRCO-, $-NRCO_2-$, $-SO_2NR-$, $-NRSO_2-$, -CONRNR-, -NRCONR-, -OCONR-, -NRNR-, $-NRSO_2NR-$, -SO-, $-SO_2-$, -PO-, $-PO_2-$, or -POR-; and each occurrence of R^7 is independently -R', halogen, $-NO_2$, -CN or =O.

2. The compound according to claim 1, wherein:

Q^1 is –CO-, $-SO_2-$, $-NR^2$, $-NR^2CO-$, $-CONR^2-$, $–SO_2NR^2-$; and

Ar^1 and Ar^2 are each independently a 5-8 membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-12 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring system having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; wherein Ar^1 and Ar^2 are each optionally substituted with 0-5 independent occurrences of TR^7; wherein T is a bond or is a C_1-C_6 alkylidene chain wherein up to two methylene units of T are optionally and independently replaced by –NR-, -S-, -O-, -CS-, $-CO_2-$, -OCO-, -CO-, -COCO-, -CONR-, -NRCO-, $-NRCO_2-$, $-SO_2NR-$, $-NRSO_2-$, -CONRNR-, -NRCONR-, -OCONR-, -NRNR-, $-NRSO_2NR-$, -SO-, $-SO_2-$, -PO-, $-PO_2-$, or -POR-; and each occurrence of R^7 is independently -R', halogen, $-NO_2$ or -CN.

3. The compound according to claim 2, wherein  is , to provide a compound of formula I-B:



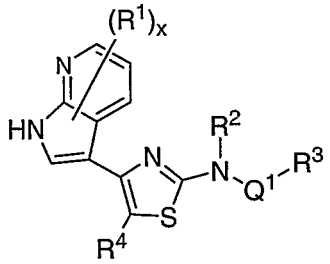
I-B.

4. The compound according to claim 3, wherein G is $-NR^2$ and Q^1 is -CO- or G is C=O and Q^1 is $-NR^2-$.

5. The compound according to claim 4, wherein G is $-NR^2$ and Q^1 is -CO-.

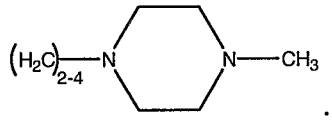
6. The compound according to claim 5, wherein X_1 is CR^4 and X_2 is CR^4 or N.

7. The compound according to claim 3, wherein X_1 is CR^4, X_2 is N and G is NR^2, to provide a compound of formula VII-A:



VII-A.

8. The compound according to claim 7, wherein Q^1 is -CO-.

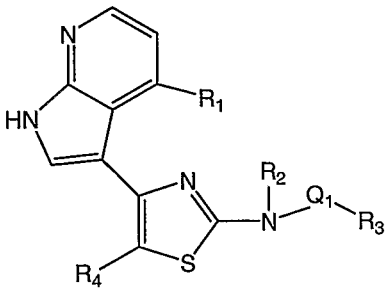
9. The compound according to claim 8, wherein R^2 is H, -C_{1-4} aliphatic, -cyclopropyl or .

10. The compound according to claim 9, wherein R^2 is H.

11. The compound according to claim 7, wherein R^4 is H or -C_{1-4} aliphatic.

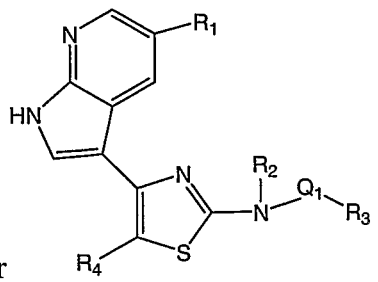
12. The compound according to claim 11, wherein R^4 is H.

13. The compound according to claim 7, wherein x is 1 and said compound has a formula selected from formulae VII-B-i or VII-B-ii:



VII-B-i

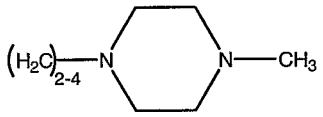
or



VII-B-ii.

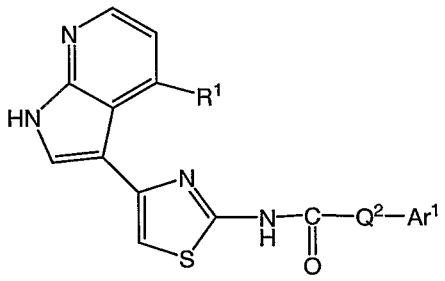
14. The compound according to claim 13, wherein R^1 is H, halogen, OH or CH_3.

15. The compound according to claim 14, wherein the compound has a structure of formulae VII-B-i, and R^1 is H or F.

16. The compound according to claim 13, wherein Q^1 is -CO-, R^1 is H, halogen, OH or CH_3, R^2 is H, $-C_{1-4}$ aliphatic, -cyclopropyl or  and R^4 is H or $-C_{1-4}$ aliphatic.

17. The compound according to claim 16, wherein R^1 is H or F, R^2 is H and R^4 is H or $-C_{1-4}$ aliphatic.

18. The compound according to claim 17, wherein R^1 is H or F, R^2 is H and R^4 is H, and the compound has a structure of formula V-B-iii:



VII-B-iii.

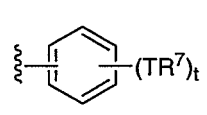
19. The compound according to any one of claims 1-18, wherein Q^2 is $-(CHR^6)_q-$, $-(CHR^6)_qO-$, $-(CHR^6)_qS-$, $-(CHR^6)_qS(O)_2-$, $-(CHR^6)_qS(O)-$, $-(CHR^6)_qNR-$, or $-(CHR^6)_qC(O)-$, wherein q is 0, 1, 2, or 3, and each R^6 is R', -N(R)(R'), $-(CH_2)_{1-4}N(R)(R')$, $-(CH_2)_{1-4}C(CH_3)_2N(R)(R')$, $-(CH_2)_{1-4}CH(CH_3)N(R)(R')$, -OR', $-(CH_2)_{1-4}OR'$, $-NR(CH_2)_{1-4}N(R)(R')$, $-NR(CH_2)_{1-4}SO_2R'$, $-NR(CH_2)_{1-4}COOR'$, or $-NR(CH_2)_{1-4}COR'$, or two occurrences of R^6, taken together with the atoms to which they are bound, form an optionally substituted 3-6-membered saturated, partially unsaturated, or fully unsaturated ring.

20. The compound according to claim 19, wherein Q^2 is $-(CHR^6)_q-$, q is 1 or 2, and R^6 is R', -N(R)(R'), $-(CH_2)_{1-4}N(R)(R')$, -OR', $-(CH_2)_{1-4}OR'$ or $-NR(CH_2)_{1-4}SO_2R'$.

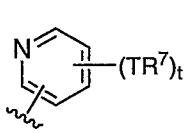
21. The compound according to claim 20, wherein Q^2 is $-(CHR^6)_q-$, q is 1 or 2, and each R^6 is H.

22. The compound according to claim 18, wherein Q^2 is $-(CHR^6)_q-$, q is 1, and R^6 is H.

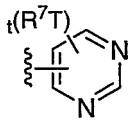
23. The compound according to any one of claims 1-18, wherein Ar^1 is



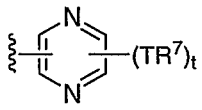
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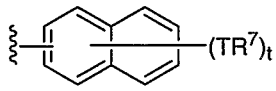
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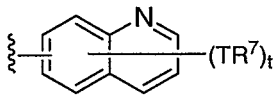
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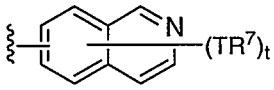
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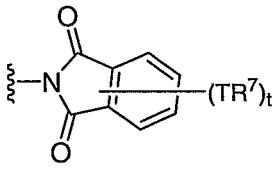
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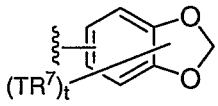
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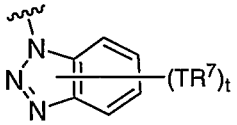
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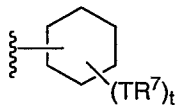
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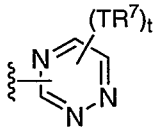
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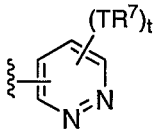
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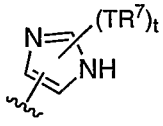
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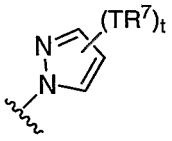
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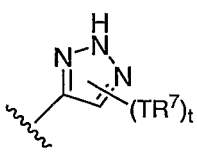
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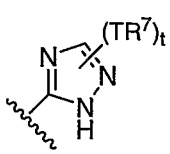
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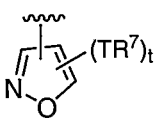
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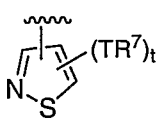
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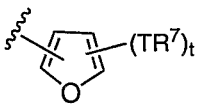
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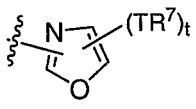
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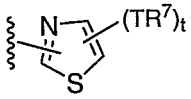
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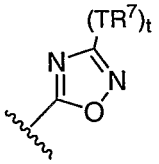
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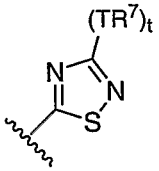
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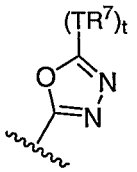
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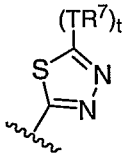
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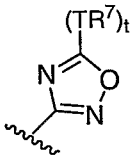
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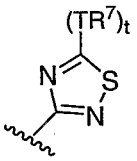
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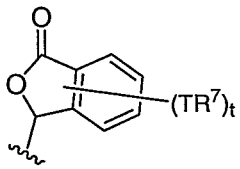
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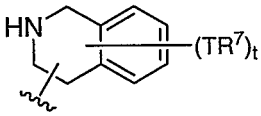
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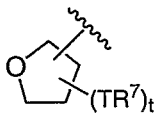
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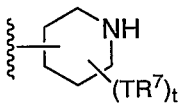
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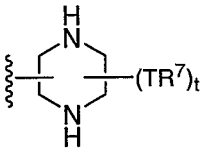
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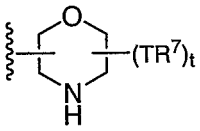
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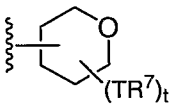
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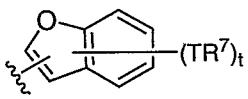
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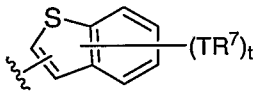
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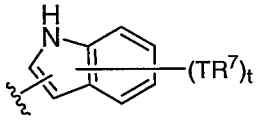
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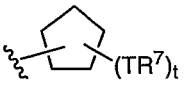
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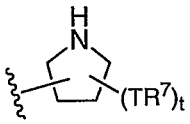
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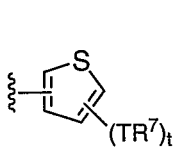
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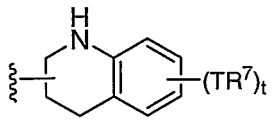
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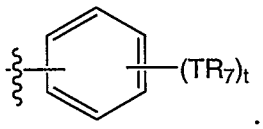


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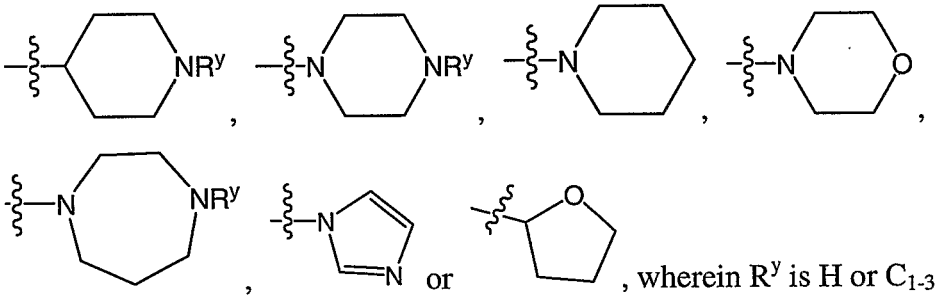
wherein t is 0, 1, 2, 3, 4, or 5, and wherein any Ar^1 is bonded to Q^2 through any substitutable nitrogen or carbon atom, and wherein one or more hydrogen atoms on any substitutable nitrogen or carbon atom is substituted with one or more independent occurrences of TR^7.

24. The compound according to claim 23, wherein Ar^1 is 

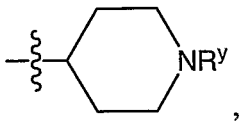
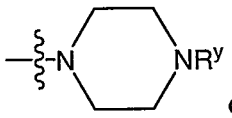
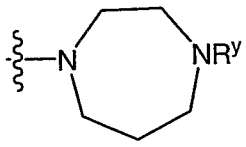
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25. The compound according to either of claims 23 or 24, wherein t is 0, 1 or 2, and each TR^7 is independently selected from halogen, -CN, -R', $-O(CH_2)_{0-5}R'$, -NRR', $-OSO_2(CH_2)_{0-4}R'$, $-NRSO_2(CH_2)_{0-5}R'$, $-NRSO_2NR(CH_2)_{0-5}R'$, $-SO_2NR(CH_2)_{0-5}R'$, -CONRR', -COR', -COOR', -NRCOR' or $-SO_2(CH_2)_{0-5}R'$.

26. The compound according to claim 25, wherein TR^7 is selected from -F, -Cl, -CN, $-NH_2$, $-CH_3$, $-CH_2CH_3$, $-CH(CH_3)_2$, -OH, $-OCH_3$, -NR"SO_2R", -NR"$SO_2N(R")_2$, $-COOC(CH_3)_3$, $-OSO_2CH_3$, -OH, $-SO_2N(R")_2$, $-SO_2NHR'$, $-SO_2R"$, -pyrollidinone, tetrahydrofuran or $-D-(CH_2)_p-Y$, wherein R" is a H or a C_{1-4} alkyl, D is $-SO_2-$, $-SO_2NH-$, $-NHSO_2-$ or -O-, p is 0-3, and Y is selected from:

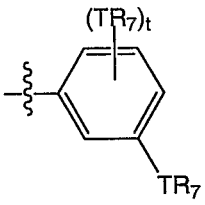


, wherein R^y is H or C_{1-3} alkyl, and wherein one or more carbon atoms of Y is optionally substituted with =O.

27. The compound according to claim 26, wherein t is 1 or 2, one TR^7 is -D-$(CH_2)_p$-Y, D is -O-, p is 2 or 3, Y is  ,  or  , and R^y is H or CH_3, and wherein one or more carbon atoms of Y is optionally substituted with =O.

28. The compound according to claim 26, wherein t is 1 or 2, and one TR^7 is -NR"SO_2R", $NHSO_2$R" or OR".

29. The compound according to claim 26, wherein t is 1 or 2, and one or both TR^7 are F or Cl.

30. The compound according to any one of claims 24-29, wherein Ar^1 is  and t is 0 or 1.

31. The compound according to claim 18, wherein Ar^1 is a C_{1-6} optionally substituted aliphatic.

32. The compound according to claim 31, wherein Ar^1 is a C_{1-3} optionally substituted alkyl and Q^2 is -$(CHR^6)_q$-, -$(CHR^6)_q$O-, -$(CHR^6)_q$S-, -$(CHR^6)_q$S(O)$_2$-, -$(CHR^6)_q$S(O)- , -$(CHR^6)_q$NR-, or –$(CHR^6)_q$C(O)-, wherein q is 0, 1, 2, or 3, and each R^6 is R', -N(R)(R'), -$(CH_2)_{1-4}$N(R)(R'), -$(CH_2)_{1-4}C(CH_3)_2$N(R)(R'), -$(CH_2)_{1-4}CH(CH_3)$N(R)(R'), -OR', -$(CH_2)_{1-4}$OR', -NR$(CH_2)_{1-4}$N(R)(R'), -NR$(CH_2)_{1-4}SO_2$R', -NR$(CH_2)_{1-4}$COOR', or -NR$(CH_2)_{1-4}$COR'.

33. The compound according to claim 32, wherein Q^2-Ar^1 is -CH_2CN.

34. The compound according to claim 3, wherein X_1 is CR^4, X_2 is CR^4 or N, G is $--NR^2-$ or -CO- and Q^1 is a bond.

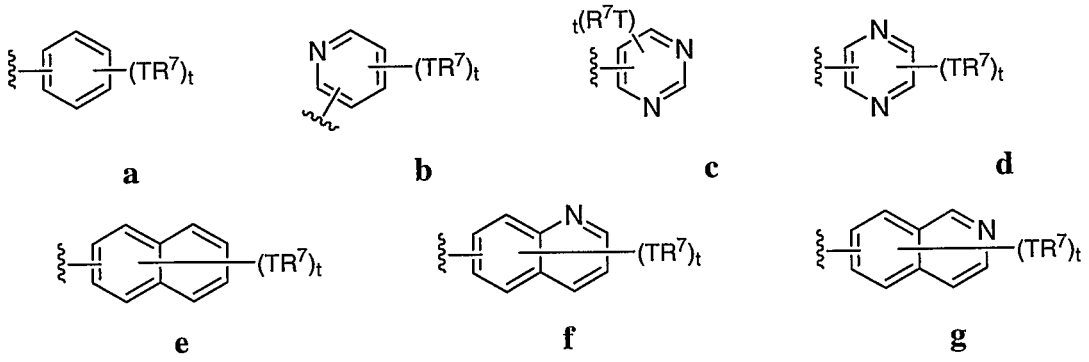
35. The compound according to claim 34, wherein Q^2 is a bond.

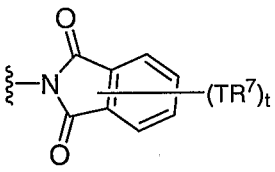
36. The compound according to claim 14, wherein the compound has a structure of formulae VII-B-i, and R^1 is Br.

37. The compound according to claim 36, wherein Q^1 is -CO-, R^2 is H and R^4 is H or $-C_{1-4}$ aliphatic.

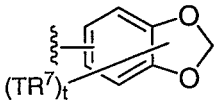
38. The compound according to claim 37, wherein Q^2 is $-(CHR^6)_q-$, $-(CHR^6)_qO-$, $-(CHR^6)_qS-$, $-(CHR^6)_qS(O)_2-$, $-(CHR^6)_qS(O)-$, $-(CHR^6)_qNR-$, or $-(CHR^6)_qC(O)-$, $-(CHR^6)NRC(O)-$ wherein q is 0, 1, 2, or 3, and each R^6 is R', -N(R)(R'), $-(CH_2)_{1-4}N(R)(R')$, $-(CH_2)_{1-4}C(CH_3)_2N(R)(R')$, $-(CH_2)_{1-4}CH(CH_3)N(R)(R')$, -OR', $-(CH_2)_{1-4}OR'$, $-NR(CH_2)_{1-4}N(R)(R')$, $-NR(CH_2)_{1-4}SO_2R'$, $-NR(CH_2)_{1-4}COOR'$, or $-NR(CH_2)_{1-4}COR'$, or two occurrences of R^6, taken together with the atoms to which they are bound, form an optionally substituted 3-6-membered saturated, partially unsaturated, or fully unsaturated ring.

39. The compound according to claim 38, wherein Ar^1 is

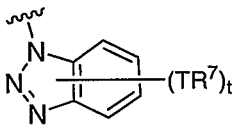




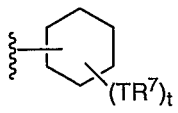
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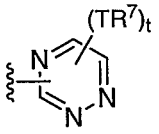
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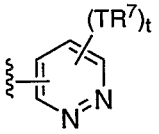
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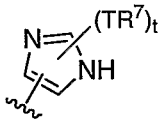
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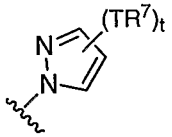
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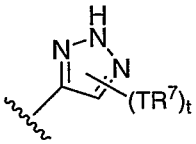
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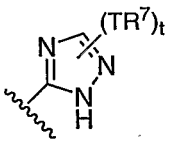
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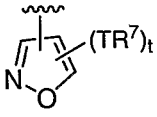
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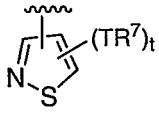
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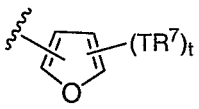
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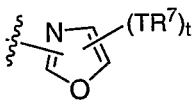
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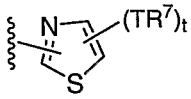
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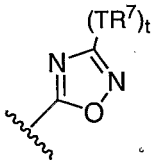
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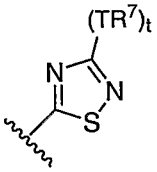
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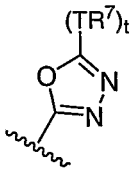
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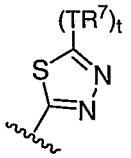
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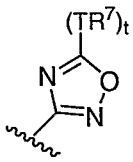
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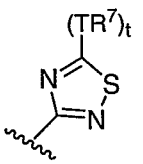
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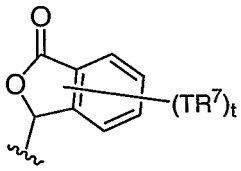
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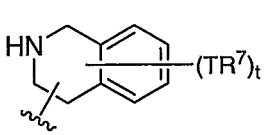
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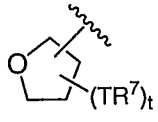
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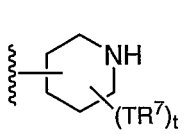
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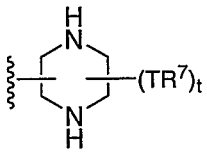
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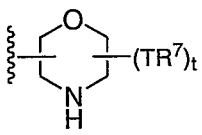
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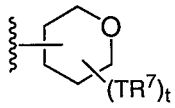
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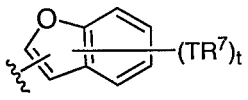
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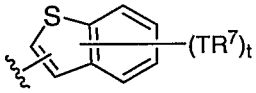
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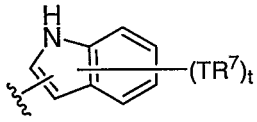
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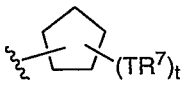
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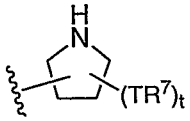
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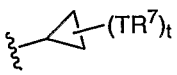
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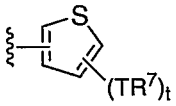
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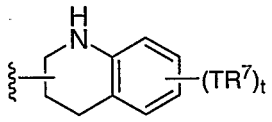
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wherein t is 0, 1, 2, 3, 4, or 5, and wherein any Ar^1 is bonded to Q^2 through any substitutable nitrogen or carbon atom, and wherein one or more hydrogen atoms on any substitutable nitrogen or carbon atom is substituted with one or more independent occurrences of TR^7.

40. The compound according to claim 1, wherein said compound has a structure depicted in Table 1 or Table 2.

41. A composition comprising an effective amount of compound according to any one of claims 1, 18, 24, 35, 37 or 40, and a pharmaceutically acceptable carrier, adjuvant, or vehicle.

42. The composition of claim 41, additionally comprising a therapeutic agent selected from a chemotherapeutic or anti-proliferative agent, an anti-inflammatory agent, an immunomodulatory or immunosuppressive agent, a neurotrophic factor, an agent for treating cardiovascular disease, an agent for treating destructive bone disorders, an agent for treating liver disease, an anti-viral agent, an agent for treating blood disorders, an agent for treating diabetes, or an agent for treating immunodeficiency disorders.

43. A method of inhibiting ROCK, ERK, GSK, AGC or Itk kinase activity in a biological sample; which method contacting said biological sample with a compound of claim 1 or a composition comprising said compound.

44. The method of claim 43, wherein the method comprises inhibiting ROCK activity.

45. A method of treating or lessening the severity of a disease condition or disorder selected from a proliferative disorder, a cardiac disorder, a neurodegenerative disorder, a psychotic disorder, an autoimmune disorder, a condition associated with organ transplant, an inflammatory disorder, an immunologically mediated disorder, a viral disease, or a bone disorder, comprising the step of administering to said patient a compound of claim 1 or a composition comprising said compound.

46. The method of claim 45, comprising the additional step of administering to said patient an additional therapeutic agent selected from a chemotherapeutic or anti-proliferative agent, an anti-inflammatory agent, an immunomodulatory or immunosuppressive agent, a neurotrophic factor, an anti-psychotic agent, an agent for treating cardiovascular disease, an agent for treating destructive bone disorders, an agent for treating liver disease, an anti-viral agent, an agent for treating blood disorders, an agent for treating diabetes, or an agent for treating immunodeficiency disorders, wherein:

said additional therapeutic agent is appropriate for the disease being treated; and

said additional therapeutic agent is administered together with said composition as a single dosage form or separately from said composition as part of a multiple dosage form.

47. The method of either of claims 45 or 46, wherein disease, condition, or disorder is allergy, asthma, diabetes, Alzheimer's disease, Huntington's disease, Parkinson's disease, AIDS-associated dementia, amyotrophic lateral sclerosis (AML, Lou Gehrig's disease), multiple sclerosis (MS), schizophrenia, cardiomyocyte hypertrophy, reperfusion/ischemia (e.g., stroke), baldness, cancer, hepatomegaly, cardiovascular disease including cardiomegaly, cystic fibrosis, viral disease, autoimmune diseases, atherosclerosis, restenosis, psoriasis, inflammation, hypertension, angina pectoris, cerebrovascular contraction, peripheral circulation disorder, premature birth, arteriosclerosis, vasospasm (cerebral vasospasm, coronary vasospasm), retinopathy, erectile dysfunction (ED), AIDS, osteoporosis, Crohn's Disease and colitis, neurite outgrowth, or Raynaud's Disease.

48. The method of claim 45, wherein the disease, condition, or disorder is hypertension, cerebral vasospasm, coronary vasospasm, bronchial asthma, preterm labor, erectile dysfunction, glaucoma, vascular smooth muscle cell proliferation, myocardial hypertrophy, malignoma, ischemia/reperfusion-induced injury, endothelial dysfunction, Crohn's Disease and colitis, neurite outgrowth, Raynaud's Disease, angina, Alzheimer's disease, benign prostatic hyperplasia, or atherosclerosis.

49. The method of claim 45, wherein disease, condition, or disorder is atherosclerosis, hypertension, erectile dysfunction (ED), reperfusion/ischemia (e.g., stroke), or vasospasm (cerebral vasospasm and coronary vasospasm).

50. A method of treating or lessening the severity of a disease of condition selected from an autoimmune, inflammatory, proliferative, or hyperproliferative disease or an immunologically-mediated disease comprising administering to a patient in need thereof a compound according to claim 1 or a composition comprising said compound.

51. The method of claim 50, comprising the further step of administering to said patient an additional therapeutic agent selected from an agent for the treatment of an autoimmune, inflammatory, proliferative, hyperproliferative disease, or an immunologically-mediated disease including rejection of transplanted organs or tissues and Acquired Immunodeficiency Syndrome (AIDS), wherein:
said additional therapeutic agent is appropriate for the disease being treated; and
said additional therapeutic agent is administered together with said composition as a single dosage form or separately from said composition as part of a multiple dosage form.

52. The method of either of claims 50 or 51, wherein the disease or disorder is asthma, acute rhinitis, allergic, atrophic rhinitis, chronic rhinitis, membranous rhinitis, seasonal rhinitis, sarcoidosis, farmer's lung, fibroid lung, idiopathic interstitial pneumonia, rheumatoid arthritis, seronegative spondyloarthropathis (including ankylosing spondylitis, psoriatic arthritis and Reiter's disease), Behcet's disease, Sjogren's syndrome, systernic sclerosis, psoriasis, systemic sclerosis, atopical dermatitis, contact dermatitis and other eczematous dermatitis, seborrhoetic dermatitis, Lichen planus, Pemphigus, bullous Pemphigus, epidermolysis bullosa, urticaria, angiodermas, vasculitides, erythemas, cutaneous eosinophilias, uveitis, Alopecia, areata vernal conjunctivitis, Coeliac disease, proctitis, eosinophilic gastro-enteritis, mastocytosis, pancreatitis, Crohn's disease, ulcerative colitis, food-related allergies, multiple sclerosis, artherosclerosis, acquired immunodeficiency syndrome (AIDS), lupus erythematosus, systemic lupus, erythematosus, Hashimoto's thyroiditis, myasthenia gravis, type I diabetes, nephrotic syndrome, eosinophilia fascitis, hyper IgE syndrome, lepromatous leprosy, sezary syndrome and idiopathic thrombocytopenia purpura, restenosis following angioplasty, tumours, artherosclerosis, systemic lupus erythematosus, allograft rejection including, without limitation, acute and chronic allograft rejection following for example transplantation of kidney, heart, liver, lung, bone marrow, skin and cornea; and chronic graft versus host disease.