INHIBITION OF FGFR3 AND TREATMENT OF MULTIPLE MYELOMA

FIELD OF THE INVENTION

[0001] This invention pertains generally to methods for inhibiting fibroblast growth factor receptor 3 and methods of treating multiple myeloma, particularly in patients or cells with a t(4;14) chromosomal translocation. This invention also pertains to the use of benzimidazole quinolinone compounds in the preparation of medicaments for use in inhibiting fibroblast growth factor receptor 3 and treating multiple myeloma, particularly in patients or cells with a t(4;14) chromosomal translocation.

BACKGROUND OF THE INVENTION

[0002] Capillaries reach into almost all tissues of the human body and supply tissues with oxygen and nutrients as well as removing waste products. Under typical conditions, the endothelial cells lining the capillaries do not divide, and capillaries, therefore, do not normally increase in number or size in a human adult. Under certain normal conditions, however, such as when a tissue is damaged, or during certain parts of the menstrual cycle, the capillaries begin to proliferate rapidly. This process of forming new capillaries from pre-existing blood vessels is known as angiogenesis or neovascularization. See Folkman, J. Scientific American 275, 150-154 (1996). Angiogenesis during wound healing is an example of pathophysiological neovascularization during adult life. During wound healing, the additional capillaries provide a supply of oxygen and nutrients, promote granulation tissue, and aid in waste removal. After termination of the healing process, the capillaries normally regress. Lymboussaki, A. "Vascular Endothelial Growth Factors and their Receptors in Embryos, Adults, and in Tumors" Academic Dissertation, University of Helsinki, Molecular/Cancer Biology Laboratory and Department of Pathology, Haartman Institute, (1999).

[0003] Angiogenesis also plays an important role in the growth of cancer cells. It is known that once a nest of cancer cells reaches a certain size, roughly 1 to 2 mm in diameter, the cancer cells must develop a blood supply in order for the tumor to grow larger as diffusion will not be sufficient to supply the cancer cells with enough oxygen and nutrients. Thus, inhibition of angiogenesis is expected to halt the growth of cancer cells.

[0004] Receptor tyrosine kinases (RTKs) are transmembrane polypeptides that regulate developmental cell growth and differentiation, remodeling and regeneration of adult tissues. Mustonen, T. et al., J. Cell Biology 129, 895-898 (1995); van der Geer, P. et al. Ann Rev. Cell Biol. 10, 251-337 (1994). Polypeptide ligands known as growth factors or cytokines, are known to activate RTKs. Signaling RTKs involves ligand binding and a shift in conformation in the external domain of the receptor resulting in its dimerization. Lymboussaki, A. "Vascular Endothelial Growth Factors and their Receptors in Embryos, Adults, and in Tumors" Academic Dissertation, University of Helsinki, Molecular/Cancer Biology Laboratory and Department of Pathology, Haartman Institute, (1999); Ullrich, A. et al., Cell 61, 203-212 (1990). Binding of the ligand to the RTK results in receptor trans-phosphorylation at specific tyrosine residues and subsequent activation of the catalytic domains for the phosphorylation of cytoplasmic substrates. Id.

[0005] Two subfamilies of RTKs are specific to the vascular endothelium. These include the vascular endothelial growth factor (VEGF) subfamily and the Tie receptor subfamily. Class V RTKs include VEGFR1 (FLT-1), VEGFR2 (KDR (human), Flk-1 (mouse)), and VEGFR3 (FLT-4). Shibuya, M. et al., Oncogene 5, 519-525 (1990); Terman, B. et al., Oncogene 6, 1677-1683 (1991); Aprelikova, O. et al., Cancer Res. 52, 746-748 (1992).

[0006] Members of the VEGF subfamily have been described as being able to induce vascular permeability and endothelial cell proliferation and further identified as a major inducer of angiogenesis and vasculogenesis. Ferrara, N. et al., Endocrinol. Rev. 18, 4-25 (1997). VEGF is known to

specifically bind to RTKs including FLT-1 and Flk-1. DeVries, C. et al., Science 255, 989-991 (1992); Quinn, T. et al., Proc. Natl. Acad. Sci. 90, 7533-7537 (1993). VEGF stimulates the migration and proliferation of endothelial cells and induces angiogenesis both *in vitro* and *in vivo*. Connolly, D. et al., J. Biol. Chem. 264, 20017-20024 (1989); Connolly, D. et al., J. Clin. Invest. 84, 1470-1478 (1989); Ferrara, N. et al., Endocrino. Rew. 18, 4-25 (1997); Leung, D. et al., Science 246, 1306-1309 (1989); Plouet, J. et al., EMBO J 8, 3801-3806 (1989).

[0007] Because angiogenesis is known to be critical to the growth of cancer and to be controlled by VEGF and VEGF-RTK, substantial efforts have been undertaken to develop compounds which inhibit or retard angiogenesis and inhibit VEGF-RTK.

[0008] Platelet derived growth factor receptor kinase (PDGFR) is another type of RTK. PDGF expression has been shown in a number of different solid tumors, from glioblastomas to prostate carcinomas. In these various tumor types, the biological role of PDGF signaling can vary from autocrine stimulation of cancer cell growth to more subtle paracrine interactions involving adjacent stroma and angiogenesis. Therefore, inhibiting the PDGFR kinase activity with small molecules may interfere with tumor growth and angiogenesis.

[0009] Tie-2 is a membrane RTK. Upon binding to its ligand, Tie-2 is activated and phosphorylates its downstream signal proteins. Tie-2 kinase activity may then trigger a pathway of cellular response that leads to stabilization of vascular vessels in cancer. Therefore, blocking kinase activity of Tie-2, in synergy with blockage of activity of other angiogenic kinases such as VEGF and FGFR1 receptor kinases, may be effective in cutting off the blood supply to cancer cells and in treating the disease.

[0010] FLT-3 is a receptor tyrosine kinase belonging to the PDGF Receptor family expressed on acute myelogenous leukemia (AML) cells in a

majority of patients and can be present in wildtype form or have activating mutations that result in constitutively active kinase function. An internal tandem repeat (ITD) mutation is expressed in about 25% of AML patients and has been associated with poor prognosis in AML patients. Levis, M et al Blood 99, 11; 2002.

[0011] c-Kit is another receptor tyrosine kinase belonging to PDGF Receptor family and is normally expressed in hematopoietic progenitor, mast and germ cells. C-kit expression has been implicated in a number of cancers including mast cell leukemia, germ cell tumors, small-cell lung carcinoma, gastroinstestinal stromal tumors, acute myelogenous leukemia (AML), neuroblastoma, melanoma, ovarian carcinoma, breast carcinoma. Heinrich, M. C. et al; J. Clin. Onc. 20, 6 1692-1703, 2002 (review article); Smolich, B. D. et al Blood, 97, 5; 1413-1421.

[0012] c-ABL is a tyrosine kinase that was originally identified as an oncogene product from the genome of the Abelson murine leukemia virus. About 90% of chronic myelogenous leukemia (CML), 20-30% of acute lymphoblastic leukemia (ALL) and about 1% of acute myeloblastic leukemia (AML) have a reciprocal translocation between chromsome 9 and 22. The translocation results in the 'Philadelphia' chromosome and is the reason for the expression of a chimeric BCR/ABL transcript.

[0013] FGFR3 is a tyrosine kinase associated with various cancers. Fibroblast growth factor receptor 3 (FGFR3) is a class IV receptor tyrosine kinase. FGFR3 is deregulated due to a t(4,14) translocation in about 15-20% of multiple myeloma patients. This translocation causes the expression of a functional FGFR3 that can respond to FGF1 in e.g. the bone microenvironment. In some cases, activating mutations that make FGFR3 ligand independent have been identified. These activating FGFR3 mutations have been found to cause Ras-like tumor progression and evidence exists that similar signaling pathways are utilized (Chesi, et al., Blood 2001 97 729-736.).

[0014] Multiple myeloma (MM), a disease of malignant B cells, is characterized by the accumulation of clonal plasma cells in the bone marrow (BM) and osteolytic bone lesions. Autologous stem cell transplant (ASCT) and advances in supportive care have had a significant impact on the disease and long-term survival. Attal, M. *et al.*, *N. Engl. J. Med.*, 1996; 335:91-97; and Barlogie, B. *et al.*, *Blood*, 1997; 89:789-793. However, patients invariably relapse, and MM remains a universal fatal disease. The identification of nonrandom chromosomal translocations in MM has resulted in the development of powerful prognostic tools and the identification of novel molecular targets. Nearly half of patients with MM overexpress a putative oncogene, dysregulated by one of five recurrent immunoglobulin heavy (IgH) translocations: 11q13 (cyclin D1), 6p21 (cyclin D3), 4p16 (FGFR3 and MMSET), 16q23 (c-maf) and 20q11 (mafB). Kuehl, W. M. *et al.*, *Nat Rev Cancer*, 2002; 2:175-187; and Avet-Loiseau, H. *et al.*, *Blood*, 2002; 99:2185-2191. These translocations likely represent an early and possibly seminal event in the development of MM. More recently, it has become clear that these specific IgH translocations impart prognostic significance. Particularly, the t(4;14) translocation with occurs in approximately 20% of patients appears to confer a particularly poor prognosis for MM, with no apparent therapeutic benefit to ASCT. Fonseca, R. *et al.*, *Blood*, 2003; 101:4569-4575; Keats, J. J. *et al.*, *Blood*, 2003; 101:1520-1529; Moreau, P. *et al.*, *Blood*, 2002; 100:1579-1583; and Chang, H. *et al.*, *Br. J. Haematol.*, 2004; 125:64-68. Clearly, novel treatment approaches are required for these patients.

[0015] The t(4;14) translocation is unusual in that it appears to dysregulate two potential oncogenes, MMSET on der(4) and FGFR3 on der(14). Chesi, M. *et al.*, *Nat. Genet.*, 1997; 16:260-265; and Chesi, M. *et al.*, *Blood*, 1998; 92:3025-3034. Whether dysregulation of either or both of these genes is critical for MM pathogenesis is not known, however several lines of evidence support a role for FGFR3 in tumor initiation and progression. Activation of WT FGFR3, a RTK, promotes proliferation and survival in myeloma cells and is weakly transforming in a hematopoetic mouse model.

Plowright, E. E. *et al.*, *Blood*, 2000; 95:992-998; Chesi, M. *et al.*, *Blood*, 2001; 97:729-736; and Pollett, J. B. *et al.*, *Blood*, 2002; 100:3819-3821. Subsequent acquisition of activating mutations of FGFR3 in some MM are associated with progression to late stage myeloma and are strongly transforming in several experimental models. Chesi, M. *et al.*, *Blood*, 2001; 97:729-736; and Li, Z. *et al.*, *Blood*, 2001; 97:2413-2419. *In vitro* studies suggest that FGFR3 can impart chemoresistance, an observation supported by clinical data that demonstrate poor responses to conventional chemotherapy and shortened median survival of t(4;14) MM patients. Fonseca, R. *et al.*, *Blood*, 2003; 101:4569-4575; Keats, J. J. *et al.*, *Blood*, 2003; 101:1520-1529; Moreau, P. *et al.*, *Blood*, 2002; 100:1579-1583; and Chang, H. *et al.*, *Br. J. Haematol.*, 2004; 125:64-68. These findings suggest that ectopic expression of FGFR3 may play a significant, albeit not a singular, role in myeloma oncogenesis thus making this RTK a target for molecular based therapy.

[0016] Inhibition of FGFR3 in t(4;14) MM cell lines induces cytotoxic responses demonstrating that these cells remain dependent on FGFR3 signaling despite the complexity of genetic alterations in these cells derived from end stage patients. Trudel, S. *et al.*, *Blood*, 2004; 103:3521-3528; Paterson, J. L. *et al.*, *Br. J. Haematol.*, 2004; 124:595-603; and Grand ,E. K. *et al.*, *Leukemia*, 2004; 18:962-966. These observations are congruent with the results of receptor tyrosine inactivation in a range of human malignancies where clinical successes have been documented and encourage the clinical development of FGFR3 inhibitors for the treatment of these poor-prognosis patients. Druker, B. J. *et al.*, *N. Engl. J. Med.*, 2001; 344:1031-1037; Demetri, G. D. *et al.*, *N. Engl. J. Med.*, 2002; 347:472-480; Slamon, D. J. *et al.*, *N. Engl. J. Med.* 2001; 344:783-792; and Smith, B. D. *et al.*, *Blood*, 2004; 103:3669-3676.

[0017] Glycogen synthase kinase 3 (GSK-3) is a serine/threonine kinase for which two isoforms, α and β, have been identified. Woodgett, *Trends Biochem. Sci.*, 16:177-81 (1991). Both GSK-3 isoforms are

constitutively active in resting cells. GSK-3 was originally identified as a kinase that inhibits glycogen synthase by direct phosphorylation. Upon insulin activation, GSK-3 is inactivated, thereby allowing the activation of glycogen synthase and possibly other insulin-dependent events, such glucose transport. Subsequently, it has been shown that GSK-3 activity is also inactivated by other growth factors that, like insulin, signal through receptor tyrosine kinases (RTKs). Examples of such signaling molecules include IGF-1 and EGF. Saito et al., *Biochem. J.*, 303:27-31 (1994); Welsh et al., *Biochem. J.* 294:625-29 (1993); and Cross et al., *Biochem. J.*, 303:21-26 (1994).

[0018] Agents that inhibit GSK-3 activity are useful in the treatment of disorders that are mediated by GSK-3 activity. In addition, inhibition of GSK-3 mimics the activation of growth factor signaling pathways and consequently GSK-3 inhibitors are useful in the treatment of diseases in which such pathways are insufficiently active. Examples of diseases that can be treated with GSK-3 inhibitors are described below.

[0019] Diabetes mellitus is a serious metabolic disease that is defined by the presence of chronically elevated levels of blood glucose (hyperglycemia). This state of hyperglycemia is the result of a relative or absolute lack of activity of the peptide hormone, insulin. Insulin is produced and secreted by the β cells of the pancreas. Insulin is reported to promote glucose utilization, protein synthesis, and the formation and storage of carbohydrate energy as glycogen. Glucose is stored in the body as glycogen, a form of polymerized glucose, which may be converted back into glucose to meet metabolism requirements. Under normal conditions, insulin is secreted at both a basal rate and at enhanced rates following glucose stimulation, all to maintain metabolic homeostasis by the conversion of glucose into glycogen.

[0020] The term diabetes mellitus encompasses several different hyperglycemic states. These states include Type 1 (insulin-dependent diabetes mellitus or IDDM) and Type 2 (non-insulin dependent diabetes

mellitus or NIDDM) diabetes. The hyperglycemia present in individuals with Type 1 diabetes is associated with deficient, reduced, or nonexistent levels of insulin that are insufficient to maintain blood glucose levels within the physiological range. Conventionally, Type 1 diabetes is treated by administration of replacement doses of insulin, generally by a parental route. Since GSK-3 inhibition stimulates insulin-dependent processes, it is useful in the treatment of type 1 diabetes.

[0021] Type 2 diabetes is an increasingly prevalent disease of aging. It is initially characterized by decreased sensitivity to insulin and a compensatory elevation in circulating insulin concentrations, the latter of which is required to maintain normal blood glucose levels. Increased insulin levels are caused by increased secretion from the pancreatic beta cells, and the resulting hyperinsulinemia is associated with cardiovascular complications of diabetes. As insulin resistance worsens, the demand on the pancreatic beta cells steadily increases until the pancreas can no longer provide adequate levels of insulin, resulting in elevated levels of glucose in the blood. Ultimately, overt hyperglycemia and hyperlipidemia occur, leading to the devastating long-term complications associated with diabetes, including cardiovascular disease, renal failure and blindness. The exact mechanism(s) causing type 2 diabetes are unknown, but result in impaired glucose transport into skeletal muscle and increased hepatic glucose production, in addition to inadequate insulin response. Dietary modifications are often ineffective, therefore the majority of patients ultimately require pharmaceutical intervention in an effort to prevent and/or slow the progression of the complications of the disease. Many patients can be treated with one or more of the many oral anti-diabetic agents available, including sulfonylureas, to increase insulin secretion. Examples of sulfonylurea drugs include metformin for suppression of hepatic glucose production, and troglitazone, an insulin-sensitizing medication. Despite the utility of these agents, 30-40% of diabetics are not adequately controlled using these medications and require subcutaneous insulin injections. Additionally, each of these therapies has

associated side effects. For example, sulfonylureas can cause hypoglycemia and troglitazone can cause severe hepatoxicity. Presently, there is a need for new and improved drugs for the treatment of prediabetic and diabetic patients.

[0022] As described above, GSK-3 inhibition stimulates insulin-dependent processes and is consequently useful in the treatment of type 2 diabetes. Recent data obtained using lithium salts provides evidence for this notion. The lithium ion has recently been reported to inhibit GSK-3 activity. Klein et al., *PNAS* 93:8455-9 (1996). Since 1924, lithium has been reported to have antidiabetic effects including the ability to reduce plasma glucose levels, increase glycogen uptake, potentiate insulin, up-regulate glucose synthase activity and to stimulate glycogen synthesis in skin, muscle and fat cells. However, lithium has not been widely accepted for use in the inhibition of GSK-3 activity, possibly because of its documented effects on molecular targets other than GSK-3. The purine analog 5-iodotubercidin, also a GSK-3 inhibitor, likewise stimulates glycogen synthesis and antagonizes inactivation of glycogen synthase by glucagon and vasopressin in rat liver cells. Fluckiger-Isler et al., *Biochem J.* 292:85-91 (1993); and Massillon et al., *Biochem J.* 299:123-8 (1994). However, this compound has also been shown to inhibit other serine/threonine and tyrosine kinases. Massillon et al., *Biochem J.* 299:123-8 (1994).

[0023] One of the main goals in the management of patients with diabetes mellitus is to achieve blood glucose levels that are as close to normal as possible. In general, obtaining normal postprandial blood glucose levels is more difficult than normalizing fasting hyperglycemia. In addition, some epidemiological studies suggest that postprandial hyperglycemia (PPHG) or hyperinsulinemia are independent risk factors for the development of macrovascular complications of diabetes mellitus. Recently, several drugs with differing pharmacodynamic profiles have been developed which target PPHG. These include insulin lispro, amylin analogues, alpha-glucosidase inhibitors and meglitinide analogues. Insulin lispro has a more rapid onset of action and shorter duration of efficacy compared with regular human insulin.

In clinical trials, the use of insulin lispro has been associated with improved control of PPHG and a reduced incidence of hypoglycemic episodes. Repaglinide, a meglitinide analogue, is a short-acting insulinotropic agent which, when given before meals, stimulates endogenous insulin secretions and lowers postprandial hyperglycaemic excursions. Both insulin lispro and repaglinide are associated with postprandial hyperinsulinaemia. In contrast, amylin analogues reduce PPHG by slowing gastric emptying and delivery of nutrients to the absorbing surface of the gut. Alpha-glucosidase inhibitors such as acarbose, miglitol and voglibose also reduce PPHG primarily by interfering with the carbohydrate-digesting enzymes and delaying glucose absorption. Yamasaki et al., *Tohoku J Exp Med* 1997;183(3):173-83. The GSK inhibitors of the present invention are also useful, alone or in combination with the agents set forth above, in the treatment of postprandial hyperglycemia as well as in the treatment of fasting hyperglycemia.

[0024] GSK-3 is also involved in biological pathways relating to Alzheimer's disease (AD). The characteristic pathological features of AD are extracellular plaques of an abnormally processed form of the amyloid precursor protein (APP), so called β-amyloid peptide (β-AP) and the development of intracellular neurofibrillary tangles containing paired helical filaments (PHF) that consist largely of hyperphosphorylated tau protein. GSK-3 is one of a number of kinases that have been found to phosphorylate tau protein *in vitro* on the abnormal sites characteristic of PHF tau, and is the only kinase also demonstrated to do this in living cells and in animals. Lovestone et al., *Current Biology* 4:1077-86 (1994); and Brownlees et al., *Neuroreport* 8: 3251-3255 (1997). Furthermore, the GSK-3 kinase inhibitor, LiCl, blocks tau hyperphosphorylation in cells. Stambolic et al., *Current Biology* 6:1664-8 (1996). Thus GSK-3 activity may contribute to the generation of neurofibrillary tangles and consequently to disease progression. Recently it has been shown that GSK-3β associates with another key protein in AD pathogenesis, presenillin 1 (PS1). Takashima et al., *PNAS* 95:9637-9641 (1998). Mutations in the PS1 gene lead to increased production of β-AP, but the authors also

demonstrate that the mutant PS1 proteins bind more tightly to GSK-3β and potentiate the phosphorylation of tau, which is bound to the same region of PS1.

[0025] It has also been shown that another GSK-3 substrate, β-catenin, binds to PS1. Zhong et al., *Nature* 395:698-702 (1998). Cytosolic β-catenin is targeted for degradation upon phosphorylation by GSK-3 and reduced β-catenin activity is associated with increased sensitivity of neuronal cells to β-AP induced neuronal apoptosis. Consequently, increased association of GSK-3β with mutant PS1 may account for the reduced levels of β-catenin that have been observed in the brains of PS1-mutant AD patients and to the disease related increase in neuronal cell-death. Consistent with these observations, it has been shown that injection of GSK-3 antisense but not sense, blocks the pathological effects of β-AP on neurons *in vitro*, resulting in a 24 hour delay in the onset of cell death and increased cell survival at 1 hour from 12 to 35%. Takashima et al., *PNAS* 90:7789-93. (1993). In these latter studies, the effects on cell-death are preceded (within 3-6 hours of β-AP administration) by a doubling of intracellular GSK-3 activity, suggesting that in addition to genetic mechanisms that increase the proximity of GSK-3 to its substrates, β-AP may actually increase GSK-3 activity. Further evidence for a role for GSK-3 in AD is provided by the observation that the protein expression level (but, in this case, not specific activity) of GSK-3 is increased by 50% in postsynaptosomal supernatants of AD vs. normal brain tissue. Pei et al., *J. Neuropathol Exp.*, 56:70-78 (1997). Thus, specific inhibitors of GSK-3 should slow the progression of Alzheimer's Disease.

[0026] In addition to the effects of lithium described above, there is a long history of the use of lithium to treat bipolar disorder (manic depressive syndrome). This clinical response to lithium may reflect an involvement of GSK-3 activity in the etiology of bipolar disorder, in which case GSK-3 inhibitors could be relevant to that indication. In support of this notion it was recently shown that valproate, another drug commonly used in the treatment

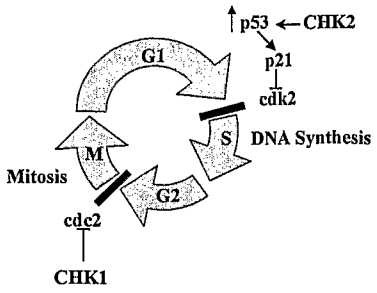
of bipolar disorder, is also a GSK-3 inhibitor. Chen et al., *J. Neurochemistry*, 72:1327-1330 (1999). One mechanism by which lithium and other GSK-3 inhibitors may act to treat bipolar disorder is to increase the survival of neurons subjected to aberrantly high levels of excitation induced by the neurotransmitter, glutamate. Nonaka et al., *PNAS* 95: 2642-2647 (1998). Glutamate-induced neuronal excitotoxicity is also believed to be a major cause of neurodegeneration associated with acute damage, such as in cerebral ischemia, traumatic brain injury and bacterial infection. Furthermore it is believed that excessive glutamate signaling is a factor in the chronic neuronal damage seen in diseases such as Alzheimer's, Huntingdon's, Parkinson's, AIDS associated dementia, amyotrophic lateral sclerosis (ALS) and multiple sclerosis (MS). Thomas, *J. Am. Geriatr. Soc.* 43: 1279-89 (1995). Consequently, GSK-3 inhibitors should provide a useful treatment in these and other neurodegenerative disorders.

[0027] GSK-3 phosphorylates transcription factor NF-AT and promotes its export from the nucleus, in opposition to the effect of calcineurin. Beals et al., *Science* 275:1930-33 (1997). Thus, GSK-3 blocks early immune response gene activation via NF-AT, and GSK-3 inhibitors may tend to permit or prolong activation of immune responses. Thus, GSK-3 inhibitors are believed to prolong and potentiate the immunostimulatory effects of certain cytokines, and such an effect may enhance the potential of those cytokines for tumor immunotherapy or indeed for immunotherapy in general.

[0028] Lithium has other biological effects. It is a potent stimulator of hematopoiesis, both *in vitro* and *in vivo*. Hammond et al., *Blood* 55: 26-28 (1980). In dogs, lithium carbonate eliminated recurrent neutropenia and normalized other blood cell counts. Doukas et al. *Exp. Hematol.* 14: 215-221 (1986). If these effects of lithium are mediated through the inhibition of GSK-3, GSK-3 inhibitors may have even broader applications. Since inhibitors of GSK-3 are useful in the treatment of many diseases, the identification of new inhibitors of GSK-3 would be highly desirable.

[0029] NEK-2 is a mammalian serine threonine kinase, which is structurally related to the NimA kinase from the fungus Aspergillus nidulans. Mutations in NimA result in G2 phase arrest of cells and overexpression of wt NimA results in premature chromatin condensation, even when ectopically expressed in mammalian cells. Both protein and kinase levels peak in S/G2 phase of the cell cycle. NimA also appears to be required for the localization of cdk1/cyclinB complex to the nucleus and spindle pole body. Histone H3 has been shown to be an *in vitro* substrate for the kinase, and if this is also the case *in vivo*, it may explain the role of the kinase in chromosome condensation. Six NimA kinases have been identified to date in mammals, and of these, NEK-2 appears to be the most closely related to NimA. It's activity is also cell cycle regulated, peaking in S/G2 phase. Overexpression of NEK-2, however, does not affect chromatin condensation but instead results in a pronounced splitting of centrosomes, possibly due to the loss of centriole/centriole adhesion. There is evidence that NEK-2 is regulated by phosphorylation and can interact with protein phosphatase PP1. NEK-2 is ubiquitously expressed and appears to be most abundant in testis. Hyseq cluster 374113, containing only NEK-2 sequences shows dramatic overexpression of NEK-2 in lymph node metastasis (13.3x) and in primary tumor (6.5x). Inhibition of NEK-2 by antisense oligonucleotides inhibited cell proliferation and reduced the capability of cells to grow in soft agar. In addition, increased cell death was observed in these cells both in the presence and absence of cisplatin.

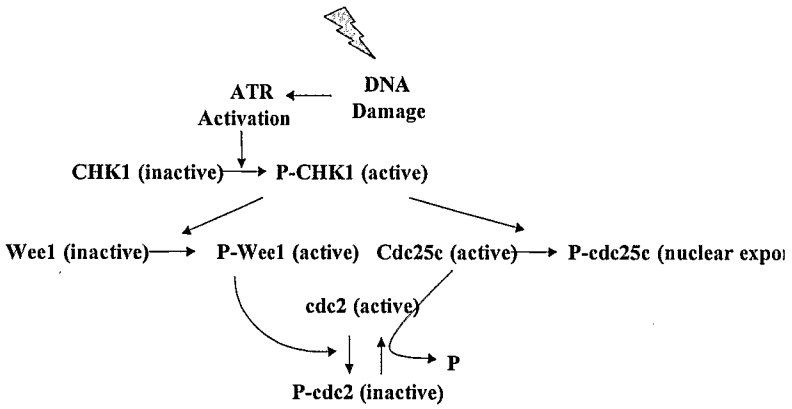
[0030] Ultraviolet light, ionizing radiation, environmental agents and cytotoxic drugs can result in damage to cellular DNA integrity. When such damage occurs during DNA replication or cell division it is potentially catastrophic and may result in cell death. The cellular response is to arrest the cell cycle at one of two checkpoints (G1/S or G2/M) to either permit DNA repair or initiate apoptosis.



[0031] The G1/S checkpoint is regulated by the p53 transcriptional activator protein and the absence of this critical protein is often an important step in tumorigenesis, thus defining p53 as a tumor suppressor. In fact, nearly 50% of all cancers are p53 defective due to mutation. T. Soussi, *Ann. N.Y. Acad Sci.*, 910, 121 (2001). In response to DNA damage, checkpoint kinase 2 (CHK-2) phosphorylates p53 and this results in stabilization of the protein and an elevation in p53 levels. A. Hirao et al., *Science*, 287, 1824 (2000). Consequently, negative cell cycle regulators, such as p21Waf1/Cip1, are activated and halt the cell cycle at the G1/S checkpoint. B. Vogelstein et al., *Nature,* 408, 307 (2000).

[0032] The G2/M checkpoint is monitored by the serine/threonine checkpoint kinase 1 (CHK1). Upon DNA damage, the protein kinase ATR (ataxia-telangiectasia mutated - rad53 related kinase) is activated. H. Zhao et al., *Mol. Cell Biol.*, 21, 4129 (2001); Q. Liu et al., *Genes Dev.,* 14, 1448 (2000). SATR-dependent phosphorylation of CHK1 promotes its phosphorylation of Cdc25 and Wee1 and ultimately inactivation of Cdc2. Thus, CHK1 phosphorylation of Cdc25c targets it for nuclear export to the cytoplasm and as a result the Cdc25c phosphatase is rendered unavailable to activate Cdc2 by dephosphorylation. Y. Sanchez et al., *Science*, 277, 1497 (1997); C. Y. Peng et al., *Science*, 277, 1501 (1997); T. A. Chen et al., *Nature*, 401, 616 (1999); and A. Lopez-Girona et al., *Nature*, 397, 172 (1999). In addition, CHK1 activates the protein kinase Wee1, which phosphorylates and inactivates Cdc2. J. Lee et al. *Mol. Biol. Cell*, 12, 551 (2001); L. L. Parker et al., *Science*, 257, 1955 (1992). These dual pathways thus converge to result in cell cycle arrest. Because cell cycle arrest is a potential

mechanism by which tumor cells can overcome the damage induced by cytotoxic agents, abrogation of these checkpoints with novel therapeutic agents should increase the sensitivity of tumors to chemotherapy. The presence of two checkpoints, coupled with the tumor specific abrogation of one of these by p53 mutations in 50% of cancers, can be exploited to design tumor-selective agents. Thus, in p53 minus tumors, therapeutic inhibition of G2/M arrest leaves cancerous cells no options for DNA damage repair and results in apoptosis. Normal cells have wild type p53 and retain an intact G1/S checkpoint. Thus these cells have an opportunity to correct DNA damage and survive. One approach to the design of chemosensitizers that abrogate the G2/M checkpoint is to identify inhibitors of the key G2/M regulatory kinase, CHK1.



[0033] It has been shown that PAR-1, also known as HDAK, a regulator of polarity, is a modulator of Wnt–β-catenin signaling, indicating a link between two important developmental pathways. See Sun, T-Q. et al. *Nature Cell Biology*, 3, 628-636 (2001). An important function of β-catenin, namely its role in cell signaling, has been elucidated in the past few years. β-Catenin is the vertebrate homologue of the *Drosophila* segment polarity gene armadillo, an important element in the Wingless/Wnt (Wg/Wnt) signaling pathway. Wingless is a cell–cell signal in *Drosophila* that triggers many key developmental processes, Wnt being the vertebrate homologue. In the absence of a mitotic signal from outside the cell β-catenin is sequestered in a complex with the adenomatous polyposis coli (APC) gene product, a serine

threonine glycogen synthetase kinase (GSK-3β) and an adapter protein axin (or a homologue conductin), enabling phosphorylation and degradation of free β-catenin by the ubiquitin–proteasome system. The function of and interactions between the proteins in the complex was something of a mystery until recently. Axin, a recently recognized component of the complex, acts as a scaffold protein in the multiprotein structure. Formation of an axin regulatory complex is critical for GSK-3β activity and β-catenin phosphorylation and degradation, since GSK-3β does not bind directly to β-catenin but requires the presence of axin, which binds to both proteins. This complex formation leads to the maintenance of low levels of free cytoplasmic β-catenin. Residual catenins hold cells together by binding to cadherins, both at the adherens junctions and the actin cytoskeleton.

[0034] When a mitotic signal is delivered by the Wnt pathway, by association of the Wg/Wnt family of secreted glycoproteins and their membrane receptor frizzled, it leads to activation of the dishevelled (Dsh) protein, which is recruited to the cell membrane. The activated Dsh downregulates the protein complex, so that it can no longer phosphorylate β-catenin, which then is not degraded. How exactly Wnt signaling leads to the stabilization of β-catenin remains unclear, although the critical step is possibly the dissociation of GSK-3β from axin with the help of Dsh. With GSK-3β no longer bound to axin, it cannot phosphorylate β-catenin, leading to an increase in β-catenin levels. Another proposed model is that inhibition of GSK-3β activity upon Wnt signaling by Dsh leads to the dephosphorylation of axin, resulting in a reduced efficiency of binding to β-catenin. The release of β-catenin from the phosphorylation and degradation complex promotes β-catenin stabilization and signaling. The resulting increase in free cytosolic β-catenin then enters the nucleus. This results in an increase of free cystolic β-catenin which translocates to the nucleus and directly binds the transcription factors Lef and Tcf, leading to the activation of gene expression. Recently, the target genes of these transcription factors have been identified. They are

thought to be involved in inhibiting apoptosis and promoting cellular proliferation and migration, and include the c-*myc* oncogene and one of the cell cycle regulators cyclin D1.

[0035] Transformation of adult mammalian cells into malignant tumors is believed to reflect an exaggeration of the Wg/Wnt pathway, at least in some tumors. The PAR-1 gene is involved in Wg/Wnt activity levels as well as production of free β-catenin in the cell. Down regulating of Wg/Wnt has been shown to limit β-catenin, which is involved in anti-apoptosis signaling. Small molecule inhibitors capable of inhibiting PAR-1 such as those disclosed herein, have been shown to be efficacious in cancer cell lines. Screens monitoring PAR-1 (HDAK) inhibition depict effective reduction of Wnt activity, with EC50 values below 10 μM in cell-based assays. Therefore, a need remains for small molecule inhibitors of the PAR-1, capable of inhibiting Wg/Wnt signaling and β-catenin production in order to reduce growth of tumor cell lines and tumors via stimulation of cellular apoptosis.

[0036] Various indolyl substituted compounds have recently been disclosed in WO 01/29025, WO 01/62251, and WO 01/62252, and various benzimidazolyl compounds have recently been disclosed in WO 01/28993. These compounds are reportedly capable of inhibiting, modulating, and/or regulating signal transduction of both receptor-type and non-receptor tyrosine kinases. Some of the disclosed compounds contain a quinolone fragment bonded to the indolyl or benzimidazolyl group.

[0037] The synthesis of 4-hydroxy quinolone and 4-hydroxy quinoline derivatives is disclosed in a number of references which are heing incorporated by reference in their entirety for all purposes as if fully set forth herein. For example, Ukrainets et al. have disclosed the synthesis of 3-(benzimidazol-2-yl)-4-hydroxy-2-oxo-1,2-dihydroquinoline. Ukrainets, I. et al., Tet. Lett. 42, 7747-7748 (1995); Ukrainets, I. et al., Khimiya Geterotsiklicheskikh Soedinii, 2, 239-241(1992). Ukrainets has also disclosed the synthesis, anticonvulsive and antithyroid activity of other 4-hydroxy

quinolones and thio analogs such as 1H-2-oxo-3-(2-benzimidazolyl)-4-hydoxyquinoline. Ukrainets, I. et al., Khimiya Geterotsiklicheskikh Soedinii, 1, 105-108 (1993); Ukrainets, I. et al., Khimiya Geterotsiklicheskikh Soedinii, 8, 1105-1108 (1993); Ukrainets, I. et al., Chem. Heterocyclic Comp. 33, 600-604, (1997).

[0038] The synthesis of various quinoline derivatives is disclosed in WO 97/48694. These compounds are disclosed as capable of binding to nuclear hormone receptors and being useful for stimulating osteoblast proliferation and bone growth. The compounds are also disclosed as being useful in the treatment or prevention of diseases associated with nuclear hormone receptor families.

[0039] Various quinoline derivatives in which the benzene ring of the quinolone is substituted with a sulfur group are disclosed in WO 92/18483. These compounds are disclosed as being useful in pharmaceutical formulations and as medicaments.

[0040] Quinolone and coumarin derivatives have been disclosed as having use in a variety of applications unrelated to medicine and pharmaceutical formulations. References that describe the preparation of quinolone derivatives for use in photopolymerizable compositions or for luminescent properties include: U.S. Patent No. 5,801,212 issued to Okamoto et al.; JP 8-29973; JP 7-43896; JP 6-9952; JP 63-258903; EP 797376; and DE 23 63 459 which are all herein incorporated by reference in their entirety for all purposes as if fully set forth herein.

[0041] Various quinolinone benzimidazole compounds described as useful in inhibiting angiogenesis and vascular endothelial growth factor receptor tyrosine kinases are disclosed in U.S. Patent Application No. 09/951,265 and WO 02/22598 (published on March 21, 2002), U.S. Patent Application No. 09/943,382 and WO 02/18383 (published on March 7, 2002), and U.S. Patent Application No. 10/116,117 filed (published on February 6,

2003 as US 20030028018 A1) each of which is incorporated herein by reference in its entirety for all purposes as if fully set forth herein.

[0042] Each of the following documents to which this application claims priority is also herein incorporated by reference in its entirety and for all purposes as if the references were fully set forth herein: U.S.S.N. 60/405,729 filed on August 23, 2002; U.S.S.N. 60/426,107 filed on November 13, 2002; U.S.S.N. 60/426,226 filed on November 13, 2002; U.S.S.N. 60/426,282 filed on November 13, 2002; U.S.S.N. 60/428,210 filed on November 21, 2002; U.S.S.N. 60/460,327 filed on April 3, 2003 U.S.S.N. 60/460,328 filed on April 3, 2003; U.S.S.N. 60/460,493 filed on April 3, 2003; U.S.S.N. 60/478,916 filed on June 16, 2003; and U.S.S.N. 60/484,048 filed on July 1, 2003.

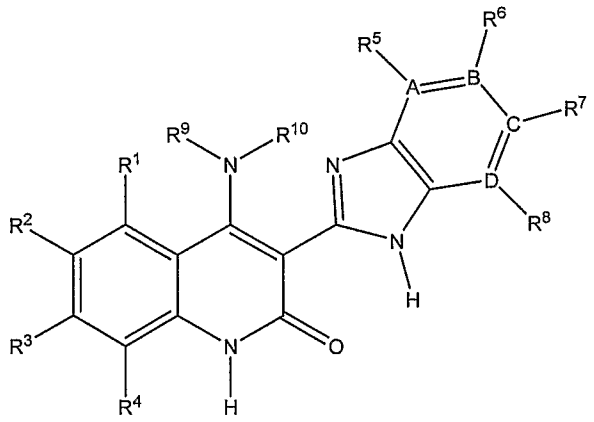
[0043] A continuing need exists for compounds that inhibit the proliferation of capillaries, inhibit the growth of tumors, treat cancer, treat diabetes, stimulate insulin-dependent processes, treat Alzheimer's disease, treat central nervous system disorders, prolong immune responses, reduce the splitting of centrosomes, block DNA repair, modulate cell cycle arrest, and/or inhibit enzymes such as FLT-1 (VEGFR1), VEGFR2 (KDR, Flk-1), VEGFR3, FGFR1, GSK-3, Cdk2, Cdk4, MEK1, CHK2, CK1ε, Raf, c-Kit, c-ABL, p60src, FGFR3, FLT-3, NEK-2, CHK1, Rsk2, PAR-1, Cdc2, Fyn, Lck, Tie-2, PDGFRα, and PDGFRβ, and pharmaceutical formulations and medicaments that contain such compounds. A need also exists for methods for administering such compounds, pharmaceutical formulations, and medicaments to patients or subjects in need thereof.

SUMMARY OF THE INVENTION

[0044] The present invention provides methods of inhibiting fibroblast growth factor receptor 3 and treating biological conditions mediated by fibroblast growth factor receptor 3. The present invention also provides the use of compounds in the preparation of medicaments for inhibiting fibroblast

growth factor receptor 3 and treating biological conditions mediated by fibroblast growth factor receptor 3.

[0045] In one aspect, the present invention provides a method of inhibiting fibroblast growth factor receptor 3 in a subject and/or a method of treating a biological condition mediated by fibroblast growth factor receptor 3 in a subject. The method includes administering to the subject a compound of Structure I, a tautomer of the compound, a pharmaceutically acceptable salt of the compound, a pharmaceutically acceptable salt of the tautomer, or a mixture thereof. The fibroblast growth factor receptor 3 is inhibited in the subject after administration. The invention also provides the use of a compound of Structure I, a tautomer of the compound, a pharmaceutically acceptable salt of the compound, a pharmaceutically acceptable salt of the tautomer, or a mixture thereof in the preparation of a medicament for inhibiting fibroblast growth factor receptor 3 in a subject and/or treating a biological condition mediated by fibroblast growth factor receptor 3 in a subject. Structure I has the following formula:



I

where:

A, B, C, and D are independently selected from carbon or nitrogen;

R^1 is selected from the group consisting of -H, -F, -Cl, -Br, -I, -CN, -NO_2, substituted and unsubstituted alkyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted alkenyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted aryl groups, substituted and unsubstituted aralkyl groups, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted heterocyclylalkyl groups, -SH, substituted and unsubstituted -S-alkyl groups, substituted and unsubstituted -S-heterocyclyl groups, -OH, substituted and unsubstituted alkoxy groups, substituted and unsubstituted heterocyclyloxy groups, substituted and unsubstituted heterocyclylalkoxy groups, -NH_2, substituted and unsubstituted -N(H)(alkyl) groups, substituted and unsubstituted -N(alkyl)$_2$ groups, substituted and unsubstituted -N(H)(heterocyclyl) groups, substituted and unsubstituted -N(alkyl)(heterocyclyl) groups, substituted and unsubstituted -N(heterocyclyl)$_2$ groups, substituted and unsubstituted -N(H)(heterocyclylalkyl) groups, substituted and unsubstituted -N(alkyl)(heterocyclylalkyl) groups, substituted and unsubstituted -N(heterocyclylalkyl)$_2$ groups, substituted and unsubstituted -N(H)-C(=O)-alkyl groups, substituted and unsubstituted -N(H)-C(=O)-heterocyclyl groups, substituted and unsubstituted -N(H)-C(=O)-heterocyclylalkyl groups, substituted and unsubstituted -N(alkyl)-S(=O)$_2$-alkyl groups, substituted and unsubstituted -N(alkyl)-S(=O)$_2$-heterocyclyl groups, substituted and unsubstituted -N(alkyl)-S(=O)$_2$-heterocyclylalkyl groups, substituted and unsubstituted -C(=O)-alkyl groups, substituted and unsubstituted -C(=O)-heterocyclyl groups, substituted and unsubstituted -C(=O)-heterocyclylalkyl groups, -C(=O)-NH_2, substituted and unsubstituted -C(=O)-N(H)(alkyl) groups, substituted and unsubstituted -C(=O)-N(alkyl)$_2$ groups, substituted and unsubstituted -C(=O)-N(H)(heterocyclyl) groups,

substituted and unsubstituted -C(=O)-N(alkyl)(heterocyclyl) groups, substituted and unsubstituted -C(=O)-N(heterocyclyl)$_2$ groups, substituted and unsubstituted -C(=O)-N(H)(heterocyclylalkyl) groups, substituted and unsubstituted -C(=O)-N(alkyl)(heterocyclylalkyl) groups, substituted and unsubstituted -C(=O)-N(heterocyclylalkyl)$_2$ groups, -CO_2H, substituted and unsubstituted -C(=O)-O-alkyl groups, substituted and unsubstituted -C(=O)-O-heterocyclyl groups, and substituted and unsubstituted -C(=O)-O-heterocyclylalkyl groups;

R^2 and R^3 are independently selected from the group consisting of -H, -F, -Cl, -Br, -I, -NO_2, -CN, substituted and unsubstituted alkyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted alkenyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted aryl groups, substituted and unsubstituted aralkyl groups, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted heterocyclylalkyl groups, -SH, substituted and unsubstituted -S-alkyl groups, substituted and unsubstituted -S(=O)$_2$-O-alkyl groups, substituted and unsubstituted -S(=O)$_2$-alkyl groups, substituted and unsubstituted -S(=O)$_2$-heterocyclyl groups, -S(=O)$_2$-NH_2, substituted and unsubstituted -S(=O)$_2$-N(H)(alkyl) groups, substituted and unsubstituted -S(=O)$_2$-N(alkyl)$_2$ groups, substituted and unsubstituted -S(=O)-alkyl groups, substituted and unsubstituted -S(=O)-heterocyclyl groups, -OH, substituted and unsubstituted alkoxy groups, substituted and unsubstituted aryloxy groups, substituted and unsubstituted heterocyclyloxy groups, substituted and unsubstituted heterocyclylalkoxy groups, -NH_2, substituted and unsubstituted -N(H)(alkyl) groups, substituted and unsubstituted -N(alkyl)$_2$ groups, substituted and unsubstituted -N(H)(aryl) groups, substituted and unsubstituted

-N(alkyl)(aryl) groups, substituted and unsubstituted -N(aryl)$_2$ groups, substituted and unsubstituted -N(H)(aralkyl) groups, substituted and unsubstituted -N(alkyl)(aralkyl) groups, substituted and unsubstituted -N(aralkyl)$_2$ groups, substituted and unsubstituted -N(H)(heterocyclyl) groups, substituted and unsubstituted -N(alkyl)(heterocyclyl) groups, substituted and unsubstituted -N(heterocyclyl)$_2$ groups, substituted and unsubstituted -N(H)(heterocyclylalkyl) groups, substituted and unsubstituted -N(alkyl)(heterocyclylalkyl) groups, substituted and unsubstituted -N(heterocyclylalkyl)$_2$ groups, substituted and unsubstituted -N(H)-C(=O)-alkyl groups, substituted and unsubstituted -N(alkyl)-C(=O)-alkyl groups, substituted and unsubstituted -N(H)-C(=O)-aryl groups, substituted and unsubstituted -N(alkyl)-C(=O)-aryl groups, substituted and unsubstituted -N(H)-C(=O)-aralkyl groups, substituted and unsubstituted -N(alkyl)-C(=O)-aralkyl groups, substituted and unsubstituted -N(H)-C(=O)-heterocyclyl groups, substituted and unsubstituted -N(alkyl)-C(=O)-heterocyclyl groups, substituted and unsubstituted -N(H)-C(=O)-heterocyclylalkyl groups, substituted and unsubstituted -N(alkyl)-C(=O)-heterocyclylalkyl groups, substituted and unsubstituted -N(H)-S(=O)$_2$-alkyl groups, substituted and unsubstituted -N(H)-S(=O)$_2$-aryl, substituted and unsubstituted -N(H)-S(=O)$_2$-heterocyclyl groups, substituted and unsubstituted -C(=O)-alkyl groups, substituted and unsubstituted -C(=O)-aryl, substituted and unsubstituted -C(=O)-aralkyl, substituted and unsubstituted -C(=O)-heterocyclyl groups, substituted and unsubstituted -C(=O)-heterocyclylalkyl groups, -C(=O)-NH$_2$, substituted and unsubstituted -C(=O)-N(H)(alkyl) groups, substituted and unsubstituted -C(=O)-N(alkyl)$_2$ groups, substituted and unsubstituted -C(=O)-N(H)(aryl) groups, substituted and unsubstituted -C(=O)-N(alkyl)(aryl) groups, substituted and

unsubstituted -C(=O)-N(aryl)$_2$ groups, substituted and unsubstituted -C(=O)-N(H)(aralkyl) groups, substituted and unsubstituted -C(=O)-N(alkyl)(aralkyl) groups, substituted and unsubstituted -C(=O)-N(aralkyl)$_2$ groups, substituted and unsubstituted -C(=O)-N(H)(heterocyclyl) groups, substituted and unsubstituted -C(=O)-N(alkyl)(heterocyclyl) groups, substituted and unsubstituted -C(=O)-N(heterocyclyl)$_2$ groups, substituted and unsubstituted -C(=O)-N(H)(heterocyclylalkyl) groups, substituted and unsubstituted -C(=O)-N(alkyl)(heterocyclylalkyl) groups, substituted and unsubstituted -C(=O)-N(heterocyclylalkyl)$_2$ groups, -CO_2H, substituted and unsubstituted -C(=O)-O-alkyl groups, C(=O)-O-aryl groups -C(=O)-O-aralkyl groups, substituted and unsubstituted -C(=O)-O-heterocyclyl groups, and substituted and unsubstituted -C(=O)-O-heterocyclylalkyl groups;

R^4 is selected from the group consisting of –H and substituted and unsubstituted alkyl groups having from 1 to 12 carbon atoms;

R^5 and R^8 are independently selected from the group consisting of -H, -F, -Cl, -Br, -I, -CN, -NO_2, substituted and unsubstituted alkyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted alkenyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted heterocyclylalkyl groups, -OH, substituted and unsubstituted alkoxy groups, substituted and unsubstituted heterocyclyloxy groups, substituted and unsubstituted heterocyclylalkoxy groups; or R^5 may be absent if A is nitrogen; or R^8 may be absent if D is nitrogen;

R^6 and R^7 are independently selected from the group consisting of -H, -F, -Cl, -Br, -I, -CN, $-NO_2$, substituted and unsubstituted alkyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted alkenyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted aryl groups, substituted and unsubstituted arylakyl groups, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted heterocyclylalkyl groups, -SH, substituted and unsubstituted -S-alkyl groups, substituted and unsubstituted -S-heterocyclyl groups, $-S(=O)_2-NH_2$, substituted and unsubstituted $-S(=O)_2-N(H)$(alkyl) groups, substituted and unsubstituted $-S(=O)_2-N(alkyl)_2$ groups, -OH, substituted and unsubstituted alkoxy groups, substituted and unsubstituted heterocyclyloxy groups, substituted and unsubstituted heterocyclylalkoxy groups, $-NH_2$, substituted and unsubstituted -N(H)(alkyl) groups, substituted and unsubstituted $-N(alkyl)_2$ groups, substituted and unsubstituted -N(H)(heterocyclyl) groups, substituted and unsubstituted -N(alkyl)(heterocyclyl) groups, substituted and unsubstituted $-N(heterocyclyl)_2$ groups, substituted and unsubstituted -N(H)(heterocyclylalkyl) groups, substituted and unsubstituted -N(alkyl)(heterocyclylalkyl) groups, substituted and unsubstituted $-N(heterocyclylalkyl)_2$ groups, substituted and unsubstituted -N(H)-C(=O)-alkyl groups, substituted and unsubstituted -N(H)-C(=O)-heterocyclyl groups, substituted and unsubstituted -N(H)-C(=O)-heterocyclylalkyl groups, substituted and unsubstituted -N(alkyl)-C(=O)-alkyl groups, substituted and unsubstituted -N(alkyl)-C(=O)-heterocyclyl groups, substituted and unsubstituted -N(alkyl)-C(=O)-heterocyclylalkyl, substituted and unsubstituted $-N(H)-S(=O)_2$-alkyl groups, substituted and unsubstituted $-N(H)-S(=O)_2$-heterocyclyl groups, substituted and unsubstituted $-N(H)-S(=O)_2$-heterocyclylalkyl groups, substituted and unsubstituted -C(=O)-alkyl groups, substituted and

unsubstituted -C(=O)-heterocyclyl groups, substituted and unsubstituted -C(=O)-heterocyclylalkyl groups, -C(=O)-NH_2, substituted and unsubstituted -C(=O)-N(H)(alkyl) groups, substituted and unsubstituted -C(=O)-N(alkyl)$_2$ groups, substituted and unsubstituted -C(=O)-N(H)(heterocyclyl) groups, substituted and unsubstituted -C(=O)-N(alkyl)(heterocyclyl) groups, substituted and unsubstituted -C(=O)-N(heterocyclyl)$_2$ groups, substituted and unsubstituted -C(=O)-N(H)(heterocyclylalkyl) groups, substituted and unsubstituted -C(=O)-N(alkyl)(heterocyclylalkyl) groups, substituted and unsubstituted -C(=O)-N(heterocyclylalkyl)$_2$ groups, -CO_2H, substituted and unsubstituted -C(=O)-O-alkyl groups, substituted and unsubstituted -C(=O)-O-heterocyclyl groups, and substituted and unsubstituted -C(=O)-O-heterocyclylalkyl groups; or R^6 is absent if B is nitrogen; or R^7 is absent if C is nitrogen;

R^9 is selected from the group consisting of -H, substituted and unsubstituted alkyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted alkenyl groups having from 1 to 12 carbons, substituted and unsubstituted aryl groups, substituted and unsubstituted aralkyl groups, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted heterocyclylalkyl groups, -OH, substituted and unsubstituted alkoxy groups, substituted and unsubstituted heterocyclyloxy groups, -NH_2, and substituted and unsubstituted heterocyclylaminoalkyl; and

R^{10} is -H.

[0046] In some embodiments, A,B,C, and D are all carbon.

[0047] In some embodiments, R^9 is H.

[0048] In some embodiments, R^1 is selected from -H, -F, -Cl, -Br, -I, substituted or unsubstituted straight or branched chain alkyl groups having from 1 to 8 carbon atoms, substituted or unsubstituted cycloalkyl groups, substituted or unsubstituted heterocyclyl groups, substituted or unsubstituted heterocyclylalkyl groups, substituted or unsubstituted alkoxy groups, substituted or unsubstituted heterocyclyloxy groups, or substituted or unsubstituted heterocyclylalkoxy groups. In some such embodiments, R^1 is -F.

[0049] In some embodiments, R^2 is selected from –H, -Cl, -F, -Br, -I, $-NO_2$, -CN, substituted or unsubstituted straight or branched chain alkyl having from 1 to 8 carbons, substituted or unsubstituted phenyl groups, substituted or unsubstituted thiophene groups, substituted or unsubstituted 1,2,3,6-tetrahydropyridinyl groups, substituted or unsubstituted pyridinyl groups, substituted or unsubstituted straight or branched chain alkoxy groups, substituted or unsubstituted pyridinylalkoxy groups, substituted or unsubstituted dialkylamino groups, or $-CO_2H$. In some such embodiments, R^2 is -H.

[0050] In some embodiments, R^3 is selected from -H, -F, -Cl, -Br, methoxy, or dimethylamino groups. In some such embodiments, R^3 is -H.

[0051] In some embodiments, R^4 is H.

[0052] In some embodiments, R^5 is H and R^8 is H.

[0053] In some embodiments, at least one of R^6 or R^7 is a substituted or unsubstituted heterocyclyl group. In some such embodiments, one of R^6 or R^7 is a substituted or unsubstituted heterocyclyl group and the heterocyclyl group is selected from morpholine, piperazine, piperidine, pyrrolidine, thiomorpholine, homopiperazine, tetrahydrothiophene, tetrahydrofuran, or tetrahydropyran. In other such embodiments, one of R^6 or R^7 is selected from substituted or unsubstituted morpholine groups, or substituted or unsubstituted piperazine groups. In other such embodiments, one of R^6 or R^7

is an N-alkyl substituted piperazine such as N-methyl piperazine. In still other such embodiments, one of R^6 or R^7 is an N-alkyl substituted piperazine and the other of R^6 or R^7 is H, and R^5 and R^8 are both H.

[0054] In some embodiments, the biological condition is multiple myeloma and the subject is a multiple myeloma patient with a t(4;14) chromosomal translocation.

[0055] In some embodiments, the biological condition is multiple myeloma, the subject is a multiple myeloma patient, and the multiple myeloma expresses fibroblast growth factor receptor 3.

[0056] In some embodiments, the subject is a multiple myeloma patient having multiple myeloma cells, and further wherein apoptotic cell death is induced in the multiple myeloma cells after administration of the compound of Structure I, the tautomer of the compound, the pharmaceutically acceptable salt of the compound, the pharmaceutically acceptable salt of the tautomer, or the mixture thereof to the subject. In some embodiments, the compound of Structure I, the tautomer of the compound, the pharmaceutically acceptable salt of the compound, the pharmaceutically acceptable salt of the tautomer, or the mixture thereof is used to prepare a medicament for inducing aptoptotic cell death in the multiple myeloma cells of a subject that is a multiple myeloma patient.

[0057] In some embodiments, the subject is a multiple myeloma patient, and further wherein osteolytic bone loss is reduced in the subject after administration of the compound of Structure I, the tautomer of the compound, the pharmaceutically acceptable salt of the compound, the pharmaceutically acceptable salt of the tautomer, or the mixture thereof to the subject. In some embodiments, the compound of Structure I, the tautomer of the compound, the pharmaceutically acceptable salt of the compound, the pharmaceutically acceptable salt of the tautomer, or the mixture thereof is used to prepare a

medicament for reducing osteolytic bone loss in a subject that is a multiple myeloma patient.

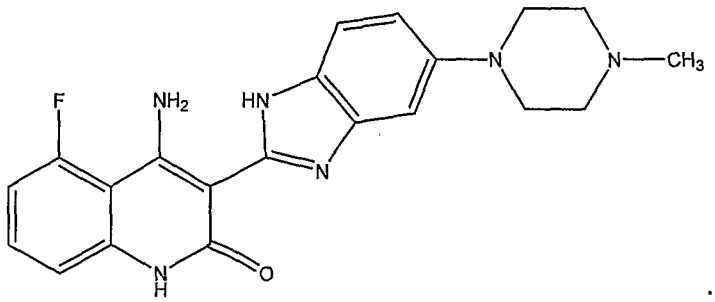
[0058] In some embodiments, the subject is a multiple myeloma patient, and the method further comprises administering dexamethasone to the subject before during or after administration of the compound of Structure I.

[0059] In some embodiments, the invention provides a composition that includes the compound of Structure I, a tautomer of the compound, a pharmaceutically acceptable salt of the compound, a pharmaceutically acceptable salt of the tautomer, or a mixture thereof and dexamethasone.

[0060] In some embodiments, the invention provides therapeutic compositions comprising a compound of Structure I, a tautomer of the compound, a pharmaceutically acceptable salt of the compound, a pharmaceutically acceptable salt of the tautomer, or a mixture thereof, and dexamethasone as a combined preparation for simultaneous, separate, or sequential use in inhibiting fibroblast growth factor receptor 3 in a subject and/or treating a biological condition mediated by fibroblast growth factor receptor 3 in a subject. In some such embodiments, the compound of Structure I, the tautomer of the compound, the pharmaceutically acceptable salt of the compound, the pharmaceutically acceptable salt of the tautomer, or the mixture thereof and the dexamethasone are provided as a single composition whereas in other embodiments, the tautomer of the compound, the pharmaceutically acceptable salt of the compound, the pharmaceutically acceptable salt of the tautomer, or the mixture thereof and the dexamethasone are provided separately as parts of a kit.

[0061] In some embodiments, the lactate salt of the compound of Structure I or the tautomer thereof is administered to the subject and/or is used to prepare the medicament.

[0062] In some embodiments, the compound of Structure I has the following formula



[0063] The invention further provides the use of the compounds of Structure I, tautomers of the compounds, pharmaceutically acceptable salts of the compounds, pharmaceutically acceptable salts of the tautomers, and mixtures thereof in inhibiting fibroblast growth factor receptor 3 or for use in treating a biological condition such as multiple myeloma that is mediated by fibroblast growth factor receptor 3. The invention further provides the use of the compounds of Structure I, tautomers of the compounds, pharmaceutically acceptable salts of the compounds, pharmaceutically acceptable salts of the tautomers, and mixtures thereof in the preparation and manufacture of medicaments for inhibiting fibroblast growth factor receptor 3 or for use in treating any biological condition mediated by fibroblast growth factor receptor 3. In some embodiments, the compounds may be used to prepare medicaments in containers such as vials, ampoules, or other pharmaceutical formulation storage devices and such storage devices may include labels which may include directions for application such as directions for inhibiting fibroblast growth factor receptor 3 or directions for treating a subject that has a biological condition mediated by fibroblast growth factor receptor 3.

[0064] Further objects, features and advantages of the invention will be apparent from the following detailed description.

BRIEF DESCRIPTION OF THE DRAWINGS

[0065] FIG. 1 is a graph of tumor growth inhibition in the presence of 4-amino-5-fluoro-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one in the KM12L4a colon tumor model in *nu/nu* mice.

[0066] FIG. 2 is a graph of inhibition of angiogenesis in the presence of 4-amino-5-fluoro-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one in the *in vivo* matrigel angiogenesis model.

[0067] FIG. 3 is a graph of tumor growth inhibition in the presence of 4-amino-5-fluoro-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one administered intermittently in the PC3 human prostate tumor model in *SCID* mice.

[0068] FIG. 4 is a graph of tumor growth inhibition in the presence of 4-amino-5-fluoro-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one.

[0069] FIG. 5 is a graph of tumor growth inhibition in the presence of 10 mg/kg/d 4-amino-5-fluoro-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one administered in combination with irinotecan in the KM12L4a colon tumor model in *nu/nu* mice.

[0070] FIG. 6 is a graph of tumor growth inhibition in the presence of 50 mg/kg/d 4-amino-5-fluoro-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one administered in combination with irinotecan in the KM12L4a colon tumor model in *nu/nu* mice.

[0071] FIG. 7. is a graph of tumor growth inhibition in the presence of 50 mg/kg/d 4-amino-5-fluoro-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one administered in combination with trastuzumab in the erbB2-overexpressing ovarian tumor model, SKOV3ip1.

[0072] FIG. 8 is a graph of tumor growth inhibition in the presence of 50 mg/kg/d 4-amino-5-fluoro-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one administered in combination with ZD1839 in the A431 epidermoid tumor model.

[0073] FIGS. 9A and 9B are graphs showing inhibition of VEGF-mediated migration of HUVEC and VEGF-mediated tube formation in the presence of 4-amino-5-fluoro-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one.

[0074] FIG. 10 is a graph showing inhibition of the sprouting of endothelial cells from rat aortic rings in the presence of 4-amino-5-fluoro-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one.

[0075] FIG. 11 is a graph of tumor growth inhibition in the presence of 10, 30, and 70 mg/kg/d 4-amino-5-fluoro-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one in the MV4-11 (FLT-3 ITD mutant) tumor model in *SCID-NOD* mice.

[0076] FIG. 12 is a graph of tumor growth inhibition starting with different tumor sizes (300, 500, 1000 mm^3) in the presence of 30 mg/kg/d 4-amino-5-fluoro-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one in the MV4-11 (FLT-3 ITD mutant) tumor model in *SCID-NOD* mice.

[0077] FIG. 13 is a graph of tumor growth inhibition in the presence of 30 mg/kg/d 4-amino-5-fluoro-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one administered daily, q.o.d., or 7 days on/7off in the MV4-11 (FLT-3 ITD mutant) tumor model in *SCID-NOD* mice.

[0078] FIG. 14 is a graph showing that 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one inhibits proliferation of multiple myeloma cell lines including KMS11, OPM-2, and H929.

[0079] FIG. 15 is a western blot showing that 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one inhibits FGFR3 phosphorylation at 0.5 μM in KMS11 cells.

[0080] FIGS. 16A, 16B, and 16C are western blots showing that 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one inhibits ERK phosphorylation at 0.5 μM in KMS11 cells (FIG. 16A), at 0.1 μM in OPM-2 cells (FIG. 16B), and has no effect on ERK phosphorylation up to 5 μM in H929 cells (FIG. 16C).

[0081] FIG. 17 is a graph showing apoptosis of KMS11 cells, as measured by AnnexinVPE staining, when such cells were incubated with 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one at various concentrations.

[0082] FIG. 18 is a graph showing that 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one has minor effects on the cell cycle of KMS11 cells when it is incubated with the cell for 72 hours but induces apoptosis.

[0083] FIG. 19 is a graph showing apoptosis of OPM-2 cells, as measured by AnnexinVPE staining, when such cells were incubated with 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one at various concentrations.

[0084] FIG. 20 is a graph showing that 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one has minor effects on the cell cycle of OPM-2 cells when it is incubated with the cells for 72 hours but induces apoptosis.

[0085] FIG. 21 is a graph showing that 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one has minor to no effect on the cell cycle of H929 cells when it is incubated with the cells.

[0086] FIG. 22 is a graph showing that M-CSF mediated proliferation of a mouse myeloblastic cell line M-NFS-60 was inhibited when the cells were incubated with 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one (EC_{50} of 220 nM).

[0087] FIG. 23 is a graph showing that 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one inhibits the viability of FGFR3 expressing B9 cells, but not parental interleukin-6 (IL6) stimulated cells. The values represent the mean +/- the standard deviation of four independent experiments.

[0088] FIG. 24 is a graph showing apoptosis in various human myeloma cell lines as assessed with a flow cytometric assay of annexin V binding and propidium iodide exclusion. KMS11, KMS18, OPM2, H929, and 8226 cells were incubated with vehicle (unshaded bar); with 100 nM (shaded bar) 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one; and with 500 nM (hatched bar) 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one. The values represent the mean +/- the standard deviation of four independent experiments.

[0089] FIGS 25A-25D are graphs showing that 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one inhibits FGF-mediated ERK1/2 phosphorylation and induces cytotoxicity in FGFR3 expressing primary multiple myeloma cells. FIG. 25A shows a graph obtained using flow cytometry of cells stained with FGFR3 antibody (open) or rabbit pre-immune serum (filled) and then stained with goat anti-rabbit FITC. Myeloma cells were identified by CD138 labeling. FIG. 25B shows a graph obtained using flow cytometry of primary myeloma cells incubated in the absence (filled) or presence of aFGF (- -) or pre-incubated with 500 nM 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one for 2 hours and then stimulated with aFGF. ERK1/2 phosphorylation was assessed using flow cytometry. FIGS. 25C and 25D are

graphs obtained using flow cytometry of primary myeloma cells cultured in growth medium in the presence of DMSO (FIG. 25C) or 500 nM 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one (FIG. 25D). Cells were harvested after 7 days and stained with annexin V-FITC and analyzed by flow cytometry. Myeloma cells were identified by $CD38^{++}/CD45^{-}$ labeling. The total percentage of $CD38^{++}/CD45^{-}$/annexin V^{+} cells is shown in upper right quadrant.

[0090] FIGS. 26A and 26B are graphs showing that 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one inhibits the viability of KMS11 cells in the presence of interleukin-6 (IL6), insulin growth factor (IGF-1), and bone marrow stroma cells (BMSCs). FIG 26A is a graph in which KMS11 cells were cultured with DMSO (unshaded bar); with 100 nM (shaded bar) 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one; and with 500 nM (hatched bar) 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one in the presence or absence of 50 ng/mL IL6 or 50 ng/mL IGF-1. Cell viability was assessed by MTT assay after 48 hours. FIG. 26B is a graph in which BMSCs alone or together with KMS11 were cultured with DMSO (unshaded bar); with 100 nM (shaded bar) 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one; and with 500 nM (hatched bar) 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one. Viability was assessed after 96 hours by MTT assay. The data represent means of quadruplicate cultures +/- standard deviations.

[0091] FIG. 27 is a graph showing that 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one inhibits proliferation of M-NFS-60, a M-CSF growth driven mouse myeloblastic cell line with an EC_{50} of 220 nM. M-NSF-60 cells were incubated with serial dilutions of 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one in the presence of M-CSF and without GM-CSF. The

number of viable cells was assessed after 72 hours using the Cell Titer-Glo™ assay.

[0092] FIG. 28 is a graph showing that 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one inhibits FGFR3 phosphorylation and demonstrates anti-tumor effects *in vivo*. When tumor size reached 200 mm^3, mice were randomly assigned (8-10/group) to receive vehicle alone or varying doses of 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one by oral gavage for 21 days. The graph shows tumor volume (mean +/- standard deviation) as a function of the days of treatment.

[0093] FIG. 29 shows KM12L4a tumor inhibition by the compound of formula I.

[0094] FIG. 30 shows the C_{max} and AUC values versus percent inhibition of KML12L4a tumor growth in KM12L4a tumor-bearing mice.

DETAILED DESCRIPTION OF THE INVENTION

[0095] The present invention relates to a novel class of compounds which act as inhibitors of serine/threonine kinases and tyrosine kinases, including inhibitors of GSK-3, Cdk2, Cdk4, MEK1, NEK-2, CHK2, CK1ε, Raf, CHK1, Rsk2, PAR-1, Cdc2 kinase, c-Kit, c-ABL, p60src, FGFR3, FLT-3, Fyn, Lck, and Tie-2. The present invention further relates to the compounds used in these methods. These compounds can be formulated into pharmaceutical formulations that are useful in treating patients with a need for such inhibitors (e.g., those suffering from cancer). The compounds described herein are also useful for reducing capillary proliferation and in the treatment of cancer and other medical or cellular conditions in human and cell subjects.

[0096] The following abbreviations and definitions are used throughout this application:

[0097] "ALS" is an abbreviation that stands for amyotropic lateral sclerosis.

[0098] "AD" is an abbreviation that stands for Alzheimer Disease.

[0099] "APP" is an abbreviation that stands for amyloid precursor protein.

[0100] "bFGF" is an abbreviation that stands for basic fibroblast growth factor.

[0101] "FGFR1", also referred to as bFGFR, is an abbreviation that stands for a tyrosine kinase that interacts with the fibroblast growth factor FGF.

[0102] "Cdc 2" is an abbreviation that stands for cell division cycle 2.

[0103] "Cdk 2" is an abbreviation that stands for cyclin dependent kinase 2.

[0104] "Cdk 4" is an abbreviation that stands for cyclin dependent kinase 4.

[0105] "Chk 1" is an abbreviation that stands for checkpoint kinase 1.

[0106] "CK1ε" is a serine/threonine kinase that stands for Casein kinase 1 (epsilon).

[0107] "c-ABL" is an abbreviation for a tyrosine kinase that stands for an oncogene product originally isolated from the Abelson leukemia virus.

[0108] "C-Kit" is also known as stem cell factor receptor or mast cell growth factor receptor.

[0109] "FGF" is an abbreviation for the fibroblast growth factor that interacts with FGFR1.

[0110] "FGFR3" is an abbreviation that stands for the tyrosine kinase fibroblast growth factor receptor 3 that is often expressed in multiple myeloma-type cancers.

[0111] "Flk-1" is an abbreviation that stands for fetal liver tyrosine kinase 1, also known as kinase-insert domain tyrosine kinase or KDR (human), also known as vascular endothelial growth factor receptor-2 or VEGFR2 (KDR (human), Flk-1 (mouse)).

[0112] "FLT-1" is an abbreviation that stands for fms-like tyrosine kinase-1, also known as vascular endothelial growth factor receptor-1 or VEGFR1.

[0113] "FLT-3" is an abbreviation that stands for fms-like tyrosine kinase-3, also known as stem cell tyrosine kinase I (STK I).

[0114] "FLT-4" is an abbreviation that stands for fms-like tyrosine kinase-4, also known as VEGFR3.

[0115] "Fyn" is an abbreviation that stands for FYN oncogene kinase related to SRC, FGR, YES.

[0116] "GSK-3" is an abbreviation that stands for glycogen synthase kinase 3.

[0117] "p60src" is a tyrosine kinase originally identified as the v-src oncogene of the rous sarcoma virus.

[0118] "PAR-1" is an abbreviation that stands for a kinase also known as disheveled associated kinase, also known as HDAK.

[0119] "Lck" is an abbreviation that stands for lymphocyte-specific protein tyrosine kinase.

[0120] "MEK1" is an abbreviation that stands for a serine threonine kinase in the MAPK (Mitogen activated protein kinase) signal transduction

pathway in a module that is formed of the Raf-MEK1-ERK. MEK1 phosphorylates ERK (extracellular regulated kinase).

[0121] "MS" is an abbreviation that stands for multiple sclerosis.

[0122] "NEK-2" is an abbreviation that stands for NIM-A related kinase.

[0123] "NIM-A" is an abbreviation that stands for never in mitosis.

[0124] "PDGF" is an abbreviation that stands for platelet derived growth factor. PDGF interacts with tyrosine kinases PDGFRα and PDGFRβ.

[0125] "PHF" is an abbreviation that stands for paired helical filaments.

[0126] "PS 1" is an abbreviation that stands for presenelin 1.

[0127] "Rsk2" is an abbreviation that stands for ribosomal S6 kinase 2.

[0128] "Raf" is a serine/threonine kinase in the MAPK signal transduction pathway.

[0129] "RTK" is an abbreviation that stands for receptor tyrosine kinase.

[0130] "Tie-2" is an abbreviation that stands for tyrosine kinase with Ig and EGF homology domains.

[0131] "VEGF" is an abbreviation that stands for vascular endothelial growth factor.

[0132] "VEGF-RTK" is an abbreviation that stands for vascular endothelial growth factor receptor tyrosine kinase.

[0133] Generally, reference to a certain element such as hydrogen or H is meant to include all isotopes of that element. For example, if an R group is defined to include hydrogen or H, it also includes deuterium and tritium.

[0134] The phrase "unsubstituted alkyl" refers to alkyl groups that do not contain heteroatoms. Thus the phrase includes straight chain alkyl groups

such as methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl, dodecyl and the like. The phrase also includes branched chain isomers of straight chain alkyl groups, including but not limited to, the following which are provided by way of example: $-CH(CH_3)_2$, $-CH(CH_3)(CH_2CH_3)$, $-CH(CH_2CH_3)_2$, $-C(CH_3)_3$, $-C(CH_2CH_3)_3$, $-CH_2CH(CH_3)_2$, $-CH_2CH(CH_3)(CH_2CH_3)$, $-CH_2CH(CH_2CH_3)_2$, $-CH_2C(CH_3)_3$, $-CH_2C(CH_2CH_3)_3$, $-CH(CH_3)CH(CH_3)(CH_2CH_3)$, $-CH_2CH_2CH(CH_3)_2$, $-CH_2CH_2CH(CH_3)(CH_2CH_3)$, $-CH_2CH_2CH(CH_2CH_3)_2$, $-CH_2CH_2C(CH_3)_3$, $-CH_2CH_2C(CH_2CH_3)_3$, $-CH(CH_3)CH_2CH(CH_3)_2$, $-CH(CH_3)CH(CH_3)CH(CH_3)_2$, $-CH(CH_2CH_3)CH(CH_3)CH(CH_3)(CH_2CH_3)$, and others. The phrase also includes cyclic alkyl groups such as cycloalkyl groups such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl and such rings substituted with straight and branched chain alkyl groups as defined above. The phrase also includes polycyclic alkyl groups such as, but not limited to, adamantyl norbornyl, and bicyclo[2.2.2]octyl and such rings substituted with straight and branched chain alkyl groups as defined above. Thus, the phrase unsubstituted alkyl groups includes primary alkyl groups, secondary alkyl groups, and tertiary alkyl groups. Unsubstituted alkyl groups may be bonded to one or more carbon atom(s), oxygen atom(s), nitrogen atom(s), and/or sulfur atom(s) in the parent compound. Preferred unsubstituted alkyl groups include straight and branched chain alkyl groups and cyclic alkyl groups having 1 to 20 carbon atoms. More preferred such unsubstituted alkyl groups have from 1 to 10 carbon atoms while even more preferred such groups have from 1 to 5 carbon atoms. Most preferred unsubstituted alkyl groups include straight and branched chain alkyl groups having from 1 to 3 carbon atoms and include methyl, ethyl, propyl, and $-CH(CH_3)_2$.

[0135] The phrase "substituted alkyl" refers to an unsubstituted alkyl group as defined above in which one or more bonds to a carbon(s) or hydrogen(s) are replaced by a bond to non-hydrogen and non-carbon atoms such as, but not limited to, a halogen atom in halides such as F, Cl, Br, and I; an oxygen atom in groups such as hydroxyl groups, alkoxy groups, aryloxy

groups, and ester groups; a sulfur atom in groups such as thiol groups, alkyl and aryl sulfide groups, sulfone groups, sulfonyl groups, and sulfoxide groups; a nitrogen atom in groups such as amines, amides, alkylamines, dialkylamines, arylamines, alkylarylamines, diarylamines, N-oxides, imides, and enamines; a silicon atom in groups such as in trialkylsilyl groups, dialkylarylsilyl groups, alkyldiarylsilyl groups, and triarylsilyl groups; and other heteroatoms in various other groups. Substituted alkyl groups also include groups in which one or more bonds to a carbon(s) or hydrogen(s) atom is replaced by a bond to a heteroatom such as oxygen in carbonyl, carboxyl, and ester groups; nitrogen in groups such as imines, oximes, hydrazones, and nitriles. Preferred substituted alkyl groups include, among others, alkyl groups in which one or more bonds to a carbon or hydrogen atom is/are replaced by one or more bonds to fluorine atoms. One example of a substituted alkyl group is the trifluoromethyl group and other alkyl groups that contain the trifluoromethyl group. Other alkyl groups include those in which one or more bonds to a carbon or hydrogen atom is replaced by a bond to an oxygen atom such that the substituted alkyl group contains a hydroxyl, alkoxy, aryloxy group, or heterocyclyloxy group. Still other alkyl groups include alkyl groups that have an amine, alkylamine, dialkylamine, arylamine, (alkyl)(aryl)amine, diarylamine, heterocyclylamine, (alkyl)(heterocyclyl)amine, (aryl)(heterocyclyl)amine, or diheterocyclylamine group.

[0136] The phrase "unsubstituted aryl" refers to aryl groups that do not contain heteroatoms. Thus the phrase includes, but is not limited to, groups such as phenyl, biphenyl, anthracenyl, naphthenyl by way of example. Although the phrase "unsubstituted aryl" includes groups containing condensed rings such as naphthalene, it does not include aryl groups that have other groups such as alkyl or halo groups bonded to one of the ring members, as aryl groups such as tolyl are considered herein to be substituted aryl groups as described below. A preferred unsubstituted aryl group is phenyl. Unsubstituted aryl groups may be bonded to one or more carbon

atom(s), oxygen atom(s), nitrogen atom(s), and/or sulfur atom(s) in the parent compound, however.

[0137] The phrase "substituted aryl group" has the same meaning with respect to unsubstituted aryl groups that substituted alkyl groups had with respect to unsubstituted alkyl groups. However, a substituted aryl group also includes aryl groups in which one of the aromatic carbons is bonded to one of the non-carbon or non-hydrogen atoms described above and also includes aryl groups in which one or more aromatic carbons of the aryl group is bonded to a substituted and/or unsubstituted alkyl, alkenyl, or alkynyl group as defined herein. This includes bonding arrangements in which two carbon atoms of an aryl group are bonded to two atoms of an alkyl, alkenyl, or alkynyl group to define a fused ring system (e.g. dihydronaphthyl or tetrahydronaphthyl). Thus, the phrase "substituted aryl" includes, but is not limited to tolyl, and hydroxyphenyl among others.

[0138] The phrase "unsubstituted alkenyl" refers to straight and branched chain and cyclic groups such as those described with respect to unsubstituted alkyl groups as defined above, except that at least one double bond exists between two carbon atoms. Examples include, but are not limited to vinyl, $-CH=C(H)(CH_3)$, $-CH=C(CH_3)_2$, $-C(CH_3)=C(H)_2$, $-C(CH_3)=C(H)(CH_3)$, $-C(CH_2CH_3)=CH_2$, cyclohexenyl, cyclopentenyl, cyclohexadienyl, butadienyl, pentadienyl, and hexadienyl among others.

[0139] The phrase "substituted alkenyl" has the same meaning with respect to unsubstituted alkenyl groups that substituted alkyl groups had with respect to unsubstituted alkyl groups. A substituted alkenyl group includes alkenyl groups in which a non-carbon or non-hydrogen atom is bonded to a carbon double bonded to another carbon and those in which one of the non-carbon or non-hydrogen atoms is bonded to a carbon not involved in a double bond to another carbon.

[0140] The phrase "unsubstituted alkynyl" refers to straight and branched chain groups such as those described with respect to unsubstituted alkyl groups as defined above, except that at least one triple bond exists between two carbon atoms. Examples include, but are not limited to –C≡C(H), -C≡C(CH_3), -C≡C(CH_2CH_3), -C(H_2)C≡C(H), -C($H)_2$C≡C(CH_3), and -C($H)_2$C≡C(CH_2CH_3) among others.

[0141] The phrase "substituted alkynyl" has the same meaning with respect to unsubstituted alkynyl groups that substituted alkyl groups had with respect to unsubstituted alkyl groups. A substituted alkynyl group includes alkynyl groups in which a non-carbon or non-hydrogen atom is bonded to a carbon triple bonded to another carbon and those in which a non-carbon or non-hydrogen atom is bonded to a carbon not involved in a triple bond to another carbon.

[0142] The phrase "unsubstituted aralkyl" refers to unsubstituted alkyl groups as defined above in which a hydrogen or carbon bond of the unsubstituted alkyl group is replaced with a bond to an aryl group as defined above. For example, methyl (-CH_3) is an unsubstituted alkyl group. If a hydrogen atom of the methyl group is replaced by a bond to a phenyl group, such as if the carbon of the methyl were bonded to a carbon of benzene, then the compound is an unsubstituted aralkyl group (*i.e.*, a benzyl group). Thus the phrase includes, but is not limited to, groups such as benzyl, diphenylmethyl, and 1-phenylethyl (-CH(C_6H_5)(CH_3)) among others.

[0143] The phrase "substituted aralkyl" has the same meaning with respect to unsubstituted aralkyl groups that substituted aryl groups had with respect to unsubstituted aryl groups. However, a substituted aralkyl group also includes groups in which a carbon or hydrogen bond of the alkyl part of the group is replaced by a bond to a non-carbon or a non-hydrogen atom. Examples of substituted aralkyl groups include, but are not limited to, -CH_2C(=O)(C_6H_5), and -CH_2(2-methylphenyl) among others.

[0144] The phrase "unsubstituted heterocyclyl" refers to both aromatic and nonaromatic ring compounds including monocyclic, bicyclic, and polycyclic ring compounds such as, but not limited to, quinuclidyl, containing 3 or more ring members of which one or more is a heteroatom such as, but not limited to, N, O, and S. Although the phrase "unsubstituted heterocyclyl" includes condensed heterocyclic rings such as benzimidazolyl, it does not include heterocyclyl groups that have other groups such as alkyl or halo groups bonded to one of the ring members as compounds such as 2-methylbenzimidazolyl are substituted heterocyclyl groups. Examples of heterocyclyl groups include, but are not limited to: unsaturated 3 to 8 membered rings containing 1 to 4 nitrogen atoms such as, but not limited to pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridinyl, dihydropyridinyl, pyrimidyl, pyrazinyl, pyridazinyl, triazolyl (e.g. 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl etc.), tetrazolyl, (e.g. 1H-tetrazolyl, 2H tetrazolyl, etc.); saturated 3 to 8 membered rings containing 1 to 4 nitrogen atoms such as, but not limited to, pyrrolidinyl, imidazolidinyl, piperidinyl, piperazinyl; condensed unsaturated heterocyclic groups containing 1 to 4 nitrogen atoms such as, but not limited to, indolyl, isoindolyl, indolinyl, indolizinyl, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl; unsaturated 3 to 8 membered rings containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms such as, but not limited to, oxazolyl, isoxazolyl, oxadiazolyl (e.g. 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, etc.); saturated 3 to 8 membered rings containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms such as, but not limited to, morpholinyl; unsaturated condensed heterocyclic groups containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, for example, benzoxazolyl, benzoxadiazolyl, benzoxazinyl (e.g. 2H-1,4-benzoxazinyl etc.); unsaturated 3 to 8 membered rings containing 1 to 3 sulfur atoms and 1 to 3 nitrogen atoms such as, but not limited to, thiazolyl, isothiazolyl, thiadiazolyl (e.g. 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, etc.); saturated 3 to 8 membered rings containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms such as, but not limited to, thiazolodinyl; saturated and unsaturated 3 to 8 membered rings

containing 1 to 2 sulfur atoms such as, but not limited to, thienyl, dihydrodithiinyl, dihydrodithionyl, tetrahydrothiophene, tetrahydrothiopyran; unsaturated condensed heterocyclic rings containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms such as, but not limited to, benzothiazolyl, benzothiadiazolyl, benzothiazinyl (e.g. 2H-1,4-benzothiazinyl, etc.), dihydrobenzothiazinyl (e.g., 2H-3,4-dihydrobenzothiazinyl, etc.), unsaturated 3 to 8 membered rings containing oxygen atoms such as, but not limited to furyl; unsaturated condensed heterocyclic rings containing 1 to 2 oxygen atoms such as benzodioxolyl (e.g., 1,3-benzodioxoyl, etc.); unsaturated 3 to 8 membered rings containing an oxygen atom and 1 to 2 sulfur atoms such as, but not limited to, dihydrooxathiinyl; saturated 3 to 8 membered rings containing 1 to 2 oxygen atoms and 1 to 2 sulfur atoms such as 1,4-oxathiane; unsaturated condensed rings containing 1 to 2 sulfur atoms such as benzothienyl, benzodithiinyl; and unsaturated condensed heterocyclic rings containing an oxygen atom and 1 to 2 oxygen atoms such as benzoxathiinyl. Heterocyclyl group also include those described above in which one or more S atoms in the ring is double-bonded to one or two oxygen atoms (sulfoxides and sulfones). For example, heterocyclyl groups include tetrahydrothiophene oxide and tetrahydrothiophene 1,1-dioxide. Preferred heterocyclyl groups contain 5 or 6 ring members. More preferred heterocyclyl groups include morpholine, piperazine, piperidine, pyrrolidine, imidazole, pyrazole, 1,2,3-triazole, 1,2,4-triazole, tetrazole, thiophene, thiomorpholine, thiomorpholine in which the S atom of the thiomorpholine is bonded to one or more O atoms, pyrrole, homopiperazine, oxazolidin-2-one, pyrrolidin-2-one, oxazole, quinuclidine, thiazole, isoxazole, furan, and tetrahydrofuran.

[0145] The phrase "substituted heterocyclyl" refers to an unsubstituted heterocyclyl group as defined above in which one or more of the ring members is bonded to a non-hydrogen atom such as described above with respect to substituted alkyl groups and substituted aryl groups. Examples, include, but are not limited to, 2-methylbenzimidazolyl, 5-methylbenzimidazolyl, 5-chlorobenzthiazolyl, N-alkyl piperazinyl groups such

as 1-methyl piperazinyl, piperazine-N-oxide, N-alkyl piperazine N-oxides, 2-phenoxy-thiophene, and 2-chloropyridinyl among others. In addition, substituted heterocyclyl groups also include heterocyclyl groups in which the bond to the non-hydrogen atom is a bond to a carbon atom that is part of a substituted and unsubstituted aryl, substituted and unsubstituted aralkyl, or unsubstituted heterocyclyl group. Examples include but are not limited to 1-benzylpiperidinyl, 3-phenythiomorpholinyl, 3-(pyrrolidin-1-yl)-pyrrolidinyl, and 4-(piperidin-1-yl)-piperidinyl. Groups such as N-alkyl substituted piperazine groups such as N-methyl piperazine, substituted morpholine groups, and piperazine N-oxide groups such as piperazine N-oxide and N-alkyl piperazine N-oxides are examples of some substituted heterocyclyl groups. Groups such as substituted piperazine groups such as N-alkyl substituted piperazine groups such as N-methyl piperazine and the like, substituted morpholine groups, piperazine N-oxide groups, and N-alkyl piperazine N-oxide groups are examples of some substituted heterocyclyl groups that are especially suited as R^6 or R^7 groups.

[0146] The phrase "unsubstituted heterocyclylalkyl" refers to unsubstituted alkyl groups as defined above in which a hydrogen or carbon bond of the unsubstituted alkyl group is replaced with a bond to a heterocyclyl group as defined above. For example, methyl ($-CH_3$) is an unsubstituted alkyl group. If a hydrogen atom of the methyl group is replaced by a bond to a heterocyclyl group, such as if the carbon of the methyl were bonded to carbon 2 of pyridine (one of the carbons bonded to the N of the pyridine) or carbons 3 or 4 of the pyridine, then the compound is an unsubstituted heterocyclylalkyl group.

[0147] The phrase "substituted heterocyclylalkyl" has the same meaning with respect to unsubstituted heterocyclylalkyl groups that substituted aralkyl groups had with respect to unsubstituted aralkyl groups. However, a substituted heterocyclylalkyl group also includes groups in which a non-hydrogen atom is bonded to a heteroatom in the heterocyclyl group of the heterocyclylalkyl group such as, but not limited to, a nitrogen atom in the

piperidine ring of a piperidinylalkyl group. In addition, a substituted heterocyclylalkyl group also includes groups in which a carbon bond or a hydrogen bond of the alkyl part of the group is replaced by a bond to a substituted and unsubstituted aryl or substituted and unsubstituted aralkyl group. Examples include but are not limited to phenyl-(piperidin-1-yl)-methyl and phenyl-(morpholin-4-yl)-methyl.

[0148] The phrase "unsubstituted alkylaminoalkyl" refers to an unsubstituted alkyl group as defined above in which a carbon or hydrogen bond is replaced by a bond to a nitrogen atom that is bonded to a hydrogen atom and an unsubstituted alkyl group as defined above. For example, methyl ($-CH_3$) is an unsubstituted alkyl group. If a hydrogen atom of the methyl group is replaced by a bond to a nitrogen atom that is bonded to a hydrogen atom and an ethyl group, then the resulting compound is $-CH_2-N(H)(CH_2CH_3)$ which is an unsubstituted alkylaminoalkyl group.

[0149] The phrase "substituted alkylaminoalkyl" refers to an unsubstituted alkylaminoalkyl group as defined above except where one or more bonds to a carbon or hydrogen atom in one or both of the alkyl groups is replaced by a bond to a non-carbon or non-hydrogen atom as described above with respect to substituted alkyl groups except that the bond to the nitrogen atom in all alkylaminoalkyl groups does not by itself qualify all alkylaminoalkyl groups as being substituted. However, substituted alkylaminoalkyl groups does include groups in which the hydrogen bonded to the nitrogen atom of the group is replaced with a non-carbon and non-hydrogen atom.

[0150] The phrase "unsubstituted dialkylaminoalkyl" refers to an unsubstituted alkyl group as defined above in which a carbon bond or hydrogen bond is replaced by a bond to a nitrogen atom which is bonded to two other similar or different unsubstituted alkyl groups as defined above.

[0151] The phrase "substituted dialkylaminoalkyl" refers to an unsubstituted dialkylaminoalkyl group as defined above in which one or more bonds to a carbon or hydrogen atom in one or more of the alkyl groups is replaced by a bond to a non-carbon and non-hydrogen atom as described with respect to substituted alkyl groups. The bond to the nitrogen atom in all dialkylaminoalkyl groups does not by itself qualify all dialkylaminoalkyl groups as being substituted.

[0152] The phrase "unsubstituted alkoxy" refers to a hydroxyl group (-OH) in which the bond to the hydrogen atom is replaced by a bond to a carbon atom of an otherwise unsubstituted alkyl group as defined above.

[0153] The phrase "substituted alkoxy" refers to a hydroxyl group (-OH) in which the bond to the hydrogen atom is replaced by a bond to a carbon atom of an otherwise substituted alkyl group as defined above.

[0154] The phrase "unsubstituted heterocyclyloxy" refers to a hydroxyl group (-OH) in which the bond to the hydrogen atom is replaced by a bond to a ring atom of an otherwise unsubstituted heterocyclyl group as defined above.

[0155] The phrase "substituted heterocyclyloxy" refers to a hydroxyl group (-OH) in which the bond to the hydrogen atom is replaced by a bond to a ring atom of an otherwise substituted heterocyclyl group as defined above.

[0156] The phrase "unsubstituted heterocyclyloxyalkyl" refers to an unsubstituted alkyl group as defined above in which a carbon bond or hydrogen bond is replaced by a bond to an oxygen atom which is bonded to an unsubstituted heterocyclyl group as defined above.

[0157] The phrase "substituted heterocyclyloxyalkyl" refers to an unsubstituted heterocyclyloxyalkyl group as defined above in which a bond to a carbon or hydrogen group of the alkyl group of the heterocyclyloxyalkyl group is bonded to a non-carbon and non-hydrogen atom as described above

with respect to substituted alkyl groups or in which the heterocyclyl group of the heterocyclyloxyalkyl group is a substituted heterocyclyl group as defined above.

[0158] The phrase "unsubstituted heterocyclylalkoxy" refers to an unsubstituted alkyl group as defined above in which a carbon bond or hydrogen bond is replaced by a bond to an oxygen atom which is bonded to the parent compound, and in which another carbon or hydrogen bond of the unsubstituted alkyl group is bonded to an unsubstituted heterocyclyl group as defined above.

[0159] The phrase "substituted heterocyclylalkoxy" refers to an unsubstituted heterocyclylalkoxy group as defined above in which a bond to a carbon or hydrogen group of the alkyl group of the heterocyclylalkoxy group is bonded to a non-carbon and non-hydrogen atom as described above with respect to substituted alkyl groups or in which the heterocyclyl group of the heterocyclylalkoxy group is a substituted heterocyclyl group as defined above. Further, a substituted heterocyclylalkoxy group also includes groups in which a carbon bond or a hydrogen bond to the alkyl moiety of the group may be substituted with one or more additional substituted and unsubstituted heterocycles. Examples include but are not limited to pyrid-2-ylmorpholin-4-ylmethyl and 2-pyrid-3-yl-2-morpholin-4-ylethyl.

[0160] The phrase "unsubstituted arylaminoalkyl" refers to an unsubstituted alkyl group as defined above in which a carbon bond or hydrogen bond is replaced by a bond to a nitrogen atom which is bonded to at least one unsubstituted aryl group as defined above.

[0161] The phrase "substituted arylaminoalkyl" refers to an unsubstituted arylaminoalkyl group as defined above except where either the alkyl group of the arylaminoalkyl group is a substituted alkyl group as defined above or the aryl group of the arylaminoalkyl group is a substituted aryl group except that the bonds to the nitrogen atom in all arylaminoalkyl groups does

not by itself qualify all arylaminoalkyl groups as being substituted. However, substituted arylaminoalkyl groups does include groups in which the hydrogen bonded to the nitrogen atom of the group is replaced with a non-carbon and non-hydrogen atom.

[0162] The phrase "unsubstituted heterocyclylaminoalkyl" refers to an unsubstituted alkyl group as defined above in which a carbon or hydrogen bond is replaced by a bond to a nitrogen atom which is bonded to at least one unsubstituted heterocyclyl group as defined above.

[0163] The phrase "substituted heterocyclylaminoalkyl" refers to unsubstituted heterocyclylaminoalkyl groups as defined above in which the heterocyclyl group is a substituted heterocyclyl group as defined above and/or the alkyl group is a substituted alkyl group as defined above. The bonds to the nitrogen atom in all heterocyclylaminoalkyl groups does not by itself qualify all heterocyclylaminoalkyl groups as being substituted. However, substituted heterocyclylaminoalkyl groups do include groups in which the hydrogen bonded to the nitrogen atom of the group is replaced with a non-carbon and non-hydrogen atom.

[0164] The phrase "unsubstituted alkylaminoalkoxy" refers to an unsubstituted alkyl group as defined above in which a carbon or hydrogen bond is replaced by a bond to an oxygen atom which is bonded to the parent compound and in which another carbon or hydrogen bond of the unsubstituted alkyl group is bonded to a nitrogen atom which is bonded to a hydrogen atom and an unsubstituted alkyl group as defined above.

[0165] The phrase "substituted alkylaminoalkoxy" refers to unsubstituted alkylaminoalkoxy groups as defined above in which a bond to a carbon or hydrogen atom of the alkyl group bonded to the oxygen atom which is bonded to the parent compound is replaced by one or more bonds to a non-carbon and non-hydrogen atoms as discussed above with respect to substituted alkyl groups and/or if the hydrogen bonded to the amino group is

bonded to a non-carbon and non-hydrogen atom and/or if the alkyl group bonded to the nitrogen of the amine is bonded to a non-carbon and non-hydrogen atom as described above with respect to substituted alkyl groups. The presence of the amine and alkoxy functionality in all alkylaminoalkoxy groups does not by itself qualify all such groups as substituted alkylaminoalkoxy groups.

[0166] The phrase "unsubstituted dialkylaminoalkoxy" refers to an unsubstituted alkyl group as defined above in which a carbon or hydrogen bond is replaced by a bond to an oxygen atom which is bonded to the parent compound and in which another carbon or hydrogen bond of the unsubstituted alkyl group is bonded to a nitrogen atom which is bonded to two other similar or different unsubstituted alkyl groups as defined above.

[0167] The phrase "substituted dialkylaminoalkoxy" refers to an unsubstituted dialkylaminoalkoxy group as defined above in which a bond to a carbon or hydrogen atom of the alkyl group bonded to the oxygen atom which is bonded to the parent compound is replaced by one or more bonds to a non-carbon and non-hydrogen atoms as discussed above with respect to substituted alkyl groups and/or if one or more of the alkyl groups bonded to the nitrogen of the amine is bonded to a non-carbon and non-hydrogen atom as described above with respect to substituted alkyl groups. The presence of the amine and alkoxy functionality in all dialkylaminoalkoxy groups does not by itself qualify all such groups as substituted dialkylaminoalkoxy groups.

[0168] The term "protected" with respect to hydroxyl groups, amine groups, and sulfhydryl groups refers to forms of these functionalities which are protected from undesirable reaction with a protecting group known to those skilled in the art such as those set forth in Protective Groups in Organic Synthesis, Greene, T.W.; Wuts, P. G. M., John Wiley & Sons, New York, NY, (3rd Edition, 1999) which can be added or removed using the procedures set forth therein. Examples of protected hydroxyl groups include, but are not limited to, silyl ethers such as those obtained by reaction of a hydroxyl group

with a reagent such as, but not limited to, *t*-butyldimethyl-chlorosilane, trimethylchlorosilane, triisopropylchlorosilane, triethylchlorosilane; substituted methyl and ethyl ethers such as, but not limited to methoxymethyl ether, methythiomethyl ether, benzyloxymethyl ether, *t*-butoxymethyl ether, 2-methoxyethoxymethyl ether, tetrahydropyranyl ethers, 1-ethoxyethyl ether, allyl ether, benzyl ether; esters such as, but not limited to, benzoylformate, formate, acetate, trichloroacetate, and trifluoracetate. Examples of protected amine groups include, but are not limited to, amides such as, formamide, acetamide, trifluoroacetamide, and benzamide; imides, such as phthalimide, and dithiosuccinimide; and others. Examples of protected sulfhydryl groups include, but are not limited to, thioethers such as S-benzyl thioether, and S-4-picolyl thioether; substituted S-methyl derivatives such as hemithio, dithio and aminothio acetals; and others.

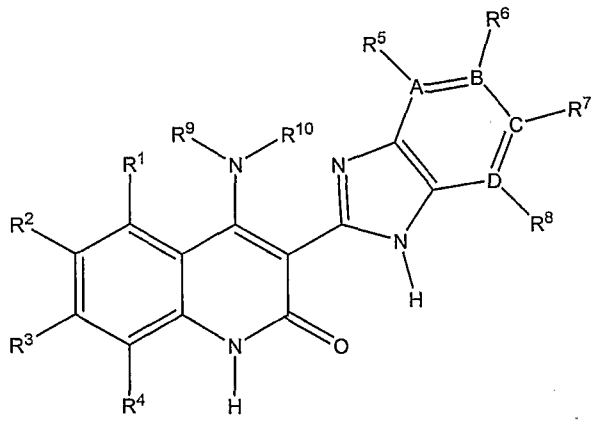
[0169] A "pharmaceutically acceptable salt" includes a salt with an inorganic base, organic base, inorganic acid, organic acid, or basic or acidic amino acid. As salts of inorganic bases, the invention includes, for example, alkali metals such as sodium or potassium; alkaline earth metals such as calcium and magnesium or aluminum; and ammonia. As salts of organic bases, the invention includes, for example, trimethylamine, triethylamine, pyridine, picoline, ethanolamine, diethanolamine, and triethanolamine. As salts of inorganic acids, the instant invention includes, for example, hydrochloric acid, hydroboric acid, nitric acid, sulfuric acid, and phosphoric acid. As salts of organic acids, the instant invention includes, for example, formic acid, acetic acid, trifluoroacetic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, lactic acid, citric acid, succinic acid, malic acid, methanesulfonic acid, benzenesulfonic acid, and p-toluenesulfonic acid. As salts of basic amino acids, the instant invention includes, for example, arginine, lysine and ornithine. Acidic amino acids include, for example, aspartic acid and glutamic acid.

[0170] The present invention provides methods of inhibiting serine/threonine and tyrosine kinases, and methods of treating biological

conditions mediated by serine/threonine and tyrosine kinases. In particular, the present invention provides methods of inhibiting serine/threonine kinases, including glycogen synthase kinase 3 (GSK-3), cyclin dependent kinase 2 (Cdk2), cyclin dependent kinase 4 (Cdk4), MEK1, NEK-2, CHK2, CK1ε, Raf, checkpoint kinase 1 (CHK1), ribosomal S6 kinase 2 (Rsk2), and PAR-1 and methods of inhibiting tyrosine kinases, including cell division cycle 2 kinase (Cdc2 kinase), c-Kit, c-ABL, p60src, VEGFR3, PDGFRα, PDGFRβ, FGFR3, FLT-3, FYN oncogene kinase related to SRC, FGR, and YES (Fyn), lymphocyte-specific protein tyrosine kinase (Lck), and tyrosine kinase with Ig and EGF homology domains (Tie-2). The present invention also provides methods of treating biological conditions mediated by serine/threonine kinases, including GSK-3, Cdk2, Cdk4, MEK1, NEK-2, CHK2, CK1ε, Raf, CHK1, Rsk2, and PAR-1, and methods of treating biological conditions mediated by tyrosine kinases, including Cdc2 kinase, c-Kit, c-ABL, p60src, VEGFR3, PDGFRα, PDGFRβ, FGFR3, FLT-3, Fyn, Lck, and Tie-2.

Methods Relating to Serine/Threonine Kinases

[0171] In one aspect, the present invention provides a method of inhibiting a serine/threonine kinase in a subject and/or a method of treating a biological condition mediated by serine/threonine kinase activity in a subject. The methods include administering to the subject a compound of Structure I, a tautomer of the compound, a pharmaceutically acceptable salt of the compound, a pharmaceutically acceptable salt of the tautomer, or mixtures thereof. In the method of inhibiting a serine/threonine kinase, the serine/threonine kinase is inhibited in the subject after administration. Structure I has the following formula:



I

where,

A, B, C, and D are independently selected from carbon or nitrogen;

R^1 is selected from -H, -F, -Cl, -Br, -I, -CN, -NO_2, substituted and unsubstituted alkyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted alkenyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted alkynyl groups having from 1 to 8 carbon atoms, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted heterocyclylalkyl groups, -SH, substituted and unsubstituted -S-

alkyl groups, substituted and unsubstituted -$S(=O)_2$-O-alkyl groups, substituted and unsubstituted -$S(=O)_2$-alkyl groups, substituted and unsubstituted -S(=O)-alkyl groups, -S(=O)-NH_2, substituted and unsubstituted -S(=O)-N(H)(alkyl) groups, substituted and unsubstituted -S(=O)-N$(alkyl)_2$ groups, -OH, substituted and unsubstituted alkoxy groups, substituted and unsubstituted aryloxy groups, substituted and unsubstituted arylalkoxy groups, substituted and unsubstituted heterocyclyloxy groups, substituted and unsubstituted heterocyclylalkoxy groups, -NH_2, substituted and unsubstituted -N(H)(alkyl) groups, substituted and unsubstituted -N$(alkyl)_2$ groups, substituted and unsubstituted -N(H)(heterocyclyl) groups, substituted and unsubstituted -N(alkyl)(heterocyclyl) groups, substituted and unsubstituted -N$(heterocyclyl)_2$ groups, substituted and unsubstituted -N(H)(heterocyclylalkyl) groups, substituted and unsubstituted -N(alkyl)(heterocyclylalkyl) groups, substituted and unsubstituted -N$(heterocyclylalkyl)_2$ groups, substituted and unsubstituted -N(H)-C(=O)-alkyl groups, substituted and unsubstituted -N(H)-C(=O)-heterocyclyl groups, substituted and unsubstituted -N(H)-C(=O)-heterocyclylalkyl groups, substituted and unsubstituted -N(H)-S(=O)-alkyl groups, substituted and unsubstituted -C(=O)-alkyl groups, substituted and unsubstituted -C(=O)-heterocyclyl groups, substituted and unsubstituted -C(=O)-heterocyclylalkyl groups, -C(=O)-NH_2, substituted and unsubstituted -C(=O)-N(H)(alkyl) groups, substituted and unsubstituted -C(=O)-N$(alkyl)_2$ groups, substituted and unsubstituted -C(=O)-N(H)(aralkyl) groups, substituted and unsubstituted -C(=O)-N(H)(heterocyclyl) groups, -C(=O)-N(H)(heterocyclylalkyl) groups, -CO_2H, substituted and unsubstituted -C(=O)-O-alkyl groups, substituted and unsubstituted -C(=O)-O-heterocyclyl groups, or substituted and unsubstituted -C(=O)-O-heterocyclylalkyl groups;

R^2 and R^3 are independently selected from -H, -F, -Cl, -Br, -I, -CN, -NO_2, substituted and unsubstituted alkyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted alkenyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted alkynyl groups having from 1 to 8 carbon atoms, substituted and unsubstituted aryl groups, substituted and unsubstituted aralkyl groups, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted heterocyclylalkyl groups, -SH, substituted and unsubstituted -S-alkyl groups, substituted and unsubstituted -S-aryl groups, substituted and unsubstituted -S-aralkyl groups, substituted and unsubstituted -$S(=O)_2$-O-alkyl groups, substituted and unsubstituted -$S(=O)_2$-alkyl groups, substituted and unsubstituted -$S(=O)_2$-heterocyclyl groups, substituted and unsubstituted -S(=O)-alkyl groups, substituted and unsubstituted -S(=O)-heterocyclyl groups, -$S(=O)_2$-NH_2, substituted and unsubstituted -$S(=O)_2$-N(H)(alkyl) groups, substituted and unsubstituted -$S(=O)_2$-$N(alkyl)_2$ groups, substituted and unsubstituted -$S(=O)_2$-N(H)(aryl) groups, substituted and unsubstituted -$S(=O)_2$-N(alkyl)(aryl) groups, substituted and unsubstituted -$S(=O)_2$-$N(aryl)_2$ groups, substituted and unsubstituted -$S(=O)_2$-N(H)(aralkyl) groups, substituted and unsubstituted -$S(=O)_2$-N(alkyl)(aralkyl) groups, substituted and unsubstituted -$S(=O)_2$-$N(aralkyl)_2$ groups, -OH, substituted and unsubstituted alkoxy groups, substituted and unsubstituted aryloxy groups, substituted and unsubstituted arylalkoxy groups, substituted and unsubstituted heterocyclyloxy groups, substituted and unsubstituted heterocyclylalkoxy groups, -NH_2, substituted and unsubstituted -N(H)(alkyl) groups, substituted and unsubstituted -$N(alkyl)_2$ groups, substituted and unsubstituted -N(H)(aryl) groups, substituted and unsubstituted -N(alkyl)(aryl) groups, substituted and unsubstituted -$N(aryl)_2$

groups, substituted and unsubstituted -N(H)(aralkyl) groups, substituted and unsubstituted -N(alkyl)(aralkyl) groups, substituted and unsubstituted -N(aralkyl)$_2$ groups, substituted and unsubstituted -N(H)(heterocyclyl) groups, substituted and unsubstituted -N(alkyl)(heterocyclyl) groups, substituted and unsubstituted -N(heterocyclyl)$_2$ groups, substituted and unsubstituted -N(H)(heterocyclylalkyl) groups, substituted and unsubstituted -N(alkyl)(heterocyclylalkyl) groups, substituted and unsubstituted -N(heterocyclylalkyl)$_2$ groups, substituted and unsubstituted -N(H)-S(=O)$_2$-alkyl groups, substituted and unsubstituted -N(H)-S(=O)$_2$-aryl groups, substituted and unsubstituted -N(H)-S(=O)$_2$-aralkyl groups, substituted and unsubstituted -N(H)-S(=O)$_2$-heterocyclyl groups, substituted and unsubstituted -N(H)-S(=O)$_2$-heterocyclylalkyl groups, substituted and unsubstituted -N(H)-C(=O)-alkyl groups, substituted and unsubstituted -N(H)-C(=O)-aryl groups, substituted and unsubstituted -N(H)-C(=O)-aralkyl groups, substituted and unsubstituted -N(H)-C(=O)-heterocyclyl groups, substituted and unsubstituted -N(H)-C(=O)-heterocyclylalkyl groups, substituted and unsubstituted -N(alkyl)-C(=O)-alkyl groups, substituted and unsubstituted -N(alkyl)-C(=O)-aryl groups, substituted and unsubstituted -N(alkyl)-C(=O)-aralkyl groups, substituted and unsubstituted -N(alkyl)-C(=O)-heterocyclyl groups, substituted and unsubstituted -N(alkyl)-C(=O)-heterocyclylalkyl groups, substituted and unsubstituted -N(alkyl)-S(=O)$_2$-alkyl groups, substituted and unsubstituted -N(alkyl)-S(=O)$_2$-aryl groups, substituted and unsubstituted -N(alkyl)-S(=O)$_2$-aralkyl groups, substituted and unsubstituted -N(alkyl)-S(=O)$_2$-heterocyclyl groups, substituted and unsubstituted -N(alkyl)-S(=O)$_2$-heterocyclylalkyl groups, -N(H)-C(=O)-NH$_2$, substituted and unsubstituted -N(H)-C(=O)-N(H)(alkyl) groups, substituted and unsubstituted -N(H)-C(=O)-N(alkyl)$_2$ groups,

substituted and unsubstituted -N(H)-C(=O)-N(H)(aryl) groups, substituted and unsubstituted -N(H)-C(=O)-N(alkyl)(aryl) groups, substituted and unsubstituted -N(H)-C(=O)-N(aryl)$_2$ groups, substituted and unsubstituted -N(H)-C(=O)-N(H)(aralkyl) groups, substituted and unsubstituted -N(H)-C(=O)-N(alkyl)(aralkyl) groups, substituted and unsubstituted -N(H)-C(=O)-N(aralkyl)$_2$ groups, substituted and unsubstituted -N(H)-C(=O)-N(H)(heterocyclyl) groups, substituted and unsubstituted -N(H)-C(=O)-N(alkyl)(heterocyclyl) groups, substituted and unsubstituted -N(H)-C(=O)-N(heterocyclyl)$_2$ groups, substituted and unsubstituted -N(H)-C(=O)-N(H)(heterocyclylalkyl) groups, substituted and unsubstituted -N(H)-C(=O)-N(alkyl)(heterocyclylalkyl) groups, substituted and unsubstituted -N(H)-C(=O)-N(heterocyclylalkyl)$_2$ groups, substituted and unsubstituted -N(alkyl)-C(=O)-NH$_2$ groups, substituted and unsubstituted -N(alkyl)-C(=O)-N(H)(alkyl) groups, substituted and unsubstituted -N(alkyl)-C(=O)-N(alkyl)$_2$ groups, substituted and unsubstituted -N(alkyl)-C(=O)-N(H)(aryl) groups, substituted and unsubstituted -N(alkyl)-C(=O)-N(alkyl)(aryl) groups, substituted and unsubstituted -N(alkyl)-C(=O)-N(aryl)$_2$ groups, substituted and unsubstituted -N(alkyl)-C(=O)-N(H)(aralkyl) groups, substituted and unsubstituted -N(alkyl)-C(=O)-N(alkyl)(aralkyl) groups, substituted and unsubstituted -N(alkyl)-C(=O)-N(aralkyl)$_2$ groups, substituted and unsubstituted -N(alkyl)-C(=O)-N(H)(heterocyclyl) groups, substituted and unsubstituted -N(alkyl)-C(=O)-N(alkyl)(heterocyclyl) groups, substituted and unsubstituted -N(alkyl)-C(=O)-N(heterocyclyl)$_2$ groups, substituted and unsubstituted -N(alkyl)-C(=O)-N(H)(heterocyclylalkyl) groups, substituted and unsubstituted -N(alkyl)-C(=O)-N(alkyl)(heterocyclylalkyl) groups,

substituted and unsubstituted -N(alkyl)-C(=O)-N(heterocyclylalkyl)$_2$ groups, substituted and unsubstituted -C(=O)-alkyl groups, substituted and unsubstituted -C(=O)-aryl groups, substituted and unsubstituted -C(=O)-aralkyl groups, substituted and unsubstituted -C(=O)-heterocyclyl groups, substituted and unsubstituted -C(=O)-heterocyclylalkyl groups, -C(=O)-NH_2, substituted and unsubstituted -C(=O)-N(H)(alkyl) groups, substituted and unsubstituted -C(=O)-N(alkyl)$_2$ groups, substituted and unsubstituted -C(=O)-N(H)(aryl) groups, substituted and unsubstituted -C(=O)-N(alkyl)(aryl) groups, substituted and unsubstituted -C(=O)-N(aryl)$_2$ groups, substituted and unsubstituted -C(=O)-N(H)(aralkyl) groups, substituted and unsubstituted -C(=O)-N(alkyl)(aralkyl) groups, substituted and unsubstituted -C(=O)-N(aralkyl)$_2$ groups, substituted and unsubstituted -C(=O)-N(H)(heterocyclyl) groups, substituted and unsubstituted -C(=O)-N(alkyl)(heterocyclyl) groups, substituted and unsubstituted -C(=O)-N(heterocyclyl)$_2$ groups, substituted and unsubstituted -C(=O)-N(H)(heterocyclylalkyl) groups, substituted and unsubstituted -C(=O)-N(alkyl)(heterocyclylalkyl) groups, substituted and unsubstituted -C(=O)-N(heterocyclylalkyl)$_2$ groups, -CO_2H, substituted and unsubstituted -C(=O)-O-alkyl groups, substituted and unsubstituted -C(=O)-O-aryl groups, substituted and unsubstituted -C(=O)-O-heterocyclyl groups, or substituted and unsubstituted -C(=O)-O-heterocyclylalkyl groups;

R^4 is selected from -H, -F, -Cl, -Br, -I, -CN, -NO_2, substituted and unsubstituted alkyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted alkenyl groups having from 1 to 8 carbon atoms, substituted and unsubstituted alkynyl groups having from 1 to 8 carbon atoms, -SH, substituted and

unsubstituted -S-alkyl groups, substituted and unsubstituted $-S(=O)_2$-O-alkyl groups, substituted and unsubstituted $-S(=O)_2$-alkyl groups, substituted and unsubstituted -S(=O)-alkyl groups, $-S(=O)_2-NH_2$, substituted and unsubstituted $-S(=O)_2$-N(H)(alkyl) groups, substituted and unsubstituted $-S(=O)_2-N(alkyl)_2$ groups, -OH, substituted and unsubstituted alkoxy groups, $-NH_2$, substituted and unsubstituted -N(H)(alkyl) groups, substituted and unsubstituted $-N(alkyl)_2$ groups, substituted and unsubstituted -N(H)-C(=O)-alkyl groups, substituted and unsubstituted -N(H)-S(=O)-alkyl groups, $-C(=O)-NH_2$, substituted and unsubstituted -C(=O)-N(H)(alkyl) groups, substituted and unsubstituted $-C(=O)-N(alkyl)_2$ groups, or substituted and unsubstituted -C(=O)-O-alkyl groups;

R^5 and R^8 are independently selected from -H, -F, -Cl, -Br, -I, -CN, $-NO_2$, substituted and unsubstituted straight and branched chain alkyl groups having from 1 to 8 carbon atoms, substituted and unsubstituted alkenyl groups having from 1 to 8 carbon atoms, substituted and unsubstituted alkynyl groups having from 1 to 8 carbon atoms, substituted and unsubstituted heterocyclyl groups, -SH, substituted and unsubstituted -S-alkyl groups, substituted and unsubstituted $-S(=O)_2$-O-alkyl groups, substituted and unsubstituted $-S(=O)_2$-alkyl groups, substituted and unsubstituted -S(=O)-alkyl groups, $-S(=O)_2-NH_2$, substituted and unsubstituted $-S(=O)_2$-N(H)(alkyl) groups, substituted and unsubstituted $-S(=O)_2-N(alkyl)_2$ groups, -OH, substituted and unsubstituted alkoxy groups, $-NH_2$, substituted and unsubstituted -N(H)(alkyl) groups, substituted and unsubstituted $-N(alkyl)_2$ groups, substituted and unsubstituted -N(H)-C(=O)-alkyl groups, substituted and unsubstituted -N(H)-S(=O)-alkyl groups, $-C(=O)-NH_2$, substituted and unsubstituted -C(=O)-N(H)(alkyl) groups, substituted and

unsubstituted -C(=O)-N(alkyl)$_2$ groups, or substituted and unsubstituted -C(=O)-O-alkyl groups; or R^5 may be absent if A is nitrogen; or R^8 may be absent if D is nitrogen;

R^6 and R^7 are independently selected from -H, -F, -Cl, -Br, -I, -NO_2, -CN, substituted and unsubstituted alkyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted alkenyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted alkynyl groups having from 1 to 8 carbon atoms, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted heterocyclylalkyl groups, -SH, substituted and unsubstituted -S-alkyl groups, substituted and unsubstituted -S(=O)$_2$-O-alkyl groups, substituted and unsubstituted -S(=O)$_2$-alkyl groups, substituted and unsubstituted -S(=O)$_2$-heterocyclyl groups, substituted and unsubstituted -S(=O)-alkyl groups, substituted and unsubstituted -S(=O)-heterocyclyl groups, -S(=O)$_2$-NH_2, substituted and unsubstituted -S(=O)$_2$-N(H)(alkyl) groups, substituted and unsubstituted -S(=O)$_2$-N(alkyl)$_2$ groups, substituted and unsubstituted -S(=O)$_2$-N(H)(heterocyclyl) groups, substituted and unsubstituted -S(=O)$_2$-N(alkyl)(heterocyclyl) groups, substituted and unsubstituted -S(=O)$_2$-N(heterocyclyl)$_2$ groups, substituted and unsubstituted -S(=O)$_2$-N(H)(heterocyclylalkyl) groups, substituted and unsubstituted -S(=O)$_2$-N(alkyl)(heterocyclylalkyl) groups, substituted and unsubstituted -S(=O)$_2$-N(heterocyclylalkyl)$_2$ groups, -OH, substituted and unsubstituted alkoxy groups, substituted and unsubstituted aryloxy groups, substituted and unsubstituted arylalkoxy groups, substituted and unsubstituted heterocyclyloxy groups, substituted and unsubstituted heterocyclylalkoxy groups, -NH_2, substituted and unsubstituted -N(H)(alkyl) groups, substituted and unsubstituted -N(alkyl)$_2$ groups, substituted and

unsubstituted -N(H)(aryl) groups, substituted and unsubstituted -N(alkyl)(aryl) groups, substituted and unsubstituted -N(aryl)$_2$ groups, substituted and unsubstituted -N(H)(aralkyl) groups, substituted and unsubstituted -N(alkyl)(aralkyl) groups, substituted and unsubstituted -N(aralkyl)$_2$ groups, substituted and unsubstituted -N(H)(heterocyclyl) groups, substituted and unsubstituted -N(alkyl)(heterocyclyl) groups, substituted and unsubstituted -N(heterocyclyl)$_2$ groups, substituted and unsubstituted -N(H)(heterocyclylalkyl) groups, substituted and unsubstituted -N(alkyl)(heterocyclylalkyl) groups, substituted and unsubstituted -N(heterocyclylalkyl)$_2$ groups, substituted and unsubstituted -N(H)-S(=O)$_2$-alkyl groups, substituted and unsubstituted -N(H)-S(=O)$_2$-heterocyclyl groups, substituted and unsubstituted -N(H)-S(=O)$_2$-heterocyclylalkyl groups, substituted and unsubstituted -N(H)-C(=O)-alkyl groups, substituted and unsubstituted -N(H)-C(=O)-heterocyclyl groups, substituted and unsubstituted -N(H)-C(=O)-heterocyclylalkyl groups, substituted and unsubstituted -N(alkyl)-C(=O)-alkyl groups, substituted and unsubstituted -N(alkyl)-C(=O)-heterocyclyl groups, substituted and unsubstituted -N(alkyl)-C(=O)-heterocyclylalkyl groups, substituted and unsubstituted -N(alkyl)-S(=O)$_2$-alkyl groups, substituted and unsubstituted -N(alkyl)-S(=O)$_2$-heterocyclyl groups, substituted and unsubstituted -N(alkyl)-S(=O)$_2$-heterocyclylalkyl groups, substituted and unsubstituted -C(=O)-alkyl groups, substituted and unsubstituted -C(=O)-heterocyclyl groups, substituted and unsubstituted -C(=O)-heterocyclylalkyl groups, -C(=O)-NH$_2$, substituted and unsubstituted -C(=O)-N(H)(alkyl) groups, substituted and unsubstituted -C(=O)-N(alkyl)$_2$ groups, substituted and unsubstituted -C(=O)-N(H)(aryl) groups, substituted and unsubstituted -C(=O)-N(alkyl)(aryl) groups, substituted and unsubstituted -C(=O)-N(aryl)$_2$ groups, substituted and

unsubstituted -C(=O)-N(H)(aralkyl) groups, substituted and unsubstituted -C(=O)-N(alkyl)(aralkyl) groups, substituted and unsubstituted -C(=O)-N(aralkyl)$_2$ groups, substituted and unsubstituted -C(=O)-N(H)(heterocyclyl) groups, substituted and unsubstituted -C(=O)-N(alkyl)(heterocyclyl) groups, substituted and unsubstituted -C(=O)-N(heterocyclyl)$_2$ groups, substituted and unsubstituted -C(=O)-N(H)(heterocyclylalkyl) groups, substituted and unsubstituted -C(=O)-N(alkyl)(heterocyclylalkyl) groups, substituted and unsubstituted -C(=O)-N(heterocyclylalkyl)$_2$ groups, -CO_2H, substituted and unsubstituted -C(=O)-O-alkyl groups, substituted and unsubstituted -C(=O)-O-heterocyclyl groups, or substituted and unsubstituted -C(=O)-O-heterocyclylalkyl groups; or R^6 may be absent if B is nitrogen; or R^7 may be absent if C is nitrogen;

R^9 is selected from –H, substituted and unsubstituted alkyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted aryl groups, substituted and unsubstituted aralkyl groups, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted heterocyclylalkyl groups, substituted and unsubstituted heterocyclylaminoalkyl groups, substituted and unsubstituted alkoxy groups, or -NH_2, or R^9 and R^{10} join together to form one or more rings, each having 5, 6, or 7 ring members; and

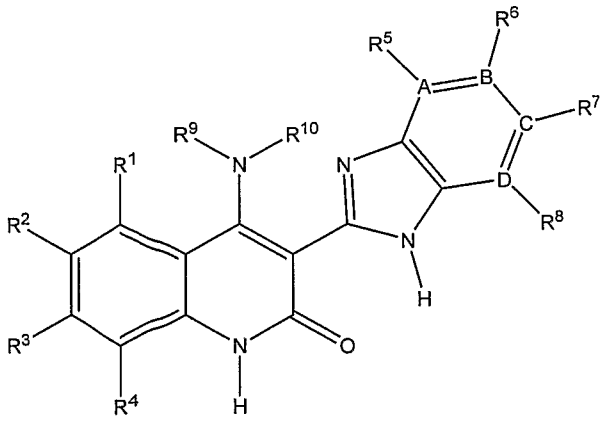
R^{10} is –H, or R^9 and R^{10} join together to form one or more rings, each having 5, 6, or 7 ring members.

[0172] In some embodiments of the method of inhibiting a serine/threonine kinase in a subject and/or the method of treating a biological condition mediated by serine/threonine kinase activity in a subject, the serine/threonine kinase is selected from glycogen synthase kinase 3, cyclin

dependent kinase 2, cyclin dependent kinase 4, MEK1, NEK-2, CHK2, CK1ε, Raf, checkpoint kinase 1, ribosomal S6 kinase 2, or disheveled associated kinase (PAR-1).

Methods Relating to Glycogen Synthase Kinase 3

[0173] In some embodiments of the method of inhibiting a serine/threonine kinase in a subject and/or the method of treating a biological condition mediated by serine/threonine kinase activity in a subject using a compound of Structure I, a tautomer of the compound, a pharmaceutically acceptable salt of the compound, a pharmaceutically acceptable salt of the tautomer, or mixtures thereof, the serine/threonine kinase is GSK-3. In some such methods the GSK-3 is inhibited in the subject after administration. Structure I has the following formula:



I

where:

A, B, C, and D are independently selected from carbon or nitrogen;

R^1 is selected from -H, -F, -Cl, -Br, -I, -CN, $-NO_2$, substituted and unsubstituted straight and branched chain alkyl groups having from 1 to 8 carbon atoms, substituted and unsubstituted alkenyl

groups having from 1 to 8 carbon atoms, substituted and unsubstituted alkynyl groups having from 1 to 8 carbon atoms, substituted and unsubstituted heterocyclyl groups, -SH, substituted and unsubstituted -S-alkyl groups, substituted and unsubstituted $-S(=O)_2$-O-alkyl groups, substituted and unsubstituted $-S(=O)_2$-alkyl groups, substituted and unsubstituted -S(=O)-alkyl groups, $-S(=O)-NH_2$, substituted and unsubstituted -S(=O)-N(H)(alkyl) groups, substituted and unsubstituted $-S(=O)-N(alkyl)_2$ groups, -OH, substituted and unsubstituted alkoxy groups, substituted and unsubstituted heterocyclyloxy groups, substituted and unsubstituted heterocyclylalkoxy groups, $-NH_2$, substituted and unsubstituted -N(H)(alkyl) groups, substituted and unsubstituted $-N(alkyl)_2$ groups, substituted and unsubstituted -N(H)-C(=O)-alkyl groups, substituted and unsubstituted -N(H)-S(=O)-alkyl groups, $-C(=O)-NH_2$, substituted and unsubstituted -C(=O)-N(H)(alkyl) groups, substituted and unsubstituted $-C(=O)-N(alkyl)_2$ groups, substituted and unsubstituted -C(=O)-N(H)(aralkyl) groups, $-CO_2H$, or substituted and unsubstituted -C(=O)-O-alkyl groups;

R^2 is selected from -H, -F, -Cl, -Br, -I, -CN, $-NO_2$, substituted and unsubstituted straight and branched chain alkyl groups having from 1 to 8 carbon atoms, substituted and unsubstituted alkenyl groups having from 1 to 8 carbon atoms, substituted and unsubstituted alkynyl groups having from 1 to 8 carbon atoms, substituted and unsubstituted cycloalkyl groups, substituted and unsubstituted cycloalkenyl groups, substituted and unsubstituted aryl groups, substituted and unsubstituted heterocyclyl groups, -SH, substituted and unsubstituted -S-alkyl groups, substituted and unsubstituted $-S(=O)_2$-O-alkyl groups, substituted and unsubstituted $-S(=O)_2$-alkyl groups, substituted and unsubstituted $-S(=O)_2$-heterocyclyl groups, substituted and

unsubstituted -S(=O)-alkyl groups, substituted and unsubstituted -S(=O)-heterocyclyl groups, -$S(=O)_2$-NH_2, substituted and unsubstituted -$S(=O)_2$-N(H)(alkyl) groups, substituted and unsubstituted -$S(=O)_2$-$N(alkyl)_2$ groups, -OH, substituted and unsubstituted alkoxy groups, substituted and unsubstituted heterocyclylalkoxy groups, -NH_2, substituted and unsubstituted -N(H)(alkyl) groups, substituted and unsubstituted -$N(alkyl)_2$ groups, substituted and unsubstituted -N(H)-C(=O)-alkyl groups, substituted and unsubstituted -N(H)-C(=O)-heterocyclyl groups, substituted and unsubstituted -N(H)-S(=O)-alkyl groups, substituted and unsubstituted -N(H)-S(=O)-heterocyclyl groups, -N(alkyl)-C(=O)-alkyl groups, substituted and unsubstituted -N(alkyl)-C(=O)-heterocyclyl groups, substituted and unsubstituted -N(alkyl)-S(=O)-alkyl groups, substituted and unsubstituted -N(alkyl)-S(=O)-heterocyclyl groups, -N(H)-C(=O)-NH_2, substituted and unsubstituted -N(H)-C(=O)-N(H)(alkyl) groups, substituted and unsubstituted -N(H)-C(=O)-$N(alkyl)_2$ groups, -N(alkyl)-C(=O)-NH_2, substituted and unsubstituted -N(alkyl)-C(=O)-N(H)(alkyl) groups, substituted and unsubstituted -N(alkyl)-C(=O)-$N(alkyl)_2$ groups, -C(=O)-NH_2, substituted and unsubstituted -C(=O)-N(H)(alkyl) groups, substituted and unsubstituted -C(=O)-$N(alkyl)_2$ groups, substituted and unsubstituted -C(=O)-alkyl groups, substituted and unsubstituted -C(=O)-heterocyclyl groups, -CO_2H, or substituted and unsubstituted -C(=O)-O-alkyl groups; or R^2 and R^3 may join together to form a cyclic group;

R^3 is selected from -H, -F, -Cl, -Br, -I, -CN, -NO_2, substituted and unsubstituted straight and branched chain alkyl groups having from 1 to 8 carbon atoms, substituted and unsubstituted alkenyl groups having from 1 to 8 carbon atoms, substituted and unsubstituted alkynyl groups having from 1 to 8 carbon atoms,

substituted and unsubstituted aryl groups, substituted and unsubstituted aralkyl groups, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted heterocyclylalkyl groups, -SH, substituted and unsubstituted -S-alkyl groups, substituted and unsubstituted $-S(=O)_2$-O-alkyl groups, substituted and unsubstituted $-S(=O)_2$-alkyl groups, substituted and unsubstituted $-S(=O)_2$-heterocyclyl groups, substituted and unsubstituted -S(=O)-alkyl groups, substituted and unsubstituted -S(=O)-heterocyclyl groups, $-S(=O)-NH_2$, substituted and unsubstituted -S(=O)-N(H)(alkyl) groups, substituted and unsubstituted $-S(=O)-N(alkyl)_2$ groups, -OH, substituted and unsubstituted alkoxy groups, substituted and unsubstituted heterocyclyloxy groups, substituted and unsubstituted heterocyclylalkoxy groups, substituted and unsubstituted -N(H)(alkyl) groups, substituted and unsubstituted -N(H)(cycloalkyl) groups, substituted and unsubstituted -N(H)(heterocyclyl) groups, substituted and unsubstituted -N(H)(heterocyclylalkyl) groups, substituted and unsubstituted $-N(alkyl)_2$ groups, $-NH_2$, substituted and unsubstituted -N(H)-C(=O)-alkyl groups, substituted and unsubstituted -N(H)-C(=O)-heterocyclyl groups, substituted and unsubstituted -N(H)-S(=O)-alkyl groups, substituted and unsubstituted -N(H)-S(=O)-heterocyclyl groups, substituted and unsubstituted -N(alkyl)-C(=O)-alkyl groups, substituted and unsubstituted -N(alkyl)-C(=O)-heterocyclyl groups, substituted and unsubstituted -N(alkyl)-S(=O)-alkyl groups, substituted and unsubstituted -N(alkyl)-S(=O)-heterocyclyl groups, $-N(H)-C(=O)-NH_2$, substituted and unsubstituted -N(H)-C(=O)-N(H)(alkyl) groups, substituted and unsubstituted $-N(H)-C(=O)-N(alkyl)_2$ groups, $-N(alkyl)-C(=O)-NH_2$, substituted and unsubstituted -N(alkyl)-C(=O)-N(H)(alkyl) groups substituted and unsubstituted $-N(alkyl)-C(=O)-N(alkyl)_2$ groups, substituted

and unsubstituted -C(=O)-alkyl groups, substituted and unsubstituted -C(=O)-heterocyclyl groups, -C(=O)-NH_2 groups, substituted and unsubstituted -C(=O)-N(H)(alkyl) groups, substituted and unsubstituted -C(=O)-N(alkyl)$_2$ groups, substituted and unsubstituted -C(=O)-N(H)(heterocyclyl) groups, substituted and unsubstituted -C(=O)-N(H)(aryl) groups, -CO_2H, or substituted and unsubstituted -C(=O)-O-alkyl groups, or R^2 and R^3 may join together to form a cyclic group;

R^4 is selected from -H, -F, -Cl, -Br, -I, -CN, -NO_2, substituted and unsubstituted straight and branched chain alkyl groups having from 1 to 8 carbon atoms, substituted and unsubstituted alkenyl groups having from 1 to 8 carbon atoms, substituted and unsubstituted alkynyl groups having from 1 to 8 carbon atoms, -SH, substituted and unsubstituted -S-alkyl groups, substituted and unsubstituted -S(=O)$_2$-O-alkyl groups, substituted and unsubstituted -S(=O)$_2$-alkyl groups, substituted and unsubstituted -S(=O)-alkyl groups, -S(=O)$_2$-NH_2, substituted and unsubstituted -S(=O)$_2$-N(H)(alkyl) groups, substituted and unsubstituted -S(=O)$_2$-N(alkyl)$_2$ groups, -OH, substituted and unsubstituted alkoxy groups, -NH_2, substituted and unsubstituted -N(H)(alkyl) groups, substituted and unsubstituted -N(alkyl)$_2$ groups, substituted and unsubstituted -N(H)-C(=O)-alkyl groups, substituted and unsubstituted -N(H)-S(=O)-alkyl groups, -C(=O)-NH_2, substituted and unsubstituted -C(=O)-N(H)(alkyl) groups, substituted and unsubstituted -C(=O)-N(alkyl)$_2$ groups, or substituted and unsubstituted -C(=O)-O-alkyl groups;

R^5 is selected from -H, -F, -Cl, -Br, -I, -CN, -NO_2, substituted and unsubstituted straight and branched chain alkyl groups having from 1 to 8 carbon atoms, substituted and unsubstituted alkenyl groups having from 1 to 8 carbon atoms, substituted and

unsubstituted alkynyl groups having from 1 to 8 carbon atoms, substituted and unsubstituted heterocyclyl groups, -SH, substituted and unsubstituted -S-alkyl groups, substituted and unsubstituted -S(=O)$_2$-O-alkyl groups, substituted and unsubstituted -S(=O)$_2$-alkyl groups, substituted and unsubstituted -S(=O)-alkyl groups, -S(=O)$_2$-NH$_2$, substituted and unsubstituted -S(=O)$_2$-N(H)(alkyl) groups, substituted and unsubstituted -S(=O)$_2$-N(alkyl)$_2$ groups, -OH, substituted and unsubstituted alkoxy groups, -NH$_2$, substituted and unsubstituted -N(H)(alkyl) groups, substituted and unsubstituted -N(alkyl)$_2$ groups, substituted and unsubstituted -N(H)-C(=O)-alkyl groups, substituted and unsubstituted -N(H)-S(=O)-alkyl groups, -C(=O)-NH$_2$, substituted and unsubstituted -C(=O)-N(H)(alkyl) groups, substituted and unsubstituted -C(=O)-N(alkyl)$_2$ groups, or substituted and unsubstituted -C(=O)-O-alkyl groups; or R^5 may be absent if A is nitrogen;

R^6 is selected from -H, –F, -Cl, -Br, -I, -CN, -NO$_2$, substituted and unsubstituted alkyl groups having from 1 to 8 carbon atoms, substituted and unsubstituted alkenyl groups having from 1 to 8 carbon atoms, substituted and unsubstituted alkynyl groups having from 1 to 8 carbon atoms, substituted and unsubstituted heterocyclyl groups, -SH, substituted and unsubstituted -S-alkyl groups, substituted and unsubstituted -S(=O)$_2$-O-alkyl groups, substituted and unsubstituted -S(=O)$_2$-alkyl groups, substituted and unsubstituted -S(=O)$_2$-heterocyclyl groups, substituted and unsubstituted -S(=O)-alkyl groups, substituted and unsubstituted -S(=O)-heterocyclyl groups, -S(=O)$_2$-NH$_2$, substituted and unsubstituted -S(=O)$_2$-N(H)(alkyl) groups, substituted and unsubstituted -S(=O)$_2$-N(alkyl)$_2$ groups, -OH, substituted and unsubstituted alkoxy groups, -NH$_2$, substituted and

unsubstituted -N(H)(alkyl) groups, substituted and unsubstituted -N(alkyl)$_2$ groups, substituted and unsubstituted -N(H)(heterocyclyl) groups, substituted and unsubstituted -N(alkyl)(heterocyclyl) groups, substituted and unsubstituted -N(H)-C(=O)-alkyl groups, substituted and unsubstituted -N(H)-C(=O)-heterocyclyl groups, substituted and unsubstituted -N(alkyl)-C(=O)-alkyl groups, substituted and unsubstituted -N(alkyl)-C(=O)-heterocyclyl groups, substituted and unsubstituted -N(H)-S(=O)$_2$-alkyl groups, substituted and unsubstituted -N(H)-S(=O)$_2$-heterocyclyl groups, substituted and unsubstituted -N(alkyl)-S(=O)$_2$-alkyl groups, substituted and unsubstituted -N(alkyl)-S(=O)$_2$-heterocyclyl groups, substituted and unsubstituted -C(=O)-alkyl groups, substituted and unsubstituted -C(=O)-heterocyclyl groups, -C(=O)-NH$_2$, substituted and unsubstituted -C(=O)-N(H)(alkyl) groups, substituted and unsubstituted -C(=O)-N(alkyl)$_2$ groups, -CO$_2$H, or substituted and unsubstituted -C(=O)-O-alkyl groups; or R^6 may be absent if B is nitrogen;

R^7 is selected from -H, -F, -Cl, -Br, -I, -CN, -NO$_2$, substituted and unsubstituted alkyl groups having from 1 to 8 carbon atoms, substituted and unsubstituted alkenyl groups having from 1 to 8 carbon atoms, substituted and unsubstituted alkynyl groups having from 1 to 8 carbon atoms, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted heterocyclylalkyl groups, -SH, substituted and unsubstituted -S-alkyl groups, substituted and unsubstituted -S(=O)$_2$-O-alkyl groups, substituted and unsubstituted -S(=O)$_2$-alkyl groups, substituted and unsubstituted -S(=O)$_2$-heterocyclyl groups, substituted and unsubstituted -S(=O)-alkyl groups, substituted and unsubstituted -S(=O)-heterocyclyl groups, -S(=O)$_2$-NH$_2$, substituted and unsubstituted -S(=O)$_2$-N(H)(alkyl) groups,

substituted and unsubstituted -$S(=O)_2$-$N(alkyl)_2$ groups, -OH, substituted and unsubstituted alkoxy groups, -NH_2, substituted and unsubstituted -N(H)(alkyl) groups, substituted and unsubstituted -$N(alkyl)_2$ groups, substituted and unsubstituted -N(H)(heterocyclyl) groups, substituted and unsubstituted -N(alkyl)(heterocyclyl) groups, substituted and unsubstituted -N(H)-C(=O)-alkyl groups, substituted and unsubstituted -N(H)-C(=O)-heterocyclyl groups, substituted and unsubstituted -N(alkyl)-C(=O)-alkyl groups, substituted and unsubstituted -N(alkyl)-C(=O)-heterocyclyl groups, substituted and unsubstituted -N(H)-S(=O)-alkyl groups, substituted and unsubstituted -N(H)-S(=O)-heterocyclyl groups, substituted and unsubstituted -N(alkyl)-S(=O)-alkyl groups, substituted and unsubstituted -N(alkyl)-S(=O)-heterocyclyl groups, substituted and unsubstituted amidine groups, -C(=O)-NH_2, substituted and unsubstituted -C(=O)-N(H)(alkyl) groups, substituted and unsubstituted -$C(=O)-N(alkyl)_2$ groups, substituted and unsubstituted -C(=O)-N(H)(heterocyclyl) groups, substituted and unsubstituted -C(=O)-N(H)(alkyl)(heterocyclyl) groups, substituted and unsubstituted -$C(=O)-N(heterocyclyl)_2$ groups, substituted and unsubstituted -C(=O)-alkyl groups, substituted and unsubstituted -C(=O)-heterocyclyl groups, -CO_2H, or substituted and unsubstituted -C(=O)-O-alkyl groups; or R^7 may be absent if C is nitrogen;

R^8 is selected from -H, -F, -Cl, -Br, -I, -CN, -NO_2, substituted and unsubstituted straight and branched chain alkyl groups having from 1 to 8 carbon atoms, substituted and unsubstituted alkenyl groups having from 1 to 8 carbon atoms, substituted and unsubstituted alkynyl groups having from 1 to 8 carbon atoms, substituted and unsubstituted heterocyclyl groups, -SH, substituted and unsubstituted -S-alkyl groups, substituted and

unsubstituted -S(=O)$_2$-O-alkyl groups, substituted and unsubstituted -S(=O)$_2$-alkyl groups, substituted and unsubstituted -S(=O)-alkyl groups, -S(=O)$_2$-NH$_2$, substituted and unsubstituted -S(=O)$_2$-N(H)(alkyl) groups, substituted and unsubstituted -S(=O)$_2$-N(alkyl)$_2$ groups, -OH, substituted and unsubstituted alkoxy groups, -NH$_2$, substituted and unsubstituted -N(H)(alkyl) groups, substituted and unsubstituted -N(alkyl)$_2$ groups, substituted and unsubstituted -N(H)-C(=O)-alkyl groups, substituted and unsubstituted -N(H)-S(=O)$_2$-alkyl groups, -C(=O)-NH$_2$, substituted and unsubstituted -C(=O)-N(H)(alkyl) groups, substituted and unsubstituted -C(=O)-N(alkyl)$_2$ groups, or substituted and unsubstituted -C(=O)-O-alkyl groups; or R^8 may be absent if D is nitrogen;

R^9 is selected from –H, substituted and unsubstituted straight and branched chain alkyl groups having from 1 to 8 carbon atoms, substituted and unsubstituted cycloalkyl groups, substituted and unsubstituted aryl groups, substituted and unsubstituted aralkyl groups, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted heterocyclylalkyl groups, substituted and unsubstituted heterocyclylaminoalkyl groups, substituted and unsubstituted alkoxy groups, or -NH$_2$, or R^9 and R^{10} join together to form a ring having 5, 6, or 7 ring members; and

R^{10} is –H, or R^9 and R^{10} join together to form a ring having 5, 6, or 7 ring members.

[0174] In some embodiments of the method of inhibiting GSK-3 in a subject and/or the method of treating a biological condition mediated by GSK-3 activity in a subject,

A, B, C, and D are independently selected from carbon or nitrogen;

R^1 is selected from -H, -F, -Cl, -Br, -I, substituted or unsubstituted straight or branched chain alkyl groups having from 1 to 8 carbon atoms, substituted or unsubstituted alkenyl groups having from 1 to 8 carbon atoms, substituted or unsubstituted alkynyl groups having from 1 to 8 carbon atoms, -CN, $-NO_2$, -OH, -SH, substituted or unsubstituted alkoxy groups, substituted or unsubstituted -S-alkyl groups, substituted or unsubstituted $-S(=O)_2$-O-alkyl groups, substituted or unsubstituted $-S(=O)_2$-alkyl groups, substituted or unsubstituted -S(=O)-alkyl groups, $-S(=O)-NH_2$, substituted or unsubstituted -S(=O)-N(H)(alkyl) groups, substituted or unsubstituted $-S(=O)-N(alkyl)_2$ groups, $-C(=O)-NH_2$, substituted or unsubstituted -C(=O)-N(H)(alkyl) groups, substituted or unsubstituted $-C(=O)-N(alkyl)_2$ groups, substituted or unsubstituted -C(=O)-O-alkyl groups, $-NH_2$, substituted or unsubstituted -N(H)(alkyl) groups, substituted or unsubstituted $-N(alkyl)_2$ groups, substituted or unsubstituted -N(H)-C(=O)-alkyl groups, or substituted or unsubstituted -N(H)-S(=O)-alkyl groups;

R^2 is selected -H, -F, -Cl, -Br, -I, $-NO_2$, -CN, $-NH_2$, $-CO_2H$, -OH, substituted or unsubstituted straight or branched chain alkyl groups having from 1 to 8 carbon atoms, substituted or unsubstituted cycloalkenyl groups, substituted or unsubstituted cycloalkyl groups, substituted or unsubstituted alkoxy groups, substituted or unsubstituted -N(H)(alkyl) groups, substituted or unsubstituted $-N(alkyl)_2$ groups, substituted or unsubstituted heterocyclyl groups, substituted or unsubstituted aryl groups, substituted or unsubstituted alkenyl groups having from 1 to 8 carbon atoms, substituted or unsubstituted alkynyl groups

having from 1 to 8 carbon atoms, -SH, substituted or unsubstituted -S-alkyl groups, substituted or unsubstituted $-S(=O)_2$-O-alkyl groups, substituted or unsubstituted $-S(=O)_2$-alkyl groups, substituted or unsubstituted $-S(=O)_2$-heterocyclyl groups, substituted or unsubstituted -S(=O)-alkyl groups, substituted or unsubstituted -S(=O)-heterocyclyl groups, $-S(=O)-NH_2$, substituted or unsubstituted -S(=O)-N(H)(alkyl) groups, substituted or unsubstituted $-S(=O)-N(alkyl)_2$ groups, $-C(=O)-NH_2$, substituted or unsubstituted -C(=O)-N(H)(alkyl) groups, substituted or unsubstituted $-C(=O)-N(alkyl)_2$ groups, substituted or unsubstituted -C(=O)-alkyl groups, substituted or unsubstituted -C(=O)-heterocyclyl groups, substituted or unsubstituted -C(=O)-O-alkyl groups, substituted or unsubstituted -N(H)-C(=O)-alkyl groups, substituted or unsubstituted -N(H)-C(=O)-heterocyclyl groups, substituted or unsubstituted -N(H)-S(=O)-alkyl groups, substituted or unsubstituted -N(H)-S(=O)-heterocyclyl groups, -N(alkyl)-C(=O)-alkyl groups, substituted or unsubstituted -N(alkyl)-C(=O)-heterocyclyl groups, substituted or unsubstituted -N(alkyl)-S(=O)-alkyl groups, substituted or unsubstituted -N(alkyl)-S(=O)-heterocyclyl groups, $-N(H)-C(=O)-NH_2$, substituted or unsubstituted -N(H)-C(=O)-N(H)(alkyl) groups, substituted or unsubstituted $-N(H)-C(=O)-N(alkyl)_2$ groups, $-N(alkyl)-C(=O)-NH_2$, substituted or unsubstituted -N(alkyl)-C(=O)-N(H)(alkyl) groups, or substituted or unsubstituted $-N(alkyl)-C(=O)-N(alkyl)_2$ groups; or R^2 and R^3 may join together to form a cyclic group;

R^3 is selected from -H, -F, -Cl, -Br, -I, -OH, substituted or unsubstituted straight or branched chain alkyl groups having from 1 to 8 carbon atoms, substituted or unsubstituted alkoxy groups, $-CO_2H$, -CN, substituted or unsubstituted -N(H)(alkyl)

groups, substituted or unsubstituted -N(H)(cycloalkyl) groups, substituted or unsubstituted -N(alkyl)$_2$ groups, substituted or unsubstituted heterocyclyl groups, substituted or unsubstituted aryl groups, substituted or unsubstituted -C(=O)-heterocyclyl groups, substituted or unsubstituted -C(=O)-alkyl groups, substituted or unsubstituted -C(=O)-N(H)(alkyl) groups, substituted or unsubstituted -C(=O)-N(alkyl)$_2$ groups, -C(=O)-NH$_2$ groups, substituted or unsubstituted -C(=O)-N(H)(heterocyclyl) groups, substituted or unsubstituted -C(=O)-N(H)(aryl) groups, substituted or unsubstituted alkenyl groups having from 1 to 8 carbon atoms, substituted or unsubstituted alkynyl groups having from 1 to 8 carbon atoms, -NO$_2$, -SH, substituted or unsubstituted -S-alkyl groups, substituted or unsubstituted -S(=O)$_2$-O-alkyl groups, substituted or unsubstituted -S(=O)$_2$-alkyl groups, substituted or unsubstituted -S(=O)$_2$-heterocyclyl groups, substituted or unsubstituted -S(=O)-alkyl groups, substituted or unsubstituted -S(=O)-heterocyclyl groups, -S(=O)-NH$_2$, substituted or unsubstituted -S(=O)-N(H)(alkyl) groups, substituted or unsubstituted -S(=O)-N(alkyl)$_2$ groups, substituted or unsubstituted -C(=O)-O-alkyl groups, -NH$_2$, substituted or unsubstituted -N(H)-C(=O)-alkyl groups, substituted or unsubstituted -N(H)-C(=O)-heterocyclyl groups, substituted or unsubstituted -N(H)-S(=O)-alkyl groups, substituted or unsubstituted -N(H)-S(=O)-heterocyclyl groups, substituted or unsubstituted -N(alkyl)-C(=O)-alkyl groups, substituted or unsubstituted -N(alkyl)-C(=O)-heterocyclyl groups, substituted or unsubstituted -N(alkyl)-S(=O)-alkyl groups, substituted or unsubstituted -N(alkyl)-S(=O)-heterocyclyl groups, -N(H)-C(=O)-NH$_2$, substituted or unsubstituted -N(H)-C(=O)-N(H)(alkyl) groups, substituted or unsubstituted -N(H)-C(=O)-N(alkyl)$_2$ groups, -N(alkyl)-C(=O)-NH$_2$, substituted

or unsubstituted -N(alkyl)-C(=O)-N(H)(alkyl) groups, or substituted or unsubstituted -N(alkyl)-C(=O)-N(alkyl)$_2$ groups; or R^2 and R^3 may join together to form a cyclic group;

R^4 is selected from of -H, -F, -Cl, -Br, -I, substituted or unsubstituted straight or branched chain alkyl groups having from 1 to 8 carbon atoms, substituted or unsubstituted alkenyl groups having from 1 to 8 carbon atoms, substituted or unsubstituted alkynyl groups having from 1 to 8 carbon atoms, -CN, -NO_2, -OH, -SH, substituted or unsubstituted alkoxy groups, substituted or unsubstituted -S-alkyl groups, substituted or unsubstituted -S(=O)$_2$-O-alkyl groups, substituted or unsubstituted -S(=O)$_2$-alkyl groups, substituted or unsubstituted -S(=O)-alkyl groups, -S(=O)-NH_2, substituted or unsubstituted -S(=O)-N(H)(alkyl) groups, substituted or unsubstituted -S(=O)-N(alkyl)$_2$ groups, -C(=O)-NH_2, substituted or unsubstituted -C(=O)-N(H)(alkyl) groups, substituted or unsubstituted -C(=O)-N(alkyl)$_2$ groups, substituted or unsubstituted -C(=O)-O-alkyl groups, -NH_2, substituted or unsubstituted -N(H)(alkyl) groups, substituted or unsubstituted -N(alkyl)$_2$ groups, substituted or unsubstituted -N(H)-C(=O)-alkyl groups, or substituted or unsubstituted -N(H)-S(=O)-alkyl groups;

R^5 is selected from -H, -F, -Cl, -Br, -I, substituted or unsubstituted straight or branched chain alkyl groups having from 1 to 8 carbon atoms, substituted or unsubstituted heterocyclyl groups, substituted or unsubstituted alkenyl groups having from 1 to 8 carbon atoms, substituted or unsubstituted alkynyl groups having from 1 to 8 carbon atoms, -CN, -NO_2, -OH, -SH, substituted or unsubstituted alkoxy groups, substituted or unsubstituted -S-alkyl groups, substituted or unsubstituted -S(=O)$_2$-O-alkyl groups, substituted or

unsubstituted -S(=O)$_2$-alkyl groups, substituted or unsubstituted -S(=O)-alkyl groups, -S(=O)-NH$_2$, substituted or unsubstituted -S(=O)-N(H)(alkyl) groups, substituted or unsubstituted -S(=O)-N(alkyl)$_2$ groups, -C(=O)-NH$_2$, substituted or unsubstituted -C(=O)-N(H)(alkyl) groups, substituted or unsubstituted -C(=O)-N(alkyl)$_2$ groups, substituted or unsubstituted -C(=O)-O-alkyl groups, -NH$_2$, substituted or unsubstituted -N(H)(alkyl) groups, substituted or unsubstituted -N(alkyl)$_2$ groups, substituted or unsubstituted -N(H)-C(=O)-alkyl groups, or substituted or unsubstituted -N(H)-S(=O)-alkyl groups; or R^5 may be absent if A is nitrogen;

R^6 is selected from -H, -Cl, -F, -Br, -OH, substituted or unsubstituted heterocyclyl groups, substituted or unsubstituted -N(H)(alkyl) groups, substituted or unsubstituted -N(H)(heterocyclyl) groups, substituted or unsubstituted -N(alkyl)(heterocyclyl) groups, substituted or unsubstituted alkoxy groups, substituted or unsubstituted alkyl groups having from 1 to 8 carbon atoms, substituted or unsubstituted alkenyl groups having from 1 to 8 carbon atoms, substituted or unsubstituted alkynyl groups having from 1 to 8 carbon atoms, -CN, -NO$_2$, -OH, -SH, substituted or unsubstituted -S-alkyl groups, substituted or unsubstituted -S(=O)$_2$-O-alkyl groups, substituted or unsubstituted -S(=O)$_2$-alkyl groups, substituted or unsubstituted -S(=O)$_2$-heterocyclyl groups, substituted or unsubstituted -S(=O)-alkyl groups, substituted or unsubstituted -S(=O)-heterocyclyl groups, -S(=O)-NH$_2$, substituted or unsubstituted -S(=O)-N(H)(alkyl) groups, substituted or unsubstituted -S(=O)-N(alkyl)$_2$ groups, -C(=O)-NH$_2$, substituted or unsubstituted -C(=O)-N(H)(alkyl) groups, substituted or unsubstituted -C(=O)-N(alkyl)$_2$ groups, substituted or unsubstituted -C(=O)-alkyl groups, substituted or unsubstituted

-C(=O)-heterocyclyl groups, substituted or unsubstituted -C(=O)-O-alkyl groups, $-NH_2$, substituted or unsubstituted $-N(alkyl)_2$ groups, substituted or unsubstituted -N(H)-C(=O)-alkyl groups, substituted or unsubstituted -N(H)-C(=O)-heterocyclyl groups, substituted or unsubstituted -N(alkyl)-C(=O)-alkyl groups, substituted or unsubstituted -N(alkyl)-C(=O)-heterocyclyl groups, substituted or unsubstituted -N(H)-S(=O)-alkyl groups, substituted or unsubstituted –N(H)-S(=O)-heterocyclyl groups, substituted or unsubstituted –N(alkyl)-S(=O)-alkyl groups, or substituted or unsubstituted –N(alkyl)-S(=O)-heterocyclyl groups; or R^6 may be absent if B is nitrogen;

R^7 is selected from -H, -Cl, -F, -Br, -OH, substituted or unsubstituted heterocyclyl groups, substituted or unsubstituted -N(H)(alkyl) groups, substituted or unsubstituted -N(H)(heterocyclyl) groups, substituted or unsubstituted -N(alkyl)(heterocyclyl) groups, substituted or unsubstituted alkoxy groups, substituted or unsubstituted alkyl groups having from 1 to 8 carbon atoms, substituted or unsubstituted alkenyl groups having from 1 to 8 carbon atoms, substituted or unsubstituted alkynyl groups having from 1 to 8 carbon atoms, -CN, $-NO_2$, -OH, -SH, substituted or unsubstituted -S-alkyl groups, substituted or unsubstituted $-S(=O)_2$-O-alkyl groups, substituted or unsubstituted $-S(=O)_2$-alkyl groups, substituted or unsubstituted $-S(=O)_2$-heterocyclyl groups, substituted or unsubstituted -S(=O)-alkyl groups, substituted or unsubstituted -S(=O)-heterocyclyl groups, $-S(=O)-NH_2$, substituted or unsubstituted -S(=O)-N(H)(alkyl) groups, substituted or unsubstituted $-S(=O)-N(alkyl)_2$ groups, $-C(=O)-NH_2$, substituted or unsubstituted -C(=O)-N(H)(alkyl) groups, substituted or unsubstituted $-C(=O)-N(alkyl)_2$ groups, substituted or unsubstituted -C(=O)-alkyl groups, substituted or unsubstituted

-C(=O)-heterocyclyl groups, substituted or unsubstituted -C(=O)-O-alkyl groups, $-NH_2$, substituted or unsubstituted $-N(alkyl)_2$ groups, substituted or unsubstituted -N(H)-C(=O)-alkyl groups, substituted or unsubstituted -N(H)-C(=O)-heterocyclyl groups, substituted or unsubstituted -N(alkyl)-C(=O)-alkyl groups, substituted or unsubstituted -N(alkyl)-C(=O)-heterocyclyl groups, substituted or unsubstituted -N(H)-S(=O)-alkyl groups, substituted or unsubstituted -N(H)-S(=O)-heterocyclyl groups, substituted or unsubstituted -N(alkyl)-S(=O)-alkyl groups, or substituted or unsubstituted -N(alkyl)-S(=O)-heterocyclyl groups; or R^7 may be absent if C is nitrogen;

R^8 is selected from -H, -F, -Cl, -Br, -I, substituted or unsubstituted straight or branched chain alkyl groups having from 1 to 8 carbon atoms, substituted or unsubstituted heterocyclyl groups, substituted or unsubstituted alkenyl groups having from 1 to 8 carbon atoms, substituted or unsubstituted alkynyl groups having from 1 to 8 carbon atoms, -CN, $-NO_2$, -OH, -SH, substituted or unsubstituted alkoxy groups, substituted or unsubstituted -S-alkyl groups, substituted or unsubstituted $-S(=O)_2$-O-alkyl groups, substituted or unsubstituted $-S(=O)_2$-alkyl groups, substituted or unsubstituted -S(=O)-alkyl groups, $-S(=O)-NH_2$, substituted or unsubstituted -S(=O)-N(H)(alkyl) groups, substituted or unsubstituted $-S(=O)-N(alkyl)_2$ groups, $-C(=O)-NH_2$, substituted or unsubstituted -C(=O)-N(H)(alkyl) groups, substituted or unsubstituted $-C(=O)-N(alkyl)_2$ groups, substituted or unsubstituted -C(=O)-O-alkyl groups, $-NH_2$, substituted or unsubstituted -N(H)(alkyl) groups, substituted or unsubstituted $-N(alkyl)_2$ groups, substituted or unsubstituted -N(H)-C(=O)-alkyl groups, or substituted or unsubstituted -N(H)-S(=O)-alkyl groups; or R^8 may be absent if D is nitrogen;

R^9 is selected from of substituted or unsubstituted heterocyclyl groups, substituted or unsubstituted aryl groups, substituted or unsubstituted alkoxy groups, $-NH_2$, substituted or unsubstituted cycloalkyl groups, or substituted or unsubstituted straight or branched chain alkyl groups having from 1 to 8 carbon atoms, or R^9 and R^{10} join together to form a ring having 5, 6, or 7 ring members; or

R^{10} is –H, or R^9 and R^{10} join together to form a ring having 5, 6, or 7 ring members.

[0175] In some embodiments of the method of inhibiting GSK-3 in a subject and/or the method of treating a biological condition mediated by GSK-3 activity in a subject,

R^1 is selected from -H, -F, -Cl, -Br, -I, and straight and branched chain alkyl groups having from 1 to 8 carbon atoms;

R^2 is selected from -H, -F, -Cl, -Br, -I, -CN, $-CO_2H$, $-NO_2$, straight and branched chain alkyl groups having from 1 to 8 carbon atoms, substituted and unsubstituted cycloalkyl groups, substituted and unsubstituted cycloalkenyl groups, substituted and unsubstituted aryl groups, substituted and unsubstituted heterocyclyl groups, -OH, substituted and unsubstituted alkoxy groups, $-NH_2$, substituted and unsubstituted -N(H)(alkyl) groups, or substituted and unsubstituted $-N(alkyl)_2$ groups;

R^3 is selected from -H, -F, -Cl, -Br, -I, -CN, straight and branched chain alkyl groups having from 1 to 8 carbon atoms, substituted and unsubstituted aryl groups, substituted and unsubstituted heterocyclyl groups, -OH, substituted and unsubstituted alkoxy groups, substituted and unsubstituted -N(H)(alkyl) groups, substituted and unsubstituted -N(H)(cycloalkyl) groups, substituted and unsubstituted

-N(H)(heterocyclyl) groups, substituted and unsubstituted -N(H)(heterocyclylalkyl) groups, substituted and unsubstituted $-N(alkyl)_2$ groups, $-CO_2H$, substituted and unsubstituted -C(=O)-heterocyclyl groups, substituted and unsubstituted -C(=O)-alkyl groups, substituted and unsubstituted -C(=O)-N(H)(alkyl) groups, substituted and unsubstituted $-C(=O)-N(alkyl)_2$ groups, $-C(=O)-NH_2$ groups, substituted and unsubstituted -C(=O)-N(H)(heterocyclyl) groups, or substituted and unsubstituted -C(=O)–N(H)(aryl) groups;

R^4 is selected from -H, -F, -Cl, -Br, -I, and straight and branched chain alkyl groups having from 1 to 8 carbon atoms;

R^5 is selected from -H, -F, -Cl, -Br, -I, straight and branched chain alkyl groups having from 1 to 8 carbon atoms, or substituted and unsubstituted heterocyclyl groups; or R^5 may be absent if A is nitrogen;

R^6 is selected from -H, -F, -Cl, -Br, substituted and unsubstituted alkyl groups having from 1 to 8 carbon atoms, substituted and unsubstituted heterocyclyl groups, -OH, substituted and unsubstituted alkoxy groups, substituted and unsubstituted -N(H)(alkyl) groups, substituted and unsubstituted -N(H)(heterocyclyl) groups, or substituted and unsubstituted -N(alkyl)(heterocyclyl) groups; or R^6 may be absent if B is nitrogen;

R^7 is selected from -H, -Cl, -F, -Br, substituted and unsubstituted alkyl groups having from 1 to 8 carbon atoms, -OH, substituted and unsubstituted alkoxy groups, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted -N(H)(alkyl) groups, substituted and unsubstituted -N(H)(heterocyclyl)

groups, or substituted and unsubstituted -N(alkyl)(heterocyclyl) groups; or R^7 may be absent if C is nitrogen; and

R^8 is selected from -H, -F, -Cl, -Br, -I, straight and branched chain alkyl groups having from 1 to 8 carbon atoms, or substituted and unsubstituted heterocyclyl groups; or R^8 may be absent if D is nitrogen.

[0176] In some embodiments of the method of inhibiting GSK-3 in a subject and/or the method of treating a biological condition mediated by GSK-3 activity in a subject, A, B, C, and D are all carbon.

[0177] In some embodiments of the method of inhibiting GSK-3 in a subject and/or the method of treating a biological condition mediated by GSK-3 activity in a subject, one of A or D is nitrogen, and B and C are both carbon.

[0178] In some embodiments of the method of inhibiting GSK-3 in a subject and/or the method of treating a biological condition mediated by GSK-3 activity in a subject, R^{10} is –H, and R^9 is selected from substituted and unsubstituted straight and branched chain alkyl groups having from 1 to 8 carbon atoms, substituted and unsubstituted cycloalkyl groups, substituted and unsubstituted aryl groups, substituted and unsubstituted aralkyl groups, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted heterocyclylalkyl groups, substituted and unsubstituted heterocyclylaminoalkyl groups, substituted and unsubstituted alkoxy groups, or $-NH_2$.

[0179] In some embodiments of the method of inhibiting GSK-3 in a subject and/or the method of treating a biological condition mediated by GSK-3 activity in a subject, R^9 is selected from unsubstituted straight and branched chain alkyl groups having from 1 to 8 carbon atoms, substituted and unsubstituted cycloalkyl groups, substituted and unsubstituted aryl groups, substituted and unsubstituted aralkyl groups, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted heterocyclylalkyl groups

wherein the heterocyclyl group is saturated, substituted and unsubstituted heterocyclylalkyl groups wherein the heterocyclyl group is unsaturated, substituted and unsubstituted alkoxy groups, $-NH_2$, substituted and unsubstituted alkoxyalkyl groups, substituted and unsubstituted hydroxyalkyl groups, substituted and unsubstituted dialkylaminoalkyl groups, substituted and unsubstituted alkylaminoalkyl groups, substituted and unsubstituted aminoalkyl groups, substituted and unsubstituted heterocyclylaminoalkyl groups, substituted and unsubstituted (heterocyclyl)(alkyl)aminoalkyl groups, or substituted and unsubstituted alkyl-(SO_2)-alkyl groups.

[0180] In some embodiments of the method of inhibiting GSK-3 in a subject and/or the method of treating a biological condition mediated by GSK-3 activity in a subject, R^{10} is –H, and R^9 is selected from substituted and unsubstituted cycloalkyl groups, substituted and unsubstituted saturated heterocyclyl groups, substituted and unsubstituted heterocyclylalkyl groups, or substituted and unsubstituted aminoalkyl groups.

[0181] In some embodiments of the method of inhibiting GSK-3 in a subject and/or the method of treating a biological condition mediated by GSK-3 activity in a subject, R^9 is selected from quinuclidinyl groups, piperidinyl groups, piperidinylalkyl groups, pyrrolidinyl groups, or aminocyclohexyl groups. In some such embodiments, R^9 is a quinuclidinyl group, and in further such embodiments R^9 is a quinuclidin-3-yl group.

[0182] In some embodiments of the method of inhibiting GSK-3 in a subject and/or the method of treating a biological condition mediated by GSK-3 activity in a subject, R^9 is selected from monocyclic, bicyclic, or polycyclic saturated heterocyclyl groups.

[0183] In some embodiments of the method of inhibiting GSK-3 in a subject and/or the method of treating a biological condition mediated by GSK-3 activity in a subject, R^1 is selected from -H, -F, -Cl, or $–CH_3$ groups. In

some such embodiments R^1 is –H or –F, and in further such embodiments, R^1 is –H.

[0184] In some embodiments of the method of inhibiting GSK-3 in a subject and/or the method of treating a biological condition mediated by GSK-3 activity in a subject, R^2 is selected from–H, -Cl, -F, -Br, -I, $-CH_3$, $-NO_2$, -OMe, -CN, $-CO_2H$, substituted and unsubstituted 1,2,3,6-tetrahydropyridine groups, substituted and unsubstituted thiophene groups, substituted and unsubstituted imidazole groups, substituted and unsubstituted pyrrole groups, substituted and unsubstituted 3-pyridinyl groups, substituted and unsubstituted 4-pyridinyl groups, phenyl, 2-substituted phenyl groups, 2,4-disubstituted phenyl groups, 4-substituted phenyl groups, 3-substituted phenyl groups, 2,6-disubstituted phenyl groups, 3,4-disubstituted phenyl groups, substituted and unsubstituted dialkylamino groups, or substituted and unsubstituted alkylamino groups.

[0185] In some embodiments of the method of inhibiting GSK-3 in a subject and/or the method of treating a biological condition mediated by GSK-3 activity in a subject, R^2 is a substituted and unsubstituted aryl group selected from phenyl, 2-chlorophenyl, 2-methylphenyl, 2-ethylphenyl, 2-hydroxyphenyl, 2-methoxyphenyl, 2-trifluoromethylphenyl, 3-methoxyphenyl, 3-nitrophenyl, 3-carboxyphenyl, 3-acetylphenyl, 3-aminophenyl, 3-hydroxyphenyl, 3-acetamidophenyl, 3-carbomethoxyphenyl, 3-trifluoromethylphenyl, 3-ureidophenyl, 4-chlorophenyl, 4-cyanophenyl, 4-hydroxyphenyl, 4-nitrophenyl, 4-ethylphenyl, 4-methylphenyl, 4-methoxyphenyl, 4-acetylphenyl, 4-acetamidophenyl, 4-carboxyphenyl, 4-formylphenyl, 4-methylthiophenyl, 4-dimethylaminophenyl, 4-carbomethoxyphenyl, 4-carboethoxyphenyl, 4-carboxamidophenyl, 4-(methylsulfonyl)phenyl, 4-trifluoromethylphenyl, 2,4-difluorophenyl, 2-fluoro-4-chlorophenyl, 2,4-dichlorophenyl, 2-amino-4-carbomethoxyphenyl, 2-amino-4-carboxyphenyl, 2,6-difluorophenyl, or 3,4-(methylenedioxy)phenyl.

[0186] In some embodiments of the method of inhibiting GSK-3 in a subject and/or the method of treating a biological condition mediated by GSK-

3 activity in a subject, R^2 is selected from–H, -Cl, -F, or $–CH_3$. In some such embodiments R^2 is –F.

[0187] In some embodiments of the method of inhibiting GSK-3 in a subject and/or the method of treating a biological condition mediated by GSK-3 activity in a subject, R^4 is selected from–H or $–CH_3$. In some such embodiments, R^4 is –H.

[0188] In some embodiments of the method of inhibiting GSK-3 in a subject and/or the method of treating a biological condition mediated by GSK-3 activity in a subject, R^5 and R^8 are independently selected from –H, saturated heterocyclyl groups, or are absent. In some such embodiments, R^5 and R^8 are independently selected from –H, or saturated heterocyclyl groups.

[0189] In some embodiments of the method of inhibiting GSK-3 in a subject and/or the method of treating a biological condition mediated by GSK-3 activity in a subject, A and D are both carbon, R^5 is –H, and R^8 is –H.

[0190] In some embodiments of the method of inhibiting GSK-3 in a subject and/or the method of treating a biological condition mediated by GSK-3 activity in a subject, R^6 and R^7 are independently selected from –H, -F, -Cl, -OH, or substituted and unsubstituted heterocyclyl groups. In some such embodiments, R^6 is –H and R^7 is –H.

[0191] In some embodiments of the method of inhibiting GSK-3 in a subject and/or the method of treating a biological condition mediated by GSK-3 activity in a subject, A, B, C, and D are all carbon, and R^5, R^6, R^7, and R^8 are all -H.

[0192] In some embodiments of the method of inhibiting GSK-3 in a subject and/or the method of treating a biological condition mediated by GSK-3 activity in a subject, R^3 is selected from –H, -F, -Cl, -Br, $-CH_3$, -OH, -CN, substituted and unsubstituted aryl groups, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted alkoxy groups, substituted

and unsubstituted alkylamino groups, substituted and unsubstituted dialkylamino groups, substituted and unsubstituted -C(=O)-heterocyclyl groups, substituted and unsubstituted -C(=O)-N(alkyl)$_2$ groups, or -C(=O)-NH_2 groups.

[0193] In some embodiments of the method of inhibiting GSK-3 in a subject and/or the method of treating a biological condition mediated by GSK-3 activity in a subject, R^3 is selected from –H, -F, -Cl, -Br, -CH_3, -CN, -OMe, hydroxyalkylamino groups, dialkylamino groups, dialkylaminoalkylamino groups, alkoxyalkylamino groups, substituted and unsubstituted heterocyclylalkylamino groups, acetamidoalkylamino groups, cyanoalkylamino groups, thioalkylamino groups, (methylsulfonyl)alkylamino groups, cycloalkylalkylamino groups, dialkylaminoalkoxy groups, heterocyclylalkoxy groups, substituted and unsubstituted piperidinyl groups, substituted and unsubstituted imidazolyl groups, substituted and unsubstituted morpholinyl groups, substituted and unsubstituted pyrrolyl groups, substituted and unsubstituted pyrrolidinyl groups, substituted and unsubstituted piperazinyl groups, substituted and unsubstituted aryl groups, substituted and unsubstituted -C(=O)-heterocyclyl groups, substituted and unsubstituted -C(=O)-N(alkyl)$_2$ groups, or -C(=O)-NH_2 groups.

[0194] In some embodiments of the method of inhibiting GSK-3 in a subject and/or the method of treating a biological condition mediated by GSK-3 activity in a subject, R^3 is selected from substituted and unsubstituted alkylamino groups or substituted and unsubstituted dialkylamino groups. In some such embodiments, R^3 is a dimethylamino group.

[0195] In some embodiments of the method of inhibiting GSK-3 in a subject and/or the method of treating a biological condition mediated by GSK-3 activity in a subject, A, B, C, and D are all carbon, and R^4, R^5, R^6, R^7, R^8, and R^{10} are all –H.

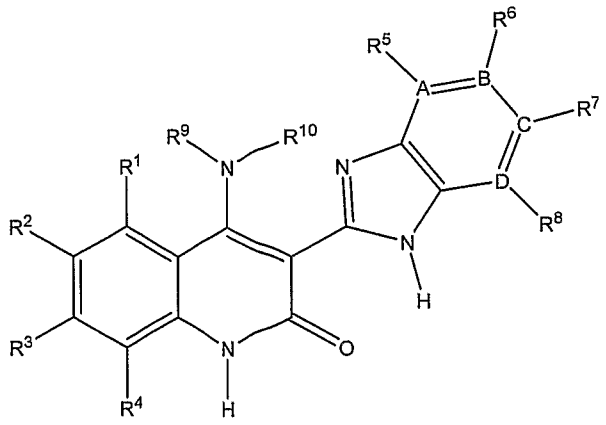
[0196] In some embodiments of the method of inhibiting GSK-3 in a subject and/or the method of treating a biological condition mediated by GSK-3 activity in a subject, the IC_{50} value of the compound is less than or equal to 10 μM with respect to GSK-3. In other such embodiments, the IC_{50} value is less than or equal to 1 μM, is less than or equal to 0.1 μM, is less than or equal to 0.050 μM, is less than or equal to 0.030 μM, is less than or equal to 0.025 μM, or is less than or equal to 0.010 μM.

[0197] In some embodiments of the method of inhibiting GSK-3 in a subject and/or the method of treating a biological condition mediated by GSK-3 activity in a subject, the subject is a mammal and in some such embodiments is a human.

[0198] In some embodiments of the method of treating a biological condition mediated by GSK-3 activity in a subject, the biological condition is diabetes, and in some such embodiments the biological condition is noninsulin dependent diabetes mellitus (NIDDM). In other such embodiments, the biological condition is Alzheimer's disease or is bipolar disorder.

Methods Relating to Cyclin Dependent Kinase 2

[0199] In some embodiments of the method of inhibiting a serine/threonine kinase in a subject and/or the method of treating a biological condition mediated by serine/threonine kinase activity in a subject using a compound of Structure I, a tautomer of the compound, a pharmaceutically acceptable salt of the compound, a pharmaceutically acceptable salt of the tautomer, or mixtures thereof, the serine/threonine kinase is Cdk2. In some such methods, the Cdk2 is inhibited in the subject after administration. In methods of inhibiting Cdk2, Structure I has the following formula:



I

where:

A, B, C, and D are independently selected from carbon or nitrogen;

R^1, R^4, R^5, and R^8 are independently selected from –H or substituted and unsubstituted straight and branched chain alkyl groups having from 1 to 8 carbon atoms; or R^5 may be absent if A is nitrogen; or R^8 may be absent if D is nitrogen;

R^2 and R^3 are independently selected from -H, -F, -Cl, -Br, -I, -CN, -NO_2, substituted and unsubstituted alkyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted alkenyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted aryl groups, substituted and unsubstituted aralkyl groups, substituted and unsubstituted heterocyclyl groups, or substituted and unsubstituted heterocyclylalkyl groups, -NH_2, substituted and unsubstituted -N(H)(alkyl) groups, substituted and unsubstituted -N(alkyl)$_2$ groups, substituted and unsubstituted -N(H)(aryl) groups, substituted and unsubstituted -N(alkyl)(aryl) groups, substituted and unsubstituted -N(aryl)$_2$ groups, substituted and unsubstituted -N(H)(heterocyclyl)

groups, substituted and unsubstituted -N(alkyl)(heterocyclyl) groups, substituted and unsubstituted -N(heterocyclyl)$_2$ groups;

R^6 and R^7 are independently selected from -H, -F, -Cl, -Br, -I, -CN, -NO_2, substituted and unsubstituted alkyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted alkenyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted heterocyclylalkyl groups, -OH, substituted and unsubstituted alkoxy groups, substituted and unsubstituted heterocyclyloxy groups, substituted and unsubstituted heterocyclylalkoxy groups, -NH_2, substituted and unsubstituted -N(H)(alkyl) groups, substituted and unsubstituted -N(alkyl)$_2$ groups, substituted and unsubstituted -N(H)(heterocyclyl) groups, substituted and unsubstituted -N(alkyl)(heterocyclyl) groups, substituted and unsubstituted -N(heterocyclyl)$_2$ groups, substituted and unsubstituted -N(H)(heterocyclylalkyl) groups, substituted and unsubstituted -N(alkyl)(heterocyclylalkyl) groups, substituted and unsubstituted -N(heterocyclylalkyl)$_2$ groups, substituted and unsubstituted -N(H)-C(=O)-alkyl groups, substituted and unsubstituted -N(H)-C(=O)-heterocyclyl groups, or substituted and unsubstituted -N(H)-C(=O)-heterocyclylalkyl groups; or R^6 may be absent if B is nitrogen; or R^7 may be absent if C is nitrogen;

R^9 is selected from -H, substituted and unsubstituted alkyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted alkenyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted heterocyclylalkyl groups, -OH, substituted and unsubstituted alkoxy groups, substituted and unsubstituted

heterocyclyloxy groups, substituted and unsubstituted heterocyclylalkoxy groups, substituted and unsubstituted -C(=O)-alkyl groups, substituted and unsubstituted -C(=O)-heterocyclyl groups, substituted and unsubstituted -C(=O)-heterocyclylalkyl groups; and

R^{10} is –H.

[0200] In some embodiments of the method of inhibiting Cdk2 in a subject and/or the method of treating a biological condition mediated by Cdk2 activity in a subject,

R^2 and R^3 are independently selected from -H, -F, -Cl, -Br, -I, -CN, -NO_2, substituted and unsubstituted alkyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted alkenyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted aryl groups, substituted and unsubstituted aralkyl groups, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted heterocyclylalkyl groups, -NH_2, substituted and unsubstituted -N(H)(alkyl) groups, substituted and unsubstituted -N(alkyl)$_2$ groups, substituted and unsubstituted -N(H)(aryl) groups, substituted and unsubstituted -N(alkyl)(aryl) groups, or substituted and unsubstituted -N(aryl)$_2$ groups;

R^6 and R^7 are independently selected from -H, -F, -Cl, -Br, -I, substituted and unsubstituted alkyl groups having from 1 to 8 carbon atoms, substituted and unsubstituted heterocyclyl groups, -OH, substituted and unsubstituted alkoxy groups, substituted and unsubstituted heterocyclyloxy groups, substituted and unsubstituted heterocyclylalkoxy groups,

substituted and unsubstituted -N(H)(heterocyclyl) groups, substituted and unsubstituted -N(alkyl)(heterocyclyl) groups, substituted and unsubstituted -N(heterocyclyl)$_2$ groups, or R^6 may be absent if B is nitrogen and R^7 may be absent if C is nitrogen..

[0201] In some embodiments of the method of inhibiting Cdk2 in a subject and/or the method of treating a biological condition mediated by Cdk2 activity in a subject, A, B, C, and D are all carbon.

[0202] In some embodiments of the method of inhibiting Cdk2 in a subject and/or the method of treating a biological condition mediated by Cdk2 activity in a subject, one of A or D is nitrogen, and B and C are both carbon.

[0203] In some embodiments of the method of inhibiting Cdk2 in a subject and/or the method of treating a biological condition mediated by Cdk2 activity in a subject, R^9 is selected from –H, substituted and unsubstituted chain alkyl groups having from 1-12 carbon atoms, substituted and unsubstituted aryl groups, substituted and unsubstituted aralkyl groups, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted heterocyclylalkyl groups, substituted and unsubstituted alkoxy groups, or substituted and unsubstituted heterocyclylalkoxy groups.

[0204] In some embodiments of the method of inhibiting Cdk2 in a subject and/or the method of treating a biological condition mediated by Cdk2 activity in a subject, R^9 is selected from –H, substituted and unsubstituted straight or branched chain alkyl groups having from 1-8 carbon atoms, substituted and unsubstituted saturated heterocyclyl groups, substituted and unsubstituted heterocyclylalkyl groups wherein the heterocyclyl moiety is saturated, substituted and unsubstituted alkoxy groups, or substituted and unsubstituted heterocyclylalkoxy groups wherein the heterocyclyl moiety is saturated.

[0205] In some embodiments of the method of inhibiting Cdk2 in a subject and/or the method of treating a biological condition mediated by Cdk2 activity in a subject, R^9 is selected from –H, unsubstituted straight or branched chain alkyl groups having from 1-8 carbon atoms, aminoalkyl groups, alkylaminoalkyl groups, dialkylaminoalkyl groups, substituted and unsubstituted saturated heterocyclyl groups, or substituted and unsubstituted heterocyclylalkyl groups wherein the heterocyclyl moiety is saturated.

[0206] In some embodiments of the method of inhibiting Cdk2 in a subject and/or the method of treating a biological condition mediated by Cdk2 activity in a subject, R^9 is selected from pyrrolidinyl, pyrrolidinylalkyl, piperidinyl, piperidinylalkyl, or quinuclidinyl.

[0207] In some embodiments of the method of inhibiting Cdk2 in a subject and/or the method of treating a biological condition mediated by Cdk2 activity in a subject, R^1 is –H.

[0208] In some embodiments of the method of inhibiting Cdk2 in a subject and/or the method of treating a biological condition mediated by Cdk2 activity in a subject, R^2 is selected from –H, -F, -Cl, -Br, -I, $-NO_2$, -CN, $-NH_2$, substituted and unsubstituted straight or branched chain alkyl groups having from 1 to 8 carbons, substituted and unsubstituted aryl groups, or substituted and unsubstituted pyridinyl groups. In some such embodiments, R^2 is selected from –H, -F, -Cl, –Br, –I, -CN, unsubstituted straight or branched chain alkyl groups having from 1 to 8 carbons, dihalophenyl, carboxyphenyl, aminophenyl, aminocarboxyphenyl, methylcarboxyphenyl, or hydroxyphenyl. In other such embodiments, R^2 is selected from –H, -F, -Cl, –Br, –I, -CN, $-CH_3$, 2,6-difluorophenyl, 4-carboxyphenyl, 3-aminophenyl, 2-amino-4-methylcarboxyphenyl, 3-methylcarboxyphenyl, or 3-hydroxyphenyl.

[0209] In some embodiments of the method of inhibiting Cdk2 in a subject and/or the method of treating a biological condition mediated by Cdk2 activity in a subject, R^3 is selected from the group consisting of -H, -F, -Cl, -Br,

-I, substituted and unsubstituted straight or branched chain alkyl groups having from 1 to 8 carbon atoms, substituted and unsubstituted aryl groups, substituted and unsubstituted aralkyl groups. In some such embodiments, R^3 is selected from -H, -F, -Cl, -Br, -I, unsubstituted straight or branched chain alkyl groups having from 1 to 8 carbon atoms, aminoalkylamino groups, or substituted aryl groups. In other such embodiments, R^3 is selected from -H, -F, -Cl, -Br, $-CH_3$, 2-aminopropylamino groups, or 4-carboxamidophenyl, or R^3 is selected from –H, -F, -Cl, -Br, or $-CH_3$.

[0210] In some embodiments of the method of inhibiting Cdk2 in a subject and/or the method of treating a biological condition mediated by Cdk2 activity in a subject, R^4 is –H.

[0211] In some embodiments of the method of inhibiting Cdk2 in a subject and/or the method of treating a biological condition mediated by Cdk2 activity in a subject, R^5 or R^8 is –H, or are both –H.

[0212] In some embodiments of the method of inhibiting Cdk2 in a subject and/or the method of treating a biological condition mediated by Cdk2 activity in a subject, R^6 and R^7 are independently selected from–H, -F, -Cl, -Br, -I, -OH, substituted and unsubstituted -N(alkyl)(piperidinyl), substituted and unsubstituted piperidinyl groups, substituted and unsubstituted morpholinyl groups, or substituted and unsubstituted piperazinyl groups; or R^6 may be absent if B is nitrogen; or R^7 may be absent if C is nitrogen. In some such embodiments, R^6 and R^7 are independently selected from –H, -F, -Cl, -OH, substituted and unsubstituted -N(methyl)(4-(N-methylpiperidinyl)), N-morpholinyl groups, or 4-N-methylpiperazinyl groups; or R^6 may be absent if B is nitrogen; or R^7 may be absent if C is nitrogen. In other such embodiments, R^6 and R^7 are both –H, and B and C are both carbon.

[0213] In some embodiments of the method of inhibiting Cdk2 in a subject and/or the method of treating a biological condition mediated by Cdk2 activity in a subject, R^5 and R^8 are both –H, and A and D are both carbon.

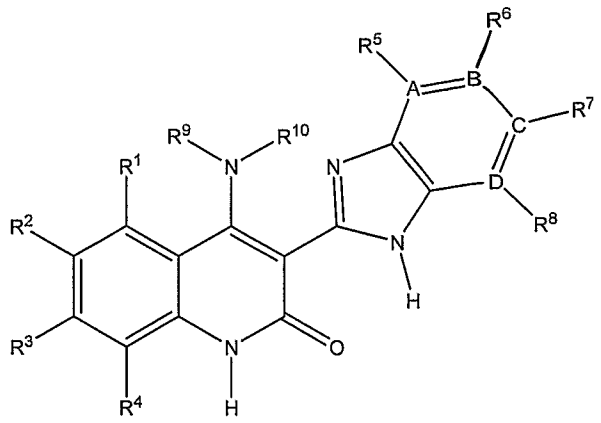
[0214] In some embodiments of the method of inhibiting Cdk2 in a subject and/or the method of treating a biological condition mediated by Cdk2 activity in a subject, the IC_{50} value of the compound is less than or equal to 10 μM with respect to Cdk2. In other such embodiments, the IC_{50} value is less than or equal to 1 μM, is less than or equal to 0.1 μM, is less than or equal to 0.050 μM, is less than or equal to 0.030 μM, is less than or equal to 0.025 μM, or is less than or equal to 0.010 μM.

[0215] In some embodiments of the method of inhibiting Cdk2 in a subject and/or the method of treating a biological condition mediated by Cdk2 activity in a subject, the subject is a mammal or is a human.

[0216] In some embodiments of the method of treating a biological condition mediated by Cdk2 activity in a subject, the biological condition is cancer.

Methods Relating to Checkpoint Kinase 1

[0217] In some embodiments of the method of inhibiting a serine/threonine kinase in a subject and/or the method of treating a biological condition mediated by serine/threonine kinase activity in a subject using a compound of Structure I, a tautomer of the compound, a pharmaceutically acceptable salt of the compound, a pharmaceutically acceptable salt of the tautomer, or mixtures thereof, the serine/threonine kinase is CHK1. In some such methods, the CHK1 is inhibited in the subject after administration. In methods of inhibiting CHK1, Structure I has the following formula:



I

where,

A, B, C, and D are independently selected from carbon or nitrogen;

R^1 is selected from -H, -F, -Cl, -Br, -I, -CN, $-NO_2$, substituted and unsubstituted alkyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted alkenyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted alkynyl groups having from 1 to 8 carbon atoms, substituted and unsubstituted heterocyclyl groups, -OH, substituted and unsubstituted alkoxy groups, substituted and unsubstituted aryloxy groups, substituted and unsubstituted arylalkoxy groups, substituted and unsubstituted heterocyclyloxy groups, substituted and unsubstituted heterocyclylalkoxy groups,-SH, substituted and unsubstituted -S-alkyl groups, $-NH_2$, substituted and unsubstituted -N(H)(alkyl) groups, substituted and unsubstituted $-N(alkyl)_2$ groups, substituted and unsubstituted -N(H)(heterocyclyl) groups, substituted and unsubstituted -N(alkyl)(heterocyclyl) groups, substituted and unsubstituted $-N(heterocyclyl)_2$ groups, substituted and unsubstituted -N(H)(heterocyclylalkyl) groups, substituted and unsubstituted

-N(alkyl)(heterocyclylalkyl) groups, or substituted and unsubstituted -N(heterocyclylalkyl)$_2$ groups;

R^2 and R^3 are independently selected from -H, -F, -Cl, -Br, -I, -NO_2, -CN, substituted and unsubstituted alkyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted alkenyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted alkynyl groups having from 1 to 8 carbon atoms, substituted and unsubstituted aryl groups, substituted and unsubstituted aralkyl groups, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted heterocyclylalkyl groups, -SH, substituted and unsubstituted -S-alkyl groups, substituted and unsubstituted -S(=O)$_2$-O-alkyl groups, substituted and unsubstituted -S(=O)$_2$-alkyl groups, substituted and unsubstituted -S(=O)$_2$-heterocyclyl groups, substituted and unsubstituted -S(=O)-alkyl groups, substituted and unsubstituted -S(=O)-heterocyclyl groups, -S(=O)$_2$-NH_2, substituted and unsubstituted -S(=O)$_2$-N(H)(alkyl) groups, substituted and unsubstituted -S(=O)$_2$-N(alkyl)$_2$ groups, substituted and unsubstituted -S(=O)$_2$-N(H)(aryl) groups, substituted and unsubstituted -S(=O)$_2$-N(alkyl)(aryl) groups, substituted and unsubstituted -S(=O)$_2$-N(aryl)$_2$ groups, substituted and unsubstituted -S(=O)$_2$-N(H)(aralkyl) groups, substituted and unsubstituted -S(=O)$_2$-N(alkyl)(aralkyl) groups, substituted and unsubstituted -S(=O)$_2$-N(aralkyl)$_2$ groups, -OH, substituted and unsubstituted alkoxy groups, substituted and unsubstituted aryloxy groups, substituted and unsubstituted arylalkoxy groups, substituted and unsubstituted heterocyclyloxy groups, substituted and unsubstituted heterocyclylalkoxy groups, -NH_2, substituted and unsubstituted -N(H)(alkyl) groups, substituted and unsubstituted -N(alkyl)$_2$ groups, substituted and unsubstituted -N(H)(aryl) groups, substituted and unsubstituted

-N(alkyl)(aryl) groups, substituted and unsubstituted -N(aryl)$_2$ groups, substituted and unsubstituted -N(H)(aralkyl) groups, substituted and unsubstituted -N(alkyl)(aralkyl) groups, substituted and unsubstituted -N(aralkyl)$_2$ groups, substituted and unsubstituted -N(H)(heterocyclyl) groups, substituted and unsubstituted -N(alkyl)(heterocyclyl) groups, substituted and unsubstituted -N(heterocyclyl)$_2$ groups, substituted and unsubstituted -N(H)(heterocyclylalkyl) groups, substituted and unsubstituted -N(alkyl)(heterocyclylalkyl) groups, substituted and unsubstituted -N(heterocyclylalkyl)$_2$ groups, substituted and unsubstituted -N(H)-S(=O)$_2$-alkyl groups, substituted and unsubstituted -N(H)-S(=O)$_2$-aryl groups, substituted and unsubstituted -N(H)-S(=O)$_2$-aralkyl groups, substituted and unsubstituted -N(H)-S(=O)$_2$-heterocyclyl groups, substituted and unsubstituted -N(H)-S(=O)$_2$-heterocyclylalkyl groups, substituted and unsubstituted -N(H)-C(=O)-alkyl groups, substituted and unsubstituted -N(H)-C(=O)-aryl groups, substituted and unsubstituted -N(H)-C(=O)-aralkyl groups, substituted and unsubstituted -N(H)-C(=O)-heterocyclyl groups, substituted and unsubstituted -N(H)-C(=O)-heterocyclylalkyl groups, substituted and unsubstituted -N(alkyl)-C(=O)-alkyl groups, substituted and unsubstituted -N(alkyl)-C(=O)-aryl groups, substituted and unsubstituted -N(alkyl)-C(=O)-aralkyl groups, substituted and unsubstituted -N(alkyl)-C(=O)-heterocyclyl groups, substituted and unsubstituted -N(alkyl)-C(=O)-heterocyclylalkyl groups, substituted and unsubstituted -N(alkyl)-S(=O)-alkyl groups, substituted and unsubstituted -N(alkyl)-S(=O)-aryl groups, substituted and unsubstituted -N(alkyl)-S(=O)-aralkyl groups, substituted and unsubstituted -N(alkyl)-S(=O)-heterocyclyl groups, substituted and unsubstituted -N(alkyl)-S(=O)-heterocyclylalkyl groups, -N(H)-C(=O)-NH$_2$, substituted and unsubstituted -N(H)-C(=O)-N(H)(alkyl) groups,

substituted and unsubstituted -N(H)-C(=O)-N(alkyl)$_2$ groups, substituted and unsubstituted -N(H)-C(=O)-N(H)(aryl) groups, substituted and unsubstituted -N(H)-C(=O)-N(alkyl)(aryl) groups, substituted and unsubstituted -N(H)-C(=O)-N(aryl)$_2$ groups, substituted and unsubstituted -N(H)-C(=O)-N(H)(aralkyl) groups, substituted and unsubstituted -N(H)-C(=O)-N(alkyl)(aralkyl) groups, substituted and unsubstituted -N(H)-C(=O)-N(aralkyl)$_2$ groups, substituted and unsubstituted -N(H)-C(=O)-N(H)(heterocyclyl) groups, substituted and unsubstituted -N(H)-C(=O)-N(alkyl)(heterocyclyl) groups, substituted and unsubstituted -N(H)-C(=O)-N(heterocyclyl)$_2$ groups, substituted and unsubstituted -N(H)-C(=O)-N(H)(heterocyclylalkyl) groups, substituted and unsubstituted -N(H)-C(=O)-N(alkyl)(heterocyclylalkyl) groups, substituted and unsubstituted -N(H)-C(=O)-N(heterocyclylalkyl)$_2$ groups, substituted and unsubstituted -N(alkyl)-C(=O)-NH$_2$ groups, substituted and unsubstituted -N(alkyl)-C(=O)-N(H)(alkyl) groups substituted and unsubstituted -N(alkyl)-C(=O)-N(alkyl)$_2$ groups, substituted and unsubstituted -N(alkyl)-C(=O)-N(H)(aryl) groups, substituted and unsubstituted -N(alkyl)-C(=O)-N(alkyl)(aryl) groups, substituted and unsubstituted -N(alkyl)-C(=O)-N(aryl)$_2$ groups, substituted and unsubstituted -N(alkyl)-C(=O)-N(H)(aralkyl) groups, substituted and unsubstituted -N(alkyl)-C(=O)-N(alkyl)(aralkyl) groups, substituted and unsubstituted -N(alkyl)-C(=O)-N(aralkyl)$_2$ groups, substituted and unsubstituted -N(alkyl)-C(=O)-N(H)(heterocyclyl) groups, substituted and unsubstituted -N(alkyl)-C(=O)-N(alkyl)(heterocyclyl) groups, substituted and unsubstituted -N(alkyl)-C(=O)-N(heterocyclyl)$_2$ groups, substituted and unsubstituted -N(alkyl)-C(=O)-N(H)(heterocyclylalkyl) groups, substituted and unsubstituted -N(alkyl)-C(=O)-N(alkyl)(heterocyclylalkyl) groups,

substituted and unsubstituted -N(alkyl)-C(=O)-N(heterocyclylalkyl)$_2$ groups, substituted and unsubstituted -C(=O)-alkyl groups, substituted and unsubstituted -C(=O)-aryl groups, substituted and unsubstituted -C(=O)-aralkyl groups, substituted and unsubstituted -C(=O)-heterocyclyl groups, substituted and unsubstituted -C(=O)-heterocyclylalkyl groups, -C(=O)-NH_2, substituted and unsubstituted -C(=O)-N(H)(alkyl) groups, substituted and unsubstituted -C(=O)-N(alkyl)$_2$ groups, substituted and unsubstituted -C(=O)-N(H)(aryl) groups, substituted and unsubstituted -C(=O)-N(alkyl)(aryl) groups, substituted and unsubstituted -C(=O)-N(aryl)$_2$ groups, substituted and unsubstituted -C(=O)-N(H)(aralkyl) groups, substituted and unsubstituted -C(=O)-N(alkyl)(aralkyl) groups, substituted and unsubstituted -C(=O)-N(aralkyl)$_2$ groups, substituted and unsubstituted -C(=O)-N(H)(heterocyclyl) groups, substituted and unsubstituted -C(=O)-N(alkyl)(heterocyclyl) groups, substituted and unsubstituted -C(=O)-N(heterocyclyl)$_2$ groups, substituted and unsubstituted -C(=O)-N(H)(heterocyclylalkyl) groups, substituted and unsubstituted -C(=O)-N(alkyl)(heterocyclylalkyl) groups, substituted and unsubstituted -C(=O)-N(heterocyclylalkyl)$_2$ groups, -CO_2H, substituted and unsubstituted -C(=O)-O-alkyl groups, substituted and unsubstituted -C(=O)-O-aryl groups, substituted and unsubstituted -C(=O)-O-heterocyclyl groups, or substituted and unsubstituted -C(=O)-O-heterocyclylalkyl groups;

R^4 is selected from –H or substituted and unsubstituted alkyl groups having from 1 to 12 carbon atoms;

R^5 and R^8 are independently selected from -H, substituted and unsubstituted alkyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted alkenyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted heterocyclyl groups; or R^5 may be absent if A is nitrogen; or R^8 may be absent if D is nitrogen;

R^6 and R^7 are independently selected from -H, -F, -Cl, -Br, -I, $-NO_2$, -CN, substituted and unsubstituted alkyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted alkenyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted alkynyl groups having from 1 to 8 carbon atoms, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted heterocyclylalkyl groups, -SH, substituted and unsubstituted -S-alkyl groups, substituted and unsubstituted $-S(=O)_2$-O-alkyl groups, substituted and unsubstituted $-S(=O)_2$-alkyl groups, substituted and unsubstituted $-S(=O)_2$-heterocyclyl groups, substituted and unsubstituted -S(=O)-alkyl groups, substituted and unsubstituted -S(=O)-heterocyclyl groups, $-S(=O)_2-NH_2$, substituted and unsubstituted $-S(=O)_2$-N(H)(alkyl) groups, substituted and unsubstituted $-S(=O)_2$-N(alkyl)$_2$ groups, substituted and unsubstituted $-S(=O)_2$-N(H)(heterocyclyl) groups, substituted and unsubstituted $-S(=O)_2$-N(alkyl)(heterocyclyl) groups, substituted and unsubstituted $-S(=O)_2$-N(heterocyclyl)$_2$ groups, substituted and unsubstituted $-S(=O)_2$-N(H)(heterocyclylalkyl) groups, substituted and unsubstituted $-S(=O)_2$-N(alkyl)(heterocyclylalkyl) groups, substituted and unsubstituted $-S(=O)_2$-N(heterocyclylalkyl)$_2$ groups, -OH, substituted and unsubstituted alkoxy groups, substituted and unsubstituted aryloxy groups, substituted and unsubstituted arylalkoxy groups, substituted and unsubstituted heterocyclyloxy

groups, substituted and unsubstituted heterocyclylalkoxy groups, $-NH_2$, substituted and unsubstituted -N(H)(alkyl) groups, substituted and unsubstituted $-N(alkyl)_2$ groups, substituted and unsubstituted -N(H)(aryl) groups, substituted and unsubstituted -N(alkyl)(aryl) groups, substituted and unsubstituted $-N(aryl)_2$ groups, substituted and unsubstituted -N(H)(aralkyl) groups, substituted and unsubstituted -N(alkyl)(aralkyl) groups, substituted and unsubstituted $-N(aralkyl)_2$ groups, substituted and unsubstituted -N(H)(heterocyclyl) groups, substituted and unsubstituted -N(alkyl)(heterocyclyl) groups, substituted and unsubstituted $-N(heterocyclyl)_2$ groups, substituted and unsubstituted -N(H)(heterocyclylalkyl) groups, substituted and unsubstituted -N(alkyl)(heterocyclylalkyl) groups, substituted and unsubstituted $-N(heterocyclylalkyl)_2$ groups, substituted and unsubstituted $-N(H)-S(=O)_2$-alkyl groups, substituted and unsubstituted $-N(H)-S(=O)_2$-heterocyclyl groups, substituted and unsubstituted $-N(H)-S(=O)_2$-heterocyclylalkyl groups, substituted and unsubstituted -N(H)-C(=O)-alkyl groups, substituted and unsubstituted -N(H)-C(=O)-heterocyclyl groups, substituted and unsubstituted -N(H)-C(=O)-heterocyclylalkyl groups, substituted and unsubstituted -N(alkyl)-C(=O)-alkyl groups, substituted and unsubstituted -N(alkyl)-C(=O)-heterocyclyl groups, substituted and unsubstituted -N(alkyl)-C(=O)-heterocyclylalkyl groups, substituted and unsubstituted $-N(alkyl)-S(=O)_2$-alkyl groups, substituted and unsubstituted $-N(alkyl)-S(=O)_2$-heterocyclyl groups, substituted and unsubstituted $-N(alkyl)-S(=O)_2$-heterocyclylalkyl groups, substituted and unsubstituted -C(=O)-alkyl groups, substituted and unsubstituted -C(=O)-heterocyclyl groups, substituted and unsubstituted -C(=O)-heterocyclylalkyl groups, $-C(=O)-NH_2$, substituted and unsubstituted -C(=O)-N(H)(alkyl) groups, substituted and unsubstituted $-C(=O)-N(alkyl)_2$ groups, substituted and

unsubstituted -C(=O)-N(H)(aryl) groups, substituted and unsubstituted -C(=O)-N(alkyl)(aryl) groups, substituted and unsubstituted -C(=O)-N(aryl)$_2$ groups, substituted and unsubstituted -C(=O)-N(H)(aralkyl) groups, substituted and unsubstituted -C(=O)-N(alkyl)(aralkyl) groups, substituted and unsubstituted -C(=O)-N(aralkyl)$_2$ groups, substituted and unsubstituted -C(=O)-N(H)(heterocyclyl) groups, substituted and unsubstituted -C(=O)-N(alkyl)(heterocyclyl) groups, substituted and unsubstituted -C(=O)-N(heterocyclyl)$_2$ groups, substituted and unsubstituted -C(=O)-N(H)(heterocyclylalkyl) groups, substituted and unsubstituted -C(=O)-N(alkyl)(heterocyclylalkyl) groups, substituted and unsubstituted -C(=O)-N(heterocyclylalkyl)$_2$ groups, -CO_2H, substituted and unsubstituted -C(=O)-O-alkyl groups, substituted and unsubstituted -C(=O)-O-heterocyclyl groups, or substituted and unsubstituted -C(=O)-O-heterocyclylalkyl groups; or R^6 may be absent if B is nitrogen; or R^7 may be absent if C is nitrogen;

R^9 is selected from –H, substituted and unsubstituted alkyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted aryl groups, substituted and unsubstituted aralkyl groups, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted heterocyclylalkyl groups, substituted and unsubstituted heterocyclylaminoalkyl groups, substituted and unsubstituted alkoxy groups, or -NH_2, or R^9 and R^{10} join together to form one or more rings, each having 5, 6, or 7 ring members; and

R^{10} is –H, or R^9 and R^{10} join together to form one or more rings, each having 5, 6, or 7 ring members.

[0218] In some embodiments of the method of inhibiting CHK1 in a subject and/or the method of treating a biological condition mediated by CHK1 activity in a subject,

R^1 is selected from -H, -F, -Cl, -Br, -I, -CN, $-NO_2$, substituted and unsubstituted straight and branched chain alkyl groups having from 1 to 8 carbon atoms, substituted and unsubstituted cycloalkyl groups, substituted and unsubstituted alkenyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted heterocyclyl groups, -OH, substituted and unsubstituted alkoxy groups, substituted and unsubstituted aryloxy groups, substituted and unsubstituted arylalkoxy groups, substituted and unsubstituted heterocyclyloxy groups, substituted and unsubstituted heterocyclylalkoxy groups, $-NH_2$, substituted and unsubstituted -N(H)(alkyl) groups, substituted and unsubstituted $-N(alkyl)_2$ groups, substituted and unsubstituted -N(H)(heterocyclyl) groups, substituted and unsubstituted -N(alkyl)(heterocyclyl) groups, substituted and unsubstituted -N(H)(heterocyclylalkyl) groups, or substituted and unsubstituted -N(alkyl)(heterocyclylalkyl) groups;

R^2 and R^3 are independently selected from -H, -F, -Cl, -Br, -I, $-NO_2$, -CN, substituted and unsubstituted alkyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted alkenyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted alkynyl groups having from 1 to 8 carbon atoms, substituted and unsubstituted aryl groups, substituted and unsubstituted aralkyl groups, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted heterocyclylalkyl groups, -OH, substituted and unsubstituted alkoxy groups, substituted and unsubstituted aryloxy groups,

substituted and unsubstituted arylalkoxy groups, substituted and unsubstituted heterocyclyloxy groups, substituted and unsubstituted heterocyclylalkoxy groups, $-NH_2$, substituted and unsubstituted -N(H)(alkyl) groups, substituted and unsubstituted $-N(alkyl)_2$ groups, substituted and unsubstituted -N(H)(aryl) groups, substituted and unsubstituted -N(alkyl)(aryl) groups, substituted and unsubstituted $-N(aryl)_2$ groups, substituted and unsubstituted -N(H)(aralkyl) groups, substituted and unsubstituted -N(alkyl)(aralkyl) groups, substituted and unsubstituted $-N(aralkyl)_2$ groups, substituted and unsubstituted -N(H)(heterocyclyl) groups, substituted and unsubstituted -N(alkyl)(heterocyclyl) groups, substituted and unsubstituted $-N(heterocyclyl)_2$ groups, substituted and unsubstituted -N(H)(heterocyclylalkyl) groups, substituted and unsubstituted -N(alkyl)(heterocyclylalkyl) groups, substituted and unsubstituted $-N(heterocyclylalkyl)_2$ groups, substituted and unsubstituted -N(H)-C(=O)-alkyl groups, substituted and unsubstituted -N(H)-C(=O)-aryl groups, substituted and unsubstituted -N(H)-C(=O)-aralkyl groups, substituted and unsubstituted -N(H)-C(=O)-heterocyclyl groups, substituted and unsubstituted -N(H)-C(=O)-heterocyclylalkyl groups, substituted and unsubstituted -N(alkyl)-C(=O)-alkyl groups, substituted and unsubstituted -N(alkyl)-C(=O)-aryl groups, substituted and unsubstituted -N(alkyl)-C(=O)-aralkyl groups, substituted and unsubstituted -N(alkyl)-C(=O)-heterocyclyl groups, substituted and unsubstituted -N(alkyl)-C(=O)-heterocyclylalkyl groups, $-N(H)-C(=O)-NH_2$, substituted and unsubstituted -N(H)-C(=O)-N(H)(alkyl) groups, substituted and unsubstituted $-N(H)-C(=O)-N(alkyl)_2$ groups, substituted and unsubstituted -N(H)-C(=O)-N(H)(aryl) groups, substituted and unsubstituted -N(H)-C(=O)-N(alkyl)(aryl) groups, substituted and unsubstituted $-N(H)-C(=O)-N(aryl)_2$ groups, substituted and unsubstituted

-N(H)-C(=O)-N(H)(aralkyl) groups, substituted and unsubstituted -N(H)-C(=O)-N(alkyl)(aralkyl) groups, substituted and unsubstituted -N(H)-C(=O)-N(aralkyl)$_2$ groups, substituted and unsubstituted -N(H)-C(=O)-N(H)(heterocyclyl) groups, substituted and unsubstituted -N(H)-C(=O)–N(alkyl)(heterocyclyl) groups, substituted and unsubstituted -N(H)-C(=O)-N(heterocyclyl)$_2$ groups, substituted and unsubstituted -N(H)-C(=O)-N(H)(heterocyclylalkyl) groups, substituted and unsubstituted -N(H)-C(=O)-N(alkyl)(heterocyclylalkyl) groups, substituted and unsubstituted -N(H)-C(=O)-N(heterocyclylalkyl)$_2$ groups, substituted and unsubstituted -N(alkyl)-C(=O)-NH$_2$ groups, substituted and unsubstituted -N(alkyl)-C(=O)-N(H)(alkyl) groups, substituted and unsubstituted -N(alkyl)-C(=O)-N(H)(aryl) groups, substituted and unsubstituted -N(alkyl)-C(=O)-N(H)(aralkyl) groups, substituted and unsubstituted -N(alkyl)-C(=O)-N(H)(heterocyclyl) groups, substituted and unsubstituted -N(alkyl)-C(=O)-N(H)(heterocyclylalkyl) groups, substituted and unsubstituted -C(=O)-alkyl groups, substituted and unsubstituted -C(=O)-aryl groups, substituted and unsubstituted -C(=O)-aralkyl groups, substituted and unsubstituted -C(=O)-heterocyclyl groups, substituted and unsubstituted -C(=O)-heterocyclylalkyl groups, -C(=O)-NH$_2$, substituted and unsubstituted -C(=O)-N(H)(alkyl) groups, substituted and unsubstituted -C(=O)-N(alkyl)$_2$ groups, substituted and unsubstituted -C(=O)-N(H)(aryl) groups, substituted and unsubstituted -C(=O)-N(alkyl)(aryl) groups, substituted and unsubstituted -C(=O)-N(aryl)$_2$ groups, substituted and unsubstituted -C(=O)-N(H)(aralkyl) groups, substituted and unsubstituted -C(=O)-N(alkyl)(aralkyl) groups, substituted and unsubstituted -C(=O)-N(aralkyl)$_2$ groups, -CO$_2$H, substituted and unsubstituted

-C(=O)-O-alkyl groups, substituted and unsubstituted
-C(=O)-O-aryl groups, substituted and unsubstituted
-C(=O)-O-heterocyclyl groups, or substituted and unsubstituted
-C(=O)-O-heterocyclylalkyl groups;

R^6 and R^7 are independently selected from -H, -F, -Cl, -Br, -I, $-NO_2$, -CN, substituted and unsubstituted alkyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted alkenyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted alkynyl groups having from 1 to 8 carbon atoms, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted heterocyclylalkyl groups, $-S(=O)_2-NH_2$, substituted and unsubstituted $-S(=O)_2-N(H)(alkyl)$ groups, substituted and unsubstituted $-S(=O)_2-N(alkyl)_2$ groups, -OH, substituted and unsubstituted alkoxy groups, substituted and unsubstituted aryloxy groups, substituted and unsubstituted arylalkoxy groups, substituted and unsubstituted heterocyclyloxy groups, substituted and unsubstituted heterocyclylalkoxy groups, $-NH_2$, substituted and unsubstituted -N(H)(alkyl) groups, substituted and unsubstituted $-N(alkyl)_2$ groups, substituted and unsubstituted -N(H)(heterocyclyl) groups, substituted and unsubstituted -N(alkyl)(heterocyclyl) groups, substituted and unsubstituted $-N(heterocyclyl)_2$ groups, substituted and unsubstituted -N(H)(heterocyclylalkyl) groups, substituted and unsubstituted -N(alkyl)(heterocyclylalkyl) groups, substituted and unsubstituted $-N(heterocyclylalkyl)_2$ groups, substituted and unsubstituted -N(H)-C(=O)-alkyl groups, substituted and unsubstituted -N(H)-C(=O)-heterocyclyl groups, substituted and unsubstituted -N(H)-C(=O)-heterocyclylalkyl groups, substituted and unsubstituted -N(alkyl)-C(=O)-alkyl groups, substituted and unsubstituted -N(alkyl)-C(=O)-heterocyclyl groups, substituted and unsubstituted -N(alkyl)-C(=O)-heterocyclylalkyl groups,

substituted and unsubstituted -C(=O)-alkyl groups, substituted and unsubstituted -C(=O)-heterocyclyl groups, substituted and unsubstituted -C(=O)-heterocyclylalkyl groups, $-C(=O)-NH_2$, substituted and unsubstituted -C(=O)-N(H)(alkyl) groups, substituted and unsubstituted $-C(=O)-N(alkyl)_2$ groups, substituted and unsubstituted -C(=O)-N(H)(heterocyclyl) groups, substituted and unsubstituted -C(=O)-N(alkyl)(heterocyclyl) groups, substituted and unsubstituted $-C(=O)-N(heterocyclyl)_2$ groups, substituted and unsubstituted -C(=O)-N(H)(heterocyclylalkyl) groups, substituted and unsubstituted -C(=O)-N(alkyl)(heterocyclylalkyl) groups, substituted and unsubstituted $-C(=O)-N(heterocyclylalkyl)_2$ groups, $-CO_2H$, substituted and unsubstituted -C(=O)-O-alkyl groups, substituted and unsubstituted -C(=O)-O-heterocyclyl groups, or substituted and unsubstituted -C(=O)-O-heterocyclylalkyl groups; or R^6 may be absent if B is nitrogen; or R^7 may be absent if C is nitrogen.

[0219] In some embodiments of the method of inhibiting CHK1 in a subject and/or the method of treating a biological condition mediated by CHK1 activity in a subject, A, B, C, and D are all carbon.

[0220] In some embodiments of the method of inhibiting CHK1 in a subject and/or the method of treating a biological condition mediated by CHK1 activity in a subject, one of A or D is nitrogen, and B and C are both carbon.

[0221] In some embodiments of the method of inhibiting CHK1 in a subject and/or the method of treating a biological condition mediated by CHK1 activity in a subject, R^{10} is –H, and R^9 is selected from substituted and unsubstituted straight and branched chain alkyl groups having from 1 to 8 carbon atoms, substituted and unsubstituted cycloalkyl groups, substituted and unsubstituted aryl groups, substituted and unsubstituted aralkyl groups,

substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted heterocyclylalkyl groups, or substituted and unsubstituted heterocyclylaminoalkyl groups.

[0222] In some embodiments of the method of inhibiting CHK1 in a subject and/or the method of treating a biological condition mediated by CHK1 activity in a subject, R^{10} is –H, and R^9 is selected from unsubstituted straight and branched chain alkyl groups having from 1 to 8 carbon atoms, substituted and unsubstituted cycloalkyl groups, substituted and unsubstituted hydroxyalkyl groups, substituted and unsubstituted dialkylaminoalkyl groups, substituted and unsubstituted alkylaminoalkyl groups, or substituted and unsubstituted aminoalkyl groups. In some such embodiments, R^{10} is –H, and R^9 is selected from 2-amino-4-methyl-pentyl, 2-amino-3-methyl-butyl, 2-amino-butyl, 2,2-dimethyl-3-amino-propyl, 1-aminomethyl-propyl, 2-hydroxy-3-amino-propyl, 3-aminopropyl, 2-dimethylamino-ethyl, 2-methylamino-ethyl, 2-hydroxy-ethyl, or 2-amino-ethyl.

[0223] In some embodiments of the method of inhibiting CHK1 in a subject and/or the method of treating a biological condition mediated by CHK1 activity in a subject, R^{10} is –H and R^9 is selected from substituted and unsubstituted cycloalkyl groups, substituted and unsubstituted aryl groups, substituted and unsubstituted aralkyl groups, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted heterocyclylalkyl groups, or substituted and unsubstituted heterocyclylaminoalkyl groups. In some such embodiments, R^{10} is –H and R^9 is selected from substituted and unsubstituted phenylpropyl groups, substituted and unsubstituted phenylmethyl groups, or substituted and unsubstituted phenyl groups. In other such embodiments, R^{10} is –H and R^9 is selected from phenyl, 4-aminomethyl-phenylmethyl, 2-(2-amino-ethyloxy)-phenylmethyl, 4-(2-amino-ethyloxy)-phenylmethyl, 4-sulfonamido-phenylmethyl, 1-benzyl-2-amino-ethyl, or 2-amino–3-phenyl-propyl.

[0224] In some embodiments of the method of inhibiting CHK1 in a subject and/or the method of treating a biological condition mediated by CHK1 activity in a subject, R^{10} is –H and R^9 is selected from substituted and unsubstituted cyclohexyl groups, substituted and unsubstituted cyclohexylalkyl groups, substituted and unsubstituted pyrrolidinyl groups, substituted and unsubstituted pyrrolidinylalkyl groups, substituted and unsubstituted tetrahydrofuranylalkyl groups, substituted and unsubstituted piperidinyl groups, substituted and unsubstituted piperidinylalkyl groups, substituted and unsubstituted piperazinylalkyl groups, substituted and unsubstituted morpholinylalkyl groups, or substituted and unsubstituted quinuclidinyl groups. In some such embodiments, R^9 is selected from cyclohexyl, cyclohexylmethyl, 1-cyclohexylethyl, 2-amino-cyclohexyl, 4-amino-cyclohexyl, pyrrolidin-3-yl, 1-methyl-pyrroldin-3-yl, 1-ethyl-pyrrolidin-2-yl, pyrrolidin-2-ylmethyl, 1-ethyl-pyrrolidin-2-ylmethyl, pyrrolidin-1-ylethyl, 1-methyl-pyrrolidin-2-ylethyl, pyrrolidin-1-ylpropyl, 2-oxo-pyrrolidin-1-ylpropyl, tetrahydrofuran-2-ylmethyl, piperidin-3-yl, 1-ethyl-piperidin-3-yl, piperidin-4-yl, 1-methyl-piperidin-4-yl, 1-benzyl-piperidin-4-yl, piperidin-2-ylmethyl, piperidin-3-ylmethyl, piperidin-4-ylmethyl, piperidin-1-ylethyl, piperidin-2-ylethyl, 4-methyl-piperazin-1-ylpropyl, morpholin-4-ylethyl, morpholin-4-ylpropyl, or quinuclidin-3-yl. In other such embodiments, R^9 is a quinuclidin-3-yl. In further such embodiments R^9 is a piperidin-3-ylmethyl. In other such embodiments, R^9 is selected from pyrrolidin-3-yl, 1-methyl-pyrrolidin-3-yl, or pyrrolidin-2-ylmethyl.

[0225] In some embodiments of the method of inhibiting CHK1 in a subject and/or the method of treating a biological condition mediated by CHK1 activity in a subject, R^{10} is –H and R^9 is selected from substituted and unsubstituted imidazolylalkyl groups, substituted and unsubstituted pyridinyl groups, substituted and unsubstituted pyridinylalkyl groups, substituted and unsubstituted pyridinylaminoalkyl groups, substituted and unsubstituted pyrimidinylalkyl groups, substituted and unsubstituted pyrazinylalkyl groups, substituted and unsubstituted indolylalkyl groups, substituted and

unsubstituted benzimidazolylalkyl groups. In some such embodiments, R^{10} is –H and R^9 is selected from 3-(imidazol-1-yl)-propyl, 3-(imidazol-4-yl)-propyl, pyridin-2-yl, pyridin-4-yl, 2-methoxy-pyridin-5-yl, 2-(piperidin-4-yloxy)-pyridin-3-yl, 2-(piperidin-3-yloxy)-pyridin-5-yl, pyridin-3-ylmethyl, pyridin-4-ylmethyl, pyridin-2-ylethyl, pyridin-3-ylethyl, 2-(5-trifluromethyl-pyridin-2-ylamino)-ethyl, 2-(2-carboxamido-pyridin-5-ylamino)-ethyl, 2-(4-amino-5-nitro-pyridin-2-ylamino)-ethyl, pyridin-2-ylpropyl, pyrazin-2-yl, 2-methyl-4-amino-pyrazin-5-yl, 5-fluoro-indol-3-ylethyl, benzimidazol-2-ylmethyl, benzimidazol-5-ylmethyl, 2-piperidin-4-yl-benzimidazol-5-ylmethyl, and benzimidazol-2-ylethyl.

[0226] In some embodiments of the method of inhibiting CHK1 in a subject and/or the method of treating a biological condition mediated by CHK1 activity in a subject, R^9 is selected from monocyclic, bicyclic, and polycyclic saturated heterocyclyl groups.

[0227] In some embodiments of the method of inhibiting CHK1 in a subject and/or the method of treating a biological condition mediated by CHK1 activity in a subject, R^9 and R^{10} join together to form one or more rings, each having 5, 6, or 7 ring members.

[0228] In some embodiments of the method of inhibiting CHK1 in a subject and/or the method of treating a biological condition mediated by CHK1 activity in a subject, R^1 is selected from -H, -F, -Cl, -Br, -I, substituted and unsubstituted straight and branched chain alkyl groups having from 1 to 4 carbon atoms, substituted and unsubstituted heterocyclyl groups, -OH, substituted and unsubstituted alkoxy groups, substituted and unsubstituted aryloxy groups, substituted and unsubstituted heterocyclyloxy groups, substituted and unsubstituted heterocyclylalkoxy groups, or substituted and unsubstituted -N(H)(alkyl) groups. In some such embodiments, R^1 is selected from -H, -F, -Cl, $-CH_3$, substituted and unsubstituted piperazinyl groups, $-OCH_3$, substituted and unsubstituted phenyloxy groups, substituted and unsubstituted piperidinyloxy groups, substituted and unsubstituted quinuclidinyloxy groups, substituted and unsubstituted morpholinylalkoxy

groups, or -NCH_3. In other such embodiments, R^1 is selected from 4-methyl-piperazin-1-yl, 4-ethyl-piperazin-1-yl, 4-amino-phenyloxy, 3-dimethylamino-phenyloxy, 3-acetamido-phenyloxy, 4-acetamido-phenyloxy, or 2-(morpholin-4-yl)-ethyloxy. In still other such embodiments, R^1 is –H.

[0229] In some embodiments of the method of inhibiting CHK1 in a subject and/or the method of treating a biological condition mediated by CHK1 activity in a subject, R^2 and R^3 are independently selected from -H, -F, –Cl, -Br, -I, -NO_2, -CN, substituted and unsubstituted straight or branched chain alkyl groups having from 1 to 8 carbon atoms, substituted and unsubstituted cycloalkyl groups, substituted and unsubstituted alkenyl groups having from 1 to 8 carbon atoms, substituted and unsubstituted aryl groups, substituted and unsubstituted aralkyl groups, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted heterocyclylalkyl groups, -OH, substituted and unsubstituted alkoxy groups, substituted and unsubstituted aryloxy groups, substituted and unsubstituted arylalkoxy groups, substituted and unsubstituted heterocyclyloxy groups, substituted and unsubstituted heterocyclylalkoxy groups, -NH_2, substituted and unsubstituted -N(H)(alkyl) groups, substituted and unsubstituted -$N(alkyl)_2$ groups, substituted and unsubstituted -N(H)(aryl) groups, substituted and unsubstituted -N(alkyl)(aryl) groups, substituted and unsubstituted -$N(aryl)_2$ groups, substituted and unsubstituted -N(H)(aralkyl) groups, substituted and unsubstituted -N(alkyl)(aralkyl) groups, substituted and unsubstituted -$N(aralkyl)_2$ groups, substituted and unsubstituted -N(H)(heterocyclyl) groups, substituted and unsubstituted -N(alkyl)(heterocyclyl) groups, substituted and unsubstituted -$N(heterocyclyl)_2$ groups, substituted and unsubstituted -N(H)(heterocyclylalkyl) groups, substituted and unsubstituted -N(alkyl)(heterocyclylalkyl) groups, substituted and unsubstituted -$N(heterocyclylalkyl)_2$ groups, substituted and unsubstituted -N(H)-C(=O)-alkyl groups, substituted and unsubstituted -N(H)-C(=O)-aryl groups, substituted and unsubstituted -N(H)-C(=O)-aralkyl groups, substituted and unsubstituted -N(H)-C(=O)-heterocyclyl groups, substituted and unsubstituted

-N(H)-C(=O)-heterocyclylalkyl groups, substituted and unsubstituted -N(alkyl)-C(=O)-alkyl groups, substituted and unsubstituted -N(alkyl)-C(=O)-aryl groups, substituted and unsubstituted -N(alkyl)-C(=O)-aralkyl groups, substituted and unsubstituted -N(alkyl)-C(=O)-heterocyclyl groups, substituted and unsubstituted -N(alkyl)-C(=O)-heterocyclylalkyl groups, $-N(H)-C(=O)-NH_2$, substituted and unsubstituted -N(H)-C(=O)-N(H)(alkyl) groups, substituted and unsubstituted $-N(H)-C(=O)-N(alkyl)_2$ groups, substituted and unsubstituted -N(H)-C(=O)-N(H)(aryl) groups, substituted and unsubstituted -N(H)-C(=O)-N(alkyl)(aryl) groups, substituted and unsubstituted $-N(H)-C(=O)-N(aryl)_2$ groups, substituted and unsubstituted -N(H)-C(=O)-N(H)(aralkyl) groups, substituted and unsubstituted -N(H)-C(=O)-N(alkyl)(aralkyl) groups, substituted and unsubstituted $-N(H)-C(=O)-N(aralkyl)_2$ groups, substituted and unsubstituted -N(H)-C(=O)-N(H)(heterocyclyl) groups, substituted and unsubstituted -N(H)-C(=O)-N(alkyl)(heterocyclyl) groups, substituted and unsubstituted $-N(H)-C(=O)-N(heterocyclyl)_2$ groups, substituted and unsubstituted -N(H)-C(=O)-N(H)(heterocyclylalkyl) groups, substituted and unsubstituted -N(H)-C(=O)-N(alkyl)(heterocyclylalkyl) groups, substituted and unsubstituted $-N(H)-C(=O)-N(heterocyclylalkyl)_2$ groups, substituted and unsubstituted -C(=O)-alkyl groups, substituted and unsubstituted -C(=O)-aryl groups, substituted and unsubstituted -C(=O)-aralkyl groups, substituted and unsubstituted -C(=O)-heterocyclyl groups, substituted and unsubstituted -C(=O)-heterocyclylalkyl groups, $-C(=O)-NH_2$, substituted and unsubstituted -C(=O)-N(H)(alkyl) groups, substituted and unsubstituted $-C(=O)-N(alkyl)_2$ groups, substituted and unsubstituted -C(=O)-N(H)(aryl) groups, substituted and unsubstituted -C(=O)-N(alkyl)(aryl) groups, substituted and unsubstituted $-C(=O)-N(aryl)_2$ groups, substituted and unsubstituted -C(=O)-N(H)(aralkyl) groups, substituted and unsubstituted -C(=O)-N(alkyl)(aralkyl) groups, substituted and unsubstituted $-C(=O)-N(aralkyl)_2$ groups, $-CO_2H$, substituted and unsubstituted -C(=O)-O-alkyl groups, substituted and unsubstituted

-C(=O)-O-aryl groups, substituted and unsubstituted -C(=O)-O-heterocyclyl groups, or substituted and unsubstituted -C(=O)-O-heterocyclylalkyl groups.

[0230] In some embodiments of the method of inhibiting CHK1 in a subject and/or the method of treating a biological condition mediated by CHK1 activity in a subject, R^2 is selected from -H, -F, -Cl, -Br, -I, $-NO_2$, -CN, substituted and unsubstituted straight or branched chain alkyl groups having from 1 to 8 carbon atoms, substituted and unsubstituted cycloalkyl groups, substituted and unsubstituted alkenyl groups having from 1 to 8 carbon atoms, substituted and unsubstituted aryl groups, substituted and unsubstituted aralkyl groups, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted heterocyclylalkyl groups, -OH, substituted and unsubstituted alkoxy groups, substituted and unsubstituted aryloxy groups, substituted and unsubstituted arylalkoxy groups, $-NH_2$, substituted and unsubstituted -N(H)(alkyl) groups, substituted and unsubstituted $-N(alkyl)_2$ groups, substituted and unsubstituted -N(H)(aryl) groups, substituted and unsubstituted -N(alkyl)(aryl) groups, substituted and unsubstituted $-N(aryl)_2$ groups, substituted and unsubstituted -N(H)(aralkyl) groups, substituted and unsubstituted -N(alkyl)(aralkyl) groups, substituted and unsubstituted $-N(aralkyl)_2$ groups, substituted and unsubstituted -N(H)(heterocyclyl) groups, substituted and unsubstituted -N(alkyl)(heterocyclyl) groups, substituted and unsubstituted $-N(heterocyclyl)_2$ groups, substituted and unsubstituted -N(H)(heterocyclylalkyl) groups, substituted and unsubstituted -N(alkyl)(heterocyclylalkyl) groups, substituted and unsubstituted $-N(heterocyclylalkyl)_2$ groups, substituted and unsubstituted -N(H)-C(=O)-alkyl groups, substituted and unsubstituted -N(H)-C(=O)-aryl groups, substituted and unsubstituted -N(H)-C(=O)-aralkyl groups, substituted and unsubstituted -N(H)-C(=O)-heterocyclyl groups, substituted and unsubstituted -N(H)-C(=O)-heterocyclylalkyl groups, $-N(H)-C(=O)-NH_2$, substituted and unsubstituted -N(H)-C(=O)-N(H)(alkyl) groups, substituted and unsubstituted -N(H)-C(=O)-N(H)(aryl) groups, substituted and unsubstituted -N(H)-C(=O)-N(H)(aralkyl) groups, substituted and unsubstituted

-N(H)-C(=O)-N(H)(heterocyclyl) groups, substituted and unsubstituted -N(H)-C(=O)-N(H)(heterocyclylalkyl) groups, substituted and unsubstituted -C(=O)-alkyl groups, substituted and unsubstituted -C(=O)-aryl groups, substituted and unsubstituted -C(=O)-aralkyl groups, substituted and unsubstituted -C(=O)-heterocyclyl groups, substituted and unsubstituted -C(=O)-heterocyclylalkyl groups, $-C(=O)-NH_2$, substituted and unsubstituted -C(=O)-N(H)(alkyl) groups, substituted and unsubstituted $-C(=O)-N(alkyl)_2$ groups, substituted and unsubstituted -C(=O)-N(H)(aryl) groups, substituted and unsubstituted -C(=O)-N(alkyl)(aryl) groups, substituted and unsubstituted $-C(=O)-N(aryl)_2$ groups, substituted and unsubstituted -C(=O)-N(H)(aralkyl) groups, substituted and unsubstituted -C(=O)-N(alkyl)(aralkyl) groups, substituted and unsubstituted $-C(=O)-N(aralkyl)_2$ groups, $-CO_2H$, or substituted and unsubstituted -C(=O)-O-alkyl groups.

[0231] In some embodiments of the method of inhibiting CHK1 in a subject and/or the method of treating a biological condition mediated by CHK1 activity in a subject, R^2 is selected from 2-substituted phenyl groups, 3-substituted phenyl groups, 4-substituted phenyl groups, 2,4-disubstituted phenyl groups, 2,6-disubstituted phenyl groups, substituted or unsubstituted pyrrole groups, substituted and unsubstituted thiophene groups, substituted and unsubstituted tetrahydropyridine groups, or substituted and unsubstituted pyridine groups.

[0232] In some embodiments of the method of inhibiting CHK1 in a subject and/or the method of treating a biological condition mediated by CHK1 activity in a subject, R^2 is a substituted and unsubstituted aryl group selected from phenyl, 2-chlorophenyl, 2-ethylphenyl, 2-hydroxyphenyl, 2-methoxyphenyl, 2-methylphenyl, 2-trifluoromethylphenyl, 3-acetylphenyl, 3-acetamidophenyl, 3-aminophenyl, 3-methoxycarbonylphenyl, 3-carboxyphenyl, 3-hydroxyphenyl, 3-methoxyphenyl, 3-nitrophenyl, 3-trifluoromethylphenyl, 4-acetylphenyl, 4-methoxycarbonylphenyl, 4-carboxamidophenyl, 4-carboxyphenyl, 4-chlorophenyl, 4-cyanophenyl, 4-dimethylaminophenyl, 4-ethylphenyl, 4-formylphenyl, 4-hydroxyphenyl, 4-

methoxyphenyl, 4-methylthiophenyl, 4-nitrophenyl, 4-(methylsulfonyl)-phenyl, 2,4-difluorophenyl, 2-fluoro-4-chlorophenyl, 2,4-dichlorophenyl, 2-amino-4-methoxycarbonylphenyl, 2-amino-4-carboxyphenyl, or 2,6-difluorophenyl. In some such embodiments, R^2 is selected from 2-hydroxyphenyl, 2-methoxyphenyl, 3-hydroxyphenyl, 3-methoxyphenyl, 3-aminophenyl, 4-cyanophenyl, 4-hydroxyphenyl, and 4-methoxyphenyl.

[0233] In some embodiments of the method of inhibiting CHK1 in a subject and/or the method of treating a biological condition mediated by CHK1 activity in a subject, R^2 is a substituted and unsubstituted heterocyclyl or heterocyclylalkyl group selected from 1-*tert*-butyloxycarbonyl-pyrrol-2-yl, thiophen-2-yl, thiophen-3-yl, 1,2,5,6-tetrahydropyridin-4-yl, 4-(*tert*-butyloxycarbonyl)-1,2,5,6-tetrahydropyridin-4-yl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, benzo[1,3]dioxol-5-yl, or benzo[b]thiophen-2-yl. In some such embodiments, R^2 is selected from thiophen-2-yl or thiophen-3-yl. In other such embodiments, R^2 is selected from pyridin-2-yl, pyridin-3-yl, or pyridin-4-yl.

[0234] In some embodiments of the method of inhibiting CHK1 in a subject and/or the method of treating a biological condition mediated by CHK1 activity in a subject, R^2 is selected from–H, -Cl, –F, -Br, -I, $-NO_2$, -CN, $–CH_3$, -OH, $-OCH_3$, $-CO_2H$, or $-CO_2CH_3$. In some such embodiments, R^2 is –Cl.

[0235] In some embodiments of the method of inhibiting CHK1 in a subject and/or the method of treating a biological condition mediated by CHK1 activity in a subject, R^2 is selected from $-NH_2$, substituted and unsubstituted -N(H)(alkyl) groups, substituted and unsubstituted $-N(alkyl)_2$ groups, substituted and unsubstituted -N(H)(aryl) groups, substituted and unsubstituted -N(alkyl)(aryl) groups, substituted and unsubstituted $-N(aryl)_2$ groups, substituted and unsubstituted -N(H)(aralkyl) groups, substituted and unsubstituted -N(alkyl)(aralkyl) groups, substituted and unsubstituted $-N(aralkyl)_2$ groups, substituted and unsubstituted -N(H)(heterocyclyl) groups, substituted and unsubstituted -N(alkyl)(heterocyclyl) groups, substituted and

unsubstituted -N(heterocyclyl)$_2$ groups, substituted and unsubstituted -N(H)(heterocyclylalkyl) groups, substituted and unsubstituted -N(alkyl)(heterocyclylalkyl) groups, substituted and unsubstituted -N(heterocyclylalkyl)$_2$ groups, substituted and unsubstituted -N(H)-C(=O)-alkyl groups, substituted and unsubstituted -N(H)-C(=O)-aryl groups, substituted and unsubstituted -N(H)-C(=O)-aralkyl groups, substituted and unsubstituted -N(H)-C(=O)-heterocyclyl groups, substituted and unsubstituted -N(H)-C(=O)-heterocyclylalkyl groups, -N(H)-C(=O)-NH_2, substituted and unsubstituted -N(H)-C(=O)-N(H)(alkyl) groups, substituted and unsubstituted -N(H)-C(=O)-N(H)(aryl) groups, substituted and unsubstituted -N(H)-C(=O)-N(H)(aralkyl) groups, substituted and unsubstituted -N(H)-C(=O)-N(H)(heterocyclyl) groups, substituted and unsubstituted -N(H)-C(=O)-N(H)(heterocyclylalkyl) groups, substituted and unsubstituted -C(=O)-N(H)(alkyl) groups, substituted and unsubstituted -C(=O)-N(H)(aryl) groups, or substituted and unsubstituted -C(=O)-N(H)(aralkyl) groups.

[0236] In some embodiments of the method of inhibiting CHK1 in a subject and/or the method of treating a biological condition mediated by CHK1 activity in a subject, R^2 is selected from -NH_2, substituted and unsubstituted -N(H)(alkyl) groups, substituted and unsubstituted -N(alkyl)$_2$ groups, substituted and unsubstituted -N(H)(aralkyl) groups, substituted and unsubstituted -N(H)(heterocyclyl) groups, substituted and unsubstituted -N(alkyl)(heterocyclyl) groups, substituted and unsubstituted -N(H)(heterocyclylalkyl) groups, or substituted and unsubstituted -N(alkyl)(heterocyclylalkyl) groups. In some such embodiments, R^2 is selected from -NH_2, -N(H)(methyl), -N(methyl)$_2$, -N(H)(2-methyl-propyl), -N(H)(2,2-dimethyl-propyl), -N(H)(2-methyl-butyl), -N(H)(heptyl), -N(H)(cyclohexylmethyl), -N(methyl)(isobutyl), -N(methyl)(cyclohexylmethyl), -N(H)(benzyl), -N(H)(piperidin-4-yl),-N(H)(pyrrolidin-2-ylmethyl), -N(H)(2-dimethylaminomethyl-furan-5-ylmethyl),-N(H)(3-methyl-thiophen-2-ylmethyl), -N(H)(3-phenyloxy-thiophen-2-ylmethyl), -N(H)(2-ethyl-5-methyl-imidazol-4-

ylmethyl), -N(H)(5-methyl-isoxazol-3-ylmethyl), -N(H)(thiazol-2-ylmethyl), -N(H)(pyrazin-2-ylmethyl), or -N(methyl)(1-methyl-piperidin-4-yl).

[0237] In some embodiments of the method of inhibiting CHK1 in a subject and/or the method of treating a biological condition mediated by CHK1 activity in a subject, R^2 is selected from substituted and unsubstituted -N(H)-C(=O)-alkyl groups, wherein the alkyl moiety is a straight or branched chain alkyl having from 1 to 8 carbon atoms, substituted and unsubstituted -N(H)-C(=O)-cycloalkyl groups, substituted and unsubstituted -N(H)-C(=O)-aryl groups, substituted and unsubstituted -N(H)-C(=O)-aralkyl groups, substituted and unsubstituted -N(H)-C(=O)-heterocyclyl groups, substituted and unsubstituted -N(H)-C(=O)-heterocyclylalkyl groups, or substituted and unsubstituted -C(=O)-N(H)(aralkyl) groups. In some such embodiments, R^2 is selected from substituted and unsubstituted -N(H)-C(=O)-methyl groups, substituted and unsubstituted -N(H)-C(=O)-cyclohexyl groups, substituted and unsubstituted -N(H)-C(=O)-phenyl groups, substituted and unsubstituted -N(H)-C(=O)-phenylalkyl groups, substituted and unsubstituted -N(H)-C(=O)-furan groups, substituted and unsubstituted -N(H)-C(=O)-thiophenylalkyl groups. In other such embodiments, R^2 is selected from -N(H)-C(=O)-methyl, -N(H)-C(=O)-propyl, -N(H)-C(=O)-isopropyl, -N(H)-C(=O)-benzyloxymethyl, N(H)-C(=O)-benzylaminomethyl, -N(H)-C(=O)-cyclohexyl groups, -N(H)-C(=O)-4-ethyl-phenyl, -N(H)-C(=O)-4-cyano-phenyl, -N(H)-C(=O)-2-phenyl-ethyl groups, -N(H)-C(=O)-furan-2-yl, -N(H)-C(=O)-thiophen-2-ylmethyl groups, or -N(H)-C(=O)-pyrazin-2-yl.

[0238] In some embodiments of the method of inhibiting CHK1 in a subject and/or the method of treating a biological condition mediated by CHK1 activity in a subject, R^2 is selected from -N(H)-C(=O)-NH_2, substituted and unsubstituted -N(H)-C(=O)-N(H)(alkyl) groups, substituted and unsubstituted -N(H)-C(=O)-N(H)(aryl) groups, substituted and unsubstituted -N(H)-C(=O)-N(H)(aralkyl) groups, substituted and unsubstituted

-N(H)-C(=O)-N(H)(heterocyclyl) groups, substituted and unsubstituted -N(H)-C(=O)-N(H)(heterocyclylalkyl) groups. In some such embodiments, R^2 is selected from substituted and unsubstituted -N(H)-C(=O)-N(H)(alkyl) groups, wherein the alkyl moiety is a straight or branched chain alkyl group having from 1 to 12 carbons, substituted and unsubstituted -N(H)-C(=O)-N(H)(phenyl) groups, or substituted and unsubstituted -N(H)-C(=O)-N(H)(phenylalkyl) groups. In other such embodiments, R^2 is selected from -N(H)-C(=O)-N(H)(isopropyl), -N(H)-C(=O)-N(H)(heptyl), -N(H)-C(=O)-N(H)(phenyl), -N(H)-C(=O)-N(H)(2-ethoxyphenyl), -N(H)-C(=O)-N(H)(2-methylthiophenyl), -N(H)-C(=O)-N(H)(3-trifluoromethylphenyl), -N(H)-C(=O)-N(H)(3,5-dimethylphenyl), or -N(H)-C(=O)-N(H)(benzyl).

[0239] In some embodiments of the method of inhibiting CHK1 in a subject and/or the method of treating a biological condition mediated by CHK1 activity in a subject, R^3 is selected from -H, -F, -Cl, -Br, -I, -CN, $-NO_2$, substituted and unsubstituted straight or branched chain alkyl groups having from 1 to 8 carbon atoms, substituted and unsubstituted cycloalkyl groups, substituted and unsubstituted aryl groups, substituted and unsubstituted aralkyl groups, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted heterocyclylalkyl groups, -OH, substituted and unsubstituted alkoxy groups, substituted and unsubstituted heterocyclyloxy groups, substituted and unsubstituted heterocyclylalkoxy groups, $-NH_2$, substituted and unsubstituted -N(H)(alkyl) groups, substituted and unsubstituted $-N(alkyl)_2$ groups, substituted and unsubstituted -N(H)(heterocyclyl) groups, substituted and unsubstituted -N(alkyl)(heterocyclyl) groups, substituted and unsubstituted $-N(heterocyclyl)_2$ groups, substituted and unsubstituted -N(H)(heterocyclylalkyl) groups, substituted and unsubstituted -N(alkyl)(heterocyclylalkyl) groups, substituted and unsubstituted $-N(heterocyclylalkyl)_2$ groups, substituted and unsubstituted -C(=O)-alkyl groups, substituted and unsubstituted -C(=O)-heterocyclyl groups, substituted and unsubstituted -C(=O)-heterocyclylalkyl groups,

-C(=O)-NH_2, substituted and unsubstituted -C(=O)-N(H)(alkyl) groups, substituted and unsubstituted -C(=O)-N(alkyl)$_2$ groups, -CO_2H, or substituted and unsubstituted -C(=O)-O-alkyl groups.

[0240] In some embodiments of the method of inhibiting CHK1 in a subject and/or the method of treating a biological condition mediated by CHK1 activity in a subject, R^3 is selected from -H, -F, -Cl, -Br, -I, -CN, -NO_2, substituted and unsubstituted straight or branched chain alkyl groups having from 1 to 8 carbon atoms, -OH, substituted and unsubstituted alkoxy groups, substituted and unsubstituted heterocyclyloxy groups, or substituted and unsubstituted heterocyclylalkoxy groups. In some such embodiments, R^3 is selected from -H, -F, -Cl, -Br, -CN, -CH_3, -OH, -OCH_3, 2-dimethylamino-ethoxy, pyrrolidin-2-ylmethoxy, or 2-oxo-pyrrolidin-1-ylethoxy.

[0241] In some embodiments of the method of inhibiting CHK1 in a subject and/or the method of treating a biological condition mediated by CHK1 activity in a subject, R^3 is selected from substituted and unsubstituted aryl groups, substituted and unsubstituted aralkyl groups, substituted and unsubstituted heterocyclyl groups, or substituted and unsubstituted heterocyclylalkyl groups.

[0242] In some embodiments of the method of inhibiting CHK1 in a subject and/or the method of treating a biological condition mediated by CHK1 activity in a subject, R^3 is selected from 2-substituted phenyl groups, 3-substituted phenyl groups, 4-substituted phenyl groups, 2,4-disubstituted phenyl groups, substituted or unsubstituted pyrrole groups, substituted and unsubstituted thiophene groups, substituted and unsubstituted piperidine groups, substituted and unsubstituted piperazine groups, substituted and unsubstituted morpholine groups, substituted and unsubstituted azepane groups, substituted and unsubstituted pyrrole groups, substituted and unsubstituted imidazole groups, substituted and unsubstituted pyridine groups, or substituted and unsubstituted benzodioxole groups.

[0243] In some embodiments of the method of inhibiting CHK1 in a subject and/or the method of treating a biological condition mediated by CHK1 activity in a subject, R^3 is a substituted and unsubstituted aryl group selected from 2-methoxy-phenyl, 2-methylphenyl, 2-trifluoromethyl-phenyl, 3-acetylphenyl, 3-acetamidophenyl, 3-methoxycarbonyl-phenyl, 3-carboxyphenyl, 4-acetylphenyl, 4-carboxamidophenyl, 4-carboxyphenyl, 4-cyanophenyl, 4-formylphenyl, 4-methoxycarbonyl-phenyl, 4-methylsulfonyl-phenyl, 2,4-dichlorophenyl, 2-amino-4-methoxycarbonylphenyl, or 2-amino-4-methoxycarbonyl-phenyl.

[0244] In some embodiments of the method of inhibiting CHK1 in a subject and/or the method of treating a biological condition mediated by CHK1 activity in a subject, R^3 is a substituted and unsubstituted heterocyclyl group selected from pyrrolidin-1-yl, 3-dimethylamino-pyrrolidin-1-yl, 3-acetamido-pyrrolidin-1-yl, 3-hydroxy-pyrrolidin-1-yl, 3-methylsulfonyl-pyrrolidin-1-yl, 3-trifluoroacetamido-pyrrolidin-1-yl, piperidin-1-yl, 2-hydroxy-piperidin-1 -yl, 3-carboxamide-piperidin-1-yl, 3-carboxy-piperidin-1-yl, 3-methoxycarbonyl-piperidin-1-yl, 3-(pyridin-4-yl)-pyrrolidin-3-yl, 4-carboxamido-piperidin-1-yl, 4-carboxy-piperidin-1-yl, 4-ethoxycarbonyl-piperidin-1-yl, 4-methyl-piperazin-1-yl, 4-(pyridin-2-ylmethyl)-piperazin-1-yl, morpholin-4-yl, azepan-1-yl, pyrrol-1-yl, 3-acetyl-pyrrol-1-yl, 3-carboxy-pyrrol-1-yl, imidazol-1-yl, 2-methyl-imidazol-1-yl, 2-ethyl-imidazol-1-yl, 2-isopropyl-imidazol-1-yl, or benzo[1,3]dioxol-5-yl.

[0245] In some embodiments of the method of inhibiting CHK1 in a subject and/or the method of treating a biological condition mediated by CHK1 activity in a subject, R^3 is selected from $-NH_2$, substituted and unsubstituted -N(H)(alkyl) groups, substituted and unsubstituted $-N(alkyl)_2$ groups, substituted and unsubstituted -N(H)(heterocyclyl) groups, substituted and unsubstituted -N(alkyl)(heterocyclyl) groups, substituted and unsubstituted $-N(heterocyclyl)_2$ groups, substituted and unsubstituted -N(H)(heterocyclylalkyl) groups, substituted and unsubstituted -N(alkyl)(heterocyclylalkyl) groups, or substituted and unsubstituted $-N(heterocyclylalkyl)_2$ groups.

[0246] In some embodiments of the method of inhibiting CHK1 in a subject and/or the method of treating a biological condition mediated by CHK1 activity in a subject, R^3 is selected from $-NH_2$, -N(H)(methyl), -N(H)(2-methylpropyl), -N(H)(2-acetamidoethyl), -N(H)(2-aminoethyl), -N(H)(2-cyanoethyl), -N(H)(2-diethylamino-ethyl), -N(H)(2-dimethylamino-ethyl), -N(H)(2-hydroxyethyl), -N(H)(2-methoxyethyl), -N(H)(2-thioethyl), -N(H)(3-dimethylaminopropyl), -N(H)(3-hydroxypropyl), -N(H)(3-methoxypropyl), -N(H)(2-methylsulfonyl-ethyl), -N(H)(cyclopropyl), -N(H)(4-hydroxy-cyclohexyl), -N(H)(1-hydroxy-cyclohexylmethyl), $-N(methyl)_2$, $-N(ethyl)_2$, -N(methyl)(ethyl), -N(methyl)(2-dimethylamino-ethyl), -N(H)(morpholin-4-ylethyl), -N(H)(pyrrolidin-1-ylethyl), -N(H)(1-methyl-pyrrolidin-2-ylethyl), -N(H)(pyrrolidin-1-ylpropyl), -N(H)(2-oxo-pyrrolidin-1-ylpropyl), -N(H)(piperidin-3-ylmethyl), -N(H)(piperidin-1-ylethyl), -N(H)(pyridin-2-ylmethyl), -N(H)(pyridin-2-ylethyl), -N(H)(pyridin-3-ylethyl), or -N(H)(pyridin-4-ylethyl).

[0247] In some embodiments of the method of inhibiting CHK1 in a subject and/or the method of treating a biological condition mediated by CHK1 activity in a subject, R^3 is selected from substituted and unsubstituted -C(=O)-heterocyclyl groups, $-C(=O)-NH_2$, substituted and unsubstituted $-C(=O)-N(alkyl)_2$ groups, or $-CO_2H$. In some such embodiments, R^3 is selected from -C(=O)-morpholin-4-yl, $-C(=O)-NH_2$, $-C(=O)-N(methyl)_2$, or $-CO_2H$.

[0248] In some embodiments of the method of inhibiting CHK1 in a subject and/or the method of treating a biological condition mediated by CHK1 activity in a subject, R^4 is selected from –H or $–CH_3$. In some such embodiments, R^4 is –H.

[0249] In some embodiments of the method of inhibiting CHK1 in a subject and/or the method of treating a biological condition mediated by CHK1 activity in a subject, R^5 and R^8 are independently selected from –H or saturated heterocyclyl groups, or are absent. In some such embodiments, A and D are both carbon, R^5 is –H, and R^8 is –H.

[0250] In some embodiments of the method of inhibiting CHK1 in a subject and/or the method of treating a biological condition mediated by CHK1 activity in a subject, R^6 and R^7 are independently selected from -H, -F, -Cl, -Br, -I, substituted and unsubstituted alkyl groups having from 1 to 8 carbon atoms, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted heterocyclylalkyl groups, $-S(=O)_2-NH_2$, substituted and unsubstituted $-S(=O)_2-N(H)(alkyl)$ groups, substituted and unsubstituted $-S(=O)_2-N(alkyl)_2$ groups, -OH, substituted and unsubstituted alkoxy groups, substituted and unsubstituted aryloxy groups, substituted and unsubstituted arylalkoxy groups, substituted and unsubstituted heterocyclyloxy groups, substituted and unsubstituted heterocyclylalkoxy groups, $-NH_2$, substituted and unsubstituted -N(H)(alkyl) groups, substituted and unsubstituted $-N(alkyl)_2$ groups, substituted and unsubstituted -N(H)(heterocyclyl) groups, substituted and unsubstituted -N(alkyl)(heterocyclyl) groups, substituted and unsubstituted -N(H)(heterocyclylalkyl) groups, substituted and unsubstituted -N(alkyl)(heterocyclylalkyl) groups, substituted and unsubstituted -C(=O)-alkyl groups, substituted and unsubstituted -C(=O)-heterocyclyl groups, substituted and unsubstituted -C(=O)-heterocyclylalkyl groups, $-C(=O)-NH_2$, substituted and unsubstituted -C(=O)-N(H)(alkyl) groups, substituted and unsubstituted $-C(=O)-N(alkyl)_2$ groups, substituted and unsubstituted -C(=O)-N(H)(heterocyclyl) groups, substituted and unsubstituted -C(=O)-N(alkyl)(heterocyclyl) groups, substituted and unsubstituted -C(=O)-N(H)(heterocyclylalkyl) groups, substituted and unsubstituted -C(=O)-N(alkyl)(heterocyclylalkyl) groups, $-CO_2H$, substituted and unsubstituted -C(=O)-O-alkyl groups, substituted and unsubstituted -C(=O)-O-heterocyclyl groups, or substituted and unsubstituted -C(=O)-O-heterocyclylalkyl groups; or R^6 may be absent if B is nitrogen; or R^7 may be absent if C is nitrogen. In some such embodiments, R^6 and R^7 are independently selected from -H, -F, -Cl, -Br, -I, or $-CH_3$.

[0251] In some embodiments of the method of inhibiting CHK1 in a subject and/or the method of treating a biological condition mediated by CHK1

activity in a subject, R^6 and R^7 are independently selected from substituted and unsubstituted heterocyclyl groups or substituted and unsubstituted heterocyclylalkyl groups; or R^6 may be absent if B is nitrogen; or R^7 may be absent if C is nitrogen.

[0252] In some embodiments of the method of inhibiting CHK1 in a subject and/or the method of treating a biological condition mediated by CHK1 activity in a subject, R^6 and R^7 are independently selected from substituted and unsubstituted pyrrolidinyl groups, substituted and unsubstituted piperidinylalkyl groups, substituted and unsubstituted piperazinyl groups, substituted and unsubstituted morpholinyl groups, substituted and unsubstituted thiomorpholinyl groups, substituted and unsubstituted dizaepanyl groups, substituted and unsubstituted oxazepanyl groups, or pyridinylalkyl groups.

[0253] In some embodiments of the method of inhibiting CHK1 in a subject and/or the method of treating a biological condition mediated by CHK1 activity in a subject, R^6 and R^7 are independently selected from 3-(acetyl-methyl-amino)-pyrrolidin-1-yl, 3-diethylamino-pyrrolidin-1-yl, 3-dimethylamino-pyrrolidin-1-yl, 3-(N-oxido-N,N-dimethylamino)-pyrrolidin-1-yl, 3-(pyrrolidin-1-yl)-pyrrolidin-1-yl, 2-(pyrrolidin-1-ylmethyl)-pyrrolidin-1-yl, 4-(piperidin-1-yl)-piperidin-1-yl, 1-acetyl-piperazin-4-yl, 1-carboxymethyl-piperazin-4-yl, 1-methyl-piperazin-4-yl, 1-ethyl-piperazin-4-yl, 1-cyclohexyl-piperazin-4-yl, 1-isopropyl-piperazin-4-yl, morpholin-4-yl, 2-dimethylamino-morpholin-4-yl, 2,6-dimethyl-morpholin-4-yl, 2-dimethylamino-5-methyl-morpholin-4-yl, thiomorpholin-4-yl, thiomorpholin-4-yl 1-oxide 1-methyl-[1,4]dizaepan-1-yl, 2-dimethylaminomethyl-[1,4]oxazepan-4-yl, or pyridin-4-ylmethyl.

[0254] In some embodiments of the method of inhibiting CHK1 in a subject and/or the method of treating a biological condition mediated by CHK1 activity in a subject, R^6 and R^7 are independently selected from -OH, substituted and unsubstituted alkoxy groups, substituted and unsubstituted aryloxy groups, substituted and unsubstituted arylalkoxy groups, substituted

and unsubstituted heterocyclyloxy groups, substituted and unsubstituted heterocyclylalkoxy groups, $-NH_2$, substituted and unsubstituted -N(H)(alkyl) groups, substituted and unsubstituted $-N(alkyl)_2$ groups, substituted and unsubstituted -N(H)(heterocyclyl) groups, substituted and unsubstituted -N(alkyl)(heterocyclyl) groups, substituted and unsubstituted -N(H)(heterocyclylalkyl) groups, or substituted and unsubstituted -N(alkyl)(heterocyclylalkyl) groups; or R^6 may be absent if B is nitrogen; or R^7 may be absent if C is nitrogen.

[0255] In some embodiments of the method of inhibiting CHK1 in a subject and/or the method of treating a biological condition mediated by CHK1 activity in a subject, R^6 and R^7 are independently selected from -OH, substituted and unsubstituted alkoxyalkoxy groups, substituted and unsubstituted pyrrolidinyloxy groups, substituted and unsubstituted tetrahydrofuranyloxy groups, substituted and unsubstituted pyrrolidinylalkoxy groups, substituted and unsubstituted morpholinylalkoxy groups, substituted and unsubstituted pyridinyloxy groups, $-NH_2$, substituted and unsubstituted -N(H)(pyrrolidinyl) groups, substituted and unsubstituted -N(H)(piperidinyl) groups, substituted and unsubstituted -N(H)(piperidinylalkyl) groups, substituted and unsubstituted -N(H)(pyridinylalkyl) groups, or substituted and unsubstituted -N(alkyl)(piperidinyl) groups.

[0256] In some embodiments of the method of inhibiting CHK1 in a subject and/or the method of treating a biological condition mediated by CHK1 activity in a subject, R^6 and R^7 are independently selected from -OH, methyloxy, 2-methyloxy-ethyloxy, 4-acetamido-phenyloxy, 1-methyl-pyrrolidin-3-yloxy, pyridin-3-yloxy, 3-(pyrrolidin-1-yl)-propyloxy, tetrahydrofuran-2-ylmethyloxy, 2-(morpholin-4-yl)-ethyloxy, 3-(morpholin-4-yl)-propyloxy, $-NH_2$, -N(H)(2-(methyloxymethyl)-pyrrolidin-4-yl), -N(H)(piperidin-3-yl), -N(H)(1,3-dimethyl-piperidin-4-yl), -N(H)(1-(ethoxycarbonyl)-piperidin-4-yl), -N(methyl)(1-methylpiperidin-1-yl), -N(H)(piperidin-1-ylethyl), or -N(H)(pyridin-2-ylmethyl). In some such embodiments, R^6 and R^7 are independently selected from –H or -N(methyl)(1-methylpiperidin-1-yl).

[0257] In some embodiments of the method of inhibiting CHK1 in a subject and/or the method of treating a biological condition mediated by CHK1 activity in a subject, R^6 and R^7 are independently selected from $-S(=O)_2-NH_2$, substituted and unsubstituted $-S(=O)_2-N(H)(alkyl)$ groups, substituted and unsubstituted $-S(=O)_2-N(alkyl)_2$ groups, substituted and unsubstituted -C(=O)-alkyl groups, substituted and unsubstituted -C(=O)-heterocyclyl groups, substituted and unsubstituted -C(=O)-heterocyclylalkyl groups, $-C(=O)-NH_2$, substituted and unsubstituted $-C(=O)-N(H)(alkyl)$ groups, substituted and unsubstituted $-C(=O)-N(alkyl)_2$ groups, substituted and unsubstituted -C(=O)-N(H)(heterocyclyl) groups, substituted and unsubstituted -C(=O)-N(alkyl)(heterocyclyl) groups, substituted and unsubstituted -C(=O)-N(H)(heterocyclylalkyl) groups, substituted and unsubstituted -C(=O)-N(alkyl)(heterocyclylalkyl) groups, or $-CO_2H$; or R^6 may be absent if B is nitrogen; or R^7 may be absent if C is nitrogen.

[0258] In some embodiments of the method of inhibiting CHK1 in a subject and/or the method of treating a biological condition mediated by CHK1 activity in a subject, R^6 and R^7 are independently selected from substituted and unsubstituted $-S(=O)_2-N(alkyl)_2$ groups, substituted and unsubstituted -C(=O)-pyrrolidinyl groups, substituted and unsubstituted -C(=O)-piperidinyl groups, substituted and unsubstituted -C(=O)-pyrazinyl groups, substituted and unsubstituted -C(=O)-diazabicycloheptanyl groups, $-C(=O)-NH_2$, substituted and unsubstituted -C(=O)-N(H)(alkyl) groups, substituted and unsubstituted $-C(=O)-N(alkyl)_2$ groups, substituted and unsubstituted -C(=O)-N(H)(piperidinyl) groups, substituted and unsubstituted -C(=O)-N(H)(pyridinyl) groups, substituted and unsubstituted -C(=O)-N(H)(pyrrolidinylalkyl) groups, substituted and unsubstituted -C(=O)-N(H)(piperidinylalkyl) groups, or substituted and unsubstituted -C(=O)-N(alkyl)(piperidinyl).

[0259] In some embodiments of the method of inhibiting CHK1 in a subject and/or the method of treating a biological condition mediated by CHK1 activity in a subject, R^6 and R^7 are independently selected from

-$S(=O)_2$-N(methyl)$_2$, -C(=O)-3-amino-pyrrolidin-1-yl, -C(=O)-3-(dimethylcarbamoyl)-pyrrolidin-1-yl, -C(=O)-3-hydroxy-pyrrolidin-1-yl, -C(=O)-4-dimethylamino-piperidin-1-yl, -C(=O)-3-hydroxy-piperidin-1-yl, -C(=O)-4-(piperidin-1-yl)-piperidin-1-yl, -C(=O)-pyridin-3-yl, -C(=O)-piperazin-1-yl, -C(=O)-1-acetyl-piperazin-4-yl, -C(=O)-1-cyclohexyl-piperazin-4-yl, -C(=O)-1-(ethoxycarbonylmethyl)-piperazin-4-yl, -C(=O)-1-hydroxyethyl-piperazin-4-yl, -C(=O)-1-isopropyl-piperazin-4-yl, -C(=O)-1-methyl-piperazin-4-yl, -C(=O)-2-methyl-piperazin-4-yl, -C(=O)-morpholin-4-yl, -C(=O)-2-methyl-2,5-diaza-bicyclo[2.2.1]heptan-5-yl, -C(=O)-N(methyl)(2-dimethylamino-ethyl), -C(=O)-N(ethyl)(2-dimethylamino-ethyl), -C(=O)-N(H)(piperidin-4-yl), -C(=O)-N(H)(piperidin-3-yl), -C(=O)-N(H)(1-ethoxycarbonyl-3-methoxy-piperidin-4-yl), -C(=O)-N(H)(1-aza-bicyclo[2.2.1]heptan-3-yl), -C(=O)-N(H)(2-(pyrrolidin-1-yl)-ethyl), -C(=O)-N(H)(2-(piperidin-1-yl)-ethyl), -C(=O)-N(methyl)(1-methyl-pyrrolidin-3-yl), or -C(=O)-N(methyl)(1-methyl-piperidin-4-yl).

[0260] In some embodiments of the method of inhibiting CHK1 in a subject and/or the method of treating a biological condition mediated by CHK1 activity in a subject, B and C are both carbon and R^6 is –H and R^7 is –H.

[0261] In some embodiments of the method of inhibiting CHK1 in a subject and/or the method of treating a biological condition mediated by CHK1 activity in a subject, A, B, C, and D are all carbon, and R^5, R^6, R^7, and R^8 are all -H.

[0262] In some embodiments of the method of inhibiting CHK1 in a subject and/or the method of treating a biological condition mediated by CHK1 activity in a subject, A, B, C, and D are all carbon, and R^4, R^5, R^6, R^7, R^8, and R^{10} are all –H.

[0263] In some embodiments of the method of inhibiting CHK1 in a subject and/or the method of treating a biological condition mediated by CHK1 activity in a subject, the IC_{50} value of the compound is less than or equal to 10

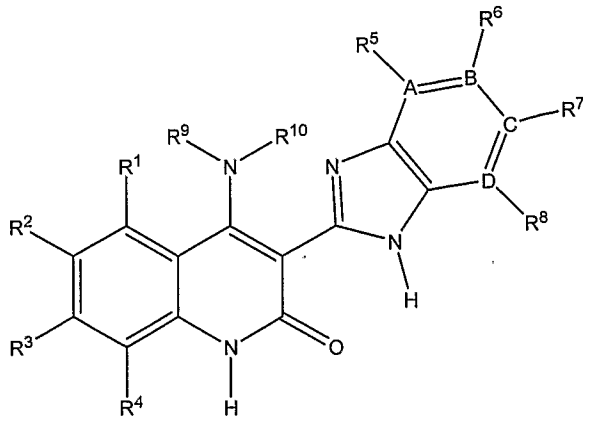
μM with respect to CHK1. In other such embodiments, the IC_{50} value is less than or equal to 1 μM, is less than or equal to 0.1 μM, is less than or equal to 0.050 μM, is less than or equal to 0.030 μM, is less than or equal to 0.025 μM, is less than or equal to 0.010 μM, or is less than or equal to 0.001 μM.

[0264] In some embodiments of the method of inhibiting CHK1 in a subject and/or the method of treating a biological condition mediated by CHK1 activity in a subject, the subject is a mammal or is a human.

[0265] In some embodiments of the method of treating a biological condition mediated by CHK1 activity in a subject, the biological condition is cancer.

Methods Relating to Ribosomal S6 Kinase 2

[0266] In some embodiments of the method of inhibiting a serine/threonine kinase in a subject and/or the method of treating a biological condition mediated by serine/threonine kinase activity in a subject using a compound of Structure I, a tautomer of the compound, a pharmaceutically acceptable salt of the compound, a pharmaceutically acceptable salt of the tautomer, or mixtures thereof, the serine/threonine kinase is Rsk2. In some such methods, the Rsk2 is inhibited in the subject after administration. In methods of inhibiting Rsk2, Structure I has the following formula:



I

where:

A, B, C, and D are independently selected from carbon or nitrogen;

R^1 is selected from -H, -F, -Cl, -Br, -I, -CN, -NO_2, substituted and unsubstituted alkyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted alkenyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted heterocyclylalkyl groups, -OH, substituted and unsubstituted alkoxy groups, substituted and unsubstituted heterocyclyloxy groups, substituted and unsubstituted heterocyclylalkoxy groups, -NH_2, substituted and unsubstituted -N(H)(alkyl) groups, substituted and unsubstituted -N(H)(heterocyclyl) groups, substituted and unsubstituted -N(H)(heterocyclylalkyl) groups, substituted and unsubstituted -N(H)-C(=O)-alkyl groups, substituted and unsubstituted -N(H)-C(=O)-heterocyclyl groups, substituted and unsubstituted -N(H)-C(=O)-heterocyclylalkyl groups, substituted and unsubstituted -C(=O)-alkyl groups, substituted and unsubstituted -C(=O)-heterocyclyl groups, substituted and unsubstituted -C(=O)-heterocyclylalkyl groups, -C(=O)-NH_2, substituted and unsubstituted -C(=O)-N(H)(alkyl) groups, substituted and

unsubstituted -C(=O)-N(alkyl)$_2$ groups, substituted and unsubstituted -C(=O)-N(H)(heterocyclyl) groups, -C(=O)-N(H)(heterocyclylalkyl) groups, -CO_2H, substituted and unsubstituted -C(=O)-O-alkyl groups, substituted and unsubstituted -C(=O)-O-heterocyclyl groups, or substituted and unsubstituted -C(=O)-O-heterocyclylalkyl groups;

R^2 and R^3 are independently selected from -H, -F, -Cl, -Br, -I, -CN, -NO_2, substituted and unsubstituted alkyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted alkenyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted aryl groups, substituted and unsubstituted aralkyl groups, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted heterocyclylalkyl groups, -SH, substituted and unsubstituted -S-alkyl groups, substituted and unsubstituted -S-aryl groups, substituted and unsubstituted -S-aralkyl groups, -OH, substituted and unsubstituted alkoxy groups, substituted and unsubstituted heterocyclyloxy groups, substituted and unsubstituted heterocyclylalkoxy groups, -NH_2, substituted and unsubstituted -N(H)(alkyl) groups, substituted and unsubstituted -N(alkyl)$_2$ groups, substituted and unsubstituted -N(H)(aryl) groups, substituted and unsubstituted -N(H)(aralkyl) groups, substituted and unsubstituted -N(H)(heterocyclyl) groups, substituted and unsubstituted -N(H)(heterocyclylalkyl) groups, substituted and unsubstituted -N(H)-C(=O)-alkyl groups, substituted and unsubstituted -N(H)-C(=O)-aryl groups, substituted and unsubstituted -N(H)-C(=O)-aralkyl groups, substituted and unsubstituted -N(H)-C(=O)-heterocyclyl groups, substituted and unsubstituted -N(H)-C(=O)-heterocyclylalkyl groups, substituted and unsubstituted -C(=O)-alkyl groups, substituted and unsubstituted -C(=O)-aryl groups, substituted and unsubstituted -C(=O)-aralkyl

groups, substituted and unsubstituted -C(=O)-heterocyclyl groups, substituted and unsubstituted -C(=O)-heterocyclylalkyl groups, -C(=O)-NH_2, substituted and unsubstituted -C(=O)-N(H)(alkyl) groups, substituted and unsubstituted -C(=O)-N(alkyl)$_2$ groups, substituted and unsubstituted -C(=O)-N(H)(aryl) groups, substituted and unsubstituted -C(=O)-N(H)(aralkyl) groups, substituted and unsubstituted -C(=O)-N(H)(heterocyclyl) groups, -C(=O)-N(H)(heterocyclylalkyl) groups, -CO_2H, substituted and unsubstituted -C(=O)-O-alkyl groups, substituted and unsubstituted -C(=O)-O-aryl groups, substituted and unsubstituted -C(=O)-O-aralkyl groups, substituted and unsubstituted -C(=O)-O-heterocyclyl groups, substituted and unsubstituted -C(=O)-O-heterocyclylalkyl groups; or R^2 and R^3 may join together to form a cyclic group,

R^4, R^5, and R^8 are independently selected from –H or substituted and unsubstituted straight and branched chain alkyl groups having from 1 to 8 carbon atoms; or R^5 may be absent if A is nitrogen; or R^8 may be absent if D is nitrogen.

R^6 is selected from -H, -F, -Cl, -Br, -I, -CN, -NO_2, substituted and unsubstituted alkyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted alkenyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted heterocyclylalkyl groups, -OH, substituted and unsubstituted alkoxy groups, substituted and unsubstituted heterocyclyloxy groups, substituted and unsubstituted heterocyclylalkoxy groups, -CO_2H, -C(=O)-NH_2, substituted and unsubstituted -C(=O)-N(H)(alkyl) groups, substituted and unsubstituted -C(=O)-N(alkyl)$_2$ groups,

substituted and unsubstituted -C(=O)-N(H)(heterocyclyl) groups, -C(=O)-N(H)(heterocyclylalkyl) groups, substituted and unsubstituted -C(=O)-O-alkyl groups, substituted and unsubstituted -C(=O)-O-heterocyclyl groups, substituted and unsubstituted -C(=O)-O-heterocyclylalkyl groups, substituted and unsubstituted -C(=O)-alkyl groups, substituted and unsubstituted -C(=O)-heterocyclyl groups, substituted and unsubstituted -C(=O)-heterocyclylalkyl groups, $-NH_2$, substituted and unsubstituted -N(H)(alkyl) groups, substituted and unsubstituted -N(H)(heterocyclyl) groups, substituted and unsubstituted -N(H)(heterocyclylalkyl) groups, substituted and unsubstituted -N(H)-C(=O)-alkyl groups, substituted and unsubstituted -N(H)-C(=O)-heterocyclyl groups, or substituted and unsubstituted -N(H)-C(=O)-heterocyclylalkyl groups;

R^7 is selected from -H, -F, -Cl, -Br, -I, -CN, $-NO_2$, substituted and unsubstituted alkyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted alkenyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted heterocyclylalkyl groups, -OH, substituted and unsubstituted alkoxy groups, substituted and unsubstituted heterocyclyloxy groups, substituted and unsubstituted heterocyclylalkoxy groups,-SH, substituted and unsubstituted -S-alkyl groups, $-CO_2H$, $-C(=O)-NH_2$, substituted and unsubstituted -C(=O)-N(H)(alkyl) groups, substituted and unsubstituted $-C(=O)-N(alkyl)_2$ groups, substituted and unsubstituted -C(=O)-N(H)(heterocyclyl) groups, -C(=O)-N(H)(heterocyclylalkyl) groups, substituted and unsubstituted -C(=O)-O-alkyl groups, substituted and unsubstituted -C(=O)-O-heterocyclyl groups, substituted and unsubstituted -C(=O)-O-heterocyclylalkyl groups, substituted and unsubstituted -C(=O)-alkyl groups, substituted and

unsubstituted -C(=O)-heterocyclyl groups, substituted and unsubstituted -C(=O)-heterocyclylalkyl groups, $-NH_2$, substituted and unsubstituted -N(H)(alkyl) groups, substituted and unsubstituted $-N(alkyl)_2$ groups, substituted and unsubstituted -N(H)(heterocyclyl) groups, substituted and unsubstituted -N(alkyl)(heterocyclyl) groups, substituted and unsubstituted $-N(heterocyclyl)_2$ groups, substituted and unsubstituted -N(H)(heterocyclylalkyl) groups, substituted and unsubstituted -N(alkyl)(heterocyclylalkyl) groups, substituted and unsubstituted $-N(heterocyclylalkyl)_2$ groups, substituted and unsubstituted -N(H)-C(=O)-alkyl groups, substituted and unsubstituted -N(H)-C(=O)-heterocyclyl groups, or substituted and unsubstituted -N(H)-C(=O)-heterocyclylalkyl groups; or R^7 may be absent if C is nitrogen;

R^9 is selected from -H, substituted and unsubstituted alkyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted alkenyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted aryl groups, substituted and unsubstituted aralkyl groups, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted heterocyclylalkyl groups, -OH, substituted and unsubstituted alkoxy groups, substituted and unsubstituted aryloxy groups, substituted and unsubstituted arylalkoxy groups, substituted and unsubstituted heterocyclyloxy groups, substituted and unsubstituted heterocyclylalkoxy groups, substituted and unsubstituted -C(=O)-alkyl groups, substituted and unsubstituted -C(=O)-aryl groups, substituted and unsubstituted -C(=O)-aralkyl groups, substituted and unsubstituted -C(=O)-heterocyclyl groups, substituted and unsubstituted -C(=O)-heterocyclylalkyl groups; or R^9 and R^{10} join together to form a ring having 5, 6, or 7 ring members; and

R^{10} is –H, or R^9 and R^{10} join together to form a ring having 5, 6, or 7 ring members.

[0267] In some embodiments of the method of inhibiting Rsk2 in a subject and/or the method of treating a biological condition mediated by Rsk2 activity in a subject,

R^1 is selected from -H, -F, -Cl, -Br, -I, substituted and unsubstituted alkyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted heterocyclylalkyl groups, -OH, substituted and unsubstituted alkoxy groups, substituted and unsubstituted heterocyclyloxy groups, or substituted and unsubstituted heterocyclylalkoxy groups;

R^2 and R^3 are independently selected from -H, -F, -Cl, -Br, -I, -CN, $-NO_2$, substituted and unsubstituted alkyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted alkenyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted aryl groups, substituted and unsubstituted aralkyl groups, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted heterocyclylalkyl groups, -OH, substituted and unsubstituted alkoxy groups, substituted and unsubstituted heterocyclyloxy groups, substituted and unsubstituted heterocyclylalkoxy groups, or $-CO_2H$; or R^2 and R^3 may join together to form a cyclic group

R^6 is selected from -H, -F, -Cl, -Br, -I, substituted and unsubstituted alkyl groups having from 1 to 8 carbon atoms, substituted and unsubstituted heterocyclyl groups, -OH, substituted and unsubstituted alkoxy groups, substituted and unsubstituted heterocyclyloxy groups, or substituted and

unsubstituted heterocyclylalkoxy groups; or R^6 may be absent if B is nitrogen;

R^7 is selected from the group consisting -H, -F, -Cl, -Br, -I, substituted and unsubstituted alkyl groups having from 1 to 8 carbon atoms, substituted and unsubstituted heterocyclyl groups, -OH, substituted and unsubstituted alkoxy groups, substituted and unsubstituted heterocyclyloxy groups, or substituted and unsubstituted heterocyclylalkoxy groups; or R^7 may be absent if C is nitrogen.

[0268] In some embodiments of the method of inhibiting Rsk2 in a subject and/or the method of treating a biological condition mediated by Rsk2 activity in a subject, A, B, C, and D are all carbon.

[0269] In some embodiments of the method of inhibiting Rsk2 in a subject and/or the method of treating a biological condition mediated by Rsk2 activity in a subject, of A or D is nitrogen, and B and C are both carbon.

[0270] In some embodiments of the method of inhibiting Rsk2 in a subject and/or the method of treating a biological condition mediated by Rsk2 activity in a subject, R^{10} is –H and R^9 is selected from –H, substituted and unsubstituted alkyl groups having from 1-12 carbon atoms, substituted and unsubstituted aryl groups, substituted and unsubstituted aralkyl groups, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted heterocyclylalkyl groups, substituted and unsubstituted alkoxy groups, or substituted and unsubstituted heterocyclylalkoxy groups.

[0271] In some embodiments of the method of inhibiting Rsk2 in a subject and/or the method of treating a biological condition mediated by Rsk2 activity in a subject, R^9 is selected from –H, substituted and unsubstituted straight or branched chain alkyl groups having from 1-12 carbon atoms, substituted and unsubstituted cycloalkyl groups, substituted and unsubstituted

aryl groups, substituted and unsubstituted aralkyl groups, substituted and unsubstituted saturated heterocyclyl groups, substituted and unsubstituted heterocyclylalkyl groups wherein the heterocyclyl moiety is saturated, substituted and unsubstituted alkoxy groups, or substituted and unsubstituted heterocyclylalkoxy groups wherein the heterocyclyl moiety is saturated.

[0272] In some embodiments of the method of inhibiting Rsk2 in a subject and/or the method of treating a biological condition mediated by Rsk2 activity in a subject, R^{10} is –H and R^9 is selected from –H, unsubstituted straight or branched chain alkyl groups having from 1-12 carbon atoms, unsubstituted cycloalkyl groups, alkoxyalkyl groups, aminoalkyl groups, alkylaminoalkyl groups, dialkylaminoalkyl groups, aminocyclohexyl groups, substituted and unsubstituted saturated heterocyclyl groups, substituted and unsubstituted heterocyclylalkoxy groups wherein the heterocyclyl moiety is saturated. In some such embodiments, R^9 is selected from pyrrolidinyl, pyrrolidinylalkyl, piperidinyl, piperidinylalkyl, quinuclidinyl, or aminocyclohexyl groups.

[0273] In some embodiments of the method of inhibiting Rsk2 in a subject and/or the method of treating a biological condition mediated by Rsk2 activity in a subject, R^1 is selected from -H, -F, -Cl, substituted and unsubstituted morpholinyl groups, substituted and unsubstituted morpholinylalkyl groups, or substituted and unsubstituted morpholinylalkoxy groups. In some such embodiments, R^1 is selected from –H or -F. In other such embodiments, R^1 is –H.

[0274] In some embodiments of the method of inhibiting Rsk2 in a subject and/or the method of treating a biological condition mediated by Rsk2 activity in a subject, R^2 is selected from –H, -F, -Cl, -Br, -I, $-NO_2$, $-CH_3$, $-OCH_3$, $-CO_2H$, substituted and unsubstituted aryl groups, or substituted and unsubstituted pyridinyl groups. In some such embodiments, R^2 is selected from –H, –Br, –I, $-CH_3$, $–CO_2H$, $–NH_2$, or 4-hydroxyphenyl.

[0275] In some embodiments of the method of inhibiting Rsk2 in a subject and/or the method of treating a biological condition mediated by Rsk2 activity in a subject, R^3 is selected from –H, -F, -Cl, -Br, -I, $-CH_3$, $-OCH_3$, substituted and unsubstituted imidazolyl, substituted and unsubstituted dialkylaminoalkoxy, or substituted and unsubstituted heterocyclylalkoxy. In some such embodiments, R^3 is selected from –H or-F.

[0276] In some embodiments of the method of inhibiting Rsk2 in a subject and/or the method of treating a biological condition mediated by Rsk2 activity in a subject, R^4 is –H.

[0277] In some embodiments of the method of inhibiting Rsk2 in a subject and/or the method of treating a biological condition mediated by Rsk2 activity in a subject, R^5 is –H; or may be absent.

[0278] In some embodiments of the method of inhibiting Rsk2 in a subject and/or the method of treating a biological condition mediated by Rsk2 activity in a subject, R^6 is selected from –H, -F, -Cl, -Me, substituted and unsubstituted morpholinyl groups, substituted and unsubstituted morpholinylalkoxy groups, substituted and unsubstituted piperidinyl groups, or substituted and unsubstituted piperazinyl groups; or may be absent.

[0279] In some embodiments of the method of inhibiting Rsk2 in a subject and/or the method of treating a biological condition mediated by Rsk2 activity in a subject, wherein R^7 is selected from –H, -F, -Me, substituted and unsubstituted morpholinyl groups, substituted and unsubstituted pyrrolidinyl groups, substituted and unsubstituted piperidinyl groups, or substituted and unsubstituted piperazinyl groups; or may be absent.

[0280] In some embodiments of the method of inhibiting Rsk2 in a subject and/or the method of treating a biological condition mediated by Rsk2 activity in a subject, R^8 is –H; or may be absent.

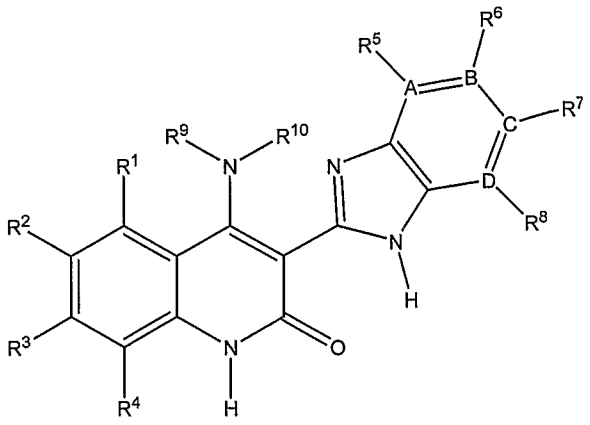
[0281] In some embodiments of the method of inhibiting Rsk2 in a subject and/or the method of treating a biological condition mediated by Rsk2 activity in a subject, the IC_{50} value of the compound is less than or equal to 10 μM with respect to CHK1. In other such embodiments, the IC_{50} value is less than or equal to 1 μM, is less than or equal to 0.1 μM, is less than or equal to 0.050 μM, is less than or equal to 0.030 μM, is less than or equal to 0.025 μM, is less than or equal to 0.010 μM, or is less than or equal to 0.001 μM.

[0282] In some embodiments of the method of inhibiting Rsk2 in a subject and/or the method of treating a biological condition mediated by Rsk2 activity in a subject, the subject is a mammal or is a human.

[0283] In some embodiments of the method of treating a biological condition mediated by Rsk2 activity in a subject, the biological condition is cancer.

Methods Relating to PAR-1

[0284] In some embodiments of the method of inhibiting a serine/threonine kinase in a subject and/or the method of treating a biological condition mediated by serine/threonine kinase activity in a subject using a compound of Structure I, a tautomer of the compound, a pharmaceutically acceptable salt of the compound, a pharmaceutically acceptable salt of the tautomer, or mixtures thereof, the serine/threonine kinase is PAR-1. In some such methods, the PAR-1 is inhibited in the subject after administration. In methods of inhibiting PAR-1, Structure I has the following formula:



I

where,

A, B, C, and D are independently selected from carbon or nitrogen;

R^1 is selected from -H, -F, -Cl, -Br, -I, -CN, $-NO_2$, substituted and unsubstituted alkyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted alkenyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted heterocyclyl groups, or substituted and unsubstituted heterocyclylalkyl groups;

R^2 is selected from -H, -F, -Cl, -Br, -I, $-NO_2$, -CN, substituted and unsubstituted alkyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted alkenyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted aryl groups, substituted and unsubstituted aralkyl groups, -OH, substituted and unsubstituted alkoxy, substituted and unsubstituted heterocyclyloxy, substituted and unsubstituted heterocyclylalkoxy, substituted and unsubstituted -C(=O)-alkyl groups, substituted and unsubstituted -C(=O)-aryl, substituted and unsubstituted -C(=O)-aralkyl, $-CO_2H$, substituted and

unsubstituted -C(=O)-O-alkyl groups, substituted and unsubstituted -C(=O)-O-aryl groups, or substituted and unsubstituted -C(=O)-O-aralkyl groups;

R^3 is selected from -H, -F, -Cl, -Br, -I, $-NO_2$, -CN, substituted and unsubstituted alkyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted alkenyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted aryl groups, substituted and unsubstituted aralkyl groups, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted heterocyclylalkyl groups, -SH, substituted and unsubstituted -S-alkyl groups, substituted and unsubstituted $-S(=O)_2$-O-alkyl groups, substituted and unsubstituted $-S(=O)_2$-alkyl groups, substituted and unsubstituted $-S(=O)_2$-heterocyclyl groups, $-S(=O)_2-NH_2$, substituted and unsubstituted $-S(=O)_2$-N(H)(alkyl) groups, substituted and unsubstituted $-S(=O)_2$-$N(alkyl)_2$ groups, substituted and unsubstituted -S(=O)-alkyl groups, substituted and unsubstituted –S(=O)-aryl groups, substituted and unsubstituted -S(=O)-heterocyclyl groups, -OH, substituted and unsubstituted alkoxy groups, substituted and unsubstituted aryloxy groups, substituted and unsubstituted heterocyclyloxy groups, substituted and unsubstituted heterocyclylalkoxy groups, $-NH_2$, substituted and unsubstituted -N(H)(alkyl) groups, substituted and unsubstituted $-N(alkyl)_2$ groups, substituted and unsubstituted -N(H)(aryl) groups, substituted and unsubstituted -N(alkyl)(aryl) groups, substituted and unsubstituted $-N(aryl)_2$ groups, substituted and unsubstituted -N(H)(aralkyl) groups, substituted and unsubstituted -N(alkyl)(aralkyl) groups, substituted and unsubstituted $-N(aralkyl)_2$ groups, substituted and unsubstituted -N(H)(heterocyclyl) groups, substituted and unsubstituted -N(alkyl)(heterocyclyl) groups, substituted and unsubstituted $-N(heterocyclyl)_2$ groups, substituted and

unsubstituted -N(H)(heterocyclylalkyl) groups, substituted and unsubstituted -N(alkyl)(heterocyclylalkyl) groups, substituted and unsubstituted -N(heterocyclylalkyl)$_2$ groups, substituted and unsubstituted -N(H)-C(=O)-alkyl groups, substituted and unsubstituted -N(alkyl)-C(=O)-alkyl groups, substituted and unsubstituted -N(H)-C(=O)-aryl groups, substituted and unsubstituted -N(alkyl)-C(=O)-aryl groups, substituted and unsubstituted -N(H)-C(=O)-aralkyl groups, substituted and unsubstituted -N(alkyl)-C(=O)-aralkyl groups, substituted and unsubstituted -N(H)-C(=O)-heterocyclyl groups, substituted and unsubstituted -N(alkyl)-C(=O)-heterocyclyl groups, substituted and unsubstituted -N(H)-C(=O)-heterocyclylalkyl groups, substituted and unsubstituted -N(alkyl)-C(=O)-heterocyclylalkyl groups, substituted and unsubstituted -N(H)-S(=O)$_2$-alkyl groups, substituted and unsubstituted -N(H)-S(=O)$_2$-aryl, substituted and unsubstituted -N(H)-S(=O)$_2$-heterocyclyl groups, substituted and unsubstituted -C(=O)-alkyl groups, substituted and unsubstituted -C(=O)-aryl, substituted and unsubstituted -C(=O)-aralkyl, substituted and unsubstituted -C(=O)-heterocyclyl groups, substituted and unsubstituted -C(=O)-heterocyclylalkyl groups, -C(=O)-NH$_2$, substituted and unsubstituted -C(=O)-N(H)(alkyl) groups, substituted and unsubstituted -C(=O)-N(alkyl)$_2$ groups, substituted and unsubstituted -C(=O)-N(H)(aryl) groups, substituted and unsubstituted -C(=O)-N(alkyl)(aryl) groups, substituted and unsubstituted -C(=O)-N(aryl)$_2$ groups, substituted and unsubstituted -C(=O)-N(H)(aralkyl) groups, substituted and unsubstituted -C(=O)-N(alkyl)(aralkyl) groups, substituted and unsubstituted -C(=O)-N(aralkyl)$_2$ groups, substituted and unsubstituted -C(=O)-N(H)(heterocyclyl) groups, substituted and unsubstituted -C(=O)-N(alkyl)(heterocyclyl) groups, substituted and unsubstituted -C(=O)-N(heterocyclyl)$_2$ groups, substituted

and unsubstituted -C(=O)-N(H)(heterocyclylalkyl) groups, substituted and unsubstituted -C(=O)-N(alkyl)(heterocyclylalkyl) groups, substituted and unsubstituted -C(=O)-N(heterocyclylalkyl)$_2$ groups, -CO_2H, substituted and unsubstituted -C(=O)-O-alkyl groups, substituted and unsubstituted -C(=O)-O-aryl groups, substituted and unsubstituted -C(=O)-O-aralkyl groups, substituted and unsubstituted -C(=O)-O-heterocyclyl groups, or substituted and unsubstituted -C(=O)-O-heterocyclylalkyl groups;

R^4, R^5 and R^8 are independently selected from –H or substituted and unsubstituted alkyl groups having from 1 to 12 carbon atoms; or R^5 may be absent if A is nitrogen; or R^8 may be absent if D is nitrogen;

R^6 and R^7 are independently selected from -H, -F, -Cl, -Br, -I, -CN, -NO_2, substituted and unsubstituted alkyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted alkenyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted heterocyclylalkyl groups, -SH, substituted and unsubstituted -S-alkyl groups, substituted and unsubstituted -S-heterocyclyl groups, -OH, substituted and unsubstituted alkoxy groups, substituted and unsubstituted heterocyclyloxy groups, substituted and unsubstituted heterocyclylalkoxy groups, -NH_2, substituted and unsubstituted -N(H)(alkyl) groups, substituted and unsubstituted -N(alkyl)$_2$ groups, substituted and unsubstituted -N(H)(heterocyclyl) groups, substituted and unsubstituted -N(alkyl)(heterocyclyl) groups, substituted and unsubstituted -N(heterocyclyl)$_2$ groups, substituted and unsubstituted -N(H)(heterocyclylalkyl) groups, substituted and

unsubstituted -N(alkyl)(heterocyclylalkyl) groups, or substituted and unsubstituted -N(heterocyclylalkyl)$_2$ groups; or R^6 is absent if B is nitrogen; or R^7 is absent if C is nitrogen;

R^9 is selected from -H, substituted and unsubstituted alkyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted alkenyl groups having from 1 to 12 carbons, substituted and unsubstituted aryl groups, substituted and unsubstituted aralkyl groups, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted heterocyclylalkyl groups, -OH, substituted and unsubstituted alkoxy groups, or substituted and unsubstituted heterocyclylalkoxy groups; and

R^{10} is -H.

[0285] In some embodiments of the method of inhibiting PAR-1 in a subject and/or the method of treating a biological condition mediated by PAR-1 activity in a subject,

R^3 is selected from -H, -F, -Cl, -Br, -I, -NO_2, -CN, substituted and unsubstituted alkyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted alkenyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted aryl groups, substituted and unsubstituted aralkyl groups, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted heterocyclylalkyl groups, -OH, substituted and unsubstituted alkoxy groups, substituted and unsubstituted aryloxy groups, substituted and unsubstituted heterocyclyloxy groups, substituted and unsubstituted heterocyclylalkoxy groups, -NH_2, substituted and unsubstituted -N(H)(alkyl) groups, substituted

and unsubstituted -N(alkyl)$_2$ groups, substituted and unsubstituted -N(H)(aryl) groups, substituted and unsubstituted -N(alkyl)(aryl) groups, substituted and unsubstituted -N(aryl)$_2$ groups, substituted and unsubstituted -N(H)(aralkyl) groups, substituted and unsubstituted -N(alkyl)(aralkyl) groups, substituted and unsubstituted -N(aralkyl)$_2$ groups, substituted and unsubstituted -N(H)(heterocyclyl) groups, substituted and unsubstituted -N(alkyl)(heterocyclyl) groups, substituted and unsubstituted -N(heterocyclyl)$_2$ groups, substituted and unsubstituted -N(H)(heterocyclylalkyl) groups, substituted and unsubstituted -N(alkyl)(heterocyclylalkyl) groups, substituted and unsubstituted -N(heterocyclylalkyl)$_2$ groups, substituted and unsubstituted -C(=O)-alkyl groups, substituted and unsubstituted -C(=O)-heterocyclyl groups, substituted and unsubstituted -C(=O)-heterocyclylalkyl groups, -C(=O)-NH$_2$, substituted and unsubstituted -C(=O)-N(H)(alkyl) groups, substituted and unsubstituted -C(=O)-N(alkyl)$_2$ groups, substituted and unsubstituted -C(=O)-N(H)(aryl) groups, substituted and unsubstituted -C(=O)-N(alkyl)(aryl) groups, substituted and unsubstituted -C(=O)-N(aryl)$_2$ groups, substituted and unsubstituted -C(=O)-N(H)(aralkyl) groups, substituted and unsubstituted -C(=O)-N(alkyl)(aralkyl) groups, substituted and unsubstituted -C(=O)-N(aralkyl)$_2$ groups, substituted and unsubstituted -C(=O)-N(H)(heterocyclyl) groups, substituted and unsubstituted -C(=O)-N(alkyl)(heterocyclyl) groups, substituted and unsubstituted -C(=O)-N(heterocyclyl)$_2$ groups, substituted and unsubstituted -C(=O)-N(H)(heterocyclylalkyl) groups, substituted and unsubstituted -C(=O)-N(alkyl)(heterocyclylalkyl) groups, substituted and unsubstituted -C(=O)-N(heterocyclylalkyl)$_2$ groups, -CO$_2$H, substituted and unsubstituted -C(=O)-O-alkyl groups, substituted and

unsubstituted -C(=O)-O-heterocyclyl groups, or substituted and unsubstituted -C(=O)-O-heterocyclylalkyl groups;

R^6 and R^7 are independently selected from -H, -F, -Cl, -Br, -I, -CN, $-NO_2$, substituted and unsubstituted alkyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted alkenyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted heterocyclylalkyl groups, -OH, substituted and unsubstituted alkoxy groups, substituted and unsubstituted heterocyclyloxy groups, or substituted and unsubstituted heterocyclylalkoxy groups; or R^6 is absent if B is nitrogen; or R^7 is absent if C is nitrogen.

[0286] In some embodiments of the method of inhibiting PAR-1 in a subject and/or the method of treating a biological condition mediated by PAR-1 activity in a subject, A, B, C, and D are all carbon.

[0287] In some embodiments of the method of inhibiting PAR-1 in a subject and/or the method of treating a biological condition mediated by PAR-1 activity in a subject, one of A or D is nitrogen, and B and C are both carbon.

[0288] In some embodiments of the method of inhibiting PAR-1 in a subject and/or the method of treating a biological condition mediated by PAR-1 activity in a subject, R^9 is selected from -H, substituted and unsubstituted straight and branched chain alkyl groups having from 1 to 8 carbon atoms, substituted and unsubstituted cycloalkyl groups, substituted and unsubstituted heterocyclyl groups, or substituted and unsubstituted heterocyclylalkyl groups.

[0289] In some embodiments of the method of inhibiting PAR-1 in a subject and/or the method of treating a biological condition mediated by PAR-

1 activity in a subject, R^9 is selected from -H, unsubstituted straight and branched chain alkyl groups having from 1 to 8 carbon atoms, substituted and unsubstituted cycloalkyl groups, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted heterocyclylalkyl groups, substituted and unsubstituted dialkylaminoalkyl groups, substituted and unsubstituted alkylaminoalkyl groups, substituted and unsubstituted aminoalkyl groups, or substituted and unsubstituted alkylsulfonylalkyl groups.

[0290] In some embodiments of the method of inhibiting PAR-1 in a subject and/or the method of treating a biological condition mediated by PAR-1 activity in a subject, R^9 is selected from -H, unsubstituted straight or branched chain alkyl groups of 1-8 carbons, substituted and unsubstituted alkylaminoalkyl groups, substituted and unsubstituted dialkylaminoalkyl groups, substituted and unsubstituted alkylsulfonylalkyl groups, substituted and unsubstituted cycloalkyl groups, substituted and unsubstituted saturated heterocyclyl groups, or substituted and unsubstituted heterocyclylalkyl groups wherein the heterocyclyl moiety is saturated.

[0291] In some embodiments of the method of inhibiting PAR-1 in a subject and/or the method of treating a biological condition mediated by PAR-1 activity in a subject, R^9 is selected from substituted and unsubstituted methylaminoethyl groups, substituted and unsubstituted dimethylaminoethyl groups, substituted and unsubstituted methylsulfonylethyl groups, substituted and unsubstituted quinuclidinyl groups, substituted and unsubstituted piperazinylalkyl groups, substituted and unsubstituted piperidinyl groups, substituted and unsubstituted piperidinylalkyl groups, substituted and unsubstituted pyrrolidinyl groups, substituted and unsubstituted pyrrolidinylalkyl groups, substituted and unsubstituted imidazolylalkyl groups, or substituted and unsubstituted cyclohexyl groups.

[0292] In some embodiments of the method of inhibiting PAR-1 in a subject and/or the method of treating a biological condition mediated by PAR-1 activity in a subject, R^9 is selected from –H, methylaminoethyl, dimethylaminoethyl, methylsulfonylethyl, 1-aminocyclohexyl, quinuclidinyl, 4-methylpiperazin-1-ylpropyl, 1-benzylpiperidinyl, piperidin-3-yl, piperidin-4-yl, piperidin-3-ylethyl, piperidin-4-ylethyl, imidazol-5-ylethyl, pyrrolidin-1-ylethyl, 1-methylpyrrolidin-2-ylethyl, or pyrrolidin-3-yl. In some such embodiments, R^9 is a quinuclidinyl group. In other such embodiments, R^9 is a quinuclidin-3-yl group. In still other such embodiments, R^9 is -H.

[0293] In some embodiments of the method of inhibiting PAR-1 in a subject and/or the method of treating a biological condition mediated by PAR-1 activity in a subject, R^9 is selected from monocyclic, bicyclic, or polycyclic saturated heterocyclyl groups.

[0294] In some embodiments of the method of inhibiting PAR-1 in a subject and/or the method of treating a biological condition mediated by PAR-1 activity in a subject, R^1 is selected from -H, -F, -Cl, -Br, -I, substituted and unsubstituted straight and branched chain alkyl groups having from 1 to 8 carbon atoms, substituted and unsubstituted cycloalkyl groups, or substituted and unsubstituted heterocyclyl groups. In some such embodiments, R^1 is selected from–H, –F, –Cl, or substituted and unsubstituted piperazinyl. In other such embodiments, R^1 is selected from –H, –F, –Cl, or 4-ethylpiperazin-1-yl. In still other such embodiments, R^1 is –H.

[0295] In some embodiments of the method of inhibiting PAR-1 in a subject and/or the method of treating a biological condition mediated by PAR-1 activity in a subject, R^2 is selected from -H, -F, -Cl, -Br, -I, $-NO_2$, -CN, substituted and unsubstituted straight and branched chain alkyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted cycloalkyl groups,

substituted and unsubstituted aryl groups, or substituted and unsubstituted aralkyl groups.

[0296] In some embodiments of the method of inhibiting PAR-1 in a subject and/or the method of treating a biological condition mediated by PAR-1 activity in a subject, R^2 is selected from –H, -Cl, -F, -Br, -I, -CN, substituted and unsubstituted straight or branched chain alkyl having from 1 to 8 carbons, or substituted and unsubstituted phenyl groups.

[0297] In some embodiments of the method of inhibiting PAR-1 in a subject and/or the method of treating a biological condition mediated by PAR-1 activity in a subject, R^2 is a substituted and unsubstituted aryl group selected from 2-amino-4-carboxymethylphenyl, 2-methylphenyl, 2-ethylphenyl, 2-methoxyphenyl, 2,4-dichlorophenyl, 2-fluoro-4-chlorophenyl, 2,6-difluorophenyl, 3-methoxyphenyl, 3-carboxyphenyl, 3-acetylphenyl, 3-acetamidophenyl, 3-methylcarboxyphenyl, 4-acetylphenyl, 4-dimethylaminophenyl, 4-cyanophenyl, 4-carboxamidophenyl, 4-carboxyphenyl, 4-methylcarboxyphenyl, 4-methylsulfonylphenyl, or phenyl.

[0298] In some embodiments of the method of inhibiting PAR-1 in a subject and/or the method of treating a biological condition mediated by PAR-1 activity in a subject, R^2 is selected from -F, -Cl, -Br, -I, -CN, methyl, methoxy, or $–CO_2H$. In some such embodiments, R^2 is –Cl.

[0299] In some embodiments of the method of inhibiting PAR-1 in a subject and/or the method of treating a biological condition mediated by PAR-1 activity in a subject, R^3 is selected from -H, -F, -Cl, -Br, -I, -CN, substituted and unsubstituted straight or branched chain alkyl groups having from 1 to 8 carbon atoms, substituted and unsubstituted cycloalkyl groups, substituted and unsubstituted aryl groups, substituted and unsubstituted aralkyl groups, substituted and unsubstituted heterocyclyl groups, substituted and

unsubstituted heterocyclylalkyl groups, -OH, substituted and unsubstituted alkoxy groups, substituted and unsubstituted heterocyclyloxy groups, substituted and unsubstituted heterocyclylalkoxy groups, substituted and unsubstituted -N(H)(alkyl) groups, substituted and unsubstituted -N(alkyl)$_2$ groups, or substituted and unsubstituted -N(H)(heterocyclylalkyl) groups.

[0300] In some embodiments of the method of inhibiting PAR-1 in a subject and/or the method of treating a biological condition mediated by PAR-1 activity in a subject, R^3 is selected from -H, -F, -Cl, -Br, -I, -CN, substituted and unsubstituted straight or branched chain alkyl groups having from 1 to 8 carbon atoms, -OH, unsubstituted straight or branched chain alkoxy groups, dialkylaminoalkoxy groups, or substituted and unsubstituted pyrrolidinylalkoxy groups. In some such embodiments, R^3 is selected from -H, -Cl, methoxy, 2-(dimethylamino)ethyl-1-oxy, and pyrrolidin-2-ylmethyloxy.

[0301] In some embodiments of the method of inhibiting PAR-1 in a subject and/or the method of treating a biological condition mediated by PAR-1 activity in a subject, R^3 is selected from substituted and unsubstituted phenyl groups or substituted and unsubstituted unsaturated heterocyclyl groups. In some such embodiments, R^3 is selected from 2-amino-4-carboxyphenyl, 3-acetamidophenyl, 3-carboxyphenyl, 4-carboxyphenyl, 4-methylsulfonylphenyl, 2-ethyl-imidazol-1-yl, 2-methyl-imidazol-1-yl, imidazol-1-yl, and 3-acetylpyrrol-1-yl.

[0302] In some embodiments of the method of inhibiting PAR-1 in a subject and/or the method of treating a biological condition mediated by PAR-1 activity in a subject, R^3 is a saturated heterocyclyl group. In some such embodiments, R^3 a saturated heterocyclyl group selected from substituted and unsubstituted thiomorpholinyl groups, substituted and unsubstituted piperazinyl groups, substituted and unsubstituted piperidinyl groups, or substituted and unsubstituted pyrrolidinyl groups. In other such embodiments,

R^3 is selected from 3-phenylthiomorpholin-4-yl groups, morpholin-4-yl, 4-methylpiperazin-1-yl groups, 4-methylcarboxypiperidin-1-yl, piperidin-1-yl, 3-dimethylaminopyrrolidin-1-yl, or 3-acetamidopyrrolidin-1-yl.

[0303] In some embodiments of the method of inhibiting PAR-1 in a subject and/or the method of treating a biological condition mediated by PAR-1 activity in a subject, R^3 is selected from substituted and unsubstituted -N(H)(alkyl) groups, substituted and unsubstituted -N(alkyl)$_2$ groups, or substituted and unsubstituted -N(H)(heterocyclylalkyl) groups, wherein the heterocyclyl moiety is saturated.

[0304] In some embodiments of the method of inhibiting PAR-1 in a subject and/or the method of treating a biological condition mediated by PAR-1 activity in a subject, R^3 is selected from substituted and unsubstituted -N(H)(hydroxyalkyl), substituted and unsubstituted -N(H)(aminoalkyl), substituted and unsubstituted -N(H)(dialkylaminoalkyl), substituted and unsubstituted -N(H)(alkylcarboxamidoalkyl), substituted and unsubstituted -N(H)(alkoxyalkyl), substituted and unsubstituted -N(H)(arylsulfonylalkyl), substituted and unsubstituted -N(H)(alkylsulfonylalkyl), substituted and unsubstituted -N(H)(cycloalkyl), substituted and unsubstituted –N(H)(morpholinylalkyl), substituted and unsubstituted -N(H)(piperidinylalkyl), or substituted and unsubstituted -N(H)(pyrrolidinonylalkyl).

[0305] In some embodiments of the method of inhibiting PAR-1 in a subject and/or the method of treating a biological condition mediated by PAR-1 activity in a subject, R^3 is selected from -N(H)(2-hydroxyethyl), -N(H)(2-aminoethyl), -N(H)(dimethylaminoethyl), -N(H)(2-diethylaminoethyl), -N(H)(3-dimethylaminopropyl), -N(H)(2-acetamidoethyl), -N(H)(2-methoxyethyl), -N(H)(2-(methylsulfonyl)ethyl), -N(H)(2-(phenylsulfonyl)ethyl), -N(H)(cyclopropyl), -N(methyl)(ethyl), -N(methyl)$_2$, -N(H)(2-morpholin-4-yl-2-phenylethyl), -N(H)(2-piperidin-1-ylethyl), or -N(H)(3-pyrrolidinon-1-ylpropyl).

[0306] In some embodiments of the method of inhibiting PAR-1 in a subject and/or the method of treating a biological condition mediated by PAR-1 activity in a subject, R^4 is –H.

[0307] In some embodiments of the method of inhibiting PAR-1 in a subject and/or the method of treating a biological condition mediated by PAR-1 activity in a subject, A and D are both carbon, R^5 is –H, and R^8 is –H.

[0308] In some embodiments of the method of inhibiting PAR-1 in a subject and/or the method of treating a biological condition mediated by PAR-1 activity in a subject, R^6 and R^7 are independently selected from -H, -F, -Cl, -Br, -I, -CN, $-NO_2$, substituted and unsubstituted straight or branched chain alkyl groups having from 1 to 8 carbon atoms, substituted and unsubstituted cycloalkyl groups, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted heterocyclylalkyl groups, -OH, substituted and unsubstituted alkoxy groups, substituted and unsubstituted heterocyclyloxy groups, or substituted and unsubstituted heterocyclylalkoxy groups; or R^6 is absent if B is nitrogen; or R^7 is absent if C is nitrogen.

[0309] In some embodiments of the method of inhibiting PAR-1 in a subject and/or the method of treating a biological condition mediated by PAR-1 activity in a subject, R^6 and R^7 are independently selected from -H, -F, -Cl, -Br, -I, substituted and unsubstituted straight or branched chain alkyl groups having from 1 to 8 carbon atoms, substituted and unsubstituted heterocyclyl groups, -OH, or substituted and unsubstituted heterocyclylalkoxy groups; or R^6 is absent if B is nitrogen; or R^7 is absent if C is nitrogen.

[0310] In some embodiments of the method of inhibiting PAR-1 in a subject and/or the method of treating a biological condition mediated by PAR-1 activity in a subject, R^6 and R^7 are independently selected from -H, -F, -Cl, -Br, -I, unsubstituted straight or branched chain alkyl groups having from 1 to

8 carbon atoms, substituted and unsubstituted morpholinyl groups, substituted and unsubstituted piperazinyl groups, substituted and unsubstituted pyrrolidinyl groups, -OH, or pyrrolidinylalkoxy; or R^6 is absent if B is nitrogen; or R^7 is absent if C is nitrogen. In some such embodiments, R^6 and R^7 are independently selected from -H, -F, methyl, morpholin-4-yl, 4-isopropyl-piperazin-1-yl, 4-methylpiperazin-1-yl, -OH; and 3-(pyrrolidin-1-yl)propyl-1-oxy; or R^6 is absent if B is nitrogen; or R^7 is absent if C is nitrogen. In other such embodiments, B and C are both carbon and R^6 and R^7 are both –H.

[0311] In some embodiments of the method of inhibiting PAR-1 in a subject and/or the method of treating a biological condition mediated by PAR-1 activity in a subject, A, B, C, and D are all carbon, and R^5, R^6, R^7, and R^8 are all -H.

[0312] In some embodiments of the method of inhibiting PAR-1 in a subject and/or the method of treating a biological condition mediated by PAR-1 activity in a subject, the IC_{50} value of the compound is less than or equal to 10 μM with respect to PAR-1. In other such embodiments, the IC_{50} value is less than or equal to 1 μM, is less than or equal to 0.1 μM, is less than or equal to 0.050 μM, is less than or equal to 0.030 μM, is less than or equal to 0.025 μM, or is less than or equal to 0.010 μM.

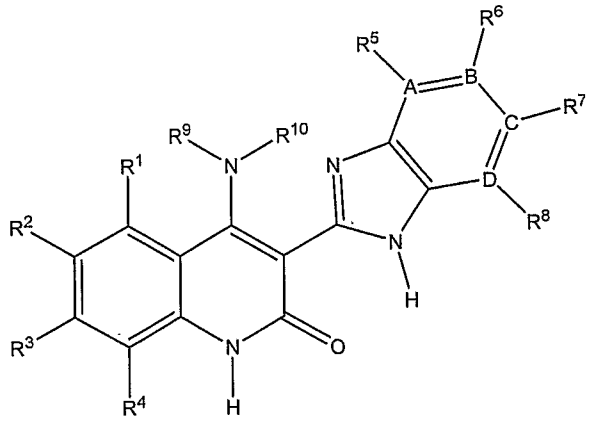
[0313] In some embodiments of the method of inhibiting PAR-1 in a subject and/or the method of treating a biological condition mediated by PAR-1 activity in a subject, the subject is a mammal or is a human.

[0314] In some embodiments of the method of treating a biological condition mediated by PAR-1 activity in a subject, the biological condition is controlled by the Wnt pathway and/or is controlled by the planar cell polarity pathway. In some cases, the biological condition is cancer which in some embodiments is caused by aberrant regulation of the Wnt pathway in a mammal such as a human. Thus, in some embodiments, the invention

provides a method of regulating the Wnt pathway in a subject. In other embodiments, the invention provides a method of modulating the Wnt β-catenin signaling.

Methods Relating to Tyrosine Kinases

[0315] In another aspect, the present invention provides a method of inhibiting a tyrosine kinase in a subject and/or a method of treating a biological condition mediated by a tyrosine kinase in a subject. The tyrosine kinase is Cdc2 kinase, Fyn, Lck, c-Kit, c-ABL, p60src, VEGFR3, PDGFRα, PDGFRβ, FGFR3, FLT-3, or Tie-2. In some embodiments, the tyrosine kinase is Cdc2 kinase, Fyn, Lck, or Tie-2 and in some other embodiments, the tyrosine kinase is c-Kit, c-ABL, p60src, FGFR3, VEGFR3, PDGFRα, PDGFRβ, or FLT-3. The methods include administering to the subject a compound of Structure I, a tautomer of the compound, a pharmaceutically acceptable salt of the compound, a pharmaceutically acceptable salt of the tautomer, or mixtures thereof. In the method of inhibiting a tyrosine kinase, the tyrosine kinase is inhibited in the subject after administration. Structure I has the following formula:



I

where,

A, B, C, and D are independently selected from carbon or nitrogen;

R^1 is selected from -H, -F, -Cl, -Br, -I, -CN, -NO_2, substituted and unsubstituted alkyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted alkenyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted aryl groups, substituted and unsubstituted aralkyl groups, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted heterocyclylalkyl groups, -SH, substituted and unsubstituted -S-alkyl groups, substituted and unsubstituted -S-heterocyclyl groups, -OH, substituted and unsubstituted alkoxy groups, substituted and unsubstituted heterocyclyloxy groups, substituted and unsubstituted heterocyclylalkoxy groups, -NH_2, substituted and unsubstituted -N(H)(alkyl) groups, substituted and unsubstituted -N(alkyl)$_2$ groups, substituted and unsubstituted -N(H)(heterocyclyl) groups, substituted and unsubstituted -N(alkyl)(heterocyclyl) groups, substituted and unsubstituted -N(heterocyclyl)$_2$ groups, substituted and unsubstituted -N(H)(heterocyclylalkyl) groups, substituted and unsubstituted -N(alkyl)(heterocyclylalkyl) groups, substituted and unsubstituted -N(heterocyclylalkyl)$_2$ groups, substituted and unsubstituted -N(H)-C(=O)-alkyl groups, substituted and unsubstituted -N(H)-C(=O)-heterocyclyl groups, substituted and unsubstituted -N(H)-C(=O)-heterocyclylalkyl groups, substituted and unsubstituted -N(alkyl)-S(=O)$_2$-alkyl groups, substituted and unsubstituted -N(alkyl)-S(=O)$_2$-heterocyclyl groups, substituted and unsubstituted -N(alkyl)-S(=O)$_2$-heterocyclylalkyl groups, substituted and unsubstituted -C(=O)-alkyl groups, substituted and unsubstituted -C(=O)-heterocyclyl groups, substituted and unsubstituted -C(=O)-heterocyclylalkyl groups, -C(=O)-NH_2, substituted and unsubstituted -C(=O)-N(H)(alkyl) groups, substituted and unsubstituted -C(=O)-N(alkyl)$_2$ groups, substituted and unsubstituted -C(=O)-N(H)(heterocyclyl) groups, substituted and unsubstituted -C(=O)-N(alkyl)(heterocyclyl)

groups, substituted and unsubstituted -C(=O)-N(heterocyclyl)$_2$ groups, substituted and unsubstituted -C(=O)-N(H)(heterocyclylalkyl) groups, substituted and unsubstituted -C(=O)-N(alkyl)(heterocyclylalkyl) groups, substituted and unsubstituted -C(=O)-N(heterocyclylalkyl)$_2$ groups, -CO_2H, substituted and unsubstituted -C(=O)-O-alkyl groups, substituted and unsubstituted -C(=O)-O-heterocyclyl groups, or substituted and unsubstituted -C(=O)-O-heterocyclylalkyl groups;

R^2 and R^3 are independently selected from -H, -F, -Cl, -Br, -I, -NO_2, -CN, substituted and unsubstituted alkyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted alkenyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted aryl groups, substituted and unsubstituted aralkyl groups, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted heterocyclylalkyl groups, -SH, substituted and unsubstituted -S-alkyl groups, substituted and unsubstituted -S(=O)$_2$-O-alkyl groups, substituted and unsubstituted -S(=O)$_2$-alkyl groups, substituted and unsubstituted -S(=O)$_2$-heterocyclyl groups, -S(=O)$_2$-NH_2, substituted and unsubstituted -S(=O)$_2$-N(H)(alkyl) groups, substituted and unsubstituted -S(=O)$_2$-N(alkyl)$_2$ groups, substituted and unsubstituted -S(=O)-alkyl groups, substituted and unsubstituted -S(=O)-heterocyclyl groups, -OH, substituted and unsubstituted alkoxy groups, substituted and unsubstituted aryloxy groups, substituted and unsubstituted heterocyclyloxy groups, substituted and unsubstituted heterocyclylalkoxy groups, -NH_2, substituted and unsubstituted -N(H)(alkyl) groups, substituted and unsubstituted -N(alkyl)$_2$ groups, substituted and unsubstituted -N(H)(aryl) groups, substituted and unsubstituted -N(alkyl)(aryl) groups, substituted and unsubstituted -N(aryl)$_2$

groups, substituted and unsubstituted -N(H)(aralkyl) groups, substituted and unsubstituted -N(alkyl)(aralkyl) groups, substituted and unsubstituted -N(aralkyl)$_2$ groups, substituted and unsubstituted -N(H)(heterocyclyl) groups, substituted and unsubstituted -N(alkyl)(heterocyclyl) groups, substituted and unsubstituted -N(heterocyclyl)$_2$ groups, substituted and unsubstituted -N(H)(heterocyclylalkyl) groups, substituted and unsubstituted -N(alkyl)(heterocyclylalkyl) groups, substituted and unsubstituted -N(heterocyclylalkyl)$_2$ groups, substituted and unsubstituted -N(H)-C(=O)-alkyl groups, substituted and unsubstituted -N(alkyl)-C(=O)-alkyl groups, substituted and unsubstituted -N(H)-C(=O)-aryl groups, substituted and unsubstituted -N(alkyl)-C(=O)-aryl groups, substituted and unsubstituted -N(H)-C(=O)-aralkyl groups, substituted and unsubstituted -N(alkyl)-C(=O)-aralkyl groups, substituted and unsubstituted -N(H)-C(=O)-heterocyclyl groups, substituted and unsubstituted -N(alkyl)-C(=O)-heterocyclyl groups, substituted and unsubstituted -N(H)-C(=O)-heterocyclylalkyl groups, substituted and unsubstituted -N(alkyl)-C(=O)-heterocyclylalkyl groups, substituted and unsubstituted -N(H)-S(=O)$_2$-alkyl groups, substituted and unsubstituted -N(H)-S(=O)$_2$-aryl, substituted and unsubstituted -N(H)-S(=O)$_2$-heterocyclyl groups, substituted and unsubstituted -C(=O)-alkyl groups, substituted and unsubstituted -C(=O)-aryl, substituted and unsubstituted -C(=O)-aralkyl, substituted and unsubstituted -C(=O)-heterocyclyl groups, substituted and unsubstituted -C(=O)-heterocyclylalkyl groups, -C(=O)-NH$_2$, substituted and unsubstituted -C(=O)-N(H)(alkyl) groups, substituted and unsubstituted -C(=O)-N(alkyl)$_2$ groups, substituted and unsubstituted -C(=O)-N(H)(aryl) groups, substituted and unsubstituted -C(=O)-N(alkyl)(aryl) groups, substituted and unsubstituted -C(=O)-N(aryl)$_2$ groups, substituted and

unsubstituted -C(=O)-N(H)(aralkyl) groups, substituted and unsubstituted -C(=O)-N(alkyl)(aralkyl) groups, substituted and unsubstituted -C(=O)-N(aralkyl)$_2$ groups, substituted and unsubstituted -C(=O)-N(H)(heterocyclyl) groups, substituted and unsubstituted -C(=O)-N(alkyl)(heterocyclyl) groups, substituted and unsubstituted -C(=O)-N(heterocyclyl)$_2$ groups, substituted and unsubstituted -C(=O)-N(H)(heterocyclylalkyl) groups, substituted and unsubstituted -C(=O)-N(alkyl)(heterocyclylalkyl) groups, substituted and unsubstituted -C(=O)-N(heterocyclylalkyl)$_2$ groups, -CO_2H, substituted and unsubstituted -C(=O)-O-alkyl groups, C(=O)-O-aryl groups -C(=O)-O-aralkyl groups, substituted and unsubstituted -C(=O)-O-heterocyclyl groups, or substituted and unsubstituted -C(=O)-O-heterocyclylalkyl groups;

R^4 is selected from –H or substituted and unsubstituted alkyl groups having from 1 to 12 carbon atoms;

R^5 and R^8 are independently selected from -H, -F, -Cl, -Br, -I, -CN, -NO_2, substituted and unsubstituted alkyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted alkenyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted heterocyclylalkyl groups, -OH, substituted and unsubstituted alkoxy groups, substituted and unsubstituted heterocyclyloxy groups, substituted and unsubstituted heterocyclylalkoxy groups; or R^5 may be absent if A is nitrogen; or R^8 may be absent if D is nitrogen;

R^6 and R^7 are independently selected from -H, -F, -Cl, -Br, -I, -CN, -NO_2, substituted and unsubstituted alkyl groups having

from 1 to 12 carbon atoms, substituted and unsubstituted alkenyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted aryl groups, substituted and unsubstituted arylakyl groups, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted heterocyclylalkyl groups, -SH, substituted and unsubstituted -S-alkyl groups, substituted and unsubstituted -S-heterocyclyl groups, $-S(=O)_2-NH_2$, substituted and unsubstituted $-S(=O)_2-N(H)(alkyl)$ groups, substituted and unsubstituted $-S(=O)_2-N(alkyl)_2$ groups, -OH, substituted and unsubstituted alkoxy groups, substituted and unsubstituted heterocyclyloxy groups, substituted and unsubstituted heterocyclylalkoxy groups, $-NH_2$, substituted and unsubstituted -N(H)(alkyl) groups, substituted and unsubstituted $-N(alkyl)_2$ groups, substituted and unsubstituted -N(H)(heterocyclyl) groups, substituted and unsubstituted -N(alkyl)(heterocyclyl) groups, substituted and unsubstituted $-N(heterocyclyl)_2$ groups, substituted and unsubstituted -N(H)(heterocyclylalkyl) groups, substituted and unsubstituted -N(alkyl)(heterocyclylalkyl) groups, substituted and unsubstituted $-N(heterocyclylalkyl)_2$ groups, substituted and unsubstituted -N(H)-C(=O)-alkyl groups, substituted and unsubstituted -N(H)-C(=O)-heterocyclyl groups, substituted and unsubstituted -N(H)-C(=O)-heterocyclylalkyl groups, substituted and unsubstituted -N(alkyl)-C(=O)-alkyl groups, substituted and unsubstituted -N(alkyl)-C(=O)-heterocyclyl groups, substituted and unsubstituted -N(alkyl)-C(=O)-heterocyclylalkyl, substituted and unsubstituted $-N(H)-S(=O)_2$-alkyl groups, substituted and unsubstituted $-N(H)-S(=O)_2$-heterocyclyl groups, substituted and unsubstituted $-N(H)-S(=O)_2$-heterocyclylalkyl groups, substituted and unsubstituted -C(=O)-alkyl groups, substituted and unsubstituted -C(=O)-heterocyclyl groups, substituted and unsubstituted -C(=O)-heterocyclylalkyl groups, $-C(=O)-NH_2$,

substituted and unsubstituted -C(=O)-N(H)(alkyl) groups, substituted and unsubstituted -C(=O)-N(alkyl)$_2$ groups, substituted and unsubstituted -C(=O)-N(H)(heterocyclyl) groups, substituted and unsubstituted -C(=O)-N(alkyl)(heterocyclyl) groups, substituted and unsubstituted -C(=O)-N(heterocyclyl)$_2$ groups, substituted and unsubstituted -C(=O)-N(H)(heterocyclylalkyl) groups, substituted and unsubstituted -C(=O)-N(alkyl)(heterocyclylalkyl) groups, substituted and unsubstituted -C(=O)-N(heterocyclylalkyl)$_2$ groups, -CO_2H, substituted and unsubstituted -C(=O)-O-alkyl groups, substituted and unsubstituted -C(=O)-O-heterocyclyl groups, or substituted and unsubstituted -C(=O)-O-heterocyclylalkyl groups; or R^6 is absent if B is nitrogen; or R^7 is absent if C is nitrogen;

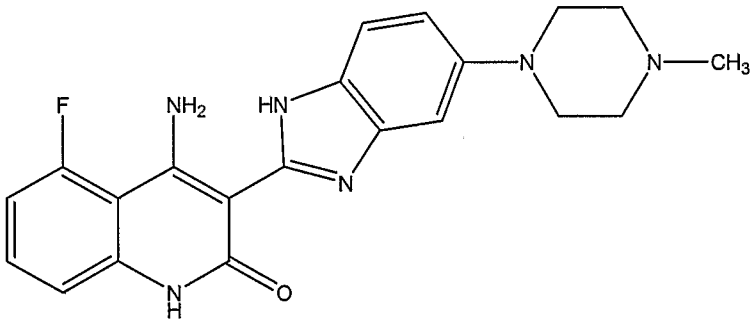
R^9 is selected from -H, substituted and unsubstituted alkyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted alkenyl groups having from 1 to 12 carbons, substituted and unsubstituted aryl groups, substituted and unsubstituted aralkyl groups, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted heterocyclylalkyl groups, -OH, substituted and unsubstituted alkoxy groups, substituted and unsubstituted heterocyclyloxy groups, -NH_2, or substituted and unsubstituted heterocyclylaminoalkyl; and

R^{10} is -H.

[0316] In some embodiments of the method of inhibiting a tyrosine kinase in a subject and/or the method of treating a biological condition mediated by tyrosine kinase activity in a subject using a compound of Structure I, a tautomer of the compound, a pharmaceutically acceptable salt

of the compound, a pharmaceutically acceptable salt of the tautomer, or mixtures thereof, the tyrosine kinase is FLT-3. In other embodiments, the tyrosine kinase is c-Kit. In still other embodiments, the tyrosine kinase is c-ABL. In still other embodiments, the tyrosine kinase is FGFR3. In still other embodiments, the tyrosine kinase is p60src. In still other embodiments, the tyrosine kinase is VEGFR3. In still other embodiments, the tyrosine kinase is PDGFRα. In other embodiments, the tyrosine kinase is PDGFRβ.

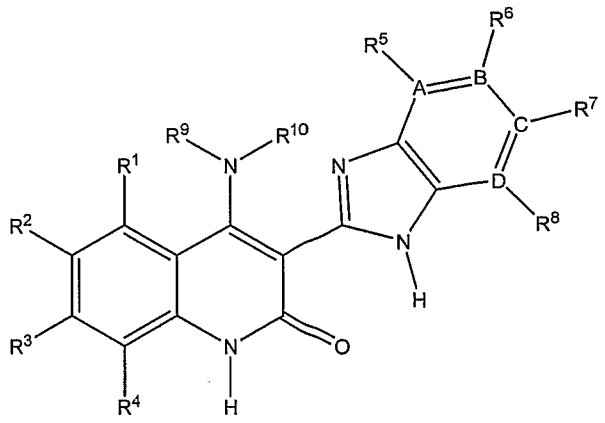
[0317] In some embodiments of the method of inhibiting a tyrosine kinase in a subject and/or the method of treating a biological condition mediated by tyrosine kinase activity in a subject using a compound of Structure I, a tautomer of the compound, a pharmaceutically acceptable salt of the compound, a pharmaceutically acceptable salt of the tautomer, or mixtures thereof, the compound of Structure I has the following formula.



Methods Relating to Fibroblast Growth Factor Receptor 3

[0318] In one aspect, the present invention provides a method of inhibiting fibroblast growth factor receptor 3 in a subject and/or a method of treating a biological condition mediated by fibroblast growth factor receptor 3 in a subject. The method includes administering to the subject a compound of Structure I, a tautomer of the compound, a pharmaceutically acceptable salt of the compound, a pharmaceutically acceptable salt of the tautomer, or a mixture thereof. The fibroblast growth factor receptor 3 is inhibited in the subject after administration. The invention also provides the use of a compound of Structure I, a tautomer of the compound, a pharmaceutically

acceptable salt of the compound, a pharmaceutically acceptable salt of the tautomer, or a mixture thereof in the preparation of a medicament for inhibiting fibroblast growth factor receptor 3 in a subject and/or treating a biological condition mediated by fibroblast growth factor receptor 3 in a subject. Structure I has the following formula:



I

where:

A, B, C, and D are independently selected from carbon or nitrogen;

R^1 is selected from the group consisting of -H, -F, -Cl, -Br, -I, -CN, -NO_2, substituted and unsubstituted alkyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted alkenyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted aryl groups, substituted and unsubstituted aralkyl groups, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted heterocyclylalkyl groups, -SH, substituted and unsubstituted -S-alkyl groups, substituted and unsubstituted -S-heterocyclyl groups, -OH, substituted and unsubstituted alkoxy groups, substituted and unsubstituted heterocyclyloxy groups, substituted and unsubstituted heterocyclylalkoxy groups, -NH_2, substituted and unsubstituted -N(H)(alkyl) groups, substituted and unsubstituted -N(alkyl)$_2$

groups, substituted and unsubstituted -N(H)(heterocyclyl) groups, substituted and unsubstituted -N(alkyl)(heterocyclyl) groups, substituted and unsubstituted -N(heterocyclyl)$_2$ groups, substituted and unsubstituted -N(H)(heterocyclylalkyl) groups, substituted and unsubstituted -N(alkyl)(heterocyclylalkyl) groups, substituted and unsubstituted -N(heterocyclylalkyl)$_2$ groups, substituted and unsubstituted -N(H)-C(=O)-alkyl groups, substituted and unsubstituted -N(H)-C(=O)-heterocyclyl groups, substituted and unsubstituted -N(H)-C(=O)-heterocyclylalkyl groups, substituted and unsubstituted -N(alkyl)-S(=O)$_2$-alkyl groups, substituted and unsubstituted -N(alkyl)-S(=O)$_2$-heterocyclyl groups, substituted and unsubstituted -N(alkyl)-S(=O)$_2$-heterocyclylalkyl groups, substituted and unsubstituted -C(=O)-alkyl groups, substituted and unsubstituted -C(=O)-heterocyclyl groups, substituted and unsubstituted -C(=O)-heterocyclylalkyl groups, -C(=O)-NH$_2$, substituted and unsubstituted -C(=O)-N(H)(alkyl) groups, substituted and unsubstituted -C(=O)-N(alkyl)$_2$ groups, substituted and unsubstituted -C(=O)-N(H)(heterocyclyl) groups, substituted and unsubstituted -C(=O)-N(alkyl)(heterocyclyl) groups, substituted and unsubstituted -C(=O)-N(heterocyclyl)$_2$ groups, substituted and unsubstituted -C(=O)-N(H)(heterocyclylalkyl) groups, substituted and unsubstituted -C(=O)-N(alkyl)(heterocyclylalkyl) groups, substituted and unsubstituted -C(=O)-N(heterocyclylalkyl)$_2$ groups, -CO$_2$H, substituted and unsubstituted -C(=O)-O-alkyl groups, substituted and unsubstituted -C(=O)-O-heterocyclyl groups, and substituted and unsubstituted -C(=O)-O-heterocyclylalkyl groups;

R^2 and R^3 are independently selected from the group consisting of -H, -F, -Cl, -Br, -I, -NO$_2$, -CN, substituted and unsubstituted

alkyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted alkenyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted aryl groups, substituted and unsubstituted aralkyl groups, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted heterocyclylalkyl groups, -SH, substituted and unsubstituted -S-alkyl groups, substituted and unsubstituted $-S(=O)_2-O$-alkyl groups, substituted and unsubstituted $-S(=O)_2$-alkyl groups, substituted and unsubstituted $-S(=O)_2$-heterocyclyl groups, $-S(=O)_2-NH_2$, substituted and unsubstituted $-S(=O)_2-N(H)$(alkyl) groups, substituted and unsubstituted $-S(=O)_2-N(alkyl)_2$ groups, substituted and unsubstituted -S(=O)-alkyl groups, substituted and unsubstituted -S(=O)-heterocyclyl groups, -OH, substituted and unsubstituted alkoxy groups, substituted and unsubstituted aryloxy groups, substituted and unsubstituted heterocyclyloxy groups, substituted and unsubstituted heterocyclylalkoxy groups, $-NH_2$, substituted and unsubstituted -N(H)(alkyl) groups, substituted and unsubstituted $-N(alkyl)_2$ groups, substituted and unsubstituted -N(H)(aryl) groups, substituted and unsubstituted -N(alkyl)(aryl) groups, substituted and unsubstituted $-N(aryl)_2$ groups, substituted and unsubstituted -N(H)(aralkyl) groups, substituted and unsubstituted -N(alkyl)(aralkyl) groups, substituted and unsubstituted $-N(aralkyl)_2$ groups, substituted and unsubstituted -N(H)(heterocyclyl) groups, substituted and unsubstituted -N(alkyl)(heterocyclyl) groups, substituted and unsubstituted $-N(heterocyclyl)_2$ groups, substituted and unsubstituted -N(H)(heterocyclylalkyl) groups, substituted and unsubstituted -N(alkyl)(heterocyclylalkyl) groups, substituted and unsubstituted $-N(heterocyclylalkyl)_2$ groups, substituted and unsubstituted -N(H)-C(=O)-alkyl groups, substituted and unsubstituted -N(alkyl)-C(=O)-alkyl groups, substituted and unsubstituted -N(H)-C(=O)-aryl groups, substituted and

unsubstituted -N(alkyl)-C(=O)-aryl groups, substituted and unsubstituted -N(H)-C(=O)-aralkyl groups, substituted and unsubstituted -N(alkyl)-C(=O)-aralkyl groups, substituted and unsubstituted -N(H)-C(=O)-heterocyclyl groups, substituted and unsubstituted -N(alkyl)-C(=O)-heterocyclyl groups, substituted and unsubstituted -N(H)-C(=O)-heterocyclylalkyl groups, substituted and unsubstituted -N(alkyl)-C(=O)-heterocyclylalkyl groups, substituted and unsubstituted -N(H)-$S(=O)_2$-alkyl groups, substituted and unsubstituted -N(H)-$S(=O)_2$-aryl, substituted and unsubstituted -N(H)-$S(=O)_2$-heterocyclyl groups, substituted and unsubstituted -C(=O)-alkyl groups, substituted and unsubstituted -C(=O)-aryl, substituted and unsubstituted -C(=O)-aralkyl, substituted and unsubstituted -C(=O)-heterocyclyl groups, substituted and unsubstituted -C(=O)-heterocyclylalkyl groups, -C(=O)-NH_2, substituted and unsubstituted -C(=O)-N(H)(alkyl) groups, substituted and unsubstituted -C(=O)-N(alkyl)$_2$ groups, substituted and unsubstituted -C(=O)-N(H)(aryl) groups, substituted and unsubstituted -C(=O)-N(alkyl)(aryl) groups, substituted and unsubstituted -C(=O)-N(aryl)$_2$ groups, substituted and unsubstituted -C(=O)-N(H)(aralkyl) groups, substituted and unsubstituted -C(=O)-N(alkyl)(aralkyl) groups, substituted and unsubstituted -C(=O)-N(aralkyl)$_2$ groups, substituted and unsubstituted -C(=O)-N(H)(heterocyclyl) groups, substituted and unsubstituted -C(=O)-N(alkyl)(heterocyclyl) groups, substituted and unsubstituted -C(=O)-N(heterocyclyl)$_2$ groups, substituted and unsubstituted -C(=O)-N(H)(heterocyclylalkyl) groups, substituted and unsubstituted -C(=O)-N(alkyl)(heterocyclylalkyl) groups, substituted and unsubstituted -C(=O)-N(heterocyclylalkyl)$_2$ groups, -CO_2H, substituted and unsubstituted -C(=O)-O-alkyl groups, C(=O)-O-aryl groups -C(=O)-O-aralkyl groups, substituted and unsubstituted

-C(=O)-O-heterocyclyl groups, and substituted and unsubstituted -C(=O)-O-heterocyclylalkyl groups;

R^4 is selected from the group consisting of –H and substituted and unsubstituted alkyl groups having from 1 to 12 carbon atoms;

R^5 and R^8 are independently selected from the group consisting of -H, -F, -Cl, -Br, -I, -CN, $-NO_2$, substituted and unsubstituted alkyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted alkenyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted heterocyclylalkyl groups, -OH, substituted and unsubstituted alkoxy groups, substituted and unsubstituted heterocyclyloxy groups, substituted and unsubstituted heterocyclylalkoxy groups; or R^5 may be absent if A is nitrogen; or R^8 may be absent if D is nitrogen;

R^6 and R^7 are independently selected from the group consisting of -H, -F, -Cl, -Br, -I, -CN, $-NO_2$, substituted and unsubstituted alkyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted alkenyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted aryl groups, substituted and unsubstituted arylakyl groups, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted heterocyclylalkyl groups, -SH, substituted and unsubstituted -S-alkyl groups, substituted and unsubstituted -S–heterocyclyl groups, $-S(=O)_2-NH_2$, substituted and unsubstituted $-S(=O)_2-N(H)(alkyl)$ groups, substituted and unsubstituted $-S(=O)_2-N(alkyl)_2$ groups, -OH, substituted and unsubstituted alkoxy groups, substituted and unsubstituted heterocyclyloxy

groups, substituted and unsubstituted heterocyclylalkoxy groups, $-NH_2$, substituted and unsubstituted -N(H)(alkyl) groups, substituted and unsubstituted $-N(alkyl)_2$ groups, substituted and unsubstituted -N(H)(heterocyclyl) groups, substituted and unsubstituted -N(alkyl)(heterocyclyl) groups, substituted and unsubstituted $-N(heterocyclyl)_2$ groups, substituted and unsubstituted -N(H)(heterocyclylalkyl) groups, substituted and unsubstituted -N(alkyl)(heterocyclylalkyl) groups, substituted and unsubstituted $-N(heterocyclylalkyl)_2$ groups, substituted and unsubstituted -N(H)-C(=O)-alkyl groups, substituted and unsubstituted -N(H)-C(=O)-heterocyclyl groups, substituted and unsubstituted -N(H)-C(=O)-heterocyclylalkyl groups, substituted and unsubstituted -N(alkyl)-C(=O)-alkyl groups, substituted and unsubstituted -N(alkyl)-C(=O)-heterocyclyl groups, substituted and unsubstituted -N(alkyl)-C(=O)-heterocyclylalkyl, substituted and unsubstituted $-N(H)-S(=O)_2$-alkyl groups, substituted and unsubstituted $-N(H)-S(=O)_2$-heterocyclyl groups, substituted and unsubstituted $-N(H)-S(=O)_2$-heterocyclylalkyl groups, substituted and unsubstituted -C(=O)-alkyl groups, substituted and unsubstituted -C(=O)-heterocyclyl groups, substituted and unsubstituted -C(=O)-heterocyclylalkyl groups, $-C(=O)-NH_2$, substituted and unsubstituted -C(=O)-N(H)(alkyl) groups, substituted and unsubstituted $-C(=O)-N(alkyl)_2$ groups, substituted and unsubstituted -C(=O)-N(H)(heterocyclyl) groups, substituted and unsubstituted -C(=O)-N(alkyl)(heterocyclyl) groups, substituted and unsubstituted $-C(=O)-N(heterocyclyl)_2$ groups, substituted and unsubstituted -C(=O)-N(H)(heterocyclylalkyl) groups, substituted and unsubstituted -C(=O)-N(alkyl)(heterocyclylalkyl) groups, substituted and unsubstituted $-C(=O)-N(heterocyclylalkyl)_2$ groups, $-CO_2H$, substituted and unsubstituted -C(=O)-O-alkyl groups, substituted and unsubstituted -C(=O)-O-heterocyclyl

groups, and substituted and unsubstituted -C(=O)-O-heterocyclylalkyl groups; or R^6 is absent if B is nitrogen; or R^7 is absent if C is nitrogen;

R^9 is selected from the group consisting of -H, substituted and unsubstituted alkyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted alkenyl groups having from 1 to 12 carbons, substituted and unsubstituted aryl groups, substituted and unsubstituted aralkyl groups, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted heterocyclylalkyl groups, -OH, substituted and unsubstituted alkoxy groups, substituted and unsubstituted heterocyclyloxy groups, $-NH_2$, and substituted and unsubstituted heterocyclylaminoalkyl; and

R^{10} is -H.

[0319] In some embodiments, A,B,C, and D are all carbon.

[0320] In some embodiments, R^9 is H.

[0321] In some embodiments, R^1 is selected from -H, -F, -Cl, -Br, -I, substituted or unsubstituted straight or branched chain alkyl groups having from 1 to 8 carbon atoms, substituted or unsubstituted cycloalkyl groups, substituted or unsubstituted heterocyclyl groups, substituted or unsubstituted heterocyclylalkyl groups, substituted or unsubstituted alkoxy groups, substituted or unsubstituted heterocyclyloxy groups, or substituted or unsubstituted heterocyclylalkoxy groups. In some such embodiments, R^1 is -F.

[0322] In some embodiments, R^2 is selected from –H, -Cl, -F, –Br, -I, $-NO_2$, -CN, substituted or unsubstituted straight or branched chain alkyl having from 1 to 8 carbons, substituted or unsubstituted phenyl groups, substituted or unsubstituted thiophene groups, substituted or unsubstituted

1,2,3,6-tetrahydropyridinyl groups, substituted or unsubstituted pyridinyl groups, substituted or unsubstituted straight or branched chain alkoxy groups, substituted or unsubstituted pyridinylalkoxy groups, substituted or unsubstituted dialkylamino groups, or $-CO_2H$. In some such embodiments, R^2 is -H.

[0323] In some embodiments, R^3 is selected from -H, -F, -Cl, -Br, methoxy, or dimethylamino groups. In some such embodiments, R^3 is -H.

[0324] In some embodiments, R^4 is H.

[0325] In some embodiments, R^5 is H and R^8 is H.

[0326] In some embodiments, at least one of R^6 or R^7 is a substituted or unsubstituted heterocyclyl group. In some such embodiments, one of R^6 or R^7 is a substituted or unsubstituted heterocyclyl group and the heterocyclyl group is selected from morpholine, piperazine, piperidine, pyrrolidine, thiomorpholine, homopiperazine, tetrahydrothiophene, tetrahydrofuran, or tetrahydropyran. In other such embodiments, one of R^6 or R^7 is selected from substituted or unsubstituted morpholine groups, or substituted or unsubstituted piperazine groups. In other such embodiments, one of R^6 or R^7 is an N-alkyl substituted piperazine such as N-methyl piperazine. In still other such embodiments, one of R^6 or R^7 is an N-alkyl substituted piperazine and the other of R^6 or R^7 is H, and R^5 and R^8 are both H.

[0327] In some embodiments, the biological condition is multiple myeloma and the subject is a multiple myeloma patient with a t(4;14) chromosomal translocation.

[0328] In some embodiments, the biological condition is multiple myeloma, the subject is a multiple myeloma patient, and the multiple myeloma expresses fibroblast growth factor receptor 3.

[0329] In some embodiments, the subject is a multiple myeloma patient having multiple myeloma cells, and further wherein apoptotic cell death is

induced in the multiple myeloma cells after administration of the compound of Structure I, the tautomer of the compound, the pharmaceutically acceptable salt of the compound, the pharmaceutically acceptable salt of the tautomer, or the mixture thereof to the subject. In some embodiments, the compound of Structure I, the tautomer of the compound, the pharmaceutically acceptable salt of the compound, the pharmaceutically acceptable salt of the tautomer, or the mixture thereof is used to prepare a medicament for inducing aptoptotic cell death in the multiple myeloma cells of a subject that is a multiple myeloma patient.

[0330] In some embodiments, the subject is a multiple myeloma patient, and further wherein osteolytic bone loss is reduced in the subject after administration of the compound of Structure I, the tautomer of the compound, the pharmaceutically acceptable salt of the compound, the pharmaceutically acceptable salt of the tautomer, or the mixture thereof to the subject. In some embodiments, the compound of Structure I, the tautomer of the compound, the pharmaceutically acceptable salt of the compound, the pharmaceutically acceptable salt of the tautomer, or the mixture thereof is used to prepare a medicament for reducing osteolytic bone loss in a subject that is a multiple myeloma patient.

[0331] In some embodiments, the subject is a multiple myeloma patient, and the method further comprises administering dexamethasone to the subject before during or after administration of the compound of Structure I.

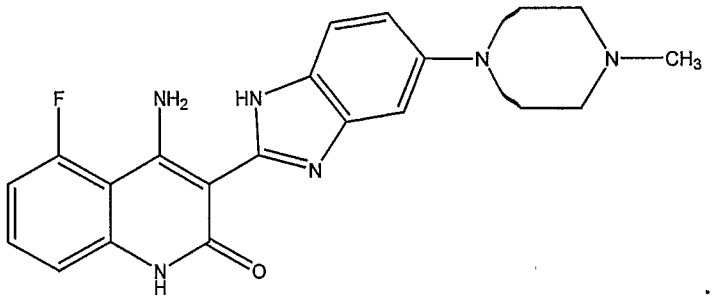
[0332] In some embodiments, the invention provides a composition that includes the compound of Structure I, a tautomer of the compound, a pharmaceutically acceptable salt of the compound, a pharmaceutically acceptable salt of the tautomer, or a mixture thereof and dexamethasone.

[0333] In some embodiments, the invention provides therapeutic compositions comprising a compound of Structure I, a tautomer of the

compound, a pharmaceutically acceptable salt of the compound, a pharmaceutically acceptable salt of the tautomer, or a mixture thereof, and dexamethasone as a combined preparation for simultaneous, separate, or sequential use in inhibiting fibroblast growth factor receptor 3 in a subject and/or treating a biological condition mediated by fibroblast growth factor receptor 3 in a subject. In some such embodiments, the compound of Structure I, the tautomer of the compound, the pharmaceutically acceptable salt of the compound, the pharmaceutically acceptable salt of the tautomer, or the mixture thereof and the dexamethasone are provided as a single composition whereas in other embodiments, the tautomer of the compound, the pharmaceutically acceptable salt of the compound, the pharmaceutically acceptable salt of the tautomer, or the mixture thereof and the dexamethasone are provided separately as parts of a kit.

[0334] In some embodiments, the lactate salt of the compound of Structure I or the tautomer thereof is administered to the subject and/or is used to prepare the medicament.

[0335] In some embodiments, the compound of Structure I has the following formula

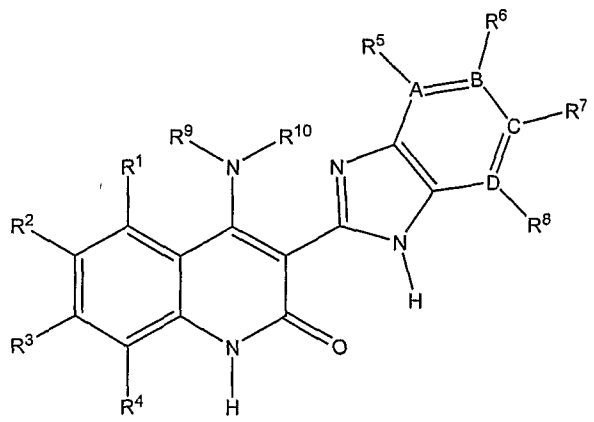


[0336] The invention further provides the use of the compounds of Structure I, tautomers of the compounds, pharmaceutically acceptable salts of the compounds, pharmaceutically acceptable salts of the tautomers, and mixtures thereof in inhibiting fibroblast growth factor receptor 3 or for use in treating a biological condition such as multiple myeloma that is mediated by fibroblast growth factor receptor 3. The invention further provides the use of the compounds of Structure I, tautomers of the compounds, pharmaceutically

acceptable salts of the compounds, pharmaceutically acceptable salts of the tautomers, and mixtures thereof in the preparation and manufacture of medicaments for inhibiting fibroblast growth factor receptor 3 or for use in treating any biological condition mediated by fibroblast growth factor receptor 3. In some embodiments, the compounds may be used to prepare medicaments in containers such as vials, ampoules, or other pharmaceutical formulation storage devices and such storage devices may include labels which may include directions for application such as directions for inhibiting fibroblast growth factor receptor 3 or directions for treating a subject that has a biological condition mediated by fibroblast growth factor receptor 3.

Methods Relating to Cell Division Cycle 2 Kinase

[0337] In some embodiments of the method of inhibiting a tyrosine kinase in a subject and/or the method of treating a biological condition mediated by tyrosine kinase activity in a subject using a compound of Structure I, a tautomer of the compound, a pharmaceutically acceptable salt of the compound, a pharmaceutically acceptable salt of the tautomer, or mixtures thereof, the tyrosine kinase is Cdc2, c-Kit, c-ABL, p60src, VEGFR3, PDGFRα, PDGFRβ, FGFR3, or FLT-3. In some such methods, the Cdc2 or other kinase is inhibited in the subject after administration. In methods of inhibiting Cdc2, Structure I has the following formula:



I

where,

A, B, C, and D are independently selected from carbon or nitrogen;

R^1 is selected from -H, -F, -Cl, -Br, -I, -CN, -NO_2, substituted and unsubstituted alkyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted alkenyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted heterocyclylalkyl groups, -SH, substituted and unsubstituted -S-alkyl groups, substituted and unsubstituted -S-heterocyclyl groups, -OH, substituted and unsubstituted alkoxy groups, substituted and unsubstituted heterocyclyloxy groups, substituted and unsubstituted heterocyclylalkoxy groups, -NH_2, substituted and unsubstituted -N(H)(alkyl) groups, substituted and unsubstituted -N(alkyl)$_2$ groups, substituted and unsubstituted -N(H)(heterocyclyl) groups, substituted and unsubstituted -N(alkyl)(heterocyclyl) groups, substituted and unsubstituted -N(heterocyclyl)$_2$ groups, substituted and unsubstituted -N(H)(heterocyclylalkyl) groups, substituted and unsubstituted -N(alkyl)(heterocyclylalkyl) groups, substituted and unsubstituted -N(heterocyclylalkyl)$_2$ groups, substituted and unsubstituted -N(H)-C(=O)-alkyl groups, substituted and unsubstituted -N(H)-C(=O)-heterocyclyl groups, substituted and unsubstituted -N(H)-C(=O)-heterocyclylalkyl groups, substituted and unsubstituted -C(=O)-alkyl groups, substituted and unsubstituted -C(=O)-heterocyclyl groups, substituted and unsubstituted -C(=O)-heterocyclylalkyl groups, -C(=O)-NH_2, substituted and unsubstituted -C(=O)-N(H)(alkyl) groups, substituted and unsubstituted -N(alkyl)$_2$ groups, substituted and unsubstituted -C(=O)-N(H)(heterocyclyl) groups, substituted and unsubstituted -C(=O)-N(alkyl)(heterocyclyl) groups, substituted and unsubstituted -C(=O)-N(heterocyclyl)$_2$ groups, substituted and unsubstituted

-C(=O)-N(H)(heterocyclylalkyl) groups, substituted and unsubstituted -C(=O)-N(alkyl)(heterocyclylalkyl) groups, substituted and unsubstituted -C(=O)-N(heterocyclylalkyl)$_2$ groups, -CO_2H, substituted and unsubstituted -C(=O)-O-alkyl groups, substituted and unsubstituted -C(=O)-O-heterocyclyl groups, or substituted and unsubstituted -C(=O)-O-heterocyclylalkyl groups;

R^2 and R^3 are independently selected from -H, -F, -Cl, -Br, -I, -NO_2, -CN, substituted and unsubstituted alkyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted alkenyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted aryl groups, substituted and unsubstituted aralkyl groups, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted heterocyclylalkyl groups, -SH, substituted and unsubstituted -S-alkyl groups, substituted and unsubstituted -S(=O)$_2$-O-alkyl groups, substituted and unsubstituted -S(=O)$_2$-alkyl groups, substituted and unsubstituted -S(=O)$_2$-heterocyclyl groups, -S(=O)$_2$-NH_2, substituted and unsubstituted -S(=O)$_2$-N(H)(alkyl) groups, substituted and unsubstituted -S(=O)$_2$-N(alkyl)$_2$ groups, substituted and unsubstituted -S(=O)-alkyl groups, substituted and unsubstituted -S(=O)-heterocyclyl groups, -OH, substituted and unsubstituted alkoxy groups, substituted and unsubstituted aryloxy groups, substituted and unsubstituted heterocyclyloxy groups, substituted and unsubstituted heterocyclylalkoxy groups, -NH_2, substituted and unsubstituted -N(H)(alkyl) groups, substituted and unsubstituted -N(alkyl)$_2$ groups, substituted and unsubstituted -N(H)(aryl) groups, substituted and unsubstituted -N(alkyl)(aryl) groups, substituted and unsubstituted -N(aryl)$_2$ groups, substituted and unsubstituted -N(H)(aralkyl) groups, substituted and unsubstituted -N(alkyl)(aralkyl) groups,

substituted and unsubstituted -N(aralkyl)$_2$ groups, substituted and unsubstituted -N(H)(heterocyclyl) groups, substituted and unsubstituted -N(alkyl)(heterocyclyl) groups, substituted and unsubstituted -N(heterocyclyl)$_2$ groups, substituted and unsubstituted -N(H)(heterocyclylalkyl) groups, substituted and unsubstituted -N(alkyl)(heterocyclylalkyl) groups, substituted and unsubstituted -N(heterocyclylalkyl)$_2$ groups, substituted and unsubstituted -N(H)-C(=O)-alkyl groups, substituted and unsubstituted -N(alkyl)-C(=O)-alkyl groups, substituted and unsubstituted -N(H)-C(=O)-aryl groups, substituted and unsubstituted -N(alkyl)-C(=O)-aryl groups, substituted and unsubstituted -N(H)-C(=O)-aralkyl groups, substituted and unsubstituted -N(alkyl)-C(=O)-aralkyl groups, substituted and unsubstituted -N(H)-C(=O)-heterocyclyl groups, substituted and unsubstituted -N(alkyl)-C(=O)-heterocyclyl groups, substituted and unsubstituted -N(H)-C(=O)-heterocyclylalkyl groups, substituted and unsubstituted -N(alkyl)-C(=O)-heterocyclylalkyl groups, substituted and unsubstituted -N(H)-S(=O)$_2$-alkyl groups, substituted and unsubstituted -N(H)-S(=O)$_2$-aryl, substituted and unsubstituted -N(H)-S(=O)$_2$-heterocyclyl groups, substituted and unsubstituted -C(=O)-alkyl groups, substituted and unsubstituted -C(=O)-aryl, substituted and unsubstituted -C(=O)-aralkyl, substituted and unsubstituted -C(=O)-heterocyclyl groups, substituted and unsubstituted -C(=O)-heterocyclylalkyl groups, -C(=O)-NH$_2$, substituted and unsubstituted -C(=O)-N(H)(alkyl) groups, substituted and unsubstituted -C(=O)-N(alkyl)$_2$ groups, substituted and unsubstituted -C(=O)-N(H)(aryl) groups, substituted and unsubstituted -C(=O)-N(alkyl)(aryl) groups, substituted and unsubstituted -C(=O)-N(aryl)$_2$ groups, substituted and unsubstituted -C(=O)-N(H)(aralkyl) groups, substituted and unsubstituted -C(=O)-N(alkyl)(aralkyl) groups, substituted and

unsubstituted -C(=O)-N(aralkyl)$_2$ groups, substituted and unsubstituted -C(=O)-N(H)(heterocyclyl) groups, substituted and unsubstituted -C(=O)-N(alkyl)(heterocyclyl) groups, substituted and unsubstituted -C(=O)-N(heterocyclyl)$_2$ groups, substituted and unsubstituted -C(=O)-N(H)(heterocyclylalkyl) groups, substituted and unsubstituted -C(=O)-N(alkyl)(heterocyclylalkyl) groups, substituted and unsubstituted -C(=O)-N(heterocyclylalkyl)$_2$ groups, -CO_2H, substituted and unsubstituted -C(=O)-O-alkyl groups, C(=O)-O-aryl groups -C(=O)-O-aralkyl groups, substituted and unsubstituted -C(=O)-O-heterocyclyl groups, or substituted and unsubstituted -C(=O)-O-heterocyclylalkyl groups;

R^4 is selected from –H or substituted and unsubstituted alkyl groups having from 1 to 12 carbon atoms;

R^5 and R^8 are independently selected from -H, -F, –Cl, -Br, -I, -CN, -NO_2, substituted and unsubstituted alkyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted alkenyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted heterocyclylalkyl groups, -OH, substituted and unsubstituted alkoxy groups, substituted and unsubstituted heterocyclyloxy groups, or substituted and unsubstituted heterocyclylalkoxy groups; or R^5 may be absent if A is nitrogen; or R^8 may be absent if D is nitrogen;

R^6 and R^7 are independently selected from -H, -F, –Cl, -Br, -I, -CN, -NO_2, substituted and unsubstituted alkyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted alkenyl groups having from 1 to 12 carbon atoms, substituted

and unsubstituted heterocyclyl groups, substituted and unsubstituted heterocyclylalkyl groups, -SH, substituted and unsubstituted -S-alkyl groups, substituted and unsubstituted -S-heterocyclyl groups, $-S(=O)_2-NH_2$, substituted and unsubstituted $-S(=O)_2-N(H)(alkyl)$ groups, substituted and unsubstituted $-S(=O)_2-N(alkyl)_2$ groups, -OH, substituted and unsubstituted alkoxy groups, substituted and unsubstituted heterocyclyloxy groups, substituted and unsubstituted heterocyclylalkoxy groups, $-NH_2$, substituted and unsubstituted -N(H)(alkyl) groups, substituted and unsubstituted $-N(alkyl)_2$ groups, substituted and unsubstituted -N(H)(heterocyclyl) groups, substituted and unsubstituted -N(alkyl)(heterocyclyl) groups, substituted and unsubstituted $-N(heterocyclyl)_2$ groups, substituted and unsubstituted -N(H)(heterocyclylalkyl) groups, substituted and unsubstituted -N(alkyl)(heterocyclylalkyl) groups, substituted and unsubstituted $-N(heterocyclylalkyl)_2$ groups, substituted and unsubstituted -N(H)-C(=O)-alkyl groups, substituted and unsubstituted -N(H)-C(=O)-heterocyclyl groups, substituted and unsubstituted -N(H)-C(=O)-heterocyclylalkyl groups, substituted and unsubstituted -C(=O)-alkyl groups, substituted and unsubstituted -C(=O)-heterocyclyl groups, substituted and unsubstituted -C(=O)-heterocyclylalkyl groups, $-C(=O)-NH_2$, substituted and unsubstituted -C(=O)-N(H)(alkyl) groups, substituted and unsubstituted $-C(=O)-N(alkyl)_2$ groups, substituted and unsubstituted -C(=O)-N(H)(heterocyclyl) groups, substituted and unsubstituted -C(=O)-N(alkyl)(heterocyclyl) groups, substituted and unsubstituted $-C(=O)-N(heterocyclyl)_2$ groups, substituted and unsubstituted -C(=O)-N(H)(heterocyclylalkyl) groups, substituted and unsubstituted -C(=O)-N(alkyl)(heterocyclylalkyl) groups, substituted and unsubstituted $-C(=O)-N(heterocyclylalkyl)_2$ groups, $-CO_2H$, substituted and unsubstituted -C(=O)-O-alkyl

groups, substituted and unsubstituted -C(=O)-O-heterocyclyl groups, or substituted and unsubstituted -C(=O)-O-heterocyclylalkyl groups; or R^6 is absent if B is nitrogen; or R^7 is absent if C is nitrogen;

R^9 is selected from -H, substituted and unsubstituted alkyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted alkenyl groups having from 1 to 12 carbons, substituted and unsubstituted aryl groups, substituted and unsubstituted aralkyl groups, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted heterocyclylalkyl groups, -OH, substituted and unsubstituted alkoxy groups, or $-NH_2$; and

R^{10} is -H.

[0338] In some embodiments of the method of inhibiting Cdc2 kinase, c-Kit, c-ABL, p60src, VEGFR3, PDGFRα, PDGFRβ, FGFR3, or FLT-3 in a subject and/or the method of treating a biological condition mediated by Cdc2 kinase, c-Kit, p60src, c-ABL, VEGFR3, PDGFRα, PDGFRβ, FGFR3, or FLT-3 activity in a subject,

R^1 is selected from -H, -F, -Cl, -Br, -I, -CN, $-NO_2$, substituted and unsubstituted alkyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted alkenyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted heterocyclylalkyl groups, -OH, substituted and unsubstituted alkoxy groups, substituted and unsubstituted heterocyclyloxy groups, substituted and unsubstituted heterocyclylalkoxy groups, $-NH_2$, substituted and unsubstituted -N(H)(alkyl) groups, substituted and unsubstituted $-N(alkyl)_2$ groups, substituted and unsubstituted

-N(H)(heterocyclyl) groups, substituted and unsubstituted -N(alkyl)(heterocyclyl) groups, substituted and unsubstituted -N(heterocyclyl)$_2$ groups, substituted and unsubstituted -N(H)(heterocyclylalkyl) groups, substituted and unsubstituted -N(alkyl)(heterocyclylalkyl) groups, or substituted and unsubstituted -N(heterocyclylalkyl)$_2$ groups;

R^2 and R^3 are independently selected from -H, -F, -Cl, -Br, -I, -NO_2, -CN, substituted and unsubstituted alkyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted alkenyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted aryl groups, substituted and unsubstituted aralkyl groups, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted heterocyclylalkyl groups, -OH, substituted and unsubstituted alkoxy groups, substituted and unsubstituted aryloxy groups, substituted and unsubstituted heterocyclyloxy groups, substituted and unsubstituted heterocyclylalkoxy groups, -NH_2, substituted and unsubstituted -N(H)(alkyl) groups, substituted and unsubstituted -N(alkyl)$_2$ groups, substituted and unsubstituted -N(H)(aryl) groups, substituted and unsubstituted -N(alkyl)(aryl) groups, substituted and unsubstituted -N(aryl)$_2$ groups, substituted and unsubstituted -N(H)(aralkyl) groups, substituted and unsubstituted -N(alkyl)(aralkyl) groups, substituted and unsubstituted -N(aralkyl)$_2$ groups, substituted and unsubstituted -N(H)(heterocyclyl) groups, substituted and unsubstituted -N(alkyl)(heterocyclyl) groups, substituted and unsubstituted -N(heterocyclyl)$_2$ groups, substituted and unsubstituted -N(H)(heterocyclylalkyl) groups, substituted and unsubstituted -N(alkyl)(heterocyclylalkyl) groups, substituted and unsubstituted -N(heterocyclylalkyl)$_2$ groups, substituted and unsubstituted -C(=O)-alkyl groups, substituted and unsubstituted

-C(=O)-heterocyclyl groups, substituted and unsubstituted -C(=O)-heterocyclylalkyl groups, -C(=O)-NH_2, substituted and unsubstituted -C(=O)-N(H)(alkyl) groups, substituted and unsubstituted -C(=O)-N(alkyl)$_2$ groups, substituted and unsubstituted -C(=O)-N(H)(aryl) groups, substituted and unsubstituted -C(=O)-N(alkyl)(aryl) groups, substituted and unsubstituted -C(=O)-N(aryl)$_2$ groups, substituted and unsubstituted -C(=O)-N(H)(aralkyl) groups, substituted and unsubstituted -C(=O)-N(alkyl)(aralkyl) groups, substituted and unsubstituted -C(=O)-N(aralkyl)$_2$ groups, substituted and unsubstituted -C(=O)-N(H)(heterocyclyl) groups, substituted and unsubstituted -C(=O)-N(alkyl)(heterocyclyl) groups, substituted and unsubstituted -C(=O)-N(heterocyclyl)$_2$ groups, substituted and unsubstituted -C(=O)-N(H)(heterocyclylalkyl) groups, substituted and unsubstituted -C(=O)-N(alkyl)(heterocyclylalkyl) groups, substituted and unsubstituted -C(=O)-N(heterocyclylalkyl)$_2$ groups, -CO_2H, substituted and unsubstituted -C(=O)-O-alkyl groups, substituted and unsubstituted -C(=O)-O-heterocyclyl groups, or substituted and unsubstituted -C(=O)-O-heterocyclylalkyl groups;

R^6 and R^7 are independently selected from -H, -F, -Cl, -Br, -I, -CN, -NO_2, substituted and unsubstituted alkyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted alkenyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted heterocyclylalkyl groups, -S(=O)$_2$-NH_2, substituted and unsubstituted -S(=O)$_2$-N(H)(alkyl) groups, substituted and unsubstituted -S(=O)$_2$-N(alkyl)$_2$ groups, -OH, substituted and unsubstituted alkoxy groups, substituted and unsubstituted heterocyclyloxy groups, substituted and unsubstituted heterocyclylalkoxy groups, -NH_2, substituted and unsubstituted

-N(H)(alkyl) groups, substituted and unsubstituted -N(alkyl)$_2$ groups, substituted and unsubstituted -N(H)(heterocyclyl) groups, substituted and unsubstituted -N(alkyl)(heterocyclyl) groups, substituted and unsubstituted -N(heterocyclyl)$_2$ groups, substituted and unsubstituted -N(H)(heterocyclylalkyl) groups, substituted and unsubstituted -N(alkyl)(heterocyclylalkyl) groups, substituted and unsubstituted -N(heterocyclylalkyl)$_2$ groups, substituted and unsubstituted -N(H)-C(=O)-alkyl groups, substituted and unsubstituted -N(H)-C(=O)-heterocyclyl groups, substituted and unsubstituted -N(H)-C(=O)-heterocyclylalkyl groups, substituted and unsubstituted -C(=O)-alkyl groups, substituted and unsubstituted -C(=O)-heterocyclyl groups, substituted and unsubstituted -C(=O)-heterocyclylalkyl groups, -C(=O)-NH_2, substituted and unsubstituted -C(=O)-N(H)(alkyl) groups, substituted and unsubstituted -C(=O)-N(alkyl)$_2$ groups, substituted and unsubstituted -C(=O)-N(H)(heterocyclyl) groups, substituted and unsubstituted -C(=O)-N(alkyl)(heterocyclyl) groups, substituted and unsubstituted -C(=O)-N(heterocyclyl)$_2$ groups, substituted and unsubstituted -C(=O)-N(H)(heterocyclylalkyl) groups, substituted and unsubstituted -C(=O)-N(alkyl)(heterocyclylalkyl) groups, substituted and unsubstituted -C(=O)-N(heterocyclylalkyl)$_2$ groups, -CO_2H, substituted and unsubstituted -C(=O)-O-alkyl groups, substituted and unsubstituted -C(=O)-O-heterocyclyl groups, or substituted and unsubstituted -C(=O)-O-heterocyclylalkyl groups; or R^6 is absent if B is nitrogen; or R^7 is absent if C is nitrogen.

[0339] In some embodiments of the method of inhibiting Cdc2 kinase, c-Kit, c-ABL, p60src, VEGFR3, PDGFRα, PDGFRβ, FGFR3, or FLT-3 in a subject and/or the method of treating a biological condition mediated by Cdc2

kinase, c-Kit, c-ABL, p60src, VEGFR3, PDGFRα, PDGFRβ, FGFR3, or FLT-3 activity in a subject, A, B, C, and D are all carbon.

[0340] In some embodiments of the method of inhibiting Cdc2 kinase, c-Kit, c-ABL, p60src, VEGFR3, PDGFRα, PDGFRβ, FGFR3, or FLT-3 in a subject and/or the method of treating a biological condition mediated by Cdc2 kinase, c-Kit, c-ABL, p60src, VEGFR3, PDGFRα, PDGFRβ, FGFR3, or FLT-3 activity in a subject, one of A or D is nitrogen, and B and C are both carbon.

[0341] In some embodiments of the method of inhibiting Cdc2 kinase, c-Kit, c-ABL, p60src, VEGFR3, PDGFRα, PDGFRβ, FGFR3, or FLT-3 in a subject and/or the method of treating a biological condition mediated by Cdc2 kinase, c-Kit, c-ABL, p60src, VEGFR3, PDGFRα, PDGFRβ, FGFR3, or FLT-3 activity in a subject, R^9 is selected from -H, substituted and unsubstituted straight and branched chain alkyl groups having from 1 to 8 carbon atoms, substituted and unsubstituted cycloalkyl groups, substituted and unsubstituted aryl groups, substituted and unsubstituted aralkyl groups, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted heterocyclylalkyl groups, substituted and unsubstituted alkoxy groups, or $-NH_2$.

[0342] In some embodiments of the method of inhibiting Cdc2 kinase, c-Kit, c-ABL, p60src, VEGFR3, PDGFRα, PDGFRβ, FGFR3, or FLT-3 in a subject and/or the method of treating a biological condition mediated by Cdc2 kinase, c-Kit, c-ABL, p60src, VEGFR3, PDGFRα, PDGFRβ, FGFR3, or FLT-3 activity in a subject, R^9 is selected from -H, unsubstituted straight and branched chain alkyl groups having from 1 to 8 carbon atoms, substituted and unsubstituted cycloalkyl groups, substituted and unsubstituted aryl groups, substituted and unsubstituted aralkyl groups, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted heterocyclylalkyl groups, substituted and unsubstituted alkoxy groups, substituted and unsubstituted hydroxyalkyl groups, $-NH_2$, substituted and unsubstituted dialkylaminoalkyl

groups, substituted and unsubstituted alkylaminoalkyl groups, or substituted and unsubstituted aminoalkyl groups.

[0343] In some embodiments of the method of inhibiting Cdc2 kinase, c-Kit, c-ABL, p60src, VEGFR3, PDGFRα, PDGFRβ, FGFR3, or FLT-3 in a subject and/or the method of treating a biological condition mediated by Cdc2 kinase, c-Kit, c-ABL, p60src, VEGFR3, PDGFRα, PDGFRβ, FGFR3, or FLT-3 activity in a subject, R^9 is selected from -H, substituted and unsubstituted cycloalkyl groups, substituted and unsubstituted aralkyl groups, substituted and unsubstituted saturated heterocyclyl groups, substituted and unsubstituted condensed unsaturated heterocyclyl groups, substituted and unsubstituted heterocyclylalkyl groups wherein the heterocyclyl moiety is saturated, or substituted and unsubstituted aminoalkyl groups.

[0344] In some embodiments of the method of inhibiting Cdc2 kinase, c-Kit, c-ABL, p60src, VEGFR3, PDGFRα, PDGFRβ, FGFR3, or FLT-3 in a subject and/or the method of treating a biological condition mediated by Cdc2 kinase, c-Kit, c-ABL, p60src, VEGFR3, PDGFRα, PDGFRβ, FGFR3, or FLT-3 activity in a subject, R^9 is selected from 4-aminomethylbenzyl groups, benzimidazolyl groups, quinuclidinyl groups, piperidinyl groups, piperidinylalkyl groups, pyrrolidinyl groups, pyrrolidinylalkyl groups, N-alkylpyrrolidinylalkyl groups, imidazolylalkyl groups, tetrahydrofuranylalkyl groups, aminocyclohexyl groups, hydroxycyclohexyl groups, or 2,2-dimethyl-3-aminopropyl groups. In some such embodiments, R^9 is a quinuclidinyl group. In other such embodiments, R^9 is a quinuclidin-3-yl group.

[0345] In some embodiments of the method of inhibiting Cdc2 kinase, c-Kit, c-ABL, p60src, VEGFR3, PDGFRα, PDGFRβ, FGFR3, or FLT-3 in a subject and/or the method of treating a biological condition mediated by Cdc2 kinase, c-Kit, c-ABL, p60src, VEGFR3, PDGFRα, PDGFRβ, FGFR3, or FLT-3 activity in a subject, R^9 is selected from monocyclic, bicyclic, and polycyclic saturated heterocyclyl groups.

[0346] In some embodiments of the method of inhibiting Cdc2 kinase, c-Kit, c-ABL, p60src, VEGFR3, PDGFRα, PDGFRβ, FGFR3, or FLT-3 in a subject and/or the method of treating a biological condition mediated by Cdc2 kinase, c-Kit, c-ABL, p60src, VEGFR3, PDGFRα, PDGFRβ, FGFR3, or FLT-3 activity in a subject, R^9 is –H.

[0347] In some embodiments of the method of inhibiting Cdc2 kinase, c-Kit, c-ABL, p60src, FGFR3, VEGFR3, PDGFRα, PDGFRβ, or FLT-3 in a subject and/or the method of treating a biological condition mediated by Cdc2 kinase, c-Kit, c-ABL, p60src, FGFR3, VEGFR3, PDGFRα, PDGFRβ, or FLT-3 activity in a subject, R^1 is selected from -H, -F, -Cl, -Br, -I, substituted and unsubstituted straight and branched chain alkyl groups having from 1 to 8 carbon atoms, substituted and unsubstituted cycloalkyl groups, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted heterocyclylalkyl groups, substituted and unsubstituted alkoxy groups, substituted and unsubstituted heterocyclyloxy groups, or substituted and unsubstituted heterocyclylalkoxy groups.

[0348] In some embodiments of the method of inhibiting Cdc2 kinase, c-Kit, c-ABL, p60src, FGFR3, VEGFR3, PDGFRα, PDGFRβ, or FLT-3 in a subject and/or the method of treating a biological condition mediated by Cdc2 kinase, c-Kit, c-ABL, p60src, FGFR3, VEGFR3, PDGFRα, PDGFRβ, or FLT-3 activity in a subject, R^1 is selected from–H, –F, –Cl, substituted and unsubstituted straight or branched chain alkoxy, substituted and unsubstituted piperidinyloxy, substituted and unsubstituted morpholinyl, or substituted and unsubstituted piperazinyl. In some such embodiments, R^1 is selected from –H, –F, –Cl. methoxy, N-methylpiperidin-3-yloxy, N-methylpiperidin-4-yloxy, morpholin-4-yl, N-methylpiperazin-4-yl, or N-ethylpiperazin-4-yl. In other such embodiments, R^1 is –H.

[0349] In some embodiments of the method of inhibiting Cdc2 kinase, c-Kit, c-ABL, p60src, FGFR3, VEGFR3, PDGFRα, PDGFRβ, or FLT-3 in a subject and/or the method of treating a biological condition mediated by Cdc2

kinase, c-Kit, c-ABL, p60src, FGFR3, VEGFR3, PDGFRα, PDGFRβ, or FLT-3 activity in a subject, R^2 is selected from -H, -F, -Cl, -Br, -I, $-NO_2$, -CN, substituted and unsubstituted straight and branched chain alkyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted cycloalkyl groups, substituted and unsubstituted aryl groups, substituted and unsubstituted aralkyl groups, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted heterocyclylalkyl groups, -OH, substituted and unsubstituted alkoxy groups, substituted and unsubstituted heterocyclylalkoxy groups, $-NH_2$, substituted and unsubstituted -N(H)(alkyl) groups, substituted and unsubstituted $-N(alkyl)_2$ groups, $-C(=O)-NH_2$, substituted and unsubstituted -C(=O)-N(H)(aryl) groups, substituted and unsubstituted -C(=O)-N(alkyl)(aryl) groups, substituted and unsubstituted $-C(=O)-N(aryl)_2$ groups, substituted and unsubstituted -C(=O)-N(H)(aralkyl) groups, substituted and unsubstituted -C(=O)-N(alkyl)(aralkyl) groups, substituted and unsubstituted $-C(=O)-N(aralkyl)_2$ groups, or $-CO_2H$.

[0350] In some embodiments of the method of inhibiting Cdc2 kinase, c-Kit, c-ABL, p60src, FGFR3, VEGFR3, PDGFRα, PDGFRβ, or FLT-3 in a subject and/or the method of treating a biological condition mediated by Cdc2 kinase, c-Kit, c-ABL, p60src, FGFR3, VEGFR3, PDGFRα, PDGFRβ, or FLT-3 activity in a subject, R^2 is selected from –H, -Cl, -F, -Br, -I, $-NO_2$, -CN, substituted and unsubstituted straight or branched chain alkyl having from 1 to 8 carbons, substituted and unsubstituted phenyl groups, substituted and unsubstituted thiophene groups, substituted and unsubstituted 1,2,3,6-tetrahydropyridinyl groups, substituted and unsubstituted pyridinyl groups, substituted and unsubstituted straight or branched chain alkoxy groups, substituted and unsubstituted pyridinylalkoxy groups, substituted and unsubstituted dialkylamino groups, or $-CO_2H$.

[0351] In some embodiments of the method of inhibiting Cdc2 kinase, c-Kit, c-ABL, p60src, FGFR3, VEGFR3, PDGFRα, PDGFRβ, or FLT-3 in a subject and/or the method of treating a biological condition mediated by Cdc2 kinase, c-Kit, c-ABL, p60src, FGFR3, VEGFR3, PDGFRα, PDGFRβ, or FLT-3

activity in a subject, R^2 is a substituted and unsubstituted aryl group selected from phenyl, 2-hydroxyphenyl, 2-amino-4-carboxyphenyl, 2, 6-difluorophenyl, 3-methoxyphenyl, 3-carboxyphenyl, 3-acetylphenyl, 3-aminophenyl, 3-hydroxyphenyl, 3-acetamidophenyl, 3-carboxamidophenyl, 4-cyanophenyl, 4-hydroxyphenyl, 4-methoxyphenyl, or 4-carboxyphenyl.

[0352] In some embodiments of the method of inhibiting Cdc2 kinase, c-Kit, c-ABL, p60src, FGFR3, VEGFR3, PDGFRα, PDGFRβ, or FLT-3 in a subject and/or the method of treating a biological condition mediated by Cdc2 kinase, c-Kit, c-ABL, p60src, FGFR3, VEGFR3, PDGFRα, PDGFRβ, or FLT-3 activity in a subject, R^2 is selected from –H, -F, -Cl, -Br, -I, methyl, methoxy, or $-CO_2H$. In some such embodiments, R^2 is $-CO_2H$.

[0353] In some embodiments of the method of inhibiting Cdc2 kinase, c-Kit, c-ABL, p60src, FGFR3, VEGFR3, PDGFRα, PDGFRβ, or FLT-3 in a subject and/or the method of treating a biological condition mediated by Cdc2 kinase, c-Kit, c-ABL, p60src, FGFR3, VEGFR3, PDGFRα, PDGFRβ, or FLT-3 activity in a subject, R^3 is selected from -H, -F, -Cl, -Br, -I, -CN, substituted and unsubstituted straight or branched chain alkyl groups having from 1 to 8 carbon atoms, substituted and unsubstituted cycloalkyl groups, substituted and unsubstituted aryl groups, substituted and unsubstituted aralkyl groups, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted heterocyclylalkyl groups, -OH, substituted and unsubstituted alkoxy groups, substituted and unsubstituted heterocyclyloxy groups, substituted and unsubstituted heterocyclylalkoxy groups, substituted and unsubstituted -N(H)(alkyl) groups, substituted and unsubstituted $-N(alkyl)_2$ groups, or substituted and unsubstituted -N(H)(heterocyclylalkyl) groups.

[0354] In some embodiments of the method of inhibiting Cdc2 kinase, c-Kit, c-ABL, p60src, FGFR3, VEGFR3, PDGFRα, PDGFRβ, or FLT-3 in a subject and/or the method of treating a biological condition mediated by Cdc2 kinase, c-Kit, c-ABL, p60src, FGFR3, or VEGFR3, PDGFRα, PDGFRβ, FLT–3 activity in a subject, R^3 is selected from -H, -F, -Cl, -Br, -I, -CN, substituted

and unsubstituted straight or branched chain alkyl groups having from 1 to 8 carbon atoms, substituted and unsubstituted phenyl groups, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted heterocyclylalkyl groups, -OH, unsubstituted straight or branched chain alkoxy groups, dialkylaminoalkoxy groups, substituted and unsubstituted pyrrolidinylalkoxy groups, substituted and unsubstituted pyrrolidinonealkoxy, substituted and unsubstituted -N(H)(alkyl) groups, substituted and unsubstituted -N(alkyl)$_2$ groups, or substituted and unsubstituted -N(H)(pyrrolidinylalkyl) groups.

[0355] In some embodiments of the method of inhibiting Cdc2 kinase, c-Kit, c-ABL, p60src, FGFR3, VEGFR3, PDGFRα, PDGFRβ, or FLT-3 in a subject and/or the method of treating a biological condition mediated by Cdc2 kinase, c-Kit, c-ABL, p60src, FGFR3, VEGFR3, PDGFRα, PDGFRβ, or FLT-3 activity in a subject, R^3 is selected from methoxy, 3-acetamidophenyl groups, 4-carboxamidophenyl groups, 4-carboxyphenyl groups, 2-alkylimidazolyl groups, N-alkylpiperazinyl groups, 3-substituted pyrrolidinyl groups, 4-carboxyamidopiperidinyl groups, dimethylamino groups, or -N(H)(cyclohexylalkyl) groups wherein the cyclohexyl moiety is substituted with hydroxy.

[0356] In some embodiments of the method of inhibiting Cdc2 kinase, c-Kit, c-ABL, p60src, FGFR3, VEGFR3, PDGFRα, PDGFRβ, or FLT-3 in a subject and/or the method of treating a biological condition mediated by Cdc2 kinase, c-Kit, c-ABL, p60src, FGFR3, VEGFR3, PDGFRα, PDGFRβ, or FLT-3 activity in a subject, R^3 is selected from -H, -F, -Cl, -Br, methoxy, and dimethylamino groups.

[0357] In some embodiments of the method of inhibiting Cdc2 kinase, c-Kit, c-ABL, p60src, FGFR3, VEGFR3, PDGFRα, PDGFRβ, or FLT-3 in a subject and/or the method of treating a biological condition mediated by Cdc2 kinase, c-Kit, c-ABL, p60src, FGFR3, VEGFR3, PDGFRα, PDGFRβ, or FLT-3

activity in a subject, R^4 is selected from -H or $-CH_3$. In some such embodiments, R^4 is –H.

[0358] In some embodiments of the method of inhibiting Cdc2 kinase, c-Kit, c-ABL, p60src, FGFR3, VEGFR3, PDGFRα, PDGFRβ, or FLT-3 in a subject and/or the method of treating a biological condition mediated by Cdc2 kinase, c-Kit, c-ABL, p60src, FGFR3, VEGFR3, PDGFRα, PDGFRβ, or FLT-3 activity in a subject, R^5 and R^8 are independently selected from –H, –F, –OH, or saturated heterocyclyl groups; or R^5 is absent if A is nitrogen; or R^8 is absent if D is nitrogen. In some such embodiments, A and D are both carbon, R^5 is –H, and R^8 is –H.

[0359] In some embodiments of the method of inhibiting Cdc2 kinase, c-Kit, c-ABL, p60src, FGFR3, VEGFR3, PDGFRα, PDGFRβ, or FLT-3 in a subject and/or the method of treating a biological condition mediated by Cdc2 kinase, c-Kit, c-ABL, p60src, FGFR3, VEGFR3, PDGFRα, PDGFRβ, or FLT-3 activity in a subject, R^6 and R^7 are independently selected from -H, -F, -Cl, -Br, -I, -CN, substituted and unsubstituted straight and branched chain alkyl groups having from 1 to 8 carbon atoms, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted heterocyclylalkyl groups, substituted and unsubstituted $-S(=O)_2-N(H)(alkyl)$ groups, substituted and unsubstituted $-S(=O)_2-N(alkyl)_2$ groups, -OH, substituted and unsubstituted alkoxy groups, substituted and unsubstituted heterocyclyloxy groups, substituted and unsubstituted heterocyclylalkoxy groups, substituted and unsubstituted -N(H)(alkyl) groups, substituted and unsubstituted $-N(alkyl)_2$ groups, substituted and unsubstituted -N(H)(heterocyclyl) groups, substituted and unsubstituted -N(alkyl)(heterocyclyl) groups, substituted and unsubstituted -N(H)(heterocyclylalkyl) groups, substituted and unsubstituted -N(alkyl)(heterocyclylalkyl) groups, substituted and unsubstituted -C(=O)-heterocyclyl groups, substituted and unsubstituted -C(=O)-N(H)(alkyl) groups, substituted and unsubstituted $-C(=O)-N(alkyl)_2$ groups, substituted and unsubstituted -C(=O)-N(H)(heterocyclyl) groups, or substituted and

unsubstituted -C(=O)-N(alkyl)(heterocyclyl) groups; or R^6 is absent if B is nitrogen; or R^7 is absent if C is nitrogen.

[0360] In some embodiments of the method of inhibiting Cdc2 kinase, c-Kit, c-ABL, p60src, FGFR3, VEGFR3, PDGFRα, PDGFRβ, or FLT-3 in a subject and/or the method of treating a biological condition mediated by Cdc2 kinase, c-Kit, c-ABL, p60src, FGFR3, VEGFR3, PDGFRα, PDGFRβ, or FLT-3 activity in a subject, R^6 and R^7 are independently selected from -H, -F, -Cl, -CN, substituted and unsubstituted straight and branched chain alkyl groups having from 1 to 8 carbon atoms, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted heterocyclylalkyl groups, substituted and unsubstituted $-S(=O)_2-N(alkyl)_2$ groups, -OH, substituted and unsubstituted straight and branched chain alkoxy groups, substituted and unsubstituted pyrrolidinyloxy groups, substituted and unsubstituted piperidinyloxy groups, substituted and unsubstituted pyrrolidinylalkoxy groups, substituted and unsubstituted tetrahydrofuranylalkoxy groups, substituted and unsubstituted morpholinylalkoxy groups, substituted and unsubstituted $-N(alkyl)_2$ groups, substituted and unsubstituted -N(H)(piperidinyl) groups, substituted and unsubstituted -N(alkyl)(piperidinyl) groups, substituted and unsubstituted -N(H)(piperidinylalkyl) groups, substituted and unsubstituted -C(=O)-heterocyclyl groups, substituted and unsubstituted $-C(=O)-N(alkyl)_2$ groups, or substituted and unsubstituted -C(=O)-N(alkyl)(heterocyclyl) groups; or R^6 is absent if B is nitrogen; or R^7 is absent if C is nitrogen.

[0361] In some embodiments of the method of inhibiting Cdc2 kinase, c-Kit, c-ABL, p60src, FGFR3, VEGFR3, PDGFRα, PDGFRβ, or FLT-3 in a subject and/or the method of treating a biological condition mediated by Cdc2 kinase, c-Kit, c-ABL, p60src, FGFR3, VEGFR3, PDGFRα, PDGFRβ, or FLT-3 activity in a subject, R^6 and R^7 are independently selected from -H, -F, -Cl, -CN, substituted and unsubstituted straight and branched chain alkyl groups having from 1 to 8 carbon atoms, substituted and unsubstituted pyrrolidinyl groups, substituted and unsubstituted morpholinyl groups, substituted and unsubstituted piperazinyl groups, substituted and unsubstituted diazepinyl

groups, substituted and unsubstituted triazolyl groups, substituted and unsubstituted thiomorpholine 1-oxide groups, substituted and unsubstituted pyridinylalkyl groups, substituted and unsubstituted $-S(=O)_2-N(alkyl)_2$ groups, -OH, substituted and unsubstituted straight and branched chain alkoxy groups, substituted and unsubstituted heterocyclyloxy groups, substituted and unsubstituted heterocyclylalkoxy groups, substituted and unsubstituted $-N(alkyl)_2$ groups, substituted and unsubstituted -N(H)(heterocyclyl) groups, substituted and unsubstituted -N(alkyl)(heterocyclyl) groups, substituted and unsubstituted -N(H)(heterocyclylalkyl) groups, substituted and unsubstituted $-C(=O)-N(alkyl)_2$ groups, substituted and unsubstituted -C(=O)-N(alkyl)(piperidinyl) groups, substituted and unsubstituted -C(=O)-(morpholin-4-yl) groups, or substituted and unsubstituted -C(=O)-(piperazin-1-yl) groups; or R^6 is absent if B is nitrogen; or R^7 is absent if C is nitrogen. In some such embodiments, R^6 and R^7 are independently selected from -H, -F, -Cl, -CN, or -OH; or R^6 is absent if B is nitrogen; or R^7 is absent if C is nitrogen. In other such embodiments, B and C are both carbon and R^6 and R^7 are both –H.

[0362] In some embodiments of the method of inhibiting Cdc2 kinase, c-Kit, c-ABL, p60src, FGFR3, VEGFR3, PDGFRα, PDGFRβ, or FLT-3 in a subject and/or the method of treating a biological condition mediated by Cdc2 kinase, c-Kit, c-ABL, p60src, FGFR3, VEGFR3, PDGFRα, PDGFRβ, or FLT-3 activity in a subject, A, B, C, and D are all carbon, and R^5, R^6, R^7, and R^8 are all –H.

[0363] In some embodiments of the method of inhibiting Cdc2 kinase, c-Kit, c-ABL, p60src, FGFR3, VEGFR3, PDGFRα, PDGFRβ, or FLT-3 in a subject and/or the method of treating a biological condition mediated by Cdc2 kinase, c-Kit, c-ABL, p60src, FGFR3, VEGFR3, PDGFRα, PDGFRβ, or FLT-3 activity in a subject, the IC_{50} value of the compound is less than or equal to 10 μM with respect to Cdc2 kinase, c-Kit, c-ABL, p60src, FGFR3, VEGFR3, PDGFRα, PDGFRβ, or FLT-3. In other such embodiments, the IC_{50} value is less than or equal to 1 μM, is less than or equal to 0.1 μM, is less than or

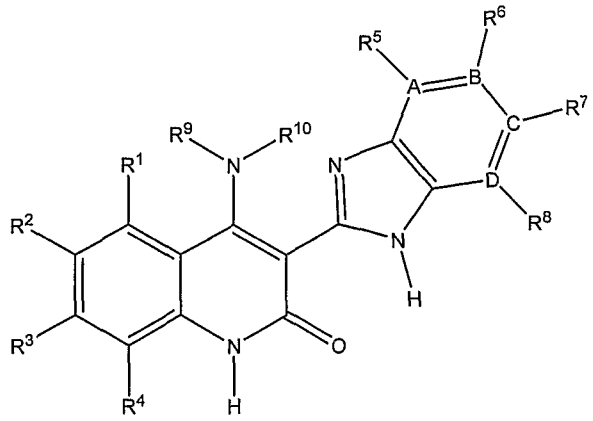
equal to 0.050 μM, is less than or equal to 0.030 μM, is less than or equal to 0.025 μM, or is less than or equal to 0.010 μM.

[0364] In some embodiments of the method of inhibiting Cdc2 kinase, c-Kit, c-ABL, p60src, FGFR3, VEGFR3, PDGFRα, PDGFRβ, or FLT-3 in a subject and/or the method of treating a biological condition mediated by Cdc2 kinase, c-Kit, c-ABL, p60src, FGFR3, VEGFR3, PDGFRα, PDGFRβ, or FLT-3 activity in a subject, the subject is a mammal or is a human.

[0365] In some embodiments of the method of treating a biological condition mediated by Cdc2 kinase, c-Kit, c-ABL, p60src, FGFR3, VEGFR3, PDGFRα, PDGFRβ, or FLT-3 activity in a subject, the biological condition is cancer.

Methods Relating to FYN Oncogene Kinase Related to SRC, FGR, YES

[0366] In some embodiments of the method of inhibiting a tyrosine kinase in a subject and/or the method of treating a biological condition mediated by tyrosine kinase activity in a subject using a compound of Structure I, a tautomer of the compound, a pharmaceutically acceptable salt of the compound, a pharmaceutically acceptable salt of the tautomer, or mixtures thereof, the tyrosine kinase is Fyn. In some such methods, the Fyn is inhibited in the subject after administration. In methods of inhibiting Fyn, Structure I has the following formula:



I

where:

A, B, C, and D are independently selected from carbon or nitrogen;

R^1 and R^3 are independently selected from -H, -F, -Cl, -Br, -I, -CN, -NO_2, or substituted and unsubstituted straight and branched chain alkyl groups having from 1 to 8 carbon atoms;

R^2 is selected from -H, -F, -Cl, -Br, -I, -CN, -NO_2, substituted and unsubstituted alkyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted aryl groups, or substituted and unsubstituted aralkyl groups;

R^4 is selected from –H or substituted and unsubstituted straight and branched chain alkyl groups having from 1 to 8 carbon atoms;

R^5 and R^8 are independently selected from –H or substituted and unsubstituted straight and branched chain alkyl groups having from 1 to 8 carbon atoms; or R^5 may be absent if A is nitrogen; or R^8 may be absent if D is nitrogen;

R^6 and R^7 are independently selected from -H, -F, -Cl, -Br, -I, -CN, -NO_2, substituted and unsubstituted alkyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted alkenyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted heterocyclylalkyl groups, -SH, substituted and unsubstituted -S-alkyl groups, -OH, substituted and unsubstituted alkoxy groups, substituted and unsubstituted heterocyclyloxy groups, substituted and unsubstituted heterocyclylalkoxy groups, -NH_2, substituted and unsubstituted -N(H)(alkyl) groups, substituted and unsubstituted -N(alkyl)$_2$ groups, substituted and unsubstituted -N(H)(heterocyclyl) groups, substituted and unsubstituted -N(alkyl)(heterocyclyl) groups, substituted and unsubstituted -N(heterocyclyl)$_2$ groups, substituted and unsubstituted -N(H)(heterocyclylalkyl) groups, substituted and unsubstituted -N(alkyl)(heterocyclylalkyl) groups, substituted and unsubstituted -N(heterocyclylalkyl)$_2$ groups, substituted and unsubstituted -N(H)-C(=O)-alkyl groups, substituted and unsubstituted -N(H)-C(=O)-heterocyclyl groups, substituted and unsubstituted -N(H)-C(=O)-heterocyclylalkyl, substituted and unsubstituted -N(alkyl)-C(=O)-alkyl groups, substituted and unsubstituted -N(alkyl)-C(=O)-heterocyclyl groups, substituted and unsubstituted -N(alkyl)-C(=O)-heterocyclylalkyl, substituted and unsubstituted -N(H)-S(=O)$_2$-alkyl groups, substituted and unsubstituted -N(H)-S(=O)$_2$-heterocyclyl groups, substituted and unsubstituted -N(H)-S(=O)$_2$-heterocyclylalkyl groups, substituted and unsubstituted -C(=O)-alkyl groups, substituted and unsubstituted -C(=O)-heterocyclyl groups, substituted and unsubstituted -C(=O)-heterocyclylalkyl groups, -C(=O)-NH_2, substituted and unsubstituted -C(=O)-N(H)(alkyl) groups, substituted and unsubstituted -C(=O)-N(alkyl)$_2$ groups, substituted and

unsubstituted -C(=O)-N(H)(heterocyclyl) groups, substituted and unsubstituted -C(=O)-N(alkyl)(heterocyclyl) groups, substituted and unsubstituted -C(=O)-N(H)(heterocyclylalkyl) groups, substituted and unsubstituted -C(=O)-N(alkyl)(heterocyclylalkyl) groups, $-CO_2H$, substituted and unsubstituted -C(=O)-O-alkyl groups, substituted and unsubstituted -C(=O)-O-heterocyclyl groups, or substituted and unsubstituted -C(=O)-O-heterocyclylalkyl groups; or R^6 may be absent if B is nitrogen; or R^7 may be absent if C is nitrogen;

R^9 is selected from –H, substituted and unsubstituted alkyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted alkenyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted heterocyclylalkyl groups, substituted and unsubstituted alkoxy groups, substituted and unsubstituted heterocyclyloxy groups, or substituted and unsubstituted heterocyclylalkoxy; and

R^{10} is –H.

[0367] In some embodiments of the method of inhibiting Fyn in a subject and/or the method of treating a biological condition mediated by Fyn activity in a subject, R^6 and R^7 are independently selected from -H, -F, -Cl, -Br, -I, substituted and unsubstituted alkyl groups having from 1 to 8 carbon atoms, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted heterocyclylalkyl groups, -OH, substituted and unsubstituted alkoxy groups, substituted and unsubstituted heterocyclyloxy, substituted and unsubstituted heterocyclylalkoxy, $-NH_2$, substituted and unsubstituted -N(H)(alkyl) groups, substituted and unsubstituted $-N(alkyl)_2$ groups, substituted and unsubstituted -N(H)(heterocyclyl) groups, substituted and unsubstituted -N(alkyl)(heterocyclyl) groups, substituted and unsubstituted

-N(heterocyclyl)$_2$ groups, substituted and unsubstituted -N(H)(heterocyclylalkyl) groups, substituted and unsubstituted -N(alkyl)(heterocyclylalkyl) groups, substituted and unsubstituted -N(heterocyclylalkyl)$_2$ groups, substituted and unsubstituted -N(H)-C(=O)-alkyl groups, substituted and unsubstituted -N(H)-C(=O)-heterocyclyl groups, substituted and unsubstituted -N(H)-C(=O)-heterocyclylalkyl, substituted and unsubstituted -N(alkyl)-C(=O)-alkyl groups, substituted and unsubstituted -N(alkyl)-C(=O)-heterocyclyl groups, substituted and unsubstituted -N(alkyl)-C(=O)-heterocyclylalkyl, -C(=O)-NH_2, substituted and unsubstituted -C(=O)-N(H)(alkyl) groups, substituted and unsubstituted -C(=O)-N(alkyl)$_2$ groups, substituted and unsubstituted -C(=O)-N(H)(heterocyclyl) groups, substituted and unsubstituted -C(=O)-N(alkyl)(heterocyclyl) groups, substituted and unsubstituted -C(=O)-N(H)(heterocyclylalkyl) groups, or substituted and unsubstituted -C(=O)-N(alkyl)(heterocyclylalkyl) groups; or R^6 may be absent if B is nitrogen; or R^7 may be absent if C is nitrogen.

[0368] In some embodiments of the method of inhibiting Fyn in a subject and/or the method of treating a biological condition mediated by Fyn activity in a subject, A, B, C, and D are all carbon.

[0369] In some embodiments of the method of inhibiting Fyn in a subject and/or the method of treating a biological condition mediated by Fyn activity in a subject, one of A or D is nitrogen, and B and C are both carbon.

[0370] In some embodiments of the method of inhibiting Fyn in a subject and/or the method of treating a biological condition mediated by Fyn activity in a subject, R^9 is selected from –H, substituted and unsubstituted straight or branched chain alkyl groups having from 1 to 8 carbons, substituted and unsubstituted cycloalkyl groups, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted heterocyclylalkyl groups, or substituted and unsubstituted heterocyclyloxy groups.

[0371] In some embodiments of the method of inhibiting Fyn in a subject and/or the method of treating a biological condition mediated by Fyn activity in a subject, R^9 is selected from –H, alkylaminoalkyl groups, substituted and unsubstituted saturated heterocyclyl groups, or substituted and unsubstituted heterocyclylalkyl groups wherein the heterocyclyl moiety is saturated.

[0372] In some embodiments of the method of inhibiting Fyn in a subject and/or the method of treating a biological condition mediated by Fyn activity in a subject, R^9 is selected from –H, substituted and unsubstituted quinuclidinyl groups, substituted and unsubstituted piperidinyl groups, substituted and unsubstituted N-alkylpiperidinyl groups, substituted and unsubstituted piperidinylalkyl groups, substituted and unsubstituted pyrrolidinyl groups, substituted and unsubstituted N-alkyl-pyrrolidinyl, or substituted and unsubstituted pyrrolidinylalkyl groups. In some such embodiments, R^9 is –H.

[0373] In some embodiments of the method of inhibiting Fyn in a subject and/or the method of treating a biological condition mediated by Fyn activity in a subject, R^9 is selected from quinuclidin-3-yl, piperidin-3-yl, piperidin-4-yl, N-methylpiperidin-4-yl, 3-piperidinylmethyl, or pyrrolidin-3-yl.

[0374] In some embodiments of the method of inhibiting Fyn in a subject and/or the method of treating a biological condition mediated by Fyn activity in a subject, R^1 and R^3 are independently selected from –H or -F. In some such embodiments, R^1 is –H.

[0375] In some embodiments of the method of inhibiting Fyn in a subject and/or the method of treating a biological condition mediated by Fyn activity in a subject, R^2 is selected from –H, -F, -Cl, -Br, -I, substituted and unsubstituted straight or branched chain alkyl groups having from 1 to 8 carbons, or substituted and unsubstituted aryl groups. In some such embodiments, R^2 is selected from –H, -F, -Cl, -Br, -I, substituted straight or

branched chain alkyl groups having from 1 to 4 carbons, or substituted aryl groups. In other such embodiments, R^2 is selected from –H, -Cl, –Br, and –I. In still other such embodiments, R^2 is -H.

[0376] In some embodiments of the method of inhibiting Fyn in a subject and/or the method of treating a biological condition mediated by Fyn activity in a subject, R^3 is -H.

[0377] In some embodiments of the method of inhibiting Fyn in a subject and/or the method of treating a biological condition mediated by Fyn activity in a subject, R^3 is –F.

[0378] In some embodiments of the method of inhibiting Fyn in a subject and/or the method of treating a biological condition mediated by Fyn activity in a subject, R^4 is -H.

[0379] In some embodiments of the method of inhibiting Fyn in a subject and/or the method of treating a biological condition mediated by Fyn activity in a subject, R^5 is –H; or where B is nitrogen and R^5 is absent.

[0380] In some embodiments of the method of inhibiting Fyn in a subject and/or the method of treating a biological condition mediated by Fyn activity in a subject, R^6 and R^7 are independently selected from -H, -F, -Cl, -Br, -I, substituted and unsubstituted alkyl groups having from 1 to 8 carbon atoms, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted heterocyclylalkyl groups, $-NH_2$, substituted and unsubstituted -N(H)(alkyl) groups, substituted and unsubstituted $-N(alkyl)_2$ groups, substituted and unsubstituted -N(H)(heterocyclyl) groups, substituted and unsubstituted -N(alkyl)(heterocyclyl) groups, substituted and unsubstituted -N(H)(heterocyclylalkyl) groups, substituted and unsubstituted -N(alkyl)(heterocyclylalkyl) groups, substituted and unsubstituted -N(H)-C(=O)-alkyl groups, substituted and unsubstituted -N(H)-C(=O)-heterocyclyl groups, substituted and unsubstituted -N(alkyl)-C(=O)-heterocyclylalkyl, substituted and unsubstituted

-N(alkyl)-C(=O)-alkyl groups, substituted and unsubstituted -N(alkyl)-C(=O)-heterocyclyl groups, or substituted and unsubstituted -N(alkyl)-C(=O)-heterocyclylalkyl; or R^6 may be absent if B is nitrogen; or R^7 may be absent if C is nitrogen.

[0381] In some embodiments of the method of inhibiting Fyn in a subject and/or the method of treating a biological condition mediated by Fyn activity in a subject, R^6 and R^7 are independently selected from -H, -F, -Cl, -Br, -I, substituted and unsubstituted alkyl groups having from 1 to 8 carbon atoms, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted heterocyclylalkyl groups, substituted and unsubstituted -N(alkyl)(heterocyclyl) groups, or substituted and unsubstituted -N(alkyl)-C(=O)-alkyl groups; or R^6 may be absent if B is nitrogen; or R^7 may be absent if C is nitrogen.

[0382] In some embodiments of the method of inhibiting Fyn in a subject and/or the method of treating a biological condition mediated by Fyn activity in a subject, R^6 and R^7 are independently selected from -H, -F, -Cl, -Br, -I, substituted and unsubstituted alkyl groups having from 1 to 8 carbon atoms, substituted and unsubstituted saturated heterocyclyl groups, substituted and unsubstituted -N(alkyl)(heterocyclyl) groups, wherein the heterocyclyl moiety is saturated, or substituted and unsubstituted -N(alkyl)-C(=O)-alkyl groups; or R^6 may be absent if B is nitrogen; or R^7 may be absent if C is nitrogen. In other such embodiments, R^6 and R^7 are independently selected from -H, -F, or –Cl; or R^6 may be absent if B is nitrogen; or R^7 may be absent if C is nitrogen. In other such embodiments, B is carbon and R^6 is –H; or C is carbon and R^7 is –H.

[0383] In some embodiments of the method of inhibiting Fyn in a subject and/or the method of treating a biological condition mediated by Fyn activity in a subject, R^6 and R^7 are independently selected from substituted and unsubstituted piperazinyl groups, substituted and unsubstituted morpholinyl groups, substituted and unsubstituted pyrrolidinyl groups,

substituted and unsubstituted -N(alkyl)(piperidinyl) groups, or substituted and unsubstituted -N(alkyl)-C(=O)-alkyl groups; or R^6 may be absent if B is nitrogen; or R^7 may be absent if C is nitrogen.

[0384] In some embodiments of the method of inhibiting Fyn in a subject and/or the method of treating a biological condition mediated by Fyn activity in a subject, R^6 and R^7 are independently selected from 4-alkylpiperazin-1-yl groups, 4-alkyl-2-alkyl-piperazin-1-yl groups, 4-alkyl-3-alkylpiperazin-1-yl groups, morpholin-4-yl groups, 2-dialkylaminoalkyl-5-alkylmorpholin-4-yl groups, 3-dialkylaminopyrrolidin-1-yl groups, 3-dialkylaminoalkylpyrrolidin-1-yl groups, -N(alkyl)(1-alkylpiperidinyl) groups, or -N(alkyl)-C(=O)-alkyl groups; or R^6 may be absent if B is nitrogen; or R^7 may be absent if C is nitrogen.

[0385] In some embodiments of the method of inhibiting Fyn in a subject and/or the method of treating a biological condition mediated by Fyn activity in a subject, R^6 and R^7 are independently selected from 4-methylpiperazin-1-yl groups, 4-ethylpiperazin-1-yl groups, 4-isopropylpiperazin-1-yl groups, 4-methyl-2-methylpiperazin-1-yl groups, 4-ethyl-2-methylpiperazin-1-yl groups, 4-isopropyl-2-methylpiperazin-1-yl groups, 4-cyclobutyl-2-methylpiperazin-1-yl groups, 4-methyl-3-methylpiperazin-1-yl groups, morpholin-4-yl groups, 2-dimethylaminomethyl-5-methylmorpholin-4-yl groups, 3-dimethylaminopyrrolidin-1-yl groups, 3-dimethylaminomethylpyrrolidin-1-yl groups, -N(methyl)(1-methylpiperidin-4-yl) groups, or -N(methyl)-C(=O)-methyl groups; or R^6 may be absent if B is nitrogen; or R^7 may be absent if C is nitrogen.

[0386] In some embodiments of the method of inhibiting Fyn in a subject and/or the method of treating a biological condition mediated by Fyn activity in a subject, the IC_{50} value of the compound is less than or equal to 10 μM with respect to Fyn. In other such embodiments, the IC_{50} value is less than or equal to 1 μM, is less than or equal to 0.1 μM, is less than or equal to 0.050

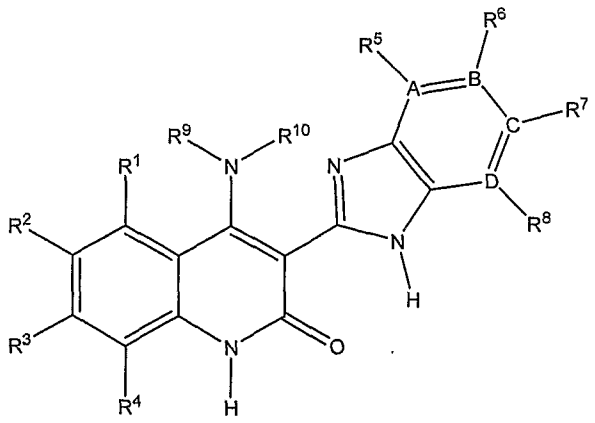
μM, is less than or equal to 0.030 μM, is less than or equal to 0.025 μM, or is less than or equal to 0.010 μM.

[0387] In some embodiments of the method of inhibiting Fyn in a subject and/or the method of treating a biological condition mediated by Fyn activity in a subject, the subject is a mammal or is a human.

[0388] In some embodiments of the method of treating a biological condition mediated by Fyn activity in a subject, the biological condition is an autoimmune disease, and in some such embodiments the biological condition is rheumatoid arthritis or systemic lupus erythematosus. In other such embodiments, the biological condition is organ transplant rejection.

Methods Relating to Lymphocyte-Specific Protein Tyrosine Kinase

[0389] In some embodiments of the method of inhibiting a tyrosine kinase in a subject and/or the method of treating a biological condition mediated by tyrosine kinase activity in a subject using a compound of Structure I, a tautomer of the compound, a pharmaceutically acceptable salt of the compound, a pharmaceutically acceptable salt of the tautomer, or mixtures thereof, the tyrosine kinase is Lck. In some such methods, the Lck is inhibited in the subject after administration. In methods of inhibiting Lck, Structure I has the following formula:



I

where,

A, B, C, and D are independently selected from carbon or nitrogen;

R^1, R^2, and R^3 are independently selected from -H, -F, -Cl, -Br, -I, -CN, -NO_2, or substituted and unsubstituted straight and branched chain alkyl groups having from 1 to 8 carbon atoms;

R^4 is selected from –H or substituted and unsubstituted straight and branched chain alkyl groups having from 1 to 8 carbon atoms;

R^5 and R^8 are independently selected from –H or substituted and unsubstituted straight and branched chain alkyl groups having from 1 to 8 carbon atoms; or R^5 may be absent if A is nitrogen; or R^8 may be absent if D is nitrogen;

R^6 and R^7 are independently selected from -H, -F, -Cl, -Br, -I, -CN, -NO_2, substituted and unsubstituted alkyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted alkenyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted heterocyclylalkyl groups, -SH, substituted and unsubstituted -S-alkyl groups, -OH, substituted and unsubstituted alkoxy groups, substituted and unsubstituted heterocyclyloxy groups, substituted and unsubstituted heterocyclylalkoxy groups, -NH_2, substituted and unsubstituted -N(H)(alkyl) groups, substituted and unsubstituted -N(alkyl)$_2$ groups, substituted and unsubstituted -N(H)(heterocyclyl) groups, substituted and unsubstituted -N(alkyl)(heterocyclyl) groups, substituted and unsubstituted -N(heterocyclyl)$_2$ groups,

substituted and unsubstituted -N(H)(heterocyclylalkyl) groups, substituted and unsubstituted -N(alkyl)(heterocyclylalkyl) groups, substituted and unsubstituted -N(heterocyclylalkyl)$_2$ groups, substituted and unsubstituted -N(H)-C(=O)-alkyl groups, substituted and unsubstituted -N(H)-C(=O)-heterocyclyl groups, substituted and unsubstituted -N(H)-C(=O)-heterocyclylalkyl, substituted and unsubstituted -N(alkyl)-C(=O)-alkyl groups, substituted and unsubstituted -N(alkyl)-C(=O)-heterocyclyl groups, substituted and unsubstituted -N(alkyl)-C(=O)-heterocyclylalkyl, substituted and unsubstituted -N(H)-S(=O)$_2$-alkyl groups, substituted and unsubstituted -N(H)-S(=O)$_2$-heterocyclyl groups, substituted and unsubstituted -N(H)-S(=O)$_2$-heterocyclylalkyl groups, substituted and unsubstituted -N(alkyl)-S(=O)$_2$-alkyl groups, substituted and unsubstituted -N(alkyl)-S(=O)$_2$-heterocyclyl groups, substituted and unsubstituted -N(alkyl)-S(=O)$_2$-heterocyclylalkyl groups, substituted and unsubstituted -C(=O)-alkyl groups, substituted and unsubstituted -C(=O)-heterocyclyl groups, substituted and unsubstituted -C(=O)-heterocyclylalkyl groups, -C(=O)-NH$_2$, substituted and unsubstituted -C(=O)-N(H)(alkyl) groups, substituted and unsubstituted -C(=O)-N(alkyl)$_2$ groups, substituted and unsubstituted -C(=O)-N(H)(heterocyclyl) groups, substituted and unsubstituted -C(=O)-N(alkyl)(heterocyclyl) groups, substituted and unsubstituted -C(=O)-N(H)(heterocyclylalkyl) groups, substituted and unsubstituted -C(=O)-N(alkyl)(heterocyclylalkyl) groups, -CO$_2$H, substituted and unsubstituted -C(=O)-O-alkyl groups, substituted and unsubstituted -C(=O)-O-heterocyclyl groups, or substituted and unsubstituted -C(=O)-O-heterocyclylalkyl groups; or R^6 may be absent if B is nitrogen; or R^7 may be absent if C is nitrogen;

R^9 is selected from –H, substituted and unsubstituted alkyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted alkenyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted heterocyclylalkyl groups, substituted and unsubstituted alkoxy groups, or substituted and unsubstituted heterocyclyloxy groups; and

R^{10} is –H.

[0390] In some embodiments of the method of inhibiting Lck in a subject and/or the method of treating a biological condition mediated by Lck activity in a subject, R^6 and R^7 are independently selected from -H, -F, -Cl, -Br, -I, substituted and unsubstituted alkyl groups having from 1 to 8 carbon atoms, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted heterocyclylalkyl groups, -OH, substituted and unsubstituted alkoxy groups, substituted and unsubstituted heterocyclyloxy, substituted and unsubstituted heterocyclylalkoxy, $-NH_2$, substituted and unsubstituted -N(H)(alkyl) groups, substituted and unsubstituted $-N(alkyl)_2$ groups, substituted and unsubstituted -N(H)(heterocyclyl) groups, substituted and unsubstituted -N(alkyl)(heterocyclyl) groups, substituted and unsubstituted $-N(heterocyclyl)_2$ groups, substituted and unsubstituted -N(H)(heterocyclylalkyl) groups, substituted and unsubstituted -N(alkyl)(heterocyclylalkyl) groups, substituted and unsubstituted $-N(heterocyclylalkyl)_2$ groups, substituted and unsubstituted -N(H)-C(=O)-alkyl groups, substituted and unsubstituted -N(H)-C(=O)-heterocyclyl groups, substituted and unsubstituted -N(H)-C(=O)-heterocyclylalkyl, substituted and unsubstituted -N(alkyl)-C(=O)-alkyl groups, substituted and unsubstituted -N(alkyl)-C(=O)-heterocyclyl groups, substituted and unsubstituted -N(alkyl)-C(=O)-heterocyclylalkyl, $-C(=O)-NH_2$, substituted and unsubstituted -C(=O)-N(H)(alkyl) groups, substituted and unsubstituted $-C(=O)-N(alkyl)_2$ groups, substituted and unsubstituted -C(=O)-N(H)(heterocyclyl) groups,

substituted and unsubstituted -C(=O)-N(alkyl)(heterocyclyl) groups, substituted and unsubstituted -C(=O)-N(H)(heterocyclylalkyl) groups, or substituted and unsubstituted -C(=O)-N(alkyl)(heterocyclylalkyl) groups; or R^6 may be absent if B is nitrogen; or R^7 may be absent if C is nitrogen.

[0391] In some embodiments of the method of inhibiting Lck in a subject and/or the method of treating a biological condition mediated by Lck activity in a subject, A, B, C, and D are all carbon.

[0392] In some embodiments of the method of inhibiting Lck in a subject and/or the method of treating a biological condition mediated by Lck activity in a subject, one of A or D is nitrogen, and B and C are both carbon.

[0393] In some embodiments of the method of inhibiting Lck in a subject and/or the method of treating a biological condition mediated by Lck activity in a subject, R^9 is selected from –H, substituted and unsubstituted straight or branched chain alkyl groups having from 1 to 8 carbons, substituted and unsubstituted cycloalkyl groups, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted heterocyclylalkyl groups, or substituted and unsubstituted heterocyclyloxy groups.

[0394] In some embodiments of the method of inhibiting Lck in a subject and/or the method of treating a biological condition mediated by Lck activity in a subject, R^9 is selected from –H, aminoalkyl groups, alkylaminoalkyl groups, dialkylaminoalkyl groups, substituted and unsubstituted saturated heterocyclyl groups, or substituted and unsubstituted heterocyclylalkyl groups wherein the heterocyclyl moiety is saturated. In some such embodiments, R^9 is selected from quinuclidinyl groups, piperidinyl groups, N-alkylpiperidinyl groups, piperidinylalkyl groups, pyrrolidinyl groups, or pyrrolidinylalkyl groups. In other such embodiments, R^9 –H.

[0395] In some embodiments of the method of inhibiting Lck in a subject and/or the method of treating a biological condition mediated by Lck

activity in a subject, R^1 and R^3 are independently selected from –H or -F. In some such embodiments, R^1 is –H.

[0396] In some embodiments of the method of inhibiting Lck in a subject and/or the method of treating a biological condition mediated by Lck activity in a subject, R^2 is selected from –H, -F, -Cl, -Br, -I, or substituted and unsubstituted straight or branched chain alkyl groups having from 1 to 4 carbons. In some such embodiments, R^2 is selected from –H, -F, -Cl, -Br, and methyl. In other such embodiments, R^2 is selected from –H, -Cl, and –Br. In still other such embodiments, R^2 is -H.

[0397] In some embodiments of the method of inhibiting Lck in a subject and/or the method of treating a biological condition mediated by Lck activity in a subject, R^3 is -H.

[0398] In some embodiments of the method of inhibiting Lck in a subject and/or the method of treating a biological condition mediated by Lck activity in a subject, R^4 is -H.

[0399] In some embodiments of the method of inhibiting Lck in a subject and/or the method of treating a biological condition mediated by Lck activity in a subject, A is carbon and R^5 is –H; or D is carbon and R^8 is –H. In some such embodiments, both A and D are carbon and both R^5 and R^8 are –H.

[0400] In some embodiments of the method of inhibiting Lck in a subject and/or the method of treating a biological condition mediated by Lck activity in a subject, R^6 and R^7 are independently selected from -H, -F, -Cl, -Br, -I, substituted and unsubstituted alkyl groups having from 1 to 8 carbon atoms, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted heterocyclylalkyl groups, $-NH_2$, substituted and unsubstituted -N(H)(alkyl) groups, substituted and unsubstituted $-N(alkyl)_2$ groups, substituted and unsubstituted -N(H)(heterocyclyl) groups, substituted and unsubstituted -N(alkyl)(heterocyclyl) groups, substituted and unsubstituted

-N(H)(heterocyclylalkyl) groups, substituted and unsubstituted -N(alkyl)(heterocyclylalkyl) groups, substituted and unsubstituted -N(H)-C(=O)-alkyl groups, substituted and unsubstituted -N(H)-C(=O)-heterocyclyl groups, substituted and unsubstituted -N(alkyl)-C(=O)-heterocyclylalkyl, substituted and unsubstituted -N(alkyl)-C(=O)-alkyl groups, substituted and unsubstituted -N(alkyl)-C(=O)-heterocyclyl groups, or substituted and unsubstituted -N(alkyl)-C(=O)-heterocyclylalkyl; or R^6 may be absent if B is nitrogen; or R^7 may be absent if C is nitrogen.

[0401] In some embodiments of the method of inhibiting Lck in a subject and/or the method of treating a biological condition mediated by Lck activity in a subject, R^6 and R^7 are independently selected from -H, -F, -Cl, -Br, -I, substituted and unsubstituted alkyl groups having from 1 to 8 carbon atoms, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted heterocyclylalkyl groups, substituted and unsubstituted -N(alkyl)(heterocyclyl) groups, or substituted and unsubstituted -N(alkyl)-C(=O)-alkyl groups; or R^6 may be absent if B is nitrogen; or R^7 may be absent if C is nitrogen.

[0402] In some embodiments of the method of inhibiting Lck in a subject and/or the method of treating a biological condition mediated by Lck activity in a subject, R^6 and R^7 are independently selected from -H, -F, -Cl, -Br, -I, substituted and unsubstituted alkyl groups having from 1 to 8 carbon atoms, substituted and unsubstituted saturated heterocyclyl groups, substituted and unsubstituted -N(alkyl)(heterocyclyl) groups, wherein the heterocyclyl moiety is saturated, substituted and unsubstituted -N(alkyl)-C(=O)-alkyl groups; or R^6 may be absent if B is nitrogen; or R^7 may be absent if C is nitrogen. In some such embodiments, R^6 and R^7 are independently selected from -H, -F, or –Cl; or R^6 may be absent if B is nitrogen; or R^7 may be absent if C is nitrogen. In other such embodiments, B is carbon and R^6 is –H; or C is carbon and R^7 is –H.

[0403] In some embodiments of the method of inhibiting Lck in a subject and/or the method of treating a biological condition mediated by Lck activity in a subject, R^6 and R^7 are independently selected from substituted and unsubstituted piperazinyl groups, substituted and unsubstituted morpholinyl groups, substituted and unsubstituted pyrrolidinyl groups, substituted and unsubstituted -N(alkyl)(piperidinyl) groups, or substituted and unsubstituted -N(alkyl)-C(=O)-alkyl groups; or R^6 may be absent if B is nitrogen; or R^7 may be absent if C is nitrogen.

[0404] In some embodiments of the method of inhibiting Lck in a subject and/or the method of treating a biological condition mediated by Lck activity in a subject, R^6 and R^7 are independently selected from 4-alkylpiperazin-1-yl groups, 4-alkyl-2-alkyl-piperazin-1-yl groups, 4-alkyl-3-alkylpiperazin-1-yl groups, morpholin-4-yl groups, 2-dialkylaminoalkyl-5-alkylmorpholin-4-yl groups, 3-dialkylaminopyrrolidin-1-yl groups, 3-dialkylaminoalkylpyrrolidin-1-yl groups, -N(alkyl)(1-alkylpiperidinyl) groups, or -N(alkyl)-C(=O)–alkyl groups; or R^6 may be absent if B is nitrogen; or R^7 may be absent if C is nitrogen.

[0405] In some embodiments of the method of inhibiting Lck in a subject and/or the method of treating a biological condition mediated by Lck activity in a subject, R^6 and R^7 are independently selected from 4-methylpiperazin–1-yl groups, 4-ethylpiperazin-1-yl groups, 4-isopropylpiperazin-1-yl groups, 4-methyl-2-methylpiperazin-1-yl groups, 4-ethyl-2-methylpiperazin-1-yl groups, 4-isopropyl-2-methylpiperazin-1-yl groups, 4-cyclobutyl-2-methylpiperazin-1-yl groups, 4-methyl-3-methylpiperazin–1-yl groups, morpholin-4-yl groups, 2-dimethylaminomethyl-5-methylmorpholin-4-yl groups, 3-dimethylaminopyrrolidin-1-yl groups, 3-dimethylaminomethylpyrrolidin-1-yl groups, -N(methyl)(1-methylpiperidin-4-yl) groups, or -N(methyl)-C(=O)-methyl groups; or R^6 may be absent if B is nitrogen; or R^7 may be absent if C is nitrogen.

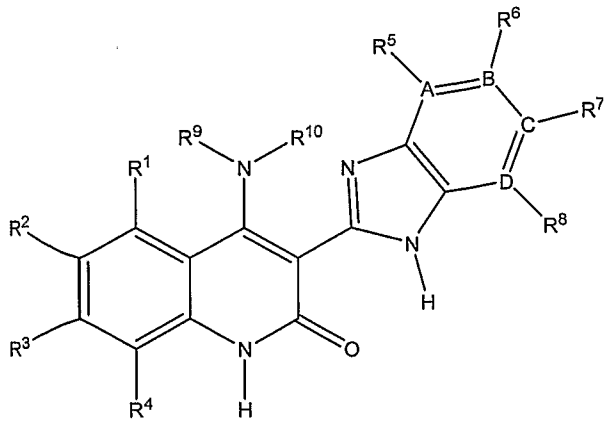
[0406] In some embodiments of the method of inhibiting Lck in a subject and/or the method of treating a biological condition mediated by Lck activity in a subject, the IC_{50} value of the compound is less than or equal to 10 μM with respect to Lck. In other such embodiments, the IC_{50} value is less than or equal to 1 μM, is less than or equal to 0.1 μM, is less than or equal to 0.050 μM, is less than or equal to 0.030 μM, is less than or equal to 0.025 μM, or is less than or equal to 0.010 μM.

[0407] In some embodiments of the method of inhibiting Lck in a subject and/or the method of treating a biological condition mediated by Lck activity in a subject, the subject is a mammal or is a human.

[0408] In some embodiments of the method of treating a biological condition mediated by Lck activity in a subject, the biological condition is an autoimmune disease, and in some such embodiments the biological condition is rheumatoid arthritis or systemic lupus erythematosus. In other such embodiments, the biological condition is organ transplant rejection.

Methods Relating to Tie-2

[0409] In some embodiments of the method of inhibiting a tyrosine kinase in a subject and/or the method of treating a biological condition mediated by tyrosine kinase activity in a subject using a compound of Structure I, a tautomer of the compound, a pharmaceutically acceptable salt of the compound, a pharmaceutically acceptable salt of the tautomer, or mixtures thereof, the tyrosine kinase is Tie-2. In some such methods, the Tie-2 is inhibited in the subject after administration. In methods of inhibiting Tie-2, Structure I has the following formula:



I

where,

A, B, C, and D are independently selected from carbon or nitrogen;

R^1 is selected from -H, -F, -Cl, -Br, -I, -CN, -NO_2, substituted and unsubstituted alkyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted alkenyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted aryl groups, substituted and unsubstituted aralkyl groups, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted heterocyclylalkyl groups, ,-SH, substituted and unsubstituted -S-alkyl groups, -OH, substituted and unsubstituted alkoxy groups, substituted and unsubstituted heterocyclyloxy groups, substituted and unsubstituted heterocyclylalkoxy groups, -NH_2, substituted and unsubstituted -N(H)(alkyl) groups, substituted and unsubstituted -N(alkyl)$_2$ groups, substituted and unsubstituted -N(H)(heterocyclyl) groups, substituted and unsubstituted -N(alkyl)(heterocyclyl) groups, substituted and unsubstituted -N(alkyl)(heterocyclylalkyl) groups, substituted and unsubstituted -N(heterocyclyl)$_2$ groups, substituted and unsubstituted -N(H)-C(=O)-alkyl groups, substituted and unsubstituted -N(H)-S(=O)$_2$-alkyl groups, substituted and

unsubstituted -C(=O)-alkyl groups, substituted and unsubstituted -C(=O)-heterocyclylalkyl groups, -C(=O)-NH_2, substituted and unsubstituted -C(=O)-N(H)(alkyl) groups, substituted and unsubstituted -C(=O)-N(alkyl)$_2$ groups, substituted and unsubstituted -C(=O)-N(H)(heterocyclyl) groups, substituted and unsubstituted -C(=O)-N(alkyl)(heterocyclyl) groups, substituted and unsubstituted -C(=O)-N(heterocyclyl)$_2$ groups, substituted and unsubstituted -C(=O)-N(H)(heterocyclylalkyl) groups, substituted and unsubstituted -C(=O)-N(alkyl)(heterocyclylalkyl) groups, substituted and unsubstituted -C(=O)-N(heterocyclylalkyl)$_2$ groups, -CO_2H, substituted and unsubstituted -C(=O)-O-alkyl groups, substituted and unsubstituted -C(=O)-O-heterocyclyl groups, or substituted and unsubstituted -C(=O)-O-heterocyclylalkyl groups;

R^2 is selected from -H, -F, -Cl, -Br, -I, -CN, -NO_2, substituted and unsubstituted alkyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted alkenyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted aryl groups, substituted and unsubstituted aralkyl groups, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted heterocyclylalkyl groups, -OH, substituted and unsubstituted alkoxy groups, substituted and unsubstituted heterocyclyloxy groups, substituted and unsubstituted heterocyclylalkoxy groups,-SH, substituted and unsubstituted -S-alkyl groups, -CO_2H, -C(=O)-NH_2, substituted and unsubstituted -C(=O)-N(H)(alkyl) groups, substituted and unsubstituted -C(=O)-N(alkyl)$_2$ groups, substituted and unsubstituted -C(=O)-N(H)(heterocyclyl) groups, substituted and unsubstituted -C(=O)-N(H)(heterocyclylalkyl) groups, substituted and unsubstituted -C(=O)-O-alkyl groups, substituted and unsubstituted -C(=O)-O-heterocyclyl groups, substituted and

unsubstituted -C(=O)-O-heterocyclylalkyl groups, substituted and unsubstituted -C(=O)-alkyl groups, substituted and unsubstituted -C(=O)-heterocyclylalkyl groups, $-NH_2$, substituted and unsubstituted -N(H)(alkyl) groups, substituted and unsubstituted -N(H)(aryl) groups, substituted and unsubstituted -N(H)(heterocyclyl) groups, substituted and unsubstituted -N(alkyl)(heterocyclyl) groups, substituted and unsubstituted -N(alkyl)(heterocyclylalkyl) groups, substituted and unsubstituted $-N(alkyl)_2$ groups, substituted and unsubstituted $-N(heterocyclyl)_2$ groups, substituted and unsubstituted -N(H)-C(=O)-alkyl groups, or substituted and unsubstituted -N(H)-S(=O)-alkyl groups; or R^2 and R^3 may join together to form a cyclic group;

R^3 and R^4 are independently selected from –H or substituted and unsubstituted straight and branched chain alkyl groups having from 1 to 8 carbon atoms;

R^5 is selected from -H, -F, -Cl, -Br, -I, or substituted and unsubstituted straight and branched chain alkyl groups having from 1 to 8 carbon atoms; or R^5 may be absent if A is nitrogen;

R^6 is selected from -H, -F, -Cl, -Br, -I, -CN, $-NO_2$, substituted and unsubstituted alkyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted alkenyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted aryl groups, substituted and unsubstituted aralkyl groups, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted heterocyclylalkyl groups, -SH, substituted and unsubstituted -S-alkyl groups, substituted and unsubstituted $-S(=O)_2$-O-alkyl groups, substituted and unsubstituted $-S(=O)_2$-alkyl groups,

substituted and unsubstituted -S(=O)$_2$-heterocyclyl groups, substituted and unsubstituted -S(=O)-alkyl groups, substituted and unsubstituted -S(=O)-heterocyclyl groups, -S(=O)$_2$-NH$_2$, substituted and unsubstituted -S(=O)$_2$-N(H)(alkyl) groups, substituted and unsubstituted -S(=O)$_2$-N(alkyl)$_2$ groups, -OH, substituted and unsubstituted alkoxy groups, substituted and unsubstituted heterocyclyloxy groups, substituted and unsubstituted heterocyclylalkoxy groups, -NH$_2$, substituted and unsubstituted -N(H)(alkyl) groups, substituted and unsubstituted -N(H)(aryl) groups, substituted and unsubstituted -N(H)(heterocyclyl) groups, substituted and unsubstituted -N(alkyl)(heterocyclyl) groups, substituted and unsubstituted -N(alkyl)(heterocyclylalkyl) groups, substituted and unsubstituted -N(alkyl)$_2$ groups, substituted and unsubstituted -N(heterocyclyl)$_2$ groups, substituted and unsubstituted -N(H)-C(=O)-alkyl groups, substituted and unsubstituted -N(H)-C(=O)-heterocyclyl groups, substituted and unsubstituted -N(alkyl)-C(=O)-alkyl groups, substituted and unsubstituted -N(alkyl)-C(=O)-heterocyclyl groups, substituted and unsubstituted -N(H)-S(=O)-alkyl groups, substituted and unsubstituted -N(H)-S(=O)-heterocyclyl groups, substituted and unsubstituted -N(alkyl)-S(=O)-alkyl groups, substituted and unsubstituted -N(alkyl)-S(=O)-heterocyclyl groups, substituted and unsubstituted -C(=O)-alkyl groups, substituted and unsubstituted -C(=O)-heterocyclylalkyl groups -C(=O)-NH$_2$, substituted and unsubstituted -C(=O)-N(H)(alkyl) groups, substituted and unsubstituted -C(=O)-N(alkyl)$_2$ groups, substituted and unsubstituted -C(=O)-N(H)(heterocyclyl) groups, -C(=O)-N(H)(heterocyclylalkyl) groups, -CO$_2$H, substituted and unsubstituted -C(=O)-O-alkyl groups, substituted and unsubstituted -C(=O)-O-heterocyclyl groups, or substituted and

unsubstituted -C(=O)-O-heterocyclylalkyl groups; or R^6 may be absent if B is nitrogen;

R^7 is selected from -H, -F, -Cl, -Br, -I, -CN, $-NO_2$, substituted and unsubstituted alkyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted alkenyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted aryl groups, substituted and unsubstituted aralkyl groups, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted heterocyclylalkyl groups, -SH, substituted and unsubstituted -S-alkyl groups, -OH, substituted and unsubstituted alkoxy groups, substituted and unsubstituted heterocyclyloxy groups, substituted and unsubstituted heterocyclylalkoxy groups, $-NH_2$, substituted and unsubstituted -N(H)(alkyl) groups, substituted and unsubstituted -N(H)(aryl) groups, substituted and unsubstituted -N(H)(heterocyclyl) groups, substituted and unsubstituted -N(alkyl)(heterocyclyl) groups, substituted and unsubstituted -N(alkyl)(heterocyclylalkyl) groups, substituted and unsubstituted $-N(alkyl)_2$ groups, substituted and unsubstituted $-N(heterocyclyl)_2$ groups, substituted and unsubstituted -N(H)-C(=O)-alkyl groups, substituted and unsubstituted $-N(H)-S(=O)_2$-alkyl groups, substituted and unsubstituted -C(=O)-alkyl groups, substituted and unsubstituted -C(=O)-heterocyclylalkyl groups $-C(=O)-NH_2$, substituted and unsubstituted -C(=O)-N(H)(alkyl) groups, substituted and unsubstituted $-C(=O)-N(alkyl)_2$ groups, substituted and unsubstituted -C(=O)-N(H)(heterocyclyl) groups, -C(=O)-N(H)(heterocyclylalkyl) groups, $-CO_2H$, substituted and unsubstituted -C(=O)-O-alkyl groups, substituted and unsubstituted -C(=O)-O-heterocyclyl groups, or substituted and unsubstituted -C(=O)-O-heterocyclylalkyl groups; or R^7 may be absent if C is nitrogen;

R^8 is selected from -H, substituted and unsubstituted alkyl groups having from 1 to 12 carbon atoms; or R^8 may be absent if D is nitrogen;

R^9 is selected from –H, substituted and unsubstituted alkyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted alkenyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted aryl groups, substituted and unsubstituted aralkyl groups, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted heterocyclylalkyl groups, substituted and unsubstituted alkoxy groups, substituted and unsubstituted heterocyclyloxy groups, $-NH_2$, or substituted and unsubstituted heterocyclylaminoalkyl; or R^9 and R^{10} join together to form a ring having 5, 6, or 7 ring members; and

R^{10} is –H.

[0410] In some embodiments of the method of inhibiting Tie-2 in a subject and/or the method of treating a biological condition mediated by Tie-2 activity in a subject,

R^1 is selected from -H, -F, -Cl, -Br, -I, substituted and unsubstituted alkyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted heterocyclylalkyl groups, -OH, substituted and unsubstituted alkoxy groups, substituted and unsubstituted heterocyclyloxy groups, or substituted and unsubstituted heterocyclylalkoxy groups;

R^2 is selected from -H, -F, -Cl, -Br, -I, substituted and unsubstituted alkyl groups having from 1 to 12 carbon atoms,

substituted and unsubstituted cycloalkenyl groups, substituted and unsubstituted aryl groups, substituted and unsubstituted heterocyclyl groups, -OH, substituted and unsubstituted alkoxy groups, substituted and unsubstituted heterocyclyloxy groups, substituted and unsubstituted heterocyclylalkoxy groups;

R^6 is selected from -H, substituted and unsubstituted alkyl groups having from 1 to 8 carbon atoms, substituted and unsubstituted heterocyclyl groups, -OH, substituted and unsubstituted alkoxy groups, substituted and unsubstituted heterocyclyloxy, substituted and unsubstituted heterocyclylalkoxy, substituted and unsubstituted -N(H)(alkyl) groups, substituted and unsubstituted -N(H)(heterocyclyl) groups, or substituted and unsubstituted -N(alkyl)(heterocyclyl) groups; or R^6 may be absent if B is nitrogen;

R^7 is selected from -H, -Cl, -F, -Br, substituted and unsubstituted alkyl groups having from 1 to 8 carbon atoms, -OH, substituted and unsubstituted alkoxy groups, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted -N(H)(alkyl) groups, substituted and unsubstituted -N(H)(heterocyclyl) groups, or substituted and unsubstituted -N(alkyl)(heterocyclyl) groups,; or R^7 may be absent if C is nitrogen.

[0411] In some embodiments of the method of inhibiting Tie-2 in a subject and/or the method of treating a biological condition mediated by Tie-2 activity in a subject, A, B, C, and D are all carbon.

[0412] In some embodiments of the method of inhibiting Tie-2 in a subject and/or the method of treating a biological condition mediated by Tie-2 activity in a subject, one of A or D is nitrogen, and B and C are both carbon.

[0413] In some embodiments of the method of inhibiting Tie-2 in a subject and/or the method of treating a biological condition mediated by Tie-2 activity in a subject, R^9 is selected from –H, substituted and unsubstituted cycloalkyl groups, substituted and unsubstituted alkoxy groups, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted heterocyclylalkyl groups, substituted and unsubstituted heterocyclylalkoxy, $-NH_2$, or substituted and unsubstituted heterocyclylaminoalkyl groups.

[0414] In some embodiments of the method of inhibiting Tie-2 in a subject and/or the method of treating a biological condition mediated by Tie-2 activity in a subject, R^9 is selected from –H, substituted and unsubstituted saturated heterocyclyl groups, substituted and unsubstituted heterocyclylalkyl groups wherein the heterocyclyl moiety is saturated, substituted and unsubstituted alkoxy groups, substituted and unsubstituted heterocyclylalkoxy groups wherein the heterocyclyl moiety is saturated, or substituted and unsubstituted heterocyclylaminoalkyl groups wherein the heterocyclyl moiety is saturated.

[0415] In some embodiments of the method of inhibiting Tie-2 in a subject and/or the method of treating a biological condition mediated by Tie-2 activity in a subject, R^9 is selected from –H, substituted and unsubstituted cycloalkyl groups, substituted and unsubstituted saturated heterocyclyl groups, or substituted and unsubstituted alkoxy groups. In some such embodiments, R^9 is selected from –H or quinuclidinyl. In other such embodiments, R^9 is –H.

[0416] In some embodiments of the method of inhibiting Tie-2 in a subject and/or the method of treating a biological condition mediated by Tie-2 activity in a subject, R^1 is selected from -H, -F, -Cl,–OCH_3 substituted and unsubstituted piperidinyloxy groups, substituted and unsubstituted piperidinylalkoxy groups, substituted and unsubstituted morpholinyloxy groups, or substituted and unsubstituted morpholinylalkoxy groups. In some

such embodiments, R^1 is selected from –H or -Cl. In other such embodiments, R^1 is –H.

[0417] In some embodiments of the method of inhibiting Tie-2 in a subject and/or the method of treating a biological condition mediated by Tie-2 activity in a subject, R^2 is selected from –H, -F, -Cl, -Br, -I, $-CH_3$, substituted and unsubstituted pyridinylalkoxy groups.

[0418] In some embodiments of the method of inhibiting Tie-2 in a subject and/or the method of treating a biological condition mediated by Tie-2 activity in a subject, R^2 is –H.

[0419] In some embodiments of the method of inhibiting Tie-2 in a subject and/or the method of treating a biological condition mediated by Tie-2 activity in a subject, R^3 is –H.

[0420] In some embodiments of the method of inhibiting Tie-2 in a subject and/or the method of treating a biological condition mediated by Tie-2 activity in a subject, R^4 is –H.

[0421] In some embodiments of the method of inhibiting Tie-2 in a subject and/or the method of treating a biological condition mediated by Tie-2 activity in a subject, R^5 is –H or is absent if A is nitrogen.

[0422] In some embodiments of the method of inhibiting Tie-2 in a subject and/or the method of treating a biological condition mediated by Tie-2 activity in a subject, R^6 is selected from –H, substituted and unsubstituted morpholinyl groups, substituted and unsubstituted morpholinylalkoxy groups, substituted and unsubstituted pyrrolidinyl groups, substituted and unsubstituted pyrrolidinylalkoxy groups, substituted and unsubstituted piperidinyl groups, substituted and unsubstituted piperidinyloxy groups, substituted and unsubstituted piperazinyl groups, or substituted and unsubstituted $-S(=O)_2-N(alkyl)_2$ groups; or may be absent if B is nitrogen.

[0423] In some embodiments of the method of inhibiting Tie-2 in a subject and/or the method of treating a biological condition mediated by Tie-2 activity in a subject, R^7 is selected from -H, -F, -Cl, substituted and unsubstituted morpholinyl groups, substituted and unsubstituted pyridinylalkyl groups, or substituted and unsubstituted piperazinyl groups; or may be absent if C is nitrogen.

[0424] In some embodiments of the method of inhibiting Tie-2 in a subject and/or the method of treating a biological condition mediated by Tie-2 activity in a subject, R^8 is –H or is absent if D is nitrogen.

[0425] In some embodiments of the method of inhibiting Tie-2 in a subject and/or the method of treating a biological condition mediated by Tie-2 activity in a subject, the IC_{50} value of the compound is less than or equal to 10 μM with respect to Tie-2. In other such embodiments, the IC_{50} value is less than or equal to 1 μM, is less than or equal to 0.1 μM, is less than or equal to 0.050 μM, is less than or equal to 0.030 μM, is less than or equal to to 0.025 μM, or is less than or equal to to 0.010 μM.

[0426] In some embodiments of the method of inhibiting Tie-2 in a subject and/or the method of treating a biological condition mediated by Tie-2 activity in a subject, the subject is a mammal or is a human.

[0427] In some embodiments of the method of treating a biological condition mediated by Tie-2 activity in a subject, the biological condition is cancer.

[0428] In some embodiments of the method of treating a biological condition mediated by serine/threonine kinase or tyrosine kinase activity in a subject, the compound, the tautomer, the pharmaceutically acceptable salt of the compound, the pharmaceutically acceptable salt of the tautomer, or mixtures thereof, is a component of a pharmaceutical formulation or a medicament that includes a pharmaceutically acceptable carrier. In some such embodiments the serine/threonine kinase or tyrosine kinase activity is

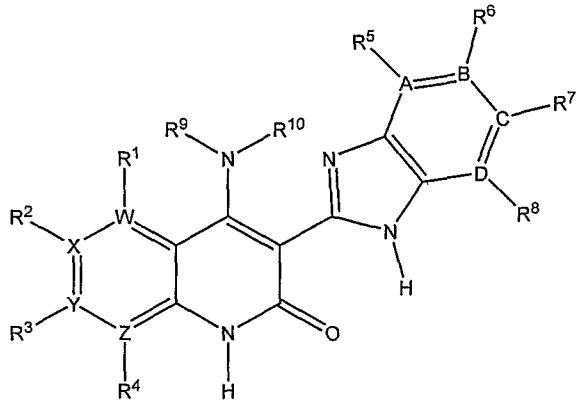
selected from FLT-1, VEGFR2, VEGFR3, FGFR1, GSK-3, Cdk2, NEK-2, CHK1, Rsk2, PAR-1, Cdc2, c-Kit, c-ABL, p60src, FGFR3, FLT-3, Fyn, Lck, Tie-2, PDGFRα, or PDGFRβ activity. In other such embodiments, the serine/threonine kinase or tyrosine kinase activity is selected from GSK-3, Cdk2, CHK1, Rsk2, PAR-1, Cdc2, c-Kit, c-ABL, p60src, FGFR3, VEGFR3, PDGFRα, PDGFRβ, FLT-3, Fyn, Lck, or Tie-2 activity. In another such embodiment the serine/threonine kinase activity is CHK1 activity.

[0429] In other aspects, the invention provides compounds of Structure I, tautomers of the compounds, pharmaceutically acceptable salts of the compounds, pharmaceutically acceptable salts of the tautomers, and mixtures thereof. The invention also provides compounds having any of the R^1 through R^{10} values described in the various embodiments described above.

[0430] The invention further provides the use of the compounds of Structure I, tautomers of the compounds, pharmaceutically acceptable salts of the compounds, pharmaceutically acceptable salts of the tautomers, and mixtures thereof in the preparation of medicaments, and in treatment of biological conditions mediated by FLT-1, VEGFR2, VEGFR3, FGFR1, GSK-3, Cdk2, NEK-2, CHK1, Rsk2, PAR-1, Cdc2, c-Kit, c-ABL, p60src, FGFR3, FLT-3, Fyn, Lck, Tie-2, PDGFRα, or PDGFRβ activity.

[0431] The present invention further provides methods of inhibiting GSK-3 and treating biological conditions mediated by GSK-3 in a subject using a compound of Structure IB. The invention also provides the use of a compound of Structure IB in preparing a medicament for use in inhibiting GSK-3 in a subject and/or for use in treating a biological condition mediated by GSK-3. In one aspect, a method of inhibiting GSK-3 or treating a biological condition mediated by GSK-3 includes administering to the subject a compound of Structure IB, a tautomer of the compound, a pharmaceutically acceptable salt of the compound, a pharmaceutically acceptable salt of the tautomer, or mixtures thereof. The invention further provides methods of inhibiting any of the other kinases described herein and methods of treating

any of the biological conditions mediated by such kinases using the compounds of Structure IB. In some embodiments, GSK-3 is inhibited in the subject after administration. Structure IB has the following formula:



IB

where:

A, B, C, and D are independently selected from carbon or nitrogen;

W, X, Y, and Z are independently selected from the group consisting of carbon and nitrogen and at least one of W, X, Y, and Z is a nitrogen;

R^1 is selected from -H, -F, -Cl, -Br, -I, substituted or unsubstituted straight or branched chain alkyl groups having from 1 to 8 carbon atoms, substituted or unsubstituted alkenyl groups having from 1 to 8 carbon atoms, substituted or unsubstituted alkynyl groups having from 1 to 8 carbon atoms, -CN, $-NO_2$, -OH, -SH, substituted or unsubstituted alkoxy groups, substituted or unsubstituted -S-alkyl groups, substituted or unsubstituted $-S(=O)_2$-O-alkyl groups, substituted or unsubstituted $-S(=O)_2$-alkyl groups, substituted or unsubstituted -S(=O)-alkyl groups, $-S(=O)-NH_2$, substituted or unsubstituted -S(=O)-N(H)(alkyl) groups, substituted or unsubstituted $-S(=O)-N(alkyl)_2$ groups, $-C(=O)-NH_2$, substituted or

unsubstituted -C(=O)-N(H)(alkyl) groups, substituted or unsubstituted -C(=O)-N(alkyl)$_2$ groups, substituted or unsubstituted -C(=O)-O-alkyl groups, -NH_2, substituted or unsubstituted -N(H)(alkyl) groups, substituted or unsubstituted -N(alkyl)$_2$ groups, substituted or unsubstituted -N(H)-C(=O)-alkyl groups, or substituted or unsubstituted -N(H)-S(=O)-alkyl groups; or R^1 may be absent if W is nitrogen;

R^2 is selected -H, -F, -Cl, -Br, -I, -NO_2, -CN, -NH_2, -CO_2H, -OH, substituted or unsubstituted straight or branched chain alkyl groups having from 1 to 8 carbon atoms, substituted or unsubstituted cycloalkenyl groups, substituted or unsubstituted cycloalkyl groups, substituted or unsubstituted alkoxy groups, substituted or unsubstituted -N(H)(alkyl) groups, substituted or unsubstituted -N(alkyl)$_2$ groups, substituted or unsubstituted heterocyclyl groups, substituted or unsubstituted aryl groups, substituted or unsubstituted alkenyl groups having from 1 to 8 carbon atoms, substituted or unsubstituted alkynyl groups having from 1 to 8 carbon atoms, -SH, substituted or unsubstituted -S-alkyl groups, substituted or unsubstituted -S(=O)$_2$-O-alkyl groups, substituted or unsubstituted -S(=O)$_2$-alkyl groups, substituted or unsubstituted -S(=O)$_2$-heterocyclyl groups, substituted or unsubstituted -S(=O)-alkyl groups, substituted or unsubstituted -S(=O)-heterocyclyl groups, -S(=O)-NH_2, substituted or unsubstituted -S(=O)-N(H)(alkyl) groups, substituted or unsubstituted -S(=O)-N(alkyl)$_2$ groups, -C(=O)-NH_2, substituted or unsubstituted -C(=O)-N(H)(alkyl) groups, substituted or unsubstituted -C(=O)-N(alkyl)$_2$ groups, substituted or unsubstituted -C(=O)-alkyl groups, substituted or unsubstituted -C(=O)-heterocyclyl groups, substituted or unsubstituted -C(=O)-O-alkyl groups, substituted or unsubstituted

-N(H)-C(=O)-alkyl groups, substituted or unsubstituted -N(H)-C(=O)-heterocyclyl groups, substituted or unsubstituted -N(H)-S(=O)-alkyl groups, substituted or unsubstituted -N(H)-S(=O)-heterocyclyl groups, -N(alkyl)-C(=O)-alkyl groups, substituted or unsubstituted -N(alkyl)-C(=O)-heterocyclyl groups, substituted or unsubstituted -N(alkyl)-S(=O)-alkyl groups, substituted or unsubstituted -N(alkyl)-S(=O)-heterocyclyl groups, $-N(H)-C(=O)-NH_2$, substituted or unsubstituted -N(H)-C(=O)-N(H)(alkyl) groups, substituted or unsubstituted $-N(H)-C(=O)-N(alkyl)_2$ groups, $-N(alkyl)-C(=O)-NH_2$, substituted or unsubstituted -N(alkyl)-C(=O)-N(H)(alkyl) groups, or substituted or unsubstituted $-N(alkyl)-C(=O)-N(alkyl)_2$ groups; or R^2 and R^3 may join together to form a cyclic group when X and Y are both carbon; or R^2 may be absent if X is nitrogen;

R^3 is selected from -H, -F, -Cl, -Br, -I, -OH, substituted or unsubstituted straight or branched chain alkyl groups having from 1 to 8 carbon atoms, substituted or unsubstituted alkoxy groups, $-CO_2H$, -CN, substituted or unsubstituted -N(H)(alkyl) groups, substituted or unsubstituted -N(H)(cycloalkyl) groups, substituted or unsubstituted $-N(alkyl)_2$ groups, substituted or unsubstituted heterocyclyl groups, substituted or unsubstituted aryl groups, substituted or unsubstituted -C(=O)-heterocyclyl groups, substituted or unsubstituted -C(=O)-alkyl groups, substituted or unsubstituted -C(=O)-N(H)(alkyl) groups, substituted or unsubstituted $-C(=O)-N(alkyl)_2$ groups, $-C(=O)-NH_2$ groups, substituted or unsubstituted -C(=O)-N(H)(heterocyclyl) groups, substituted or unsubstituted -C(=O)-N(H)(aryl) groups, substituted or unsubstituted alkenyl groups having from 1 to 8 carbon atoms, substituted or unsubstituted alkynyl groups having from 1 to 8 carbon atoms, $-NO_2$, -SH, substituted or unsubstituted -S-alkyl groups,

substituted or unsubstituted -$S(=O)_2$-O-alkyl groups, substituted or unsubstituted -$S(=O)_2$-alkyl groups, substituted or unsubstituted -$S(=O)_2$-heterocyclyl groups, substituted or unsubstituted -S(=O)-alkyl groups, substituted or unsubstituted -S(=O)-heterocyclyl groups, -S(=O)-NH_2, substituted or unsubstituted -S(=O)-N(H)(alkyl) groups, substituted or unsubstituted -S(=O)-N(alkyl)$_2$ groups, substituted or unsubstituted -C(=O)-O-alkyl groups, -NH_2, substituted or unsubstituted -N(H)-C(=O)-alkyl groups, substituted or unsubstituted -N(H)-C(=O)-heterocyclyl groups, substituted or unsubstituted -N(H)-S(=O)-alkyl groups, substituted or unsubstituted -N(H)-S(=O)-heterocyclyl groups, substituted or unsubstituted -N(alkyl)-C(=O)-alkyl groups, substituted or unsubstituted -N(alkyl)-C(=O)-heterocyclyl groups, substituted or unsubstituted -N(alkyl)-S(=O)-alkyl groups, substituted or unsubstituted -N(alkyl)-S(=O)-heterocyclyl groups, -N(H)-C(=O)-NH_2, substituted or unsubstituted -N(H)-C(=O)-N(H)(alkyl) groups, substituted or unsubstituted -N(H)-C(=O)-N(alkyl)$_2$ groups, -N(alkyl)-C(=O)-NH_2, substituted or unsubstituted -N(alkyl)-C(=O)-N(H)(alkyl) groups, or substituted or unsubstituted -N(alkyl)-C(=O)-N(alkyl)$_2$ groups; or R^2 and R^3 may join together to form a cyclic group when X and Y are both carbon; or R^3 may be absent if Y is nitrogen;

R^4 is selected from of -H, -F, -Cl, -Br, -I, substituted or unsubstituted straight or branched chain alkyl groups having from 1 to 8 carbon atoms, substituted or unsubstituted alkenyl groups having from 1 to 8 carbon atoms, substituted or unsubstituted alkynyl groups having from 1 to 8 carbon atoms, -CN, -NO_2, -OH, -SH, substituted or unsubstituted alkoxy groups, substituted or unsubstituted -S-alkyl groups, substituted or unsubstituted -$S(=O)_2$-O-alkyl groups, substituted or

unsubstituted -S(=O)$_2$-alkyl groups, substituted or unsubstituted -S(=O)-alkyl groups, -S(=O)-NH_2, substituted or unsubstituted -S(=O)-N(H)(alkyl) groups, substituted or unsubstituted -S(=O)-N(alkyl)$_2$ groups, -C(=O)-NH_2, substituted or unsubstituted -C(=O)-N(H)(alkyl) groups, substituted or unsubstituted -C(=O)-N(alkyl)$_2$ groups, substituted or unsubstituted -C(=O)-O-alkyl groups, -NH_2, substituted or unsubstituted -N(H)(alkyl) groups, substituted or unsubstituted -N(alkyl)$_2$ groups, substituted or unsubstituted -N(H)-C(=O)-alkyl groups, or substituted or unsubstituted -N(H)-S(=O)-alkyl groups; or R^4 may be absent if Z is nitrogen;

R^5 is selected from -H, -F, -Cl, -Br, -I, substituted or unsubstituted straight or branched chain alkyl groups having from 1 to 8 carbon atoms, substituted or unsubstituted heterocyclyl groups, substituted or unsubstituted alkenyl groups having from 1 to 8 carbon atoms, substituted or unsubstituted alkynyl groups having from 1 to 8 carbon atoms, -CN, -NO_2, -OH, -SH, substituted or unsubstituted alkoxy groups, substituted or unsubstituted -S-alkyl groups, substituted or unsubstituted -S(=O)$_2$-O-alkyl groups, substituted or unsubstituted -S(=O)$_2$-alkyl groups, substituted or unsubstituted -S(=O)-alkyl groups, -S(=O)-NH_2, substituted or unsubstituted -S(=O)-N(H)(alkyl) groups, substituted or unsubstituted -S(=O)-N(alkyl)$_2$ groups, -C(=O)-NH_2, substituted or unsubstituted -C(=O)-N(H)(alkyl) groups, substituted or unsubstituted -C(=O)-N(alkyl)$_2$ groups, substituted or unsubstituted -C(=O)-O-alkyl groups, -NH_2, substituted or unsubstituted -N(H)(alkyl) groups, substituted or unsubstituted -N(alkyl)$_2$ groups, substituted or unsubstituted -N(H)-C(=O)-alkyl groups, or substituted or unsubstituted -N(H)-S(=O)-alkyl groups; or R^5 may be absent if A is nitrogen;

R^6 is selected from -H, -Cl, -F, -Br, -OH, substituted or unsubstituted heterocyclyl groups, substituted or unsubstituted -N(H)(alkyl) groups, substituted or unsubstituted -N(H)(heterocyclyl) groups, substituted or unsubstituted -N(alkyl)(heterocyclyl) groups, substituted or unsubstituted alkoxy groups, substituted or unsubstituted alkyl groups having from 1 to 8 carbon atoms, substituted or unsubstituted alkenyl groups having from 1 to 8 carbon atoms, substituted or unsubstituted alkynyl groups having from 1 to 8 carbon atoms, -CN, $-NO_2$, -OH, -SH, substituted or unsubstituted -S-alkyl groups, substituted or unsubstituted $-S(=O)_2$-O-alkyl groups, substituted or unsubstituted $-S(=O)_2$-alkyl groups, substituted or unsubstituted $-S(=O)_2$-heterocyclyl groups, substituted or unsubstituted -S(=O)-alkyl groups, substituted or unsubstituted -S(=O)-heterocyclyl groups, $-S(=O)-NH_2$, substituted or unsubstituted -S(=O)-N(H)(alkyl) groups, substituted or unsubstituted $-S(=O)-N(alkyl)_2$ groups, $-C(=O)-NH_2$, substituted or unsubstituted -C(=O)-N(H)(alkyl) groups, substituted or unsubstituted $-C(=O)-N(alkyl)_2$ groups, substituted or unsubstituted -C(=O)-alkyl groups, substituted or unsubstituted -C(=O)-heterocyclyl groups, substituted or unsubstituted -C(=O)-O-alkyl groups, $-NH_2$, substituted or unsubstituted $-N(alkyl)_2$ groups, substituted or unsubstituted -N(H)-C(=O)-alkyl groups, substituted or unsubstituted -N(H)-C(=O)-heterocyclyl groups, substituted or unsubstituted -N(alkyl)-C(=O)-alkyl groups, substituted or unsubstituted -N(alkyl)-C(=O)-heterocyclyl groups, substituted or unsubstituted -N(H)-S(=O)-alkyl groups, substituted or unsubstituted -N(H)-S(=O)-heterocyclyl groups, substituted or unsubstituted -N(alkyl)-S(=O)-alkyl groups, or substituted or unsubstituted -N(alkyl)-S(=O)-heterocyclyl groups; or R^6 may be absent if B is nitrogen;

R^7 is selected from -H, -Cl, -F, -Br, -OH, substituted or unsubstituted heterocyclyl groups, substituted or unsubstituted -N(H)(alkyl) groups, substituted or unsubstituted -N(H)(heterocyclyl) groups, substituted or unsubstituted -N(alkyl)(heterocyclyl) groups, substituted or unsubstituted alkoxy groups, substituted or unsubstituted alkyl groups having from 1 to 8 carbon atoms, substituted or unsubstituted alkenyl groups having from 1 to 8 carbon atoms, substituted or unsubstituted alkynyl groups having from 1 to 8 carbon atoms, -CN, $-NO_2$, -OH, -SH, substituted or unsubstituted -S-alkyl groups, substituted or unsubstituted $-S(=O)_2$-O-alkyl groups, substituted or unsubstituted $-S(=O)_2$-alkyl groups, substituted or unsubstituted $-S(=O)_2$-heterocyclyl groups, substituted or unsubstituted -S(=O)-alkyl groups, substituted or unsubstituted -S(=O)-heterocyclyl groups, $-S(=O)-NH_2$, substituted or unsubstituted -S(=O)-N(H)(alkyl) groups, substituted or unsubstituted $-S(=O)-N(alkyl)_2$ groups, $-C(=O)-NH_2$, substituted or unsubstituted -C(=O)-N(H)(alkyl) groups, substituted or unsubstituted $-C(=O)-N(alkyl)_2$ groups, substituted or unsubstituted -C(=O)-alkyl groups, substituted or unsubstituted -C(=O)-heterocyclyl groups, substituted or unsubstituted -C(=O)-O-alkyl groups, $-NH_2$, substituted or unsubstituted $-N(alkyl)_2$ groups, substituted or unsubstituted -N(H)-C(=O)-alkyl groups, substituted or unsubstituted -N(H)-C(=O)-heterocyclyl groups, substituted or unsubstituted -N(alkyl)-C(=O)-alkyl groups, substituted or unsubstituted -N(alkyl)-C(=O)-heterocyclyl groups, substituted or unsubstituted -N(H)-S(=O)-alkyl groups, substituted or unsubstituted -N(H)-S(=O)-heterocyclyl groups, substituted or unsubstituted -N(alkyl)-S(=O)-alkyl groups, or substituted or unsubstituted -N(alkyl)-S(=O)-heterocyclyl groups; or R^7 may be absent if C is nitrogen;

R^8 is selected from -H, -F, -Cl, -Br, -I, substituted or unsubstituted straight or branched chain alkyl groups having from 1 to 8 carbon atoms, substituted or unsubstituted heterocyclyl groups, substituted or unsubstituted alkenyl groups having from 1 to 8 carbon atoms, substituted or unsubstituted alkynyl groups having from 1 to 8 carbon atoms, -CN, $-NO_2$, -OH, -SH, substituted or unsubstituted alkoxy groups, substituted or unsubstituted -S-alkyl groups, substituted or unsubstituted $-S(=O)_2$-O-alkyl groups, substituted or unsubstituted $-S(=O)_2$-alkyl groups, substituted or unsubstituted -S(=O)-alkyl groups, $-S(=O)-NH_2$, substituted or unsubstituted -S(=O)-N(H)(alkyl) groups, substituted or unsubstituted $-S(=O)-N(alkyl)_2$ groups, $-C(=O)-NH_2$, substituted or unsubstituted -C(=O)-N(H)(alkyl) groups, substituted or unsubstituted $-C(=O)-N(alkyl)_2$ groups, substituted or unsubstituted -C(=O)-O-alkyl groups, $-NH_2$, substituted or unsubstituted -N(H)(alkyl) groups, substituted or unsubstituted $-N(alkyl)_2$ groups, substituted or unsubstituted -N(H)-C(=O)-alkyl groups, or substituted or unsubstituted -N(H)-S(=O)-alkyl groups; or R^8 may be absent if D is nitrogen;

R^9 is selected from of substituted or unsubstituted heterocyclyl groups, substituted or unsubstituted aryl groups, substituted or unsubstituted alkoxy groups, $-NH_2$, substituted or unsubstituted cycloalkyl groups, or substituted or unsubstituted straight or branched chain alkyl groups having from 1 to 8 carbon atoms, or R^9 and R^{10} join together to form a ring having 5, 6, or 7 ring members; or

R^{10} is –H, or R^9 and R^{10} join together to form a ring having 5, 6, or 7 ring members.

[0432] In some embodiments of the method of inhibiting GSK-3 in a subject and/or the method of treating a biological condition mediated by GSK-3 activity in a subject using a compound of Structure IB, a tautomer of the compound, a pharmaceutically acceptable salt of the compound, a pharmaceutically acceptable salt of the tautomer, or mixtures thereof,

R^1 is selected from -H, -F, -Cl, -Br, -I, or straight or branched chain alkyl groups having from 1 to 8 carbon atoms; or R^1 may be absent if W is nitrogen

R^2 is selected from -H, -F, -Cl, -Br, -I, $-NO_2$, -CN, $-NH_2$, $-CO_2H$, -OH, straight or branched chain alkyl groups having from 1 to 8 carbon atoms, substituted or unsubstituted cycloalkenyl groups, substituted or unsubstituted cycloalkyl groups, substituted or unsubstituted alkoxy groups, substituted or unsubstituted -N(H)(alkyl) groups, substituted or unsubstituted $-N(alkyl)_2$ groups, substituted or unsubstituted heterocyclyl groups, or substituted or unsubstituted aryl groups; or R^2 may be absent if X is nitrogen;

R^3 is selected from -H, -F, -Cl, -Br, -I, -OH, straight or branched chain alkyl groups having from 1 to 8 carbon atoms, substituted or unsubstituted alkoxy groups, $-CO_2H$, -CN, substituted or unsubstituted -N(H)(alkyl) groups, substituted or unsubstituted -N(H)(cycloalkyl) groups, substituted or unsubstituted $-N(alkyl)_2$ groups, substituted or unsubstituted heterocyclyl groups, substituted or unsubstituted aryl groups, substituted or unsubstituted -C(=O)-heterocyclyl groups, substituted or unsubstituted -C(=O)-alkyl groups, substituted or unsubstituted -C(=O)-N(H)(alkyl) groups, substituted or unsubstituted $-C(=O)-N(alkyl)_2$ groups, $-C(=O)-NH_2$ groups, substituted or unsubstituted -C(=O)-N(H)(heterocyclyl) groups, or substituted

or unsubstituted -C(=O)-N(H)(aryl) groups; or R^3 may be absent if Y is nitrogen;

R^4 is selected from -H, -F, -Cl, -Br, -I, or straight or branched chain alkyl groups having from 1 to 8 carbon atoms; or R^4 may be absent if Z is nitrogen;

R^5 is selected from -H, -F, -Cl, -Br, -I, straight or branched chain alkyl groups having from 1 to 8 carbon atoms, or substituted or unsubstituted heterocyclyl groups; or R^5 may be absent if A is nitrogen;

R^6 is selected from -H, -Cl, -F, -Br, -OH, substituted or unsubstituted heterocyclyl groups, substituted or unsubstituted -N(H)(alkyl) groups, substituted or unsubstituted -N(H)(heterocyclyl) groups, substituted or unsubstituted -N(alkyl)(heterocyclyl) groups, substituted or unsubstituted alkoxy groups, or substituted or unsubstituted alkyl groups having from 1 to 8 carbon atoms; or R^6 may be absent if B is nitrogen;

R^7 is selected from -H, -Cl, -F, -Br, -OH, substituted or unsubstituted heterocyclyl groups, substituted or unsubstituted -N(H)(alkyl) groups, substituted or unsubstituted -N(H)(heterocyclyl) groups, substituted or unsubstituted -N(alkyl)(heterocyclyl) groups, substituted or unsubstituted alkoxy groups, or substituted or unsubstituted alkyl groups having from 1 to 8 carbon atoms; or R^7 may be absent if C is nitrogen; and

R^8 is selected from -H, -F, -Cl, -Br, -I, straight or branched chain alkyl groups having from 1 to 8 carbon atoms, or substituted or unsubstituted heterocyclyl groups; or R^8 may be absent if D is nitrogen.

[0433] In some embodiments of the method of inhibiting GSK-3 using a compound of Structure IB, a tautomer of the compound, a pharmaceutically acceptable salt of the compound, a pharmaceutically acceptable salt of the tautomer, or mixtures thereof, A, B, C, and D are all carbon. In some such embodiments, R^5 is -H, R^6 is -H, R^7 is -H, and R^8 is -H

[0434] In some embodiments of the method of inhibiting GSK-3 in a subject and/or the method of treating a biological condition mediated by GSK-3 activity in a subject using a compound of Structure IB, a tautomer of the compound, a pharmaceutically acceptable salt of the compound, a pharmaceutically acceptable salt of the tautomer, or mixtures thereof, one of A or D is nitrogen, and B and C are both carbon.

[0435] In some embodiments of the method of inhibiting GSK-3 in a subject and/or the method of treating a biological condition mediated by GSK-3 activity in a subject using a compound of Structure IB, a tautomer of the compound, a pharmaceutically acceptable salt of the compound, a pharmaceutically acceptable salt of the tautomer, or mixtures thereof, W is nitrogen. In some such embodiments, X, Y, and Z are all carbon.

[0436] In some embodiments of the method of inhibiting GSK-3 in a subject and/or the method of treating a biological condition mediated by GSK-3 activity in a subject using a compound of Structure IB, a tautomer of the compound, a pharmaceutically acceptable salt of the compound, a pharmaceutically acceptable salt of the tautomer, or mixtures thereof, X is nitrogen. In some such embodiments, W, Y, and Z are all carbon.

[0437] In some embodiments of the method of inhibiting GSK-3 in a subject and/or the method of treating a biological condition mediated by GSK-3 activity in a subject using a compound of Structure IB, a tautomer of the compound, a pharmaceutically acceptable salt of the compound, a pharmaceutically acceptable salt of the tautomer, or mixtures thereof, Y is nitrogen. In some such embodiments, W, X, and Z are all carbon.

[0438] In some embodiments of the method of inhibiting GSK-3 in a subject and/or the method of treating a biological condition mediated by GSK-3 activity in a subject using a compound of Structure IB, a tautomer of the compound, a pharmaceutically acceptable salt of the compound, a pharmaceutically acceptable salt of the tautomer, or mixtures thereof, Z is nitrogen. In some such embodiments, W, X, and Y are all carbon.

[0439] In some embodiments of the method of inhibiting GSK-3 in a subject and/or the method of treating a biological condition mediated by GSK-3 activity in a subject using a compound of Structure IB, a tautomer of the compound, a pharmaceutically acceptable salt of the compound, a pharmaceutically acceptable salt of the tautomer, or mixtures thereof, two of W, X, Y, and Z are nitrogen atoms. In some such embodiments, X and Z are nitrogen atoms and W and Y are carbon atoms.

[0440] In some embodiments of the method of inhibiting GSK-3 in a subject and/or the method of treating a biological condition mediated by GSK-3 activity in a subject using a compound of Structure IB, a tautomer of the compound, a pharmaceutically acceptable salt of the compound, a pharmaceutically acceptable salt of the tautomer, or mixtures thereof, R^{10} is –H and R^9 is selected from substituted or unsubstituted heterocyclyl groups, substituted or unsubstituted aryl groups, substituted or unsubstituted alkoxy groups, $-NH_2$, substituted or unsubstituted cycloalkyl groups, or substituted or unsubstituted straight or branched chain alkyl groups having from 1 to 8 carbon atoms.

[0441] In some embodiments of the method of inhibiting GSK-3 in a subject and/or the method of treating a biological condition mediated by GSK-3 activity in a subject using a compound of Structure IB, a tautomer of the compound, a pharmaceutically acceptable salt of the compound, a pharmaceutically acceptable salt of the tautomer, or mixtures thereof, R^9 is selected from substituted or unsubstituted heterocyclyl groups, substituted or unsubstituted aryl groups, unsubstituted alkoxy groups, $-NH_2$, substituted or

unsubstituted cycloalkyl groups, unsubstituted straight or branched chain alkyl groups having from 1 to 8 carbon atoms, substituted or unsubstituted heterocyclylalkyl groups wherein the heterocyclyl group is saturated, substituted or unsubstituted heterocyclylalkyl groups wherein the heterocyclyl group is unsaturated, substituted or unsubstituted aralkyl groups, substituted or unsubstituted alkoxyalkyl groups, substituted or unsubstituted hydroxyalkyl groups, substituted or unsubstituted dialkylaminoalkyl groups, substituted or unsubstituted alkylaminoalkyl groups, substituted or unsubstituted aminoalkyl groups, substituted or unsubstituted heterocyclylaminoalkyl groups, substituted or unsubstituted (heterocyclyl)(alkyl)aminoalkyl groups, or substituted or unsubstituted alkyl-(SO_2)-alkyl groups.

[0442] In some embodiments of the method of inhibiting GSK-3 in a subject and/or the method of treating a biological condition mediated by GSK-3 activity in a subject using a compound of Structure IB, a tautomer of the compound, a pharmaceutically acceptable salt of the compound, a pharmaceutically acceptable salt of the tautomer, or mixtures thereof, R^{10} is –H and R^9 is selected from substituted or unsubstituted saturated heterocyclyl groups, substituted or unsubstituted aminoalkyl groups, substituted or unsubstituted cycloalkyl groups, or substituted or unsubstituted heterocyclylalkyl groups.

[0443] In some embodiments of the method of inhibiting GSK-3 in a subject and/or the method of treating a biological condition mediated by GSK-3 activity in a subject using a compound of Structure IB, a tautomer of the compound, a pharmaceutically acceptable salt of the compound, a pharmaceutically acceptable salt of the tautomer, or mixtures thereof, R^9 is selected from quinuclidinyl groups, piperidinyl groups, pyrrolidinyl groups, and aminocyclohexyl groups. In some such embodiments, R^9 is a quinuclidinyl group and in some such embodiments, R^9 is a quinuclidin-3-yl group.

[0444] In some embodiments of the method of inhibiting GSK-3 in a subject and/or the method of treating a biological condition mediated by GSK-

3 activity in a subject using a compound of Structure IB, a tautomer of the compound, a pharmaceutically acceptable salt of the compound, a pharmaceutically acceptable salt of the tautomer, or mixtures thereof, R^9 is selected from monocyclic, bicyclic, or polycyclic saturated heterocyclyl groups.

[0445] In some embodiments of the method of inhibiting GSK-3 in a subject and/or the method of treating a biological condition mediated by GSK-3 activity in a subject using a compound of Structure IB, a tautomer of the compound, a pharmaceutically acceptable salt of the compound, a pharmaceutically acceptable salt of the tautomer, or mixtures thereof, R^1 is selected from -H, -F, -Cl, or $-CH_3$ groups. In some such embodiments, R^1 is –H or –F. In other such embodiments, R^1 is –H.

[0446] In some embodiments of the method of inhibiting GSK-3 in a subject and/or the method of treating a biological condition mediated by GSK-3 activity in a subject using a compound of Structure IB, a tautomer of the compound, a pharmaceutically acceptable salt of the compound, a pharmaceutically acceptable salt of the tautomer, or mixtures thereof, R^2 is selected from –H, -Cl, -F, -Br, -I, $-CH_3$, $-NO_2$, -OMe, -CN, $-CO_2H$, substituted or unsubstituted 1,2,3,6-tetrahydropyridine groups, substituted or unsubstituted thiophene groups, substituted or unsubstituted imidazole groups, substituted or unsubstituted 3-pyridyl groups, substituted or unsubstituted 4-pyridyl groups, 2-substituted phenyl groups, 2,4-disubstituted phenyl groups, 4-substituted phenyl groups, 3-substituted phenyl groups, 2,6-disubstituted phenyl groups, phenyl, substituted or unsubstituted dialkylamino groups, or substituted or unsubstituted alkylamino groups. In some such embodiments, R^2 is selected from –H, -Cl, -F, or $-CH_3$. In other such embodiments, R^2 is –F.

[0447] In some embodiments of the method of inhibiting GSK-3 in a subject and/or the method of treating a biological condition mediated by GSK-3 activity in a subject using a compound of Structure IB, a tautomer of the

compound, a pharmaceutically acceptable salt of the compound, a pharmaceutically acceptable salt of the tautomer, or mixtures thereof, R^2 is a substituted or unsubstituted aryl group selected from phenyl, 2-chlorophenyl, 2-methylphenyl, 2-ethylphenyl, 2-hydroxyphenyl, 2-methoxyphenyl, 2-trifluoromethylphenyl, 3-methoxyphenyl, 3-nitrophenyl, 3-carboxyphenyl, 3-acetylphenyl, 3-aminophenyl, 3-hydroxyphenyl, 3-acetamidophenyl, 3-carbomethoxyphenyl, 3-trifluoromethylphenyl, 3-ureidophenyl, 4-chlorophenyl, 4-cyanophenyl, 4-hydroxyphenyl, 4-nitrophenyl, 4-ethylphenyl, 4-methylphenyl, 4-methoxyphenyl, 4-acetylphenyl, 4-acetamidophenyl, 4-carboxyphenyl, 4-formylphenyl, 4-methylthiophenyl, 4-dimethylaminophenyl, 4-carbomethoxyphenyl, 4-carboethoxyphenyl, 4-carboxamidophenyl, 4-(methylsulfonyl)phenyl, 4-trifluoromethylphenyl, 2,4-difluorophenyl, 2-fluoro-4-chlorophenyl, 2,4-dichlorophenyl, 2-amino-4-carbomethoxyphenyl, 2-amino-4-carboxyphenyl, 2,6-difluorophenyl, or 3,4-(methylenedioxy)phenyl.

[0448] In some embodiments of the method of inhibiting GSK-3 in a subject and/or the method of treating a biological condition mediated by GSK-3 activity in a subject using a compound of Structure IB, a tautomer of the compound, a pharmaceutically acceptable salt of the compound, a pharmaceutically acceptable salt of the tautomer, or mixtures thereof, R^4 is –H or $–CH_3$. In some such embodiments, R^4 is –H.

[0449] In some embodiments of the method of inhibiting GSK-3 in a subject and/or the method of treating a biological condition mediated by GSK-3 activity in a subject using a compound of Structure IB, a tautomer of the compound, a pharmaceutically acceptable salt of the compound, a pharmaceutically acceptable salt of the tautomer, or mixtures thereof, R^5 and R^8 are independently selected from –H, or saturated heterocyclyl groups, or are absent. In some such embodiments, R^5 and R^8 are independently selected from –H or saturated heterocyclyl groups. In some such embodiments R^5 is –H and R^8 is –H.

[0450] In some embodiments of the method of inhibiting GSK-3 in a subject and/or the method of treating a biological condition mediated by GSK-3 activity in a subject using a compound of Structure IB, a tautomer of the compound, a pharmaceutically acceptable salt of the compound, a pharmaceutically acceptable salt of the tautomer, or mixtures thereof, R^6 and R^7 are independently selected from –H, -F, -Cl, -OH, or substituted or unsubstituted heterocyclyl groups. In some such embodiments, R^6 is –H and R^7 is –H.

[0451] In some embodiments of the method of inhibiting GSK-3 in a subject and/or the method of treating a biological condition mediated by GSK-3 activity in a subject using a compound of Structure IB, a tautomer of the compound, a pharmaceutically acceptable salt of the compound, a pharmaceutically acceptable salt of the tautomer, or mixtures thereof, R^5 is –H, R^6 is –H, R^7 is –H, and R^8 is –H.

[0452] In some embodiments of the method of inhibiting GSK-3 in a subject and/or the method of treating a biological condition mediated by GSK-3 activity in a subject using a compound of Structure IB, a tautomer of the compound, a pharmaceutically acceptable salt of the compound, a pharmaceutically acceptable salt of the tautomer, or mixtures thereof, R^3 is selected from –H, -F, -Cl, -Br, $-CH_3$, -OH, -CN, substituted or unsubstituted alkoxy groups, substituted or unsubstituted alkylamino groups, substituted or unsubstituted dialkylamino groups, substituted or unsubstituted heterocyclyl groups, substituted or unsubstituted aryl groups, substituted or unsubstituted -C(=O)-heterocyclyl groups, substituted or unsubstituted $-C(=O)-N(alkyl)_2$ groups, or $-C(=O)-NH_2$ groups.

[0453] In some embodiments of the method of inhibiting GSK-3 in a subject and/or the method of treating a biological condition mediated by GSK-3 activity in a subject using a compound of Structure IB, a tautomer of the compound, a pharmaceutically acceptable salt of the compound, a pharmaceutically acceptable salt of the tautomer, or mixtures thereof, R^3 is

selected from –H, -F, -Cl, -Br, -CH_3, -CN, -OMe, hydroxyalkylamino groups, dialkylamino groups, dialkylaminoalkylamino groups, alkoxyalkylamino groups, substituted or unsubstituted heterocyclylalkylamino groups, acetamidoalkylamino groups, cyanoalkylamino groups, alkoxyalkylamino groups, thioalkylamino groups, (methylsulfonyl)alkylamino groups, cycloalkylalkylamino groups, dialkylaminoalkoxy groups, heterocyclylalkoxy groups, substituted or unsubstituted piperidinyl groups, substituted or unsubstituted imidazolyl groups, substituted or unsubstituted morpholinyl groups, substituted or unsubstituted pyrrolyl groups, substituted or unsubstituted pyrrolidinyl groups, substituted or unsubstituted piperazinyl groups, substituted or unsubstituted aryl groups, substituted or unsubstituted -C(=O)-heterocyclyl groups, substituted or unsubstituted -C(=O)-N(alkyl)$_2$ groups, or -C(=O)-NH_2 groups. In some embodiments, R^3 is selected from –H, -F, -Cl, -Br, -CH_3, -OH, -CN, substituted and unsubstituted alkoxy groups, substituted and unsubstituted alkylamino groups, substituted and unsubstituted dialkylamino groups, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted aryl groups, substituted and unsubstituted -C(=O)-heterocyclyl groups, substituted and unsubstituted -C(=O)-N(alkyl)$_2$ groups, and -C(=O)-NH_2 groups.

[0454] In some embodiments of the method of inhibiting GSK-3 in a subject and/or the method of treating a biological condition mediated by GSK-3 activity in a subject using a compound of Structure IB, a tautomer of the compound, a pharmaceutically acceptable salt of the compound, a pharmaceutically acceptable salt of the tautomer, or mixtures thereof, R^3 is selected from substituted or unsubstituted alkylamino groups or substituted or unsubstituted dialkylamino groups. In some such embodiments, R^3 is a dimethylamino group.

[0455] In some embodiments of the method of inhibiting GSK-3 in a subject and/or the method of treating a biological condition mediated by GSK-3 activity in a subject using a compound of Structure IB, a tautomer of the compound, a pharmaceutically acceptable salt of the compound, a

pharmaceutically acceptable salt of the tautomer, or mixtures thereof, R^4, R^5, R^6, R^7, R^8, and R^{10} are all –H.

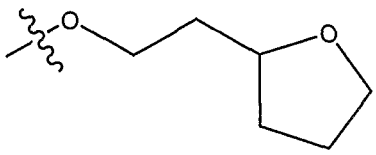
[0456] In some embodiments of the method of inhibiting GSK-3 in a subject and/or the method of treating a biological condition mediated by GSK-3 activity in a subject using a compound of Structure IB, a tautomer of the compound, a pharmaceutically acceptable salt of the compound, a pharmaceutically acceptable salt of the tautomer, or mixtures thereof, the IC_{50} value of the compound is less than or equal to 10 μM with respect to GSK-3. In other such embodiments, the IC_{50} value is less than or equal to 1 μM, is less than or equal to 0.1 μM, is less than or equal to 0.050 μM, is less than or equal to 0.030 μM, is less than or equal to 0.025 μM, or is less than or equal to 0.010 μM.

[0457] In some embodiments of the method of inhibiting GSK-3 in a subject and/or the method of treating a biological condition mediated by GSK-3 activity in a subject using a compound of Structure IB, a tautomer of the compound, a pharmaceutically acceptable salt of the compound, a pharmaceutically acceptable salt of the tautomer, or mixtures thereof, the subject is a mammal, and in some embodiments is a human.

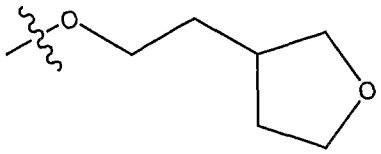
[0458] In some embodiments of the method of inhibiting GSK-3 in a subject and/or the method of treating a biological condition mediated by GSK-3 activity in a subject using a compound of Structure IB, the biological condition is diabetes, and in some such embodiments the biological condition is noninsulin dependent diabetes mellitus (NIDDM). In other such embodiments, the biological condition is Alzheimer's disease or is bipolar disorder.

[0459] In groups including heterocyclyl groups, the heterocyclyl group may be attached in various ways. For example, in a heterocycylakoxy group, the heterocyclyl group may be bonded to a methylene carbon of the alkoxy group of the heterocyclylalkoxy group through various ring members. By way

of non-limiting example, where the heterocyclyl group of the heterocyclylalkoxy group is tetrahydrofuran, the group could be represented by the formula -OCH_2CH_2(tetrahydrofuranyl) which corresponds to the following two structures:

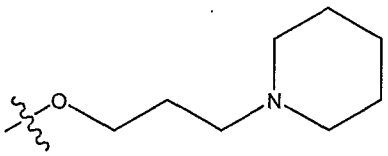


II

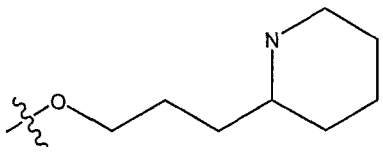


III

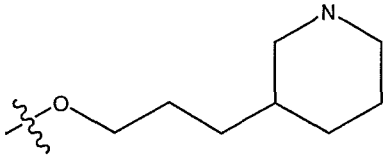
where Structure II represents the group that can be referred to as the -OCH_2CH_2(2-tetrahydrofuranyl) or –OCH_2CH_2(tetrahydrofuran-2-yl) group and Structure III represents the group that can be referred to as the –OCH_2CH_2(3-tetrahydrofuranyl) or –OCH_2CH_2(tetrahydrofuran-3-yl)group. When the heterocyclyl group is a N-containing heterocycle, such as, but not limited to piperidine, piperazine, morpholine, or pyrrolidine, the heterocycle can be bonded to the methylene carbon through a ring carbon atom or through a nitrogen atom in the ring of the N-containing heterocycle. Both of these are preferred. Where the heterocyclyl group is a piperidine for a -$OCH_2CH_2CH_2$(heterocyclyl) group, the following structures are possible and preferred:



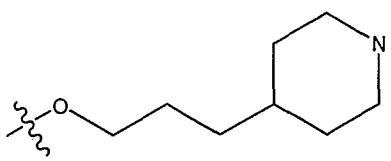
IV



V

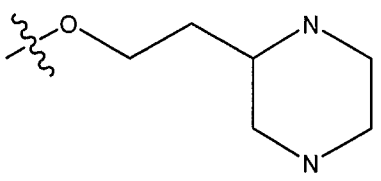


VI

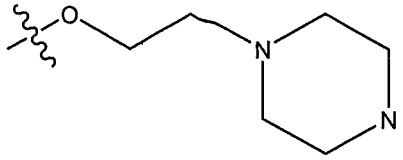


VII

[0460] Structure IV is an example of a –O(CH$_2$)$_3$(N-piperidinyl) or -O(CH$_2$)$_3$(1-piperidinyl) or -O(CH$_2$)$_3$(piperidin-1-yl) group. Structure V is an example of a –O(CH$_2$)$_3$-(2-piperidinyl) or -O(CH$_2$)$_3$(piperidin-2-yl) group. Structure VI is an example of a –O(CH$_2$)$_3$(3-piperidinyl) or -O(CH$_2$)$_3$(piperidin-3-yl) group. Structure VII is an example of a -O(CH$_2$)$_3$(4-piperidinyl) or -O(CH$_2$)$_3$(piperidin-4-yl) group. Where the heterocyclyl group is a piperazine for an -OCH$_2$CH$_2$(heterocyclyl) group, the following structures are possible and preferred:

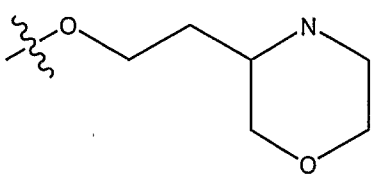


VIII

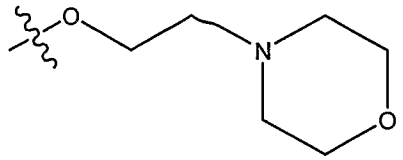


IX

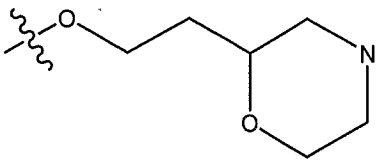
[0461] Structure VIII is an example of a –O(CH$_2$)$_2$(2-piperazinyl) or -O(CH$_2$)$_2$(piperazin-2-yl) group, and Structure IX is an example of a -O(CH$_2$)$_2$(1-piperazinyl) or -O(CH$_2$)$_2$(N-piperazinyl) or -O(CH$_2$)$_2$(piperazin-1-yl) group. Where the heterocyclyl group is a morpholine for a -OCH$_2$CH$_2$(heterocyclyl) group, the following structures are possible and preferred:



X



XI



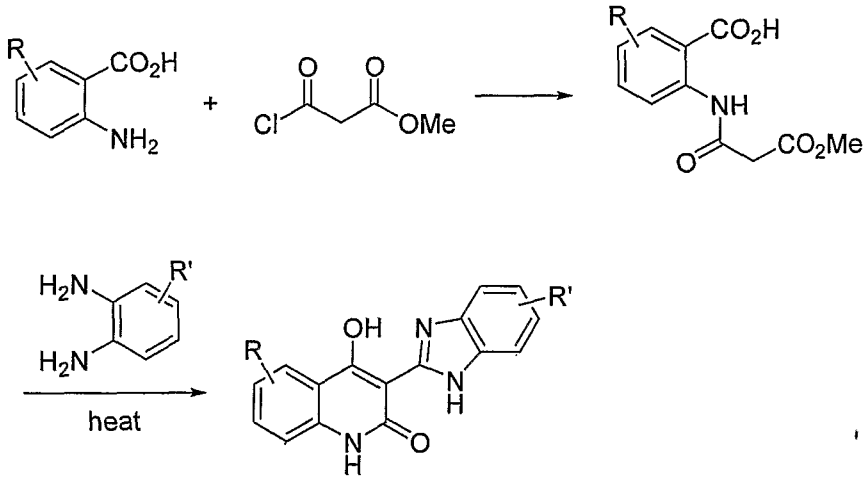
XII

[0462] Structure X is an example of a –O(CH$_2$)$_2$(3-morpholinyl) or -O(CH$_2$)$_2$(morpholin-3-yl) group, Structure XI is an example of a –O(CH$_2$)$_2$(4-

morpholinyl) or –$O(CH_2)_2$(N-morpholinyl) or -$O(CH_2)_2$(morpholin-4-yl)group, and Structure XII is an example of a –$O(CH_2)_2$(2-morpholinyl) or -$O(CH_2)_2$(morpholin-2-yl) group. It will be observed that where the heterocyclyl group is a pyrrolidine in a -OCH_2CH_2(heterocyclyl) group, the structures available include –$O(CH_2)_2$(1-pyrrolidinyl) or –$O(CH_2)_2$(N-pyrrolidinyl) or –$O(CH_2)_2$(pyrrolidin-1-yl), -$O(CH_2)_2$(2-pyrrolidinyl) or -$O(CH_2)_2$(pyrrolidin-2-yl), and –$O(CH_2)_2$(3-pyrrolidinyl) or -$O(CH_2)_2$(pyrrolidin-3-yl).

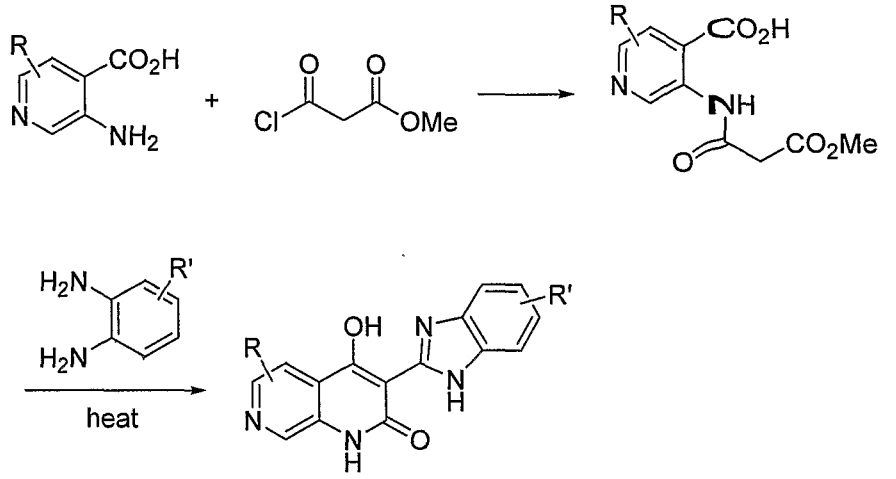
[0463] Compounds of Structure I and IB may be synthesized from simple starting molecules as shown in Schemes 1-6 and the Examples. As shown in Scheme 1, hydroxy derivatives of compounds of Structure I may generally be prepared using aromatic compounds substituted with amines and carboxylic acid groups. These compounds may then be converted to compounds of Structure I using the methods described in Schemes 3 and 5 and the Examples. Hydroxy derivatives of heterocyclic analogs of Structure I such as compounds of Structure IB may be similarly prepared using the appropriate heteroaromatic analogs of the compounds as shown in Scheme 2. These may then be converted to heterocyclic analogs of Structure I such as compounds of Structure IB using the methods described in Schemes 4 and 5.

Scheme 1.



[0464] As shown in Scheme 1, a substituted aromatic compound such as a substituted or unsubstituted 2-aminobenzoic acid may be reacted with an acyl halide such as methyl 2-(chlorocarbonyl)acetate to produce an amide that will react with a substituted or unsubstituted 1,2-diaminobenzene. The resulting product is a 4-hydroxy-substituted analog of a compound of Structure I.

Scheme 2.



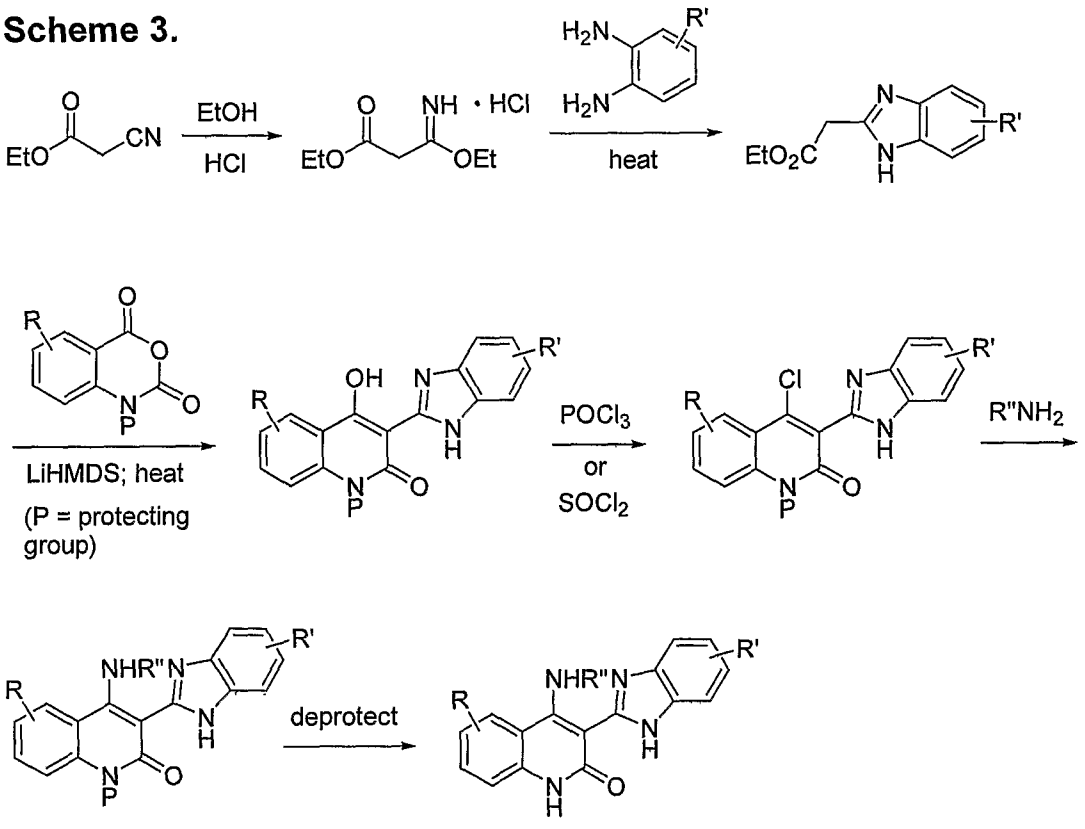
[0465] As shown in Scheme 2, a substituted pyridine such as a substituted or unsubstituted 3-amino-pyridine-4-carboxylic acid may be reacted with an acyl halide such as methyl 2-(chlorocarbonyl)acetate to produce an amide that will react with a substituted or unsubstituted 1,2-diaminobenzene or a pyridine analog. The resulting product is a 4-hydroxy-substituted heterocyclic analog of a compound of Structure I or IB. The use of starting pyridines with different substitution patterns such as 2-aminonicotinic acid (2-aminopyridine-4-carboxylic acid) provides compounds where the nitrogen is in a different position in the pyridine ring of the final compound. One skilled in the art will recognize that the procedure set forth in Scheme 2 may be modified to produce various 4-hydroxy heterocyclic analogs of compounds of Structure I and IB.

[0466] Scheme 3 illustrates a general synthetic route that allows for the synthesis of various compounds of Structure I. An inspection of Scheme 3

shows that 4-hydroxy substituted analogs of compounds of Structure I may be converted into the 4-chloro derivative by reaction with phosphorus oxychloride or thionyl chloride. The 4-chloro derivative may then be reacted with an appropriate amine such as an alkylamine, a dialkylamine, a heterocyclylamine, a cycloalkylamine, an aromatic amine, and the like to produce the corresponding protected compound of Structure I. Deprotection affords the final desired compounds of Structure I.

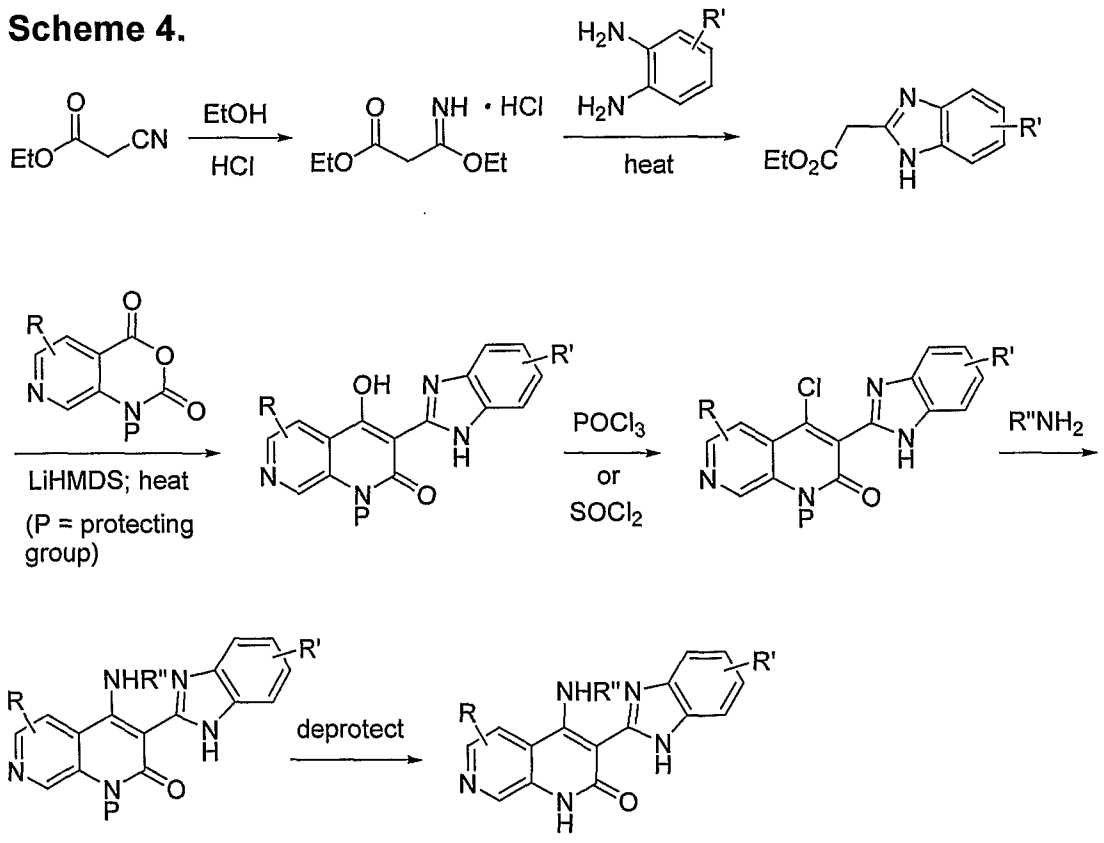
[0467] The various 2-aminobenzoic acid starting materials used to synthesize isatoic anhydrides may be obtained from commercial sources or prepared by methods known to one of skill in the art. General isatoic anhydride synthesis methods are described in *J. Med. Chem.* 1981, 24 (6), 735 and *J. Heterocycl. Chem.* 1975, 12(3), 565 which are both hereby incorporated by reference in their entirety for all purposes as if fully set forth herein.

Scheme 3.



[0468] Scheme 4 illustrates a general synthetic route that allows for the synthesis of various heterocyclic compounds of Structure IB. An inspection of Scheme 4 shows that 4-hydroxy substituted analogs of Structure IB may be converted into the 4-chloro derivative by reaction with phosphorous oxychloride or thionyl chloride. The 4-chloro derivative may then be reacted with an appropriate amine such as an alkylamine, a dialkylamine, a heterocyclylamine, a cycloalkylamine, an aromatic amine, and the like to produce the corresponding protected compounds of Structure IB. Deprotection affords the final desired heterocyclic analogs of compounds of Structure I.

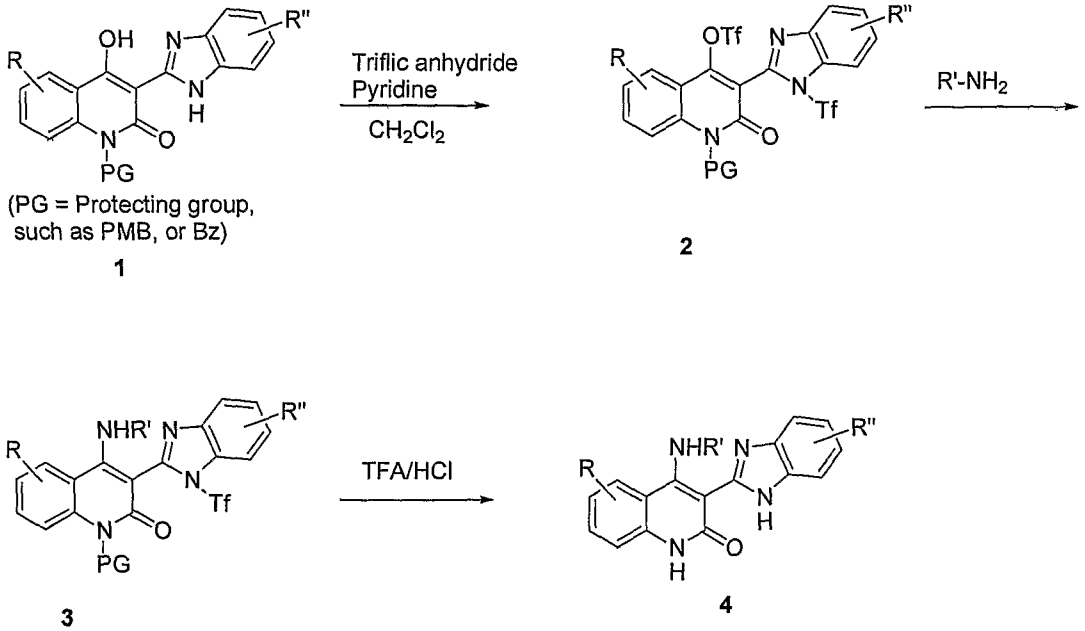
Scheme 4.



[0469] Scheme 5 depicts a general synthetic route that allows for the synthesis of various compounds of Structure I. An inspection of Scheme 5 shows that the hydroxy group of 4-hydroxy substituted analogs of compounds of Structure I may be converted to a leaving group by triflation with triflating agents such as triflic anhydride. The resulting triflates may then be reacted

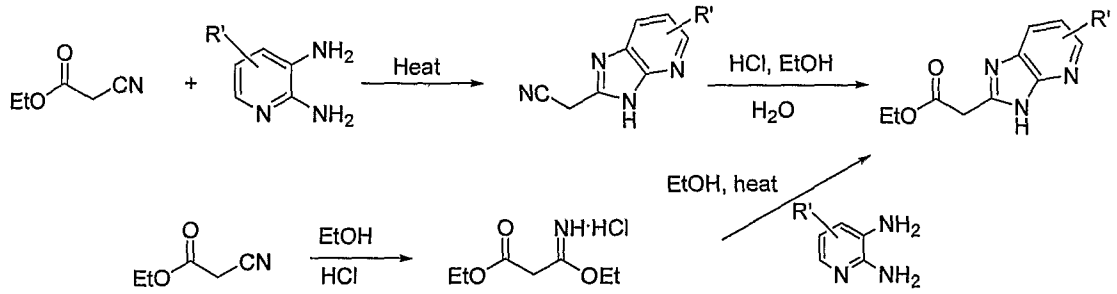
with a wide variety of nitrogen nucleophiles such as 3-aminoquinuclidine and other amines to produce protected analogs of compound of Structure I. Deprotection of the resulting products affords the desired compounds of Structure I. An analogous procedure may be used to prepare heterocyclic compounds of Structure I.

Scheme 5.



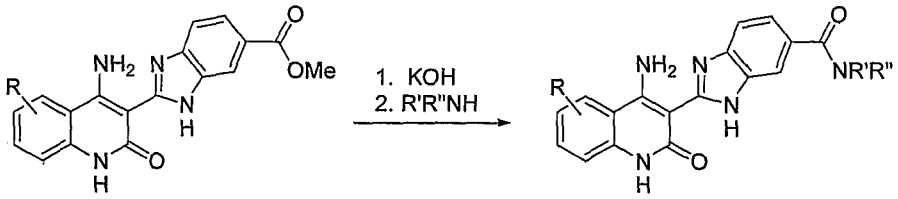
[0470] Heteroaromatic diamines may be simply prepared and used as precursors of compounds of Structure I and IB and heterocyclic analogs of compounds of Structure I and IB where one or more of A, B, C, or D is a nitrogen as shown in Scheme 6.

Scheme 6.



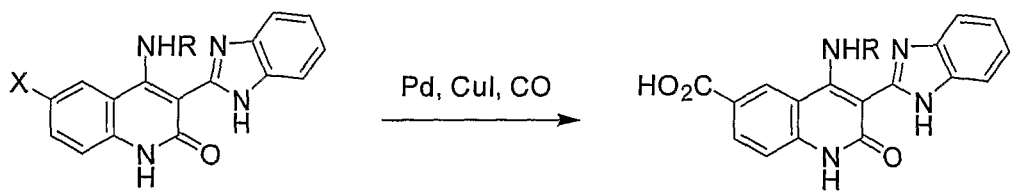
[0471] As shown in Scheme 6, a compound such as ethyl cyanoacetate may be condensed with a substituted or unsubstituted heterocycle containing two ortho amino groups such as substituted or unsubstituted 1,2-diaminopyridine to obtain a substituted or unsubstituted 2-imidazolo[5,4-b]pyridin-2-ylethanenitrile, which may subsequently be hydrolyzed in acidic medium to provide a substituted or unsubstituted ethyl 2-imidazolo[5,4-b]pyridin-2-ylacetate. As an alternate route, a substituted or unsubstituted ethyl 2-imidazolo[5,4-b]pyridin-2-ylacetate may be obtained from a compound such as the hydrochloride salt of 3-ethoxy-3-iminopropanoate and a substituted or unsubstituted 1,2-diaminopyridine. Reaction of a substituted or unsubstituted ethyl 2-imidazolo[5,4-b]pyridin-2-ylacetates with an appropriate aromatic compound provides compounds of Structure I and heterocyclic analogs of compounds of Structure I where one or more of A, B, C, or D is a nitrogen atom.

Scheme 7.



[0472] Introduction of substituents on the benzimidazole ring need not be limited to the early stages of the synthesis and may be accomplished after formation of the quinolinone ring. For example, amides can be obtained by coupling the advanced acid intermediate shown in Scheme 7 with a variety of amine.

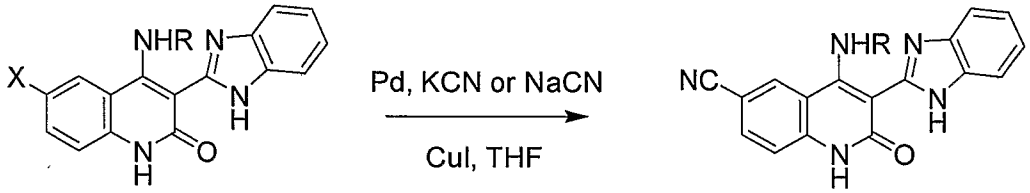
Scheme 8.



X = I, Br, TfO

[0473] Conversion of the C-6 or C-7 halides to an acid group was accomplished using procedures in the following references which are herein incorporated by reference in their entirety for all purposes as if fully set forth herein: Koga, H.; et al., *Tet. Let.*, 1995, 36, 1, 87-90; and Fukuyama, T.; et al., *J. Am. Chem. Soc.,* 1994, 116, 3125-3126.

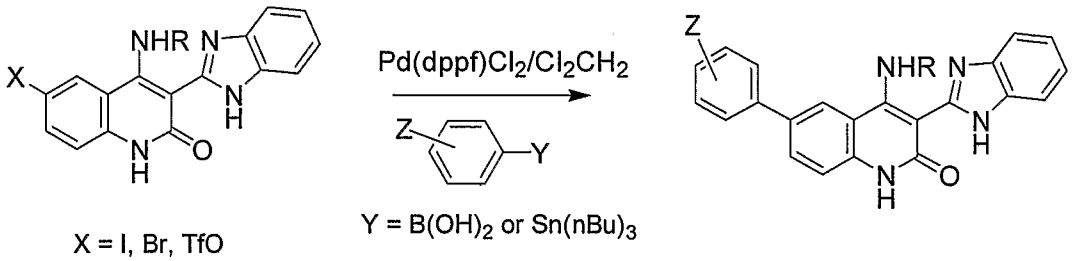
Scheme 9.



X = I, Br, TfO

[0474] Conversion of the C-6 or C-7 halides to a cyano group was accomplished using procedures in the following reference which is herein incorporated by reference in its entirety for all purposes as if fully set forth herein: Anderson, B.A.; et al., *J. Org. Chem.*, 1998, 63, 8224-828. Preferred reaction conditions for Scheme 9 are described in Method 26 below.

Scheme 10.

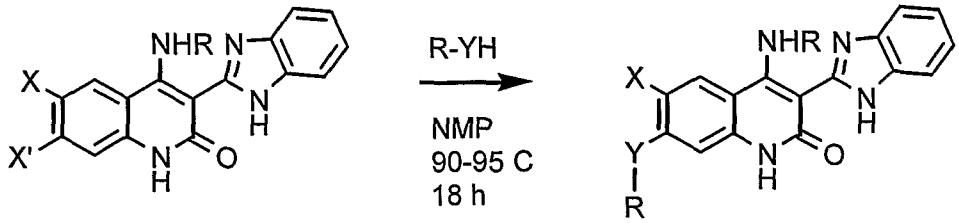


X = I, Br, TfO

Y = $B(OH)_2$ or $Sn(nBu)_3$

[0475] Conversion of the C-6 or C-7 halides to an aryl group was accomplished using standard Suzuki or Stille procedures such as described below.

Scheme 11.



X, X' = F, Cl, I
Y = NH, O, S

[0476] Additional functionalization using a dihaloquinolone was accomplished as depicted in Scheme 11 by reaction of the dihaloquinolone with nucleophiles such as amines, alcohols and thiols.

[0477] The compounds of Structure I and IB, tautomers of the compounds, pharmaceutically acceptable salts of the compounds, pharmaceutically acceptable salts of the tautomers, and mixtures thereof may be used to prepare medicaments, that may be used for the purposes described herein, and may be used to treat various biological conditions as described herein.

[0478] Pharmaceutical formulations may include any of the compounds of any of the embodiments described above in combination with a pharmaceutically acceptable carrier such as those described herein.

[0479] The instant invention also provides for compositions which may be prepared by mixing one or more compounds of the instant invention, or pharmaceutically acceptable salts tautomers thereof, or mixtures thereof with pharmaceutically acceptable carriers, excipients, binders, diluents or the like to treat or ameliorate a variety of disorders related to the activity of VEGF-RTK, more particularly angiogenesis associated with cancer or related to the activity of FLT-1, VEGFR2, VEGFR3, FGFR1, GSK-3, Cdk2, Cdk4, MEK1, NEK-2, CHK2, CK1ε, Raf, NEK-2, CHK1, Rsk2, PAR-1, Cdc2, c-Kit, c-ABL, p60src, FGFR3, FLT-3, Fyn, Lck, Tie-2, PDGFRα, and PDGFRβ. The compositions of the inventions may be used to create formulations such as medicaments and pharmaceutical formulations that inhibit tyrosine kinases and/or serine/threonine kinases and may be used to treat biological conditions

mediated by such kinases. Such compositions can be in the form of, for example, granules, powders, tablets, capsules, syrup, suppositories, injections, emulsions, elixirs, suspensions or solutions. The instant compositions can be formulated for various routes of administration, for example, by oral administration, by nasal administration, by rectal administration, subcutaneous injection, intravenous injection, intramuscular injections, or intraperitoneal injection. The following dosage forms are given by way of example and should not be construed as limiting the instant invention.

[0480] For oral, buccal, and sublingual administration, powders, suspensions, granules, tablets, pills, capsules, gelcaps, and caplets are acceptable as solid dosage forms. These can be prepared, for example, by mixing one or more compounds of the instant invention, pharmaceutically acceptable salts, tautomers, or mixtures thereof, with at least one additive such as a starch or other additive. Suitable additives are sucrose, lactose, cellulose sugar, mannitol, maltitol, dextran, starch, agar, alginates, chitins, chitosans, pectins, tragacanth gum, gum arabic, gelatins, collagens, casein, albumin, synthetic or semi-synthetic polymers or glycerides. Optionally, oral dosage forms can contain other ingredients to aid in administration, such as an inactive diluent, or lubricants such as magnesium stearate, or preservatives such as paraben or sorbic acid, or anti-oxidants such as ascorbic acid, tocopherol or cysteine, a disintegrating agent, binders, thickeners, buffers, sweeteners, flavoring agents or perfuming agents. Tablets and pills may be further treated with suitable coating materials known in the art.

[0481] Liquid dosage forms for oral administration may be in the form of pharmaceutically acceptable emulsions, syrups, elixirs, suspensions, and solutions, which may contain an inactive diluent, such as water. Pharmaceutical formulations and medicaments may be prepared as liquid suspensions or solutions using a sterile liquid, such as, but not limited to, an oil, water, an alcohol, and combinations of these. Pharmaceutically suitable

surfactants, suspending agents, emulsifying agents, may be added for oral or parenteral administration.

[0482] As noted above, suspensions may include oils. Such oil include, but are not limited to, peanut oil, sesame oil, cottonseed oil, corn oil and olive oil. Suspension preparation may also contain esters of fatty acids such as ethyl oleate, isopropyl myristate, fatty acid glycerides and acetylated fatty acid glycerides. Suspension formulations may include alcohols, such as, but not limited to, ethanol, isopropyl alcohol, hexadecyl alcohol, glycerol and propylene glycol. Ethers, such as but not limited to, poly(ethyleneglycol), petroleum hydrocarbons such as mineral oil and petrolatum; and water may also be used in suspension formulations.

[0483] For nasal administration, the pharmaceutical formulations and medicaments may be a spray or aerosol containing an appropriate solvent(s) and optionally other compounds such as, but not limited to, stabilizers, antimicrobial agents, antioxidants, pH modifiers, surfactants, bioavailability modifiers and combinations of these. A propellant for an aerosol formulation may include compressed air, nitrogen, carbon dioxide, or a hydrocarbon based low boiling solvent.

[0484] Injectable dosage forms generally include aqueous suspensions or oil suspensions which may be prepared using a suitable dispersant or wetting agent and a suspending agent. Injectable forms may be in solution phase or in the form of a suspension, which is prepared with a solvent or diluent. Acceptable solvents or vehicles include sterilized water, Ringer's solution, or an isotonic aqueous saline solution. Alternatively, sterile oils may be employed as solvents or suspending agents. Preferably, the oil or fatty acid is non-volatile, including natural or synthetic oils, fatty acids, mono-, di- or tri-glycerides.

[0485] For injection, the pharmaceutical formulation and/or medicament may be a powder suitable for reconstitution with an appropriate solution as

described above. Examples of these include, but are not limited to, freeze dried, rotary dried or spray dried powders, amorphous powders, granules, precipitates, or particulates. For injection, the formulations may optionally contain stabilizers, pH modifiers, surfactants, bioavailability modifiers and combinations of these.

[0486] For rectal administration, the pharmaceutical formulations and medicaments may be in the form of a suppository, an ointment, an enema, a tablet or a cream for release of compound in the intestines, sigmoid flexure and/or rectum. Rectal suppositories are prepared by mixing one or more compounds of the instant invention, or pharmaceutically acceptable salts or tautomers of the compound, with acceptable vehicles, for example, cocoa butter or polyethylene glycol, which is present in a solid phase at normal storing temperatures, and present in a liquid phase at those temperatures suitable to release a drug inside the body, such as in the rectum. Oils may also be employed in the preparation of formulations of the soft gelatin type and suppositories. Water, saline, aqueous dextrose and related sugar solutions, and glycerols may be employed in the preparation of suspension formulations which may also contain suspending agents such as pectins, carbomers, methyl cellulose, hydroxypropyl cellulose or carboxymethyl cellulose, as well as buffers and preservatives.

[0487] Besides those representative dosage forms described above, pharmaceutically acceptable excipients and carriers are generally known to those skilled in the art and are thus included in the instant invention. Such excipients and carriers are described, for example, in "Remingtons Pharmaceutical Sciences" Mack Pub. Co., New Jersey (1991), which is incorporated herein by reference in its entirety for all purposes as if fully set forth herein.

[0488] The formulations of the invention may be designed to be short-acting, fast-releasing, long-acting, and sustained-releasing as described

below. Thus, the pharmaceutical formulations may also be formulated for controlled release or for slow release.

[0489] The instant compositions may also comprise, for example, micelles or liposomes, or some other encapsulated form, or may be administered in an extended release form to provide a prolonged storage and/or delivery effect. Therefore, the pharmaceutical formulations and medicaments may be compressed into pellets or cylinders and implanted intramuscularly or subcutaneously as depot injections or as implants such as stents. Such implants may employ known inert materials such as silicones and biodegradable polymers.

[0490] Specific dosages may be adjusted depending on conditions of disease, the age, body weight, general health conditions, sex, and diet of the subject, dose intervals, administration routes, excretion rate, and combinations of drugs. Any of the above dosage forms containing effective amounts are well within the bounds of routine experimentation and therefore, well within the scope of the instant invention.

[0491] A therapeutically effective dose may vary depending upon the route of administration and dosage form. The preferred compound or compounds of the instant invention is a formulation that exhibits a high therapeutic index. The therapeutic index is the dose ratio between toxic and therapeutic effects which can be expressed as the ratio between LD_{50} and ED_{50}. The LD_{50} is the dose lethal to 50% of the population and the ED_{50} is the dose therapeutically effective in 50% of the population. The LD_{50} and ED_{50} are determined by standard pharmaceutical procedures in animal cell cultures or experimental animals.

[0492] "Treating" within the context of the instant invention, means an alleviation of symptoms associated with a disorder or disease, or halt of further progression or worsening of those symptoms, or prevention or prophylaxis of the disease or disorder. For example, within the context of

treating patients in need of an inhibitor of VEGF-RTK, successful treatment may include a reduction in the proliferation of capillaries feeding a tumor or diseased tissue, an alleviation of symptoms related to a cancerous growth or tumor, proliferation of capillaries, or diseased tissue, a halting in capillary proliferation, or a halting in the progression of a disease such as cancer or in the growth of cancerous cells. Treatment may also include administering the pharmaceutical formulations of the present invention in combination with other therapies. For example, the compounds and pharmaceutical formulations of the present invention may be administered before, during, or after surgical procedure and/or radiation therapy. The compounds of the invention can also be administered in conjunction with other anti-cancer drugs including those used in antisense and gene therapy. Appropriate combinations can be determined by those of skill in the oncology and medicine arts.

[0493] Pharmaceutical formulations and medicaments according to the invention include any of the compounds described above in combination with a pharmaceutically acceptable carrier. Thus, the compounds of the invention may be used to prepare medicaments and pharmaceutical formulations. In some such embodiments, the medicaments and pharmaceutical formulations comprise any of the compounds of any of the embodiments of compounds of Structure I or Structure IB or pharmaceutically acceptable salts thereof. The invention also provides for the use of any of the compounds of any of the embodiments of compounds of Structure I or IB or pharmaceutically acceptable salts thereof for the inhibition of an enzyme such as FLT-1, VEGFR2, VEGFR3, FGFR1, GSK-3, Cdk2, Cdk4, MEK1, NEK-2, CHK2, CK1ε, Raf, NEK-2, CHK1, Rsk2, PAR-1, c-Kit, c-ABL, p60src, FGFR3, FLT-3, Cdc2, Fyn, Lck, Tie-2, PDGFRα, and PDGFRβ, or for the treatment of a disease or condition associated with any of these enzymes as described in greater detail below. The invention also provides the use of any of the compounds of any of the embodiments of compounds of Structure I or IB or pharmaceutically acceptable salts thereof for the manufacture of enzyme inhibition agent such as a tyrosine kinase inhibitor or a serine/threonine

kinase inhibitor, a pharmaceutical formulation, or a medicament that inhibits enzymes such as FLT-1, VEGFR2, VEGFR3, FGFR1, GSK-3, Cdk2, Cdk4, MEK1, NEK-2, CHK2, CK1ε, Raf, NEK-2, CHK1, Rsk2, PAR-1, c-Kit, c-ABL, p60src, FGFR3, FLT-3, Cdc2, Fyn, Lck, Tie-2, PDGFRα, and PDGFRβ or treats a disease or condition associated with any of these enzymes as described in greater detail below.

[0494] A method of treating a patient in need of an inhibitor of vascular endothelial growth factor receptor tyrosine kinase includes administering an effective amount of a pharmaceutical formulation, a medicament according to the invention or any of the compounds of any of the embodiments of compounds of Structure I or IB to a patient in need thereof.

[0495] A method for inhibiting tumor growth in a patient includes administering an effective amount of the compound, a pharmaceutically acceptable salt thereof of any of the compounds of Structure I or IB , or a medicament to a patient having a tumor.

[0496] A method for inhibiting angiogenesis and tumor growth in a patient includes administering an effective amount of the compound or a pharmaceutically acceptable salt thereof according to a patient in need.

[0497] The invention provides a method of treating a subject with various tumor types. The method includes administering to the subject, such as a human subject, a compound according to any of the embodiments of compounds or a pharmaceutically acceptable salt thereof of Structure I or IB to the subject. In some such embodiments, the method includes a method of treating a cancer patient.

[0498] The invention provides a method of inhibiting an enzyme such as a tyrosine kinase. The method includes administering to a subject, such as a human subject, a mammalian subject, or a cell subject, a compound according to any of the embodiments of compounds or a pharmaceutically

acceptable salt thereof of Structure I or IB to the subject. In some such embodiments, the tyrosine kinase is VEGF.

[0499] The invention provides a method of treating a subject with type II diabetes. The method includes administering to the subject, such as a human subject, a compound according to any of the embodiments of compounds or a pharmaceutically acceptable salt thereof of Structure I or IB to the subject. In some such embodiments, the method includes a method of treating a prediabetic or diabetic patient.

[0500] The invention provides a method of stimulating insulin-dependent processes in a patient. The method includes administering to the patient, such as a human patient, a compound according to any of the embodiments of compounds of Structure I or IB , or a pharmaceutically acceptable salt thereof, to the subject. In some such embodiments, the method includes a method of reducing plasma glucose levels, increasing glycogen uptake, potentiating insulin, upregulating glucose synthase activity, and stimulating glycogen synthesis such as in skin, muscle, and fat cells.

[0501] The invention provides a method of treating a subject with Alzheimer's disease. The method includes administering to the subject, such as a human subject, a compound according to any of the embodiments of compounds of Structure I or IB, or a pharmaceutically acceptable salt thereof, to the subject. In some such embodiments, the method includes reducing tau phosphorylation, reducing the generation of neurofibrillary tangles, and slowing the progression of Alzheimer's disease.

[0502] The invention provides a method of treating a subject with a central nervous system disorder. The method includes administering to the subject, such as a human subject, a compound according to any of the embodiments of compounds of Structure I or IB, or a pharmaceutically acceptable salt thereof, to the subject. In some such embodiments, the method includes a method of treating bipolar disorder; increasing the survival

of neurons subjected to aberrantly high levels of excitation induced by glutamate; reducing neurodegeneration associated with acute damage such as in cerebral ischemia, traumatic brain injury, and bacterial injury; and reducing chronic neuronal damage associated with Alzheimer's disease, Huntington's disease, Parkinson's disease, AIDS associated dementia, amyotrophic lateral sclerosis (ALS) and multiple sclerosis.

[0503] The invention provides a method of prolonging an immune response in a subject. The method includes administering to the subject, such as a human subject, a compound according to any of the embodiments of compounds of Structure I or IB, or a pharmaceutically acceptable salt thereof, to the subject. In some such embodiments, the method includes prolonging and/or potentiating immunostimulatory effects of cytokines, and enhancing the potential of cytokines for immunotherapy such as tumor immunotherapy.

[0504] The invention provides a method of reducing the splitting of centrosomes in the cells of a subject. The method includes administering to the subject, such as a human subject, a compound according to any of the embodiments of compounds of Structure I or IB, or a pharmaceutically acceptable salt thereof, to the subject. In some such embodiments, the subject is a cancer patient.

[0505] The invention provides a method of blocking DNA repair in a cancer cell of a cancer patient. The method includes administering to the patient, such as a human patient, a compound according to any of the embodiments of compounds of Structure I or IB, or a pharmaceutically acceptable salt thereof, to the patient..

[0506] The invention provides a method of promoting phosphorylation of Cdc25 and Wee1 in a patient. The method includes administering to the patient, such as a human patient, a compound according to any of the

embodiments of compounds of Structure I or IB, or a pharmaceutically acceptable salt thereof, to the patient.

[0507] The invention provides a method of modulating and/or preventing cell cycle arrest in a cell. The method includes contacting the cell with a compound according to any of the embodiments of compounds of Structure I or IB, or a pharmaceutically acceptable salt thereof. In one method, the cells are defective in the p53 gene and/or have p53 mutations and/or are deficient in p53. In some embodiments, the cells are cancer cells such as those deficient in p53. In some embodiments, arrest at the G2/M checkpoint is prevented or inhibited. In some embodiments, the method includes treating a patient, such as a human patient with any of the compounds of the invention, and in some such further embodiments, the method further includes treating the patient with another therapeutic agent such as a chemotherapeutic agent or with radiation or heat.

[0508] A method of preparing pharmaceutical formulations and medicaments includes mixing any of the above-described compounds with a pharmaceutically acceptable carrier.

[0509] As noted above, compounds of Structure I and IB, tautomers of compounds of Structure I and IB, pharmaceutically acceptable salts of the compounds, pharmaceutically acceptable salts of the tautomers, and mixtures thereof are useful inhibitors of CHK1. One of the advantages of many of these compounds is that they exhibit selectivity for CHK1 over other enzymes such as CHK2 and FLT-1, VEGFR2, and FGFR1. In some embodiments the IC_{50} values with respect to CHK1 show that the inhibitors of the invention are 1,000 times, 100 times, or 10 times more selective towards CHK1 compared to CHK2. CHK1 inhibitors of the invention may be administered to cancer patients alone or in combination with other anti-cancer drugs or therapies. The present CHK1 inhibitors are particularly useful against p53 cancers. In some embodiments, the cancers that the CHK1 inhibitors of the invention are

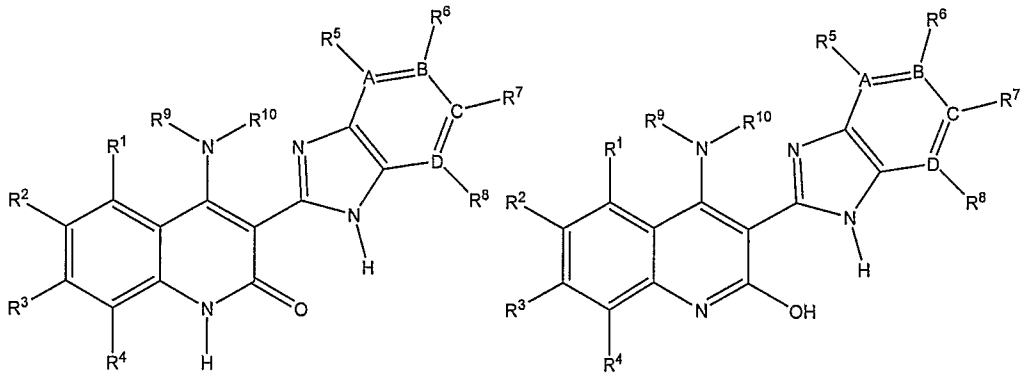
useful in treating include breast cancer, particularly human breast cancer, and colon cancer.

[0510] The CHK1 inhibitors of the present invention are particularly suitable for use in combination therapy as they have been shown to exhibit synergistic effect when used in combination with anti-cancer drugs such as camptothecin, doxorubicin, cisplatin, irinotecan (CPT-11), alkylating agents, topoisomerase I and II inhibitors, and radiation treatment. When an inhibitor of CHK1 of the present invention is used in combination therapy along with an anti-cancer drug such as camptothecin, cisplatin, irinotecan, or doxorubicin, isobolograms show that the amount of the anti-cancer drug may be reduced due to the synergistic interaction (supraadditivity) between the CHK1 inhibitor and the conventional anti-cancer drug. Therefore, the invention provides pharmaceutical formulations that include the compounds of Structure I and IB in combination with an anticancer drug, the use of the compounds in creating such formulations and medicaments.

[0511] The compounds of the invention may be used to inhibit kinases and used to treat biological conditions mediated by kinases in a variety of subjects. Suitable subjects include animals such as mammals and humans. Suitable mammals include, but are not limited to, primates such as, but not limited to lemurs, apes, and monkeys; rodents such as rats, mice, and guinea pigs; rabbits and hares; cows; horses; pigs; goats; sheep; marsupials; and carnivores such as felines, canines, and ursines. In some embodiments, the subject or patient is a human. In other embodiments, the subject or patient is a rodent such as a mouse or a rat. In some embodiments, the subject or patient is an animal other than a human and in some such embodiments, the subject or patient is a mammal other than a human.

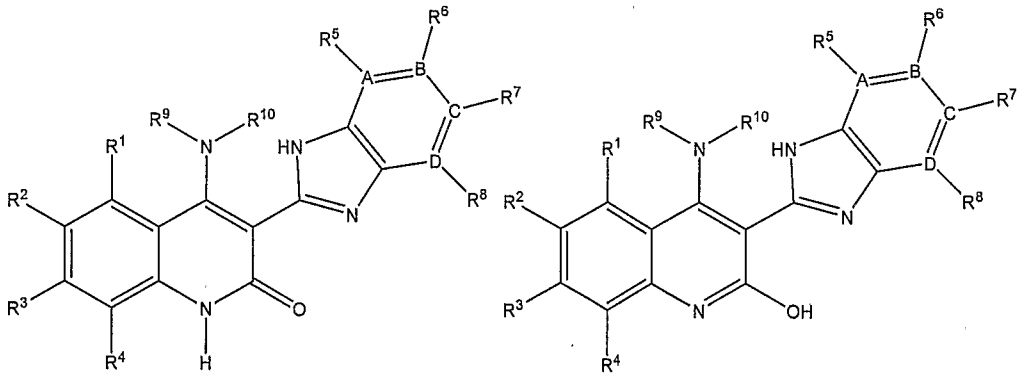
[0512] It should be understood that the organic compounds according to the invention may exhibit the phenomenon of tautomerism. As the chemical structures within this specification can only represent one of the possible tautomeric forms, it should be understood that the invention

encompasses any tautomeric form of the drawn structure. For example, Structure I is shown below with one tautomer, Tautomer Ia:



I Tautomer Ia

Other tautomers of Structure I, Tautomer Ib and Tautomer Ic, are shown below:



Tautomer Ib Tautomer Ic

Notably, the same types of tautomers occur with respect to compounds of Structure IB.

[0513] The present invention, thus generally described, will be understood more readily by reference to the following examples, which are provided by way of illustration and are not intended to be limiting of the present invention.

EXAMPLES

[0514] Nomenclature for the Example compounds was provided using ACD Name version 5.07 software (November 14, 2001) available from Advanced Chemistry Development, Inc., ChemInnovation NamExpert + Nomenclator™ brand software available from ChemInnovation Software, Inc., and AutoNom version 2.2 available in the ChemOffice® Ultra software package version 7.0 available from CambridgeSoft Corporation (Cambridge, MA). Some of the compounds and starting materials were named using standard IUPAC nomenclature.

[0515] The following abbreviations are used throughout the application with respect to chemical terminology:

AcOH:	Acetic acid
ATP:	Adenosine triphosphate
BINAP:	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
Boc:	N-*tert*-Butoxycarbonyl
Bn:	Benzyl
BSA:	Bovine Serum Albumin
Cbz:	Carbobenzyloxy
DEAD:	Diethyl azodicarboxylate
DIEA:	Diisopropylethylamine
DMA:	*N,N*-Dimethylacetamide
DMAP:	4-Dimethylaminopyridine
DMF:	*N,N*-Dimethylformamide
DMSO:	Dimethylsulfoxide
dppf:	1,1'(diphenylphosphino)ferrocene
DTT:	DL-Dithiothreitol
ED_{50}:	Dose therapeutically effective in 50% of the population
EDC or EDCI:	1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
EDTA:	Ethylene diamine tetraacetic acid

EtOAc:	Ethyl acetate
EtOH:	Ethanol
Fmoc:	9-fluorenylmethyl
HBTU:	O-Benzotriazol-1-yl-N,N,N',N'-tetramethyluronium hexafluorophosphate
HPLC:	High Pressure Liquid Chromatography
IC_{50} value:	The concentration of an inhibitor that causes a 50 % reduction in a measured activity.
KHMDS:	Potassium bis(trimethylsilyl)amide
LC/MS:	Liquid Chromatography/Mass Spectroscopy
LiHMDS:	Lithium bis(trimethylsilyl)amide
MeOH:	Methanol
NMP:	N-methylpyrrolidone
Pd(dba)2:	Bis(dibenzylideneacetone)Palladium
PPTS:	Pyridinium *p*-toluenesulfonate
Pyr:	Pyridine
SEMCl:	2-(Trimethylsilyl)ethoxymethyl chloride
TBAF:	Tetrabutylammonium fluoride
TEA:	Triethylamine
TES:	Triethylsilyl
TFAA:	Trifluoroacetic anhydride
THF:	Tetrahydrofuran
TMS:	Trimethylsilyl

Purification and Characterization of Compounds

[0516] Compounds of the present invention were characterized by high performance liquid chromatography (HPLC) using a Waters Millenium chromatography system with a 2690 Separation Module (Milford, Massachusetts). The analytical columns were Alltima C-18 reversed phase, 4.6 x 250 mm from Alltech (Deerfield, Illinois). A gradient elution was used, typically starting with 5% acetonitrile/95% water and progressing to 100% acetonitrile over a period of 40 minutes. All solvents contained 0.1%

trifluoroacetic acid (TFA). Compounds were detected by ultraviolet light (UV) absorption at either 220 or 254 nm. HPLC solvents were from Burdick and Jackson (Muskegan, Michigan), or Fisher Scientific (Pittsburg, Pennsylvania). In some instances, purity was assessed by thin layer chromatography (TLC) using glass or plastic backed silica gel plates, such as, for example, Baker-Flex Silica Gel 1B2-F flexible sheets. TLC results were readily detected visually under ultraviolet light, or by employing well known iodine vapor and other various staining techniques.

[0517] Mass spectrometric analysis was performed on one of two LCMS instruments: a Waters System (Alliance HT HPLC and a Micromass ZQ mass spectrometer; Column: Eclipse XDB-C18, 2.1 x 50 mm; Solvent system: 5-95% acetonitrile in water with 0.05% TFA; Flow rate 0.8 mL/minute; Molecular weight range 150-850; Cone Voltage 20 V; Column temperature 40°C) or a Hewlett Packard System (Series 1100 HPLC; Column: Eclipse XDB-C18, 2.1 x 50 mm; Solvent system: 1-95% acetonitrile in water with 0.05% TFA; Flow rate 0.4 mL/minute; Molecular weight range 150-850; Cone Voltage 50 V; Column temperature 30°C). All masses are reported as those of the protonated parent ions.

[0518] GCMS analysis was performed on a Hewlet Packard instrument (HP6890 Series gas chromatograph with a Mass Selective Detector 5973; Injector volume: 1 µL; Initial column temperature: 50°C; Final column temperature: 250°C; Ramp time: 20 minutes; Gas flow rate: 1 mL/minute; Column: 5% Phenyl Methyl Siloxane, Model #HP 190915-443, Dimensions: 30.0 m x 25 µm x 0.25 µm).

[0519] Preparative separations were carried out using either a Flash 40 chromatography system and KP-Sil, 60A (Biotage, Charlottesville, Virginia), or by HPLC using a C-18 reversed phase column. Typical solvents employed for the Flash 40 Biotage system were dichloromethane, methanol, ethyl acetate, hexane and triethyl amine. Typical solvents employed for the reverse

phase HPLC were varying concentrations of acetonitrile and water with 0.1% trifluoroacetic acid.

[0520] Various functionalized aryl diamines were obtained from commercial sources, prepared by methods know to those of skilled in the art, or were prepared by the following general methods. Some of the aryl diamines and Examples were prepared by the methods set forth in U.S. Provisional Application No. 60/405,729. Therefore, U.S. Provisional Application No. 60/405,729 in hereby incorporated by reference in its entirety for all purposes as if fully set forth herein including the methods and Examples set forth.

Method 1



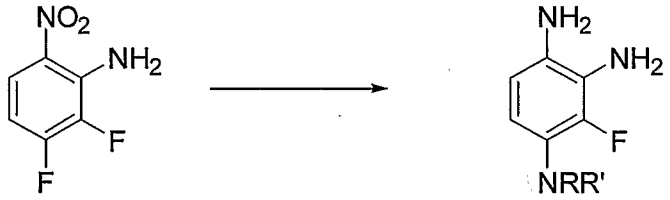
[0521] 2,4-Difluoronitrobenzene (1.0 equivalent) was placed in a dry round-bottomed flask equipped with a dry ice condenser charged with acetone and dry ice. Ammonia was condensed into the flask, and the resulting solution was stirred at reflux for 7 hours. A yellow precipitate formed within 1 hour. After 7 hours, the condenser was removed and the liquid ammonia was allowed to evaporate over several hours. The crude product was purified by flash chromatography on silica gel (85:15 hexanes:ethyl acetate, product at R_f = 0.32, contaminant at R_f = 0.51); GC/MS m/z 156.1 (M+), R_t 11.16 minutes.

[0522] The resulting 5-fluoro-2-nitrophenylamine (1.0 equivalents) and an amine (1.1 equivalents) e.g. N-methyl piperazine, were dissolved in NMP and triethylamine (2.0 equivalents) was added. The reaction mixture was heated at 100°C for 3 hours. The solution was then cooled to room temperature and diluted with water. The resulting precipitate was filtered and dried under vacuum to provide the 2-nitro-diamino product. Alternatively, the

same product may be obtained from commercially available 5-chloro-2-nitrophenylamine under identical conditions except heating at 130°C for 1-2 days. In some examples, the displacement on either 5-fluoro-2-nitrophenylamine or 5-chloro-2-nitrophenylamine can be conducted in neat amine (5 equivalents) at 100°C or 130°C, respectively. The product is isolated in an identical manner. LC/MS m/z 237.1 (MH+), R_t 1.304 minutes.

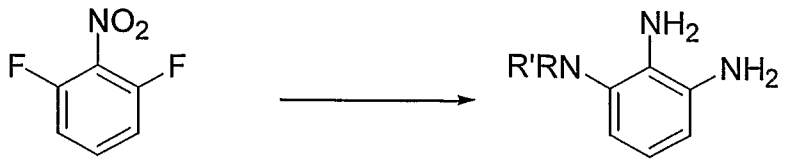
[0523] The nitroamine (1.0 equivalent) and 10% Pd/C (0.1 equivalents) was suspended in anhydrous ethanol at room temperature. The reaction flask was evacuated and subsequently filled with H_2. The resulting mixture was then stirred under a hydrogen atmosphere overnight. The resulting solution was filtered through Celite and concentrated under vacuum to provide the crude product which was used without further purification.

Method 2



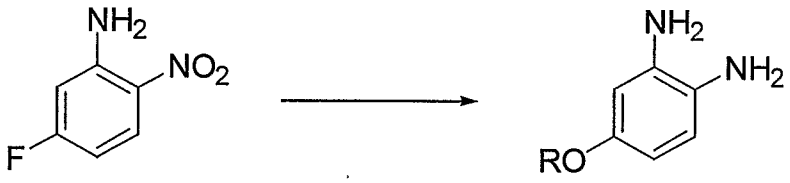
[0524] A round-bottom flask was charged with 2,3-difluoro-6-nitrophenylamine (1 equivalent) and enough NMP to make a viscous slurry. An amine (5 equivalents), e.g., N-methyl piperazine, was added and the solution was heated at 100°C. After 2 hours, the solution was cooled and poured into water. A bright yellow solid formed which was filtered and dried. The nitroamine was reduced as in Method 1 to provide the crude product which was used without further purification. LC/MS *m/z* 225.1 (MH+), R_t 0.335 minutes.

Method 3



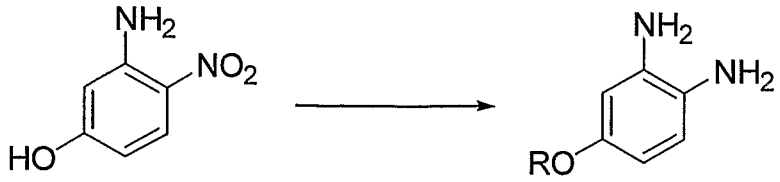
[0525] To a 0.1 M DMF solution of 1,3-difluoro-2-nitrobenzene was added Et_3N (2 equivalents) followed by an amine (1 equivalent), e.g. morpholine. The mixture was stirred for 18 hours and then diluted with water and extracted with ethyl acetate. LC/MS *m/z* 227.2 (MH+), R_t 2.522 minutes. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Ammonia was condensed into a pressure vessel containing the crude product. The pressure vessel was sealed and heated to 100°C (over 400 psi). After 72 hours, the pressure vessel was allowed to cool and the ammonia was evaporated to provide a reddish solid. The nitroamine was reduced as in Method 1 to provide the crude product which was used without further purification. LC/MS *m/z* 194.1 (MH+), R_t 1.199 minutes.

Method 4



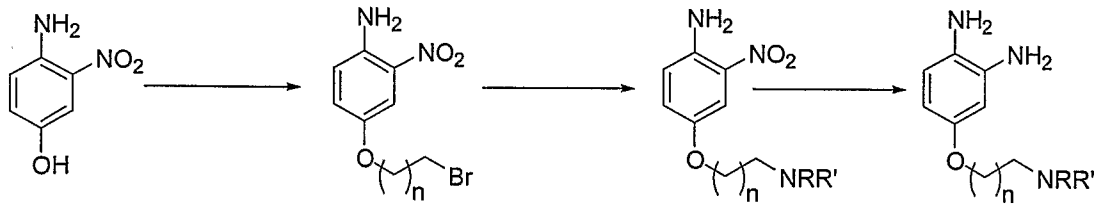
[0526] To a stirred NMP solution containing NaH (1.3 equivalents) was added an alcohol (1.0 equivalent), e.g. 2-methyloxyethanol. The resulting mixture was then stirred for 30 minutes. A slurry of 5-fluoro-2-nitrophenylamine in NMP was then added slowly. The mixture was then heated to 100°C. After 2 hours, the reaction mixture was cooled and water was added. The mixture was then filtered and the captured solid was washed with water and purified by silica gel chromatography (1:1 ethyl acetate:hexane). LC/MS *m/z* 213.2 (MH+), R_t 2.24 minutes. The nitroamine was reduced as in Method 1 to provide the crude product which was used without further purification. LC/MS *m/z* 183.1 (MH+), R_t 0.984 minutes.

Method 5



[0527] Diisopropyl azodicarboxylate (1.1 equivalents) was added dropwise to a stirred solution of 3-amino-4-nitrophenol (1.0 equivalent), triphenylphosphine (1.1 equivalents), and an alcohol, e.g. N-(2-hydroxyethyl)morpholine (1.0 equivalent), in tetrahydrofuran at 0°C. The mixture was allowed to warm to room temperature and stirred for 18 hours. The solvent was evaporated, and the product was purified by silica gel chromatography (98:2 CH_2Cl_2:methanol) to yield 4-(2-morpholin-4-ylethoxy)-2-nitrophenylamine as a dark reddish-brown oil. LC/MS *m/z* 268.0 (MH+), R_t 1.01 minutes. The nitroamine was reduced as in Method 1 to give the crude product which was used without further purification. LC/MS *m/z* 238.3 (MH+), R_t 0.295 minutes.

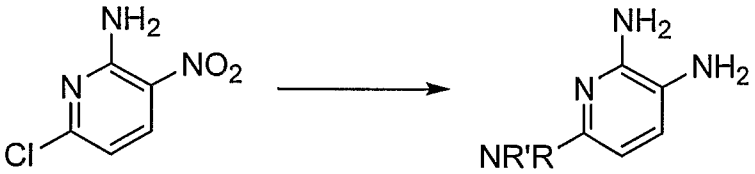
Method 6



[0528] To a flask charged with 4-amino-3-nitrophenol (1 equivalent), K_2CO_3 (2 equivalents), and 2-butanone, was added an alkyl dibromide, e.g. 1,3-dibromopropane (1.5 equivalents). The resulting mixture was then heated at 80°C for 18 hours. After cooling, the mixture was filtered, concentrated, and diluted with water. The solution was then extracted with CH_2Cl_2 (3 x) and the combined organic layers were concentrated to give a solid that was then washed with pentane. LCMS *m/z* 275.1 (MH+), R_t 2.74 minutes.

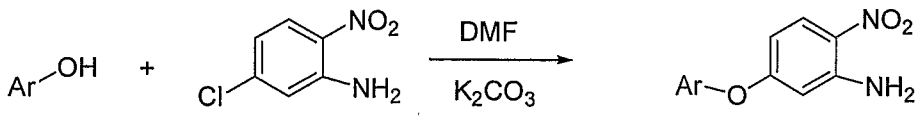
[0529] An acetonitrile solution of the bromide prepared above, an amine, e.g., pyrrolidine (5 equivalents), Cs_2CO_3 (2 equivalents) and Bu_4NI (0.1 equivalents) was heated at 70°C for 48 hours. The reaction mixture was cooled, filtered, and concentrated. The residue was dissolved in CH_2Cl_2, washed with water, and concentrated to give the desired nitroamine, 2-nitro-4-(3-pyrrolidin-1-ylpropoxy)phenylamine. LCMS *m/z* 266.2 (MH+), R_t 1.51 minutes. The nitroamine was reduced as in Method 1 to provide the crude product which was used without further purification.

Method 7



[0530] To a suspension of 6-chloro-3-nitropyridin-2-amine (1 equivalent) in acetonitrile was added an amine, e.g. morpholine (4 equivalents). The resulting reaction mixture was stirred at 70°C for 5 hours. The solvent was evaporated under reduced pressure, and the residue triturated with ether to provide the desired compound as a bright yellow powder. LC/MS *m/z* 225.0 (MH+), R_t 1.79 minutes. The nitroamine was reduced as in Method 1 to provide the crude product which was used without further purification.

Method 8



[0531] A phenol (1 equivalent) and 5-chloro-2-nitro aniline (1 equivalent) were dissolved in DMF, and solid K_2CO_3 (2 equivalents) was added in one portion. The reaction mixture was heated at 120°C overnight. The reaction mixture was cooled to room temperature, most of the DMF was distilled off, and water was added to the residue to obtain a precipitate. The

solid was dried and purified by chromatography on silicagel (2-10% $MeOH/CH_2Cl_2$) to afford the desired product. The nitroamine was reduced as in method 1 to give the crude product that was used without further purification.

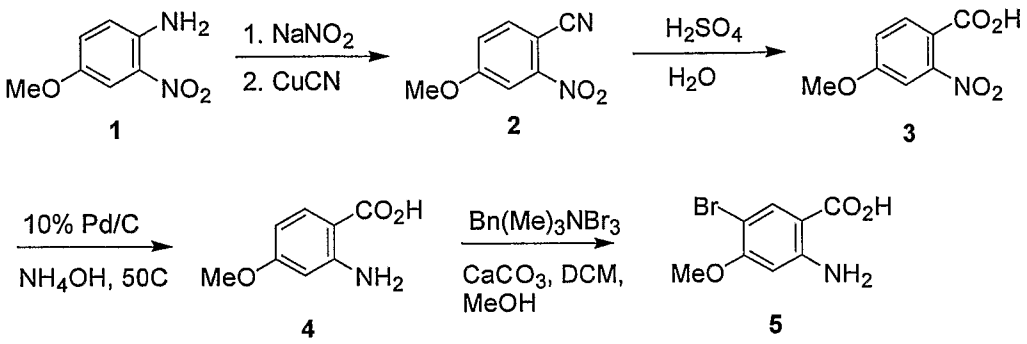
Method 9:



[0532] Morpholine (1 equivalent) and 5-chloro-2-nitroaniline (1 equivalent) were dissolved in DMF, and TEA (2 equivalents) was added. The reaction mixture was heated at 120°C overnight. The reaction mixture was then cooled to room temperature, most of the DMF was distilled off, and water was added to the residue to obtain the crude product as a precipitate. The solid was dried and purified by chromatography on silica gel (2-10% $MeOH/CH_2Cl_2$) to afford the desired product, 5-morpholin-4-yl-2-nitro-phenylamine.

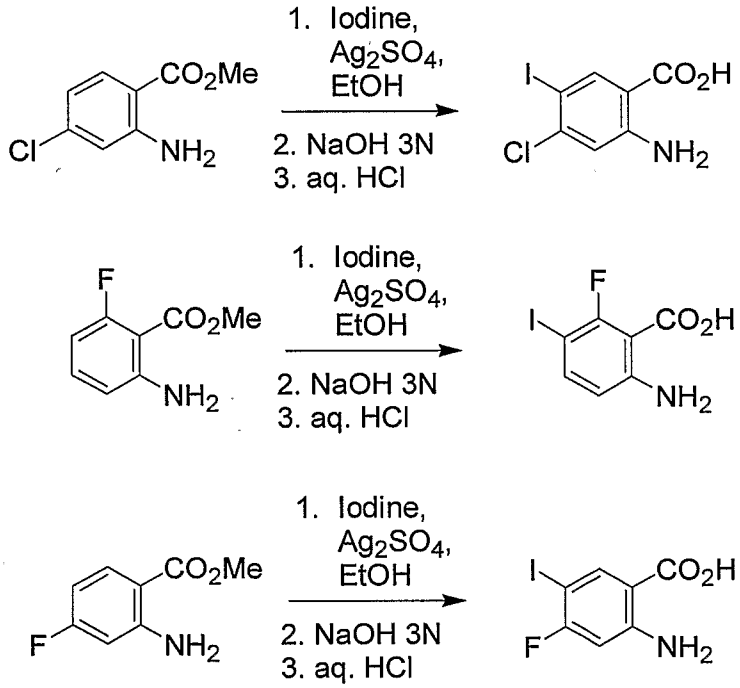
[0533] The various 2-amino benzoic acid starting materials used to synthesize isatoic anhydrides may be obtained from commercial sources, prepared by methods known to one of skill in the art, or prepared by the following general methods. General isatoic anhydride synthesis methods are described in *J. Med. Chem.* 1981, 24 (6), 735 and *J. Heterocycl. Chem.* 1975, 12(3), 565.

Method 10:



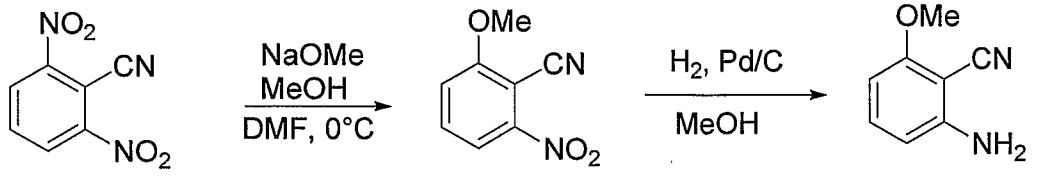
[0534] Compounds 1-3 were made using similar procedures to those in U.S. Patent No. 4,287,341 which is herein incorporated by reference in its entirety for all purposes as if fully set forth herein. Compound 3 was reduced using standard hydrogenation conditions of 10% Pd/C in NH_4OH at 50°C over 48 hours. The product was precipitated by neutralizing with glacial acetic acid, filtering, and washing with water and ether. Yields were about 50%. Compound 5 was prepared in a manner similar to that disclosed in U.S. Patent No. 5,716,993 herein incorporated by reference in its entirety for all purposes as if fully set forth herein.

Method 11:



[0535] Iodination of aniline containing compounds: Iodination was accomplished using a procedure similar to that set forth in the following reference which is herein incorporated by reference in its entirety for all purposes as if fully set forth herein: *J. Med. Chem.* 2001, 44, 6, 917-922. The anthranilic ester in EtOH was added to a mixture of silver sulfate (1 equivalent) and I_2 (1 equivalent). The reaction was typically done after 3 hours at room temperature. The reaction was filtered through Celite and concentrated. The residue was taken up in EtOAc and washed with aqueous saturated $NaHCO_3$ (3x), water (3x), brine (1x), dried ($MgSO_4$), filtered, and concentrated. The crude product (~5 g) was dissolved in MeOH (60-100 mL), NaOH 6 N (25 mL), and water (250 mL). The reactions were typically done after heating at 70-80°C for 4 hours. The reaction mixture was extracted with EtOAc (2x), neutralized with aqueous HCl, filtered to collect the solids, and the solid products were washed with water. The products were dried *in vacuo*.

Method 12:



2-Amino-6-methoxy-benzonitrile

[0536] The title compound was prepared from 2,6-dinitrobenzonitrile following literature procedures set forth in the following references which are herein incorporated by reference in their entirety for all purposes as if fully set forth herein: Harris, V.N.: Smith, C; Bowden, K.; *J. Med. Chem.* **1990**, *33*, 434; and Sellstedt, J. H. *et al. J. Med. Chem.* **1975**, *18*, 926. LC/MS *m/z* 405.4 (MH+), R_t 1.71 minutes.

Method 13:

2-Amino-4-fluorobenzenecarbonitrile

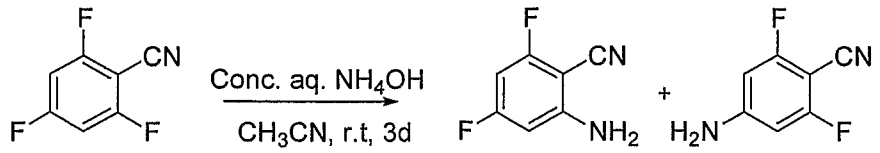
[0537] The title compound was obtained from commercially available 2-nitro-4-fluorobenzenecarbonitrile via reduction with $SnCl_2$ in concentrated HCl as previously described in the following reference which is herein incorporated by reference in its entirety for all purposes as if fully set forth herein: Hunziker, F. et Al. *Eur. J. Med. Chem., Chim. Ther.* **1981**, *16*(5), 391. GC/MS *m/z:* 136.1 (M+, 100%), R_t 9.26 minutes.

Method 14:

2-Amino-5-fluorobenzenecarbonitrile

[0538] The title compound was synthesized from commercially available 2-nitro-5-fluorobenzenecarbonitrile via reduction with $SnCl_2$ in concentrated HCl as previously described in the following reference which is herein incorporated by reference in its entirety for all purposes as if fully set forth herein: Hunziker, F. et al. *Eur. J. Med. Chem., Chim. Ther.* **1981**, *16*(5), 391. GC/MS *m/z:* 136.1 (M+, 100%), R_t 8.87 minutes.

Method 15:



[0539] The depicted compounds were synthesized following a procedure in WO 97/14686 which is herein incorporated by reference in its entirety for all purposes as if fully set forth herein. 2,4,6-Trifluorobenzonitrile was dissolved in a mixture of CH_3CN and concentrated aqueous NH_4OH (1:2) and stirred at room temperature for two days. The reaction mixture was concentrated and extracted with CH_2Cl_2. The organic extracts were collected,

dried (Na_2SO_4), and evaporated to afford an approximately 1:1 mixture of 2-amino-4,6-difluoro benzonitrile and 4-amino-2,6-difluorobenzonitrile. The desired 2-amino-4,6-difluoro benzonitrile was isolated by column chromatography on silicagel (EtOAc/Hexanes 1:2) as the compound with higher R_f; LC/MS *m/z* 155.1 (MH+), R_t 2.08 minutes; GC/MS *m/z* 154.1 (M+), R_t 9.35 minutes.

Method 16:

2-Amino-6-trifluoromethylbenzenecarbonitrile

[0540] 2-Fluoro-6-trifluoromethylbenzenecarbonitrile was heated at 100°C in a saturated solution of NH_3 in EtOH overnight. The reaction mixture was concentrated and the residue was purified by column chromatography on silicagel (EtOAc/Hexanes 1:5), to obtain the title compound as a white solid. GC/MS *m/z* 186.1 (M+), Rt 10.1 minutes.

Method 17:

5-Acetyl-2-aminobenzenecarbonitrile

[0541] The title compound was obtained from commercially available precursors as described in Goidl, J. O. and Claus, T. H., U.S. pat. No. 4,814,350 which is herein incorporated by reference in its entirety for all purposes as if fully set forth herein. GC/MS *m/z:* 160 (M+, 45%), R_t 15.04 minutes; LC/MS *m/z*: 161.2 (MH+), R_t 1.75 minutes.

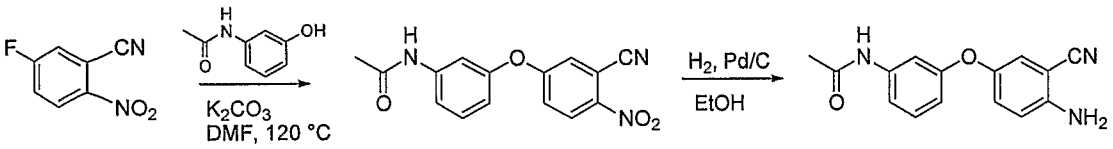
Method 18:

Dimethyl(1,4-oxazaperhydroepin-2-ylmethyl)amine

[0542] The title compound was obtained from 3-aminopropan-1-ol according to the synthetic route outlined above for (2S,5R)-2-[dimethylamino(methyl)]-5-methylmorpholine (see also: Harada H. *et al Chem. Pharm. Bull.*, **1995**, *43(8)*, 1364 and Freifelder. M. *et al*, *J. Am. Chem. Soc.*,

1958, *80,* 4320 which are both hereby incorporated by reference in their entirety for all purposes as if fully set forth herein). LC/MS *m/z* 159.1 (MH+), R_t 0.39 minutes.

Method 19:



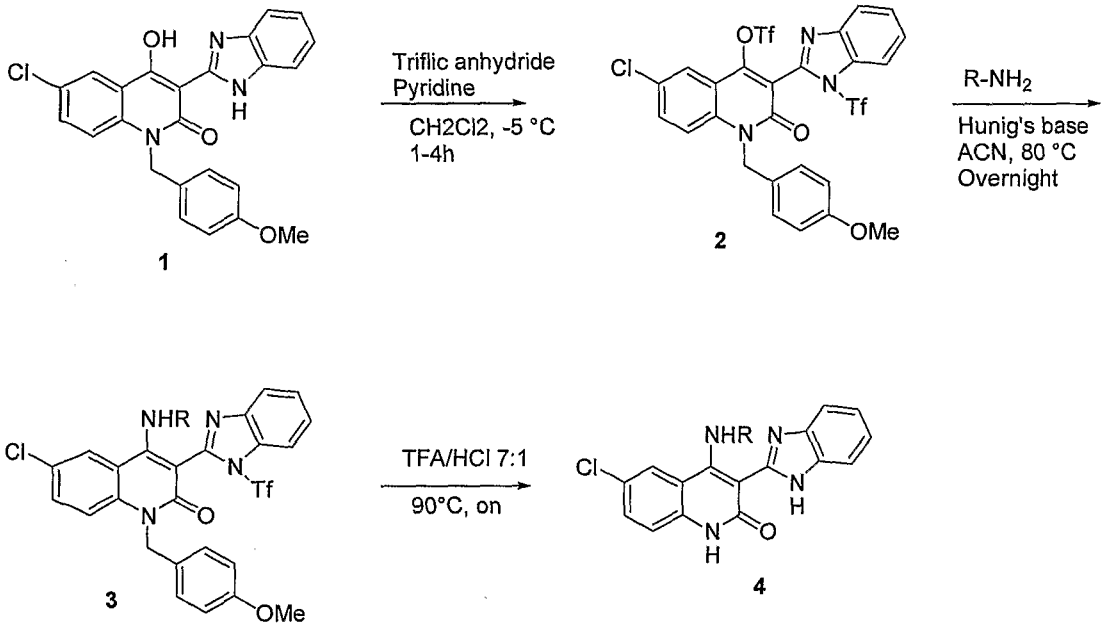
Step 1: 2-Nitro-5-(3-acetamido)phenoxybenzene carbonitrile

[0543] 5-Fluoro-2-nitrobenzenecarbonitrile and 3-acetamidophenol were dissolved in DMF, and solid K_2CO_3 (2 equivalents) was added in one portion. The reaction mixture was heated at 120°C overnight. The reaction mixture was cooled to room temperature, most of the DMF was distilled off and water was added to the residue. The solid thus obtained was filtered off and dried to afford the desired product. LC/MS *m/z:* 298.1 (MH+), R_t 2.55 minutes.

Step 2: 2-Amino-5-(3-acetamido)phenoxybenzene carbonitrile

[0544] 2-Nitro-5-(3-acetamido)phenoxybenzene carbonitrile was dissolved in EtOH, and 10% Pd/C was added. The reaction flask was evacuated and purged with H_2 three times. The reaction mixture was stirred under 1 atm of H_2 overnight, then filtered and concentrated. The residue was purified by chromatography on silicagel (2-5% MeOH/CH_2Cl_2) to afford the desired product. LC/MS *m/z:* 268.2 (MH+), R_t 2.28 minutes

Method 20:

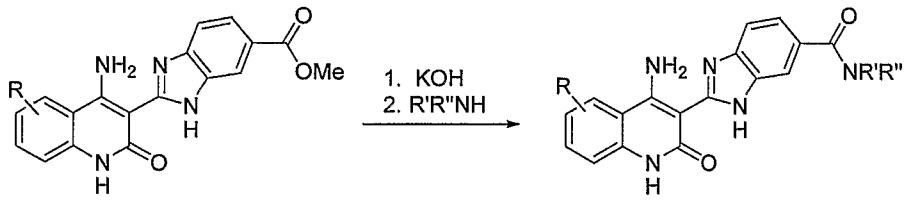


[0545] 3-(1H-Benzoimidazol-2-yl)-6-chloro-4-hydroxy-1-(4-methoxy-benzyl)-1H-quinolin-2-one (**1**) (1 equivalent) was suspended in methylene chloride or chloroform (0.01 M) in the presence of pyridine (20 equivalents). The mixture was warmed to ensure maximum solubilization. The mixture was then cooled to –5°C and triflic anhydride (8 equivalents) was added dropwise. The reaction mixture was stirred at –5°C until the reaction was complete (1 to 4 hours), and saturated aqueous $NaHCO_3$ was added. The aqueous phase was extracted with CH_2Cl_2, and the organic extracts were collected, washed with 1 M citric acid solution (x1), 1 M $NaHCO_3$ solution, water (x1), and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to afford

the title compound, 6-chloro-1-[(4-methoxyphenyl)methyl]-2-oxo-3-{1-[(trifluoromethyl)sulfonyl]-benzimidazol-2-yl}-4-hydroquinolyl (trifluoromethyl)sulfonate (**2**), as a solid.

[0546] A solution of 6-chloro-1-[(4-methoxyphenyl)methyl]-2-oxo-3-{1-[(trifluoromethyl)sulfonyl]-benzimidazol-2-yl}-4-hydroquinolyl (trifluoromethyl)sulfonate (**2**) (1 equivalent), an appropriate amine (1.2 equivalents), and Hunig's base (4 equivalents) in acetonitrile (0.15 M), was heated at 80°C for 20 hours. The reaction mixture was cooled to room temperature, diluted with EtOAc, washed with saturated aqueous $NaHCO_3$, water, and brine, and dried over Na_2SO_4. The organic solution was concentrated and the product thus obtained (**3**) was directly used in the next step. Compound **3** was dissolved in a mixture of trifluoroacetic acid and concentrated HCl (7:1) and heated at 90°C overnight. The reaction mixture was cooled to room temperature, and then water was added. The aqueous solution was washed with EtOAc and then made basic by addition of saturated $NaHCO_3$. The precipitate thus formed was collected by filtration, washed with water, and dried to afford the desired product, (**4**).

Method 21:



1 2

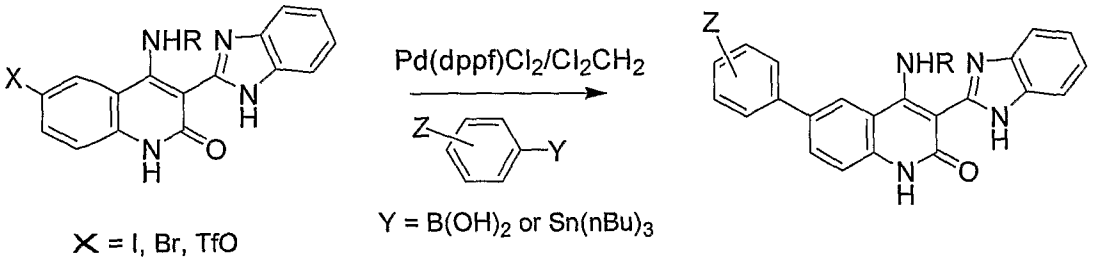
[0547] The crude methyl ester (**1**) was dissolved in a 1:1 mixture of EtOH and 30% aqueous KOH and stirred overnight at 70°C. The reaction mixture was then cooled and acidified with 1 N HCl to give a precipitate. The solid was filtered, washed with water and dried to obtain 2-(4-amino-2-oxo-1,2-dihydroquinolin-3-yl)-1*H*-benzimidazole-6-carboxylic acid as a brown solid. LC/MS *m/z:* 321.1 (MH+), R_t 2.26 minutes.

[0548] A mixture of 2-(4-amino-2-oxo-1,2-dihydroquinolin-3-yl)-1*H*-benzimidazole-6-carboxylic acid (1 equivalent) the amine (1 equivalent), EDC (1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, 1.2 equivalents), HOAT (1-hydroxy-7-azabenzotriazole, 1.2 equivalents) and triethylamine (2.5 equivalents) in DMF, was stirred at 23°C for 20 hours. The reaction mixture was partitioned between water and ethyl acetate. The combined organic layers were dried (Na_2SO_4) and concentrated. Water was added and the precipitate thus formed was filtered off and dried to afford the desired amide product (**2**).

Method 22:

[0549] A 7-Fluoroquinolinone derivative in a 8 M solution of $MeNH_2$ in EtOH:NMP (1:1), was submitted to microwave irradiation 4 times for 5 minutes at 220°C. After cooling, water was added, and the mixture was extracted with EtOAc. The organic extracts were collected and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure and purification of the residue by reverse phase preparative HPLC afforded the desired product. Other primary and secondary amines were used neat, 1:1 with NMP.

Method 23:



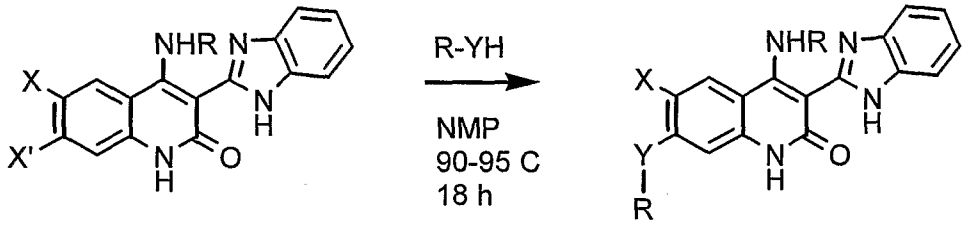
[0550] Conversion of the C-6 or C-7 halides to an aryl group was accomplished using standard Suzuki or Stille procedures such as described below.

[0551] Suzuki Method: To a 1 dram (4 mL) vial was added sequentially the quinolone (1 equivalent), boronic acid (1.2-1.5 equivalents), $Pd(dppf)Cl_2$, Cl_2CH_2 (0.2 equivalents), DMF (0.5 - 1 mL), and TEA (4 equivalents). The

reaction was flushed with argon, capped, and heated at 85°C for 12 hours. Once complete, the reaction was cooled to room temperature, and filtered with a syringe filter disk. The clear solution was then neutralized with TFA (a couple of drops) and injected directly onto a preparative HPLC. The products were lyophilized to dryness.

[0552] Stille Method: To a 1 dram (4 mL) vial was added sequentially the quinolone (1 equivalent), tin reagent (1.8 equivalent), $Pd(dppf)Cl_2 . Cl_2CH_2$ (0.2 equivalents), and DMF (0.5 - 1 mL). The reaction was flushed with argon, capped, and heated at 60-85°C for 4 hours. Once complete, the reaction was cooled to room temperature, and filtered with a syringe filter disk. The clear solution was then neutralized with TFA (a couple of drops) and injected directly onto a preparative HPLC. The products were lyophilized to dryness.

Method 24:



X, X' = F, Cl, I
Y = NH, O, S

[0553] A dihaloquinolone such as a difluoroquinolone (12-15 mg) was placed in a 1 dram (2 mL) vial. NMP (dry and pre-purged with argon for 5 minutes) was added to the vial (0.5 mL). A selected amine reagent (40-50 mg) was added next. If the amine was an HCl salt, the reaction was neutralized with TEA (~1.2-1.5 equivalents). The reaction was purged again with argon for about 5 seconds, and immediately capped. The reaction was typically heated in a heating block at 90-95°C for 18 hours. The reaction was followed by HPLC or LCMS. After taking samples for HPLC, the vial was purged with argon again and capped. Some coupling partners took 24 or 48 hours to reach completion. Less nucleophilic amines like pyrrole required the

addition of a strong base to reach completion. In these cases, cesium carbonate (2 equivalents based on the amine used) was added to the reaction. Once complete, the reaction was cooled to room temperature, and filtered with a syringe filter disk. The clear solution was then neutralized with TFA (a couple of drops) and injected directly onto a preparative HPLC. The products were lyophilized to dryness.

Example 1: Synthesis of 4-Amino-3-benzimidazol-2-yl-6-(4-methylpiperazinyl)hydroquinolin-2-one

Step 1: Ethyl 2-benzimidazol-2-ylacetate

[0554] A solution of 1,2-phenylenediamine (1.0 equivalent) and ethyl 3-ethoxy-3-iminopropanoate hydrochloride (1.3 equivalents) in ethanol was stirred at 90°C overnight. The reaction was cooled to room temperature and the solvent was removed *in vacuo*. Water and CH_2Cl_2 were added to the residue. The organic layer was separated, dried over Na_2SO_4 and the solvent removed. The solid recovered was used without purification. LC/MS *m/z* 205.2 (MH+), R_t 1.44 minutes.

Step 2: 5-(4-Methylpiperazinyl)-2-nitrobenzenecarbonitrile

[0555] 5-Fluoro-2-nitrobenzenecarbonitrile (1.02 equivalents) and N-methylpiperazine (1.0 equivalents) were dissolved in NMP. Triethylamine (2.1 equivalents) was added, and the resulting solution heated at 100°C for 1 hour. The solution was cooled to room temperature and poured into H_2O. A precipitate formed which was filtered to yield the desired product as a green solid. LC/MS *m/z* 247.3 (MH+), R_t 1.46 minutes.

Step 3: 2-Amino-5-(4-methylpiperazinyl)benzenecarbonitrile

[0556] 5-(4-Methylpiperazinyl)-2-nitrobenzenecarbonitrile (1.0 equivalent) was dissolved in EtOAc. The flask was purged with nitrogen, and 10% Pd/C (0.1 equivalents) was added. The flask was evacuated and purged with H_2 three times. The resulting mixture was stirred for three days at room temperature. The mixture was filtered through Celite and the filter pad was

washed with EtOAc. The solvent was removed *in vacuo* to give a yellow solid which was purified by silica gel chromatography (5:1:95 MeOH:Et_3N:EtOAc) to give the desired product as a yellow solid. LC/MS *m/z* 217.3 (MH+), R_t 0.95 minutes.

Step 4: 4-Amino-3-benzimidazol-2-yl-6-(4-methylpiperazinyl)hydroquinolin-2-one

[0557] Ethyl 2-benzimidazol-2-ylacetate (1.1 equivalents) and 2-amino-5-(4-methylpiperazinyl)benzenecarbonitrile (1.0 equivalent) were dissolved in 1,2-dichloroethane, and then $SnCl_4$ (11 equivalents) was added. The mixture was heated at reflux overnight. Upon cooling, the mixture was concentrated *in vacuo*. NaOH (3 M) was added to the solid, and the mixture heated at 80°C for 0.5 hours. The solid was filtered and washed sequentially with H_2O, CH_2Cl_2, and acetone. LC/MS indicated that the product was present in the acetone layer and the solid. These fractions were combined and purified by silica gel chromatography (5-10% MeOH in CH_2Cl_2 with 1% Et_3N) to give the desired product. LC/MS *m/z* 375.4 (MH+), R_t 1.65 minutes.

Example 2: Synthesis of 4-Amino-3-benzimidazol-2-yl-5-(2-morpholin-4-ylethoxy)hydroquinolin-2-one

Step 1: 6-Amino-2-(2-morpholin-4-ylethoxy)benzenecarbonitrile

[0558] 4-(Hydroxyethyl)morpholine (1.02 equivalents) was added to NaH (1.2 equivalents) in NMP. After 10 minutes, 6-amino-2-fluorobenzenecarbonitrile (1.0 equivalent) was added in NMP. The resulting mixture was heated at 100°C for 1 hour. The mixture was then cooled and poured into H_2O. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to a yield a brown gum. The crude material was purified by silica gel chromatography (5:1:95 MeOH:Et_3N:EtOAc) to give the desired product. LC/MS *m/z* 248.3 (MH+), R_t 1.26 minutes.

Step 2: 4-Amino-3-benzimidazol-2-yl-5-(2-morpholin-4-ylethoxy)hydroquinolin-2-one

[0559] The title compound was synthesized as described in Example 1 (Step 4), using 6-amino-2-(2-morpholin-4-ylethoxy)benzenecarbonitrile. LC/MS *m/z* 406.4 (MH+), R_t 1.67 minutes.

Example 3: Synthesis of 4-Amino-3-[5-(2-morpholin-4-ylethoxy)benzimidazol-2-yl]-6-nitrohydroquinolin-2-one

Step 1: 4-(2-Morpholin-4-ylethoxy)-2-nitrophenylamine

[0560] Diisopropyl azodicarboxylate (1.1 equivalents) was added dropwise to a stirred solution of 4-amino-3-nitrophenol (1.0 equivalent), triphenylphosphine (1.1 equivalents), and N-(2-hydroxyethyl)morpholine (1.0 equivalent), in THF at 0°C. The mixture was allowed to warm to room temperature and left to stir for 18 hours. The solvent was evaporated and the product was purified by silica gel chromatography (98:2 CH_2Cl_2:MeOH) to yield a dark reddish-brown oil. LC/MS *m/z* 268.0 (MH+), R_t 1.01 minutes.

Step 2: 4-(2-Morpholin-4-ylethoxy)benzene-1,2-diamine

[0561] To a solution 4-(2-morpholin-4-ylethoxy)-2-nitrophenylamine (1.0 equivalent) in EtOH was added Pd/C (0.1 equivalents). The reaction vessel was repeatedly purged with hydrogen, then stirred under a hydrogen atmosphere (1 atm) for 18 hours. The product was filtered through a Celite plug, and the plug washed with EtOH. The diamine was used without purification. LC/MS *m/z* 238.3 (MH+), R_t 0.295 minutes.

Step 3: Ethyl 2-[5-(2-morpholin-4-ylethoxy)benzimidazol-2-yl]acetate

[0562] The title compound was synthesized as described in Example 1 using 4-(2-morpholin-4-ylethoxy)benzene-1,2-diamine. The organic layer was concentrated and the residue was purified by silica gel chromatography (10:1:2 CH_2Cl_2:MeOH:EtOAc) to yield a dark reddish brown oil. LC/MS *m/z* 334.4 (MH+) R_t 1.08 minutes.

Step 4: 4-Amino-3-[5-(2-morpholin-4-ylethoxy)benzimidazol-2-yl]-6-nitrohydroquinolin-2-one

[0563] The title compound was synthesized as described in Example 1 (Step 4), using ethyl 2-[5-(2-morpholin-4-ylethoxy)benzimidazol-2-yl]acetate and 5-nitroanthranilonitrile. The crude product was purified by silica gel chromatography (5-10% MeOH in CH_2Cl_2 with 1% Et_3N) to give the desired product. LC/MS *m/z* 451.2 (MH+), R_t 1.89 minutes.

Example 4: Synthesis of 4-Amino-5-(2-morpholin-4-ylethoxy)-3-[5-(2-morpholin-4-ylethoxy)-benzimidazol-2-yl]hydroquinolin-2-one

[0564] The title compound was synthesized as described in Example 1 (Step 1), using ethyl 2-[5-(2-morpholin-4-ylethoxy)benzimidazol-2-yl]acetate and 6-amino-2-(2-morpholin-4-ylethoxy)benzenecarbonitrile. LC/MS *m/z* 535.4 (MH+), R_t 1.44 minutes.

Example 5: Synthesis of [2-(4-amino-2-oxo(3-hydroquinolyl))benzimidazol-5-yl]-N,N-dimethylcarboxamide

Step 1: 2-[(Ethoxycarbonyl)methyl]benzimidazole-5-carboxylic acid

[0565] The title compound was synthesized as described in Example 1 using 3,4-diaminobenzoic acid. The crude material was purified by silica gel chromatography (5:95 MeOH:CH_2Cl_2) to afford the desired product as a white to off-white solid. LC/MS *m/z* 249.1 (MH+), R_t 1.35 minutes.

Step 2: Ethyl 2-[5-(N,N-dimethylcarbamoyl)benzimidazol-2-yl]acetate

[0566] 2-[(Ethoxycarbonyl)methyl]benzimidazole-5-carboxylic acid (1.0 equivalent) was dissolved in THF. HBTU (1.1 equivalents) and diisopropylethylamine (2.0 equivalents) were added, followed by dimethylamine (2.0 M in THF, 1.1 equivalents). The reaction was stirred at room temperature overnight then concentrated and the resulting residue was purified by silica gel chromatography (5:95 MeOH:CH_2Cl_2) to afford the desired compound. LC/MS *m/z* 276.2 (MH+), R_t 1.18 minutes.

Step 3: [2-(4-amino-2-oxo(3-hydroquinolyl))benzimidazol-5-yl]-N,N-dimethylcarboxamide

[0567] The title compound was synthesized as described in Example 1 (Step 4), using ethyl 2-[5-(N,N-dimethylcarbamoyl)benzimidazol-2-yl]acetate and anthranilonitrile. The resulting solid was collected by filtration and washed with water followed by acetone to afford the desired product as a white solid. LC/MS *m/z* 348.3 (MH+), R_t 1.87 minutes.

Example 6: Synthesis of 4-Amino-3-[5-(morpholin-4-ylcarbonyl)benzimidazol-2-yl]hydroquinolin-2-one

[0568] 2-[(Ethoxycarbonyl)methyl]benzimidazole-5-carboxylic acid (1.0 equivalent) was dissolved in THF. HBTU (1.1 equivalents) and diisopropylethylamine (2.0 equivalents) were added, followed by morpholine (1.1 equivalents). The reaction was stirred at room temperature for 3 days then concentrated and purified by silica gel chromatography (5-10% methanol/dichloromethane). The product-containing fractions were concentrated and dissolved in anhydrous 1,2-dichloroethane. Anthranilonitrile (1.0 equivalent) was added followed by $SnCl_4$ (5.0 equivalents) and the reaction was heated at 90°C overnight. The reaction mixture was concentrated and the resulting residue was re-dissolved in NaOH (2 M) and heated at 90°C for 4 hours. After cooling to room temperature, the resulting solid was collected and washed with water followed by acetone to afford the desired product. LC/MS *m/z* 390.2 (MH+), R_t 1.95 minutes.

Example 7: Synthesis of 4-Amino-3-[5-(2-thienyl)benzimidazol-2-yl]hydroquinolin-2-one

Step 1: 4-Bromobenzene-1,2-diamine

[0569] A solution of 4-bromo-2-nitroaniline (1.0 equivalent) and $SnCl_2$ (2.2 equivalents) in EtOH was heated at reflux for 3 hours. After this time, the solution was poured onto ice, brought to pH 10 with 2 M NaOH and extracted with Et_2O. The combined organic layers were dried over $MgSO_4$ and concentrated. The resulting brown oil was purified by silica gel chromatography (0-50% EtOAc:hexanes) to provide a light yellow solid. LC/MS *m/z* 187.1 (MH+), R_t 1.33 minutes.

Step 2: 2-Nitro-4-(2-thienyl)phenylamine

[0570] 4-Bromobenzene-1,2-diamine (1.0 equivalent) and Na_2CO_3 (2.0 equivalents) were dissolved in DMF/H_2O (5:1) at room temperature. Nitrogen was bubbled through the reaction mixture for 5 minutes and $PdCl_2(dppf)_2$ (0.1 equivalents) was added. After stirring at 23°C for approximately 10 minutes, 2-thiopheneboronic acid (1.1 equivalents) in DMF was added and the reaction was heated at 90°C for 12 hours. After this time, the solution was concentrated and partitioned between EtOAc and H_2O. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The resulting black residue was purified by silica gel chromatography (0-20% EtOAc:hexanes) to yield an orange solid. LC/MS *m/z* 221.1 (MH+), R_t 2.67 minutes.

Step 3: Ethyl 2-[5-(2-thienyl)benzimidazol-2-yl]acetate

[0571] 2-Nitro-4-(2-thienyl)phenylamine (1.0 equivalent) and 10% Pd/C (0.1 equivalents) were suspended in anhydrous EtOH at room temperature. The reaction flask was evacuated and subsequently filled with H_2. The resulting mixture was allowed to stir under a hydrogen atmosphere for 3 hours. Ethyl 3-ethoxy-3-iminopropanoate hydrochloride (2.0 equivalents) was then added and the resulting mixture was heated at reflux for 12 hours. After

this time, the solution was filtered through a plug of Celite, concentrated, dissolved in 50 mL of 2 N HCl and washed with CH_2Cl_2. The aqueous layer was brought to pH 12 with concentrated NH_4OH(aq) and extracted with CH_2Cl_2. The combined organic layers were dried with $MgSO_4$ and concentrated to yield a brown oil which was purified by silica gel chromatography (5:95 MeOH:CH_2Cl_2) to provide a yellow solid. LC/MS *m/z* 287.1 (MH+), R_t 1.98 minutes.

Step 4: 4-Amino-3-[5-(2-thienyl)benzimidazol-2-yl]hydroquinolin-2-one

[0572] The title compound was synthesized as described in Example 1 (Step 4), using ethyl 2-[5-(2-thienyl)benzimidazol-2-yl]acetate and anthranilonitrile. LC/MS *m/z* 359.2 (MH+), R_t 2.68 minutes.

Example 8: Synthesis of 4-Amino-3-{5-[1-(1,2,4-triazolyl)]benzimidazol-2-yl}hydroquinolin-2-one

Step 1: 5-Fluoro-2-nitrophenylamine

[0573] The synthesis was performed according to Method 1. The crude product was purified by flash chromatography on silica gel (85:15 hexanes:EtOAc, product at R_f = 0.32, contaminant at R_f = 0.51). GC/MS *m/z* 156.1 (M+), R_t 11.16 minutes.

Step 2: 2-Nitro-5-[1-(1,2,4-triazolyl)]phenylamine

[0574] 5-Fluoro-2-nitrophenylamine (1.0 equivalent), 1*H*-1,2,4-triazole (3.0 equivalents) and NaH (3.0 equivalents) in NMP were heated at 100°C for 1 hour. The solution was cooled to room temperature and slowly poured onto ice water. The resulting precipitate was filtered and dried under vacuum to yield the desired product. The resulting solid was recrystallized from EtOH to afford pure product as a bright yellow solid. LC/MS *m/z* 206.2 (MH+), R_t 1.88 minutes.

Step 3: Ethyl 2-{5-[1-(1,2,4-triazolyl)]benzimidazol-2-yl}acetate

[0575] The title compound was synthesized as described in Example 7 using 2-nitro-5-[1-(1,2,4-triazolyl)]phenylamine. LC/MS *m/z* 272.1 (MH+), R_t 1.19 minutes.

Step 4: 4-Amino-3-{5-[1-(1,2,4-triazolyl)]benzimidazol-2-yl}hydroquinolin-2-one

[0576] The title compound was synthesized as described in Example 1 (Step 4), using ethyl 2-{5-[1-(1,2,4-triazolyl)]benzimidazol-2-yl}acetate and anthranilonitrile. The crude solid was collected and purified by silica gel chromatography (92:7:1 CH_2Cl_2:MeOH:Et_3N). LC/MS *m/z* 344.3 (MH+), R_t 2.01 minutes.

Example 9: Synthesis of 4-Amino-6-chloro-3-(5-morpholin-4-ylbenzimidazol-2-yl)hydroquinolin-2-one

***N*-(4-Chloro-2-cyanophenyl)-2-(5-morpholin-4-ylbenzimidazol-2-yl)acetamide**

[0577] LiHMDS (2.5 equivalents) was added to ethyl 2-[5-(2-morpholin-4-ylethoxy)benzimidazol-2-yl]acetate (1.0 equivalent) in THF at –78°C. After 1 hour, 2-amino-5-chlorobenzenecarbonitrile (0.82 equivalents) in THF was added. The reaction was allowed to warm to 23°C and stirred overnight. The resulting mixture was quenched with NH_4Cl (aqueous saturated solution) and extracted with EtOAc. The combined organic layers were washed with H_2O and brine, dried over Na_2SO_4, filtered and concentrated *in vacuo* to yield a brown solid. The crude material was purified by silica gel chromatography (5:1 EtOAc:hexane) to give the desired product. LC/MS *m/z* 396.1 (MH+), R_t 1.79 minutes. N-(4-chloro-2-cyanophenyl)-2-(5-morpholin-4-ylbenzimidazol-2-yl)acetamide (1.0 equivalent) was heated in NaOMe (0.5 M in MeOH, 18 equivalents) at 70°C for 2 hours. The resulting mixture was cooled, and the resulting solid was filtered and washed with water to give the desired product. LC/MS *m/z* 396.4 (MH+), R_t 2.13 minutes.

Example 10: Synthesis of 4-amino-3-(5-piperidylbenzimidazol-2-yl)hydroquinolin-2-one

Step 1: 2-Nitro-5-piperidylphenylamine

[0578] The title compound was synthesized as described in Method 1 using piperidine (3.0 equivalents). The desired product was obtained as a yellow, crystalline solid. LC/MS *m/z* 222.2 (MH+), R_t 2.53 minutes.

Step 2: Ethyl 2-(5-piperidylbenzimidazol-2-yl)acetate

[0579] The title compound was synthesized as described in Example 7 using 2-nitro-5-piperidylphenylamine. The desired product was obtained as a yellow oil. LC/MS *m/z* 288.3 (MH+), R_t 1.31 minutes.

Step 3: 4-amino-3-(5-piperidylbenzimidazol-2-yl)hydroquinolin-2-one

[0580] The title compound was synthesized as described in Example 9 using ethyl 2-(5-piperidylbenzimidazol-2-yl)acetate and anthranilonitrile. The acyclic amide was used crude in the NaOMe cyclization step. The desired product was obtained following purification by silica gel chromatography (96.5:3.0:0.5 CH_2Cl_2:MeOH:Et_3N, R_f 0.2). LC/MS *m/z* 360.4 (MH+), R_t 1.83 minutes.

Example 11: Synthesis of 4-Amino-3-{5-[3-(dimethylamino)pyrrolidinyl]benzimidazol-2-yl}-6-chlorohydroquinolin-2-one

Step 1: [1-(3-Amino-4-nitrophenyl)pyrrolidin-3-yl]dimethylamine

[0581] The title compound was synthesized as described in Method 1 using 3-(dimethylamino)pyrrolidine (3.0 equivalents). LC/MS *m/z* 251.3 (MH+), R_t 1.25 minutes.

Step 2: Ethyl 2-{5-[3-(dimethylamino)pyrrolidinyl]benzimidazol-2-yl}acetate

[0582] The title compound was synthesized as described in Example 7 using [1-(3-amino-4-nitrophenyl)pyrrolidin-3-yl]dimethylamine. The desired

product was obtained as a yellow oil. LC/MS *m/z* 317.4 (MH+), R_t 1.36 minutes.

Step 3: 4-Amino-3-{5-[3-(dimethylamino)pyrrolidinyl]benzimidazol-2-yl}-6-chlorohydroquinolin-2-one

[0583] The title compound was synthesized as described in Example 9 using 2-{5-[3-(dimethylamino)pyrrolidinyl]benzimidazol-2-yl}-*N*-(4-chloro-2-cyanophenyl)acetamide. LC/MS *m/z* 423.4 (MH+), R_t 1.71 minutes.

Example 12: Synthesis of 4-Amino-3-[5-(dimethylamino)benzimidazol-2-yl]hydroquinolin-2-one

Step 1: Ethyl 2-[5-(dimethylamino)benzimidazol-2-yl]acetate

[0584] The title compound was synthesized as described in Example 7 using (3-amino-4-nitrophenyl)dimethylamine. The resulting tan film was purified by silica gel chromatography (5:1:94 MeOH:Et_3N:CH_2Cl_2) to give the desired product. LC/MS 248.3 *m/z* (MH+), R_t 1.24 minutes.

Step 2: 4-Amino-3-[5-(dimethylamino)benzimidazol-2-yl]hydroquinolin-2-one

[0585] The title compound was synthesized as described in Example 9 using 2-[5-(dimethylamino)benzimidazol-2-yl]-*N*-(2-cyanophenyl)acetamide. LC/MS *m/z* 320.2 (MH+), R_t 1.72 minutes.

Example 13: Synthesis of 2-(4-Amino-2-oxo-3-hydroquinolyl)benzimidazole-5-carbonitrile

Step 1: Ethyl 2-(5-cyanobenzimidazol-2-yl)acetate

[0586] The title compound was synthesized as described in Example 7 using 4-amino-3-nitro-benzonitrile. LC/MS *m/z* 230.2 (MH+), R_t 1.29 minutes.

Step 2: 2-(4-Amino-2-oxo-3-hydroquinolyl)benzimidazole-5-carbonitrile

[0587] The title compound was synthesized as described in Example 9 using ethyl 2-(5-cyanobenzimidazol-2-yl)acetate and anthranilonitrile (no

acyclic amide was observed so the NaOMe step was not needed). LC/MS *m/z* 302.3 (MH+), R_t 2.62 minutes.

Example 14: Synthesis of 2-(4-Amino-2-oxo-3-hydroquinolyl)benzimidazole-5-carboxamidine

[0588] 2-(4-Amino-2-oxo-3-hydroquinolyl)benzimidazole-5-carbonitrile (Example 13) (1.0 equivalent) in EtOH was placed into a glass pressure vessel, cooled to 0°C and HCl (g) was bubbled through for 15 minutes. The pressure vessel was then sealed, brought to room temperature and stirred overnight. The solvent was removed *in vacuo*. The residue was dissolved in EtOH in a glass pressure vessel and cooled to 0°C. NH_3 (g) was bubbled through for 15 minutes and the pressure vessel was sealed and heated to 80°C for 5 hours. The solvent was removed *in vacuo* and the crude product was purified by reversed-phase HPLC. LC/MS *m/z* 319.2 (MH+), R_t 1.70 minutes.

Example 15: Synthesis of 4-Amino-3-[5-(2-morpholin-4-ylethoxy)-benzimidazol-2-yl]hydroquinolin-2-one

[0589] The title compound was synthesized as described in Example 9 (Step 1), using anthranilonitrile. The crude acyclic amide was used without purification in the NaOMe cyclization step. The crude final product was purified by reversed-phase HPLC (DMSO/5% TFA). LC/MS *m/z* 406.4 (MH+), R_t 1.56 minutes.

Example 16: Synthesis of 4-Hydroxy-3-(5-morpholin-4-ylbenzimidazol-2-yl)hydroquinolin-2-one

Step 1: 5-Morpholin-4-yl-2-nitrophenylamine

[0590] The title compound was synthesized as described in Method 9 using morpholine LC/MS *m/z* 224.1 (MH+), R_t 1.89 minutes.

Step 2: Ethyl 2-(5-morpholin-4-ylbenzimidazol-2-yl)acetate

[0591] 5-morpholin-4-yl-2-nitrophenylamine (1.0 equivalent), prepared as described in Method 9, and 10% Pd/C (0.1 equivalents) were suspended in anhydrous EtOH at room temperature. The reaction flask was evacuated and subsequently filled with H_2. The resulting mixture was stirred under a hydrogen atmosphere overnight. Ethyl 3-ethoxy-3-iminopropanoate hydrochloride (2.0 equivalents) was then added, and the resulting mixture was heated at reflux overnight. The resulting solution was filtered through Celite and evaporated under reduced pressure. The residue was suspended in CH_2Cl_2, and concentrated NH_4OH was added until a pH of 11 was achieved. The NH_4Cl thus formed was filtered off. The two phases were separated, and the organic phase was dried over Na_2SO_4. Evaporation of the solvent and trituration of the residue with ether afforded the title compound as a light green powder. LC/MS *m/z* 290.3 (MH+), R_t 1.31 minutes.

Step 3: 4-Hydroxy-3-(5-morpholin-4-ylbenzimidazol-2-yl)hydroquinolin-2-one

[0592] To a solution of ethyl 2-(5-morpholin-4-ylbenzimidazol-2-yl)acetate (1.0 equivalent) in anhydrous THF at –78°C under an atmosphere of nitrogen was added LiHMDS (1 M in THF, 3.1 equivalents) and the solution was stirred for 1 hour. A solution of 1-benzylbenzo[d]1,3-oxazaperhydroine-2,4-dione (1.05 equivalents) in anhydrous THF was then added dropwise and the resulting solution was allowed to warm to 0°C over 1 hour. The resulting mixture was quenched with a saturated aqueous solution of ammonium chloride and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (4 times). The combined organic layers were dried over Na_2SO_4, concentrated *in vacuo*, and the crude material was dissolved in toluene and heated at reflux for 16 hours. The toluene was removed *in vacuo* and the crude material was used without further purification. The product was obtained as a white solid. LC/MS *m/z* 453.1 (MH+), R_t 2.91 minutes. Crude 4-hydroxy-3-(5-morpholin-4-ylbenzimidazol-2-yl)-1-benzylhydroquinolin-2-one (1.0 equivalent) was dissolved in trifluoromethanesulfonic acid and heated at

40°C for 16 hours. The resulting solution was diluted with water and neutralized with 6 N NaOH (aq), whereupon a yellow precipitate formed. The crude solid was isolated by centrifugation and purified by reversed-phase HPLC to produce the desired product as a bright yellow solid. LC/MS *m/z* 363.3 (MH+), R_t 1.77 minutes.

Example 17: Synthesis of 3-[5-(3-aminopyrrolidinyl)benzimidazol-2-yl]-4-hydroxyhydroquinolin-2-one

Step 1: *N*-[1-(3-Amino-4-nitrophenyl)pyrrolidin-3-yl](*tert*-butoxy)carboxamide

[0593] The title compound was synthesized as described in Method 1 using 3-(*tert*-butoxycarbonylamino)pyrrolidine (1.01 equivalents) with diisopropylethylamine (2.0 equivalents). The product was obtained as an orange, crystalline solid. LC/MS *m/z* 323.3 (MH+), R_t 2.53 minutes.

Step 2: Ethyl 2-(5-{3-[(*tert*-butoxy)carbonylamino]pyrrolidinyl}benzimidazol-2-yl)acetate

[0594] The title compound was synthesized as described in Example 7 using *N*-[1-(3-amino-4-nitrophenyl)pyrrolidin-3-yl](*tert*-butoxy)carboxamide. The product was obtained as a yellow oil. LC/MS *m/z* 323.3 (MH+), R_t 2.53 minutes.

Step 3: 3-[5-(3-aminopyrrolidinyl)benzimidazol-2-yl]-4-hydroxyhydroquinolin-2-one

[0595] The title compound was synthesized following the procedure described in Example 16, using ethyl 2-(5-{3-[(*tert*-butoxy)carbonylamino]-pyrrolidinyl}benzimidazol-2-yl)acetate. The product was obtained as a yellow solid following cleavage of the benzyl group (see procedure in Example 15). LC/MS *m/e* 362.3 (MH+), R_t 1.55 minutes.

Example 18: Synthesis of 3-(5-{[2-(Dimethylamino)ethyl]methylamino}benzimidazol-2-yl)-4-hydroxyhydroquinolin-2-one

Step 1: (3-Amino-4-nitrophenyl)[2-(dimethylamino)ethyl]methylamine

[0596] The title compound was synthesized as described in Example 8 using 1,1,4-trimethylethylenediamine (1.01 equivalents) with diisopropylethylamine (2.0 equivalents). The product was obtained as a bright yellow, crystalline solid. LC/MS *m/z* 239.3 (MH+), R_t 1.29 minutes.

Step 2: Ethyl 2-(5-{[2-(dimethylamino)ethyl]methylamino}benzimidazol-2-yl)acetate

[0597] The title compound was synthesized as described in Example 7 using (3-amino-4-nitrophenyl)[2-(dimethylamino)ethyl]methylamine. The desired product was obtained as a yellow oil. LC/MS *m/z* 305.2 (MH+), R_t 1.17 minutes.

Step 3: 3-(5-{[2-(Dimethylamino)ethyl]methylamino}benzimidazol-2-yl)-4-hydroxy-1-benzylhydroquinolin-2-one

[0598] The title compound was synthesized as described in Example 16, using ethyl 2-(5-{[2-(dimethylamino)ethyl]methylamino}benzimidazol-2-yl)acetate. The product was obtained as a pale yellow solid. LC/MS *m/z* 468.4 (MH+), R_t 2.26 minutes.

Step 4: 3-(5-{[2-(Dimethylamino)ethyl]methylamino}benzimidazol-2-yl)-4-hydroxyhydroquinolin-2-one

[0599] The title compound was synthesized as described in Example 16, using 3-(5-{[2-(dimethylamino)ethyl]methylamino}benzimidazol-2-yl)-4-hydroxy-1-benzylhydroquinolin-2-one. The crude material was purified by reversed-phase HPLC to yield the product as a yellow solid. LC/MS *m/z* 378.4 (MH+), R_t 1.99 minutes.

Example 19: Synthesis of 4-[(2-methoxyethyl)amino]-3-(5-morpholin-4-ylbenzimidazol-2-yl)hydroquinolin-2-one

Step 1: 4-Chloro-3-(5-morpholin-4-ylbenzimidazol-2-yl)-1-benzylhydroquinolin-2-one

[0600] A solution of 4-hydroxy-3-(5-morpholin-4-ylbenzimidazol-2-yl)-1-benzylhydroquinolin-2-one (1.0 equivalent) and $POCl_3$ in a dry, round-bottomed flask was heated at 80°C for 2 hours. The excess $POCl_3$ was removed *in vacuo*, and the crude material was quenched with water. The crude product was collected by filtration and purified by silica gel chromatography (1:9 MeOH:CH_2Cl_2). 4-Chloro-3-(5-morpholin-4-ylbenzimidazol-2-yl)-1-benzylhydroquinolin-2-one was isolated as a red solid. LC/MS *m/z* 471.4 (MH+), R_t 2.35 minutes.

Step 2: 4-[(2-Methoxyethyl)amino]-3-(5-morpholin-4-ylbenzimidazol-2-yl)-1-benzylhydroquinolin-2-one

[0601] A solution of 4-chloro-3-(5-morpholin-4-ylbenzimidazol-2-yl)-1-benzylhydroquinolin-2-one (1.0 equivalent) and EtOH was treated with 2-methoxyethyl-amine (10 equivalents) at room temperature. The resulting solution was heated at reflux for 16 hours and then the solvent was removed *in vacuo*. The crude solid was sonicated in water, filtered, sonicated in hexanes, and filtered again. The crude product was used without further purification. LC/MS *m/z* 510.4 (MH+), R_t 2.20 minutes.

Step 3: 4-[(2-Methoxyethyl)amino]-3-(5-morpholin-4-ylbenzimidazol-2-yl)hydroquinolin-2-one

[0602] 4-[(2-methoxyethyl)amino]-3-(5-morpholin-4-ylbenzimidazol-2-yl)-1-benzylhydroquinolin-2-one was debenzylated using the procedure described in Example 16 to produce the title compound. LC/MS *m/z* 420.2 (MH+), R_t 1.57 minutes. 4-[(2-hydroxyethyl)amino]-3-(5-morpholin-4-ylbenzimidazol-2-yl)hydroquinolin-2-one was produced as a side product (see below).

Example 20: Synthesis of 4-[(2-hydroxyethyl)amino]-3-(5-morpholin-4-ylbenzimidazol-2-yl)hydroquinolin-2-one

[0603] The title compound was obtained as a side-product of the debenzylation of 4-[(2-methoxyethyl)amino]-3-(5-morpholin-4-ylbenzimidazol-2-yl)-1-benzylhydroquinolin-2-one using the procedure described in Example 16 and was isolated by reversed-phase HPLC as a yellow solid. LC/MS *m/z* 406.2 (MH+), R_t 1.39 minutes.

Example 21: Synthesis of 4-(Methoxyamino)-3-(5-morpholin-4-ylbenzimidazol-2-yl)hydroquinolin-2-one

Step 1: 4-(Methoxyamino)-3-(5-morpholin-4-ylbenzimidazol-2-yl)-1-benzylhydroquinolin-2-one

[0604] The title compound was synthesized as described in Example 19, using *O*-methylhydroxylamine. The product was used without purification.

Step 2: 4-(Methoxyamino)-3-(5-morpholin-4-ylbenzimidazol-2-yl)hydroquinolin-2-one

[0605] The title compound was obtained as a yellow solid after debenzylation of 4-(methoxyamino)-3-(5-morpholin-4-ylbenzimidazol-2-yl)-1-benzylhydroquinolin-2-one using the procedure described in Example 16. LC/MS *m/z* 392.2 (MH+), R_t 1.82 minutes.

Example 22: Synthesis of 3-(5-Morpholin-4-ylbenzimidazol-2-yl)-4-(3-piperidylamino)hydroquinolin-2-one

Step 1: *tert*-Butyl-3-{[3-(5-morpholin-4-ylbenzimidazol-2-yl)-2-oxo-1-benzyl-4-hydroquinolyl]amino}piperidinecarboxylate

[0606] The title compound was synthesized as described in Example 19 using 1-*tert*-butoxycarbonyl-3-aminopiperidine. The product was used without purification.

Step 2: 3-(5-Morpholin-4-ylbenzimidazol-2-yl)-4-(3-piperidylamino)hydroquinolin-2-one

[0607] The product was obtained as a yellow solid after debenzylation of *tert*-butyl-3-{[3-(5-morpholin-4-ylbenzimidazol-2-yl)-2-oxo-1-benzyl-4-hydroquinolyl]amino}piperidinecarboxylate using the procedure described in Example 16. The *t*-butoxycarbonyl group is removed under the reaction conditions. LC/MS *m/z* 445.4 (MH+), R_t 1.73 minutes.

Example 23: Synthesis of 3-(5-Morpholin-4-ylbenzimidazol-2-yl)-4-[(3-piperidylmethyl)amino]-hydroquinolin-2-one

Step 1: *tert*-Butyl-3-({[3-(5-morpholin-4-ylbenzimidazol-2-yl)-2-oxo-1-benzyl-4-hydroquinolyl]amino}methyl)piperidinecarboxylate

[0608] The title compound was synthesized as described in Example 19, using 1-*tert*-butoxycarbonyl-3-aminomethylpiperidine. The product was used without purification.

Step 2: 3-(5-Morpholin-4-ylbenzimidazol-2-yl)-4-[(3-piperidylmethyl)amino]-hydroquinolin-2-one

[0609] The title compound was obtained as a yellow solid after debenzylation of *tert*-butyl-3-({[3-(5-morpholin-4-ylbenzimidazol-2-yl)-2-oxo-1-benzyl-4-hydroquinolyl]amino}methyl)piperidinecarboxylate using the

procedure described in Example 16. LC/MS *m/z* 459.6 (MH+), R_t 1.71 minutes.

Example 24: Synthesis of 4-{[2-(Dimethylamino)ethyl]amino}-3-(5-morpholin-4-ylbenzimidazol-2-yl)hydroquinolin-2-one

Step 1: 4-{[2-(Dimethylamino)ethyl]amino}-3-(5-morpholin-4-ylbenzimidazol-2-yl)-1-benzylhydroquinolin-2-one

[0610] The title compound was synthesized as described in Example 19 using 1,1-dimethylethylenediamine. The product was used without purification.

Step 2: 4-{[2-(Dimethylamino)ethyl]amino}-3-(5-morpholin-4-ylbenzimidazol-2-yl)hydroquinolin-2-one

[0611] The title compound was obtained as a yellow solid after debenzylation of 4-{[2-(dimethylamino)ethyl]amino}-3-(5-morpholin-4-ylbenzimidazol-2-yl)-1-benzylhydroquinolin-2-one using the procedure described in Example 16. LC/MS *m/z* 433.4 (MH+), R_t 1.55 minutes.

Example 25: Synthesis of 3-(5-Morpholin-4-ylbenzimidazol-2-yl)-4-[(oxolan-2-ylmethyl)amino]-hydroquinolin-2-one

Step 1: 3-(5-Morpholin-4-ylbenzimidazol-2-yl)-4-[(oxolan-2-ylmethyl)amino]-1-benzylhydroquinolin-2-one

[0612] The title compound was synthesized as described in Example 19 using 2-aminomethyltetrahydrofuran. The product was used without purification.

Step 2: 3-(5-Morpholin-4-ylbenzimidazol-2-yl)-4-[(oxolan-2-ylmethyl)amino]-hydroquinolin-2-one

[0613] The title compound was obtained as a yellow solid after debenzylation of 3-(5-morpholin-4-ylbenzimidazol-2-yl)-4-[(oxolan-2-

ylmethyl)amino]-1-benzylhydroquinolin-2-one using the procedure described in Example 16. LC/MS *m/z* 446.5 (MH+), R_t 2.19 minutes.

Example 26: Synthesis of 4-{[2-(Methylamino)ethyl]amino}-3-(5-morpholin-4-ylbenzimidazol-2-yl)hydroquinolin-2-one

Step 1: 4-{[2-(Methylamino)ethyl]amino}-3-(5-morpholin-4-ylbenzimidazol-2-yl)-1-benzylhydroquinolin-2-one

[0614] The title compound was synthesized as described in Example 19 using 1-*tert*-butoxycarbonyl-1-methylethylenediamine. The product was used without purification.

Step 2: 4-{[2-(Methylamino)ethyl]amino}-3-(5-morpholin-4-ylbenzimidazol-2-yl)hydroquinolin-2-one

[0615] The title compound was obtained as a yellow solid after debenzylation of 4-{[2-(methylamino)ethyl]amino}-3-(5-morpholin-4-ylbenzimidazol-2-yl)-1-benzylhydroquinolin-2-one using the procedure described in Example 16. The *t*-butoxycarbonyl group is removed under the reaction conditions. LC/MS *m/z* 419.4 (MH+), R_t 1.50 minutes.

Example 27: Synthesis of 3-(5-Morpholin-4-ylbenzimidazol-2-yl)-4-(pyrrolidin-3-ylamino)hydroquinolin-2-one

Step 1: *tert*-Butyl-3-{[3-(5-morpholin-4-ylbenzimidazol-2-yl)-2-oxo-1-benzyl-4-hydroquinolyl]amino}pyrrolidinecarboxylate

[0616] The title compound was synthesized as described in Example 19 using 1-*tert*-butoxycarbonyl-3-aminopyrrolidine. The product was used without purification.

Step 2: 3-(5-Morpholin-4-ylbenzimidazol-2-yl)-4-(pyrrolidin-3-ylamino)hydroquinolin-2-one

[0617] The title compound was obtained as a yellow solid after debenzylation of *tert*-butyl-3-{[3-(5-morpholin-4-ylbenzimidazol-2-yl)-2-oxo-1-benzyl-4-hydroquinolyl]amino}pyrrolidinecarboxylate using the procedure described in Example 16. LC/MS *m/z* 431.4 (MH+), R_t 1.50 minutes.

Example 28: Synthesis of 4-[((2S)-2-Amino-4-methylpentyl)amino]-3-(5-morpholin-4-ylbenzimidazol-2-yl)hydroquinolin-2-one

Step 1: 4-[((2*S*)-2-Amino-4-methylpentyl)amino]-3-(5-morpholin-4-ylbenzimidazol-2-yl)-1-benzylhydroquinolin-2-one

[0618] The title compound was synthesized as described in Example 19 using (2*S*)-2-*tert*-butoxycarbonylamino-4-methylpentylamine. The product was used without purification.

Step 2: 4-[((2S)-2-Amino-4-methylpentyl)amino]-3-(5-morpholin-4-ylbenzimidazol-2-yl)hydroquinolin-2-one

[0619] The title compound was obtained as a yellow solid after debenzylation of 4-[((2*S*)-2-amino-4-methylpentyl)amino]-3-(5-morpholin-4-ylbenzimidazol-2-yl)-1-benzylhydroquinolin-2-one using the procedure described in Example 16. LC/MS *m/z* 461.4 (MH+), R_t 1.78 minutes.

Example 29: Synthesis of 4-[((2S)-2-Amino-3-methylbutyl)amino]-3-(5-morpholin-4-ylbenzimidazol-2-yl)hydroquinolin-2-one

Step 1: *t*-Butoxycarbonyl protected 4-[((2*S*)-2-amino-3-methylbutyl)amino]-3-(5-morpholin-4-ylbenzimidazol-2-yl)-1-benzylhydroquinolin-2-one

[0620] The title compound was synthesized as described in Example 19, using (2*S*)-2-*tert*-butoxycarbonylamino-3-methylbutylamine. The product was used without purification.

Step 2: 4-[((2S)-2-Amino-3-methylbutyl)amino]-3-(5-morpholin-4-ylbenzimidazol-2-yl)hydroquinolin-2-one

[0621] The title compound was obtained as a yellow solid after debenzylation of 4-[((2*S*)-2-amino-3-methylbutyl)amino]-3-(5-morpholin-4-ylbenzimidazol-2-yl)-1-benzylhydroquinolin-2-one using the procedure described in Example 16. The *t*-butoxycarbonyl group is removed under the reaction conditions. LC/MS *m/z* 447.5 (MH+), R_t 2.96 minutes.

Example 30: Synthesis of 4-Amino-3-(5-morpholin-4-ylbenzimidazol-2-yl)hydroquinolin-2-one

Step 1: 4-Amino-3-(5-morpholin-4-ylbenzimidazol-2-yl)-1-benzylhydroquinolin-2-one

[0622] The title compound was synthesized as described in Example 19, using ammonia in a sealed glass tube. The product was used without purification.

Step 2: 4-Amino-3-(5-morpholin-4-ylbenzimidazol-2-yl)hydroquinolin-2-one

[0623] The title compound was obtained as a bright yellow solid after debenzylation of 4-amino-3-(5-morpholin-4-ylbenzimidazol-2-yl)-1-benzylhydroquinolin-2-one using the procedure described in Example 16 and

purification by reversed-phase HPLC. LC/MS *m/z* 362.3 (MH+), R_t 1.61 minutes.

Example 31: Synthesis of 3-(Benzimidazol-2-yl)-4-chloro-1-benzylhydroquinolin-2-one

Step 1: 3-Benzimidazol-2-yl-4-hydroxy-1-benzylhydroquinolin-2-one

[0624] The title compound was synthesized as described in Example 16, using ethyl 2-benzimidazol-2-ylacetate. The product was obtained as a white solid and used without further purification. LC/MS *m/z* 368.4 (MH+), R_t 2.99 minutes.

Step 2: 3-(Benzimidazol-2-yl)-4-chloro-1-benzylhydroquinolin-2-one

[0625] The title compound was synthesized as described in Example 19, using 3-benzimidazol-2-yl-4-hydroxy-1-benzylhydroquinolin-2-one. The crude product was used without purification.

Example 32: Synthesis of 3-Benzimidazol-2-yl-4-(methylamino)hydroquinolin-2-one

[0626] The benzylated title compound was synthesized as described in Example 19, using methylamine and 3-(benzimidazol-2-yl)-4-chloro-1-benzylhydroquinolin-2-one. The product was obtained after debenzylation as a yellow solid using the procedure described in Example 16. LC/MS *m/z* 291.3 (MH+), R_t 1.64 minutes.

Example 33: Synthesis of 3-Benzimidazol-2-yl-4-(ethylamino)hydroquinolin-2-one

[0627] The benzylated title compound was synthesized as described in Example 19, using ethylamine and 3-(benzimidazol-2-yl)-4-chloro-1-benzylhydroquinolin-2-one. The title compound was obtained after debenzylation as a yellow solid using the procedure described in Example 16. LC/MS *m/z* 305.3 (MH+), R_t 2.01 minutes.

Example 34; Synthesis of 3-Benzimidazol-2-yl-4-[(oxolan-2-ylmethyl)amino]hydroquinolin-2-one

[0628] The benzylated title compound was synthesized as described in Example 19, using 2-aminomethyltetrahydrofuran and 3-(benzimidazol-2-yl)-4-chloro-1-benzylhydroquinolin-2-one. The title compound was obtained after debenzylation as a yellow solid using the procedure described in Example 16. LC/MS *m/z* 361.2 (MH+), R_t 1.74 minutes.

Example 35: Synthesis of 3-Benzimidazol-2-yl-4-[(4-piperidylmethyl)amino]hydroquinolin-2-one

[0629] The protected title compound was synthesized as described in Example 19, using 1-*tert*-butoxycarbonyl-4-aminomethylpiperidine and 3-(benzimidazol-2-yl)-4-chloro-1-benzylhydroquinolin-2-one. The title compound was obtained after deprotection and debenzylation as a yellow solid using the procedure described in Example 16. LC/MS *m/z* 374.3 (MH+), R_t 1.29 minutes.

Example 36: Synthesis of 3-Benzimidazol-2-yl-4-[(4-fluorophenyl)amino]hydroquinolin-2-one

[0630] The benzylated title compound was synthesized as described in Example 19, using 4-fluoroaniline and 3-(benzimidazol-2-yl)-4-chloro-1-benzylhydroquinolin-2-one. The title compound was obtained after debenzylation as a yellow solid using the procedure described in Example 16. LC/MS *m/z* 371.2 (MH+), R_t 1.92 minutes.

Example 37: Synthesis of 3-Benzimidazol-2-yl-4-(methoxyamino)hydroquinolin-2-one

3-Benzimidazol-2-yl-4-(methoxyamino)hydroquinolin-2-one

[0631] The benzylated title compound was synthesized as described in Example 19, using *O*-methylhydroxylamine and 3-(benzimidazol-2-yl)-4-chloro-1-benzylhydroquinolin-2-one. The title compound was obtained after

debenzylation as a yellow solid using the procedure described in Example 16. LC/MS *m/z* 307.3 (MH+), R_t 1.77 minutes.

Example 38: Synthesis of 3-Benzimidazol-2-yl-4-(benzimidazol-6-ylamino)hydroquinolin-2-one

3-Benzimidazol-2-yl-4-(benzimidazol-6-ylamino)hydroquinolin-2-one

[0632] The benzylated title compound was synthesized as described in Example 19, using 5-aminobenzimidazole and 3-(benzimidazol-2-yl)-4-chloro-1-benzylhydroquinolin-2-one. The title compound was obtained after debenzylation as a yellow solid using the procedure described in Example 16. LC/MS *m/z* 393.4 (MH+), R_t 1.41 minutes.

Example 39: Synthesis of 3-Benzimidazol-2-yl-4-(phenylamino)hydroquinolin-2-one

3-Benzimidazol-2-yl-4-(phenylamino)hydroquinolin-2-one

[0633] The benzylated title compound was synthesized as described in Example 19, using aniline and 3-(benzimidazol-2-yl)-4-chloro-1-benzylhydroquinolin-2-one. The title compound was obtained after debenzylation as a yellow solid using the procedure described in Example 16. LC/MS *m/z* 353.4 (MH+), R_t 2.38 minutes.

Example 40: Synthesis of 3-Benzimidazol-2-yl-4-(quinuclidin-3-ylamino)hydroquinolin-2-one

[0634] The benzylated title compound was synthesized as described in Example 19, using 3-aminoquinuclidine and 3-(benzimidazol-2-yl)-4-chloro-1-benzylhydroquinolin-2-one. The title compound was obtained after debenzylation as a yellow solid using the procedure described in Example 16. LC/MS *m/z* 386.4 (MH+), R_t 1.82 minutes.

Example 41: Synthesis of 3-Benzimidazol-2-yl-4-[(imidazol-5-ylmethyl)amino]hydroquinolin-2-one

3-Benzimidazol-2-yl-4-[(imidazol-5-ylmethyl)amino]hydroquinolin-2-one

[0635] The benzylated title compound was synthesized as described in Example 19, using 4-aminomethyl-1*H*-imidazole and 3-(benzimidazol-2-yl)-4-chloro-1-benzylhydroquinolin-2-one. The title compound was obtained after debenzylation as a yellow solid using the procedure described in Example 16. LC/MS *m/z* 357.4 (MH+), R_t 1.34 minutes.

Example 42: Synthesis of 3-Benzimidazol-2-yl-4-(morpholin-4-ylamino)hydroquinolin-2-one

[0636] The benzylated title compound was synthesized as described in Example 19, using 4-aminomorpholine and 3-(benzimidazol-2-yl)-4-chloro-1-benzylhydroquinolin-2-one. The title compound was obtained after debenzylation as a yellow solid using the procedure described in Example 16. LC/MS *m/z* 362.4 (MH+), R_t 1.42 minutes.

Example 43: Synthesis of 3-Benzimidazol-2-yl-4-hydrazinohydroquinolin-2-one

[0637] The benzylated title compound was synthesized as described in Example 19, using hydrazine and 3-(benzimidazol-2-yl)-4-chloro-1-benzylhydroquinolin-2-one. The title compound was obtained as a yellow solid after debenzylation using the procedure described in Example 16. LC/MS *m/z* 292.3 (MH+), R_t 1.19 minutes.

Example 44: Synthesis of 3-Benzimidazol-2-yl-2-oxohydroquinoline-4-carbonitrile

[0638] 3-Benzimidazol-2-yl-4-chloro-1-benzylhydroquinolin-2-one (1 equivalent) was dissolved in DMA, and CuCN (10 equivalents) was added in one portion. The reaction mixture was stirred at 90°C overnight. The resulting mixture was allowed to cool to room temperature, water was added,

and the orange precipitate was removed by filtration. The solid was treated with a solution of hydrated $FeCl_3$ at 70°C for 1 hour. The suspension was centrifuged and the solution removed. The remaining solid was washed with 6 N HCl (2 times), saturated Na_2CO_3 (2 times), water (2 times) and lyophilized. The resulting powder was dissolved in 1 mL of triflic acid and heated at 60°C overnight. The resulting mixture was cooled to 0°C and water was slowly added. Saturated LiOH was added dropwise to the suspension to a pH of 8, then the solid was filtered and washed with water (3 times). Purification by reversed-phase HPLC afforded the desired product. LC/MS *m/z* 287.1 (MH+), R_t 1.89 minutes.

Example 45: Synthesis of 3-(5,6-Dimethylbenzimidazol-2-yl)-4-(3-piperidylamino)hydroquinolin-2-one

Step 1: Ethyl 2-(5,6-dimethylbenzimidazol-2-yl)acetate

[0639] The title compound was synthesized as described in Example 1 using 4,5-dimethylbenzene-1,2-diamine. The crude yellow oil was purified first by silica gel chromatography (96.5:3.0:0.5, CH_2Cl_2:MeOH:Et_3N), and then by recrystallization from toluene to yield the title compound as a pale, yellow solid. LC/MS *m/z* 233.1 (MH+), R_t 1.73 minutes.

Step 2: 3-(5,6-Dimethylbenzimidazol-2-yl)-4-hydroxy-1-benzylhydroquinolin-2-one

[0640] The title compound was synthesized as described in Example 16, using ethyl 2-(5,6-dimethylbenzimidazol-2-yl)acetate. The crude material was purified by silica gel chromatography (98.5:1.5, CH_2Cl_2:MeOH) to yield the title compound as a yellow solid. LC/MS *m/z* 396.2 (MH+), R_t 3.60 minutes.

Step 3: 3-(5,6-Dimethylbenzimidazol-2-yl)-4-chloro-1-benzylhydroquinolin-2-one

[0641] The title compound was synthesized as described in Example 19, using 3-(5,6-dimethylbenzimidazol-2-yl)-4-hydroxy-1-benzylhydroquinolin-

2-one. The title compound was obtained as an orange-yellow solid. LC/MS *m/z* 414.2 (MH+), R_t 2.47 minutes.

Step 4: *tert*-Butyl 3-{[3-(5,6-dimethylbenzimidazol-2-yl)-2-oxo-1-benzyl-4-hydroquinolyl]amino}piperidinecarboxylate

[0642] The title compound was synthesized as described in Example 19, using 1-*tert*-butoxycarbonyl-3-aminopiperidine. The crude material was purified by silica gel chromatography (99:1 CH_2Cl_2:MeOH) to yield the title compound as a yellow solid. LC/MS *m/z* 578.5 (MH+), R_t 3.05 minutes.

Step 5: 3-(5,6-Dimethylbenzimidazol-2-yl)-4-(3-piperidylamino)hydroquinolin-2-one

[0643] *tert*-Butyl 3-{[3-(5,6-dimethylbenzimidazol-2-yl)-2-oxo-1-benzyl-4-hydroquinolyl]amino}piperidine-carboxylate was debenzylated as described in Example 16. The crude material was purified by reversed-phase HPLC to yield the title compound as a light yellow solid. LC/MS *m/z* 388.4 (MH+), R_t 1.61 minutes.

Example 46: Synthesis of 4-Amino-3-(3H-imidazo[4,5-b]pyridin-2-yl)quinolin-2(1H)-one

Step 1: 3*H*-Imidazo[4,5-*b*]pyridin-2-ylacetonitrile

[0644] Ethyl cyanoacetate (1.5 equivalents) and 2,3-diaminopyridine (1 equivalent) were heated at 185°C for 30 minutes. The reaction mixture was cooled to room temperature and the black solid was triturated with ether. The desired product was thus obtained as a dark brown powder. LC/MS *m/z* 159.1 (MH+), R_t 0.44 minutes.

Step 2: Ethyl 3*H*-imidazo[4,5-*b*]pyridin-2-ylacetate

[0645] 3*H*-Imidazo[4,5-*b*]pyridin-2-ylacetonitrile was suspended in EtOH, and gaseous HCl was bubbled through for 3 hours. The suspension initially seemed to dissolve, but a precipitate started forming almost immediately. The reaction mixture was cooled to 0°C and a cold saturated $NaHCO_3$ solution was carefully added. Solid $NaHCO_3$ was also added to bring the pH to a value of 7.6. The aqueous phase was then extracted with EtOAc, and the organic extracts were dried (Na_2SO_4). After evaporation of the solvent under reduced pressure, the residue was purified by chromatography on silicagel (10% MeOH in CH_2Cl_2 with 1% Et_3N) providing the desired product as a light brown solid. LC/MS *m/z* 206.1 (MH+), R_t 0.97 minutes.

Step 3: 4-Amino-3-(3H-imidazo[4,5-b]pyridin-2-yl)quinolin-2(1H)-one

[0646] LiHMDS (3.0 equivalents) was added to ethyl 3*H*-imidazo[4,5-*b*]pyridin-2-ylacetate (1.0 equivalent) in THF at –78°C. After 20 minutes, a solution of 2-aminobenzenecarbonitrile (1.1 equivalents) in THF was added. The resulting mixture was allowed to warm to room temperature, stirred for 3 hours, and then refluxed overnight. The mixture was cooled to 0°C and quenched with an aqueous saturated NH_4Cl solution. A precipitate formed, was filtered off, and was washed repeatedly with ether to yield the desired compound as a light brown solid. LC/MS *m/z* 278.2 (MH+), R_t 1.82 minutes.

Example 47: Synthesis of 4-Amino-3-(5-morpholin-4-yl-3H-imidazo[4,5-b]pyridin-2-yl)quinolin-2(1H)-one

Step 1: 6-Morpholin-4-yl-3-nitropyridin-2-amine

[0647] Morpholine (4 equivalents) was added to a suspension of 6-chloro-3-nitropyridin-2-amine (1 equivalent) in CH_3CN, and the reaction mixture was stirred at 70°C for 5 hours. The solvent was evaporated under reduced pressure, and the residue was triturated with ether to afford the desired compound as a bright yellow powder. LC/MS *m/z* 225.0 (MH+), R_t 1.79 minutes.

Step 2: Ethyl (5-morpholin-4-yl-3*H*-imidazo[4,5-*b*]pyridin-2-yl)acetate

[0648] To a solution 6-chloro-3-nitropyridin-2-amine (1.0 equivalent) in EtOH was added Pd/C (0.1 equivalents). The reaction vessel was repeatedly purged with hydrogen and then stirred under a hydrogen atmosphere (1 atm) for 18 hours. Ethyl 3-ethoxy-3-iminopropanoate hydrochloride (2.0 equivalents) was added in one portion, and the reaction mixture was refluxed overnight. The reaction mixture was cooled to room temperature, filtered through a Celite plug, and the plug was washed with EtOH. After evaporation of the solvent under reduced pressure, the residue was purified by silica gel chromatography (5% MeOH in CH_2Cl_2 with 1% Et_3N) providing the desired product as a brown solid. LC/MS *m/z* 291.3 (MH+), R_t 1.71 minutes.

Step 3: 4-Amino-3-(5-morpholin-4-yl-3H-imidazo[4,5-b]pyridin-2-yl)quinolin-2(1H)-one

[0649] The title compound was synthesized as described in Example 46, using ethyl 2-(5-morpholin-4-ylimidazolo[5,4-b]pyridin-2-yl)acetate and 2-aminobenzenecarbonitrile, with a modified workup procedure.. After quenching with a saturated aqueous ammonium chloride solution, the two phases were separated and the aqueous phase extracted with EtOAc. Upon standing, a solid formed and precipitated out of the organic extracts. The precipitate, a dark brown solid, was filtered off and dried. Purification by reverse phase chromatography afforded the desired product as a reddish solid. LC/MS *m/z* 363.2 (MH+), R_t 2.20 minutes.

Example 48: Synthesis of 4-Amino-5-[(2R,6S)-2,6-dimethylmorpholin-4-yl]-3-(3H-imidazo[4,5-b]pyridin-2-yl)quinolin-2(1H)-one

[0650] LiHMDS (3.0 equivalents) was added to ethyl 3*H*-imidazo[4,5-*b*]pyridin-2-ylacetate (1.0 equivalent) in THF at –78°C. After 20 minutes, a solution of 2-amino-6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]benzonitrile (1.1 equivalents) in THF was added. The resulting mixture was allowed to warm to room temperature, stirred for 2 hours, and then it was heated to 60°C overnight. The mixture was cooled to 0°C and quenched with an aqueous

saturated NH_4Cl solution. The aqueous phase was extracted with CH_2Cl_2 (5 times) and the organic extracts were collected, dried (Na_2SO_4), and concentrated. The crude product was purified by HPLC. LC/MS *m/z* 391.2 (MH+), R_t 2.35 minutes.

Example 49: Synthesis of 4-Amino-3-{5-[3-(dimethylamino)pyrrolidin-1-yl]-3H-imidazo[4,5-b]pyridin-2-yl}quinolin-2(1H)-one

Step 1: Ethyl {5-[3-(dimethylamino)pyrrolidin-1-yl]-3*H*-imidazo[4,5-*b*]pyridin-2-yl}acetate

[0651] 6-chloro-3-nitro-2-aminopyridine (1.0 equivalent) and 3-(dimethylamino)pyrrolidine (1.1 equivalents) were dissolved in CH_3CN and diisopropylethylamine(2.0 equivalents) was added. The reaction mixture was heated at 70°C overnight. The solution was cooled to room temperature, and the solvent was evaporated. The residue was triturated with ether and water and dried under vacuum (LC/MS *m/z* 252.2 (MH+), R_t 1.09 minutes). The isolated product (1.0 equivalent) and 10% Pd/C (0.1 equivalents) were suspended in anhydrous EtOH at room temperature. The reaction flask was evacuated and subsequently filled with H_2. The resulting mixture was allowed to stir under a hydrogen atmosphere overnight. Ethyl 3-ethoxy-3-iminopropanoate hydrochloride (2.0 equivalents) was then added and the resulting mixture was heated at reflux overnight. The solution was then filtered through Celite and evaporated under reduced pressure. The residue was suspended in CH_2Cl_2 and concentrated NH_4OH was added until a pH of 11 was achieved. The NH_4Cl thus formed was filtered off. The two phases were separated, and the organic phase was dried (Na_2SO_4). Evaporation of the solvent and trituration of the residue with ether gave a light green powder. LC/MS *m/z* 318.1 (MH+), R_t 1.11 minutes.

Step 2: 4-Amino-3-{5-[3-(dimethylamino)pyrrolidin-1-yl]-3H-imidazo[4,5-b]pyridin-2-yl}quinolin-2(1H)-one

[0652] LiHMDS (3.5 equivalents) was added to ethyl {5-[3-(dimethylamino)pyrrolidin-1-yl]-3*H*-imidazo[4,5-*b*]pyridin-2-yl}acetate (1.0 equivalent) in THF at –40°C. After 10 minutes, a solution of 2-aminobenzenecarbonitrile (1.1 equivalents) in THF was added. The resulting mixture was allowed to warm to room temperature, stirred for 1 hour, and then heated to 60°C overnight. The mixture was cooled to room temperature and quenched with NH_4Cl (aqueous saturated). The aqueous phase was extracted with CH_2Cl_2 (5 times). The product crashed out of the organic solution during the extractions. Evaporation of the solvent under reduced pressure afforded a brown solid that was triturated repeatedly with MeOH and acetone to obtain a yellow greenish powder. LC/MS *m/z* 390.2 (MH+), R_t 1.48 minutes.

Example 50: Synthesis of 4-Amino-3-(1H-benzimidazol-2-yl)-5-(4-ethylpiperazin-1-yl)quinolin-2(1H)-one

Step 1: 2-(4-Ethylpiperazinyl)-6-nitrobenzenecarbonitrile

[0653] 2,6-Dinitrobenzenecarbonitrile (1.0 equivalent) and ethylpiperazine (3.6 equivalents) were dissolved in DMF. The resulting solution was heated at 90°C for 2 hours. The solution was cooled to room temperature and poured into H_2O. A precipitate formed which was filtered to yield the desired product as a brown solid. LC/MS *m/z* 260.1 (MH+), R_t 1.69 minutes.

Step 2: 6-Amino-2-(4-ethylpiperazinyl)benzenecarbonitrile

[0654] 2-(4-Ethylpiperazinyl)-6-nitrobenzenecarbonitrile (1.0 equivalent) was dissolved in EtOH and EtOAc. The flask was purged with N_2, and 10% Pd/C (0.1 equivalents) was added. The flask was evacuated and purged with H_2 three times. The resulting mixture was stirred overnight at room temperature. The mixture was filtered through Celite, and the filter pad was

washed with EtOAc. The solvent was removed *in vacuo* to provide the desired product as a yellow solid. LC/MS *m/z* 231.2 (MH+), R_t 1.42 minutes.

Step 3: 4-Amino-3-(1H-benzimidazol-2-yl)-5-(4-ethylpiperazin-1-yl)quinolin-2(1H)-one

[0655] *t*-BuLi (3.1 equivalents) was added to ethyl 2-benzimidazol-2-ylacetate (1.0 equivalent) and 6-amino-2-(4-ethylpiperazinyl) benzenecarbonitrile (1.0 equivalent) in THF at 0°C. The reaction was stirred overnight. The resulting mixture was quenched with NH_4Cl (aqueous saturated) and extracted with EtOAc. The combined organic layers were washed with H_2O and brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to yield a brown solid. The crude material was triturated with CH_2Cl_2 and MeOH to provide a tan solid. LC/MS *m/z* 389.1 (MH+), R_t 1.80 minutes.

Example 51: Synthesis of 3-(1H-Benzoimidazol-2-yl)-4-hydroxy-1H-[1,7]naphthyridin-2-one

Step 1: 3-[2-(Methoxycarbonyl)acetylamino]pyridine-4-carboxylic acid

[0656] A solution of 3-aminopyridine-4-carboxylic acid (1.0 equivalent), methyl 2-(chlorocarbonyl)acetate (1.1 equivalents), and triethylamine (2.0 equivalents) in acetone was stirred overnight at room temperature. The solvent was removed *in vacuo*. The product was used without further purification. LC/MS *m/z* 239.2 (MH+), R_t 1.40 minutes.

Step 2: 3-(1H-Benzoimidazol-2-yl)-4-hydroxy-1H-[1,7]naphthyridin-2-one

[0657] 3-[2-(Methoxycarbonyl)acetylamino]pyridine-4-carboxylic acid (1.1 equivalents) was combined with 1,2-phenylenediamine (1.0 equivalent) and heated at 150°C for 3 hours. The crude product was purified by reversed-phase HPLC (DMSO/ 5% TFA). LC/MS *m/z* 279.3 (MH+), R_t 1.73 minutes.

Example 52: Synthesis of 4-Hydroxy-3-(6-methyl-1H-benzoimidazol-2-yl)-1H-[1,7]naphthyridin-2-one

[0658] The title compound was synthesized as described in Example 50 using 3-[2-(methoxycarbonyl)acetylamino]-pyridine-4-carboxylic acid and 4-methyl-1,2-phenylenediamine. The crude product was purified by reversed-phase HPLC (DMSO/ 5% TFA). LC/MS *m/z* 293.3 (MH+), R_t 1.99 minutes.

Example 53: Synthesis of 4-[(2-Hydroxyethyl)amino]-3-(5-morpholin-4-ylbenzimidazol-2-yl)hydroquinolin-2-one

[0659] The title compound was obtained as a side-product of the debenzylation of 4-[(2-methoxyethyl)amino]-3-(5-morpholin-4-ylbenzimidazol-2-yl)-1-benzylhydroquinolin-2-one (Example 52) using the procedure described in Example 16 and was isolated by reverse-phase HPLC as a yellow solid. LC/MS *m/z* 406.2 (MH+), R_t 1.39 minutes.

Example 54: Synthesis of 4-(Methoxyamino)-3-(5-morpholin-4-ylbenzimidazol-2-yl)hydroquinolin-2-one

Step 1: 4-(Methoxyamino)-3-(5-morpholin-4-ylbenzimidazol-2-yl)-1-benzylhydroquinolin-2-one

[0660] The title compound was synthesized as described in Example 19 using *O*-methylhydroxylamine as the nucleophile. The product was used without purification.

Step 2: 4-(Methoxyamino)-3-(5-morpholin-4-ylbenzimidazol-2-yl)hydroquinolin-2-one

[0661] The title compound was obtained as a yellow solid after debenzylation of 4-(methoxyamino)-3-(5-morpholin-4-ylbenzimidazol-2-yl)-1-benzylhydroquinolin-2-one using the procedure described in Example 16. LC/MS *m/z* 392.2 (MH+), R_t 1.82 minutes.

Example 55: Synthesis of 3-(5-Morpholin-4-ylbenzimidazol-2-yl)-4-(3-piperidylamino) hydroquinolin-2-one

Step 1: *tert*-Butyl-3-{[3-(5-morpholin-4-ylbenzimidazol-2-yl)-2-oxo-1-benzyl-4-hydroquinolyl]amino}piperidinecarboxylate

[0662] The title compound was synthesized as described in Example 19 using 1-*tert*-butoxycarbonyl-3-aminopiperidine as the amine. The product was used without purification.

Step 2: 3-(5-Morpholin-4-ylbenzimidazol-2-yl)-4-(3-piperidylamino) hydroquinolin-2-one

[0663] The product was obtained as a yellow solid after debenzylation of *tert*-butyl-3-{[3-(5-morpholin-4-ylbenzimidazol-2-yl)-2-oxo-1-benzyl-4-hydroquinolyl]amino}piperidinecarboxylate using the procedure described in Example 16. The *t*-butoxycarbonyl group was removed under the reaction conditions. LC/MS *m/z* 445.4 (MH+), R_t 1.73 minutes.

Example 56: Synthesis of 3-(5-Morpholin-4-ylbenzimidazol-2-yl)-4-[(3-piperidylmethyl)amino]-hydroquinolin-2-one

Step 1: *tert*-Butyl-3-({[3-(5-morpholin-4-ylbenzimidazol-2-yl)-2-oxo-1-benzyl-4-hydroquinolyl]amino}methyl)piperidinecarboxylate

[0664] The title compound was synthesized as described in Example 19 using 1-*tert*-butoxycarbonyl-3-aminomethylpiperidine as the amine. The product was used without purification.

Step 2: 3-(5-Morpholin-4-ylbenzimidazol-2-yl)-4-[(3-piperidylmethyl)amino]-hydroquinolin-2-one

[0665] The title compound was obtained as a yellow solid after debenzylation of *tert*-butyl-3-({[3-(5-morpholin-4-ylbenzimidazol-2-yl)-2-oxo-1-benzyl-4-hydroquinolyl]amino}methyl)piperidinecarboxylate using the procedure described in Example 16. LC/MS *m/z* 459.6 (MH+), R_t 1.71 minutes.

Example 57: Synthesis of 3-(5-Morpholin-4-ylbenzimidazol-2-yl)-4-[(oxolan-2-ylmethyl)amino]-hydroquinolin-2-one

Step 1: 3-(5-Morpholin-4-ylbenzimidazol-2-yl)-4-[(oxolan-2-ylmethyl)amino]-1-benzylhydroquinolin-2-one

[0666] The title compound was synthesized as described in Example 19 using 2-aminomethyltetrahydrofuran as the amine. The product was used without purification.

Step 2: 3-(5-Morpholin-4-ylbenzimidazol-2-yl)-4-[(oxolan-2-ylmethyl)amino]-hydroquinolin-2-one

[0667] The title compound was obtained as a yellow solid after debenzylation of 3-(5-morpholin-4-ylbenzimidazol-2-yl)-4-[(oxolan-2-ylmethyl)amino]-1-benzylhydroquinolin-2-one using the procedure described in Example 16. LC/MS *m/z* 446.5 (MH+), R_t 2.19 minutes.

Example 58: Synthesis of 3-(5-Morpholin-4-ylbenzimidazol-2-yl)-4-(pyrrolidin-3-ylamino)hydroquinolin-2-one

Step 1: *tert*-Butyl-3-{[3-(5-morpholin-4-ylbenzimidazol-2-yl)-2-oxo-1-benzyl-4-hydroquinolyl]amino}pyrrolidinecarboxylate

[0668] The title compound was synthesized as described in Example 19 using 1-*tert*-butoxycarbonyl-3-aminopyrrolidine as the amine. The product was used without purification.

Step 2: 3- (5-Morpholin-4-ylbenzimidazol-2-yl)-4-(pyrrolidin-3-ylamino)hydroquinolin-2-one

[0669] The title compound was obtained as a yellow solid after debenzylation of *tert*-butyl-3-{[3-(5-morpholin-4-ylbenzimidazol-2-yl)-2-oxo-1-benzyl-4-hydroquinolyl]amino}pyrrolidinecarboxylate using the procedure described in Example 16. LC/MS *m/z* 431.4 (MH+), R_t 1.50 minutes.

Example 59: Synthesis of 3-Benzimidazol-2-yl-4-(ethylamino)hydroquinolin-2-one

[0670] The benzylated title compound was synthesized as described in Example 19 using ethylamine as the amine and 3-(benzimidazol-2-yl)-4-chloro-1-benzylhydroquinolin-2-one. The title compound was obtained after debenzylation as a yellow solid using the procedure described in Example 16. LC/MS *m/z* 305.3 (MH+), R_t 2.01 minutes.

Example 60: Synthesis of 3-Benzimidazol-2-yl-4-[(oxolan-2-ylmethyl)amino]hydroquinolin-2-one

[0671] The benzylated title compound was synthesized as described in Example 19 using 2-aminomethyltetrahydrofuran as the amine and 3-(benzimidazol-2-yl)-4-chloro-1-benzylhydroquinolin-2-one. The title compound was obtained after debenzylation as a yellow solid using the procedure described in Example 16. LC/MS *m/z* 361.2 (MH+), R_t 1.74 minutes.

Example 61: Synthesis of 3-Benzimidazol-2-yl-4-[(4-piperidylmethyl)amino]hydroquinolin-2-one

[0672] The protected title compound was synthesized as described in Scheme 11 using 1-*tert*-butoxycarbonyl-4-aminomethylpiperidine as the amine and 3-(benzimidazol-2-yl)-4-chloro-1-benzylhydroquinolin-2-one. The title compound was obtained after deprotection and debenzylation as a yellow solid using the procedure described in Example 16. LC/MS *m/z* 374.3 (MH+), R_t 1.29 minutes.

Example 62: Synthesis of 3-Benzimidazol-2-yl-4-[(4-fluorophenyl)amino]hydroquinolin-2-one

[0673] The benzylated title compound was synthesized as described in Example 19 using 4-fluoroaniline as the amine and 3-(benzimidazol-2-yl)-4-chloro-1-benzylhydroquinolin-2-one. The title compound was obtained after

debenzylation as a yellow solid using the procedure described in Example 16. LC/MS *m/z* 371.2 (MH+), R_t 1.92 minutes.

Example 63: Synthesis of 3-Benzimidazol-2-yl-4-(methoxyamino)hydroquinolin-2-one

[0674] The benzylated title compound was synthesized as described in Example 19 using *O*-methylhydroxylamine as the amine and 3-(benzimidazol-2-yl)-4-chloro-1-benzylhydroquinolin-2-one. The title compound was obtained after debenzylation as a yellow solid using the procedure described in Example 16. LC/MS *m/z* 307.3 (MH+), R_t 1.77 minutes.

Example 64: Synthesis of 3-Benzimidazol-2-yl-4-(benzimidazol-6-ylamino)hydroquinolin-2-one

[0675] The benzylated title compound was synthesized as described in Example 19 using 5-aminobenzimidazole as the amine and 3-(benzimidazol-2-yl)-4-chloro-1-benzylhydroquinolin-2-one. The title compound was obtained after debenzylation as a yellow solid using the procedure described in Example 16. LC/MS *m/z* 393.4 (MH+), R_t 1.41 minutes.

Example 65: Synthesis of 3-Benzimidazol-2-yl-4-(phenylamino)hydroquinolin-2-one

[0676] The benzylated title compound was synthesized as described in Example 19 using aniline as the amine and 3-(benzimidazol-2-yl)-4-chloro-1-benzylhydroquinolin-2-one. The title compound was obtained after debenzylation as a yellow solid using the procedure described in Example 16. LC/MS *m/z* 353.4 (MH+), R_t 2.38 minutes.

Example 66: Synthesis of 3-Benzimidazol-2-yl-4-(quinuclidin-3-ylamino)hydroquinolin-2-one

[0677] The benzylated title compound was synthesized as described in Example 19 using 3-aminoquinuclidine as the amine and 3-(benzimidazol-2-yl)-4-chloro-1-benzylhydroquinolin-2-one. The title compound was obtained after debenzylation as a yellow solid using the procedure described in Example 16. LC/MS *m/z* 386.4 (MH+), R_t 1.82 minutes.

Example 67: Synthesis of 3-Benzimidazol-2-yl-4-[(imidazol-5-ylmethyl)amino]hydroquinolin-2-one

[0678] The benzylated title compound was synthesized as described in Example 19 using 4-aminomethyl-1*H*-imidazole as the amine and 3-(benzimidazol-2-yl)-4-chloro-1-benzylhydroquinolin-2-one. The title compound was obtained after debenzylation as a yellow solid using the procedure described in Example 16. LC/MS *m/z* 357.4 (MH+), R_t 1.34 minutes.

Example 68: 3-Benzimidazol-2-yl-4-(morpholin-4-ylamino)hydroquinolin-2-one

[0679] The benzylated title compound was synthesized as described in Example 19 using 4-aminomorpholine as the amine and 3-(benzimidazol-2-yl)-4-chloro-1-benzylhydroquinolin-2-one. The title compound was obtained after debenzylation as a yellow solid using the procedure described in Example 16. LC/MS *m/z* 362.4 (MH+), R_t 1.42 minutes.

Example 69: Synthesis of 3-Benzimidazol-2-yl-4-hydrazinohydroquinolin-2-one

[0680] The benzylated title compound was synthesized as described in Example 19 using hydrazine as the nucleophile and 3-(benzimidazol-2-yl)-4-chloro-1-benzylhydroquinolin-2-one. The title compound was obtained as a

yellow solid after debenzylation using the procedure described in Example 16. LC/MS *m/z* 292.3 (MH+), R_t 1.19 minutes.

Example 70: Synthesis of 3-(5,6-Dimethylbenzimidazol-2-yl)-4-(3-piperidylamino)hydroquinolin-2-one

Step 1: Ethyl 2-(5,6-dimethylbenzimidazol-2-yl)acetate

[0681] The title compound was synthesized as described in Example 16 using 4,5-dimethylbenzene-1,2-diamine as the diamine. The crude yellow oil was purified by silica gel chromatography (96.5:3.0:0.5, CH_2Cl_2:MeOH:TEA), and then by recrystallization from toluene to yield the title compound as a pale, yellow solid. LC/MS *m/z* 233.1 (MH+), R_t 1.73 minutes.

Step 2: 3-(5,6-Dimethylbenzimidazol-2-yl)-4-hydroxy-1-benzylhydroquinolin-2-one

[0682] The title compound was synthesized as described in Example 16 using ethyl 2-(5,6-dimethylbenzimidazol-2-yl)acetate. The crude material was purified by silica gel chromatography (98.5:1.5, CH_2Cl_2:MeOH) to yield the title compound as a yellow solid. LC/MS *m/z* 396.2 (MH+), R_t 3.60 minutes.

Step 3: 3-(5,6-Dimethylbenzimidazol-2-yl)-4-chloro-1-benzylhydroquinolin-2-one

[0683] The title compound was synthesized as described in Example 19, using 3-(5,6-dimethylbenzimidazol-2-yl)-4-hydroxy-1-benzylhydroquinolin-2-one. The title compound was obtained as an orange-yellow solid. LC/MS *m/z* 414.2 (MH+), R_t 2.47 minutes.

Step 4: *tert*-Butyl 3-{[3-(5,6-dimethylbenzimidazol-2-yl)-2-oxo-1-benzyl-4-hydroquinolyl]amino}piperidinecarboxylate

[0684] The title compound was synthesized as described in Example 19, using 1-*tert*-butoxycarbonyl-3-aminopiperidine as the amine and 3-(5,6-dimethylbenzimidazol-2-yl)-4-chloro-1-benzylhydroquinolin-2-one. The crude

material was purified by silica gel chromatography (99:1 CH_2Cl_2:MeOH) to yield the title compound as a yellow solid. LC/MS *m/z* 578.5 (MH+), R_t 3.05 minutes.

Step 5: 3-(5,6-Dimethylbenzimidazol-2-yl)-4-(3-piperidylamino)hydroquinolin-2-one

[0685] *tert*-Butyl 3-{[3-(5,6-dimethylbenzimidazol-2-yl)-2-oxo-1-benzyl-4-hydroquinolyl]amino}piperidine-carboxylate was debenzylated as described in Example 16. The crude material was purified by reversed-phase HPLC to yield the title compound as a light yellow solid. LC/MS *m/z* 388.4 (MH+), R_t 1.61 minutes.

Example 71: Synthesis of 4-[(3S)-1-Azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-(4-methoxyphenyl)quinolin-2(1H)-one

[0686] A vial was charged with the hydrochloride salt of 4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-bromoquinolin-2(1H)-one (1.0 equivalent) and 4-methoxyphenyl boronic acid (1.3 equivalents). To this solution was added DME and 2 M aqueous Na_2CO_3 (10%). The mixture was degassed by bubbling argon through the solution for 5 minutes. $Pd(dppf)_2Cl_2.CH_2Cl_2$ (0.2 equivalents) was then added to the degassed solution. The mixture was heated at 90°C for 16 hours, and the top organic layer was separated and filtered. The solvent was removed, and the residue was purified by reverse phase HPLC affording the desired product. MS *m/z* 492.6 (M+H).

Example 72: Synthesis of 4-[(3S)-1-Azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-(4-hydroxyphenyl)quinolin-2(1H)-one

[0687] 4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-(4-methoxyphenyl)quinolin-2(1H)-one (Example 70) was dissolved in 30% HBr/AcOH and heated at 60°C until the reaction was complete. The resulting mixture was allowed to cool, and it was then neutralized with 2 M NaOH. The resulting mixture was extracted with EtOAc, and the organic

layers were dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The residue was purified by reverse phase HPLC to give the desired product. MS *m/z* 478.6 (M+H).

Example 73: Synthesis of 4-[((3S)-Quinuclidin-3-yl)amino]-3-benzimidazol-2-yl-6-chloro-hydropyridino[3,4-b]pyridin-2-one

Step 1: Methyl 5-[(*tert*-butoxy)carbonylamino]-2-chloropyridine-4-carboxylate

[0688] 5-[(*tert*-butoxy)carbonylamino]-2-chloropyridine-4-carboxylic acid (1 equivalent) was dissolved in THF and MeOH. The mixture was heated to 50°C to completely dissolve the starting material. The solution was then cooled to 0°C, and $TMSCHN_2$ (2 M in THF, 2 equivalents) was added. The reaction was allowed to warm to room temperature and stirred overnight. The reaction was the concentrated to yield the methyl ester (100 %) as a brown solid.

Step 2: Methyl 5-{(*tert*-butoxy)-N-[(4-methoxyphenyl)methyl]carbonylamino}-2-chloropyridine-4-carboxylate

[0689] NaH (60% in oil, 1.5 equivalents) in a round bottom flask was washed with hexanes to remove mineral oil. DMF was then added to the washed NaH. A solution of methyl 5-[(*tert*-butoxy)carbonylamino]-2-chloropyridine-4-carboxylate (1 equivalent) in DMF, in an addition funnel, was added to the mixture of NaH in DMF followed by stirring at room temperature for 15 minutes. The mixture was heated at 50°C for 1.5 hours. The reaction was then cooled to room temperature, and 4-methoxybenzyl chloride (1.3 equivalents) dissolved in DMF was added through an addition funnel. The reaction was stirred overnight at 50°C. Upon cooling, water was added to the reaction mixture. Ethyl acetate was then added, and the mixture was stirred for 15 minutes. The aqueous layer was extracted with ethyl acetate. The organic layers were combined, washed with water and brine, dried over $MgSO_4$, filtered, and concentrated to yield methyl 5-{(*tert*-butoxy)-N-{(4-

methoxyphenyl)-methyl]-carbonylamino}-2-chloropyridine-4-carboxylate (81 %) as a brown oil.

Step 3: Methyl 2-chloro-5-{(4-methoxyphenyl)methyl]amino}pyridine-4-carboxylate

[0690] To a solution of crude methyl 5-{(*tert*-butoxy)-N-[(4-methoxyphenyl)methyl]carbonylamino}-2-chloropyridine-4-carboxylate (1 equivalent) in CH_2Cl_2, was added 1 M HCl (2 equivalents). The reaction was stirred overnight and then concentrated to yield crude methyl 2-chloro-5-{(4-methoxyphenyl)methyl]-amino}pyridine-4-carboxylate (80 %).

Step 4: 2-Chloro-5-{[(4-methoxyphenyl)methyl]amino}pyridine-4-carboxylic acid

[0691] To a solution of methyl 5-{(*tert*-butoxy)-N-[(4-methoxyphenyl)-methyl]carbonylamino}-2-chloropyridine-4-carboxylate (1 equivalent) in MeOH, was added an aqueous solution of NaOH (3 equivalents). A precipitate formed immediately. The reaction was heated until the solution was clear and was then stirred for 1 hour at room temperature. Aqueous citric acid (1 M) was then added causing the product to crash out of solution. The product was then collected to afford the title compound in 77 % yield.

Step 5: 6-Chloro-1-[(4-methoxyphenyl)methyl]pyridino[3,4-d]-1,3-oxazaperhydroine-2,4-dione

[0692] To a solution of 2-chloro-5-{[(4-methoxyphenyl)methyl]-amino}pyridine-4-carboxylic acid (1 equivalent) in dioxane, was added phosgene/toluene (excess). The reaction was stirred overnight and then evaporated to yield the desired product (63%).

Step 6: 3-Benzimidazol-2-yl-6-chloro-4-hydroxy-1-[(4-methoxyphenyl)-methyl]hydropyridino[3,4-b]pyridin-2-one

[0693] To a solution of ethyl 2-benzimidazol-2-ylacetate (1 equivalent) in DMF and THF (2:1) at –78°C, was added LiHMDS (3 equivalents) dropwise. After being stirred for 1 hour, a solution of 6-chloro-1-[(4-

methoxyphenyl)methyl]pyridino-[3,4-d]-1,3-oxazaperhydroine-2,4-dione in DMF and THF (1:2) was added dropwise, and the reaction was stirred for 1.5 hours. The reaction was quenched with aqueous NH_4Cl and allowed to warm to room temperature. The aqueous phase was extracted with EtOAc, and the organic layers were combined, washed with H_2O and brine, dried over $MgSO_4$, and concentrated. Toluene was added to the residue, and the reaction was refluxed overnight. The mixture was then cooled allowing the product to crash out. The reaction was filtered, and the product was washed with toluene and EtOH to give the product (45 %).

Step 7: 6-Chloro-1-[(4-methoxyphenyl)methyl]-2-oxo-3-{1-[(trifluoromethyl)sulfonyl]-benzimidazol-2-yl}hydropyridino[3,4-b]pyridin-4-yl (trifluoromethyl)sulfonate

[0694] A solution of 3-benzimidazol-2-yl-6-chloro-4-hydroxy-1-[(4-methoxyphenyl)methyl]hydropyridino[3,4-b]pyridin-2-one (1 equivalent) in CH_2Cl_2 was cooled to –10°C, and pyridine (16 equivalents) was added. Trifluoromethane-sulfonic anhydride (8 equivalents) was then slowly added dropwise, using a syringe, so that the temperature did not exceed –4°C. The reaction was stirred for 2 hours at -4°C. The reaction was allowed to warm to room temperature and stirred until clear (4 hours). The reaction was then quenched with saturated $NaHCO_3$. The organic layer was washed with saturated aqueous $NaHCO_3$, 1.0 M citric acid, H_2O, saturated aqueous $NaHCO_3$, H_2O, and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated to yield the product (96%) as a yellow solid.

Step 8: 4-[((3S)-Quinuclidin-3-yl)amino]-6-chloro-1-[(4-methoxyphenyl)methyl]-3-{1-[(trifluoromethyl)sulfonyl]benzimidazol-2-yl}hydropyridino[3,4-b]pyridin-2-one

[0695] To a solution of 6-chloro-1-[(4-methoxyphenyl)methyl]-2-oxo-3-{1-[(trifluoromethyl)sulfonyl]benzimidazol-2-yl}hydropyridino[3,4-b]pyridin-4-yl (trifluoromethyl)sulfonate (1 equivalent) in CH_3CN was added triethylamine (4 equivalents), followed by the (3S)-aminoquinuclidine (3 equivalents). The

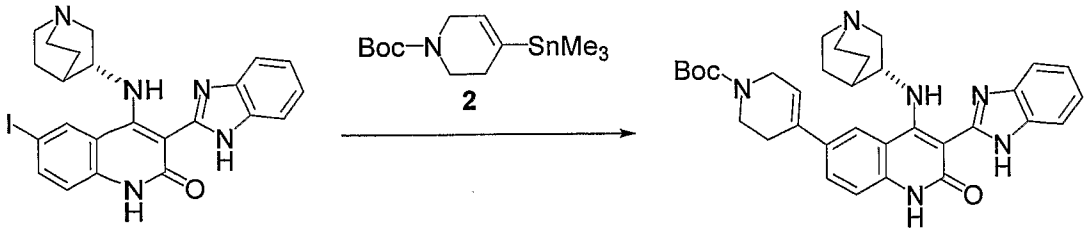
reaction was then stirred at 80°C for 2 hours. The reaction was cooled to room temperature and evaporated. The crude material was carried on to the next step.

Step 9: 4-[((3S)-Quinuclidin-3-yl)amino]-3-benzimidazol-2-yl-6-chloro-hydropyridino[3,4-b]pyridin-2-one

[0696] Crude 4-[((3S)quinuclidin-3-yl)amino]-6-chloro-1-[(4-methoxyphenyl)methyl]-3-{1-[(trifluoromethyl)sulfonyl]benzimidazol-2-yl}hydropyridino[3,4-b]pyridin-2-one was dissolved in a mixture of TFA and HCl (8:1 ratio, premixed). The reaction was stirred overnight at 80°C. The reaction was then cooled to room temperature, and the solvent was evaporated. The crude product was neutralized and subsequently purified using prep HPLC. The combined fractions from the prep. LC were made basic with NaOH first and then with $NaHCO_3$(sat) causing the free base to precipitate. After 30 minutes, the precipitate was collected and washed several times with water. The precipitate was placed in a flask, and a solution of H_2O/CH_3CN (1:1) was added. To this solution was added HCl (1 M), and the solution was lyophilized to yield the product salt (17 % over 2 steps). MS m/z 421.9 (M+H).

Example 74: Synthesis of 4-(R)-(1-Aza-bicyclo[2.2.2]oct-3-ylamino)-3-(1H-benzoimidazol-2-yl)-6-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-quinolin-2-one

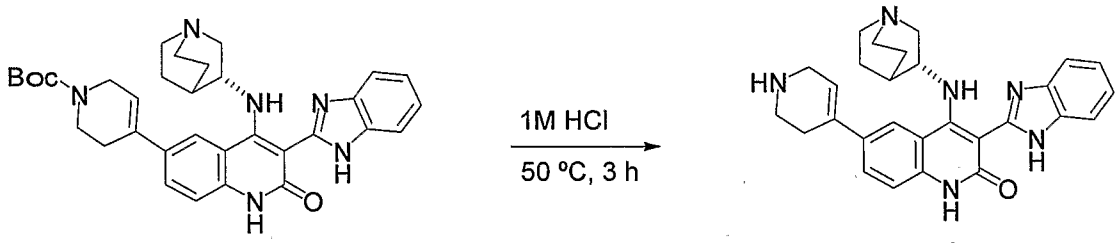
Step 1: 4(R)-[4-(1-Aza-bicyclo[2.2.2]oct-3-ylamino)-3-(1H-benzoimidazol-2-yl)-2-oxo-1,2-dihydro-quinolin-6-yl]-3,6-dihydro-2H-pyridine-1-carboxylic acid *tert*-butyl ester (3).



1 3

[0697] For similar procedures see the following reference, herein incorporated by reference in its entirety for all purposes as if fully set forth herein, and references therein: Eastwood, P.R. *Tetrahedron Letters* **2000**, *41*, 3705-3708. The palladium catalyst, $Pd(dppf)_2Cl_2.CH_2Cl_2$ (6 mg, 0.007 mmol) was added in one portion to a stirred and argon sparged (1 minute) solution of 6-iodoquinolinone (**1**) (25 mg, 0.049 mmol) and 4-trimethylstannyl-3,6-dihydro-2H-pyridine-1-carboxylic acid *tert*-butyl ester (**2**) (24 mg, 0.069 mmol) in DMF at room temperature. The reaction heated to 85°C under argon for 2 hours. The product was purified by prep. HPLC using a reverse phase Ultro 120 C18 column running a 2% gradient (AcCN/water, 0.1% TFA). The purified fractions were lyophilized to dryness to give 6 mg of white powder in 21% yield and >97% purity.

Step 2: 4-(R)-(1-Aza-bicyclo[2.2.2]oct-3-ylamino)-3-(1H-benzoimidazol-2-yl)-6-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-quinolin-2-one



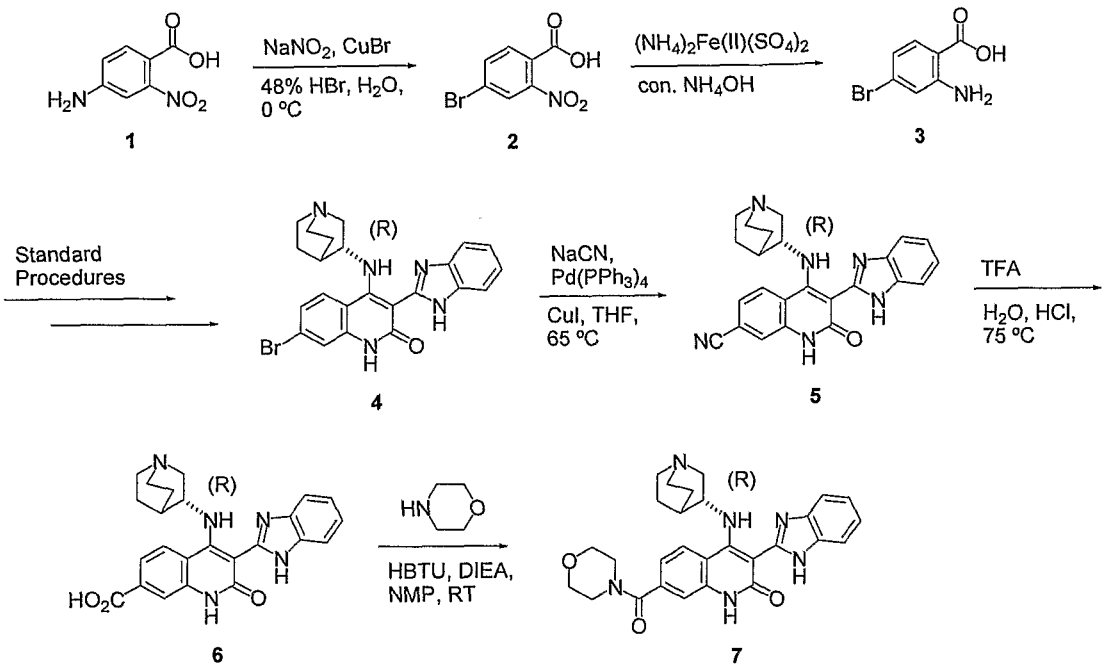
[0698] 1 M aqueous HCl (1 mL) was added to lyophilized Boc-piperidine quinolone (**3**) powder (5 mg, 0.009 mmol). The resulting solution was stirred for 3 hours at 50°C. The product was purified by prep. HPLC using a reverse phase Ultro 120 C18 column running a 2% gradient (AcCN/water, 0.1% TFA). The purified fractions were lyophilized to dryness affording 4 mg of white powder in 78% yield and >98% purity.

Example 75: Synthesis of 4-(R)-(1-Aza-bicyclo[2.2.2]oct-3-ylamino)-3-(1H-benzoimidazol-2-yl)-6,7-dihydroxy-1H-quinolin-2-one



[0699] BCl_3 (1 M in CH_2Cl_2) (5 mL) was added to 6,7-Dimethoxyquinolone (**1**) powder (20 mg, 0.045 mmol) in an 8 mL vial. The vial was capped, and the resulting solution was stirred for 2 days at 40°C. The progress of the reaction was monitored by HPLC and LCMS. More BCl_3 was added if needed. The reaction was concentrated to dryness, and the residue was dissolved in DMSO (1 mL). The product was purified by prep. HPLC using a reverse phase Ultro 120 C18 column running a 2% gradient (AcCN/water, 0.1% TFA). The purified fractions were lyophilized to dryness to give 6 mg of white powder in 32% yield and >98% purity.

Example 76: Synthesis of 4-(R)-(1-Aza-bicyclo[2.2.2]oct-3-ylamino)-3-(1H-benzoimidazol-2-yl)-7-(morpholine-4-carbonyl)-1H-quinolin-2-one



Step 1: 4-Bromo-2-nitro-benzoic acid

[0700] A modification of a procedure in the following reference which is herein incorporated by reference in its entirety, for all purposes as if fully set forth herein, was used: Boojamra, C.G.; Burow, K.M.; Thompson, L.A.; Ellman, J.A. *J. Org. Chem.*, **1997**, *62*, 1240-1256. A solution of $NaNO_2$ (1.9 g, 27.4 mmol) in water (65 mL) was added to a stirred solution of 4-amino-2-nitro-benzoic acid (**1**) (5 g, 27.4 mmol) in aqueous 48% HBr (40 mL) and water (82 mL) at 0°C. The cloudy reaction mixture turned into a clear orange-yellow solution after about 15 minutes. After stirring for 25 minutes, the solution was added dropwise to a solution of CuBr (5.2 g, 36.3 mmol) in aqueous 48% HBr (90 mL) at 0°C. A yellow foam developed and gas was evolved from the purple-brown mixture. After stirring at 0°C for 1 hour, the mixture was concentrated under reduced pressure. The aqueous layer was extracted with EtOAc (4 x 300 mL) which was dried with Na_2SO_4 and concentrated to dryness giving a dark solid. The crude product was filtered through a plug of florisil (~20 g) eluting with EtOAc. The combined organic

fractions were evaporated to approx. 200 mL and washed with 1 M HCl (2x50 mL), brine (50 mL), dried with Na_2SO_4, filtered and concentrated to dryness giving 6.1 g of a light yellow solid product (**2**) in 91% yield and >90% purity by HPLC.

Step 2: 2-Amino-4-bromo-benzoic acid

[0701] A modification of a procedure in the following reference herein incorporated by reference in its entirety, for all purposes as if fully set forth herein, was used: Boojamra, C.G.; Burow, K.M.; Thompson, L.A.; Ellman, J.A. *J. Org. Chem.*, **1997**, *62*, 1240-1256. A solution of $(NH_4)_2Fe^{(II)}(SO_4)_2 \cdot 6 H_2O$ (24.4 g, 63 mmol) in water (60 mL) was added to a stirred solution of 4-bromo-2-nitro-benzoic acid (**2**) (3.05 g, 12.45 mmol) in concentrated aqueous NH_4OH (40 mL) at room temperature. The iron sulfate solution flask was washed with an additional portion of water (20 mL) which was added to the reaction. After 16 hours, the reaction had changed from a dark green solution to a rusty-brown mixture which was filtered through a plug of Celite and washed with concentrated aqueous NH_4OH (80 mL) and water (4 x 80 mL). The combined aqueous fractions were acidified to pH 1-2 with aqueous concentrated HCl and extracted with EtOAc (4 x 500 mL). The organic fractions were evaporated under reduced pressure to a brown solid. The crude product was dissolved in EtOAc (300 mL), washed with water (40 mL), brine (40 mL), dried with Na_2SO_4, filtered, and concentrated to dryness giving 2.47 g of product (**3**) as a brown solid in 91% yield and >90% purity by HPLC.

Step 3: 4-(R)-(1-Aza-bicyclo[2.2.2]oct-3-ylamino)-3-(1H-benzoimidazol-2-yl)-7-bromo-1H-quinolin-2-one

[0702] The (R)-quinolone **4** was prepared using the standard methods described in the other Examples set forth herein.

Step 4: 4-(R)-(1-Aza-bicyclo[2.2.2]oct-3-ylamino)-3-(1H-benzoimidazol-2-yl)-2-oxo-1,2-dihydro-quinoline-7-carbonitrile

[0703] A modification of a procedure described in the following reference incorporated herein in its entirety, for all purposes as if fully set forth herein, was used: Anderson, B.A.; Bell, E.C.; Ginah, F.O.; Harn, N.K.; Pagh, L.M.; Wepsiec, J.P. *J. Org. Chem.*, **1998**, 63, 8224-8228. A mixture of 6-bromo-(R)-quinolone (**4**) (99 mg, 0.21 mmol), KCN (85 mg, 1.3 mmol), CuI (70 mg, 0.37 mmol), $Pd(PPh_3)_4$ (207 mg, 0.18 mmol) in THF (20 mL) and CH_3CH_2CN (5 mL) was sparged with dry argon (1 minute) and sonicated until a homogeneous cloudy yellow suspension was formed. The reaction was stirred under argon at 85°C for 4 days until complete as determined using HPLC and LCMS. The milky greenish-yellow mixture was filtered, and the filter was washed with AcCN (100 mL). The filtrate was evaporated under reduced pressure to give a yellow solid. The crude product was dissolved in DMSO (1 mL). The product was purified by prep. HPLC using a reverse phase Ultro 120 C18 column running a 1% gradient (AcCN/water, 0.1% TFA). The purified fractions were then lyophilized to dryness to give 60 mg of **5** as a white solid in 70% yield and 98% purity.

Step 5a: 4-(S)-(1-Aza-bicyclo[2.2.2]oct-3-ylamino)-3-(1H-benzoimidazol-2-yl)-2-oxo-1,2-dihydro-quinoline-7-carboxylic acid

[0704] A solution of 6-cyano-quinolone (**5 (S)**) (12 mg, 0.029 mmol) in TFA (3.75 mL), aqueous concentrated HCl (1.25 mL) and water (2.5 mL) was stirred at 75°C for 20 hours. LCMS analysis showed the formation of the product acid (**6**) and the primary amide. The yellow solution was stirred at 75°C for an additional 20 hours until most of the primary amide was hydrolyzed. The reaction was evaporated under reduced pressure to give a yellow glass. The crude product was dissolved in DMSO (1 mL). The product was purified by prep. HPLC using a reverse phase BDX C18 (20 x 50 mm) column running a 3% gradient (AcCN/water, 0.1% TFA). The purified fractions were lyophilized to dryness to give 2.5 mg of yellow solid **6 (S)** in 16% yield and >95% purity.

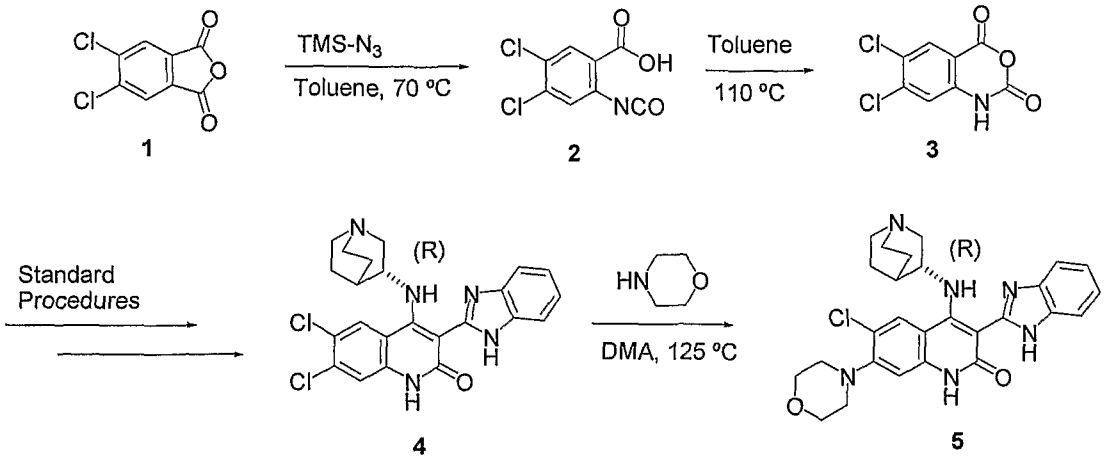
Step 5b: 4-(R)-(1-Aza-bicyclo[2.2.2]oct-3-ylamino)-3-(1H-benzoimidazol-2-yl)-2-oxo-1,2-dihydro-quinoline-7-carboxylic acid

[0705] A solution of 6-cyano-quinolone (**5 (R)**) (56 mg, 0.136 mmol) in TFA (7.5 mL), aqueous concentrated HCl (5.0 mL), and water (2.5 mL) was stirred at 85°C for 40 hours. HPLC and LCMS analysis showed the formation of the product acid (**6 (R)**) 85% and the primary amide about 15%. The yellow solution was evaporated under reduced pressure to give a yellow solid. The crude product was lyophilized from AcCN/water (1:1) twice to give 51 mg of yellow solid as the TFA salt in 69% yield and 85% purity.

Step 6: 4-(R)-(1-Aza-bicyclo[2.2.2]oct-3-ylamino)-3-(1H-benzoimidazol-2-yl)-7-(morpholine-4-carbonyl)-1H-quinolin-2-one

[0706] Morpholine (30 µL, 0.34 mmol) was added to a pre-mixed (20 minutes of stirring) solution of 6-carboxy-(R)-quinolone (**6**) (15 mg, 0.035 mmol), HBTU (19 mg, 0.05 mmol), and DIEA (18 µL, 0.1 mmol) in NMP (0.5 mL). After stirring 12 hours, the crude product was purified by prep. HPLC using a reverse phase BDX C18 column running a 1.5% gradient (AcCN/water, 0.1% TFA). The purified fractions were lyophilized to dryness affording 4 mg of product **7** as a white solid TFA salt in 19% yield and 97% purity.

Example 77: Synthesis of 4-(R)-(1-Aza-bicyclo[2.2.2]oct-3-ylamino)-3-(1H-benzoimidazol-2-yl)-6,7-dichloro-1H-quinolin-2-one



Step 1: 6,7-Dichloro-1H-benzo[d][1,3]oxazine-2,4-dione

[0707] A solution of 6,7-dichloro-1H-benzo[d][1,3]oxazine-2,4-dione (**1**) (4.34 g, 20 mmol) and TMS-azide (4 mL, 30 mmol) in toluene (60 mL) was stirred at 80°C for 3 hours. The cloudy solution was then heated at 110°C for 16 hours. After cooling, the reaction had produced some of the desired product (**3**) by LCMS. An additional aliquot of TMS-azide (4 mL, 30 mmol) was added to the reaction which was again heated with stirring under nitrogen to 80°C for 2 hours and 110°C for 16 hours. HPLC and LCMS showed that the reaction had proceeded to near completion. The reaction was concentrated under reduced pressure to give a yellow slurry which was diluted with absolute EtOH (8 mL). An ivory-colored solid formed and was collected by suction filtration. The solid was washed with absolute EtOH (50 mL) and dried *in vacuo* to give 2.9 g of pure product **3** in 63% yield.

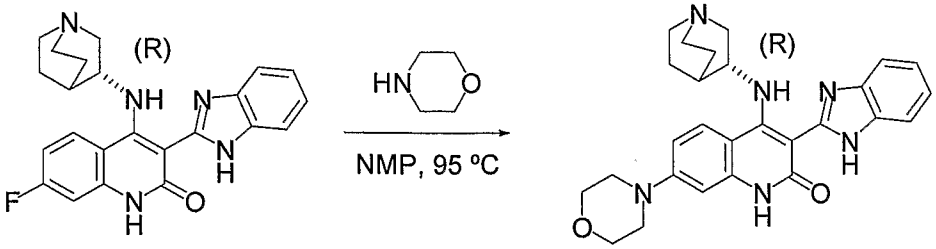
Step 2: 4-(R)-(1-Aza-bicyclo[2.2.2]oct-3-ylamino)-3-(1H-benzoimidazol-2-yl)-6,7-dichloro-1H-quinolin-2-one

[0708] 4-(R)-(1-Aza-bicyclo[2.2.2]oct-3-ylamino)-3-(1H-benzoimidazol-2-yl)-6,7-dichloro-1H-quinolin-2-one (**4**) was prepared using the standard methods described in previous Examples.

Step 3: 4-(R)-(1-Aza-bicyclo[2.2.2]oct-3-ylamino)-3-(1H-benzoimidazol-2-yl)-6,7-dichloro-1H-quinolin-2-one

[0709] An argon sparged (1 minute) solution of 6,7-Dichloro-quinolone (**4**) (20 mg, 0.044 mmol) and morpholine (1 mL) in DMA (2 mL) was stirred at 120°C for 48 hours. HPLC and LCMS showed that the reaction had proceeded to approximately 60% completion. Heating at 120°C seemed to cause some loss of chlorine. The reaction was again sparged with argon, capped and heated to 100°C for 3 days until complete as determined by LCMS. The crude product was purified by prep. HPLC using a reverse phase BDX C18 column running a 4% gradient (AcCN/water, 0.1% TFA). The purified fractions were lyophilized to dryness to give 7 mg of product **5** as white solid TFA salt in 25% yield and 97% purity.

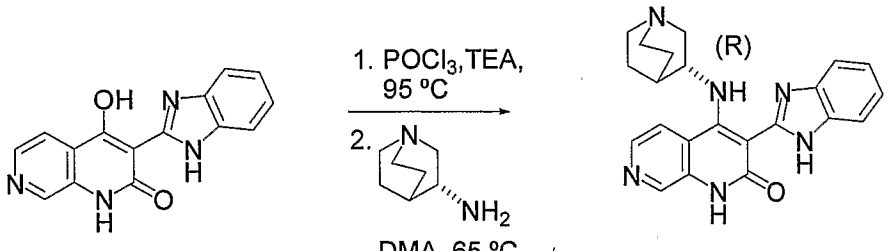
Example 78: 4-(R)-(1-Aza-bicyclo[2.2.2]oct-3-ylamino)-3-(1H-benzoimidazol-2-yl)-6,7-dichloro-1H-quinolin-2-one



1 2

[0710] An argon sparged (1 minute) solution of 6,7-Dichloro-quinolone (**4**) (20 mg, 0.044 mmol) and morpholine (100 µL) in NMP (800 µL) was stirred at 95°C for 48 hours. HPLC and LCMS showed that the reaction had proceeded to completion. The crude product was purified by prep. HPLC using a reverse phase BDX C18 column running a 3% gradient (AcCN/water, 0.1% TFA). The purified fractions were lyophilized to dryness to give 9 mg of product **2** as white solid TFA salt in 35% yield and 97% purity.

Example 79: Synthesis of 4-(R)-(1-Aza-bicyclo[2.2.2]oct-3-ylamino)-3-(1H-benzoimidazol-2-yl)-1H-[1,7]naphthyridin-2-one



1 2

[0711] $POCl_3$ (1.5 mL, 5.94 mmol) was added to the 3-(1H-benzoimidazol-2-yl)-4-hydroxy-1H-[1,7]naphthyridin-2-one (**1**) (200 mg, 0.72 mmol) with stirring. TEA (153 µL, 1.1 mmol) was added to the reaction, and the reaction was heated to 60°C for 1.5 hours. The brown solution was concentrated under reduced pressure to provide a brown solid. The solid was dissolved in EtOAc (100 mL) and washed with saturated $NaHCO_3$ (50 mL). The organic layer was evaporated under reduced pressure to a light yellow

solid which was dissolved in DMA (5 mL). After adding 3-(R)-Aminoquinuclidine dihydrochloride salt (200 mg, 1.0 mmol) and DIEA (430 µL), the solution was stirred at 65°C for 10 hours. LCMS showed that product had formed. The crude product was purified by prep. HPLC using a reverse phase BDX C18 column running a 3% gradient (AcCN/water, 0.1% TFA). The purified fractions were lyophilized to dryness to give product **2** as a yellow solid TFA salt.

Example 80: Synthesis of 4-amino-3-{6-[(2,4-dimethylmorpholin-2-yl)methylamino]benzimidazol-2-yl}hydroquinolin-2-one

Step 1: 2-(methylamino)methyl-4-benzyl morpholine

[0712] Commercially available 2-chloromethyl-4-benzyl morpholine was dissolved in an 8 M solution of NH_2Me in EtOH and heated in a glass pressure vessel at 110°C overnight. The solvent was removed *in vacuo*, and the compound was used in the next step without further purification. LC/MS *m/z:* 221.2 (MH+), R_t 0.55 minutes.

Step 2: 2-[(3-amino-4-nitrophenyl)methylamino]-2-methylmorpholin-4-yl phenyl ketone

[0713] The title compound was synthesized using the procedure set forth in Example 46) LC/MS *m/z:* 357.3 (MH+), R_t 1.98 minutes.

Step 3: ethyl 2-(6-{methyl[2-methyl-4-(phenylcarbonyl)morpholin-2-yl]amino}benzimidazol-2-yl)acetate

[0714] The synthesis of the title compound was conducted using the procedure set forth in Example 46. LC/MS *m/z:* 317.3 (MH+), R_t 2.45 minutes.

Step 4: 4-amino-3-(6-{methyl[2-methyl-4-(phenylcarbonyl)morpholin-2-yl]amino}benzimidazol-2-yl)hydroquinolin-2-one

[0715] The synthesis of 4-amino-3-(6-{methyl[2-methyl-4-(phenylcarbonyl)morpholin-2-yl]amino}benzimidazol-2-yl)hydroquinolin-2-one

was performed according to the general synthesis procedure described in Example 19.

Step 5: 4-amino-3-{6-[(2,4-dimethylmorpholin-2-yl)methylamino]benzimidazol-2-yl}hydroquinolin-2-one

[0716] a) Debenzylation of the compound of Step 4 above was accomplished using the following procedure. The benzylated compound (1.0 equivalent) and 10% Pd/C (0.1 equivalents) were suspended in 1:1 ethanol and 1 N aqueous HCl at room temperature. The reaction flask was evacuated and subsequently filled with H_2. The resulting mixture was stirred under a hydrogen atmosphere overnight. The resulting solution was filtered through Celite and concentrated under vacuum. The water was then made basic with 30% aqueous KOH, and the product was extracted with EtOAc. The combined organic layers were concentrated. The resulting residue was dissolved in CH_2Cl_2:MeOH:AcOH (2:2:1).

[0717] b) Methylation was accomplished using the following procedure. Paraformaldehyde (1.2 equivalents) and BH_3·pyridine (3 equivalents, 8 M solution) were added, and the mixture was stirred overnight at room temperature. The solvent was removed *in vacuo,* and water was added. The product was extracted with EtOAc (3x). The combined organic layers were concentrated. The residue was purified by chromatography on silicagel (10% MeOH/CH_2Cl_2) to afford the desired product.

Example 81: Synthesis of 2-(4-Amino-5-fluoro-2-oxo-3-hydroquinolyl)benzimidazole-6-carboxylic acid

Step 1: 2-[5-(methoxycarbonyl)benzimidazol-2-yl]acetate

[0718] Methyl 3,4-diaminobenzoate (1 equivalent), was stirred with ethyl-3-ethoxy-3-iminopropanoate hydrochloride (2 equivalents) in EtOH at 70°C overnight. The reaction mixture was cooled to room temperature, and the EtOH was removed under reduced pressure. The residue was taken up in water and extracted with CH_2Cl_2 (3x). The organic extracts were dried over

Na_2SO_4, and the solvent was removed. The solid was triturated with Et_2O to yield the desired ethyl 2-[5-(methoxycarbonyl)-benzimidazol-2-yl]acetate as an off-white solid. LC/MS *m/z*: 263.2 (MH+), R_t 1.80 minutes.

Step 2: Methyl 2-(4-amino-5-fluoro-2-oxo-3-hydroquinolyl) benzimidazole-6-carboxylate

[0719] In a procedure similar to that described in Example 9, LiHMDS (1.0 N solution in THF, 4.0 equivalents) was added to a solution of 2-[5-(methoxycarbonyl) benzimidazol-2-yl]acetate (1.0 equivalent) and 2-amino-6-fluorobenzene carbonitrile (1.1 equivalents) in anhydrous THF in a flame dried round bottom flask at 0°C. The resulting mixture was allowed to warm to room temperature, was stirred overnight, and was then heated at 55°C for 8 hours. The mixture was cooled to 0°C and quenched with saturated NH_4Cl. The aqueous phase was extracted with EtOAc (3x), and the organic extracts were collected and dried (Na_2SO_4). The solvent was removed under reduced pressure, and the residue was triturated with MeOH to obtain a white solid containing 50% of methyl 2-(4-amino-5-fluoro-2-oxo-3-hydroquinolyl) benzimidazole-6-carboxylate and 50% of its uncyclized isomer. LC/MS *m/z* 353.2 (MH+), R_t 2.14 minutes.

Step 3: 2-(4-Amino-5-fluoro-2-oxo-3-hydroquinolyl)benzimidazole-6-carboxylic acid

[0720] The crude product obtained in Step 2 was dissolved in a 1:1 mixture of EtOH and 30% aqueous KOH and stirred overnight at 70°C. The reaction mixture was cooled and acidified with 1 N HCl. A crash out formed. The solid was filtered, washed with water and dried providing 190 mg (40%) of 2-(4-amino-5-fluoro-2-oxo-3-hydroquinolyl)benzimidazole-6-carboxylic acid as a brown solid. LC/MS *m/z:* 339.1 (MH+), R_t 2.41 minutes.

Step 4: Amide Functionalization of 2-(4-amino-2-oxo-3-hydroquinolyl)-benzimidazole-6-carboxylic acid

[0721] A mixture of 2-(4-amino-2-oxo-3-hydroquinolyl)benzimidazole-6-carboxylic acid (1 equivalent), primary or secondary amine (1 equivalent),

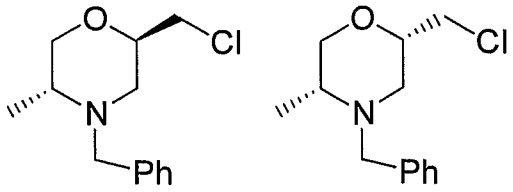
EDC (1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, 1.2 equivalents), HOAT (1-hydroxy-7-azabenzotriazole, 1.2 equivalents), and triethylamine (2.5 equivalents) in DMF, was stirred at 23°C for 20 hours. The reaction mixture was partitioned between water and ethyl acetate. The combined organic layers were dried (Na_2SO_4), and concentrated. Water was added, and the precipitate thus formed was filtered and dried. The crude was purified by reverse phase prep. HPLC to afford the desired carboxamide.

Examples 82 and 83: Synthesis of 3-(6-{(2R,5R)-2-[(dimethylamino)methyl]-5-methylmorpholin-4-yl}benzimidazol-2-yl)-4-aminohydroquinolin-2-one (7a) and 3-(6-{(2S,5R)-2-[(dimethylamino)methyl]-5-methylmorpholin-4-yl}benzimidazol-2-yl)-4-aminohydroquinolin-2-one

Step 1: (2R)-2-[Benzylamino]propan-1-ol

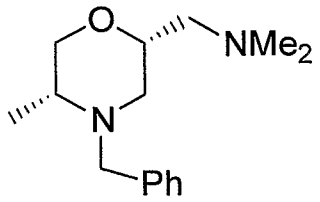
[0722] A mixture of (2R)-2-amino propanol (1.2 equivalents), benzaldehyde (1 equivalent), $NaHCO_3$ (1.5 equivalents), and MeOH, (~1 M) was heated at reflux for 4 hours and then cooled to 0°C. Sodium borohydride (4.8 equivalents) was added portionwise to the stirred reaction mixture during a period of 2 hours at *ca.* 10°C. The whole was stirred at room temperature for 4 hours. The insoluble materials were filtered off and then the filtrate was concentrated to dryness. The residue was dissolved in CH_2Cl_2, and the solution was washed successively with water (2x) and brine (1x). The organic extracts were collected and dried (Na_2SO_4). The solvent was evaporated to give the desired product as a colorless oil, which solidified on standing and was used in the next step without further purification. GC/MS : 134 (100%, M+-CH_2OH), R_t 11.57 minutes.

Step 2a and 2b: (2S,5R)-2-(chloromethyl)-5-methyl-4-benzylmorpholine and (2R,5R)-2-(chloromethyl)-5-methyl-4-benzylmorpholine



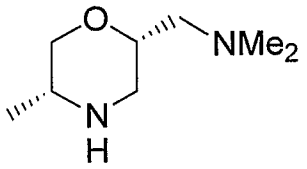
[0723] A mixture of (2R)-2-[benzylamino]propan-1-ol (1 equivalent) and epichlorohydrin (2 equivalents) was stirred at 40°C for 2.5 hours and concentrated at reduced pressure. The residue was cooled to 0° C and cold trifluoromethanesulfonic acid (3 equivalents) was added very slowly. The flask was equipped with a reflux condenser and the mixture was stirred at 160°C overnight. The reaction mixture was cooled to room temperature, and the black tar thus formed was dissolved in CH_2Cl_2 and transferred to an Erlenmeyer flask equipped with a magnetic stir bar. The solution was then cooled to 0°C, and ice water was slowly added. The dark biphasic mixture was made basic (pH= 12) with 30% NaOH solution. The two phases were separated, and the aqueous phase was further extracted with CH_2Cl_2. The organic layer was washed with water, treated with brine, dried (Na_2SO_4), and concentrated to afford a dark brown oil. The crude product mixture contained a mixture of (2S,5R)-2-(chloromethyl)-5-methyl-4-benzylmorpholine and (2R,5R)-2-(chloromethyl)-5-methyl-4-benzylmorpholine which were separated by chromatography on silicagel (EtOAc/Hexanes 1:20 to 1:8). *(2S,5R) isomer:* TLC (EtOAc/Hexanes 1: 8): R_f= 0.75; GC/MS: 239 (10%, M+), R_t 15.17 minutes; LC/MS *m/z* 240.0 (MH+), R_t 1.60 minutes. *(2R,5R) isomer:* TLC (EtOAc/Hexanes 1: 8): R_f 0.60; GC/MS: 239 (15%, M+), R_t 15.08 minutes; LC/MS *m/z* 240.0 (MH+), R_t 1.56 minutes.

Step 3a: (2S,5R)-2-[dimethylamino(methyl)]-5-methyl-4-benzylmorpholine



[0724] A mixture of (2S,5R)-2-(chloromethyl)-5-methyl-4-benzylmorpholine (1 equivalent) and dimethylamine in ethanol (33%, approx. 5.6 M, 5 equivalents) was heated at 150°C over 2 days in a glass pressure vessel. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was dissolved in 1 N HCl, and the solution was washed with CH_2Cl_2. The water phase was made basic with 30% NaOH solution (to pH=12) and extracted with CH_2Cl_2. The organic extracts were collected and dried (Na_2SO_4). Evaporation of the solvent under reduced pressure afforded (2S,5R)-2-[dimethylamino(methyl)]-5-methyl-4-benzylmorpholine as a brown oil which was used in the next step without purification. GC/MS: 247 (2%, M-H), 204 (55%, M-NMe_2), R_t 15.5 minutes; LC/MS *m/z* 249.2 (MH+), R_t 0.72 minutes.

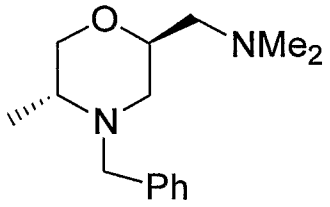
Step 4a: (2S,5R)-2-[dimethylamino(methyl)]-5-methylmorpholine



[0725] (2S,5R)-2-[Dimethylamino(methyl)]-5-methyl-4-benzylmorpholine (28 g, 113 mmol, 1 equivalent), was dissolved in EtOH (1 M), and the solution was transferred to a stainless steel high pressure vessel equipped with a pressure gauge. 10% Pd/C was added (2.8 g, 10 wt.%), and the vessel charged with H_2. The reaction mixture was stirred at 130°C and 200 psi of H_2 overnight. The reaction mixture was cooled to room temperature, filtered and evaporated. The desired amine was obtained in

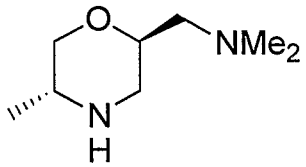
quantitative yield as a yellow oil. GC/MS : 128 (10%, M+-2xCH_3), 58 (100%, $NHCH_2CHO$), R_t 8.16 minutes.

Step 3b: (2R,5R)-2-[dimethylamino(methyl)]-5-methyl-4-benzylmorpholine



[0726] The title compound was obtained by treating (2R,5R)-2-(chloromethyl)-5-methyl-4-benzylmorpholine with dimethylamine in EtOH, as described above (Step 3a) diastereomer. GC/MS: 247 (2%, M-H), 204 (55%, M-NMe_2), R_t 15.40 minutes; LC/MS *m/z* 249.2 (MH+), R_t 0.79 minutes.

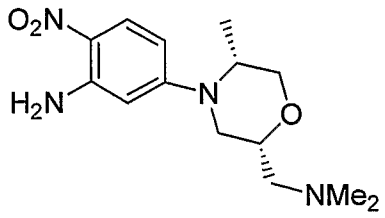
Step 4b: (2R,5R)-2-[dimethylamino(methyl)]-5-methylmorpholine



[0727] The title product was obtained by debenzylating (2R,5R)-2-[dimethylamino(methyl)]-5-methyl-4-benzylmorpholine as described earlier (Step 4a). GC/MS : 158 (1%, M+), 128 (3%, M+-2xCH_3), 58 (100%, $NHCH_2CHO$), R_t 7.64 minutes.

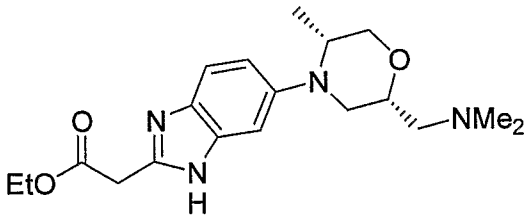
[0728] The same procedure can be employed to prepare (2S,5S)-2-[dimethylamino(methyl)]-5-methylmorpholine and (2R,5S)-2-[dimethylamino(methyl)]-5-methylmorpholine provided that (2S)-2-aminopropanol is used as starting material.

Step 5a: {[(2S,5R)-4-(3-amino-4-nitrophenyl)-5-methylmorpholin-2-yl]methyl}dimethylamine



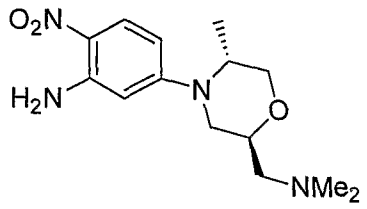
[0729] A mixture of 5-fluoro-2-nitroaniline (1.1 equivalents), [((2S,5R)-5-methylmorpholin-2-yl)methyl]dimethylamine (1 equivalent), triethylamine (3 equivalents), and NMP was heated at 140°C for 48 hours in a sealed high pressure vessel. The reaction mixture was cooled to 25°C and dissolved in CH_2Cl_2. The solution was washed with water (2x) and dried (Na_2SO_4). Purification *via* chromatography on silicagel (10% MeOH in dichloromethane), afforded the desired product as a dark yellow foam. LC/MS *m/z* 295.2 (MH+) R_t 1.86 minutes.

Step 6a: Ethyl 2-(6-{(2R,5R)-2-[(dimethylamino)methyl]-5-methylmorpholin-4-yl}benzimidazol-2-yl)acetate



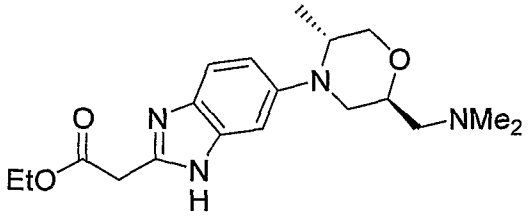
[0730] The title compound was synthesized using the general procedure for synthesis of benzimidazoles, but at room temperature for two days. Purification by column chromatography on silicagel afforded the purified product. LC/MS *m/z* 361.2 (MH+) R_t 1.27 minutes.

Step 5b: {[(2R,5R)-4-(3-amino-4-nitrophenyl)-5-methylmorpholin-2-yl]methyl}dimethylamine



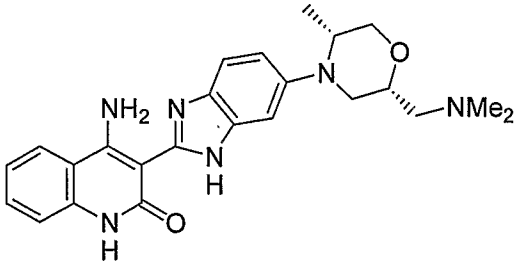
[0731] A mixture of 5-fluoro-2-nitroaniline (1.1 equivalents), [((2R,5R)-5-methylmorpholin-2-yl)methyl]dimethylamine (1 equivalent), triethylamine (3 equivalents), and NMP was heated at 140°C for 48 hours in a sealed high pressure vessel. The reaction mixture was cooled to 25°C and dissolved in CH_2Cl_2. The solution was washed with water (2x) and dried (Na_2SO_4). Purification *via* chromatography on silicagel (10% MeOH in dichloromethane), afforded the desired product as a dark yellow foam. LC/MS *m/z* 295.1 (MH+) R_t 1.85 minutes.

Step 6b: Ethyl 2-(6-{(2R,5R)-2-[(dimethylamino)methyl]-5-methylmorpholin-4-yl}benzimidazol-2-yl)acetate



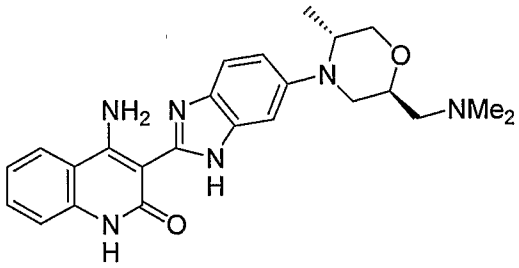
[0732] The title compound was prepared using the general procedure for synthesis of benzimidazoles, but at room temperature for two days. Purification by column chromatography on silicagel afforded the purified product. LC/MS *m/z* 361.2 (MH+) R_t 1.20 minutes.

Step 7a; 3-(6-{(2R,5R)-2-[(dimethylamino)methyl]-5-methylmorpholin-4-yl}benzimidazol-2-yl)-4-aminohydroquinolin-2-one



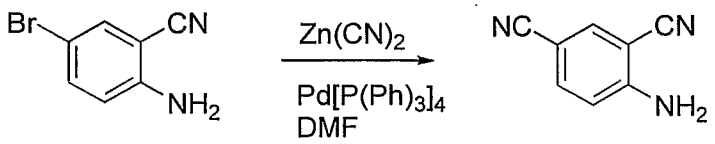
[0733] The title compound was synthesized according to Example 46 (LC/MS *m/z* 433.1 (MH+) R_t 1.58 minutes).

Step 7b: 3-(6-{(2S,5R)-2-[(dimethylamino)methyl]-5-methylmorpholin-4-yl}benzimidazol-2-yl)-4-aminohydroquinolin-2-one



[0734] The title compound was synthesized according to Example 46 (LC/MS *m/z* 433.1 (MH+) R_t 1.58 minutes).

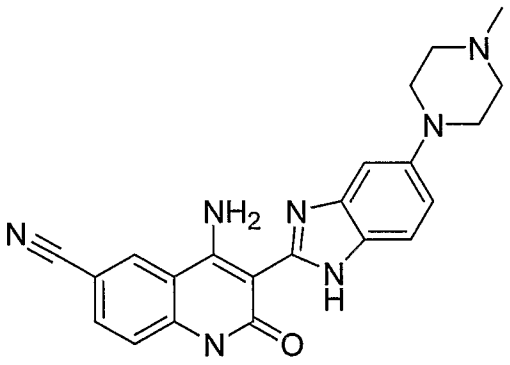
Example 84: Synthesis of 4-amino-3-[5-(4-methylpiperazinyl)benzimidazol-2-yl]-2-oxohydroquinoline-6-carbonitrile



[0735] Using a literature procedure described in the following literature reference which is herein incorporated by reference in its entirety for all purposes as if fully set forth herein, a dry round bottom flask was charged with 2-amino-5-bromo benzonitrile (1 equivalent) and zinc cyanide (2 equivalents), and DMF was added: *J. Med. Chem.* **2000**, *43*, 4063. Nitrogen was bubbled

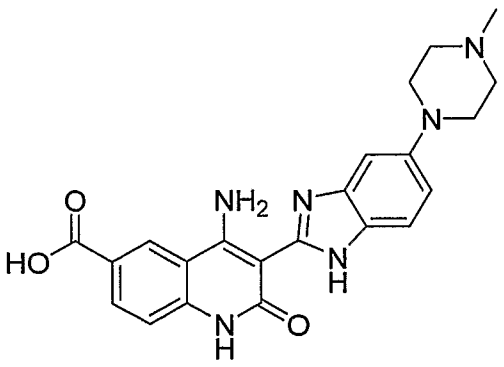
through the solution for 5 minutes, and $Pd[P(Ph)_3]_4$ was added in one portion. The reaction mixture was stirred at 90°C overnight. After cooling to room temperature, saturated $NaHCO_3$ was added, and the mixture was extracted with EtOAc. The organic extracts were collected and dried (Na_2SO_4). Evaporation of the solvent under reduced pressure and purification by column chromatography on silicagel (2% methanol in methylene chloride) afforded the desired 4-aminobenzene-1,3-dicarbonitrile as a white solid. GC/MS *m/z*: 143 (M+, 100%), R_t 14.7 minutes

4-amino-3-[5-(4-methylpiperazinyl)benzimidazol-2-yl]-2-oxohydroquinoline-6-carbonitrile



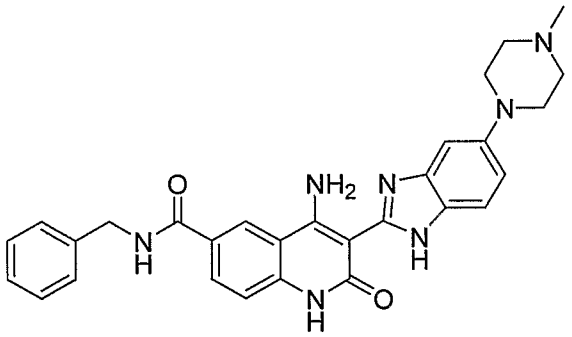
[0736] 4-Amino-isophthalonitrile and ethyl 2-[5-(4-methylpiperazinyl) benzimidazol-2-yl]acetate were reacted according to Example 46. LC/MS *m/z* 400.1 (MH+), R_t 1.54 minutes.

Example 85: Synthesis of 4-amino-3-[5-(4-methylpiperazinyl)benzimidazol-2-yl]-2-oxohydroquinoline-6-carboxylic acid



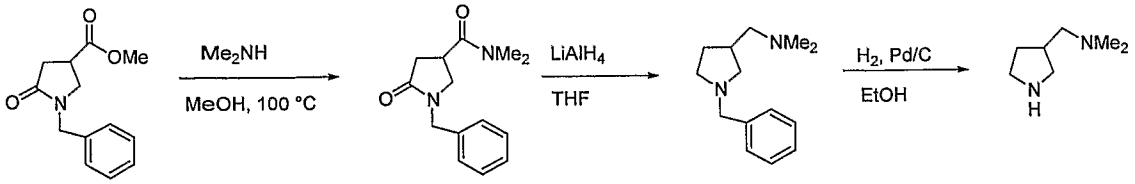
[0737] 4-amino-3-[5-(4-methylpiperazinyl)benzimidazol-2-yl]-2-oxohydroquinoline-6-carbonitrile (Example 84) derivative was dissolved in a 1:1 mixture of EtOH and 30% aqueous NaOH. The solution was heated to 100°C for 2 hours. The mixture was cooled to room temperature, concentrated, and neutralized with 1 N HCl until the product precipitated from solution. The solid was washed with water twice and dried to afford the desired product. The HCl salt was then obtained by lyophilization from a 1:1 mixture of CH_3CN and 1 N HCl (LC/MS *m/z* 331.3 (MH+) R_t 1.60 minutes).

Example 86: Synthesis of {4-amino-3-[5-(4-methylpiperazinyl)benzimidazol-2-yl]-2-oxo(6-hydroquinolyl)}-N-benzylcarboxamide



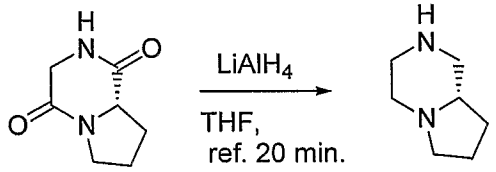
[0738] 4-amino-3-[5-(4-methylpiperazinyl)benzimidazol-2-yl]-2-oxohydroquinoline-6-carboxylic acid (Example 85), as the HCl salt (1 equivalent), was suspended in DMF. Et_3N (2 equivalents) and a primary or secondary amine (1.2 equivalents) were added, followed by EDC (1.2 equivalents) and HOAT (1.2 equivalents). The reaction mixture was stirred at room temperature for 2 days. Water was added, and the mixture was extracted with EtOAc. The residue was purified by prep. HPLC obtaining the desired product.

Example 87: Synthesis of 4-amino-3-(6-{3-[(dimethylamino)methyl]pyrrolidinyl}benzimidazol-2-yl)hydroquinolin-2-one



[0739] Dimethyl(pyrrolidin-3-ylmethyl)amine was synthesized from commercially available methyl-5-oxo-1-(phenylmethyl)pyrrolidine carboxylate following a procedure previously described in the literature (Domagala, J.M. U.S. Pat. No. 5,281,612, hereby incorporated by reference in its entirety for all purposes as if fully set forth herein). LC/MS *m/z* 265.1 (MH+), 1.62 minutes. Conversion to the concomitant 4-amino-3-(6-{3-[(dimethylamino)methyl] pyrrolidinyl}benzimidazol-2-yl)hydroquinolin-2-one was performed according to the procedure in Example 8 (LC/MS *m/z* 403.2 (MH+), R_t 1.64 minutes).

Example 88: Synthesis of 3-[6-((1S)-3,6-diazabicyclo[4.3.0]non-3-yl)benzimidazol-2-yl]-4-amino-5-fluorohydroquinolin-2-one



[0740] (6S)-1,4-diazabicyclo[4.3.0]nonane was synthesized as shown above by LAH (lithium aluminum hydride) reduction of commercially available Cyclo-Gly-Pro, employing the literature procedure set forth in the following reference which is herein incorporated by reference in its entirety for all purposes as if fully set forth herein: de Costa B. R. *et al. J. Med. Chem.*, **1993**, *36*, 2311. Conversion to the concomitant 3-[6-((1S)-3,6-diazabicyclo[4.3.0]non-3-yl)benzimidazol-2-yl]-4-amino-5-fluorohydroquinolin-2-one was performed according to the procedure in Example 8 (LC/MS *m/z* 419.1 (MH+), R_t 1.96 minutes).

Example 89: Synthesis of 4-amino-3-[6-(2,4-dimethylpiperazinyl)benzimidazol-2-yl]-5-fluorohydroquinolin-2-one

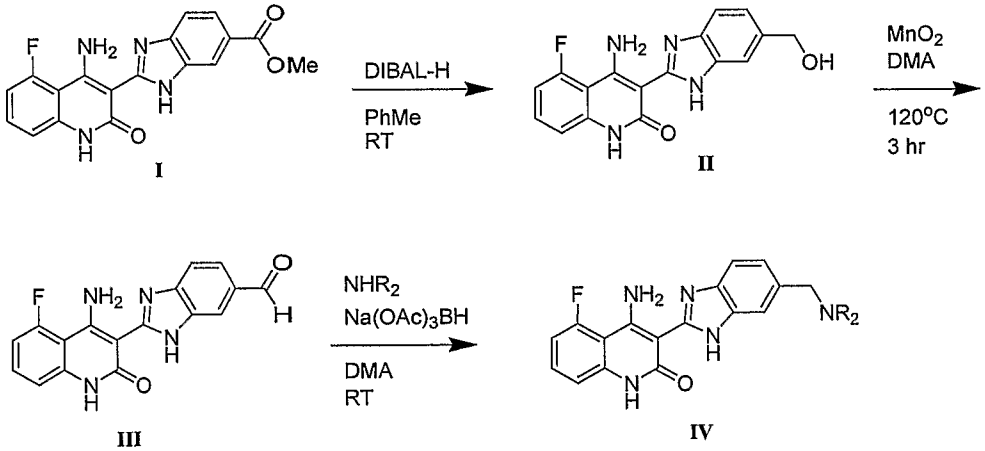
[0741] To a stirred solution of 2-methylpiperazine (2 equivalents) in dichloromethane at –10°C, was added di-*tert*-butyl dicarbonate (1 equivalent). The mixture was stirred for 10 minutes at –10°C and was then quenched with saturated aqueous $NaHCO_3$. The two phases were separated, and the organic layer was extracted with methylene chloride. The organic extracts were collected, dried (Na_2SO_4), and concentrated to give the desired *tert*-butyl 3-methylpiperazine-carboxylate (LC/MS *m/z* 201.0 (MH +), R_t 1.67 minutes). Conversion to *tert*-butyl 4-[2-(4-amino-5-fluoro-2-oxo(3-hydroquinolyl))benzimidazol-6-yl]-3-methylpiperazinecarboxylate was performed according to the procedure in Example 8 (LC/MS *m/z* 493.3 (MH+), R_t 2.45 minutes). Subsequent removal of the Boc group was preformed by bubbling HCl gas into a MeOH solution until saturated (LC/MS *m/z* 393.2 (MH +), R_t 1.95 minutes). The free amine was subsequently reacted with paraformaldehyde (5 equivalents) in MeOH:AcOH (5:1) and $NaCNBH_4$ (4 equivalents) over molecular sieves at 80°C. After 10 hours, the mixture was cooled, filtered, and concentrated. The residue was dissolved in CH_2Cl_2, washed with saturated $NaHCO_3$, and dried with Na_2SO_4 to give the desired 4-amino-3-[6-(2,4-dimethylpiperazinyl)benzimidazol-2-yl]-5-fluorohydroquinolin-2-one (LC/MS *m/z* 407.3 (MH +), R_t 2.03 minutes). Further purification was performed *via* reverse phase prep. HPLC.

Example 90: 4-amino-3-[6-(3,4-dimethylpiperazinyl)benzimidazol-2-yl]hydroquinolin-2-one

[0742] *tert*-Butyl-3-methylpiperazine carboxylate (see Example 89; 1 equivalent) and paraformaldehyde (5 equivalents) were dissolved in a mixture of MeOH and AcOH (5:1) on molecular sieves. $NaCNBH_3$ (4 equivalents) was added to the suspension at 25°C. The slurry was subsequently heated to 80°C. After 10 hours, the mixture was cooled, filtered, and concentrated. The residue was dissolved in dichloromethane and washed with saturated

aqueous $NaHCO_3$. The organic solution was dried (Na_2SO_4), and concentrated. The *tert*-butoxycarbonyl group was removed by treating the crude amine with saturated HCl in MeOH, at room temperature for 30 minutes. The mixture was then concentrated and excess HCl was removed *in-vacuo*. The desired 1,2-dimethylpiperazine was obtained as the bis HCl salt (LC/MS *m/z* 115.0 (MH+), R_t 0.33 minutes). Concomitant conversion to *tert*-butyl 4-[2-(4-amino-2-oxo(3-hydroquinolyl))benzimidazol-6-yl]-3-methylpiperazinecarboxylate was performed according to the procedure in Example 8 (LC/MS *m/z* 389.2 (MH+), R_t 1.84 minutes).

Example 91: General Synthesis of 4-amino-5-fluoro-3-(6-aminomethyl-1H-benzimidazol-2-yl)quinolin-2(1H)-ones



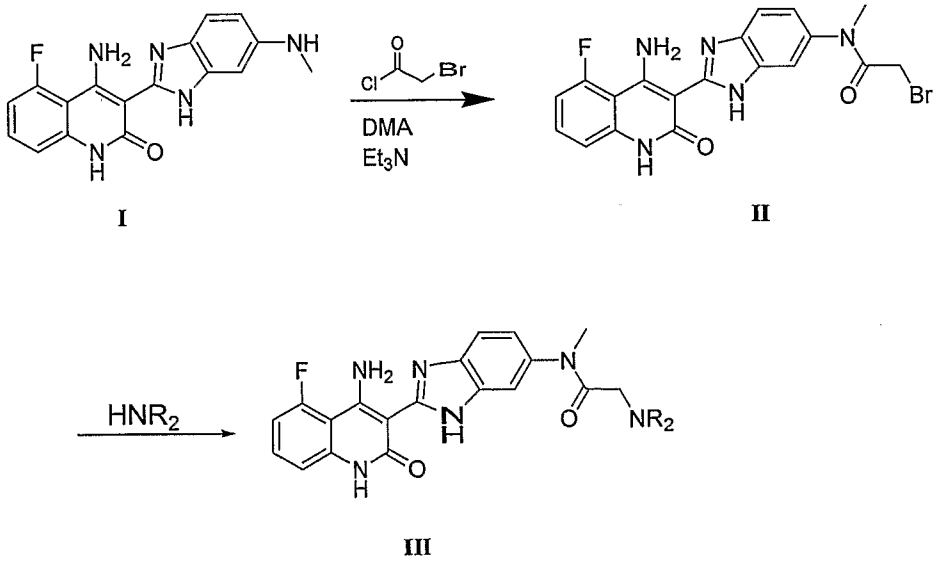
[0743] Methyl ester I was suspended as a fine powder in Toluene. To this room temperature suspension was added DIBAL-H (10 equivalents, 1 M in toluene) via an addition funnel at a rate in which gas evolution was steady and controllable. After complete addition, the homogeneous solution was allowed to stir for 10 hours. After this time, NaF (40 equivalents) and water (10 equivalents) were added. The resulting mixture was stirred at room temperature for 4 hours during which time a solid precipitate formed. This solid was collected and heated in dimethyl acetamide (DMA) at 120°C for 2 hours after which time the remaining solid was filtered away and resulting solution concentrated to a thick oil. The resulting oil was treated with water

and the resulting solid collected and dried to provide compound II as a yellow solid. MH+ = 325.1.

[0744] Alcohol II was dissolved in DMA at room temperature and treated with MnO_2 (15 equivalents). The reaction was heated at 120°C for 3 hours and the mixture was filtered hot through a pad of Celite. The resulting solution was concentrated in vacuo to provide a yellow solid identified as aldehyde III MH+ = 323.1.

[0745] Aldehyde III was dissolved in DMA and treated with an appropriate amine (2.0 equivalent) followed by sodium triacetoxyborohydride (2.5 equivalents). The reaction stirred at room temperature for 12 hours and was concentrated to provide a thick oil. This oil was purified by reverse phase HPLC to yield the desired compounds.

Example 92: General Synthesis of 4-amino-5-fluoro-3-(6-amido-1H-benzimidazol-2-yl)quinolin-2(1H)-ones



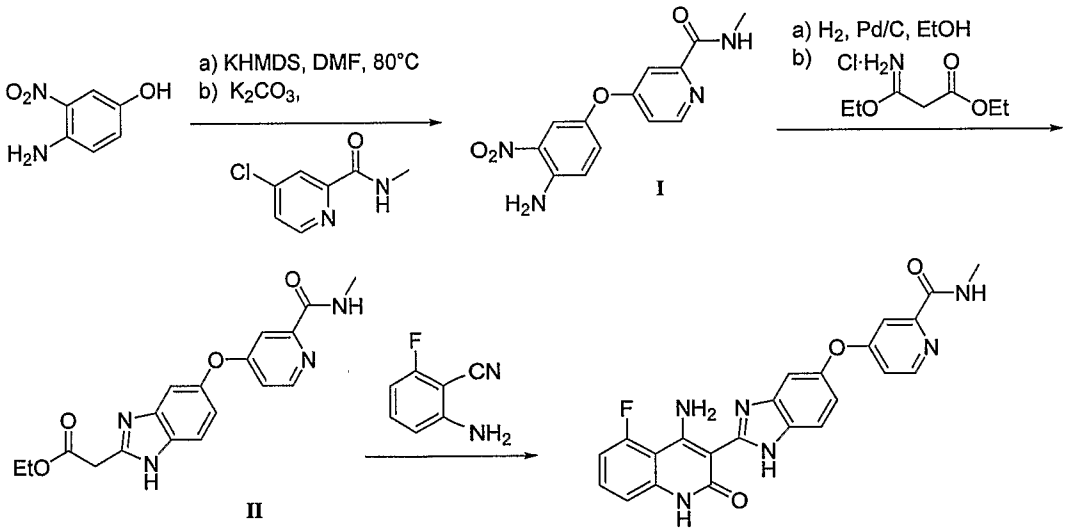
I II III

[0746] Amine I was dissolved in DMA and treated sequentially with bromoacetyl chloride (1.5 equivalents) and triethylamine (5 equivalents) at room temperature. The reaction was stirred for 2 hours and was then poured

into water. The resulting solid was collected and dried to give the desired bromide **II**. MH+ = 444.

[0747] Bromide **II** was dissolved in DMA and the appropriate amine (10 equivalents) was added at room temperature. The reaction was stirred for 12 hours and was then concentrated to a dark oil which was purified by reverse phase HPLC to provide the desired product.

Example 93: Synthesis of 4-{[2-(4-amino-5-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)-1H-benzimidazol-6-yl]oxy}-N-methylpyridine-2-carboxamide

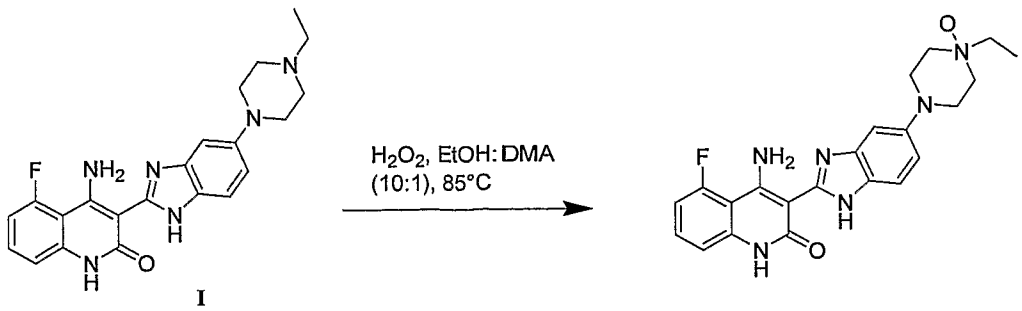


[0748] 4-Amino-3-nitrophenol (1.0 equivalent) and potassium bis(trimethylsilyl)amide (2.0 equivalents) were stirred in DMF for 2 hours. To this mixture was added (4-chloro(2-pyridyl))-N-methoxycarboxamide (1.0 equivalent) and K_2CO_3 (1.2 equivalents). The mixture was heated at 90°C overnight. The solvent was then removed and the mixture was diluted with H_2O. The aqueous layer was extracted with EtOAc. The organic layer was washed with and brine (2 x), dried over Na_2SO_4, filtered and concentrated to give a brown solid. The crude material was purified by column chromatography (50% EtOAc/hexane with 2% Et_3N to give compound **I**. MH+ = 289.2.

[0749] Compound **I** (1.0 equivalent) and 10% Pd/C (0.1 equivalents) were suspended in anhydrous EtOH at room temperature. The reaction flask was evacuated and subsequently filled with H_2. The resulting mixture was allowed to stir under a hydrogen atmosphere for 2 days. Ethyl 3-ethoxy-3-iminopropanoate hydrochloride (2.0 equivalents) was then added and the resulting mixture was heated at reflux overnight. After this time, the solution was filtered through a plug of Celite, concentrated and dissolved in CH_2Cl_2. The organic layer was washed with NH_4OH(aq, conc.), H_2O (3 x) and brine and then dried over Na_2SO_4, filtered and concentrated to yield a brown gum which was purified by silica gel chromatography (EtOAc to 10% MeOH in CH_2Cl_2 with 2% Et_3N) to provide the product **II** as a tan solid. MH+ = 287.1.

[0750] KHMDS (4.2 equivalents) was added to compound **II** (1.4 equivalents) and 2-amino-6-fluorobenzenecarbonitrile (1.0 equivalent) in DMF at room temperature. The reaction was heated at 50°C overnight. The resulting mixture was poured into EtOAc and extracted with H_2O (3 x). The organic layer was washed brine, dried over Na_2SO_4, filtered and concentrated in vacuo to yield a brown solid. The crude material was sonicated in 5% acetone/94.5% Et2O/0.5% MeOH to give the desired product as a tan solid. The solid was further purified by reverse phase HPLC. MH+ = 445.2.

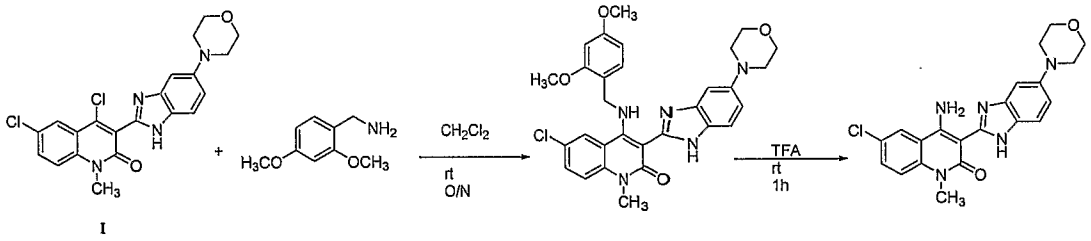
Example 94: Synthesis of 4-amino-3-[5-(4-ethyl-4-oxidopiperazin-1-yl)-1H-benzimidazol-2-yl]-5-fluoroquinolin-2(1H)-one



[0751] Piperazine **I** was suspended in EtOH:DMA (10:1). Hydrogen peroxide (10 equivalents) was added, and the reaction was heated to 85°C

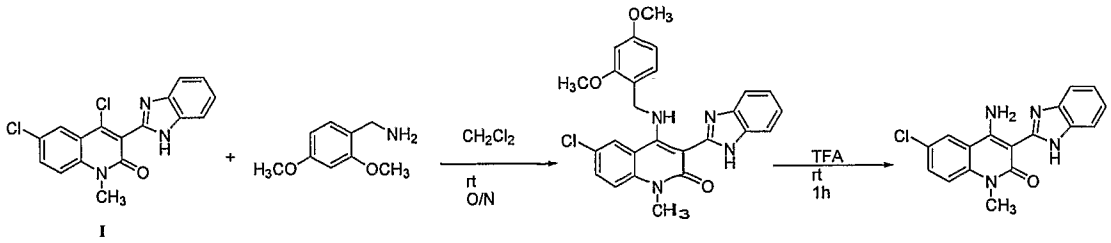
during which time a homogeneous solution formed. After 1 hour, the reaction was complete by LC/MS. The reaction was stirred at room temperature overnight during which a precipitate formed. The solid was filtered and washed with EtOH and then Et_2O to give 4-amino-3-[5-(4-ethyl-4-oxidopiperazin-1-yl)-1H-benzimidazol-2-yl]-5-fluoroquinolin-2(1H)-one. MH+ = 423.3.

Example 95: Synthesis of 4-amino-6-chloro-1-methyl-3-(5-morpholin-4-yl-1H-benzimidazol-2-yl)quinolin-2(1H)-one



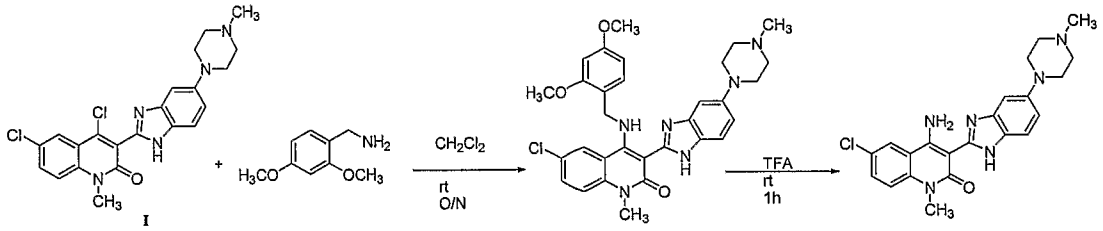
[0752] Quinolinone I (10 mg, 1 equivalent) was reacted with 2,4-dimethoxy benzylamine (10 µL, 2.7 equivalents) in 1 mL of dichloromethane at room temperature overnight. The solvent was later evaporated and the product taken up in ethyl acetate. The ethyl acetate layer was washed with water, saturated sodium bicarbonate, saturated sodium chloride and then dried. The benzylated material was treated with 1 mL of 5% trifluoroacetic acid in dichloromethane for 1 hour and evaporated. The final product was purified by HPLC and resulted in 5 mg of the amino quinolinone product as the trifluoroacetic acid salt. MH+ = 410.2.

Example 96: Synthesis of 4-amino-3-(1H-benzimidazol-2-yl)-6-chloro-1-methylquinolin-2(1H)-one



[0753] Quinolinone I (20 mg, 1 equivalent) was reacted with 2,4-dimethoxy benzylamine (20 µL, 2 equivalents) in 1 mL of dichloromethane at room temperature overnight. The solvent was later evaporated and the product taken up in ethyl acetate. The ethyl acetate layer was washed with water, saturated sodium bicarbonate, saturated sodium chloride and then dried. The benzylated material was treated with 1 mL of 5% trifluoroacetic acid in dichloromethane for 1 hour and evaporated. The final product was purified by HPLC and resulted in 17.2 mg of the amino quinolinone as the trifluoroacetic acid salt. MH+ = 325.1.

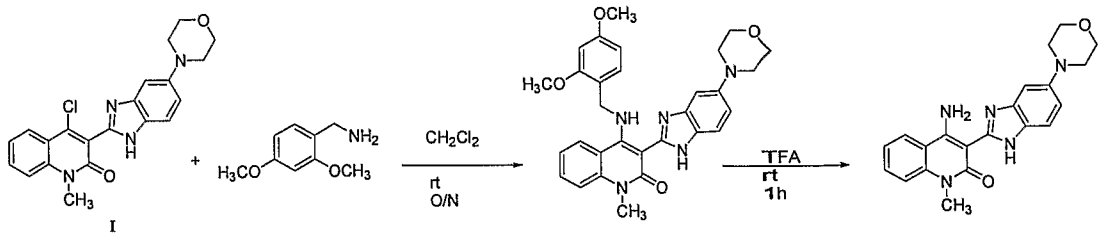
Example 97: Synthesis of 4-amino-6-chloro-1-methyl-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one



I

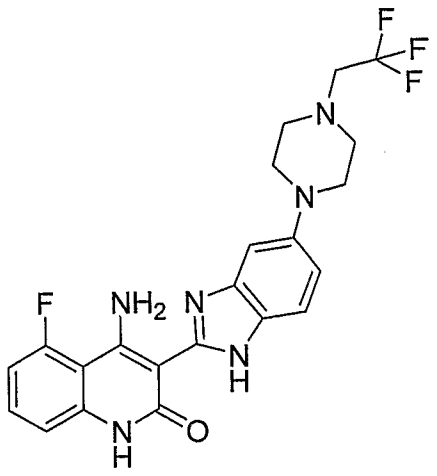
[0754] Quinolinone I (20 mg, 1 equivalent) was reacted with 2,4-dimethoxy benzylamine (20 µL, 2 equivalents) in 1 mL of dichloromethane at room temperature overnight. The solvent was later evaporated and the product taken up in ethyl acetate. The ethyl acetate layer was washed with water, saturated sodium bicarbonate, saturated sodium chloride and then dried. The benzylated material was treated with 1 mL of 5% trifluoroacetic acid in dichloromethane for 1 hour and evaporated. The final product was purified by HPLC and resulted in 11.5 mg of the amino quinolinone as the trifluoroacetic acid salt. MH+ = 423.1.

Example 98: Synthesis of 4-amino-1-methyl-3-(5-morpholin-4-yl-1H-benzimidazol-2-yl)quinolin-2(1H)-one



[0755] The quinolinone starting material I (20 mg, 1 equivalent) was reacted with 2,4-dimethoxy benzylamine (20 µL, 2 equivalents) in 1 mL of dichloromethane at room temperature overnight. The solvent was later evaporated and the product taken up in ethyl acetate. The ethyl acetate layer was washed with water, saturated sodium bicarbonate, saturated sodium chloride and then dried. The benzylated material was treated with 1 mL of 5% trifluoroacetic acid in dichloromethane for 1 hour and evaporated. The final product was purified by HPLC and resulted in 16.6 mg of the amino quinolinone as the trifluoroacetic acid salt. MH+=376.3.

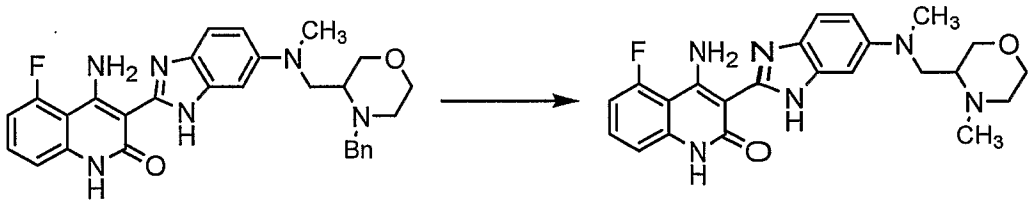
Example 99: Synthesis of 4-amino-5-fluoro-3-{5-[4-(2,2,2-trifluoroethyl)piperazin-1-yl]-1H-benzimidazol-2-yl}quinolin-2(1H)-one



[0756] 4-Amino-5-fluoro-3-(6-piperazin-1-yl-1H-benzoimidazol-2-yl)-1H-quinolin-2-one was taken up in ethyl trifluoroacetate and N,N-

dimethylacetamide (DMA). The resulting solution was heated at 130°C in a sealed tube for 30 minutes. The reaction was cooled to room temperature and quenched by addition of saturated aqueous sodium bicarbonate followed by pouring the mixture into water. The resulting solid was collected by filtration and washed with diethyl ether to afford 4-amino-5-fluoro-3-{6-[4-(2,2,2-trifluoro-acetyl)-piperazin-1-yl]-1H-benzoimidazol-2-yl}-1H-quinolin-2-one (R_t 2.63 minutes, MH+ = 457.1), which was immediately taken up in THF. Borane-THF complex (3.3 equivalents) was added and the reaction was stirred at room temperature overnight. After quenching the excess borane with water, the mixture was extracted into ethyl acetate, dried over magnesium sulfate, filtered and concentrated to a brown solid which was purified by reverse phase HPLC to yield the desired compound. MH+ = 461.1.

Example 100: Synthesis of 4-amino-5-fluoro-3-(6-{methyl[(4-methylmorpholin-3-yl)methyl]amino}-1H-benzimidazol-2-yl)quinolin-2(1H)-one

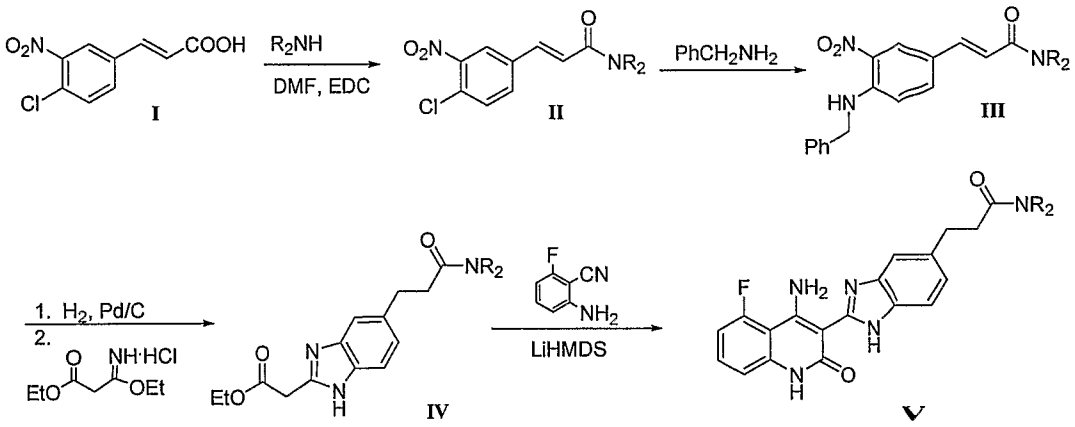


I

[0757] Quinolinone I was synthesized from commercially available 2-chloromethyl-4-benzyl morpholine, methylamine, 4-chloro-2-nitroaniline, and 2-amino-6-fluorobenzonitrile following the general procedure of Example 49. (2-(methylamino)methyl-4-benzyl morpholine was dissolved in an 8 M solution of NH_2Me in EtOH and heated in a glass bomb at 110°C overnight to form the product 2-(methylamino)methyl-4-benzyl morpholine following removal of the solvent). Compound I (1.0 equivalent) and 10% Pd/C (0.1 equivalents) were suspended in 1:1 ethanol and 1 N aqueous HCl at room temperature. The reaction flask was evacuated and subsequently filled with H_2. The resulting

mixture was stirred under a hydrogen atmosphere overnight, filtered through Celite, and concentrated under vacuum. The solution was made basic with 30% aq. KOH and the product was extracted with EtOAc. The combined organic layers were concentrated and resuspended in CH_2Cl_2:MeOH:AcOH (2:2:1). Paraformaldehyde (1.2 equivalents) and BH_3 .pyridine (3 equivalents, 8 M) was then added and the mixture was stirred overnight at room temperature. The solvent was removed in vacuo and washed with water. The aqueous layer was extracted with EtOAc (3x), and the combined organic layers were concentrated and purified by silica gel chromatography (10% MeOH/CH_2Cl_2) to afford the desired product. MH+ = 437.4.

Example 101: General synthesis of 4-amino-3-1H-benzimidazol-2-yl-5-fluoroquinolin-2(1H)-one propionamides



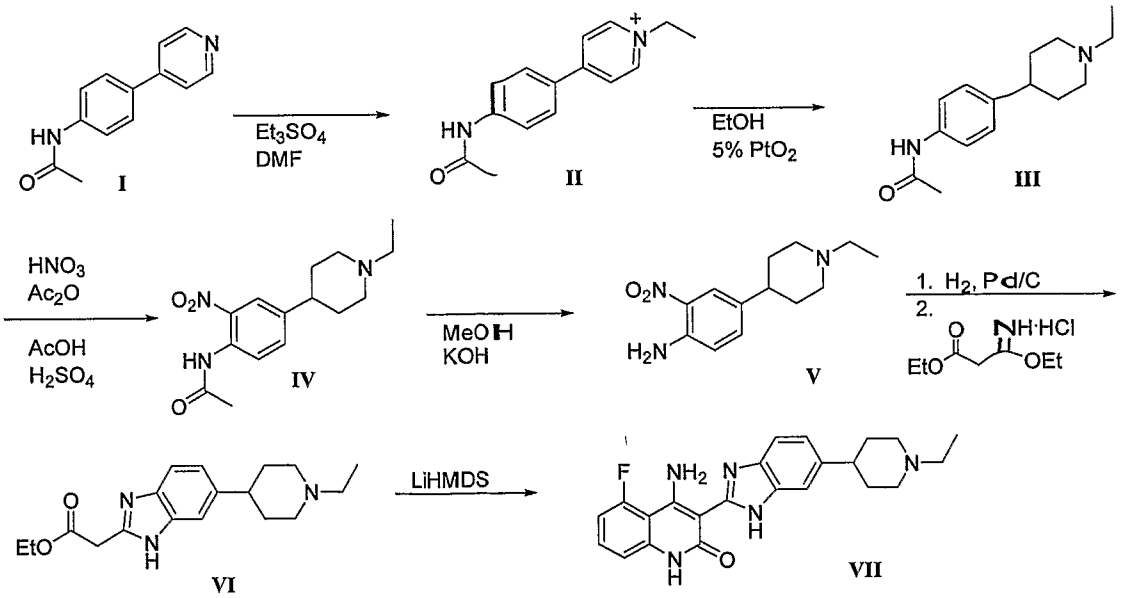
[0758] To a DMF solution of compound **I** (1 equivalent) in DMF was added an amine (1.1 equivalents) and EDC (1.1 equivalents). The solution was left to stir for 2 hours at room temperature. The reaction mixture was quenched with water and filtered to give the desired product II.

[0759] In a microwave tube, compound **II** (1 equivalent) was suspended in benzyl amine and heated in a microwave at 150°C for five minutes. The resulting crude product **III** was sonicated in ether and filtered.

[0760] To a high pressure stainless steel vessel charged with compound **III** (1 equivalent) in a solution of EtOH was added 10% Pd/C

followed by 120 psi H_2. The mixture was left at 100°C for one day followed by addition of ethyl 3-ethoxy-3-iminopropanoate hydrochloride (2.5 equivalents). The reaction was left at 80°C under nitrogen for one additional day. The palladium was then filtered off through a pad of Celite, and the resulting EtOH mixture was evaporated in vacuo. The product was then taken up in a generous amount of CH_2Cl_2, made basic, filtered over a pad of sodium sulfate, and concentrated in vacuo. Purification by silica gel chromatography (10%MeOH:CH_2Cl_2) gave compound **IV**, which was coupled with 2-amino-6-fluorobenzenecarbonitrile following the general procedure of Example 49 to give propionamide **V**.

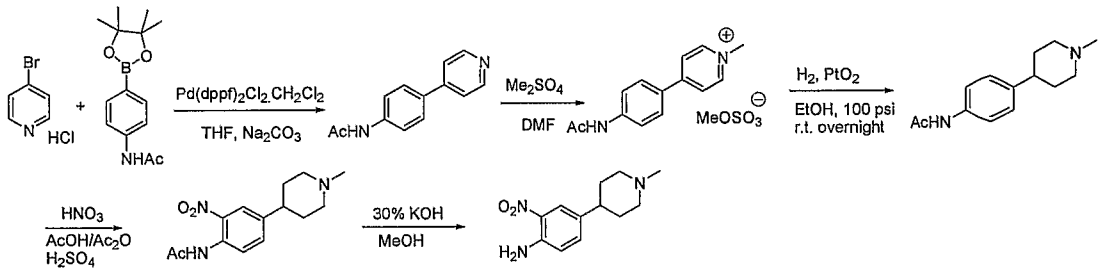
Example 102: Synthesis of 4-amino-3-[5-(1-ethylpiperidin-4-yl)-1H-benzimidazol-2-yl]-5-fluoroquinolin-2(1H)-one



[0761] Compound **I** (1 equivalent) was dissolved in DMF and Et_3SO_4 (4 equivalents) was added slowly at 0°C. The solution was left to stir overnight at room temperature. The resulting mixture was poured into Et_2O while stirring. The solid, compound **II**, was filtered off, washed once with EtOH, and resuspended in EtOH. To this mixture was added 5% PtO_2, and the resulting mixture was left under 1 atmosphere of H_2 overnight. The PtO_2 was filtered off using a pad of Celite to afford the desired product as an orange solid **III**

that was used without further purification. Compound **III** was nitrated and used in the next step without further purification. To a MeOH solution of compound **IV** was added excess 30% KOH to give a bright yellow solution that was allowed to stir overnight. MeOH was removed in vacuo and the residue was taken up in CH_2Cl_2 and extracted with water to give compound **V** that was then converted to desired product **VII** following the procedure described in Example 49. The product was purified by sonicating in ether:acetone:ethanol (10:1:1) and then refluxing in acetonitrile overnight. MH+ = 406.3.

Example 103: Synthesis of 4-(1-methylpiperidin-4-yl)-2-nitroaniline



Step 1: N-(4-(4-pyridyl)phenyl)acetamide

[0762] A round bottom flask was charged with a 2 N Na_2CO_3 solution (4 equivalents) and THF and the mixture was sparged with N_2 through a dispersion tube. 4-Bromopyridine hydrochloride (1 equivalent) and N-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]acetamide (1.2 equivalents) were subsequently added, followed by $Pd(dppf)_2Cl_2$ (2.5 mol %). The reaction mixture was refluxed overnight, cooled to room temperature and diluted with EtOAc. The two phases were separated and the organic phase was washed with a 2 N Na_2CO_3 solution, brine, and dried (Na_2SO_4). Evaporation of the solvent under reduced pressure and purification by silica gel chromatography afforded the desired product as a white solid. MH+ = 213.1.

Step 2: N-[4-(1-methyl-4-piperidyl)phenyl]acetamide

[0763] N-(4-(4-pyridyl)phenyl)acetamide (1.0 equivalent) was dissolved in DMF and dimethyl sulfate (1.5 equivalent) was added dropwise. After an initial induction period a solid crashed out. The reaction mixture was stirred for 6 hour at room temperature and then poured into diethyl ether. After a sticky solid crashed out, the ether was decanted and the residue was triturated with EtOH, filtered, and washed with EtOH to give a light yellow solid. The pyridinium salt thus obtained (MH+ = 227.3) was suspended in EtOH and PtO_2 (5 mol%) was added, and the mixture was hydrogenated at atmospheric pressure for 3 days. After the catalyst was filtered off over a pad of Celite, the filter cake was washed repeatedly with water and the resulting EtOH/water mixture was concentrated under reduced pressure. The solution was made basic with 30% NaOH and extracted with CH_2Cl_2. The organic extracts were collected and dried (Na_2SO_4). Evaporation of the solvent under reduced pressure afforded the desired product as a white solid. MH+ = 233.1.

Step 3: N-[4-(1-methyl(4-piperidyl))-2-nitrophenyl]acetamide

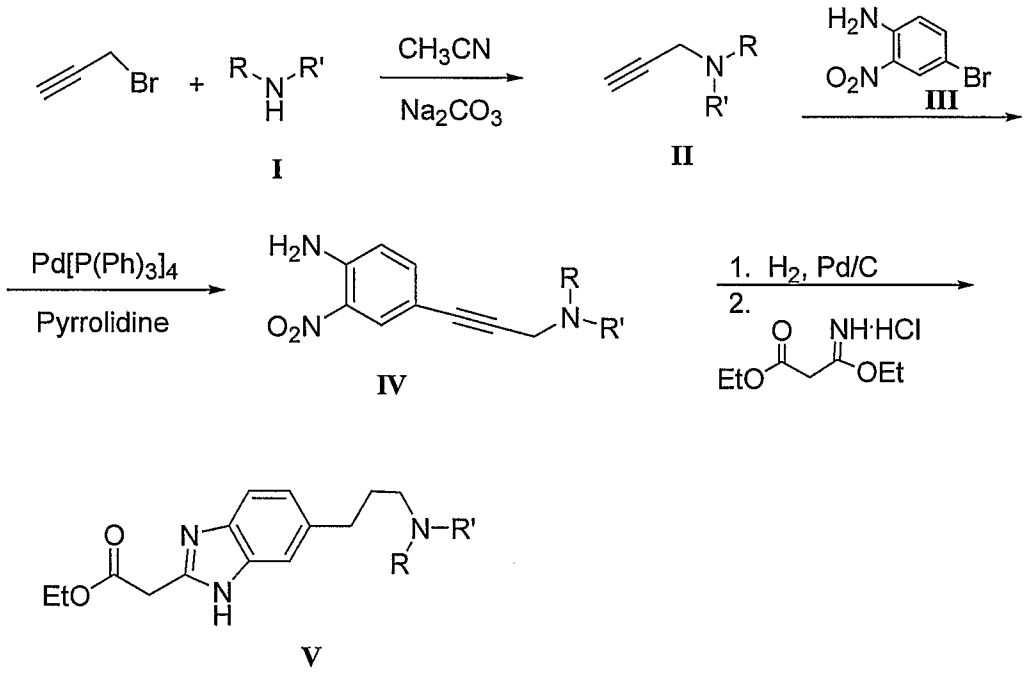
[0764] A round bottom flask was charged with acetic anhydride and acetic acid, and the mixture was cooled down to –10°C with and ice/ salt bath. HNO_3 (2 equivalents) was added, followed by 2 drops of H_2SO_4. N-[4-(1-Methyl-4-piperidyl)phenyl]acetamide (1 equivalent) in acetic acid (in such an amount as to obtain a final 1:1 ratio between AcO_2 and AcOH) was added dropwise to the cold solution. The reaction mixture was allowed to warm to room temperature and stirred for 6 hours. The reaction was then poured into diethyl ether. A sticky solid crashed out, the ether was decanted, and the residue was dissolved in water. The water solution was made basic with 30% NaOH and an orange solid precipitated. The solid was filtered off and dried to afford the desired product. MH+ = 278.3.

Step 4: 4-(1-methylpiperidin-4-yl)-2-nitroaniline

[0765] N-[4-(1-methyl(4-piperidyl))-2-nitrophenyl]acetamide (1 equivalent) was dissolved in methanol and 30% KOH (2.5 equivalents) was added dropwise with vigorous stirring. The reaction mixture was stirred at

room temperature for 3 hours and then concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 and washed with water (2x) and brine (1x). The organic solution was dried (Na_2SO_4) and evaporated to obtain the desired product as an orange brown solid. MH+ = 236.2.

Example 104: General synthesis of 5-aminopropyl benzimidazoles

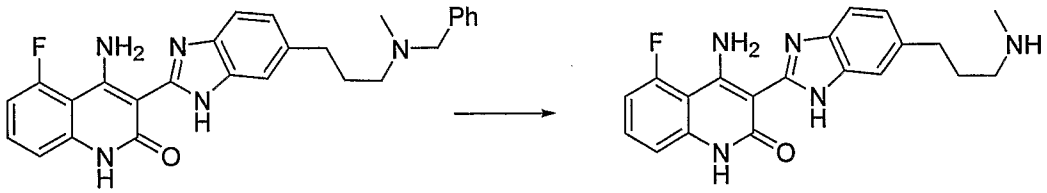


[0766] Propargyl amines may be obtained commercially or generally prepared as shown (see Banholzer, R. et. al. U.S. Patent No. 4,699,910 which is herein incorporated in its entirety and for all purposes as is fully set forth herein). A mixture of propargyl bromide (70% in toluene, 1.1 equivalents), the amine 1 (1 equivalents), Na_2CO_3 (2.5 equivalents) in acetonitrile, (about 0.2 M) was refluxed overnight. The reaction mixture was cooled to room temperature and the solid was filtered off. The solution was evaporated under reduced pressure, and the residue was dissolved in EtOAc (or CH_2Cl_2) and washed with water. The organic solution was dried (Na_2SO_4). The solvent was evaporated under reduced pressure to give the desired propargyl amine **II** as a brown oil which was used in the next step without further purification.

[0767] Aryl alkynes may be made by following a modified procedure (Jon L. Wright et al. J. Med. Chem. 2000, 43, 3408-3419 which is hereby incorporated by reference in its entirety and for all purposes as if fully set forth herein). A round bottom flask was charged with THF and the solvent was sparged with nitrogen for 10 minutes using a dispersion tube. The propargylamine **II** (1 equivalent), pyrrolidine (2 equivalents) and 2-nitro-4-bromoaniline **III** (1 equivalent) were added, while still bubbling nitrogen through the solution. $Pd[P(Ph)_3]_4$ (2.5 mol%) was added last, and the sparging was then discontinued. The flask was equipped with a reflux condenser, and the reaction mixture was refluxed overnight under nitrogen and then cooled down room temperature. The THF was evaporated and the desired product **IV** was obtained by silica gel chromatography of the crude mixture (usually EtOAc/hexane 1:1).

[0768] Exposure of **IV** to catalytic hydrogenation conditions typically gave the fully reduced alkane, which was then converted to ester **V** as described in Example 49.

Example 105: Synthesis of 4-amino-5-fluoro-3-{5-[3-(methylamino)propyl]-1H-benzimidazol-2-yl}quinolin-2(1H)-one

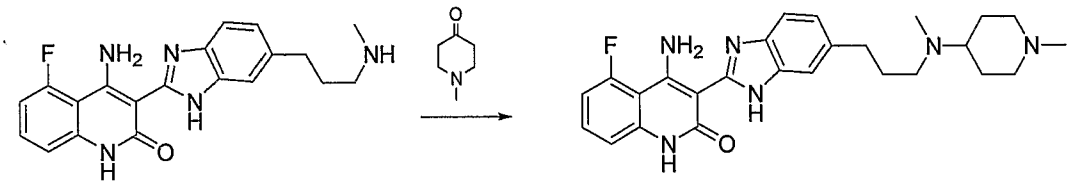


I

[0769] Benzyl quninolinone I (1.0 equivalent) was suspended in EtOH and 1 N HCl (1.1 equivalent) was added providing a clear solution. 10% Pd/C (12 wt %) was added, and the reaction mixture was hydrogenated in a steel bomb at 200 psi of H_2 and 60°C for two days. The reaction mixture was cooled to room temperature, filtered, and the solvent was evaporated under

reduced pressure. The residue was purified by reverse phase preparative HPLC to give the desired product. MH+ = 366.1.

Example 106: Synthesis of 4-amino-5-fluoro-3-(5-{3-[methyl(1-methylpiperidin-4-yl)amino]propyl}-1H-benzimidazol-2-yl)quinolin-2(1H)-one



I

[0770] To a MeOH solution of quinolinone **I** (1.0 equivalent) was added 1-methyl-4-piperidinone (1.5 equivalents) followed by $NaCNBH_3$ (3 equivalents). The reaction mixture was then refluxed overnight and cooled to room temperature. 15% NaOH was added, and the reaction mixture was stirred for 1 hour at room temperature. The solvent was concentrated under reduced pressure and the residue was dissolved in DMSO and purified by reverse phase preparative HPLC to give the desired product. MH+ = 463.2.

Examples 107-211

[0771] Each of the compounds in the following table was synthesized following procedures described in the Examples and Methods described above. Starting materials used to synthesize the following compounds are readily recognizable by one skilled in the art in light of the previous disclosure.

Table 1. Table of Examples 107-211.

Example	Name	LC/MS m/z (MH+)
107	4-amino-3-{5-[(3S)-3-(dimethylamino)pyrrolidin-1-yl]-1H-benzimidazol-2-yl}quinolin-2(1H)-one	389.4
108	4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-chloroquinolin-2(1H)-one	420
109	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-chloroquinolin-2(1H)-one	420

110	3-(1H-benzimidazol-2-yl)-4-[(3R)-3-(dimethylamino)pyrrolidin-1-yl]quinolin-2(1H)-one	374.2
111	3-(1H-benzimidazol-2-yl)-6-chloro-4-[(3R)-3-(dimethylamino)pyrrolidin-1-yl]quinolin-2(1H)-one	408.1
112	4-amino-3-[5-(4-ethylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1-methylquinolin-2(1H)-one	403.2
113	4-amino-3-(6-piperazin-1-yl-1H-benzimidazol-2-yl)quinolin-2(1H)-one	361.2
114	4-amino-3-[6-(pyridin-4-ylmethyl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one	368.2
115	4-amino-3-{5-[(3R,5S)-3,5-dimethylpiperazin-1-yl]-1H-benzimidazol-2-yl}quinolin-2(1H)-one	389.4
116	4-amino-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one	375.2
117	4-amino-3-(6-methyl-5-morpholin-4-yl-1H-benzimidazol-2-yl)quinolin-2(1H)-one	376
118	4-amino-3-{5-[(1-methylpiperidin-3-yl)oxy]-1H-benzimidazol-2-yl}quinolin-2(1H)-one	390.1
119	4-amino-3-{5-[(2R,6S)-2,6-dimethylmorpholin-4-yl]-6-fluoro-1H-benzimidazol-2-yl}quinolin-2(1H)-one	408.2
120	4-amino-3-{5-[(1-methylpyrrolidin-3-yl)oxy]-1H-benzimidazol-2-yl}quinolin-2(1H)-one	376.2
121	4-amino-3-[5-(4-methyl-1,4-diazepan-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one	389.2
122	4-amino-3-{5-[(3R)-3-(dimethylamino)pyrrolidin-1-yl]-1H-benzimidazol-2-yl}quinolin-2(1H)-one	389.2
123	4-amino-6-chloro-3-{5-[(3R)-3-(dimethylamino)pyrrolidin-1-yl]-1H-benzimidazol-2-yl}quinolin-2(1H)-one	423
124	ethyl {4-[2-(4-amino-2-oxo-1,2-dihydroquinolin-3-yl)-1H-benzimidazol-6-yl]piperazin-1-yl}acetate	447.2
125	4-amino-3-{6-[methyl(1-methylpiperidin-4-yl)amino]-1H-benzimidazol-2-yl}quinolin-2(1H)-one	403.1
126	3-[6-(4-acetylpiperazin-1-yl)-1H-benzimidazol-2-yl]-4-aminoquinolin-2(1H)-one	403.3
127	4-amino-3-[6-(1,4'-bipiperidin-1'-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one	443.3
128	2-(4-amino-2-oxo-1,2-dihydroquinolin-3-yl)-1H-benzimidazole-6-carboxylic acid	321.2
129	4-amino-5-(methyloxy)-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one	405.3
130	4-amino-3-{6-[4-(1-methylethyl)piperazin-1-yl]-1H-benzimidazol-2-yl}quinolin-2(1H)-one	403.3
131	{4-[2-(4-amino-2-oxo-1,2-dihydroquinolin-3-yl)-1H-benzimidazol-6-yl]piperazin-1-yl}acetic acid	419.2
132	4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)quinolin-2(1H)-one	386.1
133	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)quinolin-2(1H)-one	386.1

134	4-amino-3-[5-(4-ethylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one	389.1
135	4-amino-3-(5-{(2S,5S)-2-[(dimethylamino)methyl]-5-methylmorpholin-4-yl}-1H-benzimidazol-2-yl)quinolin-2(1H)-one	433.3
136	4-amino-6-chloro-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one	409.2
137	4-amino-6-chloro-3-{5-[(3S)-3-(dimethylamino)pyrrolidin-1-yl]-1H-benzimidazol-2-yl}quinolin-2(1H)-one	423.1
138	4-amino-5,6-dichloro-3-{5-[(3S)-3-(dimethylamino)pyrrolidin-1-yl]-1H-benzimidazol-2-yl}quinolin-2(1H)-one	457.2
139	4-amino-5,6-dichloro-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one	443.2
140	4-amino-3-(1H-benzimidazol-2-yl)-6-[(pyridin-2-ylmethyl)oxy]quinolin-2(1H)-one	384.2
141	4-amino-3-(1H-benzimidazol-2-yl)-6-[(2R,6S)-2,6-dimethylmorpholin-4-yl]quinolin-2(1H)-one	390.1
142	4-amino-3-(1H-benzimidazol-2-yl)-6-morpholin-4-ylquinolin-2(1H)-one	362.2
143	4-amino-3-(1H-benzimidazol-2-yl)-5-[(1-methylpiperidin-3-yl)oxy]quinolin-2(1H)-one	390.2
144	4-amino-3-(1H-benzimidazol-2-yl)-5-[(pyridin-2-ylmethyl)oxy]quinolin-2(1H)-one	384.1
145	4-amino-3-(5-morpholin-4-yl-1H-benzimidazol-2-yl)-5-[(pyridin-4-ylmethyl)oxy]quinolin-2(1H)-one	469.2
146	4-amino-3-(1H-benzimidazol-2-yl)-5-(methyloxy)quinolin-2(1H)-one	307.1
147	4-amino-3-(5-methyl-1H-benzimidazol-2-yl)-5-(methyloxy)quinolin-2(1H)-one	321.1
148	4-amino-3-{5-[(2R,6S)-2,6-dimethylmorpholin-4-yl]-1H-benzimidazol-2-yl}-5-(methyloxy)quinolin-2(1H)-one	420.2
149	4-amino-3-(1H-benzimidazol-2-yl)-5-morpholin-4-ylquinolin-2(1H)-one	362.2
150	4-amino-3-(1H-benzimidazol-2-yl)-5-[(2R,6S)-2,6-dimethylmorpholin-4-yl]quinolin-2(1H)-one	390.2
151	4-amino-3-(1H-benzimidazol-2-yl)-5-(4-methylpiperazin-1-yl)quinolin-2(1H)-one	375.1
152	4-amino-5,6-dichloro-3-(5-morpholin-4-yl-1H-benzimidazol-2-yl)quinolin-2(1H)-one	430
153	3-{5-[(2-morpholin-4-ylethyl)oxy]-1H-benzimidazol-2-yl}quinolin-2(1H)-one	391.3
154	4-amino-3-{5-[(3-pyrrolidin-1-ylpropyl)oxy]-1H-benzimidazol-2-yl}quinolin-2(1H)-one	404
155	4-amino-3-{5-[(3-morpholin-4-ylpropyl)oxy]-1H-benzimidazol-2-yl}quinolin-2(1H)-one	420.4

156	4-amino-6-fluoro-3-(5-morpholin-4-yl-1H-benzimidazol-2-yl)quinolin-2(1H)-one	380
157	4-amino-3-{5-[3-(dimethylamino)pyrrolidin-1-yl]-1H-benzimidazol-2-yl}-6-fluoroquinolin-2(1H)-one	407
158	4-amino-3-(1H-benzimidazol-2-yl)-6-fluoroquinolin-2(1H)-one	295
159	4-amino-3-(6-fluoro-5-morpholin-4-yl-1H-benzimidazol-2-yl)quinolin-2(1H)-one	380
160	4-amino-3-{5-[(tetrahydrofuran-2-ylmethyl)oxy]-1H-benzimidazol-2-yl}quinolin-2(1H)-one	377
161	4-amino-6-fluoro-3-(6-fluoro-5-morpholin-4-yl-1H-benzimidazol-2-yl)quinolin-2(1H)-one	398
162	4-amino-3-[6-fluoro-5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one	393
163	4-amino-3-(5-{[2-(methyloxy)ethyl]oxy}-1H-benzimidazol-2-yl)quinolin-2(1H)-one	351
164	4-amino-3-[4,6-difluoro-5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one	411
165	4-amino-3-{5-[3-(dimethylamino)pyrrolidin-1-yl]-1H-benzimidazol-2-yl}-5-fluoroquinolin-2(1H)-one	407.1
166	4-amino-5-fluoro-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one	393.1
167	4-amino-5-chloro-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one	409.1
168	4-amino-3-{5-[3-(dimethylamino)pyrrolidin-1-yl]-6-fluoro-1H-benzimidazol-2-yl}quinolin-2(1H)-one	407.1
169	4-amino-5-chloro-3-{5-[3-(dimethylamino)pyrrolidin-1-yl]-1H-benzimidazol-2-yl}quinolin-2(1H)-one	423.1
170	4-amino-6-chloro-3-{5-[3-(dimethylamino)pyrrolidin-1-yl]-6-fluoro-1H-benzimidazol-2-yl}quinolin-2(1H)-one	441
171	4-amino-5-[(2R,6S)-2,6-dimethylmorpholin-4-yl]-3-(3H-imidazo[4,5-b]pyridin-2-yl)quinolin-2(1H)-one	391.2
172	4-amino-3-(6-thiomorpholin-4-yl-1H-benzimidazol-2-yl)quinolin-2(1H)-one	378.4
173	4-amino-3-[5-(4-cyclohexylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one	443.1
174	4-amino-3-{6-[3-(diethylamino)pyrrolidin-1-yl]-1H-benzimidazol-2-yl}quinolin-2(1H)-one	417.1
175	4-amino-3-[6-(4-pyridin-2-ylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one	438.3
176	4-amino-3-[5-(4-methylpiperazin-1-yl)-3H-imidazo[4,5-b]pyridin-2-yl]quinolin-2(1H)-one	376.3

177	4-amino-6-chloro-3-[5-(4-methylpiperazin-1-yl)-1H-imidazo[4,5-b]pyridin-2-yl]quinolin-2(1H)-one	410.2
178	2-(4-amino-2-oxo-1,2-dihydroquinolin-3-yl)-N-methyl-N-(1-methylpiperidin-4-yl)-1H-benzimidazole-5-carboxamide	431.3
179	4-amino-3-(5-{[4-(1-methylethyl)piperazin-1-yl]carbonyl}-1H-benzimidazol-2-yl)quinolin-2(1H)-one	431.3
180	4-amino-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-6-nitroquinolin-2(1H)-one	420.2
181	4-amino-3-[5-(1,4'-bipiperidin-1'-ylcarbonyl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one	471.1
182	4-amino-3-{5-[(4-methylpiperazin-1-yl)carbonyl]-1H-benzimidazol-2-yl}quinolin-2(1H)-one	403.3
183	4-amino-3-[5-(1-oxidothiomorpholin-4-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one	394.5
184	3-{5-[(4-acetylpiperazin-1-yl)carbonyl]-1H-benzimidazol-2-yl}-4-aminoquinolin-2(1H)-one	431.3
185	4-amino-3-(5-{[(3R)-3-(dimethylamino)pyrrolidin-1-yl]carbonyl}-1H-benzimidazol-2-yl)quinolin-2(1H)-one	417.4
186	4-amino-3-(5-{[(3S)-3-(dimethylamino)pyrrolidin-1-yl]carbonyl}-1H-benzimidazol-2-yl)quinolin-2(1H)-one	417.4
187	4-amino-3-(5-{[4-(dimethylamino)piperidin-1-yl]carbonyl}-1H-benzimidazol-2-yl)quinolin-2(1H)-one	431.4
188	methyl 2-(4-amino-5-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)-1H-benzimidazole-6-carboxylate	353.2
189	4-amino-3-[5-(1,3'-bipyrrolidin-1'-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one	415.5
190	4-amino-3-[5-(pyridin-3-yloxy)-1H-benzimidazol-2-yl]quinolin-2(1H)-one	370.2
191	4-amino-5,6-bis(methyloxy)-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one	435.5
192	2-(4-amino-2-oxo-1,2-dihydroquinolin-3-yl)-N-[2-(dimethylamino)ethyl]-N-methyl-1H-benzimidazole-5-carboxamide	405.3

193	2-(4-amino-2-oxo-1,2-dihydroquinolin-3-yl)-N-methyl-N-(1-methylpyrrolidin-3-yl)-1H-benzimidazole-5-carboxamide	417.2
194	4-amino-3-{5-[(5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl)carbonyl]-1H-benzimidazol-2-yl}quinolin-2(1H)-one	415.2
195	4-amino-3-{5-[(4-cyclohexylpiperazin-1-yl)carbonyl]-1H-benzimidazol-2-yl}quinolin-2(1H)-one	471.6
196	4-amino-3-{5-[(2-piperidin-1-ylethyl)amino]-1H-benzimidazol-2-yl}quinolin-2(1H)-one	403.2
197	ethyl 4-{[2-(4-amino-2-oxo-1,2-dihydroquinolin-3-yl)-1H-benzimidazol-5-yl]amino}piperidine-1-carboxylate	447.3
198	4-amino-3-[5-({(5R)-5-[(methyloxy)methyl]pyrrolidin-3-yl}amino)-1H-benzimidazol-2-yl]quinolin-2(1H)-one	405.2
199	4-amino-3-{5-[(pyridin-2-ylmethyl)amino]-1H-benzimidazol-2-yl}quinolin-2(1H)-one	383.3
200	4-amino-3-[5-(piperidin-3-ylamino)-1H-benzimidazol-2-yl]quinolin-2(1H)-one	375.2
201	4-amino-5-fluoro-3-{5-[(pyridin-2-ylmethyl)amino]-1H-benzimidazol-2-yl}quinolin-2(1H)-one	401.3
202	ethyl 4-{[2-(4-amino-5-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)-1H-benzimidazol-5-yl]amino}piperidine-1-carboxylate	465.5
203	4-amino-5-fluoro-3-[5-(piperidin-3-ylamino)-1H-benzimidazol-2-yl]quinolin-2(1H)-one	393.3
204	4-amino-3-(1H-benzimidazol-2-yl)-6-bromoquinolin-2(1H)-one	357.1
205	4-amino-3-(1H-benzimidazol-2-yl)-7-bromoquinolin-2(1H)-one	357.1
206	4-amino-3-(5-bromo-1H-benzimidazol-2-yl)quinolin-2(1H)-one	357.1
207	N,N-dimethyl-2-(2-oxo-1,2-dihydroquinolin-3-yl)-1H-benzimidazole-5-carboxamide	333.1
208	4-amino-3-(5-thien-2-yl-1H-benzimidazol-2-yl)quinolin-2(1H)-one	359.2

209	2-(4-amino-2-oxo-1,2-dihydroquinolin-3-yl)-N,N-dimethyl-1H-benzimidazole-5-sulfonamide	384.1
210	4-amino-6-iodo-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one	501.1
211	4-amino-3-(5-{2-[(dimethylamino)methyl]-morpholin-4-yl}-1H-benzimidazol-2-yl)quinolin-2(1H)-one	419.2

Examples 212-338

Examples 212 to 338 listed in Table 2 were synthesized using the methods described above such as Methods 1-24 and those set forth in the Schemes and other Examples or modified as apparent to one of reasonable skill in the art using commercially available materials.

Table 2. Table of Examples 212-338.

Example	Name	LC/MS m/z (MH+)
212	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-chloro-6-iodoquinolin-2(1H)-one	547
213	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-nitroquinolin-2(1H)-one	431
214	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-methylquinolin-2(1H)-one	401
215	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6,7-difluoroquinolin-2(1H)-one	422
216	4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-chloroquinolin-2(1H)-one	421
217	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-bromoquinolin-2(1H)-one	465
218	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-2-oxo-1,2-dihydroquinoline-6-carbonitrile	411
219	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-fluoroquinolin-2(1H)-one	404
220	4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6,7-bis(methyloxy)quinolin-2(1H)-one	447
221	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6,7-dichloroquinolin-2(1H)-one	455
222	1-[4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-fluoro-2-oxo-1,2-dihydroquinolin-7-yl]piperidine-4-carboxamide	531

223	4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-fluoro-7-[(3-hydroxypropyl)amino]quinolin-2(1H)-one	478
224	4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-(dimethylamino)-6-fluoroquinolin-2(1H)-one	448
225	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-5-fluoroquinolin-2(1H)-one	404
226	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-(4-nitrophenyl)quinolin-2(1H)-one	508
227	4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-{[2-(dimethylamino)ethyl]amino}-6-fluoroquinolin-2(1H)-one	491
228	4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-fluoro-7-(1H-imidazol-1-yl)quinolin-2(1H)-one	471
229	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-[4-(methyloxy)phenyl]quinolin-2(1H)-one	493
230	4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-fluoro-7-morpholin-4-ylquinolin-2(1H)-one	490
231	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-6,7-difluoro-3-(3H-imidazo[4,5-b]pyridin-2-yl)quinolin-2(1H)-one	423
232	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-(3-nitrophenyl)quinolin-2(1H)-one	508
233	1-[4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-fluoro-2-oxo-1,2-dihydroquinolin-7-yl]piperidine-3-carboxamide	531
234	4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-5-methylquinolin-2(1H)-one	401
235	6-(3-acetylphenyl)-4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(3H-imidazo[4,5-b]pyridin-2-yl)quinolin-2(1H)-one	506
236	4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-5-chloroquinolin-2(1H)-one	421
237	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-6-fluoro-3-(3H-imidazo[4,5-b]pyridin-2-yl)-7-morpholin-4-ylquinolin-2(1H)-one	491
238	4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-(cyclopropylamino)-6-fluoroquinolin-2(1H)-one	460
239	N-{3-[4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(3H-imidazo[4,5-b]pyridin-2-yl)-2-oxo-1,2-dihydroquinolin-6-yl]phenyl}acetamide	521
240	4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-fluoro-7-(4-methylpiperazin-1-yl)quinolin-2(1H)-one	503

241	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-6-fluoro-7-(1H-imidazol-1-yl)-3-(3H-imidazo[4,5-b]pyridin-2-yl)quinolin-2(1H)-one	472
242	4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-fluoro-7-[(2-pyridin-2-ylethyl)amino]quinolin-2(1H)-one	525
243	4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-fluoro-7-piperidin-1-ylquinolin-2(1H)-one	488
244	6-chloro-3-(3H-imidazo[4,5-b]pyridin-2-yl)quinolin-2(1H)-one	298
245	ethyl 1-[4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-fluoro-2-oxo-1,2-dihydroquinolin-7-yl]piperidine-4-carboxylate	560
246	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-(1-benzothien-2-yl)quinolin-2(1H)-one	519
247	4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-fluoro-7-pyrrolidin-1-ylquinolin-2(1H)-one	474
248	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(3H-imidazo[4,5-b]pyridin-2-yl)-6-[2-(trifluoromethyl)phenyl]quinolin-2(1H)-one	532
249	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(3H-imidazo[4,5-b]pyridin-2-yl)-6-[2-(methyloxy)phenyl]quinolin-2(1H)-one	494
250	ethyl 1-[4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-fluoro-2-oxo-1,2-dihydroquinolin-7-yl]piperidine-3-carboxylate	560
251	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-(4-ethylphenyl)quinolin-2(1H)-one	491
252	4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-fluoro-7-[(2-methylpropyl)amino]quinolin-2(1H)-one	476
253	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-5-methylquinolin-2(1H)-one	401
254	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-6-(2,4-dichlorophenyl)-3-(3H-imidazo[4,5-b]pyridin-2-yl)quinolin-2(1H)-one	532
255	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-[3-(trifluoromethyl)phenyl]quinolin-2(1H)-one	531
256	3-(1H-benzimidazol-2-yl)-4-(dimethylamino)quinolin-2(1H)-one	305
257	4-hydroxy-3-(1H-imidazo[4,5-f]quinolin-2-yl)quinolin-2(1H)-one	329
258	4-hydroxy-3-(1H-imidazo[4,5-b]pyridin-2-yl)quinolin-2(1H)-one	279

259	4-[4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-5-fluoro-2-oxo-1,2-dihydroquinolin-6-yl]benzoic acid	525
260	4-[4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-5-fluoro-2-oxo-1,2-dihydroquinolin-6-yl]benzamide	524
261	N-{3-[4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-5-fluoro-2-oxo-1,2-dihydroquinolin-6-yl]phenyl}acetamide	538
262	3-[4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-5-fluoro-2-oxo-1,2-dihydroquinolin-6-yl]benzoic acid	525
263	4-[4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-fluoro-2-oxo-1,2-dihydroquinolin-6-yl]benzoic acid	525
264	N-{3-[4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-fluoro-2-oxo-1,2-dihydroquinolin-6-yl]phenyl}acetamide	538
265	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-chloro-6-(2-methylphenyl)quinolin-2(1H)-one	511
266	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-2-oxo-1,2-dihydroquinoline-7-carbonitrile	411
267	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-(methyloxy)quinolin-2(1H)-one	417
268	4-[4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-2-oxo-1,2-dihydroquinolin-7-yl]benzamide	506
269	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-fluoro-7-(methyloxy)quinolin-2(1H)-one	434
270	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-chloro-7-(dimethylamino)quinolin-2(1H)-one	464
271	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-(dimethylamino)-6-iodoquinolin-2(1H)-one	555
272	3-[4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-(1H-imidazol-1-yl)-2-oxo-1,2-dihydroquinolin-6-yl]benzoic acid	573
273	4-[4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-2-oxo-7-piperidin-1-yl-1,2-dihydroquinolin-6-yl]benzoic acid	590
274	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-(methyloxy)-6-[4-(methylsulfonyl)phenyl]quinolin-2(1H)-one	571
275	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-8-methylquinolin-2(1H)-one	401
276	4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6,7-difluoroquinolin-2(1H)-one	422

277	3-(1H-benzimidazol-2-yl)-6-methyl-4-(piperidin-3-ylamino)quinolin-2(1H)-one	374
278	4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-[2-(methyloxy)phenyl]quinolin-2(1H)-one	493
279	4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-[3-(methyloxy)phenyl]quinolin-2(1H)-one	493
280	3-(1H-benzimidazol-2-yl)-6,7-difluoro-4-(piperidin-4-ylamino)quinolin-2(1H)-one	396
281	3-(1H-benzimidazol-2-yl)-6,7-difluoro-4-(pyrrolidin-3-ylamino)quinolin-2(1H)-one	382
282	3-(1H-benzimidazol-2-yl)-6-chloro-4-[(3-morpholin-4-ylpropyl)amino]quinolin-2(1H)-one	439
283	6-chloro-3-(5-morpholin-4-yl-1H-benzimidazol-2-yl)-4-(piperidin-4-ylamino)quinolin-2(1H)-one	480
284	6-chloro-3-(5-morpholin-4-yl-1H-benzimidazol-2-yl)-4-[(piperidin-2-ylmethyl)amino]quinolin-2(1H)-one	494
285	4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-6-chloro-3-(5-morpholin-4-yl-1H-benzimidazol-2-yl)quinolin-2(1H)-one	506
286	6-chloro-3-(5-morpholin-4-yl-1H-benzimidazol-2-yl)-4-(piperidin-3-ylamino)quinolin-2(1H)-one	480
287	6-chloro-4-{[2-(dimethylamino)ethyl]amino}-3-(5-morpholin-4-yl-1H-benzimidazol-2-yl)quinolin-2(1H)-one	468
288	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-6-chloro-3-(5-morpholin-4-yl-1H-benzimidazol-2-yl)quinolin-2(1H)-one	506
289	6-chloro-3-(5-morpholin-4-yl-1H-benzimidazol-2-yl)-4-[(piperidin-3-ylmethyl)amino]quinolin-2(1H)-one	494
290	6-chloro-3-(5-morpholin-4-yl-1H-benzimidazol-2-yl)-4-[(piperidin-4-ylmethyl)amino]quinolin-2(1H)-one	494
291	4-{[(1R,2R)-2-aminocyclohexyl]amino}-6-chloro-3-(5-morpholin-4-yl-1H-benzimidazol-2-yl)quinolin-2(1H)-one	494
292	4-[(4-aminocyclohexyl)amino]-6-chloro-3-(5-morpholin-4-yl-1H-benzimidazol-2-yl)quinolin-2(1H)-one	494
293	4-{[(2S)-2-amino-3-methylbutyl]amino}-6-chloro-3-(5-morpholin-4-yl-1H-benzimidazol-2-yl)quinolin-2(1H)-one	482
294	4-({[4-(aminomethyl)phenyl]methyl}amino)-6-chloro-3-(5-morpholin-4-yl-1H-benzimidazol-2-yl)quinolin-2(1H)-one	516
295	6-chloro-3-(5-morpholin-4-yl-1H-benzimidazol-2-yl)-4-[(pyrrolidin-2-ylmethyl)amino]quinolin-2(1H)-one	480
296	4-{[(1R)-1-(aminomethyl)propyl]amino}-6-chloro-3-(5-morpholin-4-yl-1H-benzimidazol-2-yl)quinolin-2(1H)-one	468
297	4-{[(1S)-2-amino-1-(phenylmethyl)ethyl]amino}-6-chloro-3-(5-morpholin-4-yl-1H-benzimidazol-2-yl)quinolin-2(1H)-one	530
298	6-chloro-4-{[3-(4-methylpiperazin-1-yl)propyl]amino}-3-(5-morpholin-4-yl-1H-benzimidazol-2-yl)quinolin-2(1H)-one	537
299	6-chloro-3-(5-morpholin-4-yl-1H-benzimidazol-2-yl)-4-{[1-(phenylmethyl)piperidin-4-yl]amino}quinolin-2(1H)-one	570

300	6-chloro-3-(5-morpholin-4-yl-1H-benzimidazol-2-yl)-4-[(3-morpholin-4-ylpropyl)amino]quinolin-2(1H)-one	524
301	6-chloro-3-(5-morpholin-4-yl-1H-benzimidazol-2-yl)-4-[(2-piperidin-1-ylethyl)amino]quinolin-2(1H)-one	508
302	6-chloro-3-(5-morpholin-4-yl-1H-benzimidazol-2-yl)-4-[(pyridin-3-ylmethyl)amino]quinolin-2(1H)-one	488
303	6-chloro-4-{[3-(1H-imidazol-1-yl)propyl]amino}-3-(5-morpholin-4-yl-1H-benzimidazol-2-yl)quinolin-2(1H)-one	505
304	6-chloro-3-(5-morpholin-4-yl-1H-benzimidazol-2-yl)-4-[(pyridin-4-ylmethyl)amino]quinolin-2(1H)-one	488
305	6-chloro-4-{[2-(methylamino)ethyl]amino}-3-(5-morpholin-4-yl-1H-benzimidazol-2-yl)quinolin-2(1H)-one	454
306	6-chloro-4-{[(2-methyl-1-piperidin-4-yl-1H-benzimidazol-5-yl)methyl]amino}-3-(5-morpholin-4-yl-1H-benzimidazol-2-yl)quinolin-2(1H)-one	624
307	6-chloro-3-(5-morpholin-4-yl-1H-benzimidazol-2-yl)-4-[(2-pyrrolidin-1-ylethyl)amino]quinolin-2(1H)-one	494
308	6-chloro-3-(5-morpholin-4-yl-1H-benzimidazol-2-yl)-4-(pyrrolidin-3-ylamino)quinolin-2(1H)-one	466
309	4-{[(1R,2R)-2-aminocyclohexyl]amino}-6-chloro-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one	507
310	4-[(4-aminocyclohexyl)amino]-6-chloro-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one	507
311	4-({[4-(aminomethyl)phenyl]methyl}amino)-6-chloro-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one	529
312	6-chloro-4-{[2-(methylamino)ethyl]amino}-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one	467
313	6-chloro-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-4-{[3-(4-methylpiperazin-1-yl)propyl]amino}quinolin-2(1H)-one	550
314	6-chloro-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-4-{[1-(phenylmethyl)piperidin-4-yl]amino}quinolin-2(1H)-one	583
315	6-chloro-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-4-[(2-pyrrolidin-1-ylethyl)amino]quinolin-2(1H)-one	507
316	6-chloro-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-4-(pyrrolidin-3-ylamino)quinolin-2(1H)-one	479
317	6-chloro-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-4-(piperidin-4-ylamino)quinolin-2(1H)-one	493
318	6-chloro-3-(5-morpholin-4-yl-1H-benzimidazol-2-yl)-4-[(2-piperidin-2-ylethyl)amino]quinolin-2(1H)-one	508
319	4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-7-chloro-3-(5-morpholin-4-yl-1H-benzimidazol-2-yl)quinolin-2(1H)-one	506
320	7-chloro-3-(5-morpholin-4-yl-1H-benzimidazol-2-yl)-4-(piperidin-3-ylamino)quinolin-2(1H)-one	480

321	6-chloro-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-4-[(piperidin-2-ylmethyl)amino]quinolin-2(1H)-one	507
322	6-chloro-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-4-{[(2S)-pyrrolidin-2-ylmethyl]amino}quinolin-2(1H)-one	493
323	6-chloro-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-4-{[(2R)-pyrrolidin-2-ylmethyl]amino}quinolin-2(1H)-one	493
324	6-chloro-4-({[(2S)-1-ethylpyrrolidin-2-yl]methyl}amino)-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one	521
325	6-chloro-4-({[(2R)-1-ethylpyrrolidin-2-yl]methyl}amino)-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one	521
326	4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-[4-(methyloxy)phenyl]quinolin-2(1H)-one	493
327	6-(3-aminophenyl)-4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)quinolin-2(1H)-one	478
328	4-amino-3-(1H-benzimidazol-2-yl)-1,7-naphthyridin-2(1H)-one	278.3
329	4-amino-3-(5-methyl-1H-benzimidazol-2-yl)-1,7-naphthyridin-2(1H)-one	292.4
330	4-amino-3-[5-(2-morpholin-4-ylethoxy)-1H-benzimidazol-2-yl]-1,7-naphthyridin-2(1H)-one	407.4
331	2-(4-amino-2-oxo-1,2-dihydro-1,7-naphthyridin-3-yl)-N,N-dimethyl-1H-benzimidazole-5-carboxamide	349.3
332	4-amino-3-(5-morpholin-4-yl-1H-benzimidazol-2-yl)-1,7-naphthyridin-2(1H)-one	363.2
333	4-amino-3-{5-[3-(dimethylamino)pyrrolidin-1-yl]-1H-benzimidazol-2-yl}-1,7-naphthyridin-2(1H)-one	390.2
334	4-amino-3-(3H-imidazo[4,5-b]pyridin-2-yl)-1,7-naphthyridin-2(1H)-one	279.0
335	4-amino-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1,7-naphthyridin-2(1H)-one	376.3
336	4-amino-3-(5-morpholin-4-yl-1H-benzimidazol-2-yl)-1,6-naphthyridin-2(1H)-one	363.2
337	4-amino-3-{5-[3-(dimethylamino)pyrrolidin-1-yl]-1H-benzimidazol-2-yl}-1,5-naphthyridin-2(1H)-one	390.2
338	4-amino-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1,5-naphthyridin-2(1H)-one	376.1

Examples 339-1273

Examples 339 to 1273 listed in Table 3 were synthesized using the methods described above such as Methods 1-24 and those set forth in the Schemes and other Examples or modified as apparent to one of reasonable skill in the art using commercially available materials.

Table 3. Table of Examples 339-1273.

Example	Name	LC/MS m/z (MH^+)
339	4-amino-3-(1H-benzimidazol-2-yl)quinolin-2(1H)-one	277.3
340	4-amino-3-(1H-benzimidazol-2-yl)-6,7-dimethoxyquinolin-2(1H)-one	337.3
341	3-(1H-benzimidazol-2-yl)-4-(dimethylamino)-1-methylquinolin-2(1H)-one	319.4
342	3-(1H-benzimidazol-2-yl)-4-{[2-(dimethylamino)ethyl]amino}-1-methylquinolin-2(1H)-one	362.4
343	4-amino-3-(1H-benzimidazol-2-yl)-1-methylquinolin-2(1H)-one	291.3
344	4-amino-3-(6-methyl-1H-benzimidazol-2-yl)quinolin-2(1H)-one	291.3
345	3-(1H-benzimidazol-2-yl)-4-{[3-(1H-imidazol-1-yl)propyl]amino}quinolin-2(1H)-one	385.4
346	3-(1H-benzimidazol-2-yl)-4-[(pyridin-3-ylmethyl)amino]quinolin-2(1H)-one	368.4
347	4-amino-3-(1H-benzimidazol-2-yl)-5-fluoroquinolin-2(1H)-one	295.3
348	3-(1H-benzimidazol-2-yl)-4-pyrrolidin-1-ylquinolin-2(1H)-one	331.4
349	3-(1H-benzimidazol-2-yl)-4-[(pyridin-4-ylmethyl)amino]quinolin-2(1H)-one	368.4
350	3-(1H-benzimidazol-2-yl)-4-{[2-(1-methylpyrrolidin-2-yl)ethyl]amino}quinolin-2(1H)-one	388.5
351	4-amino-3-(1H-benzimidazol-2-yl)-7-methylquinolin-2(1H)-one	291.3
352	4-amino-3-(1H-benzimidazol-2-yl)-7-chloroquinolin-2(1H)-one	311.7
353	4-amino-3-(1H-benzimidazol-2-yl)-6-chloroquinolin-2(1H)-one	311.7
354	4-amino-3-[6-(3-aminopyrrolidin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one	361.4
355	3-(1H-benzimidazol-2-yl)-4-(diethylamino)quinolin-2(1H)-one	333.4
356	3-(1H-benzimidazol-2-yl)-4-(1,2-dimethylhydrazino)quinolin-2(1H)-one	320.4

357	4-amino-3-[5-(trifluoromethyl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one	345.3
358	4-amino-3-(5,6-dichloro-1H-benzimidazol-2-yl)quinolin-2(1H)-one	346.2
359	4-(3-aminopyrrolidin-1-yl)-3-(5-morpholin-4-yl-1H-benzimidazol-2-yl)quinolin-2(1H)-one	431.5
360	4-amino-5-fluoro-3-(5-methyl-1H-benzimidazol-2-yl)quinolin-2(1H)-one	309.3
361	4-amino-3-(1H-benzimidazol-2-yl)-6-nitroquinolin-2(1H)-one	322.3
362	4-amino-3-(4-methyl-1H-benzimidazol-2-yl)quinolin-2(1H)-one	291.3
363	4-amino-3-(6-ethoxy-1H-benzimidazol-2-yl)quinolin-2(1H)-one	321.4
364	4-amino-3-(7-hydroxy-1H-benzimidazol-2-yl)quinolin-2(1H)-one	293.3
365	4-amino-3-(6-*tert*-butyl-1H-benzimidazol-2-yl)quinolin-2(1H)-one	333.4
366	2-(4-amino-2-oxo-1,2-dihydroquinolin-3-yl)-1H-benzimidazole-5-carbonitrile	302.3
367	4-amino-3-(5,6-dimethyl-1H-benzimidazol-2-yl)quinolin-2(1H)-one	305.4
368	4-amino-3-(4,5-dimethyl-1H-benzimidazol-2-yl)quinolin-2(1H)-one	305.4
369	4-amino-6-chloro-3-(5-methyl-1H-benzimidazol-2-yl)quinolin-2(1H)-one	325.8
370	4-amino-3-(1H-benzimidazol-2-yl)-6,8-dichloroquinolin-2(1H)-one	346.2
371	4-amino-3-(1H-benzimidazol-2-yl)-5-chloroquinolin-2(1H)-one	311.7
372	2-(4-amino-2-oxo-1,2-dihydroquinolin-3-yl)-N,N-dimethyl-1H-benzimidazole-5-carboxamide	348.4
373	4-amino-3-{5-[3-(dimethylamino)pyrrolidin-1-yl]-1H-benzimidazol-2-yl}quinolin-2(1H)-one	389.5
374	4-amino-3-(6-methoxy-5-methyl-1H-benzimidazol-2-yl)quinolin-2(1H)-one	321.4
375	2-(4-amino-2-oxo-1,2-dihydroquinolin-3-yl)-1H-benzimidazole-6-carboximidamide	319.3
376	4-amino-7-(3-aminophenyl)-3-(1H-benzimidazol-2-yl)quinolin-2(1H)-one	368.4
377	4-amino-3-(1H-benzimidazol-2-yl)-7-thien-2-ylquinolin-2(1H)-one	359.4
378	4-amino-3-(5-thien-3-yl-1H-benzimidazol-2-yl)quinolin-2(1H)-one	359.4
379	4-amino-3-(1H-benzimidazol-2-yl)-7-thien-3-ylquinolin-2(1H)-one	359.4
380	4-{[(1S,2R)-2-aminocyclohexyl]amino}-3-(5-morpholin-4-yl-1H-benzimidazol-2-yl)quinolin-2(1H)-one	459.6
381	4-{[(1R,2R)-2-aminocyclohexyl]amino}-3-(5-morpholin-4-yl-1H-benzimidazol-2-yl)quinolin-2(1H)-one	459.6

382	4-{[(1S,2S)-2-aminocyclohexyl]amino}-3-(5-morpholin-4-yl-1H-benzimidazol-2-yl)quinolin-2(1H)-one	459.6
383	4-amino-3-{5-[(2R,6S)-2,6-dimethylmorpholin-4-yl]-1H-benzimidazol-2-yl}quinolin-2(1H)-one	390.5
384	3-(1H-benzimidazol-2-yl)-4-morpholin-4-ylquinolin-2(1H)-one	347.4
385	3-(1H-benzimidazol-2-yl)-4-(piperidin-3-ylamino)quinolin-2(1H)-one	360.4
386	4-(1-azabicyclo[2.2.2]oct-3-ylamino)-3-(5-chloro-1H-benzimidazol-2-yl)quinolin-2(1H)-one	420.9
387	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-6-chloro-3-(5-methyl-1H-benzimidazol-2-yl)quinolin-2(1H)-one	434.9
388	6-chloro-3-(5-methyl-1H-benzimidazol-2-yl)-4-(piperidin-3-ylamino)quinolin-2(1H)-one	408.9
389	3-(1H-benzimidazol-2-yl)-4-[(2-hydroxyethyl)amino]quinolin-2(1H)-one	321.4
390	3-(1H-benzimidazol-2-yl)-6-chloro-4-(piperidin-3-ylamino)quinolin-2(1H)-one	394.9
391	3-(1H-benzimidazol-2-yl)-6-chloro-4-{[(1S)-1-cyclohexylethyl]amino}quinolin-2(1H)-one	421.9
392	3-(1H-benzimidazol-2-yl)-6-chloro-4-[(piperidin-3-ylmethyl)amino]quinolin-2(1H)-one	408.9
393	3-(1H-benzimidazol-2-yl)-6-chloro-4-(pyridin-4-ylamino)quinolin-2(1H)-one	388.8
394	3-(1H-benzimidazol-2-yl)-6-chloro-4-[(piperidin-4-ylmethyl)amino]quinolin-2(1H)-one	408.9
395	3-(1H-benzimidazol-2-yl)-6-chloro-4-[(2-morpholin-4-ylethyl)amino]quinolin-2(1H)-one	424.9
396	3-(1H-benzimidazol-2-yl)-6-chloro-4-(cyclohexylamino)quinolin-2(1H)-one	393.9
397	3-(1H-benzimidazol-2-yl)-6-chloro-4-{[3-(1H-imidazol-1-yl)propyl]amino}quinolin-2(1H)-one	419.9
398	3-(1H-benzimidazol-2-yl)-6-chloro-4-{[2-(dimethylamino)ethyl]amino}quinolin-2(1H)-one	382.9
399	3-(1H-benzimidazol-2-yl)-6-chloro-4-[(cyclohexylmethyl)amino]quinolin-2(1H)-one	407.9
400	3-(1H-benzimidazol-2-yl)-6-chloro-4-[(tetrahydrofuran-2-ylmethyl)amino]quinolin-2(1H)-one	395.9
401	3-(1H-benzimidazol-2-yl)-6-chloro-4-[(pyridin-4-ylmethyl)amino]quinolin-2(1H)-one	402.9
402	3-(1H-benzimidazol-2-yl)-6,7-difluoro-4-(piperidin-3-ylamino)quinolin-2(1H)-one	396.4
403	4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-bromoquinolin-2(1H)-one	465.4
404	3-(1H-benzimidazol-2-yl)-6-fluoro-4-(piperidin-3-ylamino)quinolin-2(1H)-one	378.4
405	4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-methylquinolin-2(1H)-one	400.5
406	4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-fluoroquinolin-2(1H)-one	404.5

407	4-amino-3-[6-(4-methylpiperazin-1-yl)-1 H-benzimidazol-2-yl]-1-propylquinolin-2(1H)-one	417.5
408	3-(1H-benzimidazol-2-yl)-6-chloro-4-{[(1-ethylpyrrolidin-2-yl)methyl]amino}quinolin-2(1H)-one	422.9
409	3-(1H-benzimidazol-2-yl)-6-chloro-4-{[3-(2-oxopyrrolidin-1-yl)propyl]amino}quinolin-2(1H)-one	436.9
410	3-(1H-benzimidazol-2-yl)-6-chloro-4-[(piperidin-2-ylmethyl)amino]quinolin-2(1H)-one	408.9
411	3-(1H-benzimidazol-2-yl)-6-chloro-4-(4-methyl-1,4-diazepan-1-yl)quinolin-2(1H)-one	408.9
412	3-(1H-benzimidazol-2-yl)-6-chloro-4-[(pyridin-3-ylmethyl)amino]quinolin-2(1H)-one	402.9
413	4-anilino-3-(1H-benzimidazol-2-yl)-6-chloroquinolin-2(1H)-one	387.8
414	3-(1H-benzimidazol-2-yl)-6-chloro-4-{[(5-methylpyrazin-2-yl)methyl]amino}quinolin-2(1H)-one	417.9
415	3-(1H-benzimidazol-2-yl)-6-chloro-4-(piperidin-4-ylamino)quinolin-2(1H)-one	402.9
416	3-(1H-benzimidazol-2-yl)-6-chloro-4-{[2-(1-methylpyrrolidin-2-yl)ethyl]amino}quinolin-2(1H)-one	422.9
417	3-(1H-benzimidazol-2-yl)-4-[(1H-benzimidazol-5-ylmethyl)amino]-6-chloroquinolin-2(1H)-one	441.9
418	3-(1H-benzimidazol-2-yl)-6-chloro-4-(piperidin-4-ylamino)quinolin-2(1H)-one	394.9
419	3-(1H-benzimidazol-2-yl)-6-chloro-4-[(4-hydroxycyclohexyl)amino]quinolin-2(1H)-one	409.9
420	4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-5-fluoroquinolin-2(1 H)-one	404.5
421	3-(1H-benzimidazol-2-yl)-6,8-dimethyl-4-(piperidin-3-ylamino)quinolin-2(1H)-one	388.5
422	3-(1H-benzimidazol-2-yl)-5-fluoro-4-(piperidin-3-ylamino)quinolin-2(1H)-one	378.4
423	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6,8-dimethylquinolin-2(1H)-one	414.5
424	4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6,8-dimethylquinolin-2(1H)-one	414.5
425	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-chloroquinolin-2(1H)-one	420.9
426	3-(1H-benzimidazol-2-yl)-6-chloro-4-[(2-piperidin-1-ylethyl)amino]quinolin-2(1H)-one	422.9
427	4-({2-[(4-amino-5-nitropyridin-2-yl)amino]ethyl}amino)-3-(1H-benzimidazol-2-yl)-6-chloroquinolin-2(1H)-one	491.9
428	3-(1H-benzimidazol-2-yl)-6-chloro-4-({2-[(5-nitropyridin-2-yl)amino]ethyl}amino)quinolin-2(1H)-one	476.9
429	3-(1H-benzimidazol-2-yl)-4-[(1H-benzimidazol-2-ylmethyl)amino]-6-chloroquinolin-2(1H)-one	441.9
430	3-(1H-benzimidazol-2-yl)-6-chloro-4-(2,5-diazabicyclo[2.2.1]hept-2-yl)quinolin-2(1H)-one	392.9
431	3-(1H-benzimidazol-2-yl)-6-chloro-4-[(2-{[5-(trifluoromethyl)pyridin-2-yl]amino}ethyl)amino]quinolin-2(1H)-one	499.9

432	4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-methylquinolin-2(1H)-one	400.5
433	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-methylquinolin-2(1H)-one	400.5
434	3-(1H-benzimidazol-2-yl)-7-chloro-4-{[(2R)-pyrrolidin-2-ylmethyl]amino}quinolin-2(1H)-one	394.9
435	3-(1H-benzimidazol-2-yl)-6-chloro-4-[(pyrrolidin-2-ylmethyl)amino]quinolin-2(1H)-one	394.9
436	6-[(2-{[3-(1H-benzimidazol-2-yl)-6-chloro-2-oxo-1,2-dihydroquinolin-4-yl]amino}ethyl)amino]nicotinamide	474.9
437	3-(1H-benzimidazol-2-yl)-6-chloro-4-(pyrrolidin-3-ylamino)quinolin-2(1H)-one	380.8
438	4-{[(2R)-2-aminobutyl]amino}-3-(1H-benzimidazol-2-yl)-6-chloroquinolin-2(1H)-one	382.9
439	4-{[(2S)-2-amino-3-phenylpropyl]amino}-3-(1H-benzimidazol-2-yl)-6-chloroquinolin-2(1H)-one	444.9
440	4-[(4-aminocyclohexyl)amino]-3-(1H-benzimidazol-2-yl)-6-chloroquinolin-2(1H)-one	408.9
441	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-iodoquinolin-2(1H)-one	512.4
442	4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-iodoquinolin-2(1H)-one	512.4
443	3-(1H-benzimidazol-2-yl)-6,7-dimethoxy-4-(piperidin-3-ylamino)quinolin-2(1H)-one	420.5
444	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6,7-dimethoxyquinolin-2(1H)-one	446.5
445	4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-nitroquinolin-2(1H)-one	431.5
446	3-(1H-benzimidazol-2-yl)-6-iodo-4-(piperidin-3-ylamino)quinolin-2(1H)-one	486.3
447	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-5-chloroquinolin-2(1H)-one	420.9
448	3-(1H-benzimidazol-2-yl)-6-chloro-4-{[(1-piperidin-4-yl-1H-benzimidazol-6-yl)methyl]amino}quinolin-2(1H)-one	525.0
449	3-(1H-benzimidazol-2-yl)-6-methyl-4-[(piperidin-3-ylmethyl)amino]quinolin-2(1H)-one	388.5
450	3-(1H-benzimidazol-2-yl)-6-methyl-4-(piperidin-4-ylamino)quinolin-2(1H)-one	374.5
451	3-(1H-benzimidazol-2-yl)-6-methyl-4-[(piperidin-4-ylmethyl)amino]quinolin-2(1H)-one	388.5
452	3-(1H-benzimidazol-2-yl)-6-methyl-4-[(piperidin-2-ylmethyl)amino]quinolin-2(1H)-one	388.5
453	4-{[4-(2-aminoethoxy)benzyl]amino}-3-(1H-benzimidazol-2-yl)-6-chloroquinolin-2(1H)-one	460.9
454	4-{[2-(2-aminoethoxy)benzyl]amino}-3-(1H-benzimidazol-2-yl)-6-chloroquinolin-2(1H)-one	460.9
455	4-(1-azabicyclo[2.2.2]oct-3-ylamino)-3-(5-hydroxy-1H-benzimidazol-2-yl)quinolin-2(1H)-one	402.5
456	4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-2-oxo-1,2-dihydroquinoline-6-carbonitrile	411.5

457	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6,7-dihydroxyquinolin-2(1H)-one	418.5
458	4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6,7-dihydroxyquinolin-2(1H)-one	418.5
459	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-2-oxo-1,2-dihydroquinoline-6-carboxylic acid	430.5
460	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-fluoroquinolin-2(1H)-one	404.5
461	4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-fluoroquinolin-2(1H)-one	404.5
462	2-(4-amino-2-oxo-1-propyl-1,2-dihydroquinolin-3-yl)-1H-benzimidazole-6-carbonitrile	344.4
463	*tert*-butyl 4-[4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-2-oxo-1,2-dihydroquinolin-6-yl]-3,6-dihydropyridine-1(2H)-carboxylate	567.7
464	*tert*-butyl 4-[4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-2-oxo-1,2-dihydroquinolin-6-yl]-3,6-dihydropyridine-1(2H)-carboxylate	567.7
465	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-(1,2,3,6-tetrahydropyridin-4-yl)quinolin-2(1H)-one	467.6
466	4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-thien-2-ylquinolin-2(1H)-one	468.6
467	4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-(1,2,3,6-tetrahydropyridin-4-yl)quinolin-2(1H)-one	467.6
468	4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-(2,4-difluorophenyl)quinolin-2(1H)-one	498.5
469	*tert*-butyl 2-[4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-2-oxo-1,2-dihydroquinolin-6-yl]-1H-pyrrole-1-carboxylate	551.7
470	*tert*-butyl 2-[4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-2-oxo-1,2-dihydroquinolin-6-yl]-1H-pyrrole-1-carboxylate	551.7
471	4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-pyridin-2-ylquinolin-2(1H)-one	463.6
472	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-thien-2-ylquinolin-2(1H)-one	468.6
473	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-(2,4-difluorophenyl)quinolin-2(1H)-one	498.5
474	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-thien-3-ylquinolin-2(1H)-one	468.6
475	4-[4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-2-oxo-1,2-dihydroquinolin-6-yl]benzonitrile	487.6
476	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-(2-chlorophenyl)quinolin-2(1H)-one	497.0

477	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-[2-(trifluoromethyl)phenyl]quinolin-2(1H)-one	530.6
478	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-(3-methoxyphenyl)quinolin-2(1H)-one	492.6
479	4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-pyridin-3-ylquinolin-2(1H)-one	463.6
480	4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-pyridin-4-ylquinolin-2(1H)-one	463.6
481	4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-2-oxo-1,2-dihydroquinoline-6-carboxylic acid	430.5
482	3-(5-hydroxy-1H-benzimidazol-2-yl)-4-(piperidin-3-ylamino)quinolin-2(1H)-one	376.4
483	4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-8-methylquinolin-2(1H)-one	400.5
484	4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-(2-chlorophenyl)quinolin-2(1H)-one	497.0
485	4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-[2-(trifluoromethyl)phenyl]quinolin-2(1H)-one	530.6
486	4-[4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-2-oxo-1,2-dihydroquinolin-6-yl]benzonitrile	487.6
487	4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-thien-3-ylquinolin-2(1H)-one	468.6
488	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-pyridin-4-ylquinolin-2(1H)-one	463.6
489	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-(2-methoxyphenyl)quinolin-2(1H)-one	492.6
490	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-(2-methylphenyl)quinolin-2(1H)-one	476.6
491	6-(3-acetylphenyl)-4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)quinolin-2(1H)-one	504.6
492	6-(4-acetylphenyl)-4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)quinolin-2(1H)-one	504.6
493	4-[4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-2-oxo-1,2-dihydroquinolin-6-yl]benzoic acid	506.6
494	N-{3-[4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-2-oxo-1,2-dihydroquinolin-6-yl]phenyl}acetamide	519.6
495	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-(2,6-difluorophenyl)quinolin-2(1H)-one	498.5
496	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-(1,3-benzodioxol-5-yl)quinolin-2(1H)-one	506.6

497	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-(4-chlorophenyl)quinolin-2(1H)-one	497.0
498	4-[4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-2-oxo-1,2-dihydroquinolin-6-yl]benzaldehyde	490.6
499	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-[4-(methylthio)phenyl]quinolin-2(1H)-one	508.7
500	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-[4-(dimethylamino)phenyl]quinolin-2(1H)-one	505.6
501	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-(4-chloro-2-fluorophenyl)quinolin-2(1H)-one	515.0
502	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-(2,4-dichlorophenyl)quinolin-2(1H)-one	531.5
503	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-phenylquinolin-2(1H)-one	462.6
504	3-(1H-benzimidazol-2-yl)-6-chloro-4-[(1-ethylpiperidin-3-yl)amino]quinolin-2(1H)-one	422.9
505	1-[4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-fluoro-2-oxo-1,2-dihydroquinolin-7-yl]piperidine-4-carboxamide	530.6
506	ethyl 1-[4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-fluoro-2-oxo-1,2-dihydroquinolin-7-yl]piperidine-4-carboxylate	559.7
507	1-[4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-fluoro-2-oxo-1,2-dihydroquinolin-7-yl]piperidine-3-carboxamide	530.6
508	ethyl 1-[4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-fluoro-2-oxo-1,2-dihydroquinolin-7-yl]piperidine-3-carboxylate	559.7
509	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-fluoro-7-(1H-imidazol-1-yl)quinolin-2(1H)-one	470.5
510	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-{[2-(dimethylamino)ethyl]amino}-6-fluoroquinolin-2(1H)-one	490.6
511	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-fluoro-7-morpholin-4-ylquinolin-2(1H)-one	489.6
512	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-(dimethylamino)-6-fluoroquinolin-2(1H)-one	447.5
513	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-bromoquinolin-2(1H)-one	465.4
514	1-[4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-fluoro-2-oxo-1,2-dihydroquinolin-7-yl]piperidine-4-carboxylic acid	531.6

515	1-[4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-fluoro-2-oxo-1,2-dihydroquinolin-7-yl]piperidine-3-carboxylic acid	531.6
516	methyl 4-[4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-2-oxo-1,2-dihydroquinolin-6-yl]benzoate	520.6
517	4-[4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-chloro-2-oxo-1,2-dihydroquinolin-6-yl]benzamide	505.6
518	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-[4-(methylsulfonyl)phenyl]quinolin-2(1H)-one	540.7
519	methyl 3-amino-4-[4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-2-oxo-1,2-dihydroquinolin-6-yl]benzoate	535.6
520	4-[4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-chloro-2-oxo-1,2-dihydroquinolin-6-yl]benzoic acid	541.0
521	N-{3-[4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-chloro-2-oxo-1,2-dihydroquinolin-6-yl]phenyl}acetamide	554.1
522	6-(3-acetylphenyl)-4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-chloroquinolin-2(1H)-one	539.0
523	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-chloro-6-(2-methoxyphenyl)quinolin-2(1H)-one	527.0
524	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-chloro-6-(2,4-dichlorophenyl)quinolin-2(1H)-one	565.9
525	6-(4-acetylphenyl)-4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-chloroquinolin-2(1H)-one	539.0
526	4-[4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-chloro-2-oxo-1,2-dihydroquinolin-6-yl]benzamide	540.0
527	methyl 4-[4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-chloro-2-oxo-1,2-dihydroquinolin-6-yl]benzoate	555.0
528	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-[[2-(dimethylamino)ethyl](methyl)amino]-6-fluoroquinolin-2(1H)-one	504.6
529	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-fluoro-7-[(3-methoxypropyl)amino]quinolin-2(1H)-one	491.6
530	N-{(3R)-1-[4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-fluoro-2-oxo-1,2-dihydroquinolin-7-yl]pyrrolidin-3-yl}acetamide	530.6

531	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-fluoro-7-{[3-(2-oxopyrrolidin-1-yl)propyl]amino}quinolin-2(1H)-one	544.6
532	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-7-azepan-1-yl-3-(1H-benzimidazol-2-yl)-6-fluoroquinolin-2(1H)-one	501.6
533	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-fluoro-7-(1H-pyrrol-1-yl)quinolin-2(1H)-one	469.5
534	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-fluoro-7-(2-methyl-1H-imidazol-1-yl)quinolin-2(1H)-one	484.5
535	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-fluoro-7-pyrrolidin-1-ylquinolin-2(1H)-one	473.6
536	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-fluoro-7-piperidin-1-ylquinolin-2(1H)-one	487.6
537	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-fluoro-7-(4-methylpiperazin-1-yl)quinolin-2(1H)-one	502.6
538	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-fluoro-7-[(3-hydroxypropyl)amino]quinolin-2(1H)-one	477.6
539	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-chloro-7-morpholin-4-ylquinolin-2(1H)-one	506.0
540	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-chloro-7-(4-methylpiperazin-1-yl)quinolin-2(1H)-one	519.1
541	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-chloro-7-piperidin-1-ylquinolin-2(1H)-one	504.0
542	4-[4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-2-oxo-1,2-dihydroquinolin-7-yl]benzoic acid	506.6
543	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-(2,4-dichlorophenyl)quinolin-2(1H)-one	531.5
544	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-(dimethylamino)quinolin-2(1H)-one	429.5
545	7-(4-acetylphenyl)-4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)quinolin-2(1H)-one	504.6
546	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-(2-methylphenyl)quinolin-2(1H)-one	476.6
547	7-(3-acetylphenyl)-4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)quinolin-2(1H)-one	504.6
548	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-(2-methoxyphenyl)quinolin-2(1H)-one	492.6
549	3-(1H-benzimidazol-2-yl)-6,7-difluoro-4-[(piperidin-2-ylmethyl)amino]quinolin-2(1H)-one	410.4

550	N-[3-(1H-benzimidazol-2-yl)-6,7-difluoro-2-oxo-1,2-dihydroquinolin-4-yl]glycine	371.3
551	N-[3-(1H-benzimidazol-2-yl)-6,7-difluoro-2-oxo-1,2-dihydroquinolin-4-yl]-beta-alanine	385.3
552	4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(6-fluoro-1H-benzimidazol-2-yl)-6,7-dimethoxyquinolin-2(1H)-one	464.5
553	3-(6-fluoro-1H-benzimidazol-2-yl)-6,7-dimethoxy-4-(piperidin-3-ylamino)quinolin-2(1H)-one	438.5
554	3-(6-fluoro-1H-benzimidazol-2-yl)-6,7-dimethoxy-4-(pyrrolidin-3-ylamino)quinolin-2(1H)-one	424.4
555	4-[(4-aminocyclohexyl)amino]-3-(6-fluoro-1H-benzimidazol-2-yl)-6,7-dimethoxyquinolin-2(1H)-one	452.5
556	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(6-fluoro-1H-benzimidazol-2-yl)-6,7-dimethoxyquinolin-2(1H)-one	464.5
557	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-[ethyl(methyl)amino]-6-fluoroquinolin-2(1H)-one	461.6
558	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-(diethylamino)-6-fluoroquinolin-2(1H)-one	475.6
559	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-[(3R)-3-(dimethylamino)pyrrolidin-1-yl]-6-fluoroquinolin-2(1H)-one	516.6
560	7-(3-acetyl-1H-pyrrol-1-yl)-4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-fluoroquinolin-2(1H)-one	511.6
561	ethyl 4-[4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-2-oxo-1,2-dihydroquinolin-6-yl]benzoate	534.6
562	methyl 3-[4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-2-oxo-1,2-dihydroquinolin-6-yl]benzoate	520.6
563	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-{[2-(diethylamino)ethyl]amino}-6-fluoroquinolin-2(1H)-one	518.6
564	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-fluoro-7-[(2-pyrrolidin-1-ylethyl)amino]quinolin-2(1H)-one	516.6
565	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-fluoro-7-[(2-piperidin-1-ylethyl)amino]quinolin-2(1H)-one	530.7
566	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-{[3-(dimethylamino)propyl]amino}-6-fluoroquinolin-2(1H)-one	504.6
567	N-(2-{[4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-fluoro-2-oxo-1,2-dihydroquinolin-7-yl]amino}ethyl)acetamide	504.6
568	N-{1-[4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-fluoro-2-oxo-1,2-dihydroquinolin-7-yl]pyrrolidin-3-yl}-2,2,2-trifluoroacetamide	584.6

569	3-{[4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-fluoro-2-oxo-1,2-dihydroquinolin-7-yl]amino}propanenitrile	472.5
570	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-fluoro-7-[(2-hydroxyethyl)amino]quinolin-2(1H)-one	463.5
571	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-fluoro-7-[(2-methoxyethyl)amino]quinolin-2(1H)-one	477.6
572	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-fluoro-7-(3-hydroxypiperidin-1-yl)quinolin-2(1H)-one	503.6
573	4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-[[2-(dimethylamino)ethyl](methyl)amino]-6-fluoroquinolin-2(1H)-one	504.6
574	4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-{[3-(dimethylamino)propyl]amino}-6-fluoroquinolin-2(1H)-one	504.6
575	4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-{[2-(diethylamino)ethyl]amino}-6-fluoroquinolin-2(1H)-one	518.6
576	4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-fluoro-7-[(2-pyrrolidin-1-ylethyl)amino]quinolin-2(1H)-one	516.6
577	4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-fluoro-7-(3-hydroxypiperidin-1-yl)quinolin-2(1H)-one	530.7
578	4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-fluoro-7-{[3-(2-oxopyrrolidin-1-yl)propyl]amino}quinolin-2(1H)-one	544.6
579	N-(2-{[4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-fluoro-2-oxo-1,2-dihydroquinolin-7-yl]amino}ethyl)acetamide	504.6
580	4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-fluoro-7-[(3-methoxypropyl)amino]quinolin-2(1H)-one	491.6
581	4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-fluoro-7-[(2-methoxyethyl)amino]quinolin-2(1H)-one	477.6
582	4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-fluoro-7-[(2-hydroxyethyl)amino]quinolin-2(1H)-one	463.5
583	4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-[ethyl(methyl)amino]-6-fluoroquinolin-2(1H)-one	461.6
584	4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-(diethylamino)-6-fluoroquinolin-2(1H)-one	475.6

585	N-{(3R)-1-[4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-fluoro-2-oxo-1,2-dihydroquinolin-7-yl]pyrrolidin-3-yl}acetamide	530.6
586	N-{(3S)-1-[4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-fluoro-2-oxo-1,2-dihydroquinolin-7-yl]pyrrolidin-3-yl}acetamide	530.6
587	4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-[(3R)-3-(dimethylamino)pyrrolidin-1-yl]-6-fluoroquinolin-2(1H)-one	516.6
588	N-{1-[4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-fluoro-2-oxo-1,2-dihydroquinolin-7-yl]pyrrolidin-3-yl}-2,2,2-trifluoroacetamide	584.6
589	4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-7-azepan-1-yl-3-(1H-benzimidazol-2-yl)-6-fluoroquinolin-2(1H)-one	501.6
590	4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-fluoro-7-(3-hydroxypiperidin-1-yl)quinolin-2(1H)-one	503.6
591	3-{[4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-fluoro-2-oxo-1,2-dihydroquinolin-7-yl]amino}propanenitrile	472.5
592	4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-fluoro-7-(1H-pyrrol-1-yl)quinolin-2(1H)-one	469.5
593	7-(3-acetyl-1H-pyrrol-1-yl)-4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-fluoroquinolin-2(1H)-one	511.6
594	4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-fluoro-7-(2-methyl-1H-imidazol-1-yl)quinolin-2(1H)-one	484.5
595	4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-[(3S)-3-(dimethylamino)pyrrolidin-1-yl]-6-fluoroquinolin-2(1H)-one	516.6
596	4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-fluoro-7-methoxyquinolin-2(1H)-one	434.5
597	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-[(3S)-3-(dimethylamino)pyrrolidin-1-yl]-6-fluoroquinolin-2(1H)-one	516.6
598	N-{(3S)-1-[4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-fluoro-2-oxo-1,2-dihydroquinolin-7-yl]pyrrolidin-3-yl}acetamide	530.6
599	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-fluoro-7-[(2-pyridin-2-ylethyl)amino]quinolin-2(1H)-one	524.6
600	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-fluoro-7-(isobutylamino)quinolin-2(1H)-one	475.6
601	methyl 3-amino-4-[4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-chloro-2-oxo-1,2-dihydroquinolin-6-yl]benzoate	570.1

602	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-chloro-6-[4-(methylsulfonyl)phenyl]quinolin-2(1H)-one	575.1
603	methyl 3-[4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-chloro-2-oxo-1,2-dihydroquinolin-6-yl]benzoate	555.0
604	1-[4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-fluoro-2-oxo-1,2-dihydroquinolin-7-yl]piperidine-4-carboxylic acid	531.6
605	1-[4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-fluoro-2-oxo-1,2-dihydroquinolin-7-yl]piperidine-3-carboxylic acid	531.6
606	4-[(4-aminobenzyl)amino]-3-(1H-benzimidazol-2-yl)-6,7-dimethoxyquinolin-2(1H)-one	442.5
607	4-(2-{[3-(1H-benzimidazol-2-yl)-6,7-dimethoxy-2-oxo-1,2-dihydroquinolin-4-yl]amino}ethyl)benzenesulfonamide	520.6
608	4-[(3-aminopropyl)amino]-3-(1H-benzimidazol-2-yl)-6,7-dimethoxyquinolin-2(1H)-one	394.4
609	4-[(2-aminoethyl)amino]-3-(1H-benzimidazol-2-yl)-6,7-dimethoxyquinolin-2(1H)-one	380.4
610	3-(1H-benzimidazol-2-yl)-4-{[2-(1H-imidazol-5-yl)ethyl]amino}-6,7-dimethoxyquinolin-2(1H)-one	431.5
611	3-(1H-benzimidazol-2-yl)-4-{[2-(1H-benzimidazol-2-yl)ethyl]amino}-6,7-dimethoxyquinolin-2(1H)-one	481.5
612	4-{[(4-amino-2-methylpyrimidin-5-yl)methyl]amino}-3-(1H-benzimidazol-2-yl)-6,7-dimethoxyquinolin-2(1H)-one	458.5
613	3-(1H-benzimidazol-2-yl)-4-{[2-(5-fluoro-1H-indol-3-yl)ethyl]amino}-6,7-dimethoxyquinolin-2(1H)-one	498.5
614	4-{[2-(4-aminophenyl)ethyl]amino}-3-(1H-benzimidazol-2-yl)-6,7-dimethoxyquinolin-2(1H)-one	456.5
615	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-morpholin-4-ylquinolin-2(1H)-one	471.6
616	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(5,6-difluoro-1H-benzimidazol-2-yl)-6,7-dimethoxyquinolin-2(1H)-one	430.5
617	methyl 3-amino-4-[4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-2-oxo-1,2-dihydroquinolin-7-yl]benzoate	535.6
618	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-[4-(methylsulfonyl)phenyl]quinolin-2(1H)-one	540.7
619	methyl 4-[4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-2-oxo-1,2-dihydroquinolin-7-yl]benzoate	520.6
620	methyl 3-[4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-2-oxo-1,2-dihydroquinolin-7-yl]benzoate	520.6
621	N-{3-[4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-2-oxo-1,2-dihydroquinolin-7-yl]phenyl}acetamide	519.6
622	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(5,6-difluoro-1H-benzimidazol-2-yl)-6,7-dimethoxyquinolin-2(1H)-one	482.5

623	3-(5,6-difluoro-1H-benzimidazol-2-yl)-6,7-dimethoxy-4-(piperidin-3-ylamino)quinolin-2(1H)-one	456.5
624	4-[(4-aminocyclohexyl)amino]-3-(5,6-difluoro-1H-benzimidazol-2-yl)-6,7-dimethoxyquinolin-2(1H)-one	470.5
625	3-(5,6-difluoro-1H-benzimidazol-2-yl)-6,7-dimethoxy-4-(pyrrolidin-3-ylamino)quinolin-2(1H)-one	442.4
626	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-chloro-7-(1H-imidazol-1-yl)quinolin-2(1H)-one	487.0
627	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-[(3-hydroxypropyl)amino]quinolin-2(1H)-one	459.6
628	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-{[3-(2-oxopyrrolidin-1-yl)propyl]amino}quinolin-2(1H)-one	526.7
629	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-(4-methylpiperazin-1-yl)quinolin-2(1H)-one	484.6
630	4-[4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-2-oxo-1,2-dihydroquinolin-7-yl]benzonitrile	487.6
631	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-[2-(trifluoromethyl)phenyl]quinolin-2(1H)-one	530.6
632	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-(1,3-benzodioxol-5-yl)quinolin-2(1H)-one	506.6
633	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-(morpholin-4-ylcarbonyl)quinolin-2(1H)-one	499.6
634	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-N,N-dimethyl-2-oxo-1,2-dihydroquinoline-7-carboxamide	457.5
635	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-2-oxo-1,2-dihydroquinoline-7-carboxamide	429.5
636	3-[4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-2-oxo-1,2-dihydroquinolin-7-yl]benzoic acid	506.6
637	4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-bromoquinolin-2(1H)-one	465.4
638	4-{4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-[4-(ethoxycarbonyl)piperidin-1-yl]-2-oxo-1,2-dihydroquinolin-6-yl}benzoic acid	661.8
639	4-[7-(3-acetyl-1H-pyrrol-1-yl)-4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-2-oxo-1,2-dihydroquinolin-6-yl]benzoic acid	613.7
640	4-[4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-(dimethylamino)-2-oxo-1,2-dihydroquinolin-6-yl]benzoic acid	549.6

641	4-[4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-(1H-imidazol-1-yl)-2-oxo-1,2-dihydroquinolin-6-yl]benzoic acid	572.6
642	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-fluoro-6-iodoquinolin-2(1H)-one	530.4
643	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-fluoro-6-[4-(methylsulfonyl)phenyl]quinolin-2(1H)-one	558.6
644	4-[4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-fluoro-2-oxo-1,2-dihydroquinolin-6-yl]benzamide	523.6
645	6-(4-acetylphenyl)-4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-fluoroquinolin-2(1H)-one	522.6
646	methyl 4-[4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-fluoro-2-oxo-1,2-dihydroquinolin-6-yl]benzoate	538.6
647	methyl 3-amino-4-[4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-fluoro-2-oxo-1,2-dihydroquinolin-6-yl]benzoate	553.6
648	6-(3-acetylphenyl)-4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-fluoroquinolin-2(1H)-one	522.6
649	methyl 3-[4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-fluoro-2-oxo-1,2-dihydroquinolin-6-yl]benzoate	538.6
650	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-fluoro-6-(2-methylphenyl)quinolin-2(1H)-one	494.6
651	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-fluoro-6-(2-methoxyphenyl)quinolin-2(1H)-one	510.6
652	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-(2,4-dichlorophenyl)-7-fluoroquinolin-2(1H)-one	549.4
653	ethyl 1-[4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-iodo-2-oxo-1,2-dihydroquinolin-7-yl]piperidine-4-carboxylate	667.6
654	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-(1H-imidazol-1-yl)-6-iodoquinolin-2(1H)-one	578.4
655	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-(2-ethylphenyl)-7-(1H-imidazol-1-yl)quinolin-2(1H)-one	556.7
656	4-[4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-(1H-imidazol-1-yl)-2-oxo-1,2-dihydroquinolin-6-yl]benzamide	571.7
657	6-(4-acetylphenyl)-4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-(1H-imidazol-1-yl)quinolin-2(1H)-one	570.7

658	6-(3-acetylphenyl)-4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-(1H-imidazol-1-yl)quinolin-2(1H)-one	587.7
659	N-{3-[4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-(1H-imidazol-1-yl)-2-oxo-1,2-dihydroquinolin-6-yl]phenyl}acetamide	585.7
660	6-(3-acetylphenyl)-4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-(1H-imidazol-1-yl)quinolin-2(1H)-one	570.7
661	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-(1H-imidazol-1-yl)-6-(2-methylphenyl)quinolin-2(1H)-one	542.7
662	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-(1H-imidazol-1-yl)-6-(2-methoxyphenyl)quinolin-2(1H)-one	558.7
663	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-(2,4-dichlorophenyl)-7-(1H-imidazol-1-yl)quinolin-2(1H)-one	597.5
664	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-(2-ethylphenyl)quinolin-2(1H)-one	490.6
665	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-(2-ethylphenyl)-7-fluoroquinolin-2(1H)-one	508.6
666	3-[4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-2-oxo-1,2-dihydroquinolin-6-yl]benzoic acid	506.6
667	3-amino-4-[4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-chloro-2-oxo-1,2-dihydroquinolin-6-yl]benzoic acid	556.0
668	3-[4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-chloro-2-oxo-1,2-dihydroquinolin-6-yl]benzoic acid	541.0
669	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-fluoro-7-[(pyridin-2-ylmethyl)amino]quinolin-2(1H)-one	510.6
670	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-fluoro-7-[(3-pyrrolidin-1-ylpropyl)amino]quinolin-2(1H)-one	527.6
671	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-fluoro-7-[(pyridin-3-ylmethyl)amino]quinolin-2(1H)-one	510.6
672	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-fluoro-7-[(3-pyrrolidin-1-ylpropyl)amino]quinolin-2(1H)-one	530.7
673	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-fluoro-7-[(3R)-3-hydroxypyrrolidin-1-yl]quinolin-2(1H)-one	489.6
674	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-fluoro-7-{[2-(1-methylpyrrolidin-2-yl)ethyl]amino}quinolin-2(1H)-one	530.7

675	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-fluoro-7-[(pyridin-4-ylmethyl)amino]quinolin-2(1H)-one	510.6
676	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-fluoro-7-[3-(methylsulfonyl)pyrrolidin-1-yl]quinolin-2(1H)-one	551.7
677	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-fluoro-7-(3-pyridin-4-ylpyrrolidin-1-yl)quinolin-2(1H)-one	550.7
678	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-fluoro-7-[(2-morpholin-4-ylethyl)amino]quinolin-2(1H)-one	532.6
679	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-fluoro-7-[4-(pyridin-4-ylmethyl)piperazin-1-yl]quinolin-2(1H)-one	579.7
680	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-(benzylamino)-6-fluoroquinolin-2(1H)-one	509.6
681	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-fluoro-7-(2-pyridin-3-ylpyrrolidin-1-yl)quinolin-2(1H)-one	550.7
682	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-fluoro-7-[(2-pyridin-4-ylethyl)amino]quinolin-2(1H)-one	524.6
683	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-fluoro-7-[(3-morpholin-4-ylpropyl)amino]quinolin-2(1H)-one	546.7
684	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-fluoro-7-[(4-hydroxycyclohexyl)amino]quinolin-2(1H)-one	524.6
685	7-{[2-(4-aminophenyl)ethyl]amino}-4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-fluoroquinolin-2(1H)-one	538.6
686	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-fluoro-7-[(4-hydroxycyclohexyl)amino]quinolin-2(1H)-one	517.6
687	4-(1-azabicyclo[2.2.2]oct-3-ylamino)-3-(1H-benzimidazol-2-yl)-6-fluoro-7-[(piperidin-3-ylmethyl)amino]quinolin-2(1H)-one	516.6
688	4-(1-azabicyclo[2.2.2]oct-3-ylamino)-3-(1H-benzimidazol-2-yl)-6-fluoro-7-(pyrrolidin-3-ylamino)quinolin-2(1H)-one	488.6
689	4-[4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-(2-methyl-1H-imidazol-1-yl)-2-oxo-1,2-dihydroquinolin-6-yl]benzoic acid	586.7
690	1-[4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-chloro-2-oxo-1,2-dihydroquinolin-7-yl]piperidine-4-carboxamide	547.1
691	ethyl 1-[4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-chloro-2-oxo-1,2-dihydroquinolin-7-yl]piperidine-4-carboxylate	576.1

692	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-(1H-imidazol-1-yl)quinolin-2(1H)-one	452.5
693	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-(2-methyl-1H-imidazol-1-yl)quinolin-2(1H)-one	466.6
694	ethyl 1-[4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-2-oxo-1,2-dihydroquinolin-7-yl]piperidine-4-carboxylate	541.7
695	1-[4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-2-oxo-1,2-dihydroquinolin-7-yl]piperidine-4-carboxamide	512.6
696	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-fluoro-7-[(2-mercaptoethyl)amino]quinolin-2(1H)-one	479.6
697	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-fluoro-7-[4-(pyridin-3-ylmethyl)piperazin-1-yl]quinolin-2(1H)-one	579.7
698	3-(1H-benzimidazol-2-yl)-4-[(2-hydroxyethyl)amino]-6,7-dimethoxyquinolin-2(1H)-one	381.4
699	3-(1H-benzimidazol-2-yl)-4-[(3-hydroxypropyl)amino]-6,7-dimethoxyquinolin-2(1H)-one	395.4
700	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-fluoro-7-{[(1-hydroxycyclohexyl)methyl]amino}quinolin-2(1H)-one	531.6
701	3-(1H-benzimidazol-2-yl)-6,7-dimethoxy-4-[(3-pyrrolidin-1-ylpropyl)amino]quinolin-2(1H)-one	448.5
702	4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-2-oxo-1,2-dihydroquinoline-7-carbonitrile	411.5
703	3-(1H-benzimidazol-2-yl)-6-chloro-4-(pyridin-3-ylamino)quinolin-2(1H)-one	388.8
704	3-(1H-benzimidazol-2-yl)-4-[(1-benzylpiperidin-4-yl)amino]-6-chloroquinolin-2(1H)-one	485.0
705	4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-methoxyquinolin-2(1H)-one	416.5
706	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-bromo-7-methoxyquinolin-2(1H)-one	495.4
707	3-(1H-benzimidazol-2-yl)-6,7-dimethoxy-4-{[(5-methylpyrazin-2-yl)methyl]amino}quinolin-2(1H)-one	443.5
708	4-[(3-amino-2-hydroxypropyl)amino]-3-(1H-benzimidazol-2-yl)-6,7-dimethoxyquinolin-2(1H)-one	410.4
709	3-(1H-benzimidazol-2-yl)-6,7-dimethoxy-4-[(2-methoxyethyl)amino]quinolin-2(1H)-one	395.4
710	{[3-(1H-benzimidazol-2-yl)-6,7-dimethoxy-2-oxo-1,2-dihydroquinolin-4-yl]amino}acetonitrile	376.4
711	3-(1H-benzimidazol-2-yl)-4-{[2-(2-hydroxyethoxy)ethyl]amino}-6,7-dimethoxyquinolin-2(1H)-one	425.5
712	3-(1H-benzimidazol-2-yl)-4-[(3R)-3-hydroxypyrrolidin-1-yl]-6,7-dimethoxyquinolin-2(1H)-one	407.4

713	4-[4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-2-oxo-1,2-dihydroquinolin-7-yl]benzonitrile	487.6
714	4-[4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-2-oxo-1,2-dihydroquinolin-7-yl]benzoic acid	506.6
715	4-[4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-2-oxo-1,2-dihydroquinolin-7-yl]benzamide	505.6
716	methyl 3-[4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-2-oxo-1,2-dihydroquinolin-7-yl]benzoate	520.6
717	6-chloro-3-(5-morpholin-4-yl-1H-benzimidazol-2-yl)-4-({[6-(piperidin-3-yloxy)pyridin-3-yl]methyl}amino)quinolin-2(1H)-one	587.1
718	6-chloro-3-(5-morpholin-4-yl-1H-benzimidazol-2-yl)-4-{[3-(2-oxopyrrolidin-1-yl)propyl]amino}quinolin-2(1H)-one	488.0
719	6-chloro-3-(5-morpholin-4-yl-1H-benzimidazol-2-yl)-4-[(2-pyridin-2-ylethyl)amino]quinolin-2(1H)-one	502.0
720	6-chloro-3-(5-morpholin-4-yl-1H-benzimidazol-2-yl)-4-{[3-(2-oxopyrrolidin-1-yl)propyl]amino}quinolin-2(1H)-one	522.0
721	6-chloro-4-[(6-methoxypyridin-3-yl)amino]-3-(5-morpholin-4-yl-1H-benzimidazol-2-yl)quinolin-2(1H)-one	504.0
722	6-chloro-3-(5-morpholin-4-yl-1H-benzimidazol-2-yl)-4-[(3-pyridin-2-ylpropyl)amino]quinolin-2(1H)-one	516.0
723	6-chloro-3-(5-morpholin-4-yl-1H-benzimidazol-2-yl)-4-(pyridin-4-ylamino)quinolin-2(1H)-one	473.9
724	6-chloro-3-(5-morpholin-4-yl-1H-benzimidazol-2-yl)-4-({[6-(piperidin-3-ylmethoxy)pyridin-3-yl]methyl}amino)quinolin-2(1H)-one	601.1
725	6-chloro-3-(5-morpholin-4-yl-1H-benzimidazol-2-yl)-4-(pyridin-2-ylamino)quinolin-2(1H)-one	473.9
726	1-[4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-chloro-2-oxo-1,2-dihydroquinolin-7-yl]piperidine-4-carboxylic acid	548.1
727	1-[4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-2-oxo-1,2-dihydroquinolin-7-yl]piperidine-4-carboxylic acid	513.6
728	3-[4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-2-oxo-1,2-dihydroquinolin-7-yl]benzoic acid	506.6
729	6-chloro-3-(5-morpholin-4-yl-1H-benzimidazol-2-yl)-4-({[2-(piperidin-4-yloxy)pyridin-3-yl]methyl}amino)quinolin-2(1H)-one	430.5
730	4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6,7-dichloroquinolin-2(1H)-one	455.4
731	6-chloro-3-(5-morpholin-4-yl-1H-benzimidazol-2-yl)-4-({[2-(piperidin-4-yloxy)pyridin-3-yl]methyl}amino)quinolin-2(1H)-one	587.1
732	6-chloro-3-(5-morpholin-4-yl-1H-benzimidazol-2-yl)-4-(pyrazin-2-ylamino)quinolin-2(1H)-one	474.9

733	4-amino-3-(6-thiomorpholin-4-yl-1H-benzimidazol-2-yl)quinolin-2(1H)-one	378.5
734	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-fluoro-7-(3-pyridin-3-ylpyrrolidin-1-yl)quinolin-2(1H)-one	550.7
735	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-5-fluoro-6-[4-(methylsulfonyl)phenyl]quinolin-2(1H)-one	558.6
736	6-(4-acetylphenyl)-4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-5-fluoroquinolin-2(1H)-one	522.6
737	methyl 4-[4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-5-fluoro-2-oxo-1,2-dihydroquinolin-6-yl]benzoate	538.6
738	methyl 3-amino-4-[4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-5-fluoro-2-oxo-1,2-dihydroquinolin-6-yl]benzoate	553.6
739	methyl 3-[4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-5-fluoro-2-oxo-1,2-dihydroquinolin-6-yl]benzoate	538.6
740	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-5-fluoro-6-(2-methylphenyl)quinolin-2(1H)-one	494.6
741	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-(2-ethylphenyl)-5-fluoroquinolin-2(1H)-one	508.6
742	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-5-fluoro-6-(2-methoxyphenyl)quinolin-2(1H)-one	510.6
743	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-(2,4-dichlorophenyl)-5-fluoroquinolin-2(1H)-one	549.4
744	4-[4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-fluoro-2-oxo-1,2-dihydroquinolin-6-yl]benzoic acid	524.6
745	4-[4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-fluoro-2-oxo-1,2-dihydroquinolin-6-yl]benzamide	523.6
746	N-{3-[4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-fluoro-2-oxo-1,2-dihydroquinolin-6-yl]phenyl}acetamide	537.6
747	3-[4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-fluoro-2-oxo-1,2-dihydroquinolin-6-yl]benzoic acid	524.6
748	4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-fluoro-6-(2-methylphenyl)quinolin-2(1H)-one	494.6
749	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-(2-methyl-1H-imidazol-1-yl)-6-[4-(methylsulfonyl)phenyl]quinolin-2(1H)-one	620.7

750	N-{3-[4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-(2-methyl-1H-imidazol-1-yl)-2-oxo-1,2-dihydroquinolin-6-yl]phenyl}acetamide	599.7
751	N-{3-[4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-2-oxo-7-piperidin-1-yl-1,2-dihydroquinolin-6-yl]phenyl}acetamide	602.8
752	N-{3-[7-(3-acetyl-1H-pyrrol-1-yl)-4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-2-oxo-1,2-dihydroquinolin-6-yl]phenyl}acetamide	626.7
753	N-{3-[4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-(dimethylamino)-2-oxo-1,2-dihydroquinolin-6-yl]phenyl}acetamide	562.7
754	N-{3-[4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-(2-ethyl-1H-imidazol-1-yl)-2-oxo-1,2-dihydroquinolin-6-yl]phenyl}acetamide	613.7
755	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-(2-ethyl-1H-imidazol-1-yl)-6-fluoroquinolin-2(1H)-one	498.6
756	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-fluoro-7-(2-isopropyl-1H-imidazol-1-yl)quinolin-2(1H)-one	512.6
757	1-[4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-fluoro-2-oxo-1,2-dihydroquinolin-7-yl]-1H-pyrrole-3-carboxylic acid	513.5
758	4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-chloro-6-iodoquinolin-2(1H)-one	546.8
759	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-5-fluoro-6-iodoquinolin-2(1H)-one	530.4
760	4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-fluoro-6-iodoquinolin-2(1H)-one	530.4
761	6-chloro-3-(5-morpholin-4-yl-1H-benzimidazol-2-yl)-4-[(2-pyridin-3-ylethyl)amino]quinolin-2(1H)-one	502.0
762	4-{[4-(aminomethyl)benzyl]amino}-3-(1H-benzimidazol-2-yl)-7-chloroquinolin-2(1H)-one	430.9
763	3-(1H-benzimidazol-2-yl)-7-chloro-4-{[2-(dimethylamino)ethyl]amino}quinolin-2(1H)-one	382.9
764	3-(1H-benzimidazol-2-yl)-4-(1,4'-bipiperidin-1'-yl)-7-chloroquinolin-2(1H)-one	463.0
765	3-(1H-benzimidazol-2-yl)-7-chloro-4-{[3-(4-methylpiperazin-1-yl)propyl]amino}quinolin-2(1H)-one	452.0
766	3-(1H-benzimidazol-2-yl)-7-chloro-4-[(2-piperidin-1-ylethyl)amino]quinolin-2(1H)-one	422.9
767	3-(1H-benzimidazol-2-yl)-7-chloro-4-{[3-(1H-imidazol-1-yl)propyl]amino}quinolin-2(1H)-one	419.9
768	3-(1H-benzimidazol-2-yl)-7-chloro-4-(pyridin-3-ylamino)quinolin-2(1H)-one	388.8
769	3-(1H-benzimidazol-2-yl)-7-chloro-4-(pyridin-4-ylamino)quinolin-2(1H)-one	388.8
770	3-(1H-benzimidazol-2-yl)-7-chloro-4-({[6-(piperidin-3-yloxy)pyridin-3-yl]methyl}amino)quinolin-2(1H)-one	502.0

771	3-(1H-benzimidazol-2-yl)-7-chloro-4-{[3-(2-oxopyrrolidin-1-yl)propyl]amino}quinolin-2(1H)-one	436.9
772	4-[4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-methoxy-2-oxo-1,2-dihydroquinolin-6-yl]benzoic acid	536.6
773	4-[4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-methoxy-2-oxo-1,2-dihydroquinolin-6-yl]benzamide	535.6
774	6-(4-acetylphenyl)-4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-methoxyquinolin-2(1H)-one	534.6
775	methyl 4-[4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-methoxy-2-oxo-1,2-dihydroquinolin-6-yl]benzoate	550.6
776	methyl 3-amino-4-[4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-methoxy-2-oxo-1,2-dihydroquinolin-6-yl]benzoate	565.6
777	N-{3-[4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-methoxy-2-oxo-1,2-dihydroquinolin-6-yl]phenyl}acetamide	549.6
778	6-(3-acetylphenyl)-4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-methoxyquinolin-2(1H)-one	534.6
779	methyl 3-[4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-methoxy-2-oxo-1,2-dihydroquinolin-6-yl]benzoate	550.6
780	3-[4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-methoxy-2-oxo-1,2-dihydroquinolin-6-yl]benzoic acid	536.6
781	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-methoxy-6-(2-methylphenyl)quinolin-2(1H)-one	506.6
782	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-(2-ethylphenyl)-7-methoxyquinolin-2(1H)-one	520.6
783	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-methoxy-6-(2-methoxyphenyl)quinolin-2(1H)-one	522.6
784	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-(2,4-dichlorophenyl)-7-methoxyquinolin-2(1H)-one	561.5
785	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-[2-(dimethylamino)ethoxy]-6-fluoroquinolin-2(1H)-one	491.6
786	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-fluoro-7-[(2S)-pyrrolidin-2-ylmethoxy]quinolin-2(1H)-one	503.6
787	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-fluoro-7-[2-(2-oxopyrrolidin-1-yl)ethoxy]quinolin-2(1H)-one	531.6

788	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-fluoro-7-{[(2S)-1-(4-nitrophenyl)pyrrolidin-2-yl]methoxy}quinolin-2(1H)-one	624.7
789	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-fluoro-7-[(1-methylpiperidin-2-yl)methoxy]quinolin-2(1H)-one	531.6
790	3-(1H-benzimidazol-2-yl)-6,7-dimethoxy-4-{[2-(1-methylpyrrolidin-2-yl)ethyl]amino}quinolin-2(1H)-one	448.5
791	3-(1H-benzimidazol-2-yl)-6,7-dimethoxy-4-{[2-(methylsulfonyl)ethyl]amino}quinolin-2(1H)-one	443.5
792	3-(1H-benzimidazol-2-yl)-6,7-dimethoxy-4-[(2-morpholin-4-yl-2-pyridin-3-ylethyl)amino]quinolin-2(1H)-one	527.6
793	7-[(2-aminoethyl)amino]-4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-fluoroquinolin-2(1H)-one	462.5
794	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-fluoro-7-(3-phenylthiomorpholin-4-yl)quinolin-2(1H)-one	581.7
795	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-fluoro-7-(2-phenylthiomorpholin-4-yl)quinolin-2(1H)-one	581.7
796	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-fluoro-7-{[2-(phenylsulfonyl)ethyl]amino}quinolin-2(1H)-one	587.7
797	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-fluoro-7-{[2-(methylsulfonyl)ethyl]amino}quinolin-2(1H)-one	525.6
798	7-{[(2R)-2-aminopropyl]amino}-4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-fluoroquinolin-2(1H)-one	476.6
799	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-fluoro-7-[(2-morpholin-4-yl-2-pyridin-3-ylethyl)amino]quinolin-2(1H)-one	609.7
800	3-[4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-fluoro-2-oxo-1,2-dihydroquinolin-6-yl]benzoic acid	524.6
801	4-[4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-(1H-imidazol-1-yl)-2-oxo-1,2-dihydroquinolin-6-yl]benzoic acid	572.6
802	4-[4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-(2-methyl-1H-imidazol-1-yl)-2-oxo-1,2-dihydroquinolin-6-yl]benzoic acid	586.7
803	4-[4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-2-oxo-7-piperidin-1-yl-1,2-dihydroquinolin-6-yl]benzoic acid	589.7
804	4-[4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-(2-ethyl-1H-imidazol-1-yl)-2-oxo-1,2-dihydroquinolin-6-yl]benzoic acid	600.7
805	3-[4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-(2-methyl-1H-imidazol-1-yl)-2-oxo-1,2-dihydroquinolin-6-yl]benzoic acid	586.7

806	3-[4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-2-oxo-7-piperidin-1-yl-1,2-dihydroquinolin-6-yl]benzoic acid	589.7
807	6-chloro-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-4-[(piperidin-3-ylmethyl)amino]quinolin-2(1H)-one	507.1
808	3-[4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-(1H-imidazol-1-yl)-2-oxo-1,2-dihydroquinolin-6-yl]benzoic acid	572.6
809	6-chloro-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-4-[(piperidin-4-ylmethyl)amino]quinolin-2(1H)-one	507.1
810	3-[4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-(2-methyl-1H-imidazol-1-yl)-2-oxo-1,2-dihydroquinolin-6-yl]benzoic acid	586.7
811	6-chloro-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-4-[(pyrrolidin-2-ylmethyl)amino]quinolin-2(1H)-one	493.0
812	3-[4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-2-oxo-7-piperidin-1-yl-1,2-dihydroquinolin-6-yl]benzoic acid	589.7
813	4-{[(2R)-2-aminobutyl]amino}-6-chloro-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one	481.0
814	4-{[(2S)-2-amino-3-methylbutyl]amino}-6-chloro-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one	495.0
815	4-{[(1S)-2-amino-1-benzylethyl]amino}-6-chloro-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one	543.1
816	4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-6-chloro-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one	519.1
817	6-chloro-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-4-(piperidin-3-ylamino)quinolin-2(1H)-one	493.0
818	6-chloro-4-{[2-(dimethylamino)ethyl]amino}-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one	481.0
819	7-chloro-3-(5-morpholin-4-yl-1H-benzimidazol-2-yl)-4-(piperidin-4-ylamino)quinolin-2(1H)-one	480.0
820	4-{[(1R,2R)-2-aminocyclohexyl]amino}-3-(1H-benzimidazol-2-yl)-7-chloroquinolin-2(1H)-one	408.9
821	3-(1H-benzimidazol-2-yl)-7-chloro-4-[(3-morpholin-4-ylpropyl)amino]quinolin-2(1H)-one	438.9
822	3-(1H-benzimidazol-2-yl)-7-chloro-4-[(pyridin-3-ylmethyl)amino]quinolin-2(1H)-one	402.9
823	3-(1H-benzimidazol-2-yl)-7-chloro-4-[(2-pyridin-3-ylethyl)amino]quinolin-2(1H)-one	416.9
824	4-{[(1R,2R)-2-aminocyclohexyl]amino}-7-chloro-3-(5-morpholin-4-yl-1H-benzimidazol-2-yl)quinolin-2(1H)-one	494.0
825	4-[(4-aminocyclohexyl)amino]-7-chloro-3-(5-morpholin-4-yl-1H-benzimidazol-2-yl)quinolin-2(1H)-one	494.0
826	7-chloro-4-{[2-(methylamino)ethyl]amino}-3-(5-morpholin-4-yl-1H-benzimidazol-2-yl)quinolin-2(1H)-one	453.9

827	7-chloro-3-(5-morpholin-4-yl-1H-benzimidazol-2-yl)-4-[(pyrrolidin-2-ylmethyl)amino]quinolin-2(1H)-one	480.0
828	4-{[(1S)-2-amino-1-benzylethyl]amino}-7-chloro-3-(5-morpholin-4-yl-1H-benzimidazol-2-yl)quinolin-2(1H)-one	530.0
829	7-chloro-3-(5-morpholin-4-yl-1H-benzimidazol-2-yl)-4-(pyrrolidin-3-ylamino)quinolin-2(1H)-one	466.0
830	3-(1H-benzimidazol-2-yl)-7-chloro-4-[(2-pyrrolidin-1-ylethyl)amino]quinolin-2(1H)-one	408.9
831	3-(1H-benzimidazol-2-yl)-7-chloro-4-[(2-piperidin-2-ylethyl)amino]quinolin-2(1H)-one	422.9
832	3-(1H-benzimidazol-2-yl)-7-chloro-4-[(piperidin-3-ylmethyl)amino]quinolin-2(1H)-one	408.9
833	3-(1H-benzimidazol-2-yl)-7-chloro-4-[(piperidin-4-ylmethyl)amino]quinolin-2(1H)-one	408.9
834	3-(1H-benzimidazol-2-yl)-7-chloro-4-{[(2-methyl-1-piperidin-4-yl-1H-benzimidazol-5-yl)methyl]amino}quinolin-2(1H)-one	539.1
835	4-[(4-aminocyclohexyl)amino]-3-(1H-benzimidazol-2-yl)-7-chloroquinolin-2(1H)-one	408.9
836	3-(1H-benzimidazol-2-yl)-7-chloro-4-(pyrrolidin-3-ylamino)quinolin-2(1H)-one	380.8
837	4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-[4-(trifluoromethyl)phenyl]quinolin-2(1H)-one	530.6
838	4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-[3-(trifluoromethyl)phenyl]quinolin-2(1H)-one	530.6
839	4-amino-5-fluoro-3-[6-(4-isopropylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one	421.5
840	7-chloro-3-(5-morpholin-4-yl-1H-benzimidazol-2-yl)-4-{[(2S)-pyrrolidin-2-ylmethyl]amino}quinolin-2(1H)-one	480.0
841	7-chloro-3-(5-morpholin-4-yl-1H-benzimidazol-2-yl)-4-{[(2R)-pyrrolidin-2-ylmethyl]amino}quinolin-2(1H)-one	480.0
842	7-chloro-4-({[(2S)-1-ethylpyrrolidin-2-yl]methyl}amino)-3-(5-morpholin-4-yl-1H-benzimidazol-2-yl)quinolin-2(1H)-one	508.0
843	7-chloro-4-({[(2R)-1-ethylpyrrolidin-2-yl]methyl}amino)-3-(5-morpholin-4-yl-1H-benzimidazol-2-yl)quinolin-2(1H)-one	508.0
844	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-7-chloro-3-(5-morpholin-4-yl-1H-benzimidazol-2-yl)quinolin-2(1H)-one	506.0
845	7-chloro-3-(5-morpholin-4-yl-1H-benzimidazol-2-yl)-4-[(piperidin-3-ylmethyl)amino]quinolin-2(1H)-one	494.0
846	7-chloro-3-(5-morpholin-4-yl-1H-benzimidazol-2-yl)-4-[(piperidin-4-ylmethyl)amino]quinolin-2(1H)-one	494.0
847	4-{[(2S)-2-amino-3-methylbutyl]amino}-7-chloro-3-(5-morpholin-4-yl-1H-benzimidazol-2-yl)quinolin-2(1H)-one	482.0
848	4-{[4-(aminomethyl)benzyl]amino}-7-chloro-3-(5-morpholin-4-yl-1H-benzimidazol-2-yl)quinolin-2(1H)-one	516.0
849	4-{[(1R)-1-(aminomethyl)propyl]amino}-7-chloro-3-(5-morpholin-4-yl-1H-benzimidazol-2-yl)quinolin-2(1H)-one	468.0

850	7-chloro-4-{[3-(4-methylpiperazin-1-yl)propyl]amino}-3-(5-morpholin-4-yl-1H-benzimidazol-2-yl)quinolin-2(1H)-one	537.1
851	7-chloro-4-{[3-(1H-imidazol-1-yl)propyl]amino}-3-(5-morpholin-4-yl-1H-benzimidazol-2-yl)quinolin-2(1H)-one	505.0
852	7-chloro-3-(5-morpholin-4-yl-1H-benzimidazol-2-yl)-4-[(2-pyrrolidin-1-ylethyl)amino]quinolin-2(1H)-one	494.0
853	7-chloro-3-(5-morpholin-4-yl-1H-benzimidazol-2-yl)-4-[(piperidin-2-ylmethyl)amino]quinolin-2(1H)-one	494.0
854	7-chloro-4-{[2-(dimethylamino)ethyl]amino}-3-(5-morpholin-4-yl-1H-benzimidazol-2-yl)quinolin-2(1H)-one	468.0
855	7-chloro-3-(5-morpholin-4-yl-1H-benzimidazol-2-yl)-4-[(3S)-pyrrolidin-3-ylamino]quinolin-2(1H)-one	466.0
856	4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-(4-hydroxyphenyl)quinolin-2(1H)-one	478.6
857	4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-(3-hydroxyphenyl)quinolin-2(1H)-one	478.6
858	4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-(2-hydroxyphenyl)quinolin-2(1H)-one	478.6
859	3-(1H-benzimidazol-2-yl)-7-chloro-4-{[(2S)-pyrrolidin-2-ylmethyl]amino}quinolin-2(1H)-one	394.9
860	3-(1H-benzimidazol-2-yl)-7-chloro-4-({[(2S)-1-ethylpyrrolidin-2-yl]methyl}amino)quinolin-2(1H)-one	422.9
861	3-(1H-benzimidazol-2-yl)-7-chloro-4-({[(2R)-1-ethylpyrrolidin-2-yl]methyl}amino)quinolin-2(1H)-one	422.9
862	3-(1H-benzimidazol-2-yl)-7-chloro-4-[(3S)-pyrrolidin-3-ylamino]quinolin-2(1H)-one	380.8
863	3-(1H-benzimidazol-2-yl)-6-chloro-4-{[(2S)-pyrrolidin-2-ylmethyl]amino}quinolin-2(1H)-one	394.9
864	3-(1H-benzimidazol-2-yl)-6-chloro-4-{[(2R)-pyrrolidin-2-ylmethyl]amino}quinolin-2(1H)-one	394.9
865	3-(1H-benzimidazol-2-yl)-6-chloro-4-({[(2S)-1-ethylpyrrolidin-2-yl]methyl}amino)quinolin-2(1H)-one	422.9
866	3-(1H-benzimidazol-2-yl)-6-chloro-4-({[(2R)-1-ethylpyrrolidin-2-yl]methyl}amino)quinolin-2(1H)-one	422.9
867	4-amino-3-[5-(1,4'-bipiperidin-1'-ylcarbonyl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one	380.8
868	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-7-bromo-3-(5-morpholin-4-yl-1H-benzimidazol-2-yl)quinolin-2(1H)-one	550.5
869	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-7-bromo-3-(6-methoxy-1H-benzimidazol-2-yl)quinolin-2(1H)-one	495.4
870	3-{[3-(1H-benzimidazol-2-yl)-6,7-dimethoxy-2-oxo-1,2-dihydroquinolin-4-yl]amino}bicyclo[2.2.1]heptane-2-carboxamide	474.5
871	4-[(3-amino-2,2-dimethylpropyl)amino]-3-(1H-benzimidazol-2-yl)-6,7-dimethoxyquinolin-2(1H)-one	422.5
872	3-(1H-benzimidazol-2-yl)-4-{[3-(dimethylamino)-2,2-dimethylpropyl]amino}-6,7-dimethoxyquinolin-2(1H)-one	450.6

873	3-(1H-benzimidazol-2-yl)-7-chloro-4-[(pyridin-2-ylmethyl)amino]quinolin-2(1H)-one	402.9
874	3-(1H-benzimidazol-2-yl)-7-chloro-4-[(2-pyridin-2-ylethyl)amino]quinolin-2(1H)-one	416.9
875	3-(1H-benzimidazol-2-yl)-7-chloro-4-{[2-(methylamino)ethyl]amino}quinolin-2(1H)-one	368.8
876	3-(1H-benzimidazol-2-yl)-7-chloro-4-[(piperidin-2-ylmethyl)amino]quinolin-2(1H)-one	408.9
877	3-(1H-benzimidazol-2-yl)-7-chloro-4-(piperidin-4-ylamino)quinolin-2(1H)-one	394.9
878	4-amino-3-[5-(1,4'-bipiperidin-1'-ylcarbonyl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one	471.6
879	4-amino-3-{5-[(3S)-3-(dimethylnitroryl)pyrrolidin-1-yl]-1H-benzimidazol-2-yl}quinolin-2(1H)-one	405.5
880	4-amino-3-(5-{2-[(dimethylamino)methyl]morpholin-4-yl}-1H-benzimidazol-2-yl)quinolin-2(1H)-one	419.5
881	methyl 4-[4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-5-methyl-2-oxo-1,2-dihydroquinolin-6-yl]benzoate	534.6
882	3-[4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-5-methyl-2-oxo-1,2-dihydroquinolin-6-yl]benzoic acid	520.6
883	4-[4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-5-methyl-2-oxo-1,2-dihydroquinolin-6-yl]benzamide	519.6
884	4-[4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-5-methyl-2-oxo-1,2-dihydroquinolin-6-yl]benzoic acid	520.6
885	4-amino-3-{5-[(2S)-2-(pyrrolidin-1-ylmethyl)pyrrolidin-1-yl]-1H-benzimidazol-2-yl}quinolin-2(1H)-one	429.5
886	2-(4-amino-5-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)-N-methyl-N-(1-methylpiperidin-4-yl)-1H-benzimidazole-6-carboxamide	449.5
887	4-amino-3-(1H-benzimidazol-2-yl)-5-[(1-methylpiperidin-4-yl)oxy]quinolin-2(1H)-one	390.5
888	4-amino-5-(1-azabicyclo[2.2.2]oct-3-yloxy)-3-(1H-benzimidazol-2-yl)quinolin-2(1H)-one	402.5
889	4-amino-5-fluoro-3-{6-[(2-piperidin-1-ylethyl)amino]-1H-benzimidazol-2-yl}quinolin-2(1H)-one	421.5
890	4,6-diamino-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one	390.5
891	2-(4-amino-5-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)-1H-benzimidazole-5-carboxylic acid	339.3
892	2-(4-amino-2-oxo-1,2-dihydroquinolin-3-yl)-N-pyridin-3-yl-1H-benzimidazole-5-carboxamide	397.4
893	4-amino-3-(5-{[(3R)-3-hydroxypyrrolidin-1-yl]carbonyl}-1H-benzimidazol-2-yl)quinolin-2(1H)-one	390.4
894	N-{4-amino-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-2-oxo-1,2-dihydroquinolin-6-yl}acetamide	432.5

895	4-amino-5-fluoro-3-(6-morpholin-4-yl-1H-benzimidazol-2-yl)quinolin-2(1H)-one	380.4
896	3-(5-chloro-1H-benzimidazol-2-yl)-4-{[2-(dimethylamino)ethyl]amino}-6-methylquinolin-2(1H)-one	396.9
897	4-{[(1R,2R)-2-aminocyclohexyl]amino}-3-(5-chloro-1H-benzimidazol-2-yl)-6-methylquinolin-2(1H)-one	422.9
898	3-(5-chloro-1H-benzimidazol-2-yl)-6-methyl-4-[(piperidin-3-ylmethyl)amino]quinolin-2(1H)-one	422.9
899	3-(5-chloro-1H-benzimidazol-2-yl)-6-methyl-4-[(piperidin-4-ylmethyl)amino]quinolin-2(1H)-one	422.9
900	4-[(4-aminocyclohexyl)amino]-3-(5-chloro-1H-benzimidazol-2-yl)-6-methylquinolin-2(1H)-one	422.9
901	3-(5-chloro-1H-benzimidazol-2-yl)-6-methyl-4-{[2-(methylamino)ethyl]amino}quinolin-2(1H)-one	382.9
902	3-(5-chloro-1H-benzimidazol-2-yl)-6-methyl-4-(pyrrolidin-3-ylamino)quinolin-2(1H)-one	394.9
903	3-(5-chloro-1H-benzimidazol-2-yl)-6-methyl-4-[(piperidin-2-ylmethyl)amino]quinolin-2(1H)-one	422.9
904	4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(5-chloro-1H-benzimidazol-2-yl)-6-methylquinolin-2(1H)-one	434.9
905	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(5-chloro-1H-benzimidazol-2-yl)-6-methylquinolin-2(1H)-one	434.9
906	4-amino-3-(6-{(2R,5R)-2-[(dimethylamino)methyl]-5-methylmorpholin-4-yl}-1H-benzimidazol-2-yl)quinolin-2(1H)-one	433.5
907	4-amino-3-(5-{[(3R)-3-hydroxypiperidin-1-yl]carbonyl}-1H-benzimidazol-2-yl)quinolin-2(1H)-one	404.4
908	2-(4-amino-2-oxo-1,2-dihydroquinolin-3-yl)-N-(2-piperidin-1-ylethyl)-1H-benzimidazole-5-carboxamide	431.5
909	4-amino-3-[5-(piperazin-1-ylcarbonyl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one	389.4
910	N-{4-amino-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-2-oxo-1,2-dihydroquinolin-6-yl}-2,2-dimethylpropanamide	474.6
911	N-{4-amino-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-2-oxo-1,2-dihydroquinolin-6-yl}-3-phenylpropanamide	522.6
912	N-{4-amino-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-2-oxo-1,2-dihydroquinolin-6-yl}-2-(benzyloxy)acetamide	538.6
913	N-{4-amino-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-2-oxo-1,2-dihydroquinolin-6-yl}-2-thien-2-ylacetamide	514.6
914	N-{4-amino-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-2-oxo-1,2-dihydroquinolin-6-yl}-2-furamide	484.5
915	2-(4-amino-2-oxo-1,2-dihydroquinolin-3-yl)-N-(2-pyrrolidin-1-ylethyl)-1H-benzimidazole-5-carboxamide	417.5
916	ethyl (4-{[2-(4-amino-2-oxo-1,2-dihydroquinolin-3-yl)-1H-benzimidazol-5-yl]carbonyl}piperazin-1-yl)acetate	475.5

917	N-{4-amino-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-2-oxo-1,2-dihydroquinolin-6-yl}-N'-phenylurea	509.6
918	N-{4-amino-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-2-oxo-1,2-dihydroquinolin-6-yl}-N'-benzylurea	523.6
919	N-{4-amino-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-2-oxo-1,2-dihydroquinolin-6-yl}-N'-(2-phenylethyl)urea	537.6
920	N-{4-amino-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-2-oxo-1,2-dihydroquinolin-6-yl}benzamide	494.6
921	2-(4-amino-2-oxo-1,2-dihydroquinolin-3-yl)-N-piperidin-3-yl-1H-benzimidazole-5-carboxamide	403.5
922	2-(4-amino-2-oxo-1,2-dihydroquinolin-3-yl)-N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-1H-benzimidazole-6-carboxamide	429.5
923	2-(4-amino-2-oxo-1,2-dihydroquinolin-3-yl)-N-[2-(diethylamino)ethyl]-N-ethyl-1H-benzimidazole-5-carboxamide	447.6
924	4-amino-3-[6-(pyridin-4-yloxy)-1H-benzimidazol-2-yl]quinolin-2(1H)-one	370.4
925	4-amino-5-fluoro-3-{6-[(4-methylpiperazin-1-yl)carbonyl]-1H-benzimidazol-2-yl}quinolin-2(1H)-one	421.4
926	4-amino-5-fluoro-3-{6-[(4-isopropylpiperazin-1-yl)carbonyl]-1H-benzimidazol-2-yl}quinolin-2(1H)-one	449.5
927	4-amino-3-{6-[(4-cyclohexylpiperazin-1-yl)carbonyl]-1H-benzimidazol-2-yl}-5-fluoroquinolin-2(1H)-one	489.6
928	4-amino-6-(isobutylamino)-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one	446.6
929	2-(4-amino-5-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)-N-methyl-N-(1-methylpyrrolidin-3-yl)-1H-benzimidazole-6-carboxamide	488.6
930	4-amino-6-[(2-methylbutyl)amino]-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one	460.6
931	4-amino-6-[(cyclohexylmethyl)amino]-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one	486.6
932	4-amino-3-(6-{[(3S)-3-methylpiperazin-1-yl]carbonyl}-1H-benzimidazol-2-yl)quinolin-2(1H)-one	403.5
933	2-(4-amino-2-oxo-1,2-dihydroquinolin-3-yl)-N-[(3S)-1-azabicyclo[2.2.2]oct-3-yl]-1H-benzimidazole-6-carboxamide	429.5
934	4-amino-3-[6-(1,4'-bipiperidin-1'-ylcarbonyl)-1H-benzimidazol-2-yl]-5-fluoroquinolin-2(1H)-one	489.6
935	2-(4-amino-5-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)-N-methyl-N-(1-methylpyrrolidin-3-yl)-1H-benzimidazole-6-carboxamide	435.5
936	4-amino-3-(1H-benzimidazol-2-yl)-5-[(4-methoxyphenyl)thio]quinolin-2(1H)-one	415.5

937	4-amino-3-(1H-benzimidazol-2-yl)-5-[(4-methoxyphenyl)sulfonyl]quinolin-2(1H)-one	447.5
938	4-amino-3-(1H-benzimidazol-2-yl)-5-[(2-methoxyphenyl)thio]quinolin-2(1H)-one	415.5
939	N-(4-{[2-(4-amino-2-oxo-1,2-dihydroquinolin-3-yl)-1H-benzimidazol-5-yl]oxy}phenyl)acetamide	426.4
940	4-amino-6-(benzylamino)-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one	480.6
941	4-amino-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-6-{[(3-phenoxythien-2-yl)methyl]amino}quinolin-2(1H)-one	578.7
942	4-amino-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-6-{[(3-methylthien-2-yl)methyl]amino}quinolin-2(1H)-one	500.6
943	4-amino-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-6-[(1,3-thiazol-2-ylmethyl)amino]quinolin-2(1H)-one	487.6
944	4-amino-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-6-[(pyrazin-2-ylmethyl)amino]quinolin-2(1H)-one	482.6
945	4-amino-3-(5-{2-[(dimethylamino)methyl]-1,4-oxazepan-4-yl}-1H-benzimidazol-2-yl)-5-fluoroquinolin-2(1H)-one	433.5
946	4-amino-3-(5-{2-[(dimethylamino)methyl]-1,4-oxazepan-4-yl}-1H-benzimidazol-2-yl)-5-fluoroquinolin-2(1H)-one	451.5
947	6-chloro-4-{[2-(dimethylamino)-2-pyridin-3-ylethyl]amino}-3-(5-morpholin-4-yl-1H-benzimidazol-2-yl)quinolin-2(1H)-one	545.1
948	6-amino-4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)quinolin-2(1H)-one	401.5
949	6-chloro-3-(5-chloro-1H-benzimidazol-2-yl)-4-{[2-(dimethylamino)ethyl]amino}quinolin-2(1H)-one	417.3
950	4-{[(1R,2R)-2-aminocyclohexyl]amino}-6-chloro-3-(5-chloro-1H-benzimidazol-2-yl)quinolin-2(1H)-one	443.3
951	6-chloro-3-(5-chloro-1H-benzimidazol-2-yl)-4-[(piperidin-3-ylmethyl)amino]quinolin-2(1H)-one	443.3
952	6-chloro-3-(5-chloro-1H-benzimidazol-2-yl)-4-[(piperidin-4-ylmethyl)amino]quinolin-2(1H)-one	443.3
953	4-[(4-aminocyclohexyl)amino]-6-chloro-3-(5-chloro-1H-benzimidazol-2-yl)quinolin-2(1H)-one	443.3
954	6-chloro-3-(5-chloro-1H-benzimidazol-2-yl)-4-{[2-(methylamino)ethyl]amino}quinolin-2(1H)-one	403.3
955	6-chloro-3-(5-chloro-1H-benzimidazol-2-yl)-4-(pyrrolidin-3-ylamino)quinolin-2(1H)-one	415.3
956	6-chloro-3-(5-chloro-1H-benzimidazol-2-yl)-4-[(piperidin-2-ylmethyl)amino]quinolin-2(1H)-one	443.3
957	4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-6-chloro-3-(5-chloro-1H-benzimidazol-2-yl)quinolin-2(1H)-one	455.4
958	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-6-chloro-3-(5-chloro-1H-benzimidazol-2-yl)quinolin-2(1H)-one	455.4
959	4-amino-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-6-{[(2S)-pyrrolidin-2-ylmethyl]amino}quinolin-2(1H)-one	473.6

960	4-amino-6-{[(5-methylisoxazol-3-yl)methyl]amino}-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one	485.6
961	4-amino-3-(5-{(2S,5R)-2-[(dimethylamino)methyl]-5-methylmorpholin-4-yl}-1H-benzimidazol-2-yl)quinolin-2(1H)-one	433.5
962	3-(5-chloro-1H-benzimidazol-2-yl)-4-{[2-(dimethylamino)ethyl]amino}-6,7-difluoroquinolin-2(1H)-one	418.8
963	4-{[(1R,2R)-2-aminocyclohexyl]amino}-3-(5-chloro-1H-benzimidazol-2-yl)-6,7-difluoroquinolin-2(1H)-one	444.9
964	3-(5-chloro-1H-benzimidazol-2-yl)-6,7-difluoro-4-[(piperidin-3-ylmethyl)amino]quinolin-2(1H)-one	444.9
965	3-(5-chloro-1H-benzimidazol-2-yl)-6,7-difluoro-4-[(piperidin-4-ylmethyl)amino]quinolin-2(1H)-one	444.9
966	4-[(4-aminocyclohexyl)amino]-3-(5-chloro-1H-benzimidazol-2-yl)-6,7-difluoroquinolin-2(1H)-one	444.9
967	3-(5-chloro-1H-benzimidazol-2-yl)-6,7-difluoro-4-{[2-(methylamino)ethyl]amino}quinolin-2(1H)-one	404.8
968	3-(5-chloro-1H-benzimidazol-2-yl)-6,7-difluoro-4-(pyrrolidin-3-ylamino)quinolin-2(1H)-one	416.8
969	3-(5-chloro-1H-benzimidazol-2-yl)-6,7-difluoro-4-[(piperidin-2-ylmethyl)amino]quinolin-2(1H)-one	444.9
970	4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(5-chloro-1H-benzimidazol-2-yl)-6,7-difluoroquinolin-2(1H)-one	456.9
971	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(5-chloro-1H-benzimidazol-2-yl)-6,7-difluoroquinolin-2(1H)-one	456.9
972	4-amino-3-(6-{[(3R)-3-methylpiperazin-1-yl]carbonyl}-1H-benzimidazol-2-yl)quinolin-2(1H)-one	403.5
973	4-amino-3-(5-{[(3S)-3-hydroxypyrrolidin-1-yl]carbonyl}-1H-benzimidazol-2-yl)quinolin-2(1H)-one	390.4
974	4-amino-3-(5-{[4-(2-hydroxyethyl)piperazin-1-yl]carbonyl}-1H-benzimidazol-2-yl)quinolin-2(1H)-one	433.5
975	4-amino-3-[6-(4-isopropylpiperazin-1-yl)-1H-benzimidazol-2-yl]-5-methoxyquinolin-2(1H)-one	433.5
976	4-amino-3-(5-{3-[(dimethylamino)methyl]pyrrolidin-1-yl}-1H-benzimidazol-2-yl)quinolin-2(1H)-one	403.5
977	4-amino-3-(5-{3-[(dimethylamino)methyl]pyrrolidin-1-yl}-1H-benzimidazol-2-yl)-5-fluoroquinolin-2(1H)-one	421.5
978	4-amino-3-(6-{(2R,5S)-2-[(dimethylamino)methyl]-5-methylmorpholin-4-yl}-1H-benzimidazol-2-yl)quinolin-2(1H)-one	433.5
979	4-amino-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-6-(piperidin-4-ylamino)quinolin-2(1H)-one	473.6
980	6-chloro-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-4-[(3S)-pyrrolidin-3-ylamino]quinolin-2(1H)-one	479.0
981	4-amino-3-{5-[(3R)-3-(dimethylamino)pyrrolidin-1-yl]-1H-benzimidazol-2-yl}-5-fluoroquinolin-2(1H)-one	407.5
982	4-amino-3-{5-[(3S)-3-(dimethylamino)pyrrolidin-1-yl]-1H-benzimidazol-2-yl}-5-fluoroquinolin-2(1H)-one	407.5

983	4-amino-3-[6-(2,6-dimethylmorpholin-4-yl)-1H-benzimidazol-2-yl]-5-fluoroquinolin-2(1H)-one	408.4
984	4-amino-3-{6-[(3-aminopyrrolidin-1-yl)carbonyl]-1H-benzimidazol-2-yl}quinolin-2(1H)-one	389.4
985	ethyl (3S,4R)-4-({[2-(4-amino-2-oxo-1,2-dihydroquinolin-3-yl)-1H-benzimidazol-6-yl]carbonyl}amino)-3-methoxypiperidine-1-carboxylate	505.5
986	6-amino-3-(1H-benzimidazol-2-yl)-4-[(3S)-pyrrolidin-3-ylamino]quinolin-2(1H)-one	361.4
987	4-amino-3-(6-{(2R,5S)-2-[(dimethylamino)methyl]-5-methylmorpholin-4-yl}-1H-benzimidazol-2-yl)-5-fluoroquinolin-2(1H)-one	451.5
988	N-{(3S)-1-[2-(4-amino-2-oxo-1,2-dihydroquinolin-3-yl)-1H-benzimidazol-6-yl]pyrrolidin-3-yl}-N-methylacetamide	417.5
989	2-(4-amino-2-oxo-1,2-dihydroquinolin-3-yl)-N-piperidin-4-yl-1H-benzimidazole-6-carboxamide	403.5
990	2-(4-amino-2-oxo-1,2-dihydroquinolin-3-yl)-N-[2-(1-methylpyrrolidin-2-yl)ethyl]-1H-benzimidazole-6-carboxamide	431.5
991	N-{4-amino-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-2-oxo-1,2-dihydroquinolin-6-yl}-N'-isopropylurea	475.6
992	N-{4-amino-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-2-oxo-1,2-dihydroquinolin-6-yl}-N'-(3,5-dimethylphenyl)urea	537.6
993	N-allyl-N'-{4-amino-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-2-oxo-1,2-dihydroquinolin-6-yl}urea	473.6
994	N-{4-amino-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-2-oxo-1,2-dihydroquinolin-6-yl}-N'-(*tert*-butyl)urea	489.6
995	N-{4-amino-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-2-oxo-1,2-dihydroquinolin-6-yl}-N'-[2-(methylthio)phenyl]urea	555.7
996	N-{4-amino-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-2-oxo-1,2-dihydroquinolin-6-yl}heptanamide	502.6
997	4-amino-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-6-(neopentylamino)quinolin-2(1H)-one	460.6
998	N-{4-amino-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-2-oxo-1,2-dihydroquinolin-6-yl}-N'-(3,4-dichlorophenyl)urea	578.5
999	N-{4-amino-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-2-oxo-1,2-dihydroquinolin-6-yl}-N'-[3-(trifluoromethyl)phenyl]urea	577.6
1000	N-{4-amino-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-2-oxo-1,2-dihydroquinolin-6-yl}-N'-heptylurea	531.7
1001	N-{4-amino-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-2-oxo-1,2-dihydroquinolin-6-yl}-N'-(2-ethoxyphenyl)urea	553.6

1002	N-{4-amino-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-2-oxo-1,2-dihydroquinolin-6-yl}-2-methylpropanamide	460.6
1003	N-{4-amino-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-2-oxo-1,2-dihydroquinolin-6-yl}-4-ethylbenzamide	522.6
1004	N-{4-amino-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-2-oxo-1,2-dihydroquinolin-6-yl}-4-cyanobenzamide	519.6
1005	N-{4-amino-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-2-oxo-1,2-dihydroquinolin-6-yl}cyclohexanecarboxamide	500.6
1006	N-{4-amino-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-2-oxo-1,2-dihydroquinolin-6-yl}pyrazine-2-carboxamide	496.5
1007	N-{4-amino-3-[6-(4-methylpiperazinyl)benzimidazol-2-yl]-2-oxo(6-hydroquinolyl)}-2-[benzylamino]acetamide	537.6
1008	4-amino-6-[methyl(1-methylpiperidin-4-yl)amino]-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one	501.6
1009	4-amino-6-[({5-[(dimethylamino)methyl]-2-furyl}methyl)amino]-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one	527.6
1010	4-amino-6-{[(2-ethyl-5-methyl-4H-imidazol-4-yl)methyl]amino}-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one	512.6
1011	N-{4-amino-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-2-oxo-1,2-dihydroquinolin-6-yl}butanamide	460.6
1012	4-amino-3-(5-{[(2R)-2-(pyrrolidin-1-ylmethyl)pyrrolidin-1-yl]carbonyl}-1H-benzimidazol-2-yl)quinolin-2(1H)-one	457.5
1013	4-amino-3-[5-({(2R,5R)-2-[(dimethylamino)methyl]-5-methylmorpholin-4-yl}carbonyl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one	461.5
1014	4-amino-3-[5-({(2S,5R)-2-[(dimethylamino)methyl]-5-methylmorpholin-4-yl}carbonyl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one	461.5
1015	4-amino-5-fluoro-3-(6-{[(3S)-3-methylpiperazin-1-yl]carbonyl}-1H-benzimidazol-2-yl)quinolin-2(1H)-one	421.4
1016	4-amino-5-fluoro-3-(6-{[(3R)-3-methylpiperazin-1-yl]carbonyl}-1H-benzimidazol-2-yl)quinolin-2(1H)-one	421.4
1017	4-amino-5-fluoro-3-(5-{[(2R)-2-(pyrrolidin-1-ylmethyl)pyrrolidin-1-yl]carbonyl}-1H-benzimidazol-2-yl)quinolin-2(1H)-one	475.5
1018	4-amino-6-(dimethylamino)-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one	418.5
1019	4-amino-6-(methylamino)-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one	404.5
1020	4-amino-5-fluoro-3-[5-fluoro-6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one	411.4

1021	4-amino-3-[6-({(2R,5S)-2-[(dimethylamino)methyl]-5-methylmorpholin-4-yl}carbonyl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one	461.5
1022	4-amino-3-[6-({(2S,5S)-2-[(dimethylamino)methyl]-5-methylmorpholin-4-yl}carbonyl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one	461.5
1023	4-amino-3-{6-[(3,5-dimethylpiperazin-1-yl)carbonyl]-1H-benzimidazol-2-yl}quinolin-2(1H)-one	417.5
1024	4-amino-3-[5-(4-ethylpiperazin-1-yl)-1H-benzimidazol-2-yl]-5-fluoroquinolin-2(1H)-one	407.5
1025	4-amino-3-[6-({(2R,5S)-2-[(dimethylamino)methyl]-5-methylmorpholin-4-yl}carbonyl)-1H-benzimidazol-2-yl]-5-fluoroquinolin-2(1H)-one	479.5
1026	4-amino-3-[6-({(2S,5S)-2-[(dimethylamino)methyl]-5-methylmorpholin-4-yl}carbonyl)-1H-benzimidazol-2-yl]-5-fluoroquinolin-2(1H)-one	479.5
1027	4-amino-3-[5-({(2R,5R)-2-[(dimethylamino)methyl]-5-methylmorpholin-4-yl}carbonyl)-1H-benzimidazol-2-yl]-5-fluoroquinolin-2(1H)-one	479.5
1028	4-amino-3-[5-({(2S,5R)-2-[(dimethylamino)methyl]-5-methylmorpholin-4-yl}carbonyl)-1H-benzimidazol-2-yl]-5-fluoroquinolin-2(1H)-one	479.5
1029	N-[3-({4-amino-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-2-oxo-1,2-dihydroquinolin-5-yl}oxy)phenyl]acetamide	524.6
1030	4-amino-3-{6-[(4-ethylpiperazin-1-yl)carbonyl]-1H-benzimidazol-2-yl}quinolin-2(1H)-one	417.5
1031	2-(4-amino-2-oxo-1,2-dihydroquinolin-3-yl)-N,N'-dimethyl-1H-benzimidazole-6-carbohydrazide	363.4
1032	2-(4-amino-2-oxo-1,2-dihydroquinolin-3-yl)-N-(tetrahydrofuran-2-ylmethyl)-1H-benzimidazole-6-carboxamide	404.4
1033	4-amino-5-[3-(dimethylamino)phenoxy]-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one	510.6
1034	4-amino-5-(4-aminophenoxy)-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one	482.6
1035	6-chloro-4-{[2-(dimethylamino)ethyl]amino}-3-(6-fluoro-1H-benzimidazol-2-yl)quinolin-2(1H)-one	400.9
1036	4-{[(1R,2R)-2-aminocyclohexyl]amino}-6-chloro-3-(6-fluoro-1H-benzimidazol-2-yl)quinolin-2(1H)-one	426.9
1037	6-chloro-3-(6-fluoro-1H-benzimidazol-2-yl)-4-[(piperidin-3-ylmethyl)amino]quinolin-2(1H)-one	426.9
1038	6-chloro-3-(6-fluoro-1H-benzimidazol-2-yl)-4-[(piperidin-4-ylmethyl)amino]quinolin-2(1H)-one	426.9
1039	4-[(4-aminocyclohexyl)amino]-6-chloro-3-(6-fluoro-1H-benzimidazol-2-yl)quinolin-2(1H)-one	426.9
1040	6-chloro-3-(6-fluoro-1H-benzimidazol-2-yl)-4-{[2-(methylamino)ethyl]amino}quinolin-2(1H)-one	386.8
1041	6-chloro-3-(6-fluoro-1H-benzimidazol-2-yl)-4-[(3S)-pyrrolidin-3-ylamino]quinolin-2(1H)-one	398.8

1042	6-chloro-3-(6-fluoro-1H-benzimidazol-2-yl)-4-[(3R)-pyrrolidin-3-ylamino]quinolin-2(1H)-one	398.8
1043	6-chloro-3-(6-fluoro-1H-benzimidazol-2-yl)-4-[(piperidin-2-ylmethyl)amino]quinolin-2(1H)-one	426.9
1044	4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-6-chloro-3-(6-fluoro-1H-benzimidazol-2-yl)quinolin-2(1H)-one	438.9
1045	6-bromo-4-{[2-(dimethylamino)ethyl]amino}-3-(6-fluoro-1H-benzimidazol-2-yl)quinolin-2(1H)-one	445.3
1046	4-{[(1R,2R)-2-aminocyclohexyl]amino}-6-bromo-3-(6-fluoro-1H-benzimidazol-2-yl)quinolin-2(1H)-one	471.3
1047	6-bromo-3-(6-fluoro-1H-benzimidazol-2-yl)-4-[(piperidin-3-ylmethyl)amino]quinolin-2(1H)-one	471.3
1048	6-bromo-3-(6-fluoro-1H-benzimidazol-2-yl)-4-[(piperidin-4-ylmethyl)amino]quinolin-2(1H)-one	471.3
1049	4-[(4-aminocyclohexyl)amino]-6-bromo-3-(6-fluoro-1H-benzimidazol-2-yl)quinolin-2(1H)-one	471.3
1050	6-bromo-3-(6-fluoro-1H-benzimidazol-2-yl)-4-{[2-(methylamino)ethyl]amino}quinolin-2(1H)-one	431.3
1051	6-bromo-3-(6-fluoro-1H-benzimidazol-2-yl)-4-[(3S)-pyrrolidin-3-ylamino]quinolin-2(1H)-one	443.3
1052	6-bromo-3-(6-fluoro-1H-benzimidazol-2-yl)-4-[(piperidin-2-ylmethyl)amino]quinolin-2(1H)-one	471.3
1053	4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-6-bromo-3-(6-fluoro-1H-benzimidazol-2-yl)quinolin-2(1H)-one	483.4
1054	6-bromo-3-(6-fluoro-1H-benzimidazol-2-yl)-4-[(3R)-pyrrolidin-3-ylamino]quinolin-2(1H)-one	443.3
1055	N-[4-({4-amino-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-2-oxo-1,2-dihydroquinolin-5-yl}oxy)phenyl]acetamide	524.6
1056	4-amino-3-{6-[(4-ethylpiperazin-1-yl)carbonyl]-1H-benzimidazol-2-yl}-5-fluoroquinolin-2(1H)-one	435.5
1057	ethyl (3S,4R)-4-({[2-(4-amino-5-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)-1H-benzimidazol-6-yl]carbonyl}amino)-3-methoxypiperidine-1-carboxylate	523.5
1058	2-(4-amino-5-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)-N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-1H-benzimidazole-6-carboxamide	447.5
1059	2-(4-amino-5-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)-N-[(3S)-1-azabicyclo[2.2.2]oct-3-yl]-1H-benzimidazole-6-carboxamide	447.5
1060	4-amino-5-fluoro-3-{5-[(5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl)carbonyl]-1H-benzimidazol-2-yl}quinolin-2(1H)-one	433.5
1061	4-amino-3-[5-(1,4'-bipiperidin-1'-yl)-1H-benzimidazol-2-yl]-5-fluoroquinolin-2(1H)-one	461.6
1062	4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-6-chloro-3-(7-morpholin-4-yl-1H-benzimidazol-2-yl)quinolin-2(1H)-one	506.0
1063	6-chloro-3-(7-morpholin-4-yl-1H-benzimidazol-2-yl)-4-(piperidin-4-ylamino)quinolin-2(1H)-one	480.0
1064	6-chloro-3-(7-morpholin-4-yl-1H-benzimidazol-2-yl)-4-[(3S)-pyrrolidin-3-ylamino]quinolin-2(1H)-one	466.0

1065	4-amino-7-fluoro-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one	393.4
1066	4-amino-3-{6-[(2,6-dimethylpiperazin-1-yl)carbonyl]-1H-benzimidazol-2-yl}quinolin-2(1H)-one	417.5
1067	4-amino-3-(5-{(2S,5R)-2-[(dimethylamino)methyl]-5-methylmorpholin-4-yl}-1H-benzimidazol-2-yl)-5-fluoroquinolin-2(1H)-one	451.5
1068	6-chloro-3-(5-morpholin-4-yl-1H-benzimidazol-2-yl)-4-[(3S)-pyrrolidin-3-ylamino]quinolin-2(1H)-one	466.0
1069	4-amino-3-(5-{(2S,5S)-2-[(dimethylamino)methyl]-5-methylmorpholin-4-yl}-1H-benzimidazol-2-yl)-5-fluoroquinolin-2(1H)-one	451.5
1070	4-amino-3-(1H-benzimidazol-2-yl)-6-[methyl(1-methylpiperidin-4-yl)amino]quinolin-2(1H)-one	403.5
1071	4-amino-6-[isobutyl(methyl)amino]-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one	460.6
1072	4-amino-6-[(cyclohexylmethyl)(methyl)amino]-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one	500.7
1073	4,6-diamino-3-(6,7-dimethyl-1H-benzimidazol-2-yl)quinolin-2(1H)-one	320.4
1074	4-amino-3-(6,7-dimethyl-1H-benzimidazol-2-yl)-6-(methylamino)quinolin-2(1H)-one	334.4
1075	4-amino-3-(5,6-dimethyl-1H-benzimidazol-2-yl)-6-(methylamino)quinolin-2(1H)-one	334.4
1076	4,6-diamino-3-(1H-benzimidazol-2-yl)quinolin-2(1H)-one	292.3
1077	4-amino-3-(6,7-dimethyl-1H-benzimidazol-2-yl)-6-(isobutylamino)quinolin-2(1H)-one	376.5
1078	4-amino-3-(5,6-dimethyl-1H-benzimidazol-2-yl)-6-(isobutylamino)quinolin-2(1H)-one	376.5
1079	N-(3-{[2-(4-amino-2-oxo-1,2-dihydroquinolin-3-yl)-1H-benzimidazol-6-yl]oxy}phenyl)acetamide	426.4
1080	4-amino-3-[6-(3,4-dimethylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one	389.5
1081	N-[3-({4-amino-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-2-oxo-1,2-dihydroquinolin-6-yl}oxy)phenyl]acetamide	524.6
1082	4-amino-3-(6-{(2R,5R)-2-[(dimethylamino)methyl]-5-methylmorpholin-4-yl}-1H-benzimidazol-2-yl)-5-fluoroquinolin-2(1H)-one	451.5
1083	4-{[(1R,2R)-2-aminocyclohexyl]amino}-6-bromo-3-(6-chloro-5-fluoro-1H-benzimidazol-2-yl)quinolin-2(1H)-one	505.8
1084	6-bromo-3-(6-chloro-5-fluoro-1H-benzimidazol-2-yl)-4-[(piperidin-4-ylmethyl)amino]quinolin-2(1H)-one	505.8
1085	4-[(4-aminocyclohexyl)amino]-6-bromo-3-(6-chloro-5-fluoro-1H-benzimidazol-2-yl)quinolin-2(1H)-one	505.8
1086	6-bromo-3-(6-chloro-5-fluoro-1H-benzimidazol-2-yl)-4-{[2-(methylamino)ethyl]amino}quinolin-2(1H)-one	465.7
1087	6-bromo-3-(6-chloro-5-fluoro-1H-benzimidazol-2-yl)-4-(pyrrolidin-3-ylamino)quinolin-2(1H)-one	477.7

1088	6-bromo-3-(6-chloro-5-fluoro-1H-benzimidazol-2-yl)-4-[(3R)-pyrrolidin-3-ylamino]quinolin-2(1H)-one	477.7
1089	6-bromo-3-(6-chloro-5-fluoro-1H-benzimidazol-2-yl)-4-[(piperidin-2-ylmethyl)amino]quinolin-2(1H)-one	505.8
1090	4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-6-bromo-3-(6-chloro-5-fluoro-1H-benzimidazol-2-yl)quinolin-2(1H)-one	517.8
1091	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-6-bromo-3-(6-chloro-5-fluoro-1H-benzimidazol-2-yl)quinolin-2(1H)-one	517.8
1092	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-6-bromo-3-(6-fluoro-1H-benzimidazol-2-yl)quinolin-2(1H)-one	483.4
1093	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-6-chloro-3-(6-fluoro-1H-benzimidazol-2-yl)quinolin-2(1H)-one	438.9
1094	4-amino-6-[bis(cyclohexylmethyl)amino]-3-(6,7-dimethyl-1H-benzimidazol-2-yl)quinolin-2(1H)-one	512.7
1095	4-amino-6-[bis(cyclohexylmethyl)amino]-3-(5,6-dimethyl-1H-benzimidazol-2-yl)quinolin-2(1H)-one	512.7
1096	4-amino-5-(methylamino)-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one	404.5
1097	4-amino-6-[(cyclohexylmethyl)amino]-3-(6,7-dimethyl-1H-benzimidazol-2-yl)quinolin-2(1H)-one	416.5
1098	4-amino-6-[(cyclohexylmethyl)amino]-3-(5,6-dimethyl-1H-benzimidazol-2-yl)quinolin-2(1H)-one	416.5
1099	4-amino-6,7-difluoro-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one	411.4
1100	4-amino-5-fluoro-3-[6-(2-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one	393.4
1101	4-amino-7-fluoro-3-{6-[(4-isopropylpiperazin-1-yl)carbonyl]-1H-benzimidazol-2-yl}quinolin-2(1H)-one	449.5
1102	4-amino-3-[6-(2,4-dimethylpiperazin-1-yl)-1H-benzimidazol-2-yl]-5-fluoroquinolin-2(1H)-one	407.5
1103	2-(4-amino-7-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)-N-methyl-N-(1-methylpiperidin-4-yl)-1H-benzimidazole-5-carboxamide	449.5
1104	6-chloro-3-(5-chloro-1H-benzimidazol-2-yl)-4-[(3S)-pyrrolidin-3-ylamino]quinolin-2(1H)-one	415.3
1105	4-amino-7-fluoro-3-(5-{[(2R)-2-(pyrrolidin-1-ylmethyl)pyrrolidin-1-yl]carbonyl}-1H-benzimidazol-2-yl)quinolin-2(1H)-one	475.5
1106	4-amino-3-{6-[4-(2-methoxyethyl)piperazin-1-yl]-1H-benzimidazol-2-yl}quinolin-2(1H)-one	419.5
1107	4-amino-3-[5-(methylamino)-1H-benzimidazol-2-yl]quinolin-2(1H)-one	306.3
1108	6-chloro-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-4-{[(3S)-1-methylpyrrolidin-3-yl]amino}quinolin-2(1H)-one	493.0
1109	6-chloro-3-(5-chloro-1H-benzimidazol-2-yl)-4-{[(3S)-1-methylpyrrolidin-3-yl]amino}quinolin-2(1H)-one	429.3
1110	3-(1H-benzimidazol-2-yl)-6-chloro-4-{[(3S)-1-methylpyrrolidin-3-yl]amino}quinolin-2(1H)-one	394.9
1111	3-(1H-benzimidazol-2-yl)-6-chloro-4-[(1-methylpiperidin-4-yl)amino]quinolin-2(1H)-one	408.9

1112	6-chloro-3-(5-chloro-1H-benzimidazol-2-yl)-4-[(1-methylpiperidin-4-yl)amino]quinolin-2(1H)-one	443.3
1113	6-chloro-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-4-[(1-methylpiperidin-4-yl)amino]quinolin-2(1H)-one	507.1
1114	6-chloro-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-4-{[(1-methylpiperidin-2-yl)methyl]amino}quinolin-2(1H)-one	521.1
1115	4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-6-chloro-3-{5-[methyl(1-methylpiperidin-4-yl)amino]-1H-benzimidazol-2-yl}quinolin-2(1H)-one	547.1
1116	6-chloro-3-{5-[methyl(1-methylpiperidin-4-yl)amino]-1H-benzimidazol-2-yl}-4-(piperidin-4-ylamino)quinolin-2(1H)-one	521.1
1117	6-chloro-3-{5-[methyl(1-methylpiperidin-4-yl)amino]-1H-benzimidazol-2-yl}-4-[(3S)-pyrrolidin-3-ylamino]quinolin-2(1H)-one	507.1
1118	4-{[(2R)-2-aminobutyl]amino}-6-chloro-3-{5-[methyl(1-methylpiperidin-4-yl)amino]-1H-benzimidazol-2-yl}quinolin-2(1H)-one	509.1
1119	4-amino-3-{6-[(3S)-3,4-dimethylpiperazin-1-yl]-1H-benzimidazol-2-yl}quinolin-2(1H)-one	389.5
1120	4-amino-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-2-oxo-1,2-dihydroquinoline-6-carbonitrile	400.5
1121	4-amino-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-2-oxo-1,2-dihydroquinoline-6-carboxylic acid	419.5
1122	4-amino-5-fluoro-3-{5-[(8aS)-hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl]-1H-benzimidazol-2-yl}quinolin-2(1H)-one	419.5
1123	4-amino-3-{6-[(3S)-3,4-dimethylpiperazin-1-yl]-1H-benzimidazol-2-yl}-5-fluoroquinolin-2(1H)-one	407.5
1124	4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-6-chloro-3-{6-[(3R)-3-(dimethylamino)pyrrolidin-1-yl]-1H-benzimidazol-2-yl}quinolin-2(1H)-one	533.1
1125	6-chloro-3-{6-[(3R)-3-(dimethylamino)pyrrolidin-1-yl]-1H-benzimidazol-2-yl}-4-(piperidin-4-ylamino)quinolin-2(1H)-one	507.1
1126	6-chloro-3-{6-[(3R)-3-(dimethylamino)pyrrolidin-1-yl]-1H-benzimidazol-2-yl}-4-[(3S)-pyrrolidin-3-ylamino]quinolin-2(1H)-one	493.0
1127	4-{[(2R)-2-aminobutyl]amino}-6-chloro-3-{6-[(3R)-3-(dimethylamino)pyrrolidin-1-yl]-1H-benzimidazol-2-yl}quinolin-2(1H)-one	495.0
1128	6-chloro-3-{6-[(3R)-3-(dimethylamino)pyrrolidin-1-yl]-1H-benzimidazol-2-yl}-4-{[(3S)-1-methylpyrrolidin-3-yl]amino}quinolin-2(1H)-one	507.1
1129	6-chloro-3-{6-[(3R)-3-(dimethylamino)pyrrolidin-1-yl]-1H-benzimidazol-2-yl}-4-[(1-methylpiperidin-4-yl)amino]quinolin-2(1H)-one	521.1
1130	4-amino-7-(methylamino)-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one	404.5

1131	3-(1H-benzimidazol-2-yl)-6-chloro-4-[(2-morpholin-4-yl-2-pyridin-3-ylethyl)amino]quinolin-2(1H)-one	502.0
1132	3-(1H-benzimidazol-2-yl)-6-chloro-4-{[2-(dimethylamino)-2-pyridin-3-ylethyl]amino}quinolin-2(1H)-one	460.0
1133	4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-6-chloro-3-(6-{3-[(dimethylamino)methyl]pyrrolidin-1-yl}-1H-benzimidazol-2-yl)quinolin-2(1H)-one	547.1
1134	6-chloro-3-(6-{3-[(dimethylamino)methyl]pyrrolidin-1-yl}-1H-benzimidazol-2-yl)-4-(piperidin-4-ylamino)quinolin-2(1H)-one	521.1
1135	6-chloro-3-(6-{3-[(dimethylamino)methyl]pyrrolidin-1-yl}-1H-benzimidazol-2-yl)-4-[(3S)-pyrrolidin-3-ylamino]quinolin-2(1H)-one	507.1
1136	4-{[(2R)-2-aminobutyl]amino}-6-chloro-3-(6-{3-[(dimethylamino)methyl]pyrrolidin-1-yl}-1H-benzimidazol-2-yl)quinolin-2(1H)-one	509.1
1137	6-chloro-3-(6-{3-[(dimethylamino)methyl]pyrrolidin-1-yl}-1H-benzimidazol-2-yl)-4-{[(3S)-1-methylpyrrolidin-3-yl]amino}quinolin-2(1H)-one	521.1
1138	6-chloro-3-(6-{3-[(dimethylamino)methyl]pyrrolidin-1-yl}-1H-benzimidazol-2-yl)-4-[(1-methylpiperidin-4-yl)amino]quinolin-2(1H)-one	535.1
1139	3-(1H-benzimidazol-2-yl)-6-chloro-4-{[(3S)-piperidin-3-ylmethyl]amino}quinolin-2(1H)-one	408.9
1140	3-(1H-benzimidazol-2-yl)-6-chloro-4-{[(3R)-piperidin-3-ylmethyl]amino}quinolin-2(1H)-one	408.9
1141	N-(3-{[4-amino-3-(1H-benzimidazol-2-yl)-2-oxo-1,2-dihydroquinolin-5-yl]oxy}phenyl)acetamide	426.4
1142	4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-6-chloro-3-{6-[3-(dimethylamino)pyrrolidin-1-yl]-1H-benzimidazol-2-yl}quinolin-2(1H)-one	533.1
1143	6-chloro-3-{6-[3-(dimethylamino)pyrrolidin-1-yl]-1H-benzimidazol-2-yl}-4-(piperidin-4-ylamino)quinolin-2(1H)-one	507.1
1144	4-{[(2R)-2-aminobutyl]amino}-6-chloro-3-{6-[3-(dimethylamino)pyrrolidin-1-yl]-1H-benzimidazol-2-yl}quinolin-2(1H)-one	495.0
1145	6-chloro-3-{6-[3-(dimethylamino)pyrrolidin-1-yl]-1H-benzimidazol-2-yl}-4-[(1-methylpiperidin-4-yl)amino]quinolin-2(1H)-one	521.1
1146	4-amino-7-[[2-(dimethylamino)ethyl](methyl)amino]-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one	475.6
1147	4-amino-5-fluoro-3-[6-(1,4-oxazepan-4-ylcarbonyl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one	422.4
1148	methyl 4-amino-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-2-oxo-1,2-dihydroquinoline-6-carboxylate	433.5
1149	4-amino-N-benzyl-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-2-oxo-1,2-dihydroquinoline-6-carboxamide	508.6

1150	4-amino-3-{6-[4-(2-morpholin-4-ylethyl)piperazin-1-yl]-1H-benzimidazol-2-yl}quinolin-2(1H)-one	474.6
1151	4-amino-7-fluoro-3-[6-(4-isopropylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one	421.5
1152	4-amino-3-[5-(4-ethylpiperazin-1-yl)-1H-benzimidazol-2-yl]-7-fluoroquinolin-2(1H)-one	407.5
1153	4-amino-3-{6-[(2-aminoethyl)(methyl)amino]-1H-benzimidazol-2-yl}quinolin-2(1H)-one	349.4
1154	4-amino-3-{6-[[(2-ethyl-4-methyl-1H-imidazol-5-yl)methyl](methyl)amino]-1H-benzimidazol-2-yl}quinolin-2(1H)-one	428.5
1155	4-amino-3-[6-(hydroxymethyl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one	307.3
1156	4-amino-3-(6-{methyl[(2R)-pyrrolidin-2-ylmethyl]amino}-1H-benzimidazol-2-yl)quinolin-2(1H)-one	389.5
1157	4-amino-3-{6-[(1H-imidazol-2-ylmethyl)(methyl)amino]-1H-benzimidazol-2-yl}quinolin-2(1H)-one	386.4
1158	4-amino-3-{6-[(2-furylmethyl)(methyl)amino]-1H-benzimidazol-2-yl}quinolin-2(1H)-one	386.4
1159	4-amino-3-{6-[methyl(piperidin-4-ylmethyl)amino]-1H-benzimidazol-2-yl}quinolin-2(1H)-one	403.5
1160	4-amino-3-{6-[methyl(piperidin-3-ylmethyl)amino]-1H-benzimidazol-2-yl}quinolin-2(1H)-one	403.5
1161	4-amino-3-(6-{methyl[2-(methylamino)ethyl]amino}-1H-benzimidazol-2-yl)quinolin-2(1H)-one	363.4
1162	6-acetyl-4-amino-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one	417.5
1163	4-amino-5-[2-(methylamino)phenoxy]-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one	496.6
1164	3-(1H-benzimidazol-2-yl)-6-chloro-4-{[(2S)-piperidin-2-ylmethyl]amino}quinolin-2(1H)-one	408.9
1165	4-amino-3-[6-(1,4-oxazepan-4-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one	376.4
1166	4-amino-3-[5-(4-ethylpiperazin-1-yl)-1H-benzimidazol-2-yl]-6-fluoroquinolin-2(1H)-one	407.5
1167	6-chloro-3-(5-chloro-1H-benzimidazol-2-yl)-4-[(3R)-pyrrolidin-3-ylamino]quinolin-2(1H)-one	415.3
1168	4-amino-6-fluoro-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-7-morpholin-4-ylquinolin-2(1H)-one	478.5
1169	4-amino-6-fluoro-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-7-pyrrolidin-1-ylquinolin-2(1H)-one	462.5
1170	4-amino-7-(dimethylamino)-6-fluoro-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one	436.5
1171	4-amino-6-fluoro-7-(4-methylpiperazin-1-yl)-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one	491.6
1172	4-amino-6-fluoro-7-[(4-methoxybenzyl)amino]-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one	528.6

1173	4-amino-6-fluoro-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-7-[(pyridin-4-ylmethyl)amino]quinolin-2(1H)-one	499.6
1174	4-amino-7-[[2-(dimethylamino)ethyl](methyl)amino]-6-fluoro-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one	493.6
1175	4-amino-3-[6-(4-cyclopentylpiperazin-1-yl)-1H-benzimidazol-2-yl]-5-fluoroquinolin-2(1H)-one	447.5
1176	4-amino-6-[1-(methylamino)ethyl]-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one	432.5
1177	4-amino-5-fluoro-3-[6-(1,4-oxazepan-4-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one	394.4
1178	4-amino-3-{6-[methyl(pyridin-3-ylmethyl)amino]-1H-benzimidazol-2-yl}quinolin-2(1H)-one	397.5
1179	4-amino-3-{6-[({5-[(dimethylamino)methyl]-2-furyl}methyl)(methyl)amino]-1H-benzimidazol-2-yl}quinolin-2(1H)-one	443.5
1180	4-amino-3-[6-(4-oxopiperidin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one	374.4
1181	4-amino-3-{6-[4-(4-methylpiperazin-1-yl)piperidin-1-yl]-1H-benzimidazol-2-yl}quinolin-2(1H)-one	458.6
1182	4-amino-3-[6-(4-{[(4-benzylmorpholin-2-yl)methyl]amino}piperidin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one	564.7
1183	3-(1H-benzimidazol-2-yl)-6-bromo-4-{[2-(dimethylamino)ethyl]amino}quinolin-2(1H)-one	427.3
1184	4-{[(1R,2R)-2-aminocyclohexyl]amino}-3-(1H-benzimidazol-2-yl)-6-bromoquinolin-2(1H)-one	453.4
1185	3-(1H-benzimidazol-2-yl)-6-bromo-4-[(piperidin-4-ylmethyl)amino]quinolin-2(1H)-one	453.4
1186	4-[(4-aminocyclohexyl)amino]-3-(1H-benzimidazol-2-yl)-6-bromoquinolin-2(1H)-one	453.4
1187	3-(1H-benzimidazol-2-yl)-6-bromo-4-{[2-(methylamino)ethyl]amino}quinolin-2(1H)-one	413.3
1188	3-(1H-benzimidazol-2-yl)-6-bromo-4-[(3S)-pyrrolidin-3-ylamino]quinolin-2(1H)-one	425.3
1189	3-(1H-benzimidazol-2-yl)-6-bromo-4-[(3R)-pyrrolidin-3-ylamino]quinolin-2(1H)-one	425.3
1190	3-(1H-benzimidazol-2-yl)-6-bromo-4-[(piperidin-2-ylmethyl)amino]quinolin-2(1H)-one	453.4
1191	4-amino-N-[(3S)-1-azabicyclo[2.2.2]oct-3-yl]-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-2-oxo-1,2-dihydroquinoline-6-carboxamide	527.6
1192	4-amino-N-methyl-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-N-(1-methylpiperidin-4-yl)-2-oxo-1,2-dihydroquinoline-6-carboxamide	529.7
1193	4-amino-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-2-oxo-N-(tetrahydrofuran-2-ylmethyl)-1,2-dihydroquinoline-6-carboxamide	502.6

1194	3-(1H-benzimidazol-2-yl)-6-chloro-4-[(3R)-pyrrolidin-3-ylamino]quinolin-2(1H)-one	380.8
1195	3-(1H-benzimidazol-2-yl)-6-chloro-4-{[(2R)-piperidin-2-ylmethyl]amino}quinolin-2(1H)-one	408.9
1196	4-amino-3-{6-[(3R)-3,4-dimethylpiperazin-1-yl]-1H-benzimidazol-2-yl}-5-fluoroquinolin-2(1H)-one	407.5
1197	6-chloro-3-(6-chloro-5-fluoro-1H-benzimidazol-2-yl)-4-{[2-(dimethylamino)ethyl]amino}quinolin-2(1H)-one	435.3
1198	4-{[(1R,2R)-2-aminocyclohexyl]amino}-6-chloro-3-(6-chloro-5-fluoro-1H-benzimidazol-2-yl)quinolin-2(1H)-one	461.3
1199	6-chloro-3-(6-chloro-5-fluoro-1H-benzimidazol-2-yl)-4-[(piperidin-4-ylmethyl)amino]quinolin-2(1H)-one	461.3
1200	4-[(4-aminocyclohexyl)amino]-6-chloro-3-(6-chloro-5-fluoro-1H-benzimidazol-2-yl)quinolin-2(1H)-one	461.3
1201	6-chloro-3-(6-chloro-5-fluoro-1H-benzimidazol-2-yl)-4-{[2-(methylamino)ethyl]amino}quinolin-2(1H)-one	421.3
1202	6-chloro-3-(6-chloro-5-fluoro-1H-benzimidazol-2-yl)-4-[(3S)-pyrrolidin-3-ylamino]quinolin-2(1H)-one	433.3
1203	6-chloro-3-(6-chloro-5-fluoro-1H-benzimidazol-2-yl)-4-[(3R)-pyrrolidin-3-ylamino]quinolin-2(1H)-one	433.3
1204	6-chloro-3-(6-chloro-5-fluoro-1H-benzimidazol-2-yl)-4-[(piperidin-2-ylmethyl)amino]quinolin-2(1H)-one	461.3
1205	4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-6-chloro-3-(6-chloro-5-fluoro-1H-benzimidazol-2-yl)quinolin-2(1H)-one	473.3
1206	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-6-chloro-3-(6-chloro-5-fluoro-1H-benzimidazol-2-yl)quinolin-2(1H)-one	473.3
1207	4-amino-6-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one	393.4
1208	4-amino-3-(1H-benzimidazol-2-yl)-5-(methylamino)quinolin-2(1H)-one	306.3
1209	4-amino-3-{6-[(2S)-2,4-dimethylpiperazin-1-yl]-1H-benzimidazol-2-yl}-5-fluoroquinolin-2(1H)-one	407.5
1210	4-amino-5-fluoro-3-{6-[(2S)-2-methylpiperazin-1-yl]-1H-benzimidazol-2-yl}quinolin-2(1H)-one	393.4
1211	4-amino-3-{6-[(2S)-4-isopropyl-2-methylpiperazin-1-yl]-1H-benzimidazol-2-yl}quinolin-2(1H)-one	417.5
1212	4-amino-5,7-difluoro-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one	411.4
1213	3-(1H-benzimidazol-2-yl)-6-bromo-4-{[(2S)-piperidin-2-ylmethyl]amino}quinolin-2(1H)-one	453.4
1214	3-(1H-benzimidazol-2-yl)-6-bromo-4-{[(2R)-piperidin-2-ylmethyl]amino}quinolin-2(1H)-one	453.4
1215	4-amino-3-{6-[methyl(1,3-thiazol-2-ylmethyl)amino]-1H-benzimidazol-2-yl}quinolin-2(1H)-one	403.5
1216	4-amino-3-{6-[(1-ethylpiperidin-4-yl)(methyl)amino]-1H-benzimidazol-2-yl}quinolin-2(1H)-one	417.5
1217	4-amino-3-[6-(4-morpholin-4-ylpiperidin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one	445.5
1218	4-amino-3-[6-(4-isopropylpiperazin-1-yl)-1H-benzimidazol-2-yl]-5-(methylamino)quinolin-2(1H)-one	432.5

1219	4-amino-3-{6-[methyl(pyridin-2-ylmethyl)amino]-1H-benzimidazol-2-yl}quinolin-2(1H)-one	397.5
1220	4-amino-3-{6-[(2S)-2,4-dimethylpiperazin-1-yl]-1H-benzimidazol-2-yl}quinolin-2(1H)-one	389.5
1221	4-amino-3-{6-[(2S)-2-methylpiperazin-1-yl]-1H-benzimidazol-2-yl}quinolin-2(1H)-one	375.4
1222	N-[2-(4-amino-2-oxo-1,2-dihydroquinolin-3-yl)-1H-benzimidazol-6-yl]-N-methylacetamide	348.4
1223	4-amino-5-fluoro-3-{6-[(2S)-4-isopropyl-2-methylpiperazin-1-yl]-1H-benzimidazol-2-yl}quinolin-2(1H)-one	435.5
1224	4-amino-3-{6-[(3R)-3,4-dimethylpiperazin-1-yl]-1H-benzimidazol-2-yl}quinolin-2(1H)-one	389.5
1225	4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-(dimethylamino)quinolin-2(1H)-one	429.5
1226	4-amino-3-{6-[(2S)-4-cyclobutyl-2-methylpiperazin-1-yl]-1H-benzimidazol-2-yl}quinolin-2(1H)-one	429.5
1227	4-amino-5-fluoro-3-[6-(methylamino)-1H-benzimidazol-2-yl]quinolin-2(1H)-one	324.3
1228	4-amino-3-(1H-benzimidazol-2-yl)-5-(dimethylamino)quinolin-2(1H)-one	320.4
1229	4-amino-3-(1H-benzimidazol-2-yl)-5-{[2-(dimethylamino)ethyl]amino}quinolin-2(1H)-one	363.4
1230	4-amino-5-fluoro-3-(5-piperazin-1-yl-1H-benzimidazol-2-yl)quinolin-2(1H)-one	379.4
1231	4-amino-3-{5-[[2-(dimethylamino)ethyl](methyl)amino]-1H-benzimidazol-2-yl}-5-fluoroquinolin-2(1H)-one	395.5
1232	4-amino-5-fluoro-3-{5-[methyl(piperidin-3-ylmethyl)amino]-1H-benzimidazol-2-yl}quinolin-2(1H)-one	421.5
1233	4-amino-3-(1H-benzimidazol-2-yl)-5-[[2-(dimethylamino)ethyl](methyl)amino]quinolin-2(1H)-one	377.5
1234	4-amino-5-fluoro-3-{5-[(2R)-4-isopropyl-2-methylpiperazin-1-yl]-1H-benzimidazol-2-yl}quinolin-2(1H)-one	435.5
1235	4-amino-3-{5-[(2S)-4-ethyl-2-methylpiperazin-1-yl]-1H-benzimidazol-2-yl}-5-fluoroquinolin-2(1H)-one	421.5
1236	4-amino-3-(5-{[(1-ethylpyrrolidin-2-yl)methyl]amino}-1H-benzimidazol-2-yl)-5-fluoroquinolin-2(1H)-one	421.5
1237	4-amino-3-(5-{[2-(dimethylamino)-1-methylethyl]amino}-1H-benzimidazol-2-yl)-5-fluoroquinolin-2(1H)-one	395.5
1238	4-amino-3-{5-[[2-(dimethylamino)-1-methylethyl](methyl)amino]-1H-benzimidazol-2-yl}-5-fluoroquinolin-2(1H)-one	409.5
1239	4-amino-3-(1H-benzimidazol-2-yl)-5-(1,2-dimethylhydrazino)quinolin-2(1H)-one	335.4
1240	4-amino-5-fluoro-3-{6-[4-(2-methoxyethyl)piperazin-1-yl]-1H-benzimidazol-2-yl}quinolin-2(1H)-one	437.5
1241	4-amino-5-fluoro-3-{6-[methyl(1-methylpiperidin-4-yl)amino]-1H-benzimidazol-2-yl}quinolin-2(1H)-one	421.5
1242	4-amino-5-fluoro-3-(6-{[3-(4-methylpiperazin-1-yl)propyl]amino}-1H-benzimidazol-2-yl)quinolin-2(1H)-one	450.5

1243	4-amino-5-fluoro-3-(6-{methyl[3-(4-methylpiperazin-1-yl)propyl]amino}-1H-benzimidazol-2-yl)quinolin-2(1H)-one	464.6
1244	N-[2-(4-amino-5-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)-1H-benzimidazol-6-yl]-N-methylacetamide	366.4
1245	4-amino-6-fluoro-3-(5-{[(2R)-2-(pyrrolidin-1-ylmethyl)pyrrolidin-1-yl]carbonyl}-1H-benzimidazol-2-yl)quinolin-2(1H)-one	475.5
1246	4-amino-3-(1H-benzimidazol-2-yl)-5-(ethylamino)quinolin-2(1H)-one	320.4
1247	4-amino-3-{5-[(2R)-2,4-dimethylpiperazin-1-yl]-1H-benzimidazol-2-yl}-5-fluoroquinolin-2(1H)-one	407.5
1248	4-amino-5-fluoro-3-{5-[(2R)-2-methylpiperazin-1-yl]-1H-benzimidazol-2-yl}quinolin-2(1H)-one	393.4
1249	4-amino-3-{5-[(2R)-4-cyclobutyl-2-methylpiperazin-1-yl]-1H-benzimidazol-2-yl}-5-fluoroquinolin-2(1H)-one	447.5
1250	4-amino-5-(dimethylamino)-3-[6-(4-isopropylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one	446.6
1251	4-amino-5-{[2-(dimethylamino)ethyl]amino}-3-[6-(4-isopropylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one	489.6
1252	4-amino-5-[[2-(dimethylamino)ethyl](methyl)amino]-3-[6-(4-isopropylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one	503.7
1253	4-amino-5-(ethylamino)-3-[6-(4-isopropylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one	446.6
1254	N-[2-(4-amino-2-oxo(3-hydroquinolyl))benzimidazol-6-yl]-2-(dimethylamino)-N-methylacetamide	391.4
1255	4-amino-5-fluoro-3-[6-(9-isopropyl-1-oxa-4,9-diazaspiro[5.5]undec-4-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one	491.6
1256	4-amino-7-fluoro-3-[6-fluoro-5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one	411.4
1257	4-amino-3-(5-{(2S,5S)-2-[(dimethylamino)methyl]-5-methylmorpholin-4-yl}-6-fluoro-1H-benzimidazol-2-yl)-5-fluoroquinolin-2(1H)-one	469.5
1258	4-amino-3-(5-{(2S,5S)-2-[(dimethylamino)methyl]-5-methylmorpholin-4-yl}-6-fluoro-1H-benzimidazol-2-yl)quinolin-2(1H)-one	451.5
1259	4-amino-5-methyl-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one	389.5
1260	4-amino-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-5-(trifluoromethyl)quinolin-2(1H)-one	443.4
1261	4-amino-5-fluoro-3-[6-(2-isopropyl-5-oxa-2,8-diazaspiro[3.5]non-8-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one	463.5
1262	4-amino-6-fluoro-3-[5-(4-isopropylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one	421.5
1263	N-[2-(4-amino-5-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)-1H-benzimidazol-6-yl]-N-methyl-2-(4-methylpiperazin-1-yl)acetamide	464.5

1264	N-[2-(4-amino-5-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)-1H-benzimidazol-6-yl]-N-methyl-2-morpholin-4-ylacetamide	451.5
1265	N-[2-(4-amino-5-fluoro-2-oxo(3-hydroquinolyl))benzimidazol-6-yl]-N-methyl-2-morpholin-4-ylacetamide	492.6
1266	4-amino-5-fluoro-3-(6-methyl-1H-benzimidazol-2-yl)quinolin-2(1H)-one	309.3
1267	4-amino-3-[5-(4-ethylpiperazin-1-yl)-1H-benzimidazol-2-yl]-5-methylquinolin-2(1H)-one	403.5
1268	4-amino-3-{6-[(4-methylpiperazin-1-yl)methyl]-1H-benzimidazol-2-yl}quinolin-2(1H)-one	389.5
1269	4-amino-3-[6-(1,4-diazepan-1-yl)-1H-benzimidazol-2-yl]-5-fluoroquinolin-2(1H)-one	393.4
1270	4-amino-5-fluoro-3-[6-(4-methyl-1,4-diazepan-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one	407.5
1271	3-[6-(4-acetylpiperazin-1-yl)-1H-benzimidazol-2-yl]-4-amino-5-fluoroquinolin-2(1H)-one	421.4
1272	4-amino-3-[6-(4-ethyl-1,4-diazepan-1-yl)-1H-benzimidazol-2-yl]-5-fluoroquinolin-2(1H)-one	421.5
1273	4-amino-5-fluoro-3-[6-(4-isopropyl-1,4-diazepan-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one	435.5

Examples 1274-1404

Examples 1274 to 1404 listed in Table 4 were synthesized using the methods described above such as Methods 1-24 and those set forth in the Schemes and other Examples or modified as apparent to one of reasonable skill in the art using commercially available materials.

Table 4. Table of Examples 1274-1415.

Example	Name	LC/MS m/z (MH+)
1274	4-amino-5-fluoro-3-{6-[(4-methylpiperazin-1-yl)methyl]-1H-benzimidazol-2-yl}quinolin-2(1H)-one	407.4
1275	N-[2-(4-amino-5-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)-1H-benzimidazol-6-yl]-N-(1-methylpiperidin-4-yl)acetamide	449.2
1276	N-[2-(4-amino-5-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)-1H-benzimidazol-6-yl]-2-[(2R,6S)-2,6-dimethylmorpholin-4-yl]-N-methylacetamide	479.3
1277	N-[2-(4-amino-5-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)-1H-benzimidazol-6-yl]-N-methyl-2-piperidin-1-ylacetamide	449.2
1278	N-[2-(4-amino-5-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)-1H-benzimidazol-6-yl]-N-methyl-2-pyrrolidin-1-ylacetamide	435.2

1279	N-[2-(4-amino-5-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)-1H-benzimidazol-6-yl]-2-[(2S)-2-(methoxymethyl)pyrrolidin-1-yl]-N-methylacetamide	479.2
1280	N~1~-[2-(4-amino-5-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)-1H-benzimidazol-6-yl]-N~1~-methyl-N~2~-(1-methylpiperidin-4-yl)glycinamide	478.6
1281	N-[2-(4-amino-5-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)-1H-benzimidazol-6-yl]-2-{(2R,5S)-2-[(dimethylamino)methyl]-5-methylmorpholin-4-yl}-N-methylacetamide	522.7
1282	N-[2-(4-amino-5-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)-1H-benzimidazol-6-yl]-N-methyl-2-(4-methyl-1,4-diazepan-1-yl)acetamide	478.6
1283	N-[2-(4-amino-5-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)-1H-benzimidazol-6-yl]-2-[3-(dimethylamino)pyrrolidin-1-yl]-N-methylacetamide	478.6
1284	4-amino-5-fluoro-3-{6-[4-(methylsulfonyl)piperazin-1-yl]-1H-benzimidazol-2-yl}quinolin-2(1H)-one	457.3
1285	N-[2-(4-amino-5-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)-1H-benzimidazol-6-yl]-N-[3-(4-methylpiperazin-1-yl)propyl]acetamide	492.2
1286	4-amino-5-fluoro-3-(6-{[4-(methylsulfonyl)piperazin-1-yl]methyl}-1H-benzimidazol-2-yl)quinolin-2(1H)-one	471.1
1287	4-amino-5-fluoro-3-(6-{[(2-methoxyethyl)amino]methyl}-1H-benzimidazol-2-yl)quinolin-2(1H)-one	382.2
1288	4-amino-3-{6-[(4-cyclohexylpiperazin-1-yl)methyl]-1H-benzimidazol-2-yl}-5-fluoroquinolin-2(1H)-one	475.2
1289	4-amino-3-{6-[(3,5-dimethylpiperazin-1-yl)methyl]-1H-benzimidazol-2-yl}-5-fluoroquinolin-2(1H)-one	421.1
1290	4-amino-5-fluoro-3-(6-{[(2-morpholin-4-ylethyl)amino]methyl}-1H-benzimidazol-2-yl)quinolin-2(1H)-one	437.2
1291	4-amino-5-fluoro-3-[6-({[2-(2-oxoimidazolidin-1-yl)ethyl]amino}methyl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one	436.3
1292	4-amino-5-fluoro-3-[6-({[3-(1H-imidazol-1-yl)propyl]amino}methyl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one	432.3
1293	4-amino-5-fluoro-3-{6-[(4-pyrrolidin-1-ylpiperidin-1-yl)methyl]-1H-benzimidazol-2-yl}quinolin-2(1H)-one	461.4
1294	4-amino-3-[6-({[(3R)-1-benzylpyrrolidin-3-yl]amino}methyl)-1H-benzimidazol-2-yl]-5-fluoroquinolin-2(1H)-one	483.3
1295	4-amino-5-fluoro-3-(6-{[(1-methylpiperidin-4-yl)amino]methyl}-1H-benzimidazol-2-yl)quinolin-2(1H)-one	421.5
1296	4-amino-5-fluoro-3-(6-{[4-(hydroxymethyl)piperidin-1-yl]methyl}-1H-benzimidazol-2-yl)quinolin-2(1H)-one	422.4
1297	4-amino-5-fluoro-3-[6-({[2-(1H-imidazol-4-yl)ethyl]amino}methyl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one	418.4
1298	4-amino-5-fluoro-3-(6-{[(2-pyridin-4-ylethyl)amino]methyl}-1H-benzimidazol-2-yl)quinolin-2(1H)-one	429.4

1299	4-amino-5-fluoro-3-(6-{[(2-pyridin-3-ylethyl)amino]methyl}-1H-benzimidazol-2-yl)quinolin-2(1H)-one	429.3
1300	4-amino-5-fluoro-3-(6-{[methyl(2-pyridin-2-ylethyl)amino]methyl}-1H-benzimidazol-2-yl)quinolin-2(1H)-one	443.3
1301	4-amino-5-fluoro-3-(6-{[(pyridin-4-ylmethyl)amino]methyl}-1H-benzimidazol-2-yl)quinolin-2(1H)-one	415.3
1302	4-amino-5-fluoro-3-(6-{[(pyridin-3-ylmethyl)amino]methyl}-1H-benzimidazol-2-yl)quinolin-2(1H)-one	415.4
1303	4-amino-5-fluoro-3-(6-{[(pyridin-2-ylmethyl)amino]methyl}-1H-benzimidazol-2-yl)quinolin-2(1H)-one	415.4
1304	4-amino-3-[6-(anilinomethyl)-1H-benzimidazol-2-yl]-5-fluoroquinolin-2(1H)-one	400.4
1305	4-amino-5-fluoro-3-[6-(morpholin-4-ylmethyl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one	394.4
1306	N~1~-[2-(4-amino-5-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)-1H-benzimidazol-6-yl]-N~2~-(2-methoxyethyl)-N~1~-methylglycinamide	439.4
1307	N-[2-(4-amino-5-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)-1H-benzimidazol-6-yl]-2-(4-cyclohexylpiperazin-1-yl)-N-methylacetamide	532.5
1308	N-[2-(4-amino-5-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)-1H-benzimidazol-6-yl]-2-(3,5-dimethylpiperazin-1-yl)-N-methylacetamide	478.4
1309	N~1~-[2-(4-amino-5-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)-1H-benzimidazol-6-yl]-N~1~-methyl-N~2~-(2-morpholin-4-ylethyl)glycinamide	494.4
1310	N~1~-[2-(4-amino-5-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)-1H-benzimidazol-6-yl]-N~1~-methyl-N~2~-[2-(2-oxoimidazolidin-1-yl)ethyl]glycinamide	493.4
1311	N~1~-[2-(4-amino-5-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)-1H-benzimidazol-6-yl]-N~2~-[3-(1H-imidazol-1-yl)propyl]-N~1~-methylglycinamide	489.4
1312	N-[2-(4-amino-5-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)-1H-benzimidazol-6-yl]-N-methyl-2-(4-pyrrolidin-1-ylpiperidin-1-yl)acetamide	518.4
1313	N~1~-[2-(4-amino-5-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)-1H-benzimidazol-6-yl]-N~2~-[(3R)-1-benzylpyrrolidin-3-yl]-N~1~-methylglycinamide	540.4
1314	N-[2-(4-amino-5-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)-1H-benzimidazol-6-yl]-2-[4-(hydroxymethyl)piperidin-1-yl]-N-methylacetamide	479.4
1315	N~1~-[2-(4-amino-5-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)-1H-benzimidazol-6-yl]-N~2~-[2-(1H-imidazol-4-yl)ethyl]-N~1~-methylglycinamide	475.4
1316	N~1~-[2-(4-amino-5-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)-1H-benzimidazol-6-yl]-N~1~-methyl-N~2~-(2-pyridin-4-ylethyl)glycinamide	486.4
1317	N~1~-[2-(4-amino-5-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)-1H-benzimidazol-6-yl]-N~1~-methyl-N~2~-(2-pyridin-3-ylethyl)glycinamide	486.4

1318	N~1~-[2-(4-amino-5-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)-1H-benzimidazol-6-yl]-N~1~,N~2~-dimethyl-N~2~-(2-pyridin-2-ylethyl)glycinamide	500.4
1319	N~1~-[2-(4-amino-5-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)-1H-benzimidazol-6-yl]-N~1~-methyl-N~2~-(pyridin-4-ylmethyl)glycinamide	472.4
1320	N~1~-[2-(4-amino-5-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)-1H-benzimidazol-6-yl]-N~1~-methyl-N~2~-(pyridin-3-ylmethyl)glycinamide	472.4
1321	N~1~-[2-(4-amino-5-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)-1H-benzimidazol-6-yl]-N~1~-methyl-N~2~-(pyridin-2-ylmethyl)glycinamide	472.4
1322	N~1~-[2-(4-amino-5-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)-1H-benzimidazol-6-yl]-N~2~-[(1-ethylpyrrolidin-3-yl)methyl]-N~1~-methylglycinamide	492.3
1323	N~1~-[2-(4-amino-5-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)-1H-benzimidazol-6-yl]-N~1~-methyl-N~2~-[3-(4-methylpiperazin-1-yl)propyl]glycinamide	521.3
1324	N~1~-[2-(4-amino-5-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)-1H-benzimidazol-6-yl]-N~1~-methyl-N~2~-1,3-thiazol-2-ylglycinamide	464.2
1325	N~1~-[2-(4-amino-5-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)-1H-benzimidazol-6-yl]-N~1~-methyl-N~2~-[2-(1-methylpyrrolidin-3-yl)ethyl]glycinamide	492.4
1326	N~1~-[2-(4-amino-5-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)-1H-benzimidazol-6-yl]-N~1~-methyl-N~2~-(2-pyrrolidin-1-ylethyl)glycinamide	478.3
1327	N~1~-[2-(4-amino-5-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)-1H-benzimidazol-6-yl]-N~1~,N~2~-dimethyl-N~2~-[2-(methylamino)ethyl]glycinamide	452.4
1328	N~1~-[2-(4-amino-5-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)-1H-benzimidazol-6-yl]-N~2~-(2-hydroxyethyl)-N~1~-methylglycinamide	425.3
1329	N~1~-[2-(4-amino-5-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)-1H-benzimidazol-6-yl]-N~1~-methyl-N~2~-(2-piperidin-1-ylethyl)glycinamide	492.4
1330	N~1~-[2-(4-amino-5-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)-1H-benzimidazol-6-yl]-N~1~-methyl-N~2~-(3-piperidin-1-ylpropyl)glycinamide	506.4
1331	N~1~-[2-(4-amino-5-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)-1H-benzimidazol-6-yl]-N~1~-methyl-N~2~-(3-pyrrolidin-1-ylpropyl)glycinamide	492.4
1332	N~1~-[2-(4-amino-5-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)-1H-benzimidazol-6-yl]-N~2~-(3-methoxypropyl)-N~1~-methylglycinamide	453.4
1333	N~1~-[2-(4-amino-5-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)-1H-benzimidazol-6-yl]-N~2~,N~2~-diisopropyl-N~1~-methylglycinamide	465.4
1334	N-[2-(4-amino-5-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)-1H-benzimidazol-6-yl]-N-methyl-2-(2-methylaziridin-1-yl)acetamide	421.3

1335	4-amino-3-[6-({[(1-ethylpyrrolidin-3-yl)methyl]amino}methyl)-1H-benzimidazol-2-yl]-5-fluoroquinolin-2(1H)-one	435.4
1336	4-amino-5-fluoro-3-[6-({[3-(4-methylpiperazin-1-yl)propyl]amino}methyl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one	464.4
1337	4-amino-5-fluoro-3-{6-[(1,3-thiazol-2-ylamino)methyl]-1H-benzimidazol-2-yl}quinolin-2(1H)-one	407.3
1338	4-amino-5-fluoro-3-[6-({[2-(1-methylpyrrolidin-3-yl)ethyl]amino}methyl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one	435.4
1339	4-amino-5-fluoro-3-(6-{[(2-pyrrolidin-1-ylethyl)amino]methyl}-1H-benzimidazol-2-yl)quinolin-2(1H)-one	421.4
1340	4-amino-5-fluoro-3-[6-({methyl[2-(methylamino)ethyl]amino}methyl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one	395.4
1341	4-amino-5-fluoro-3-(6-{[(2-hydroxyethyl)amino]methyl}-1H-benzimidazol-2-yl)quinolin-2(1H)-one	368.3
1342	4-amino-5-fluoro-3-(6-{[(2-piperidin-1-ylethyl)amino]methyl}-1H-benzimidazol-2-yl)quinolin-2(1H)-one	435.4
1343	4-amino-5-fluoro-3-(6-{[(3-piperidin-1-ylpropyl)amino]methyl}-1H-benzimidazol-2-yl)quinolin-2(1H)-one	449.4
1344	4-amino-5-fluoro-3-(6-{[(3-pyrrolidin-1-ylpropyl)amino]methyl}-1H-benzimidazol-2-yl)quinolin-2(1H)-one	435.4
1345	4-amino-5-fluoro-3-(6-{[(3-methoxypropyl)amino]methyl}-1H-benzimidazol-2-yl)quinolin-2(1H)-one	396.4
1346	N-[2-({[2-(4-amino-5-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)-1H-benzimidazol-6-yl]methyl}amino)ethyl]acetamide	409.4
1347	4-amino-3-{6-[(diisopropylamino)methyl]-1H-benzimidazol-2-yl}-5-fluoroquinolin-2(1H)-one	408.4
1348	4-amino-3-{6-[(dimethylamino)methyl]-1H-benzimidazol-2-yl}-5-fluoroquinolin-2(1H)-one	352.3
1349	4-amino-3-{6-[(4-ethylpiperazin-1-yl)methyl]-1H-benzimidazol-2-yl}-5-fluoroquinolin-2(1H)-one	421.1
1350	4-amino-5-fluoro-3-{6-[methyl(piperidin-4-yl)amino]-1H-benzimidazol-2-yl}quinolin-2(1H)-one	407.2
1351	4-amino-5-fluoro-3-[6-(piperazin-1-ylmethyl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one	493.2
1352	4-amino-5-fluoro-3-[5-(4-pyrrolidin-1-ylpiperidin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one	447.1
1353	4-amino-5-fluoro-3-{5-[4-(trifluoromethyl)piperidin-1-yl]-1H-benzimidazol-2-yl}quinolin-2(1H)-one	446.1
1354	4-amino-5-fluoro-3-{6-[3-(trifluoromethyl)piperidin-1-yl]-1H-benzimidazol-2-yl}quinolin-2(1H)-one	446.1
1355	4-amino-7-fluoro-3-{6-[3-(trifluoromethyl)piperidin-1-yl]-1H-benzimidazol-2-yl}quinolin-2(1H)-one	446.1
1356	4-amino-5-fluoro-3-[5-fluoro-6-(4-isopropylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one	439.1
1357	4-amino-3-[5-fluoro-6-(4-isopropylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one	421.4

1358	4-amino-3-[6-(4,4-difluoropiperidin-1-yl)-1H-benzimidazol-2-yl]-5-fluoroquinolin-2(1H)-one	414.1
1359	4-amino-6-fluoro-3-[5-fluoro-6-(4-isopropylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one	439.2
1360	4-amino-3-[5,7-difluoro-6-(4-isopropylpiperazin-1-yl)-1H-benzimidazol-2-yl]-6-fluoroquinolin-2(1H)-one	457.1
1361	4-amino-3-[5,7-difluoro-6-(4-isopropylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one	439.1
1362	4-amino-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-5-(2,2,2-trifluoroethoxy)quinolin-2(1H)-one	473.3
1363	4-amino-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-6-(2,2,2-trifluoroethoxy)quinolin-2(1H)-one	473.3
1364	4-amino-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-7-(2,2,2-trifluoroethoxy)quinolin-2(1H)-one	473.3
1365	4-amino-3-{5-[2-(dimethylamino)ethoxy]-6-methoxy-1H-benzimidazol-2-yl}-5-fluoroquinolin-2(1H)-one	412.3
1366	3-[6-(4-acetyl-1,4-diazepan-1-yl)-1H-benzimidazol-2-yl]-4-amino-5-fluoroquinolin-2(1H)-one	435.3
1367	4-amino-5-fluoro-3-{6-[(2-methoxyethyl)(methyl)amino]-1H-benzimidazol-2-yl}quinolin-2(1H)-one	382.3
1368	4-amino-6-fluoro-3-[5-fluoro-6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one	411.3
1369	4-amino-3-{6-[4-(N,N-dimethylglycyl)-1,4-diazepan-1-yl]-1H-benzimidazol-2-yl}-5-fluoroquinolin-2(1H)-one	478.3
1370	4-amino-5-fluoro-3-{5-fluoro-6-[methyl(1-methylpiperidin-4-yl)amino]-1H-benzimidazol-2-yl}quinolin-2(1H)-one	439.3
1371	4-amino-3-{5-[3-(dimethylamino)propyl]-1H-benzimidazol-2-yl}-5-fluoroquinolin-2(1H)-one	380.3
1372	4-amino-3-{5-fluoro-6-[methyl(1-methylpiperidin-4-yl)amino]-1H-benzimidazol-2-yl}quinolin-2(1H)-one	421.3
1373	4-amino-5-fluoro-3-{6-[4-(2-furoyl)piperazin-1-yl]-1H-benzimidazol-2-yl}quinolin-2(1H)-one	473.3
1374	4-amino-5-fluoro-3-[5-(3-morpholin-4-ylpropyl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one	422.3
1375	4-amino-3-{6-[4-(N,N-dimethylglycyl)piperazin-1-yl]-1H-benzimidazol-2-yl}-5-fluoroquinolin-2(1H)-one	464.3
1376	2-{4-[2-(4-amino-5-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)-1H-benzimidazol-6-yl]piperazin-1-yl}-N,N-dimethylacetamide	464.3
1377	3-{5-[3-(4-acetylpiperazin-1-yl)propyl]-1H-benzimidazol-2-yl}-4-amino-5-fluoroquinolin-2(1H)-one	463.3
1378	4-amino-3-{5-[3-(4-ethylpiperazin-1-yl)propyl]-1H-benzimidazol-2-yl}-5-fluoroquinolin-2(1H)-one	449.4
1379	4-amino-3-(6-{(2R,5R)-2-[(diethylamino)methyl]-5-methylmorpholin-4-yl}-1H-benzimidazol-2-yl)-5-fluoroquinolin-2(1H)-one	479.3
1380	4-amino-3-[5-(4-ethylpiperazin-1-yl)-6-fluoro-1H-benzimidazol-2-yl]-5-fluoroquinolin-2(1H)-one	425.1
1381	4-amino-3-{6-[(2R,5R)-5-methyl-2-(pyrrolidin-1-ylmethyl)morpholin-4-yl]-1H-benzimidazol-2-yl}-1,7-naphthyridin-2(1H)-one	460.2

1382	4-amino-3-[5-(4-ethylpiperazin-1-yl)-6-fluoro-1H-benzimidazol-2-yl]-6-fluoroquinolin-2(1H)-one	425.1
1383	4-amino-3-[5-(4-ethylpiperazin-1-yl)-6-fluoro-1H-benzimidazol-2-yl]-1,7-naphthyridin-2(1H)-one	408.2
1384	4-amino-5-fluoro-3-{6-[(2R,5R)-5-methyl-2-(pyrrolidin-1-ylmethyl)morpholin-4-yl]-1H-benzimidazol-2-yl}quinolin-2(1H)-one	477.2
1385	4-amino-8-fluoro-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one	393.3
1386	4-amino-5-fluoro-3-[6-(4-methyl-5-oxo-1,4-diazepan-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one	421.1
1387	4-amino-3-(5-{(2R,5S)-2-[(dimethylamino)methyl]-5-methylmorpholin-4-yl}-6-fluoro-1H-benzimidazol-2-yl)-1,7-naphthyridin-2(1H)-one	452.1
1388	4-amino-5-fluoro-3-{5-[3-(4-methylpiperazin-1-yl)-3-oxopropyl]-1H-benzimidazol-2-yl}quinolin-2(1H)-one	449.2
1389	4-amino-3-{5-[3-(4-ethylpiperazin-1-yl)-3-oxopropyl]-1H-benzimidazol-2-yl}-5-fluoroquinolin-2(1H)-one	463.2
1390	ethyl {[2-(4-amino-5-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)-1H-benzimidazol-6-yl]oxy}acetate	397.1
1391	4-amino-3-[5-(4-ethylpiperazin-1-yl)-1H-benzimidazol-2-yl]-6-fluoro-1,7-naphthyridin-2(1H)-one	408.3
1392	4-amino-3-(5-{(2S,5R)-2-[(dimethylamino)methyl]-5-methylmorpholin-4-yl}-1H-benzimidazol-2-yl)-1,7-naphthyridin-2(1H)-one	434.2
1393	4,5-diamino-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one	390.2
1394	N-{4-amino-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-2-oxo-1,2-dihydroquinolin-5-yl}methanesulfonamide	468.1
1395	4-amino-5-fluoro-3-{5-[3-(4-methylpiperazin-1-yl)propyl]-1H-benzimidazol-2-yl}quinolin-2(1H)-one	435.2
1396	4-amino-5-fluoro-3-[5-(2-pyrrolidin-1-ylethoxy)-1H-benzimidazol-2-yl]quinolin-2(1H)-one	408.1
1397	N-({(2R,5S)-4-[2-(4-amino-5-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)-1H-benzimidazol-5-yl]-5-methylmorpholin-2-yl}methyl)-N-methylacetamide	479.2
1398	4-amino-5-fluoro-3-(5-{(2S,5S)-5-methyl-2-[(methylamino)methyl]morpholin-4-yl}-1H-benzimidazol-2-yl)quinolin-2(1H)-one	437.2
1399	4-amino-3-(5-{(1E)-3-[benzyl(methyl)amino]prop-1-enyl}-1H-benzimidazol-2-yl)-5-fluoroquinolin-2(1H)-one	454.2
1400	4-amino-3-(5-{3-[benzyl(methyl)amino]propyl}-1H-benzimidazol-2-yl)-5-fluoroquinolin-2(1H)-one	456.3
1401	4-amino-5-fluoro-3-(5-{3-[methyl(piperidin-4-yl)amino]propyl}-1H-benzimidazol-2-yl)quinolin-2(1H)-one	449.2
1402	4-amino-5-fluoro-3-(5-{3-[(1-isopropylpiperidin-4-yl)(methyl)amino]propyl}-1H-benzimidazol-2-yl)quinolin-2(1H)-one	491.3
1403	4-amino-3-(5-{3-[(1-ethylpiperidin-4-yl)(methyl)amino]propyl}-1H-benzimidazol-2-yl)-5-fluoroquinolin-2(1H)-one	477.3

1404	4-amino-5-fluoro-3-[5-(1-methylpiperidin-4-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one	392.1
1405	4-amino-5-fluoro-3-[5-(4-methyl-4-oxidopiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one	409.2
1406	N-[2-(4-amino-5-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)-1H-benzimidazol-6-yl]-N,4-dimethylpiperazine-1-carboxamide	450.1
1407	4-amino-3-(5-{2-[(dimethylamino)methyl]morpholin-4-yl}-1H-benzimidazol-2-yl)-5-fluoroquinolin-2(1H)-one	437.2
1408	4-amino-5-ethoxy-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one	419.3
1409	4-amino-3-[5-(4-ethylpiperazin-1-yl)-6-fluoro-1H-benzimidazol-2-yl]-6,7-dimethoxyquinolin-2(1H)-one	467.3
1410	4-amino-6,7-dimethoxy-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one	435.3
1411	4-amino-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-7-(trifluoromethyl)quinolin-2(1H)-one	443.3
1412	4-amino-3-(5-{(2R,5S)-2-[(dimethylamino)methyl]-5-methylmorpholin-4-yl}-6-fluoro-1H-benzimidazol-2-yl)-6,7-dimethoxyquinolin-2(1H)-one	511.4
1413	4-amino-3-[5-(4-ethyl-1,4-diazepan-1-yl)-1H-benzimidazol-2-yl]-6,7-dimethoxyquinolin-2(1H)-one	463.3
1414	4-amino-3-{6-[(1-ethylpiperidin-4-yl)methyl]-1H-benzimidazol-2-yl}-5-fluoroquinolin-2(1H)-one	420.5
1415	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-1,7-naphthyridin-2(1H)-one	387.4

Examples 1416-1457

Examples 1416 to 1457 listed in Table 5 were synthesized using the methods described above such as Methods 1-24 and those set forth in the Schemes and other Examples or modified as apparent to one of reasonable skill in the art using commercially available materials.

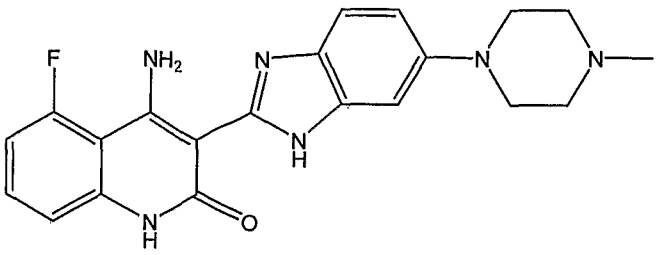
Table 5. Table of Examples 1416-1457.

Example	Name	LC/MS m/z (MH+)
1416	3-(1H-benzimidazol-2-yl)-6-chloro-4-[(pyridin-2-ylmethyl)amino]quinolin-2(1H)-one	402.9
1417	4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6,7-dimethoxyquinolin-2(1H)-one	446.5
1418	4-[4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-2-oxo-1,2-dihydroquinolin-6-yl]benzonitrile	487.6
1419	4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-(3-methoxyphenyl)quinolin-2(1H)-one	492.6

1420	4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-(2-methoxyphenyl)quinolin-2(1H)-one	492.6
1421	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-(4-methoxyphenyl)quinolin-2(1H)-one	492.6
1422	4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-fluoro-7-(isobutylamino)quinolin-2(1H)-one	475.6
1423	4-[4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-2-oxo-1,2-dihydroquinolin-6-yl]benzamide	505.6
1424	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-fluoro-7-methoxyquinolin-2(1H)-one	434.5
1425	4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-fluoro-7-[(2-piperidin-1-ylethyl)amino]quinolin-2(1H)-one	530.7
1426	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-2-oxo-1,2-dihydroquinoline-7-carboxylic acid	430.5
1427	3-amino-4-[4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-(1H-imidazol-1-yl)-2-oxo-1,2-dihydroquinolin-6-yl]benzoic acid	587.7
1428	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-fluoro-7-{[3-(1H-imidazol-1-yl)propyl]amino}quinolin-2(1H)-one	527.6
1429	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-fluoro-7-[(2-pyridin-3-ylethyl)amino]quinolin-2(1H)-one	524.6
1430	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-methoxyquinolin-2(1H)-one	416.5
1431	6-chloro-3-(5-morpholin-4-yl-1H-benzimidazol-2-yl)-4-[(pyridin-2-ylmethyl)amino]quinolin-2(1H)-one	488.0
1432	4-{[(1S)-2-amino-1-benzylethyl]amino}-6-chloro-3-(5-morpholin-4-yl-1H-benzimidazol-2-yl)quinolin-2(1H)-one	530.0
1433	4-[(1-benzylpiperidin-4-yl)amino]-6-chloro-3-(5-morpholin-4-yl-1H-benzimidazol-2-yl)quinolin-2(1H)-one	570.1
1434	4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-2-oxo-1,2-dihydroquinoline-7-carboxylic acid	430.5
1435	4-{[4-(aminomethyl)benzyl]amino}-6-chloro-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one	529.1
1436	4-[(1-benzylpiperidin-4-yl)amino]-6-chloro-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one	583.1
1437	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-methoxy-6-[4-(methylsulfonyl)phenyl]quinolin-2(1H)-one	570.7
1438	3-(1H-benzimidazol-2-yl)-6-chloro-4-[(3S)-pyrrolidin-3-ylamino]quinolin-2(1H)-one	380.8
1439	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-6-bromo-3-(3H-imidazo[4,5-b]pyridin-2-yl)quinolin-2(1H)-one	466.3
1440	4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-6-bromo-3-(3H-imidazo[4,5-b]pyridin-2-yl)quinolin-2(1H)-one	466.3
1441	6-bromo-3-(3H-imidazo[4,5-b]pyridin-2-yl)-4-(piperidin-3-ylamino)quinolin-2(1H)-one	440.3

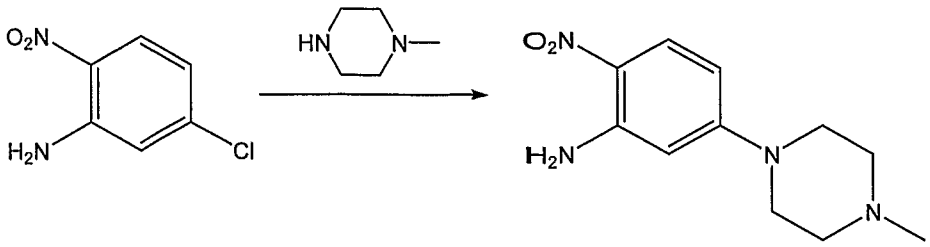
1442	4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-6,7-difluoro-3-(3H-imidazo[4,5-b]pyridin-2-yl)quinolin-2(1H)-one	423.4
1443	6,7-difluoro-3-(3H-imidazo[4,5-b]pyridin-2-yl)-4-(piperidin-3-ylamino)quinolin-2(1H)-one	397.4
1444	4-[4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(3H-imidazo[4,5-b]pyridin-2-yl)-2-oxo-1,2-dihydroquinolin-6-yl]benzoic acid	507.6
1445	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(3H-imidazo[4,5-b]pyridin-2-yl)-6-[2-(trifluoromethyl)phenyl]quinolin-2(1H)-one	531.6
1446	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(3H-imidazo[4,5-b]pyridin-2-yl)-6-(2-methoxyphenyl)quinolin-2(1H)-one	493.6
1447	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-7-(dimethylamino)-6-fluoro-3-(3H-imidazo[4,5-b]pyridin-2-yl)quinolin-2(1H)-one	448.5
1448	5-(1-azabicyclo[2.2.2]oct-3-ylamino)-6-(1H-benzimidazol-2-yl)-2-(methylthio)pyrido[2,3-d]pyrimidin-7(8H)-one	434.5
1449	5-(1-azabicyclo[2.2.2]oct-3-ylamino)-6-(1H-benzimidazol-2-yl)-2-hydroxypyrido[2,3-d]pyrimidin-7(8H)-one	404.4
1450	5-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-6-(1H-benzimidazol-2-yl)-2-hydroxypyrido[2,3-d]pyrimidin-7(8H)-one	404.4
1451	4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-fluoro-1,7-naphthyridin-2(1H)-one	405.4
1452	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-fluoro-1,7-naphthyridin-2(1H)-one	405.4
1453	4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-chloro-1,7-naphthyridin-2(1H)-one	421.9
1454	3-(1H-benzimidazol-2-yl)-6-chloro-4-{[2-(dimethylamino)ethyl]amino}-1,7-naphthyridin-2(1H)-one	383.9
1455	4-{[(1R,2R)-2-aminocyclohexyl]amino}-3-(1H-benzimidazol-2-yl)-6-chloro-1,7-naphthyridin-2(1H)-one	409.9
1456	3-(1H-benzimidazol-2-yl)-6-chloro-4-[(piperidin-3-ylmethyl)amino]-1,7-naphthyridin-2(1H)-one	409.9
1457	3-(1H-benzimidazol-2-yl)-6-chloro-4-[(3S)-pyrrolidin-3-ylamino]-1,7-naphthyridin-2(1H)-one	381.8

Synthesis of 4-Amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-quinolin-2-one



A. Synthesis of 5-(4-Methyl-piperazin-1-yl)-2-nitroaniline

Procedure A



[0772] 5-Chloro-2-nitroaniline (500 g, 2.898 mol) and 1-methyl piperazine (871 g, 8.693 mol) were placed in a 2000 mL flask fitted with a condenser and purged with N_2. The flask was placed in an oil bath at 100°C and heated until the 5-chloro-2-nitroaniline was completely reacted (typically overnight) as determined by HPLC. After HPLC confirmed the disappearance of the 5-chloro-2-nitroaniline, the reaction mixture was poured directly (still warm) into 2500 mL of room temperature water with mechanical stirring. The resulting mixture was stirred until it reached room temperature and then it was filtered. The yellow solid thus obtained was added to 1000 mL of water and stirred for 30 minutes. The resulting mixture was filtered, and the resulting solid was washed with TBME (500 mL, 2X) and then was dried under vacuum for one hour using a rubber dam. The resulting solid was transferred to a drying tray and dried in a vacuum oven at 50°C to a constant weight to yield 670 g (97.8%) of the title compound as a yellow powder.

Procedure B

[0773] 5-Chloro-2-nitroaniline (308.2 g, 1.79 mol) was added to a 4-neck 5000 mL round bottom flask fitted with an overhead stirrer, condenser, gas inlet, addition funnel, and thermometer probe. The flask was then purged with N_2. 1-Methylpiperazine (758.1 g, 840 mL, 7.57 mol) and 200 proof ethanol (508 mL) were added to the reaction flask with stirring. The flask was again purged with N_2, and the reaction was maintained under N_2. The flask was heated in a heating mantle to an internal temperature of 97°C (+/- 5°C) and maintained at that temperature until the reaction was complete (typically about 40 hours) as determined by HPLC. After the reaction was complete,

heating was discontinued and the reaction was cooled to an internal temperature of about 20°C to 25°C with stirring, and the reaction was stirred for 2 to 3 hours. Seed crystals (0.20 g, 0.85 mmol) of 5-(4-methyl-piperazin-1-yl)-2-nitroaniline were added to the reaction mixture unless precipitation had already occurred. Water (2,450 mL) was added to the stirred reaction mixture over a period of about one hour while the internal temperature was maintained at a temperature ranging from about 20°C to 30°C. After the addition of water was complete, the resulting mixture was stirred for about one hour at a temperature of 20°C to 30°C. The resulting mixture was then filtered, and the flask and filter cake were washed with water (3 x 2.56 L). The golden yellow solid product was dried to a constant weight of 416 g (98.6% yield) under vacuum at about 50°C in a vacuum oven.

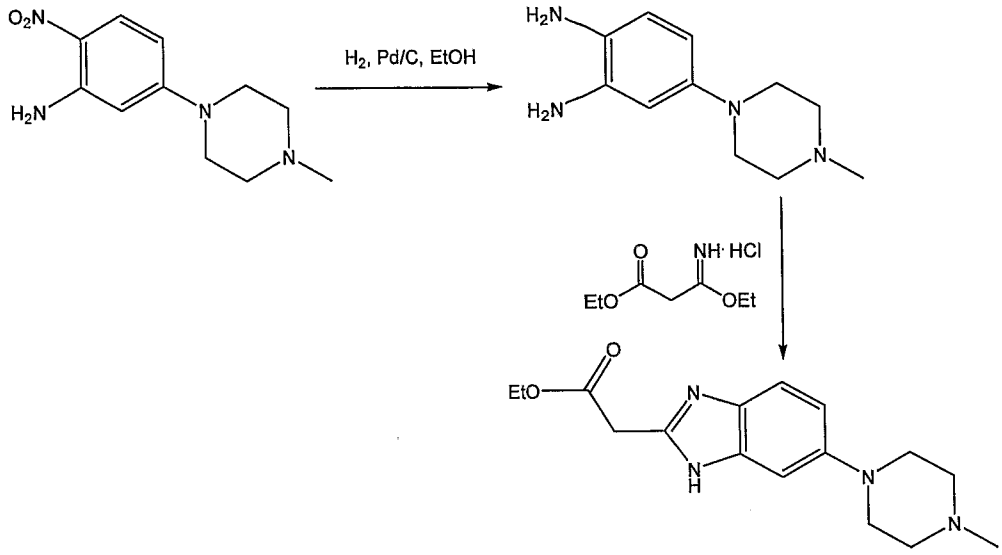
Procedure C

[0774] 5-Chloro-2-nitroaniline (401 g, 2.32 mol) was added to a 4-neck 12 L round bottom flask fitted with an overhead stirrer, condenser, gas inlet, addition funnel, and thermometer probe. The flask was then purged with N_2. 1-Methylpiperazine (977 g, 1.08 L, 9.75 mol) and 100% ethanol (650 mL) were added to the reaction flask with stirring. The flask was again purged with N_2, and the reaction was maintained under N_2. The flask was heated in a heating mantle to an internal temperature of 97°C (+/- 5°C) and maintained at that temperature until the reaction was complete (typically about 40 hours) as determined by HPLC. After the reaction was complete, heating was discontinued and the reaction was cooled to an internal temperature of about 80°C with stirring, and water (3.15 L) was added to the mixture via an addition funnel over the period of 1 hour while the internal temperature was maintained at 82°C (+/- 3°C). After water addition was complete, heating was discontinued and the reaction mixture was allowed to cool over a period of no less than 4 hours to an internal temperature of 20-25°C. The reaction mixture was then stirred for an additional hour at an internal temperature of 20-30°C. The resulting mixture was then filtered, and the flask and filter cake were washed with water (1 x 1 L), 50% ethanol (1 x 1L), and 95% ethanol (1 x 1L).

The golden yellow solid product was placed in a drying pan and dried to a constant weight of 546 g (99% yield) under vacuum at about 50°C in a vacuum oven.

B. Synthesis of [6-(4-Methyl-piperazin-1-yl)-1H-benzimidazol-2-yl]-acetic acid ethyl ester

Procedure A



[0775] A 5000 mL, 4-neck flask was fitted with a stirrer, thermometer, condenser, and gas inlet/outlet. The equipped flask was charged with 265.7 g (1.12 mol. 1.0 eq) of 5-(4-methyl-piperazin-1-yl)-2-nitroaniline and 2125 mL of 200 proof EtOH. The resulting solution was purged with N_2 for 15 minutes. Next, 20.0 g of 5% Pd/C (50% H_2O w/w) was added. The reaction was vigorously stirred at 40-50°C (internal temperature) while H_2 was bubbled through the mixture. The reaction was monitored hourly for the disappearance of 5-(4-methyl-piperazin-1-yl)-2-nitroaniline by HPLC. The typical reaction time was 6 hours.

[0776] After all the 5-(4-methyl-piperazin-1-yl)-2-nitroaniline had disappeared from the reaction, the solution was purged with N_2 for 15 minutes. Next, 440.0 g (2.25 mol) of ethyl 3-ethoxy-3-iminopropanoate hydrochloride was added as a solid. The reaction was stirred at 40-50°C (internal temperature) until the reaction was complete. The reaction was

monitored by following the disappearance of the diamino compound by HPLC. The typical reaction time was 1-2 hours. After the reaction was complete, it was cooled to room temperature and filtered through a pad of Celite filtering material. The Celite filtering material was washed with absolute EtOH (2 x 250 mL), and the filtrate was concentrated under reduced pressure providing a thick brown/orange oil. The resulting oil was taken up in 850 mL of a 0.37% HCl solution. Solid NaOH (25 g) was then added in one portion, and a precipitate formed. The resulting mixture was stirred for 1 hour and then filtered. The solid was washed with H_2O (2 x 400 mL) and dried at 50°C in a vacuum oven providing 251.7 g (74.1%) of [6-(4-methyl-piperazin-1-yl)-1H-benzoimidazol-2-yl]-acetic acid ethyl ester as a pale yellow powder.

Procedure B

[0777] A 5000 mL, 4-neck jacketed flask was fitted with a mechanical stirrer, condenser, temperature probe, gas inlet, and oil bubbler. The equipped flask was charged with 300 g (1.27 mol) of 5-(4-methyl-piperazin-1-yl)-2-nitroaniline and 2400 mL of 200 proof EtOH (the reaction may be and has been conducted with 95% ethanol and it is not necessary to use 200 proof ethanol for this reaction). The resulting solution was stirred and purged with N_2 for 15 minutes. Next, 22.7 g of 5% Pd/C (50% H_2O w/w) was added to the reaction flask. The reaction vessel was purged with N_2 for 15 minutes. After purging with N_2, the reaction vessel was purged with H_2 by maintaining a slow, but constant flow of H_2 through the flask. The reaction was stirred at 45-55°C (internal temperature) while H_2 was bubbled through the mixture until the 5-(4-methyl-piperazin-1-yl)-2-nitroaniline was completely consumed as determined by HPLC. The typical reaction time was 6 hours.

[0778] After all the 5-(4-methyl-piperazin-1-yl)-2-nitroaniline had disappeared from the reaction, the solution was purged with N_2 for 15 minutes. The diamine intermediate is air sensitive so care was taken to avoid exposure to air. 500 g (2.56 mol) of ethyl 3-ethoxy-3-iminopropanoate hydrochloride was added to the reaction mixture over a period of about 30 minutes. The reaction was stirred at 45-55°C (internal temperature) under N_2

until the diamine was completely consumed as determined by HPLC. The typical reaction time was about 2 hours. After the reaction was complete, the reaction was filtered while warm through a pad of Celite. The reaction flask and Celite were then washed with 200 proof EtOH (3 x 285 mL). The filtrates were combined in a 5000 mL flask, and about 3300 mL of ethanol was removed under vacuum producing an orange oil. Water (530 mL) and then 1M HCL (350 mL) were added to the resulting oil, and the resulting mixture was stirred. The resulting solution was vigorously stirred while 30% NaOH (200 mL) was added over a period of about 20 minutes maintaining the internal temperature at about 25-30°C while the pH was brought to between 9 and 10. The resulting suspension was stirred for about 4 hours while maintaining the internal temperature at about 20-25°C. The resulting mixture was filtered, and the filter cake was washed with H_2O (3 x 300 mL). The collected solid was dried to a constant weight at 50°C under vacuum in a vacuum oven providing 345.9 g (90.1%) of [6-(4-methyl-piperazin-1-yl)-1H-benzoimidazol-2-yl]-acetic acid ethyl ester as a pale yellow powder. In an alternative work up procedure, the filtrates were combined and the ethanol was removed under vacuum until at least about 90% had been removed. Water at a neutral pH was then added to the resulting oil, and the solution was cooled to about 0°C. An aqueous 20% NaOH solution was then added slowly with rapid stirring to bring the pH up to 9.2 (read with pH meter). The resulting mixture was then filtered and dried as described above. The alternative work up procedure provided the light tan to light yellow product in yields as high as 97%.

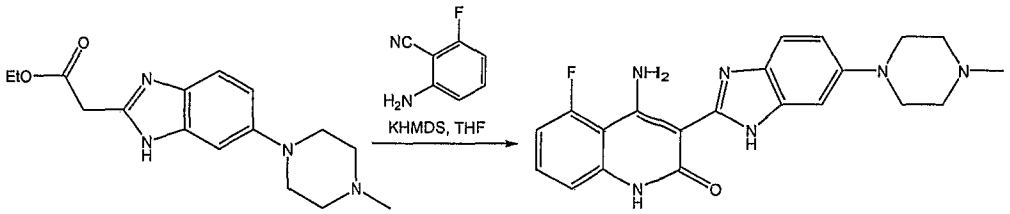
Method for Reducing Water Content of [6-(4-Methyl-piperazin-1-yl)-1H-benzoimidazol-2-yl]-acetic acid ethyl ester

[0779] [6-(4-Methyl-piperazin-1-yl)-1H-benzimidazol-2-yl]-acetic acid ethyl ester (120.7 grams) that had been previously worked up and dried to a water content of about 8-9% H_2O was placed in a 2000 mL round bottom flask and dissolved in absolute ethanol (500 mL). The amber solution was concentrated to a thick oil using a rotary evaporator with heating until all

solvent was removed. The procedure was repeated two more times. The thick oil thus obtained was left in the flask and placed in a vacuum oven heated at 50°C overnight. Karl Fisher analysis results indicated a water content of 5.25%. The lowered water content obtained by this method provided increased yields in the procedure of the following Example. Other solvents such as toluene and THF may be used in place of the ethanol for this drying process.

C. Synthesis of 4-Amino-5-fluoro-3-[6-(4-methyl-piperazin-1-yl)-1H-benzimidazol-2-yl]-1H-quinolin-2-one

Procedure A



[0780] [6-(4-Methyl-piperazin-1-yl)-1H-benzimidazol-2-yl]-acetic acid ethyl ester (250 g, 820 mmol) (dried with ethanol as described above) was dissolved in THF (3800 mL) in a 5000 mL flask fitted with a condenser, mechanical stirrer, temperature probe, and purged with argon. 2-Amino-6-fluoro-benzonitrile (95.3 g, 700 mmol) was added to the solution, and the internal temperature was raised to 40°C. When all the solids had dissolved and the solution temperature had reached 40°C, solid KHMDS (376.2 g, 1890 mmol) was added over a period of 5 minutes. When addition of the potassium base was complete, a heterogeneous yellow solution was obtained, and the internal temperature had risen to 62°C. After a period of 60 minutes, the internal temperature decreased back to 40°C, and the reaction was determined to be complete by HPLC (no starting material or uncyclized intermediate was present). The thick reaction mixture was then quenched by pouring it into H_2O (6000 mL) and stirring the resulting mixture until it had reached room temperature. The mixture was then filtered, and the filter pad was washed with water (1000 mL 2X). The bright yellow solid was placed in a drying tray and dried in a vacuum oven at 50°C overnight providing 155.3 g

(47.9%) of the desired 4-amino-5-fluoro-3-[6-(4-methyl-piperazin-1-yl)-1H-benzimidazol-2-yl]-1H-quinolin-2-one.

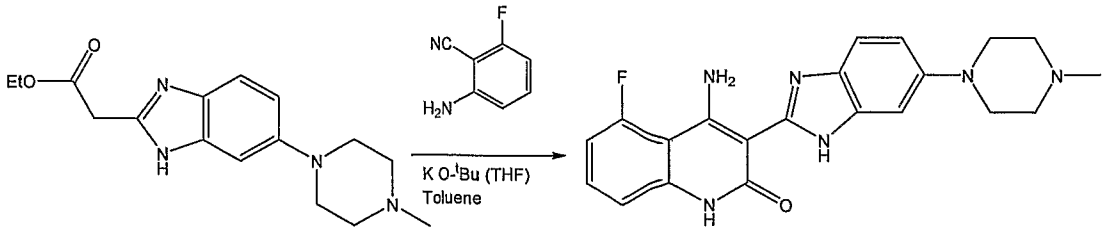
Procedure B

[0781] A 5000 mL 4-neck jacketed flask was equipped with a distillation apparatus, a temperature probe, a N_2 gas inlet, an addition funnel, and a mechanical stirrer. [6-(4-Methyl-piperazin-1-yl)-1H-benzimidazol-2-yl]-acetic acid ethyl ester (173.0 g, 570 mmol) was charged into the reactor, and the reactor was purged with N_2 for 15 minutes. Dry THF (2600 mL) was then charged into the flask with stirring. After all the solid had dissolved, solvent was removed by distillation (vacuum or atmospheric (the higher temperature helps to remove the water) using heat as necessary. After 1000 mL of solvent had been removed, distillation was stopped and the reaction was purged with N_2. 1000 mL of dry THF was then added to the reaction vessel, and when all solid was dissolved, distillation (vacuum or atmospheric) was again conducted until another 1000 mL of solvent had been removed. This process of adding dry THF and solvent removal was repeated at least 4 times (on the 4th distillation, 60% of the solvent is removed instead of just 40% as in the first 3 distillations) after which a 1 mL sample was removed for Karl Fischer analysis to determine water content. If the analysis showed that the sample contained less than 0.20% water, then reaction was continued as described in the next paragraph. However, if the analysis showed more than 0.20% water, then the drying process described above was continued until a water content of less than 0.20% was achieved.

[0782] After a water content of less than or about 0.20% was achieved using the procedure described in the previous paragraph, the distillation apparatus was replaced with a reflux condenser, and the reaction was charged with 2-amino-6-fluoro-benzonitrile (66.2 g, 470 mmol) (in some procedures 0.95 equivalents is used). The reaction was then heated to an internal temperature of 38-42°C. When the internal temperature had reached 38-42°C, KHMDS solution (1313 g, 1.32 mol, 20% KHMDS in THF) was added to the reaction via the additional funnel over a period of 5 minutes

maintaining the internal temperature at about 38-50°C during the addition. When addition of the potassium base was complete, the reaction was stirred for 3.5 to 4.5 hours (in some examples it was stirred for 30 to 60 minutes and the reaction may be complete within that time) while maintaining the internal temperature at from 38-42°C. A sample of the reaction was then removed and analyzed by HPLC. If the reaction was not complete, additional KHMDS solution was added to the flask over a period of 5 minutes and the reaction was stirred at 38-42°C for 45-60 minutes (the amount of KHMDS solution added was determined by the following: If the IPC ratio is < 3.50, then 125 mL was added; if 10.0 ≥ IPC ratio ≥ 3.50, then 56 mL was added; if 20.0 ≥ IPC ratio ≥ 10, then 30 mL was added. The IPC ratio is equal to the area corresponding to 4-amino-5-fluoro-3-[6-(4-methyl-piperazin-1-yl)-1H-benzimidazol-2-yl]-1H-quinolin-2-one) divided by the area corresponding to the uncyclized intermediate). Once the reaction was complete (IPC ratio > 20), the reactor was cooled to an internal temperature of 25-30°C, and water (350 mL) was charged into the reactor over a period of 15 minutes while maintaining the internal temperature at 25-35°C (in one alternative, the reaction is conducted at 40°C and water is added within 5 minutes. The quicker quench reduces the amount of impurity that forms over time). The reflux condenser was then replaced with a distillation apparatus and solvent was removed by distillation (vacuum or atmospheric) using heat as required. After 1500 mL of solvent had been removed, distillation was discontinued and the reaction was purged with N_2. Water (1660 mL) was then added to the reaction flask while maintaining the internal temperature at 20-30°C. The reaction mixture was then stirred at 20-30°C for 30 minutes before cooling it to an internal temperature of 5-10°C and then stirring for 1 hour. The resulting suspension was filtered, and the flask and filter cake were washed with water (3 x 650 mL). The solid thus obtained was dried to a constant weight under vacuum at 50°C in a vacuum oven to provide 103.9 g (42.6% yield) of 4-amino-5-fluoro-3-[6-(4-methyl-piperazin-1-yl)-1H-benzimidazol-2-yl]-1H-quinolin-2-one as a yellow powder.

Procedure C



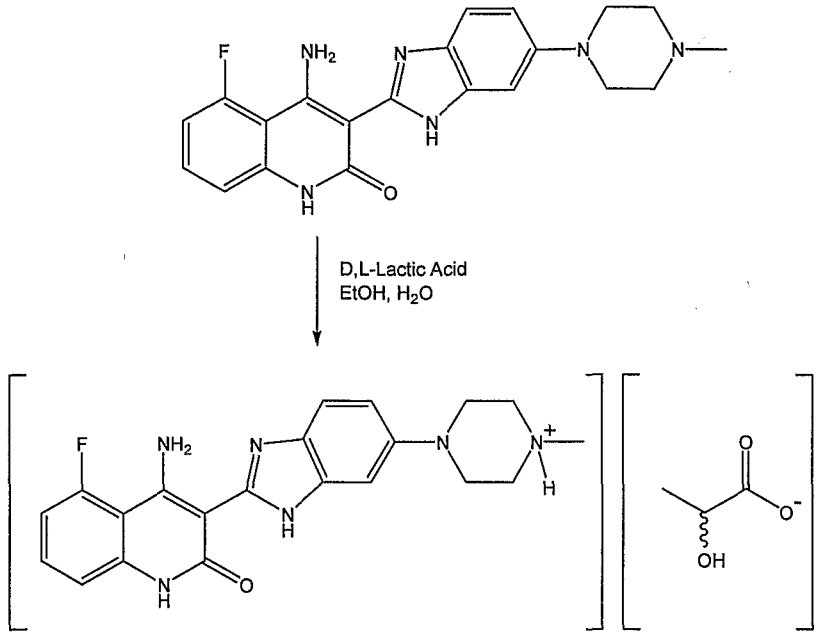
[0783] [6-(4-Methyl-piperazin-1-yl)-1H-benzimidazol-2-yl]-acetic acid ethyl ester (608 g, 2.01 mol) (dried) and 2-amino-6-fluoro-benzonitrile (274 g, 2.01 mol) were charged into a 4-neck 12 L flask seated on a heating mantle and fitted with a condenser, mechanical stirrer, gas inlet, and temperature probe. The reaction vessel was purged with N_2, and toluene (7.7 L) was charged into the reaction mixture while it was stirred. The reaction vessel was again purged with N_2 and maintained under N_2. The internal temperature of the mixture was raised until a temperature of 63°C (+/- 3°C) was achieved. The internal temperature of the mixture was maintained at 63°C (+/- 3°C) while approximately 2.6 L of toluene was distilled from the flask under reduced pressure (380 +/- 10 torr, distilling head t = 40°C (+/- 10°C) (Karl Fischer analysis was used to check the water content in the mixture. If the water content was greater than 0.03%, then another 2.6 L of toluene was added and distillation was repeated. This process was repeated until a water content of less than 0.03% was achieved). After a water content of less than 0.03% was reached, heating was discontinued, and the reaction was cooled under N_2 to an internal temperature of 17-19°C. Potassium t-butoxide in THF (20% in THF; 3.39 kg, 6.04 moles potassium t-butoxide) was then added to the reaction under N_2 at a rate such that the internal temperature of the reaction was kept below 20°C. After addition of the potassium t-butoxide was complete, the reaction was stirred at an internal temperature of less than 20°C for 30 minutes. The temperature was then raised to 25°C, and the reaction was stirred for at least 1 hour. The temperature was then raised to 30°C, and the reaction was stirred for at least 30 minutes. The reaction was then monitored for completion using HPLC to check for consumption of the starting materials (typically in 2-3 hours, both starting materials were consumed (less

than 0.5% by area % HPLC)). If the reaction was not complete after 2 hours, another 0.05 equivalents of potassium t-butoxide was added at a time, and the process was completed until HPLC showed that the reaction was complete. After the reaction was complete, 650 mL of water was added to the stirred reaction mixture. The reaction was then warmed to an internal temperature of 50°C and the THF was distilled away (about 3 L by volume) under reduced pressure from the reaction mixture. Water (2.6 L) was then added dropwise to the reaction mixture using an addition funnel. The mixture was then cooled to room temperature and stirred for at least 1 hour. The mixture was then filtered, and the filter cake was washed with water (1.2 L), with 70% ethanol (1.2 L), and with 95% ethanol (1.2 L). The bright yellow solid was placed in a drying tray and dried in a vacuum oven at 50°C until a constant weight was obtained providing 674 g (85.4%) of the desired 4-amino-5-fluoro-3-[6-(4-methyl-piperazin-1-yl)-1H-benzimidazol-2-yl]-1H-quinolin-2-one.

Purification of 4-Amino-5-fluoro-3-[6-(4-methyl-piperazin-1-yl)-1H-benzimidazol-2-yl]-1H-quinolin-2-one

[0784] A 3000 mL 4-neck flask equipped with a condenser, temperature probe, N_2 gas inlet, and mechanical stirrer was placed in a heating mantle. The flask was then charged with 4-amino-5-fluoro-3-[6-(4-methyl-piperazin-1-yl)-1H-benzimidazol-2-yl]-1H-quinolin-2-one (101.0 g, 0.26 mol), and the yellow solid was suspended in 95% ethanol (1000 mL) and stirred. In some cases an 8:1 solvent ratio is used. The suspension was then heated to a gentle reflux (temperature of about 76°C) with stirring over a period of about 1 hour. The reaction was then stirred for 45-75 minutes while refluxed. At this point, the heat was removed from the flask and the suspension was allowed to cool to a temperature of 25-30°C. The suspension was then filtered, and the filter pad was washed with water (2 x 500 mL). The yellow solid was then placed in a drying tray and dried in a vacuum oven at 50°C until a constant weight was obtained (typically 16 hours) to obtain 97.2 g (96.2%) of the purified product as a yellow powder.

D. Preparation of Lactic Acid Salt of 4-Amino-5-fluoro-3-[6-(4-methyl-piperazin-1-yl)-1H-benzimidazol-2-yl]-1H-quinolin-2-one



[0785] A 3000 mL 4-necked jacketed flask was fitted with a condenser, a temperature probe, a N_2 gas inlet, and a mechanical stirrer. The reaction vessel was purged with N_2 for at least 15 minutes and then charged with 4-amino-5-fluoro-3-[6-(4-methyl-piperazin-1-yl)-1H-benzimidazol-2-yl]-1H-quinolin-2-one (484 g, 1.23 mol). A solution of D,L-Lactic acid (243.3 g, 1.72 mol of monomer-see the following paragraph), water (339 mL), and ethanol (1211 mL) was prepared and then charged to the reaction flask. Stirring was initiated at a medium rate, and the reaction was heated to an internal temperature of 68-72°C. The internal temperature of the reaction was maintained at 68-72°C for 15-45 minutes and then heating was discontinued. The resulting mixture was filtered through a 10-20 micron frit collecting the filtrate in a 12 L flask. The 12 L flask was equipped with an internal temperature probe, a reflux condenser, an addition funnel, a gas inlet an outlet, and an overhead stirrer. The filtrate was then stirred at a medium rate and heated to reflux (internal temperature of about 78°C). While maintaining a gentle reflux, ethanol (3,596 mL) was charged to the flask over a period of about 20 minutes. The reaction flask was then cooled to an internal temperature ranging from about 64-70°C within 15-25 minutes and this

temperature was maintained for a period of about 30 minutes. The reactor was inspected for crystals. If no crystals were present, then crystals of the lactic acid salt of 4-amino-5-fluoro-3-[6-(4-methyl-piperazin-1-yl)-1H-benzimidazol-2-yl]-1H-quinolin-2-one (484 mg, 0.1 mole %) were added to the flask, and the reaction was stirred at 64-70°C for 30 minutes before again inspecting the flask for crystals. Once crystals were present, stirring was reduced to a low rate and the reaction was stirred at 64-70°C for an additional 90 minutes. The reaction was then cooled to about 0°C over a period of about 2 hours, and the resulting mixture was filtered through a 25-50 micron fritted filter. The reactor was washed with ethanol (484 mL) and stirred until the internal temperature was about 0°C. The cold ethanol was used to wash the filter cake, and this procedure was repeated 2 more times. The collected solid was dried to a constant weight at 50°C under vacuum in a vacuum oven yielding 510.7 g (85.7%) of the crystalline yellow lactic acid salt of 4-amino-5-fluoro-3-[6-(4-methyl-piperazin-1-yl)-1H-benzimidazol-2-yl]-1H-quinolin-2-one. A rubber dam or inert conditions were typically used during the filtration process. While the dry solid did not appear to be very hygroscopic, the wet filter cake tends to pick up water and become sticky. Precautions were taken to avoid prolonged exposure of the wet filter cake to the atmosphere.

[0786] Commercial lactic acid generally contains about 8-12% w/w water, and contains dimers and trimers in addition to the monomeric lactic acid. The mole ratio of lactic acid dimer to monomer is generally about 1.0:4.7. Commercial grade lactic acid may be used in the process described in the preceding paragraph as the monolactate salt preferentially precipitates from the reaction mixture.

Assay Procedures

Serine/Threonine Kinases

[0787] The kinase activity of various protein serine/threonine kinases was measured by providing ATP and a suitable peptide or protein containing a serine or threonine amino acid residue for phosphorylation, and assaying for

the transfer of phosphate moiety to the serine or threonine residue. Recombinant proteins containing the kinase domains of GSK-3, RSK-2, PAR-1, NEK-2, and CHK1 enzymes were expressed in Sf9 insect cells using a Baculovirus expression system (InVitrogen) and purified via Glu antibody interaction (for Glu-epitope tagged constructs) or by Metal Ion Chromatography (for His_6 (SEQ ID NO: 1) tagged constructs). Cdc2 (GST fusion construct) and cyclin B were co-expressed in Sf9 insect cells using a Baculovirus expression system. Recombinant, active Cdk2/cyclin A is available commercially and was purchased from Upstate Biotechnology. The purified Cdc2 enzyme used in the assay was commercially available, and it may be purchased from New England Bio Labs. For each assay, test compounds were serially diluted in DMSO and then mixed with the appropriate kinase reaction buffer plus 5-10 nM of ^{33}P gamma-labeled ATP. The kinase protein and the appropriate biotinylated peptide substrate were added to give a final volume of 150 μL. Reactions were incubated for 3-4 hours at room temperature and then stopped by transferring to a streptavidin-coated white microtiter plate (Thermo Labsystems) containing 100 μL of stop reaction buffer. The stop reaction buffer consists of 50 mM unlabeled ATP and 30 mM EDTA. After 1 hour of incubation, streptavidin plates were washed with PBS, and 200 μL Microscint 20 scintillation fluid was added per well. The plates were sealed and counted using TopCount. The concentration of each compound for 50% inhibition (IC_{50}) was calculated employing non-linear regression using XL Fit data analysis software.

[0788] The reaction buffer contained 30 mM Tris-HCl_2 pH 7.5, 10 mM $MgCl_2$, 2 mM DTT, 4 mM EDTA, 25 mM beta-glycerophosphate, 5 mM $MnCl_2$, 0.01% BSA/PBS, 0.5 μM peptide substrate, and 1 μM unlabeled ATP. GSK-3 enzyme was used at 27 nM, CHK1 at 5 nM, Cdc2 at 1 nM, Cdk2 at 5 nM, and Rsk2 at 0.044 units/mL. For the GSK-3 assay, biotin-CREB peptide (Biotin-SGSGKRREILSRRP(pS)YR-NH_2 (SEQ ID NO: 4)) was used. For the CHK1 assay, a biotin-Cdc25c peptide (Biotin-[AHX]SGSGSGLYRSPSMPENLNRPR[$CONH_2$] (SEQ ID NO: 5)) was

used. For the Cdc2 and the Cdk2 assays, a biotin-Histone H1 peptide ([IcBiotin]GGGGPKTPKKAKKL[$CONH_2$] (SEQ ID NO: 6)) was used. In the Rsk2 assay, a biotin-p70 peptide, 15 mM $MgCl_2$, 1 mM DTT, 5 mM EDTA, 2.7 μM PKC inhibitor peptide, and 2.7 μM PKA inhibitor peptide were used.

Tyrosine Kinases

[0789] The kinase activity of a number of protein tyrosine kinases was measured by providing ATP and an appropriate peptide or protein containing a tyrosine amino acid residue for phosphorylation, and assaying for the transfer of phosphate moiety to the tyrosine residue. Recombinant proteins corresponding to the cytoplasmic domains of the FLT-1 (VEGFR1), VEGFR2, VEGFR3, Tie-2, PDGFRα, PDGFRβ, and FGFR1 receptors were expressed in Sf9 insect cells using a Baculovirus expression system (InVitrogen) and may be purified via Glu antibody interaction (for Glu-epitope tagged constructs) or by Metal Ion Chromatography (for His_6 (SEQ ID NO: 1) tagged constructs). For each assay, test compounds were serially diluted in DMSO and then mixed with an appropriate kinase reaction buffer plus ATP. Kinase protein and an appropriate biotinylated peptide substrate were added to give a final volume of 50-100 μL, reactions were incubated for 1-3 hours at room temperature and then stopped by addition of 25-50 μL of 45 mM EDTA, 50 mM Hepes pH 7.5. The stopped reaction mixture (75 μL) was transferred to a streptavidin-coated microtiter plate (Boehringer Mannheim) and incubated for 1 hour. Phosphorylated peptide product was measured with the DELFIA time-resolved fluorescence system (Wallac or PE Biosciences), using a Europium labeled anti-phosphotyrosine antibody PT66 with the modification that the DELFIA assay buffer was supplemented with 1 mM $MgCl_2$ for the antibody dilution. Time resolved fluorescence was read on a Wallac 1232 DELFIA fluorometer or a PE Victor II multiple signal reader. The concentration of each compound for 50% inhibition (IC_{50}) was calculated employing non-linear regression using XL Fit data analysis software.

[0790] FLT-1, VEGFR2, VEGFR3, FGFR3, Tie-2, and FGFR1 kinases were assayed in 50 mM Hepes pH 7.0, 2 mM $MgCl_2$, 10 mM $MnCl_2$, 1 mM NaF, 1 mM DTT, 1 mg/mL BSA, 2 μM ATP, and 0.20-0.50 μM corresponding biotinylated peptide substrate. FLT-1, VEGFR2, VEGFR3, Tie-2, and FGFR1 kinases were added at 0.1 μg/mL, 0.05 μg/mL, or 0.1 μg/mL respectively. For the PDGFR kinase assay, 120 μg/mL enzyme with the same buffer conditions as above was used except for changing ATP and peptide substrate concentrations to 1.4 μM ATP, and 0.25 μM biotin-GGLFDDPSYVNVQNL-NH_2 (SEQ ID NO: 2) peptide substrate. Each of the above compounds displayed an IC_{50} value of less than 10 μM with respect to FLT-1, VEGFR2, VEGFR3, and FGFR1.

[0791] Recombinant and active tyrosine kinases Fyn, and Lck are available commercially and were purchased from Upstate Biotechnology. For each assay, test compounds were serially diluted in DMSO and then mixed with an appropriate kinase reaction buffer plus 10 nM ^{33}P gamma-labeled ATP. The kinase protein and the appropriate biotinylated peptide substrate were added to give a final volume of 150 μL. Reactions were incubated for 3-4 hours at room temperature and then stopped by transferring to a streptavidin-coated white microtiter plate (Thermo Labsystems) containing 100 μL of stop reaction buffer of 100 mM EDTA and 50 μM unlabeled ATP. After 1 hour incubation, the streptavidin plates were washed with PBS and 200 μL Microscint 20 scintillation fluid was added per well. The plates were sealed and counted using TopCount. The concentration of each compound for 50% inhibition (IC_{50}) was calculated employing non-linear regression using XL Fit data analysis software.

[0792] The kinase reaction buffer for Fyn, Lck, and c-ABL contained 50 mM Tris-HCl pH 7.5, 15 mM MgCl2, 30 mM $MnCl_2$, 2 mM DTT, 2 mM EDTA, 25 mM beta-glycerol phosphate, 0.01% BSA/PBS, 0.5 μM of the appropriate peptide substrate (biotinylated Src peptide substrate: biotin-

GGGGKVEKIGEGTYGVVYK-NH_2 (SEQ ID NO: 3) for Fyn and Lck), 1 μM unlabeled ATP, and 1 nM kinase.

[0793] The kinase activity of c-Kit and FLT-3 were measured by providing ATP and a peptide or protein containing a tyrosine amino acid residue for phosphorylation, and assaying for the transfer of phosphate moiety to the tyrosine residue. Recombinant proteins corresponding to the cytoplasmic domains of the c-Kit and FLT-3 receptors were purchased (Proquinase). For testing, an exemplary compound, for example 4-amino-5-fluoro-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one, was diluted in DMSO and then mixed with the kinase reaction buffer described below plus ATP. The kinase protein (c-Kit or FLT-3) and the biotinylated peptide substrate (biotin-GGLFDDPSYVNVQNL-NH2 (SEQ ID NO: 2)) were added to give a final volume of 100 μL. These reactions were incubated for 2 hours at room temperature and then stopped by addition of 50 μL of 45 mM EDTA, 50 mM HEPES, pH 7.5. The stopped reaction mixture (75 μL) was transferred to a streptavidin-coated microtiter plate (Boehringer Mannheim) and incubated for 1 hour. Phosphorylated peptide product was measured with the DELPHIA time-resolved fluorescence system (Wallac or PE Biosciences), using a Europium-labeled anti-phosphotyrosine antibody, PT66, with the modification that the DELFIA assay buffer was supplemented with 1 mM $MgCl_2$ for the antibody dilution. Time resolved fluorescence values were determined on a Wallac 1232 DELFIA fluorometer or a PE Victor II multiple signal reader. The concentration of each compound for 50% inhibition (IC_{50}) was calculated employing non-linear regression using XL Fit data analysis software.

[0794] FLT-3 and c-Kit kinases were assayed in 50 mM Hepes pH 7.5, 1 mM NaF, 2 mM $MgCl_2$, 10 mM $MnCl_2$ and 1mg/mL BSA, 8 μM ATP and 1 μM of corresponding biotinylated peptide substrate (biotin-GGLFDDPSYVNVQNL-NH2 (SEQ ID NO: 2)). The concentration of FLT-3 and c-Kit kinases were assayed at 2 nM.

[0795] Each of the compounds produced in the Examples was synthesized and assayed using the procedures described above. The majority of the exemplary compounds displayed an IC_{50} value of less than 10 μM with respect to VEGFR1, VEGFR2, VEGFR3, FGFR1, CHK1, Cdc2, GSK-3, NEK-2, Cdk2, Cdk4, MEK1, NEK-2, CHK2, CK1ε, Raf, Fyn, Lck, Rsk2, PAR-1, c-Kit, c-ABL, p60src, FGFR3, FLT-3, PDGFRα, and PDGFRβ. In addition, many of the exemplary compounds exhibited IC_{50} values in the nM range and show potent activity with respect to VEGFR1, VEGFR2, VEGFR3, FGFR1, FGFR3, c-Kit, c-ABL, FLT-3, CHK1, Cdc2, GSK-3, NEK-2, Cdk2, MEK1, NEK-2, CHK2, Fyn, Lck, Rsk2, PAR-1, PDGFRα, and PDGFRβ with IC_{50} values of less than 1 μM. The other examples also exhibited such activity with respect to VEGFR1, VEGFR2, VEGFR3, FGFR1, FGFR3, c-Kit, c-ABL, p60src, FLT-3, CHK1, Cdc2, GSK-3, NEK-2, Cdk2, Cdk4, MEK1, NEK-2, CHK2, CK1ε, Raf, Fyn, Lck, Rsk2, PAR-1, PDGFRα, and PDGFRβ or will be shown to exhibit such activity. The exemplary compounds also exhibited inhibition activity with respect to VEGFR2. In some embodiments, the invention provides a compound, a tautomer of the compound, a pharmaceutically acceptable salt of the compound, a pharmaceutically acceptable salt of the tautomer, an enantiomer or diastereomer of the compound, an enantiomer or diastereomer of the tautomer, an enantiomer or diastereomer of the pharmaceutically acceptable salt of the compound, an enantiomer or diastereomer of the pharmaceutically acceptable salt of the tautomer, or a mixture of the compounds, enantiomers, tautomers, or salts, wherein the compound is selected from the group consisting of the title compounds of Examples 51-90, Examples 93-100, Example 102, Example 104, Example 105, and Examples 339-1457. Such embodiments are directed to the specific compound, salts, enantiomers, and mixtures of the title compounds and are not limited to the procedures used to make such compounds, for example, the procedures described in Examples 51-90, 93-100, 102, 104, and 105. In some such embodiments, the invention provides the compound, the tautomer of the compound, the pharmaceutically acceptable salt of the compound, or the pharmaceutically acceptable salt of

the tautomer, wherein the compound is selected from the group consisting of Examples 51-90, Examples 93-100, Example 102, Example 104, Example 105, and Examples 339-1457. In some such embodiments, the compound is selected from those named in Table 3, Table 4, and Table 5. In some embodiments, the compound is selected from those named in Table 3. In other embodiments, the compound is selected from those named in Table 4. In other embodiments, the compound is selected from those named in Table 5. The invention further provides the use of such compounds in the manufacture of a medicament or pharmaceutical formulation for inhibiting the kinase activity of the serine/threonine or tyrosine kinases described herein; the use of such compounds in the manufacture of a medicament or pharmaceutical formulation for treating a biological condition mediated by any of the of the serine/threonine or tyrosine kinases described herein. The invention further provides methods for inhibiting any of the serine/threonine kinases or tyrosine kinases described herein utilizing these compounds and methods of treating biological conditions mediated by any of the serine/threonine kinases or tyrosine kinases described herein utilizing these compounds.

[0796] In one embodiment, the invention provides a method of inhibiting FLT-1 (VEGFR1). The method includes administering an effective amount of a compound, or a pharmaceutically acceptable salt thereof, of any of the embodiments of the compounds of Structure I or IB to a subject, such as a human, in need thereof.

[0797] In one embodiment, the invention provides a method of inhibiting VEGFR2 (KDR (human), Flk-1 (mouse)). The method includes administering an effective amount of a compound, or a pharmaceutically acceptable salt thereof, of any of the embodiments of compounds of Structure I or IB to a subject, such as a human, in need thereof.

[0798] In one embodiment, the invention provides a method of inhibiting VEGFR3 (FLT-4). The method includes administering an effective

amount of a compound, or a pharmaceutically acceptable salt thereof, of any of the embodiments of compounds of Structure I or IB to a subject, such as a human, in need thereof.

[0799] In one embodiment, the invention provides a method of inhibiting FGFR1. The method includes administering an effective amount of a compound, or a pharmaceutically acceptable salt thereof, of any of the embodiments of compounds of Structure I or IB to a subject, such as a human, in need thereof.

[0800] In one embodiment, the invention provides a method of inhibiting NEK-2. The method includes administering an effective amount of a compound of compounds of Structure I or IB to a subject, such as a human, in need thereof.

[0801] In one embodiment, the invention provides a method of inhibiting PDGFRα and PDGFRβ. The method includes administering an effective amount of a compound, or a pharmaceutically acceptable salt thereof, of any of the embodiments of compounds of Structure I or IB to a subject, such as a human, in need thereof.

[0802] In one embodiment, the invention provides a method of inhibiting FGFR3. The method includes administering an effective amount of a compound, or a pharmaceutically acceptable salt thereof, of any of the embodiments of compounds of Structure I or IB to a subject, such as a human, in need thereof.

[0803] In one embodiment, the invention provides a method of inhibiting FLT-3. The method includes administering an effective amount of a compound, or a pharmaceutically acceptable salt thereof, of any of the embodiments of compounds of Structure I or IB to a subject, such as a human, in need thereof.

[0804] In another embodiment, the invention provides a method of inhibiting FLT-3 or Stat5 phosphorylation. The method includes administering an effective amount of a compound, or a pharmaceutically acceptable salt thereof, of any of the embodiments of compounds of Structure I or IB to a subject, such as a human, in need thereof.

[0805] In one embodiment, the invention provides a method of inhibiting c-Kit. The method includes administering an effective amount of a compound, or a pharmaceutically acceptable salt thereof, of any of the embodiments of compounds of Structure I or IB to a subject, such as a human, in need thereof.

[0806] In one embodiment, the invention provides a method of inhibiting c-ABL. The method includes administering an effective amount of a compound, or a pharmaceutically acceptable salt thereof, of any of the embodiments of compounds of Structure I or IB to a subject, such as a human, in need thereof.

[0807] In one embodiment, the invention provides a method of inhibiting p60src. The method includes administering an effective amount of a compound, or a pharmaceutically acceptable salt thereof, of any of the embodiments of compounds of Structure I or IB to a subject, such as a human, in need thereof.

[0808] In one embodiment, the invention provides a method of inhibiting FGFR3. The method includes administering an effective amount of a compound, or a pharmaceutically acceptable salt thereof, of any of the embodiments of compounds of Structure I or IB to a subject, such as a human, in need thereof.

[0809] In one embodiment, the invention provides a method of inhibiting ErB2. The method includes administering an effective amount of a compound, or a pharmaceutically acceptable salt thereof, of any of the

embodiments of compounds of Structure I or IB to a subject, such as a human, in need thereof.

[0810] In one embodiment, the invention provides a method of inhibiting Cdk 2. The method includes administering an effective amount of a compound, or a pharmaceutically acceptable salt thereof, of any of the embodiments of compounds of Structure I or IB to a subject, such as a human, in need thereof.

[0811] In one embodiment, the invention provides a method of inhibiting Cdk 4. The method includes administering an effective amount of a compound, or a pharmaceutically acceptable salt thereof, of any of the embodiments of compounds of Structure I or IB to a subject, such as a human, in need thereof.

[0812] In one embodiment, the invention provides a method of inhibiting MEK1. The method includes administering an effective amount of a compound, or a pharmaceutically acceptable salt thereof, of any of the embodiments of compounds of Structure I or IB to a subject, such as a human, in need thereof.

[0813] In one embodiment, the invention provides a method of inhibiting NEK-2. The method includes administering an effective amount of a compound, or a pharmaceutically acceptable salt thereof, of any of the embodiments of compounds of Structure I or IB to a subject, such as a human, in need thereof.

[0814] In one embodiment, the invention provides a method of inhibiting CHK2. The method includes administering an effective amount of a compound, or a pharmaceutically acceptable salt thereof, of any of the embodiments of compounds of Structure I or IB to a subject, such as a human, in need thereof.

[0815] In one embodiment, the invention provides a method of inhibiting CK1ε. The method includes administering an effective amount of a compound, or a pharmaceutically acceptable salt thereof, of any of the embodiments of compounds of Structure I or IB to a subject, such as a human, in need thereof.

[0816] In one embodiment, the invention provides a method of inhibiting Raf. The method includes administering an effective amount of a compound, or a pharmaceutically acceptable salt thereof, of any of the embodiments of compounds of Structure I or IB to a subject, such as a human, in need thereof.

[0817] As noted above, the exemplary compounds exhibited activity in one or more important assay or will be found to exhibit such activity. For this reason, each of the exemplary compounds is both individually preferred and is preferred as a group. One, two, or more compounds of the invention may be used in combination in pharmaceutical formulations, medicaments, and in methods of treating subjects. Furthermore, each of the R^1-R^{10} groups of the exemplary compounds is preferred individually and as a member of a group.

Small Molecule Inhibitors of Growth Factor Tyrosine Kinase Receptors Involved in Angiogenesis and Tumor Cell Proliferation

Inhibition of Kinases

[0818] 4-Amino-5-fluoro-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one is an orally bioavailable benzimidazole-quinolinone that exhibits potent inhibition of receptor tyrosine kinases that drive both endothelial and tumor cell proliferation. The inhibitory effect of 4-amino-5-fluoro-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one on nine tyrosine kinases, FGFR1, FGFR3, VEGFR1, VEGFR2, VEGFR3, PDGFRβ, c-Kit, p60src, and FLT-3 was determined using the assay procedures described above. The IC_{50}s for these tyrosine kinases were found to be less than 30 nM. The compound also displays IC_{50}s of less than 1 μM

against fyn, p^{56}lck, c-ABL, CHK1, CHK2, PAR-1, MEK, and RSK2. 4-Amino-5-fluoro-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one does not significantly inhibit EGFR family kinases or insulin receptor kinase at these concentrations (IC_{50}s >2 μM). The inhibitory effect of 4-Amino-5-fluoro-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one on phosphorylation of FLT-3 in MV4-11 cells, a tumor cell line, is described below.

Antiproliferative Effects in Cell Lines

[0819] The antiproliferative activity of 4-Amino-5-fluoro-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one (Example 166) was assessed in 27 different cancer and primary cell lines and displayed EC_{50} values of less than 10 μM in 26 out of the 27 cell lines. The antiproliferative activity of the exemplary compound was tested by adding a MTS tetrazolium compound (available from Promega, Madison, Wisconsin) that is bioreduced by metabolically-active cells into a soluble colored formazan product, which was recorded by measuring the absorbance at 490 nm with a spectrophotometer. In order to determine EC_{50} values for the exemplary compound in each of the cell lines, the appropriate number of cells was determined to give an optimal signal (see Table 6) and plated in 100 μL of growth media in a 96 well plate. Serially-diluted exemplary compound in a DMSO stock solution was added to the plate in 100 μL growth media typically at a starting concentration of 20 μM and incubated for 72 hours at 37°C and 5% CO_2. The final DMSO concentration was 0.5% or less for each cell line (see Table 6). The cell lines used to determine EC_{50} values of the exemplary compounds are listed in Table 6 and were of human origin unless otherwise noted. For the HMVEC and TF-1 cell lines, the EC_{50} were determined as inhibition of VEGF and SCF (Stem cell factor) mediated proliferation, respectively. After the 72 hours of incubation, 40 μL of MTS solution was added to the wells and the OD measured after 3-5 hours at 490 nm. The EC_{50} values were calculated using nonlinear regression. The exemplary compound had antiproliferative effects with EC_{50}s <10 μM for all the cell lines

tested with the exception of the U87MG cell line in which the EC_{50} was calculated to be about 10 μM for the exemplary compound.

Table 6. Cell Lines and Conditions Employed to Determine the Antiproliferative Activity of Exemplary Compounds.

Cell Line	Origin*	Cells/ well of 96 well plate	Final DMSO conc. (%)	MTS incubation	Medium
4T1	mouse breast	500	0.5	4-5H	DMEM + 10%FBS + Pen/Strep + SodiumPyruvate + 2 mM L-Glut
ARH-77	blood	10,000	0.5	4H	RPMI-1640 + 10% Heat Inactivated FBS + 2 mM L-Glut + Pen/Strep
DU145	prostate	500	0.5	3-4H	EMEM + 10% FBS + 2 mM L-Glut + Pen/Strep
HCT-116	colon	500	0.5	5H	McCoy's5A with 2 mM L-Glut + 10% FBS + Pen/Strep
HMVECd	endothelium	2,000	0.5	4H	EGM-2-MV (Biowhittaker #cc-3202)
K-562	blood	5,000	0.2	3H	RPMI-1640 + 10% FBS+2 mM L-Glut + Pen/Strep
KM12L4A	colon	500	0.5	5H	EMEM + 10% FBS +2 mM L-Glut + 2xVitamins + NEAA + Sodium Pyruvate + Pen/Strep
KU812	blood	10,000	0.2	6H	RPMI-1640 + 10%FBS + 2 mM L-Glut + Pen/Strep
MOLT4	blood	5,000	0.5	4H	RPMI-1640 + 10% FBS + 2 mM L-Glut + Pen/Strep
MV4-11	blood	10,000	0.2	6H	IMDM + 10% FBS + 5 ng/ml GM-CSF + 2 mM L-Glut+Pen/Strep
NCI-H209	lung	10,000	0.5	5H	IMDM + 10% FBS + 2 mM L-Glut + Pen/Strep
NCI-H526	lung	10,000	0.5	5H	RPMI-1640 + 10% FBS + 2 mM L-Glut + Pen/Strep
PC-3P	prostate	500	0.5	5H	EMEM + 10% FBS + vit 2% 100x + L-L-Glut 200 mM 1% + NaPy100mM 1% + NEAA100x 1%
RS4;11	blood	10,000	0.2	6H	RPMI-1640+10%FBS + 10mM HEPES + 1mM SodiumPyruvate+Pen/Strep
SK-OV-3	ovary	2,500	0.5	4H	McCoy's 5A + 10% FBS + 2 mM L-Glut+Pen/Strep
TF-1	blood	10,000	0.2	6H	RPMI-1640 + 10% FBS + 0.044 mM BME + 2 mM L-Glut + Pen/Strep + 5ng/ml GM-CSF
U-87MG	brain	500	0.5	5H	EMEM + 10% FBS + NEAA + SodiumPyruvate + Earle's BSS
HL60	blood	12,500	0.5	5H	RPMI-1640 + 10% FBS + 2

					mM L-Glut + Pen/Strep
M-NFS-60	blood	5,000	0.5	4-5H	RPMI-1640 + 10% FBS + 0.044mM BME + 2 mM L-Glut + Pen/Strep + 67.1 ng/ml GM-CSF
GH3	rat pituitary	10,000	0.5	4H	Ham's F10 + 2mM L-Glut + 15% Horse Serum (HS) + 2.5% Fetal Bovine Serum (FBS)
HP75	pituitary	5,000	0.5	4H	DMEM 15% Horse Serum, 2.5% Fetal Bovine Serum, 1 µg/ml Insulin, Pen/Strep
HMEC	mammary epithelium	2,000	0.5	4H	MEGM (Biowhittaker #CC-3051)
PrEC	prostate epithelium	2,000	0.5	4H	PrEGM (Cambrex #CC3166)
MDA-MB435	breast	500	0.5	4H	DMEM/F12 (1:1) 10% FBS
SW620	colon	500	0.5	4H	Leibovitz's L-15 medium with 2 mM L-Glut 10% fetal bovine serum
HT29	colon	5,000	0.5	4H	McCoy's 5A + 10% FBS

*Origin was human unless otherwise noted.

[0820] Significant anti-proliferative effects were observed in endothelial cells and a subset of tumor cell lines. Several human cancer cell lines have been identified that are at least 10 fold more sensitive to the anti-proliferative effects of 4-amino-5-fluoro-3-[5-(4–methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one than the rest of the cell lines tested. The compound inhibited VEGF mediated proliferation in HMVEC (human microvascular endothelial cells) with an IC_{50} of 25 nM and the compound inhibited KM12L4a, a human colon cancer cell line, in a dose-dependent manner with an EC_{50} of 9 nM. SCF (Stem Cell Factor) mediated proliferation of TF-1 cells was inhibited by 4-amino-5-fluoro-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one indicating that c-Kit RTK activity is modulated. The compound displayed antiproliferative activity in FLT-3 mutant and wild-type cells: EC_{50}s of 13 nM against MV4-11 (FLT-3 ITD mutant), and 510 nM against RS4 (FLT-3 wild-type). Reduced tumor cell proliferation was documented *in vivo* by immunohistochemistry staining with Ki67. Thus, 4-amino-5-fluoro-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one is not a general "non-specific" cytotoxic agent, but has potent activity against many cancer cell lines.

Inhibition of Phosphorylation in Cell-Based Assays

[0821] Studies with plasma and tumors collected from mice following treatment with 4-amino-5-fluoro-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one were performed to evaluate potential pharmacodynamic endpoints. Analysis of target modulation in KM12L4a tumors after 4-amino-5-fluoro-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one treatment indicated that phosphorylation of VEGFR1, VEGFR2, PDGFRβ, and FGFR1 were inhibited in a time- and dose-dependent manner. For example, HMVEC cells showed inhibition of VEGF mediated VEGFR2 phosphorylation with an IC_{50} of about 0.1 μM. In addition, treatment of endothelial cells with 4-amino-5-fluoro-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one inhibited MAPK and Akt phosphorylation mediated by VEGF.

[0822] Furthermore, a time- and dose- dependent inhibition of ERK (MAPK) activation, a downstream target of receptor tyrosine kinases, was observed with IC_{50}s ranging from 0.1 to 0.5 μM in KM12L4A cells. (KM12L4A cells express PDGFRβ and VEGFR1/2 on their surfaces.) The inhibitory effects of 4-amino-5-fluoro-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one on receptor phosphorylation and ERK activation were maintained for 24 hours after treatment. Phosphorylation of ERK1/2 in MV4-11 cells was inhibited by the exemplary compound at IC_{50}s of 0.01 to 0.1 μM in a dose-dependent manner.

[0823] FLT-3 and Stat5 phosphorylation was inhibited at concentrations of 0.1 and 0.5 μM of 4-amino-5-fluoro-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one when MV4-11 cells are treated for 1 hour. A dose response study of the exemplary compound showed full inhibition of Stat5 phosphorylation in MV4-11 cells at 0.1 μM. A pulse-washout experiment in MV4-11 cells with the exemplary compound showed full inhibition of Stat5 phosphorylation for at least 4 hours and partial inhibition

at 24 and 44 hours. FLT-3 phosphorylation in RS4 cells was inhibited at 0.1, 1 and 3 μM concentrations of the exemplary compound.

[0824] Significant activity was observed *in vivo* in the HCT116 human colon tumor model. In HCT116 tumors, 4-amino-5-fluoro-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one inhibited the phosphorylation of ERK (MAPK) in a dose- and time-dependent manner and significant changes in histology analyses of the tumors was observed.

[0825] These PK/PD evaluations in preclinical models indicate that 4-amino-5-fluoro-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one showed a dose- and time-dependent inhibition of both the target receptors and the downstream signaling molecule, ERK (MAPK). These studies will aid in the identification of potential biomarkers to support the monitoring of biological activity of 4-amino-5-fluoro-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one in clinical trials.

In Vivo Tumor Model Studies

[0826] *In vivo* daily oral dosing of 4-amino-5-fluoro-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one resulted in significant anti-tumor activity in a broad range of human and murine tumor models. Established tumor xenografts of prostate, colon, ovarian and hematologically-derived cancer cells have all demonstrated responsiveness to treatment in a dose-dependent manner, with ED_{50s} ranging from 4-65 mg/kg/d. The *in vivo* activity ranges from growth inhibition to stable disease and tumor regressions. For example, the compound induces regression and growth inhibition in subcutaneous KM12L4a human colon tumor xenografts in *nu/nu* mice. FIG. 1 shows tumor volume over time at various doses of 4-amino-5-fluoro-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one. Dosing started when tumor xenografts reached 125 mm^3. The results show significant tumor growth inhibition after 4 doses of greater than or equal to 30 mg/kg, and tumor regressions at 60 and 100 mg/kg. Similar

results were observed in 90-100% of animals with larger KM12L4a colon tumor xenografts. Treatment started when tumor size reached 500 and 1000 mm^3. Tissue concentration studies showed that 4-amino-5-fluoro-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one was retained in the tumor with levels up to 65-300 fold higher than plasma at 24 hours after dosing. In addition, target modulation studies showed inhibition was maintained for more than 24 hours.

[0827] Example 166 also displayed an ED_{50} of 4 mg/kg/d in a subcutaneous MV4-11 (FLT-3 ITD mutant) tumor model in SCID-NOD mice (treatment initiated when tumor volume at 300 mm^3; see FIG. 11). A dose of 30 mg/kg/d inhibited the growth of larger MV4-11 tumors (>86% for 500 mm^3; >80% for 1000 mm^3 tumor volume at treatment start) and resulted in several complete regressions (see FIG. 12). Regressions were found to be stable after cessation of dosing. In those tumors that recurred, a second cycle of 30 mg/kg/d of the exemplary compound again caused partial regression, indicating a lack of acquired resistance to the compound.

[0828] 4-Amino-5-fluoro-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one also proved efficacious in a tumor metastasis study in which 4T1 murine breast tumor cells were implanted subcutaneously in BALB/c mice. Treatment was begun when the tumors reached 150 mm^3, and the mice were given oral daily doses for 17 days. Study endpoints at 30 days after cell implant were primary tumor growth inhibition versus vehicle and macroscopic counts of gross liver metastases. Example 166 inhibited the primary tumor up to 82% and inhibited liver metastases by more than 75% at all doses above 10 mg/kg/d.

Antiangiogenic Effects

[0829] 4-Amino-5-fluoro-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one was assayed in several *in vitro* angiogenesis assays including endothelial cell migration and tube formation on fibrin gels (see

FIGS. 9A and 9B) as well as in the *ex vivo* rat aortic ring assay (see FIG. 10). It showed dose-dependent inhibition of the respective assay endpoints compared to the control.

[0830] 4-Amino-5-fluoro-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one induces dose-dependent inhibition of angiogenesis in the *in vivo* matrigel model. Matrigel supplemented with bFGF was injected subcutaneously into mice. The compound was orally administered to the mice for 8 days. The matrigel plug was removed and the hemoglobin concentration therein was quantitated. As shown in FIG. 2, significant inhibition of neovascularization was observed, with an ED_{50} of 3 mg/kg/day. In addition, all doses were well tolerated by the animals in the 8-day studies.

Dosing Scheduling Effects

[0831] Dose scheduling studies were done to evaluate the relationship of the extended tumor half-life and prolonged biological activity to the anti-tumor efficacy. Significant activity was observed with several intermittent and cyclic dosing regimens. For example, in an intermittent dosing regime, 4-amino-5-fluoro-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one was administered to *SCID* mice having subcutaneous PC3 human prostate tumor xenografts. Treatment was started when tumors reached 150 mm^3 in size. Dosing was performed at 100 mg/kg orally qd, q2d, q3d, and q4d. Significant and similar tumor inhibition was observed in all treatment groups as shown in FIG. 3.

[0832] In a cyclic dosing experiment, 4-amino-5-fluoro-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one was administered to *nu/nu* mice having KM12L4a human colon tumor xenografts. Treatment was started when tumors reached 500 mm^3. Doses were administered at 100 or 150 mg/kg on days 1-5, 18-22, and 26-30. Compared to vehicle, tumor regression of 50% or more was seen. At the higher dose, tumors continued to regress and then stabilize for about 10 days. In another

dosing study, the effect of the exemplary compound was examined in the human MV4-11 (FLT-3 ITD mutant) subcutaneous tumor model in *SCID-NOD* mice. Alternate dosing schedules (q.o.d. or 7days on/7 off) of 30 mg/kg 4-amino-5-fluoro-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one were equally potent (see FIG. 13).

Combination Therapy Results

[0833] Combination therapy studies were done using the standard cytotoxics, irinotecan and 5-FU, in the KM12L4a colon tumor model. Significant potentiation of activity was seen, with the most dramatic effects at low, inactive doses of 4-amino-5-fluoro-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one as shown in FIG. 5. A cyclic dosing regimen of the compound at 50 mg/kg in combination with irinotecan gave excellent results, with 3 complete regressions and 7 partial regressions, as shown in FIG. 6. Synergistic and greater than additive effects were also seen with trastuzumab combined with 4-amino-5-fluoro-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one in the erbB2-overexpressing ovarian tumor model, SKOV3ip1 (see FIG. 7). Additionally, tumor responses and regressions were significantly improved over each single agent treatment in the A431 epidermoid tumor model when 4-amino-5-fluoro-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one was combined with ZD1839 (Iressa) (see FIG. 8). These data suggest that 4-amino-5-fluoro-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one has the potential to be a broadly applicable and effective therapy for solid and hematological cancers.

Metabolism and Pharmacokinetic Studies

[0834] Metabolism and pharmacokinetic studies were carried out on 4-amino-5-fluoro-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one. The compound was stable in human liver microsomes. It did not demonstrate a significant potential for inhibition of five common cDNA derived

CYP isozymes (1A2, 2C9, 2C19, 2D6, 3A4) having IC_{50}s of greater than 25 μM for each. In addition, the compound displays a half life adequate for once daily dosing. Thus, the compound displays favorable metabolic and pharmacokinetic properties.

Inhibition of CSF-1 Mediated Growth by 4-Amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-quinolin-2-one

[0835] The antiproliferative activity of 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-quinolin-2-one was shown to inhibit CSF-1 (Colony Stimulating Factor-1) mediated proliferation of M-NFS-60 cells (mouse myeloblast cell line) with an EC_{50} of 300 nM. The assay was run by plating 5000 cells/well in 50 uL assay media (growth media without 67.1 ng/ml GM-CSF: RPMI-1640+10% FBS+0.044 mM beta Mercaptoethanol+2 mM L-Glut+Pen/Strep) in a 96 well plate. Serially-diluted 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-quinolin-2-one in a DMSO stock solution starting at 20 μM was added to the plate in 50 μL assay media containing CSF-1 to make a final concentration of 10 ng/ml and then incubated for 72 hours at 37°C and 5% CO_2. The final DMSO concentration was 0.2%. After 72 hours of incubation, 100 μL of Cell Titer Glo (Promega #G755B) was added to the plate and, after shaking and a 10 minute incubation time, the luminescence was measured. The EC_{50} was calculated using nonlinear regression.

[0836] Autophosphorylation of CSFR1 is inhibited by 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-quinolin-2-one with concentrations < 1 μM. Treatment of M-NFS-60 cells with 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-quinolin-2-one and treatment of the cells with CSF-1 for 5 minutes at the end of the incubation time, resulted in inhibition of receptor tyrosine phosphorylation detected by immunoprecipitation of CSFR1 and western blotting with an anti-phosphotyrosine antibody.

Inhibition of FGFR3 by 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-quinolin-2-one

[0837] The t(4;14) translocation that occurs uniquely in a subset (15-20%) of multiple myeloma (MM) patients results in the ectopic expression of the receptor tyrosine kinase (RTK), FGFR3. The subsequent acquisition of FGFR3 activating mutations in some MM is associated with disease progression and is strongly transforming in experimental models.

[0838] 4-Amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-quinolin-2-one inhibited proliferation of OPM-2 cells that express constitutively activated FGFR3 due to a K650E mutation with an EC_{50} of 100 nM. The assay was run by plating 8000 cells/well in 50 μL assay media (RPMI-1640+10%FBS+Pen/Strep) in a 96 well plate. Serially-diluted 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-quinolin-2-one in a DMSO stock solution starting at 20 μM was added to the plate in 50 μL assay media and then incubated for 72 hours at 37C and 5% CO_2. The final DMSO concentration was 0.2%. After 72 hours of incubation, 100 μL of Cell Titer Glo (Promega #G755B) was added to the plate and, after shaking and a 10 minute incubation time, the luminescence was read. The EC_{50} was calculated using nonlinear regression. The EC_{50} for 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-quinolin-2-one in the H929 cell line (IMDM+10%FBS+Pen/Strep) that expresses WT FGFR3 receptor was 0.63 μM. The EC_{50} was determined as described above using assay media that contained 50 ng/ml aFGF, 10 μg/ml Heparin and 1% FBS). The EC_{50} was calculated using nonlinear regression from the ODs at 490 nm which were determined after adding MTS tetrazolium reagent (Promega) for 4 hours.

[0839] Significant apoptosis was seen after 6 days of treatment of OPM-2 cells with 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-quinolin-2-one (>60% of the cells were AnnexinV

positive using the protocol and instrument from Guava Technologies for detection of Annexin V positive cells).

[0840] The phosphorylation of downstream signaling component ERK was completely inhibited after incubation of OPM-2 cells with 0.1 μM of 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1 H-benzimidazol-2-yl]-1H-quinolin-2-one. Western blotting was used to show inhibition of ERK phosphorylation.

Inhibition of C-Met by 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-quinolin-2-one

[0841] 4-Amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-quinolin-2-one inhibited c-MET with an IC_{50}>3 μM. The kinase activity of c-MET was measured by providing ATP at a final concentration of 25 μM and 10 nM of the c-MET enzyme (Upstate#14-526) in the presence of 1 μM biotinylated substrate (KKKSPGEYVNIEFG (SEQ ID NO: 8)). Substrate bound to Streptavidin plates was detected with Europium labeled antiphosphotyrosine Antibody PT66. Phosphorylated peptide substrate was measured with the DELPHIA time resolved fluorescence system, and the IC_{50} was calculated employing non-linear regression using XL Fit data analysis software. C-MET was constitutively activated in KM12L4A cells which is one of the most sensitive cell lines with respect to inhibition of proliferation by 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-quinolin-2-one (EC_{50} 20 nM). This suggests that 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-quinolin-2-one either inhibits mutated c-MET or a kinase in the downstream signaling pathway of c-MET.

***In Vitro* Activity of 4-Amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one Against Various RTKs**

[0842] 4-Amino substituted quinolinone benzimidazolyl compounds such as 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one and tautomers and salts thereof are potent inhibitors of

various kinases such as VEGFR2 (KDR, Flk-1), FGFR1 and PDGFRβ with IC_{50}s ranging from 10-27 nM. See U.S. Patent No. 6,605,617, U.S. Patent Application No. 10/644,055, and U.S. Patent Application No. 10/706,328, each of which is hereby incorporated by reference in its entirety and for all purposes as if fully set forth herein, for a list of various tyrosine and serine/threonine kinases for which 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one has shown activity and for assay procedures. These RTKs are important for the initiation and maintenance of new blood vessel growth as well as tumor proliferation. Systematic profiling against class III-IV RTKs as well as a subset of RTKs from other classes shows potent inhibition of CSF-R1/c-fms, c-kit, flt3 and FGFR3. FGFR3 is abnormally expressed and in some cases constitutively activated in a subset of multiple myeloma patients as a consequence of the t(4;14) translocation (about 15-20%).

[0843] The effects of 4-amino substituted quinolinone benzimidazolyl compounds such as 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one on multiple myeloma cell lines with the t(4;14) translocation were investigated with respect to effects on proliferation, cell cycle, apoptosis, and FGFR3 and ERK (extracellular regulated kinase) phosphorylation. Multiple myeloma presents with detrimental bone loss mainly mediated by the large increase in IL6 production and concomitant activation of osteoclasts responsible for bone resorption. M-CSF has a role in recruitment of osteoclast precursors and may promote their survival. Blocking signaling through the CSF-1R may thus provide additional benefit to multiple myeloma patients. Inhibition of M-CSF mediated proliferation of the murine myeloid cell line M-NFS-60 correlated with inhibition of *in vitro* kinase activity against c-fms/CSF-1R.

[0844] 4-Amino substituted quinolinone benzimidazolyl compounds such as 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one and tautomers and salts thereof act as potent inhibitors of Class III-V RTKs. IC_{50} values of 4-amino-5-fluoro-3-[6-(4-methylpiperazin-

1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one are presented in the following table.

Table 7. Activity of 4-Amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one Against Various RTKs

RTK	IC_{50} (μM)
FLT3	0.001
c-KIT	0.002
CSFR1/c-fms	0.036
FGFR1	0.008
FGFR3	0.009
VEGFR1/Flt1	0.01
VEGFR2/Flk1	0.013
VEGFR3/Flt4	0.008
PDGFRβ	0.027
PDGFRα	0.21
EGFR1	2
c-MET	>3
EphA2	4
TIE2	4
IGFR1	>10
HER2	>10

[0845] The *in vitro* RTK assays used to prepare the above table were run in the presence of an ATP concentration that was within three-fold or at K_m of enzymes used (for enzymes where the K_m was available). Phosphorylated peptide substrate was detected with a Europium labeled anti-phospho-tyrosine Antibody (PT66). The Europium was then detected using time resolved fluorescence. For some assays, γ-P^{33} ATP was incubated with the enzyme and the radioactivity of phosphorylated peptide substrate was quantified in the presence of various concentration of 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one and used to calculate the IC_{50}.

[0846] FIG. 14 shows that 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one inhibits proliferation of multiple myeloma cell lines. KMS11, OPM-2, and H929 are multiple myeloma cell lines that were incubated with serial dilutions of 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one. After 72 hours, the number of viable cells left was determined using the CellTiter-Glo™ Assay (Promega). KMS11 and OPM-2 have activating mutations in the FGFR3 receptor, and H929 expresses WT FGFR3. 4-Amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one inhibited FGFR3 receptor kinase (IC_{50} = 9 nM, Table 7) and blocked proliferation of two cell lines with activating FGFR3 mutations: KMS11 (Y373C) and OPM-2 (K650E) cells with EC_{50}s of 60 nM and 87 nM, respectively (see FIG. 14). H929 cells express WT FGFR3 and mutant N-ras (1 3G>D), and proliferation was inhibited, but less potently, by 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one in this cell line (EC_{50} = 2.6 μM, EC_{50} in serum reduced growth media = 0.6 μM).

[0847] FGFR3 tyrosine phosphorylation was inhibited by 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one at 0.5 μM in KMS11 cells (see FIG. 15). KMS11 cells were starved for two hours in growth media containing 1% FBS. The cells were then incubated with different concentrations of 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one for two hours in growth media without FBS, washed and lysed for immunoprecipitation with FGFR3 Ab (sc123 Santa Cruz Biotech). Lysates were analyzed by western blotting and probed with anti-phosphotyrosine Antibody 4G10 (Upstate Biotech). The lower panel showed total FGFR3 after stripping the western blot and reprobing with FGFR3 Ab (See FIG. 15).

[0848] 4-Amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one was found to inhibit ERK phosphorylation at 0.5 μM in KMS11 cells. KMS11 cells were starved for two hours in growth media containing 1% FBS. The cells were then incubated with different

concentrations of 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one for two hours in growth media without FBS, washed, lysed, and analyzed by western blotting and probed with anti phospho-ERK Antibody (Cell Signaling). The lower panel of FIG. 16A shows cyclophilin protein (Upstate Biotech) as a loading control. 4-Amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one also inhibited ERK phosphorylation at 0.1 μM in OPM-2 cells. OPM-2 cells were incubated with different concentration of 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one for one hour in growth media with 1% FBS, washed, lysed, and analyzed by western blotting and probed with anti phospho-ERK Antibody (Cell Signaling). The lower panel of FIG. 16B shows 14-3-3 protein (Santa Cruz Biotech) as a loading control. ERK in the MAPK pathway is a downstream FGFR3 signaling component and phosphorylation of ERK was inhibited in both OPM-2 and KMS11 cells at 0.5 μM 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one (See FIGS. 16A and 16B). In contrast, the compound had no effect on phospho-ERK levels up to 5 μM in H929 cells. H929 cells were starved for two days in growth media without FBS. The cells were then incubated with different concentrations of 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one for one hour in growth media without FBS, washed, stimulated for 5 minutes with 50 ng/mL aFGF and 10 μg/mL Heparin, lysed, and analyzed by western blotting and probed with anti phospho-ERK Ab (Cell Signaling). Only a minor change in phospho-ERK in response to stimulation with aFGF after two days of serum starvation indicated that the pathway is constitutively activated due to the Ras mutation (See FIG. 16C).

[0849] KMS11 cells were incubated with 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one at various concentrations for 96 hours. The incubated KMS11 cells were washed and stained with AnnexinVPE and 7AAD according to the Nexin assay protocol (Guava Technologies). Samples were run on Guava PCA™ instrument and

percentage of cells in each category were analyzed with the Guava Nexin™ software. OPM-2 cells were incubated with 4-amino–5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one at various concentrations for 72 hours. The incubated OPM-2 cells were washed and stained with AnnexinVPE and 7AAD according to the Nexin assay protocol (Guava Technologies). Samples were run on Guava PCA™ instrument and percentage of cells in each category were analyzed with the Guava Nexin™ software. Results of the above experiments show that 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one induced apoptosis as measured by AnnexinVPE staining in KMS11 and OPM-2 cells starting at concentrations of 0.1 μM and 0.5 μM respectively (FIGS. 17 and 19).

[0850] The experimental data regarding induction of apoptosis by 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one in KMS11 and OPM-2 cells was confirmed by significant increases in the sub G1 population of cells in a cell cycle analysis observed at concentrations of 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one of 0.1 μM and higher (FIG. 18). KMS11 cells were incubated with 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one at concentrations of 0.001 μM, 0.01 μM, 0.1 μM, and 1 μM for 72 hours. Cells were then fixed and stained with propidium iodide before analyzing the samples by FACS (See FIG. 18). These results showed that the compound has minor effects on the cell cycle, but induced apoptosis in KMS11 cells at 0.1 μM. OPM-2 cells were also incubated with 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one at concentrations of 0.001 μM, 0.01 μM, 0.1 μM, and 1 μM for 72 hours. Cells were similarly fixed and stained with propidium iodide before analyzing the samples by FACS (See FIG. 20). These results showed that the compound has minor effects on the cell cycle, but induced apoptosis in OPM-2 cells at 0.5 μM. Other effects on the cell cycle by the compound were minor e.g., there was no significant G1 arrest.

Increases in the sub G1 population were less significant in the OPM-2 cell line compared to the KMS11 cells and started at 0.5 μM (FIG. 20).

[0851] H929 cells were incubated with 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one at concentrations of 0.01 μM, 0.1 μM, 0.5 μM, and 1 μM for 72 hours. Cells were then fixed and stained with propidium iodide before analyzing the samples by FACS (See FIG. 21). 4-Amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one had no effects on the cell cycle in H929 cells with concentrations up to 1 μM confirming that the FGFR3 expressing N-ras mutant cell line is less sensitive to 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one (FIG. 21) than are the KMS11 and OPM-2 cells.

[0852] Osteolytic bone loss is one of the major complications in multiple myeloma disease. The major cytokines involved in bone resorption are IL1β and IL6. In addition, increased serum concentrations of M-CSF have been detected in patients. 4-Amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one inhibits CSF-1R activity, the only known receptor for M-CSF with an IC_{50} of 36 nM (See Table 7). M-CSF mediated proliferation of a mouse myeloblastic cell line M-NFS-60 was inhibited with an EC_{50} of 220 nM (FIG. 22). Murine M-NFS-60 cells were incubated with serial dilutions of 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one in assay media with 10 ng/mL M-CSF and without GM-CSF. Cells in control wells were incubated with assay media only. After 72 hours incubation time, the number of viable cells left was determined using the CellTiter-Glo™ Assay (Promega). EC_{50} values were determined using nonlinear regression (FIG. 22).

[0853] 4-Amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one has significant antiproliferative activity and inhibits FGFR3 receptor phosphorylation and ERK phosphorylation in multiple myeloma cell lines with activating FGFR3 mutations. Therefore, the invention

provides a method for inhibiting FGFR3 receptor phosphorylation and ERK phosphorylation in multiple myeloma cell lines with activating FGFR3 mutations which includes administering an effective amount of a 4-amino substituted quinolinone benzimidazolyl compound, a tautomer thereof, a salt of the 4-amino substituted quinolinone benzimidazolyl compound, a salt of the tautomer, a combination thereof, or a pharmaceutical formulation comprising the 4-amino substituted quinolinone benzimidazolyl compound, the tautomer thereof, the salt of the 4-amino substituted quinolinone benzimidazolyl compound, the salt of the tautomer, or the combination thereof to a subject with a multiple myeloma cell line with activating FGFR3 mutations, wherein inhibition of FGFR3 receptor phosphorylation and/or ERK phosphorylation is inhibited after administration of the compound or the pharmaceutical formulation. In some embodiments, the 4-amino substituted quinolinone benzimidazolyl compound is 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one. In some embodiments, the subject is a mammal such as a rodent or primate. In some such embodiments, the subject is a mouse, whereas in other embodiments the subject is a human. The invention further provides the use of a 4-amino substituted quinolinone benzimidazolyl compound, a tautomer thereof, a salt of the 4-amino substituted quinolinone benzimidazolyl compound, a salt of the tautomer, or a combination thereof, in the preparation of a medicament for inhibiting the FGFR3 receptor phosphorylation and/or ERK phosphorylation. In some such embodiments, the 4-amino substituted quinolinone benzimidazolyl compound is 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one.

[0854] 4-Amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one caused apoptosis, but had minor effects on the cell cycle in FGFR3 mutant cell lines at concentrations of < 0.5 μM. Therefore, the invention provides a method of inducing apoptosis in FGFR3 mutant cell lines which, in some embodiments, is not accompanied by a large effect on the cell cycle. The method includes administering an effective amount of an

effective amount of a 4-amino substituted quinolinone benzimidazolyl compound, a tautomer thereof, a salt of the 4-amino substituted quinolinone benzimidazolyl compound, a salt of the tautomer, a combination thereof, or a pharmaceutical formulation comprising the 4-amino substituted quinolinone benzimidazolyl compound, the tautomer thereof, the salt of the 4-amino substituted quinolinone benzimidazolyl compound, the salt of the tautomer, or the combination thereof to a subject with a multiple myeloma cell line with activating FGFR3 mutations, wherein apoptosis in FGFR3 mutant cell lines is induced following administration. In some embodiments, the 4-amino substituted quinolinone benzimidazolyl compound is 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one. In some embodiments, the subject is a mammal such as a rodent or primate. In some such embodiments, the subject is a mouse, whereas in other embodiments the subject is a human. The invention further provides the use of a 4-amino substituted quinolinone benzimidazolyl compound, a tautomer thereof, a salt of the 4-amino substituted quinolinone benzimidazolyl compound, a salt of the tautomer, or a combination thereof, in the preparation of a medicament for inducing apoptosis in FGFR3 mutant cell lines, which in some embodiments, is not accompanied by a large effect on the cell cycle when incubated for the indicated times. In some such embodiments, the 4-amino substituted quinolinone benzimidazolyl compound is 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one.

[0855] Inhibition of M-CSF mediated proliferation of the murine myeloid cell line M-NFS-60 correlated with inhibition of the *in vitro* kinase activity of CSF-1R by 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one. Potent activity of 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one against t(4:14) multiple myeloma cell lines especially those with activating FGFR3 were observed. Furthermore, this compound and salts and tautomers thereof may be used to protect patients with multiple myeloma from osteolytic bone loss and lesions. Therefore, in some embodiments, the invention provides a

method of inhibiting M-CSF mediated proliferation of myeloid cell lines and inhibiting CSF-1R activity. The method comprises administering an effective amount of an effective amount of a 4-amino substituted quinolinone benzimidazolyl compound, a tautomer thereof, a salt of the 4-amino substituted quinolinone benzimidazolyl compound, a salt of the tautomer, a combination thereof, or a pharmaceutical formulation comprising the 4-amino substituted quinolinone benzimidazolyl compound, the tautomer thereof, the salt of the 4-amino substituted quinolinone benzimidazolyl compound, the salt of the tautomer, or the combination thereof to a subject with a myeloid cell line, wherein M-CSF mediated proliferation of myeloid cell lines and/or CSF-1R activity is inhibited. In some embodiments, the 4-amino substituted quinolinone benzimidazolyl compound is 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one. The invention further provides the use of a 4-amino substituted quinolinone benzimidazolyl compound, a tautomer thereof, a salt of the 4-amino substituted quinolinone benzimidazolyl compound, a salt of the tautomer, or a combination thereof, in the preparation of a medicament for inhibiting M-CSF mediated proliferation of myeloid cell lines and/or CSF-1R activity. In some such embodiments, the 4-amino substituted quinolinone benzimidazolyl compound is 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one. The invention also provides a method of reducing osteolytic bone loss or lesions in subjects with multiple myeloma, the method comprising administering effective amount of an effective amount of a 4-amino substituted quinolinone benzimidazolyl compound, a tautomer thereof, a salt of the 4-amino substituted quinolinone benzimidazolyl compound, a salt of the tautomer, a combination thereof, or a pharmaceutical formulation comprising the 4-amino substituted quinolinone benzimidazolyl compound, the tautomer thereof, the salt of the 4-amino substituted quinolinone benzimidazolyl compound, the salt of the tautomer, or the combination thereof to a subject with multiple myeloma, wherein a reduction in osteolytic bone loss or lesions is observed in the subject after administration. In some embodiments, the 4-amino substituted quinolinone benzimidazolyl compound is 4-amino-5-fluoro-3-[6-(4-

methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one. In some embodiments, the subject is a mammal such as a rodent or primate. In some such embodiments, the subject is a mouse, whereas in other embodiments the subject is a human. The invention further provides the use of a 4-amino substituted quinolinone benzimidazolyl compound, a tautomer thereof, a salt of the 4-amino substituted quinolinone benzimidazolyl compound, a salt of the tautomer, or a combination thereof, in the preparation of a medicament for reducing osteolytic bone loss or lesions in subjects with multiple myeloma. In some such embodiments, the 4-amino substituted quinolinone benzimidazolyl compound is 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one.

INHIBITION OF FGF3 AND TREATMENT OF MULTIPLE MYELOMA

[0856] The t(4: 14) translocation that occurs uniquely in a subset (20%) of multiple myeloma (MM) patients results in the ectopic expression of the receptor tyrosine kinase (RTK), fibroblast growth factor receptor 3 (FGFR3). Inhibition of activated FGFR3 in MM cells induces apoptosis, validating FGFR3 as a therapeutic target in t(4;14) MM and encouraging the clinical development of FGFR3 inhibitors for the treatment of these poor-prognosis patients. 4-Amino substituted quinolinone benzimidazolyl compounds such as 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one, act as inhibitors of FGFR3. 4-Amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one potently inhibits FGFR3 with IC50 of 5 nM in in vitro kinase assays and selectively inhibited the growth of B9 cells and human myeloma cell lines expressing wild-type (WT) or activated mutant FGFR3. In responsive cell lines, 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one induced cytostatic and cytotoxic effects. Importantly, addition of interleukin-6 (IL-6), insulin growth factor 1 (IGF-1) or co-culture on stroma did not confer resistance to 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one. In primary myeloma cells from t(4;14) patients, 4-

amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one inhibited downstream ERK1/2 phosphorylation with an associated cytotoxic response. Finally, therapeutic efficacy of 4-Amino substituted quinolinone benzimidazolyl compounds such as 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one was demonstrated in a xenograft mouse model of FGFR3 MM. 4-Amino substituted quinolinone benzimidazolyl compounds such as 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one are potent inhibitors of FGFR3-transformed hematopoietic cell lines and human multiple myeloma cell lines expressing either WT or mutant FGFR3. In addition, these compounds are potent inhibitors in a mouse model of FGFR3-mediated MM and are cytotoxic to primary myeloma cells from t(4;14) patients. Taken together, these data indicate that 4-amino substituted quinolinone benzimidazolyl compounds such as 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one have significant potential in treating MM associated with FGFR3 expression.

METHODS

Chemical Compounds and Biological Reagents

[0857] 4-Amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one was dissolved in DMSO at a stock concentration of 20 mM. For animal experiments, 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one was formulated in 5 mM citrate buffer. Acidic FGF (aFGF) and heparin were purchased from R&D Systems (Minneapolis, MN) and Sigma (Ontario, Canada), respectively. FGFR3 antibodies (C15, H100 and B9) were obtained from Santa Cruz Biotechnology (Santa Cruz, CA), and 4G10 from Upstate Biotechnology (Lake Placid, NY).

In Vitro Kinase Assays

[0858] The IC_{50} values for the inhibition of RTKs by 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one were

determined in a time resolved fluorescence (TRF) or radioactive format, measuring the inhibition by 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one of phosphate transfer to a substrate by the respective enzyme. Briefly, the respective RTK domain was expressed or purchased as recombinant protein and incubated with serial dilutions of 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one in the presence of substrate and ATP concentrations within 2-3 times the K_m of the enzyme. IC_{50} values were calculated using non-linear regression and represent the average of at least 2 experiments.

FGFR3 Expression Vectors and B9 Cell Transfectants

[0859] B9 cells expressing WT FGFR3 (B9-WT), FGFR3-K650E (B9-K650E) and empty retrovirus (B9-MINV) have been described previously. Plowright, E. E. *et al.*, *Blood*, 2000; 95:992-998. Full-length FGFR3 cDNAs, containing F384L, Y373C, or J807C (gift of Marta Chesi, Weill Medical College of Cornell, New York, NY) were cloned into an MSCV-based retroviral vector containing a green fluorescent protein (GFP) cassette. A construct carrying the G384D mutation was created from the FGFR3-WT by replacing the PmlI-BglII fragment between amino acid 290 and 413 with the same fragment obtained from the KMS18 as previously described. Ronchetti, D. *et al.*, *Oncogene*, 2001; 20:3553-3562. The constructed retroviral vectors were transfected into GP-E ecotropic packaging cells. The resulting retroviruses were used to introduce FGFR3 into the IL-6 dependent murine myeloma cell line, B9. A limiting cell dilution was further performed to generate single cell clones. A high-expressing clone for each construct (B9-F384L, B9-Y373C, B9-G384D and B9-J807C) was cryopreserved.

Cell Lines and Tissue Culture

[0860] All human MM cell lines and B9 cells were maintained in Iscove's Modified Dulbecco's Medium (IMDM) supplemented with 5% FCS, 100 μg/ml penicillin and 100 μg/ml streptomycin (Gibco, Invitrogen Canada, Ontario) and 1% IL-6 conditioned medium (B9 cells only). BM stroma cells

(BMSCs) were derived from BM specimens obtained from MM patients. Mononuclear cells separated by Ficoll-Hipaque density sedimentation were used to establish long-term cultures, as described previously. Hideshima, T. *et al.*, *Blood*, 2000; 96:2943-2950. For the purposes of viability assays BMSCs were irradiated with 20 Gy after plating on 96 well plates.

Viability Assay

[0861] Cell viability was assessed by 3-(4,5-dimethylthiazol)-2,5-diphenyl tetrazolium (MTT) dye absorbance. Cells were seeded in 96-well plates at a density of 5,000 (B9 cells) or 20,000 (MM cell lines) cells per well in IMDM with 5% FCS. Cells were incubated with 30 ng/ml aFGF and 100 μg/ml heparin or 1% IL-6 where indicated and increasing concentrations of 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one. For each concentration of 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1 H-benzimidazol-2-yl]quinolin-2(1H)-one, 10 μl aliquots of drug or DMSO diluted in culture medium was added. For drug combination studies, cells were incubated with 0.5 μM dexamethasone, 100 nM 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one or both simultaneously where indicated. To evaluate the effect of 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one on growth of MM cells adherent to BMSCs, 10,000 KMS11 cells were cultured on BMSC-coated 96-well plates, in the presence or absence of 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one. Plates were incubated for 48 to 96 hours at 37°C, 5% CO_2. The MTT assay was performed according to the manufacturer's instruction (Boehringer Mannheim, Mannheim, Germany). For assessment of macrophage-colony stimulating factor (M-CSF) mediated growth, 5000 M-NFS-60 cells per well were incubated with serial dilutions of 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one in media with 10 ng/ml M-CSF and without granulocytemacrophage-colony stimulating factor (GM-CSF). After 72 hours, cell viability was determined using Cell Titer-Glo™ Assay (Promega, Madison, WI). EC_{50} values were determined

using non-linear regression. Each experimental condition was performed in triplicate.

Intracellular Phospho-Protein Staining

[0862] Determination of ERK1/2 phosphorylation by flow cytometry has been described previously. Chow, S. *et al.*, *Cytometry*, 2001; 46:72-78; and Irish, J. M. *et al.*, *Cell*, 2004; 118:217-228Briefly, cells were serum starved overnight and then stimulated with 30 ng/ml aFGF and 10 μg/ml heparin for 10 minutes at 37°C. The cells were immediately fixed by adding 10% formaldehyde directly into the culture medium to obtain a final concentration of 2%. Cells were incubated in fixative for 10 minutes at 37°C then on ice for an additional 2 minutes. The cells were permeabilized by adding ice-cold methanol (final concentration of 90%) and incubated on ice for 30 minutes. Cells were stained with anti-ERK1/2 (Cell Signaling Technology, Beverly, MA) for 15 minutes and labeled with FITC-conjugated goat anti-rabbit and anti-CD138-PE (PharMinogen, San Diego, CA) where indicated. Malignant cells were identified as cells that express high levels of CD138. Flow cytometry was performed on a FACS Caliber flow cytometer (BD Biosciences, San Jose, CA) and analyzed using Cellquest software (Becton Dickinson).

Apoptosis Analysis

[0863] For studies of apoptosis, cells were seeded at an initial density of 2 x 10^5/ml medium supplemented with DMSO, 100 nM or 500 nM 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one and cultured for up to 6 days. The medium and drug were replenished every 3 days, and the cell density was adjusted to 2 x 10^5/ml. Apoptosis was determined by Annexin V staining (Boehringer Mannheim, Indianapolis, IN) and analyzed by flow cytometry.

Primary Patient Samples

[0864] Patients identified for the study were determined to possess a t(4;14) translocation by fluorescence in situ hybridization (FISH). Expression

of FGFR3 was confirmed by flow cytometry as described previously. Chesi, M. *et al.*, *Blood*, 2001; 97:729-736. Briefly, erythrocytes were lysed and BM mononuclear cells were incubated on ice for 30 minutes with rabbit anti-FGFR3 (H100) or rabbit preimmune serum. The cells were stained with FITC-conjugated goat antirabbit IgG and mouse anti-CD138-PE to identify MM cells. The samples were then analyzed by flow cytometry.

[0865] All t(4;14) positive samples were further analyzed for the presence of FGFR3 or Ras mutations. Four pairs of primers were designed to amplify the regions of FGFR3-containing codons of the extracellular (EC) domain, transmembrane (TM) domain tyrosine kinase (TK) domain and stop codon (SC), known hot spots for activating mutations. Two pairs of primers were designed to amplify regions of codons 12, 13, and 61 of N-*ras* and K-*ras*. Chesi, M. *et al.*, *Blood*, 2001; 97:729-736. A first PCR reaction was performed on genomic DNA extracted from CD138 purified myeloma cells and amplicons were used for DHPLC analysis. Results were confirmed by sequence analysis of the PCR products.

[0866] For cell death analysis, mononuclear cells were separated by Ficoll-Hipaque gradient sedimentation and plated at a cell density of 5×10^5 cells/ml in IMDM supplemented with 20% FCS and 30 ng/ml aFGF and 10 μg/ml heparin. Cells were cultured in the presence of DMSO or 500 nM 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one for up to 12 days. The medium, aFGF/heparin and drug were replenished every 3 days. After 3, 7 and 12 days, cells were triple stained with anti-CD38-PE, anti-CD45-CyChrome (PharMinogen) and FITC-conjugated Annexin V as previously described. LeBlanc, R. *et al.*, *Cancer Res.*, 2002; 62:4996-5000. Controls included unstained cells, isotype control stained cells, and single-stained cells. Malignant cells plasma cells were defined as cells that express high levels of CD38 and no or low levels of CD45 ($CD38^{++}/CD45^{-}$). Samples were analyzed by FACScan analysis using Cellquest software. BM aspirates were obtained by consent under an IRB-approved protocol.

Xenograft Mouse Model

[0867] The xenograft mouse model was prepared as previously described. Mohammadi, M. *et a.,I Embo. J.*, 1998; 17:5896-5904. Briefly, six to eight week old female BNX mice obtained from Frederick Cancer Research and Development Centre (Frederick, MD) were inoculated s.c. into the right flank with 3 x 10^7 KMS11 cells in 150 µl of IMDM, together with 150 µl of matrigel basement membrane matrix (Becton Dickinson, Bedford, MA). Treatment was initiated when tumors reached volumes of approximately 200 mm^3 at which time mice were randomized to receive 10, 30 or 60 mg/kg 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one or 5 mM citrate buffer. Dosing was performed daily by gavage and continued for 21 days. Eight to 10 mice were included in each treatment group. Calliper measurements were performed twice weekly to estimate tumor volume, using the formula: $4\pi/3$ x $(width/2)^2$ x (length/2). One way analysis of variance was used to compare differences between vehicle and 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one treated groups.

Immunoprecipitation and Immunoblotting

[0868] Immunoprecipitation and immunoblotting were performed as described previously. LeBlanc, R. *et al.*, *Cancer Res.*, 2002; 62:4996-5000. Briefly, tumors from sacrificed mice were immediately homogenized on ice and lysed in detergent buffer. Clarified cell extracts (1 mg/sample) were incubated for 6 hours with C15 FGFR3 antibody, then protein A/G agarose (Santa Cruz) was added for an additional 2 hours. Immunoblotting was performed with anti-phosphotyrosine antibody, 4G10 to assess phosphorylated FGFR3, or with anti-FGFR3 (B9) to measure total FGFR3.

Histopathology and Immunohistochemical Analysis

[0869] Tissue samples were fixed in 10% formalin and embedded in paraffin, from which 5 µm histologic sections were cut and stained with hematoxylin and eosin. Immunohistochemistry (IHC) studies were performed

by indirect immunoperoxidase staining of paraffin tissue sections using a TechMate500™ BioTek automated immunostainer (Ventana Medical Systems, Inc., Tucson, AZ) and antibodies recognizing FGFR3 (C15), Ki-67 (Zymed, San Francisco, CA), and cleaved caspase 3 (Signaling Cell Technology) as previously described.

RESULTS OF FGFR3 AND MULTIPLE MYELOMA STUDIES

Selective Kinase Inhibition of 4-Amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one

[0870] The ability of 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one to inhibit exogenous substrate phosphorylation was tested against a wide range of kinases. The concentration of 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one resulting in a 50% reduction in the activity of receptor tyrosine kinases (IC_{50}) is reported in Table 7. 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one inhibited members of the class III RTKs including FLT3, c-Kit, CSF-R1 and PDGFRα/βwith IC_{50} values of 0.001-0.21 mM as assessed by *in vitro* kinase assays. In addition, 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one potently inhibited class IV (FGFR1 and 3) and class V (VEGFR1-4) RTKs with IC_{50} values of 0.008-0.013 mM. When similar kinase assays for InsR, EGFR, c-MET, EphA2, TIE2, IGFR1 and HER2 were performed, significant inhibition was observed only at >10-fold higher concentrations. These studies demonstrated that 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one is a selective but multi-targeted inhibitor of class III, IV and V RTKs with high potency against FGFRs.

4-Amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one Inhibits the Growth of WT and Mutant FGFR3 Transformed Cells

[0871] The ability of 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one to inhibit constitutively activated FGFR3 mutants identified in MM patients (Y373C, G384D, K650E, J807C) was also tested. Chesi, M. *et al.*, *Blood*, 2001; 97:729-736; and Ely, S. A. *et al.*, *Cancer*, 2000; 89:445-452. Stable expression of these cDNAs conferred IL-6 independent growth to B9 cells, demonstrating that these mutants retain biologic activity and providing a platform for testing potential FGFR3 inhibitors against various classes of FGFR3 mutations. To determine the effect of 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one on FGFR3-mediated cell growth, B9 cells expressing FGFR3-WT, FGFR3-F384L (a non-transforming polymorphism) and the FGFR3-activated mutants were grown in increasing concentrations of inhibitor for 48 hours exposure following which viability was determined by MTT assay (FIG. 23). As expected, 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one potently inhibited the FGF-stimulated growth of WT and F384L-FGFR3 expressing B9 cells with IC_{50} values of 25 nM. In addition, 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one inhibited proliferation of B9 cells expressing each of the various activated mutants of FGFR3. Interestingly, there were minimal observed differences in the sensitivity of the different FGFR3 mutations to 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one, with the IC_{50} ranging from 70-90 nM for each of the various mutations. IL-6 dependent B9 cells 11 containing vector only (B9-MINV) were used to detect non-specific toxicity. B9-MINV cells were resistant to the inhibitory activity of 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one at concentrations up to 1 μM. These data further confirm the *in vitro* kinase data demonstrating inhibition of FGFR3 by 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one and indicate that nonspecific cytotoxic effects are not observed within the effective range of drug concentration. These results also indicate that 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one has potent activity against a variety of activated mutants of FGFR3 described in MM.

4-Amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one is Cytotoxic to FGFR3-Expressing Myeloma Cells

[0872] To assess the potential of 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one as a therapeutic agent in MM, the effect of 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one on the growth and survival of human myeloma cell lines was also investigated. FGFR3 positive cell lines (KMS11, KMS18, OPM2, H929) and the FGFR3 negative cell lines, U266 and 8226 were incubated with increasing concentrations of 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one and cell viability was monitored (Table 8). 4-Amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one inhibited cell proliferation of KMS11 (FGFR3-Y373C) and OPM2 (FGFR3-K650E), and KMS18 (FGFR3-G384D) cells with IC_{50} of values of 90 nM (KMS11 and OPM2) and 550 nM respectively. FGFR3 negative cell lines and H929 (FGFR3-WT), a cell line that harbors a downstream activating mutation of N-Ras (Chesi, M. *et al.*, *Blood*, 2001; 97:729-736), were resistant, requiring greater than 5-fold higher concentrations to inhibit cell growth. Inhibition of cellular growth was associated with disappearance of downstream ERK1/2 phosphorylation as determined by flow cytometry. The 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one sensitive cell lines (KMS11, KMS18, OPM2) all demonstrated loss of ERK1/2 phosphorylation in the presence of effective doses of 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one. In contrast, H929 cells, which displayed minimal cytostatic response to 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one, demonstrated high basal levels of MAP kinase activation as a result of constitutive Ras activation and showed no change in ERK1/2 phosphorylation, indicating that 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one is acting upstream of Ras.

Table 8. IC_{50} values (in nM) of 4-Amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one Against Human Myeloma Cell Lines.

Cell line	T(4;14)	FGFR3 genotype	IC_{50}(nM)
KMS11	+	Y373C	90
KMS18	+	G384D	550
OPM2	+	K650E	90
H929	+	WT	>2500
8226	-	N/D	>2500
U266	-	N/D	>2500

Listed are MM cell lines and the presence (+) or absence (-) of the t(4;14) translocation and the FGFR3 mutations. WT denotes the wild-type genotype and N/D means not determined. The concentration of 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one that inhibits 50% viability (IC_{50}) as compared to DMSO control (MTT assay or Cell titer Glo) after 72 hours incubation with 4-Amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one was determined.

[0873] 4-Amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one also induced apoptosis in responsive FGFR3 expressing cell lines. Treatment of KMS11, OPM2, and KMS18 cells with 500 nM 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one for 96 hours resulted in a significant increase in the percentage of annexin-V binding cells when compared to DMSO controls (FIG. 24). The delayed induction of apoptosis observed in some myeloma cell lines is similar to that previously reported with the more selective FGFR3 inhibitor, PD173074. Trudel, S. *et al.*, *Blood*, 2004; 103:3521-3528. Treatment of FGFR3-negative cells (U266 not shown) had no effect on annexin V-binding suggesting that class III and V RTKs that can potentially be inhibited by 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one are not expressed or are not essential for survival of these myeloma cells.

[0874] The cytotoxic potential of 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one was assessed against primary human myeloma cells. Freshly isolated BM mononuclear cells were obtained from patients previously identified by FISH as t(4;14)

positive or negative. Chang, H. *et al.*, *Br. J. Haematol.*, 2004; 125:64-68. The presence or absence of FGFR3 expression was confirmed by flow cytometry (FIG. 25A). Of the five t(4;14) positive samples, all but one demonstrated high level expression of FGFR3 on CD138 positive myeloma cells (Table 8). In addition, these samples were screened by DHPLC for FGFR3 mutations and downstream mutations of N and K-Ras. Results were confirmed by sequence analysis. No mutations were identified. FGF stimulation of primary cells in culture resulted in upregulation of ERK1/2 phosphorylation in CD138 positive myeloma cells demonstrating biological activity of FGFR3 in these cells (FIG. 25B). 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one at 500 nM fully inhibited ERK1/2 phosphorylation in all samples. In addition, mononuclear cells were cultured with 500 nM 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one or DMSO vehicle and apoptosis was determined by annexin V staining. Four of five t(4;14) myeloma samples demonstrated a cytotoxic response to 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one when compared to vehicle control whereas none of the other myeloma samples were affected (FIGS. 25C and 12D and Table 9). Interestingly, the t(4;14) positive sample that demonstrated low level FGFR3 expression was 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one resistant implying that only high level of WT FGFR3 expression can confer dependence. Support for this hypothesis is provided by studies of c-KIT (Rubin, B. P. *et al.*, *Cancer Res.*, 2001; 61:8118-8121) in gastrointestinal tumors and FLT3 (Armstrong, S. A. *et al.*, *Cancer Cell*, 2003; 3:173-183) in AML where high level expression of the WT receptor, as well as receptor mutation, lead to constitutive activity and inhibitor sensitivity. Furthermore, sensitivity to Herceptin in breast cancer correlates with the level of HER2/neu expression. Vogel, C. L. *et al.*, *J. Clin. Oncol.*, 2002; 20:719-726. Alternatively, MM cells from this patient may have activation of additional pathways, that circumvent dependency on FGFR3 signaling.

Table 9. Summary of Expression of FGFR3 on Primary MM Cells in Relation to Sensitivity to 4-Amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one (Compound).

Patient	FGFR3 (flow cytometry)	FGFR3 genotype	N & K-Ras genotype	% Annexin V DMSO	% Annexin V Compound (500 nM)	% Increase Annexin V
1	N/D	WT	WT	9.0	21.8	20.9
2	+	WT	WT	10.4	8.6	-1.8
3	++	WT	WT	9.8	42.1	32.3
4	++	WT	WT	6.8	25.7	18.9
5	+++	WT	WT	10.1	24.5	14.4
6	-	N/D	N/D	8.8	10.2	1.4
7	-	N/D	N/D	15.3	16.0	0.7
8	-	N/D	N/D	20.9	20.7	-0.2
9	-	N/D	N/D	12.8	13.4	0.6
10	-	N/D	N/D	15.0	17.1	2.1

FGFR3 expression on CD138 primary MM cells was analyzed by flow cytometry and the fluorescence was expressed as follows: +, weak; ++ intermediate; +++ strong; -, absent. CD138 selected cells were screened for the FGFR3 and N and K-Ras mutations. WT denotes wild-type status and N/D indicates not determined.

Effect of IL-6, IGF-1 and Stroma on Response of MM cells to 4-Amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one

[0875] Given the known role of IL-6 (Klein, B. *et al.*, *Blood*, 1995; 85:863-872; and Anderson, K. C. *et al.*, *Semin. Hematol.*, 1999; 36:14-20) and more recently, IGF-1 (Ogawa, M. *et al.*, *Cancer Res.*, 2000; 60:4262-4269; and Mitsiades, C. S. *et al.*, *Cancer Cell*, 2004; 5:221-230) in tumor cell proliferation, survival and drug resistance in MM, experiments were performed to determine whether exogenous IL-6 and IGF-1 could overcome the growth inhibitory effects produced by 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one. Inhibition with 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one was still observed when KMS11 cells were grown in the presence of 50 ng/ml IL-6 or 50 ng/ml IGF-1 and was comparable to that of cells cultured in the presence of aFGF (FIG. 26A). These studies highlight the critical role of FGFR3 function in the hierarchy of growth factor receptors in these cells.

[0876] Because the BM microenvironment has been shown to confer drug resistance in MM cells (Dalton, W. S. *et al.*, *Semin Hematol.*, 2004; 41:1-5; and Hideshima, T. *et al.*, *Semin. Oncol.*, 2001; 28:607-612), the effect of 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one on MM cell growth was investigated in the BM milieu. The direct toxicity of 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one on BMSCs was determined using the MTT assay, and no significant difference in cell viability of 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one treated cells compared to DMSO controls (FIG. 26B) was observed. KMS11 cells were then cultured with or without BMSCs in the presence or absence of 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one. BMSCs did confer a modest degree of resistance with 44.6% growth inhibition for cells treated with 500 nM 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one and cultured on stroma compared to with 71.6% growth inhibition for cells grown without BMSCs. However, cell growth was still significantly inhibited by the 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one despite the presence of stroma.

4-Amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one Augments Dexamethasone Cytotoxicity in Multiple Myeloma

[0877] FGFR3 expression results in increased STAT3 phosphorylation and higher levels of Bcl-x_L expression than that observed in parental B9 cells after IL-6 withdrawas. Plowright, E. E. *et al.*, *Blood*, 2000; 95:992-998; and Pollett, J. B. *et al.*, *Blood*, 2002; 100:3819-3821. These findings were associated with inhibition of dexamethasone-induced apoptosis, a phenomenon that was reversed by Bcl-x_L anti-sense oligonucleotide. Treatment of FGFR3 expressing MM cells may, thus overcome resistance to dexamethasone. As shown in Table 10, KMS11 cells are relatively resistant to dexamethasone; however, when combined with 4-amino-5-fluoro-3-[6-(4-

methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one, synergistic inhibitory effects were observed. These data indicates the usefulness of combining dexamethasone with 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one as a therapeutic strategy.

Table 10. Effect of 4-Amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one (Compound) and/or Dexamethasone on KSM11 Viability.

Treatment (concentration)	Viability (% of control) ± SD
DMSO	100%
Dexamethasone (0.5 μM)	87% ± 4.74
Compound (100 nM)	49% ± 4.64
Dexamethasone (0.5 μM) and Compound (100 nM)	10% ± 6.48

4-Amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one Inhibits M-CSF Mediated Cell Growth

[0878] Osteolytic bone loss is one of the major complications in MM. The major osteoclast activating factors involved in bone resorption are IL-1β, IL-6, RANK-L and M-CSF. Croucher, P. I. *et al.*, *Br. J. Haemaatol.*, 1998; 103:902-910. MM cells, osteoblasts and stromal cells in the BM express M-CSF which together with RANK-L is essential for osteoclast formation. Quinn, J. M. *et al.*, *Endocrinology*, 1998; 139:4424-4427. Increased serum concentrations of MCSF have been detected in MM patients. Janowska-Wieczorek, A. *et al.*, *Blood*, 1991; 77:1796-1803. *In vitro* kinase assays demonstrate potent activity of 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one against CSF-1R, the only known receptor for M-CSF with an IC_{50} of 36 nM (Table 7). 4-Amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one inhibited proliferation of M-NFS-60, a M-CSF growth driven mouse myeloblastic cell line with an EC_{50} of 220 nM (FIG. 27). It would appear, therefore, that in addition to inhibiting MM cell growth, 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one has the advantage of potentially inhibiting tumor-associated osteolysis.

Evaluation of 4-Amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one *in vivo* in a Xenograft Mouse Model

[0879] The efficacy of 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one was tested in a murine model in which KMS11 cells are injected subcutaneously into BNX mice. Grad, J. M. *et al.*, *Blood*, 2001; 805-813; and Lentzsch, S. *et al.*, *Leukemia*, 2003; 17:41-44. A similar plasmacytoma xenograft mouse model has been used in pre-clinical studies of Bortezomib and IMiDs in MM. Each of 36 BNX mice were injected in the flank with 3 x 10^7 KMS11 cells together with matrigel by s.c. injection. When the tumors reached approximately 200 mm^3, mice were randomized (n=8-10) to receive vehicle or 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one at 10 mg/kg, 30 mg/kg and 60 mg/kg, administered by oral gavage once daily for 21 days. When compared to vehicle controls, a significant ($p<0.001$) anti-tumor effect was observed in all three 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one dose groups with a minimum effective dose of 10 mg/kg/d (FIG. 28). Specifically, 48%, 78.5% and 94% growth inhibition was calculated in the 10 mg/kg, 30 mg/kg and 60 mg/kg treatment arms, respectively, compared to the placebo treated mice. On the last day of dosing, 7 of 10 mice in the highest treatment group had achieved and maintained a partial remission with > 50% reduction in tumor volumes compared to day 1 of drug administration. Weight loss, as a marker of significant toxicity, was not observed in any of the treatment groups.

[0880] To demonstrate that the observed responses correlated with FGFR3 inhibition, mice were sacrificed 4 hours after receiving the last dose of 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one and tumors were harvested for analysis of *in vivo* inhibition of FGFR3 phosphorylation. FGFR3 was immunoprecipitated from tumor cell lysates and the level of expression and phosphorylation was determined on immunoblots. *In vivo* inhibition of FGFR3 was observed, with complete inhibition of FGFR3 occurring at the 60 mg/kg dose. Inhibition of FGFR3

phosphorylation was dose dependent and correlated with the anti-tumor response.

[0881] Histopathologic examination of the tumors from representative animals further supported the interpretation of tumor reduction in the drug-treated mice compared to the placebo controls. Tumors from the drug-treated mice showed large areas of tumor necrosis. Immunohistochemistry for expression of the proliferative antigen, Ki-67, and for cleaved caspase 3, demonstrated that 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one inhibited cell growth and induced apoptosis. These findings suggest that 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one induces both cytostatic and cytotoxic responses *in vivo* resulting in regression of FGFR3 expressing tumors.

DISCUSSION OF FGFR3 INHIBITION AND MULTIPLE MYELOMA EXAMPLES

[0882] The identification of recurrent cytogenetic abnormalities in MM and characterization of the translocation partners has identified novel molecular targets and presents the potential for molecular targeted therapy for this universally fatal disease. Kuehl, W. M. *et al.*, *Nat Rev Cancer*, 2002; 2:175-187; and Chesi, M. *et al.*, *Nat. Genet.*, 1997; 16:260-265. Nearly 20% of newly diagnosed cases of MM harbor the t(4;14) translocation as detected by the presence of IgH-MMSET hybrid transcript (Santra, M. *et al.*, *Blood,* 2003; 101:2374-2376), the presence of which has generally been reported to be associated with a poor-prognosis. Fonseca, R. *et al.*, *Blood*, 2003; 101:4569-4575; Keats, J. J. *et al.*, *Blood*, 2003; 101:1520-1529; Moreau, P. *et al.*, *Blood*, 2002; 100:1579-1583.; and Chang, H. *et al.*, *Br. J. Haematol.*, 2004; 125:64-68. FGFR3 is expressed in approximately 70% (Keats, J. J. *et al.*, *Blood*, 2003; 101:1520-1529; and Quinn, J. M. *et al.*, *Endocrinology*, 1998; 139:4424-4427) of these cases and 10% (Intini, D. *et al.*, *Br. J. Haematol.*,

2001; 114:362-364) of patients will acquire an activating mutation of FGFR3 with disease progression.

[0883] An understanding of the genetic defects that are causally implicated in oncogenesis has led to targeted therapy for the treatment of a number of cancers. Druker, B. J. *et al.*, *N. Engl. J. Med.*, 2001; 344:1031-1037; Demetri, G. D. *et al.*, *N. Engl. J. Med.*, 2002; 347:472-480; Slamon, D. J. *et al.*, *N. Engl. J. Med.* 2001; 344:783-792; and Smith, B. D. *et al.*, *Blood*, 2004; 103:3669-3676. Most notably, the inhibition of BCR-ABL kinase activity by STI571 has produced major cytogenetic remissions in chronic myelogenous leukemia (CML). Druker, B. J. *et al.*, *N. Engl. J. Med.*, 2001; 344:1031-1037. Inhibition of activated c-Kit in gastrointestinal stromal tumors by STI571 has also been effective against this chemoresistant tumor. Demetri, G. D. *et al.*, *N. Engl. J. Med.*, 2002; 347:472-480. In addition, Herceptin, a monoclonal antibody targeting HER2/neu, has resulted in improved chemotherapy responses and prolonged survival of breast cancer patients. Slamon, D. J. *et al.*, *N. Engl. J. Med.* 2001; 344:783-792. A similar kinase inhibitor strategy targeting FLT3 in acute myeloid leukemia (AML) is also showing promising results in Phase II clinical trial. Smith, B. D. *et al.*, *Blood*, 2004; 103:3669-3676. Pre-clinical studies of FGFR3 inhibition in t(4;14) myeloma have likewise identified this RTK as a plausible candidate for targeted therapy. Two antagonists of FGFR3, PD173074 and SU5402 inhibited the growth and induced apoptosis of MM cells expressing mutant FGFR3. Trudel, S. *et al.*, *Blood*, 2004; 103:3521-3528; Paterson, J. L. *et al.*, *Br. J. Haematol.*, 2004; 124:595-603; and Grand ,E. K. *et al.*, *Leukemia*, 2004; 18:962-966. Together these studies support the clinical development of FGFR3 inhibitors for these patients. Unfortunately, PD173074 is not a candidate compound for the clinic and the IC_{50} of SU5402, required to inhibit FGFR3 is not likely to the achieved *in vivo*.

[0884] 4-Amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one is a potent inhibitor of FGFR3 and class III, IV and V RTKs including, FLT3, c-Kit, c-Fms, PDGFR and VEGFR. In this study, 4-

amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one was demonstrated to be a highly active inhibitor of both WT and mutant FGFR3 17 tyrosine kinases. The activity of this inhibitor against a broad spectrum of RTKs implies that 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one requires less stringent conformation requirements for binding to the kinase domain and is consistent with the retained activity of 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one against many FGFR3 mutants. 4-Amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one treatment selectively induced apoptotic cell death of MM cell lines and primary patient samples that harbor FGFR3. The potential clinical application of 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one for the treatment of MM was further validated using a xenograft mouse model in which 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one treatment inhibited FGFR3 activity *in vivo* and produced tumor regression and significantly decrease disease progression.

[0885] Although the data suggests that FGFR3 is the primary target of 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one in MM cells, it is important to note that OPM2 cells responded to this broadly active RTK inhibitor when they did not respond to the more selective FGFR3 inhibitor PD173074. Trudel, S. *et al.*, *Blood*, 2004; 103:3521-3528; and Paterson, J. L. *et al.*, *Br. J. Haematol.*, 2004; 124:595-603. This cell line is characterized by high basal levels of AKT phosphorylation (data not shown) and biallelic PTEN deletion. Consistent with our results, Grand et al. demonstrated that the multi-targeted RTK inhibitor, SU5402 induced cytotoxic responses in OPM2 cells whereas PD173074 failed to induce apoptosis. Grand ,E. K. *et al.*, *Leukemia*, 2004; 18:962-966. These findings also raise the possibility that 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one is targeting other, as yet to be defined, targets important for myeloma cell

viability, a fact that is of further relevance given the demonstration that FGFR3 is sometimes lost during disease progression and may, therefore, be supplanted by other downstream signaling mediators.

[0886] With the latter point in mind, it is important to note that the clinical relevance of FGFR3 in t(4;14) myeloma has been questioned by observations that the der(14) chromosome is lost in some myeloma patients suggesting that FGFR3 is dispensible and that MMSET is the true causal target of t(4;14) in MM. Keats, J. J. *et al.*, *Blood*, 2003; 101:1520-1529; and Intini, D. *et al.*, *Br. J. Haematol.*, 2001; 114:362-364. Moreover, studies in model systems indicate that WT FGFR3 is not dominantly transforming, requiring additional cooperating oncogenic events to complement transformation. Chesi, M. *et al.*, *Blood*, 2001; 97:729-736; and Li, Z. *et al.*, *Blood*, 2001; 97:2413-2419. The data presented above, however, indicates that primary MM cells that definitively express FGFR3 remain dependent on this pathway for survival despite the presence of additional genetic events. It is likely, therefore, that FGFR3 acts in concert with TACC3 and MMSET providing survival signals through the stimulation by FGF ligands expressed in the BM microenvironment. Along these lines, FLT3 mutations and high level expression of FLT3 have been described in acute lymphoblastic leukemia where MLL, a gene similar to MMSET, is also expressed. Armstrong, S. A. *et al.*, *Cancer Cell*, 2003; 3:173-183. These observations suggest a possible mechanism of complementation between tyrosine kinases and trithorax genes.

[0887] Studies of FGFR3 inhibition in MM cell lines indicated that only cell lines expressing the constitutively active receptor responded to FGFR3 inhibition. Trudel, S. *et al.*, *Blood*, 2004; 103:3521-3528; and Paterson, J. L. *et al.*, *Br. J. Haematol.*, 2004; 124:595-603. This highlights the limitation of using MM cell lines that grow independently of BM microenvironment and, thus, are no longer reliant on FGF produced by the stroma for growth and survival. Studies using primary patient material are therefore critical. The cytotoxic effect demonstrated by primary MM cells exposed to 4-amino-5-

fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one indicates that this drug will be an effective therapy in patients expressing either WT or mutant FGFR3. Nevertheless, the only modest and delayed cytotoxic response to 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one observed in primary MM cells may imply that inhibition of WT FGFR3 does not itself introduce proapoptotic signal, but more likely results in the withdrawal of strong anti-apoptotic signals. One would predict, therefore, the most effective use of 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one may be in combination with chemotherapeutic agents such as dexamethasone as demonstrated in KMS11 cells.

[0888] The importance of the BM microenvironment in supporting tumor growth is becoming increasingly clear. Mitsiades, C. S. *et al., Cancer Cell*, 2004; 5:221-230; and Dalton, W. S. *et al.*, *Semin Hematol.*, 2004; 41:1-5. In particular, cytokines such as IL-6 and IGF-1 and direct interaction with BMSCs have been shown to confer drug resistance. The *in vitro* experiments demonstrate that these paracrine factors failed to overcome the anti-tumor effects of 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one. Given its target profile, 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one may also impact host-derived tumor-associated cells within the BM that have implications in supporting tumor growth. 4-Amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one exhibits potent anti-angiogenic activity in several angiogenesis assays including endothelial cell migration and tube formation on fibrin gels as well as in the ex vivo rat aortic ring assay. Wiesmann, M. *et al.*, *Proc AACR*, 2003; 44:934a. In agreement, tumors from 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one treated mice were less vascular when compared to controls (data not shown). It has been demonstrated that 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one also inhibits CSF-1R activity, the receptor for M-CSF, an osteoclast

activating factor that may contribute to pathogenesis of bone disease in MM. Taken together, the data suggests that 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one can potentially target both the MM cell within the BM milieu and the BM microenvironment directly.

[0889] In summary, 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one represents a novel and potent small molecule inhibitor of FGFR3 for the treatment of t(4;14) myeloma. The cytotoxic effects of 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one on MM cell lines and primary patient samples, and a target profile that suggests the potential to favorably modulate the BM milieu, lead to the prediction that this will be an effective therapy in this poor-prognosis group, particularly in combination therapies. The ultimate success of this therapeutic strategy now awaits the outcome of clinical trials of that are soon to be underway to evaluate the efficacy of 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one of the treatment of t(4;14) MM.

TREATMENT OF CANCER AND PHARMACOKINETIC STUDIES

[0890] The antiproliferative activities of 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one (compound **1**) were tested against a large number of cancer cell lines and primary non-malignant cell lines. Methods were as follows: Cells were plated in 96-well plates; after three to five hours gelling time for adherent cell lines dilutions of the compounds were added, three days later viable cells were determined by adding MTS solution (Promega). Absorbance at 490 nm was measured and EC_{50} values calculated using non linear regression. For the HMVEC assay, compounds were incubated with the cells for three days in the presence of five ng/mL recombinant VEGF. For the SCF/c-KIT assay the TF-1 and H526 cells were incubated for three days in the presence of 40 ng/mL and 100 ng/mL recombinant SCF, respectively. Proliferation was assayed by adding

MTS solution and measuring the absorbance at 490 nm. EC_{50}s were calculated by non-linear regression. Results are shown in Table 11.

[0891] In a subset of the cancer cell lines and the endothelial cells, proliferation was inhibited with $EC_{50} \leq 50$ nM, consistent with their dependence on an RTK targeted by compound **1** (MV4; 11: expression of constitutively active FLT3; HMVEC: VEGFR2 mediated proliferation; TF-1: c-KIT mediated proliferation) with the exception of the KM12L4a cell line. Even though this cell line does express some of the targeted RTKs (e.g., VEGFR ½ and PDGFR determined by RT-PCR), experiments showed that the inhibition of these individual RTKs does not fully explain the potent antiproliferative effects observed with compound **1**. This finding suggests that either the inhibition of multiple RTKs or as yet unidentified effects may be responsible for the antiproliferative effect mediated by compound **1** in this cell line.

[0892] The majority of cell lines showed an antiproliferative response when incubated with compound **1** with EC_{50}s between 1 and 10 μM including two primary cell lines HMEC (human normal mammary epithelial cells) and PrEC (normal human prostate epithelial cells). Consistent with *in vitro* results, the growth of both the KM12L4a and MV4;11 xenografts in mice were potently inhibited by compound **1** *in vivo*.

Table 11

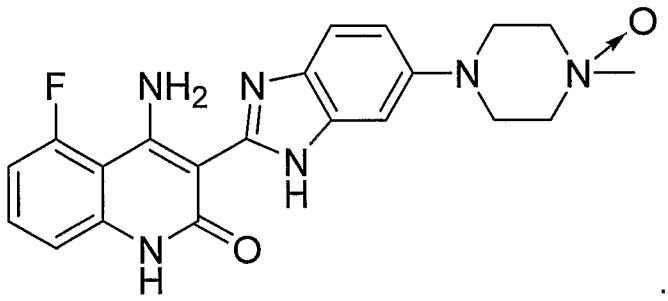
EC_{50}≤50 nM	EC_{50} 0.4-1μM	EC_{50} 1-10 μM	EC_{50} 10 μM
MV4; 11 (AML) KM12L4a (colon cancer) HMVEC (VEGF/VEGF R2 mediated; endothelium) TF-1 (SCF/ c-KIT mediated; AML)	RS4 (ALL) 4T1 (mouse breast cancer)	MDA-MB435 (breast cancer) SKOV3 (ovarian cancer) K562 (CML) Ku812 (CML) MOLT-4 (ALL) ARH77 (multiple myeloma) HCT116 (colon cancer) Du145 (prostate cancer) PC3 (prostate cancer) H209 (lung cancer) H226 (lung cancer) HT29 (colon cancer) SW620 (colon cancer) PrC (normal prostate epithelium) HMEC (normal mammary epithelium)	U87 (brain cancer)

[a]all cell lines tested were of human origin unless otherwise noted.

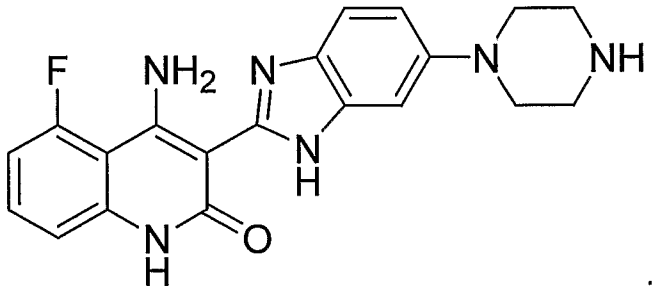
Identification of Metabolites

[0893] Two metabolites of compound **1** were identified and partially characterized in pooled rat plasma from a 2 week toxicology study. Day 1 and day 14 dosed animal plasmas were analyzed by UV and LC/MS from once a day 30 or 80 mg/kg, PO, dose groups. The two identified metabolites were the piperazine N-oxide compound (compound **2**) and the N-demethylated compound (compound **3**) (see following procedures for synthesis and characterization of these compounds). Estimated levels of the

metabolites (based on UV absorbance and in comparison to known levels of compound **1** quantified in the same samples from previous analyses) are given in Table 12. The N-desmethyl metabolite was found to be in substantially lower abundance than compound **1** in all samples of post dosed pooled plasmas. The N-oxide metabolite was observed to be present in lower abundance than compound **1** except at 24 hours on day 14 in the 80 mg/kg dose group and 1-2 hours on day 1 in the 30 mg/kg dose group (Table 12). The metabolic profile does not change with dose or duration of dose. Generally the metabolite levels increase in tandem with compound **1** levels with dose escalation.



Compound 2



Compound 3

[0894] With both dose groups the duration of dose, Day 1 vs 14 , does not appear to result in an increase in plasma levels of metabolites alone (Table 12) or as compared to compound **1** levels. Compound **1** levels decrease with duration of dose and this is reflected by a decrease in metabolite levels as well. This suggests that if induction is occurring, it is not reflected in increased metabolism of compound **1** to these two circulating phase I metabolites. The day 14, 24 hr samples contained compound **1** and

metabolites at lower levels than the 24 hour samples on day 1 indicating that there is no accumulation of metabolites or compound **1** with a once a day dosage regimen of 30 or 80 mg/kg. The N-oxide metabolite is present in higher abundance than the N-desmethyl metabolite at all assayed time points in the 80 mg/kg dose group and in all but the 24 hr time points after day 1 in the 30 mg/kg dose group. The N-desmethyl metabolite levels appear to fall more slowly than that of compound **1** suggesting a longer $T_{1/2}$ and indicating that the plasma levels of this metabolite are likely determined by its rate of elimination and not its rate of formation as is, in contrast, likely for the N-oxide.

Table 12.: Compound **1** Levels and Estimated Compound **1** Metabolite Levels in Rat Plasma

Dose (mg/kg)	Day	Sample Time (hr)	Des-CH_3 (ng/ml)[1]	N-oxide (ng/ml)[1]	Compound **1** (ng/ml)[2]
30	1	0	0	0	0
30	1	1-2	14	1090	635
30	1	4-8	48	310	943
30	1	24	22	25	54
30	14	0	6	1.3	20
30	14	1-2	6	135	467
30	14	4-8	12	220	442
30	14	24	4	0.4	8
100	1	0	0	0	0
100	1	1-2	35	424	1212
100	1	4-8	84	779	2075
100	1	24	83	137	500
100	14	0	15	67	162
100	14	1-2	17	122	628
100	14	4-8	19	533	1099
100	14	24	10	102	33

1 : Metabolite levels estimated based on metabolite UV absorbance areas in comparison to compound **1** UV areas and using previously reported compound **1** levels. 2: Compound **1** levels previously quantified in a separate study from the same plasma samples analyzed herein.

IC_{50}s of Compounds 1-3

[0895] The kinase activity of a number of protein tyrosine kinases was measured using the procedures set forth above for Compounds 1-3 to provide the IC_{50} values shown in Table 13.

Table 13.

Compound	IC_{50} (μM)					
	VEGFR flt	VEGFR flk1	bFGFR	PDGFR	Flt3	c-kit
Compound **1**	0.010	0.013	0.008	0.027	0.0001	0.0015
Compound **2**	0.004	0.009	0.005	0.010	0.0004	0.0002
Compound **3**	0.019	0.012	0.019	0.037	0.0001	0.0002

Oral Dosing in the KM12L4a Human Colon Tumor Model

[0896] This single agent study evaluated daily oral dosing of compound **1** in the KM12L4a human colon tumor model.

[0897] Female Nu/Nu mice, aged 7-8 weeks (Charles River), were implanted with $2x10^6$ KM12L4a cells subcutaneously in the right flank. Treatment began 7 days later when average tumor volume was $125mm^3$. This was designated as study day 1. Compound **1** was formulated as a solution in 10 mM H_3PO_4 and administered by oral gavage.

[0898] Seven treatment groups were included in the study, (n=10/group): vehicle (water) *p.o., q.d.*; and six groups of compound **1** doses: 3, 10, 30, 100, 200, 300 mg/kg *p.o., q.d.*

[0899] Plasma samples were drawn from satellite animals in each dose group on various days to characterize the pharmacokinetics of compound **1** in tumor-bearing mice (N=2/timepoint/dose group). Tissue and tumor concentrations of compound **1** were determined in samples collected from animals in the 100 and 200 mg/kg dose group at 8 and 24 hours post-dose on Day 22 (N=2/timepoint/dose group).

[0900] Plasma compound **1** concentrations were determined by a non-validated LC/MS/MS assay with a calibration range of 1 to 8000 ng/mL and a lower limit of quantitation (LLOQ) of 1 ng/mL (Charles River Laboratories, Worcester, MA. Tissue and tumor compound **1** concentrations were also determined using a non-validated LC/MS/MS assay with a calibration range of 20 to 43740 ng/g and a LLOQ of 20 ng/g.

[0901] Composite pharmacokinetic parameters (C_{max} and AUC) were obtained using standard noncompartmental analysis from mean plasma compound concentration-time data in each dose group on each sampling day (WinNonlin Professional, version 4). The reported AUC values were determined using 3 concentration-time data points. Predose concentration values were reported as those observed immediately prior to dosing.

[0902] Significant dose-dependent inhibition in tumor growth was observed at all doses by 4-7 days of treatment (see Table 14). The calculated ED_{50} was 17 mg/kg. Tumor regressions of > 50% of initial size were observed in the majority of mice dosed with compound **1** at 200 and 300 mg/kg, however these doses were not tolerated for the entire study duration. By days 12-16, mice treated with 300 mg/kg lost 20-30% body weight and were euthanized. In those treated with 200 mg/kg, 1 of 10 was euthanized on day 14 with 22% wt loss, and the remaining mice were euthanized days 21-24 with > 25% weight loss. Mice were dosed for 37 days with 100 mg/kg and remained at 98% of initial weight; tumors remained stable at this dose (FIG. 29). The vehicle group was taken down on day 9, and tumor growth inhibition (TGI) was calculated. (Table 14).

Table 14. Dose response activity of Compound **1**

Daily dose compound **1** (n=9-10/gp)	Tumor Vol Day 9 Mean ± SD (mm^3)	Treated/ Control	% Tumor Growth Inhibition	P value vs. Vehicle
Vehicle	1333 ± 283	-	-	-
3 mg/kg	1168 ± 202	0.88	12	0.1519
10 mg/kg	861 ± 321	0.65	35	0.0037
30 mg/kg	553 ± 213	0.42	58	≤0.00001
100 mg/kg	263 ± 108	0.20	80	≤0.00001
200 mg/kg	98 ± 40	0.07	93	≤0.00001
300 mg/kg	74 ± 30	0.06	94	≤0.00001

[0903] On the second day of dosing (Day 2), plasma concentrations of compound **1** increased proportionally with dose (Table 15) in all dosing groups. Following multiple dosing for at least 2 weeks, plasma concentrations were comparable to those on Day 2, suggesting no accumulation upon once daily dosing in mice (Table 15). Similarly, predose plasma concentration of compound **1** collected on Days 3, 8, and 15 were similar within each dose group, suggesting that steady state was reached after Day 2. Therefore, these data suggest that compound **1** follows dose-and time-independent pharmacokinetics in tumor-bearing mice.

[0904] Tumor growth inhibition of 35-60% was observed at doses of 10 and 30 mg/kg, respectively. The corresponding plasma exposure of compound **1**, as assessed by C_{max} and AUC values, ranged from 163-742 ng/mL and 1420-5540 ng*hr/mL, respectively (FIG. 30). The corresponding plasma predose concentration values ranged from 2-135 ng/mL.

Table 15. Composite Compound 1 Pharmacokinetic Parameters and Plasma Concentrations-Time Data Following Once-Daily Oral Dosing of Compound 1 to Mice Bearing SC KM1214a Tumors

Dose (mg/kg/day)	Day	Composite Pharmacokinetic Parameters		Mean Plasma Concentrations (ng/mL)			
				Time (hr)			
		C_{max} (ng/mL)	AUC (ng*hr/mL)[1]	0*	2	8	24*
3	2	48	420		48.0	12.7	11.1
	8	--	--	1.55			
10	2	163	1420		163	67.3	2.72
	8	--	--	2.37			
	15	--	--	3.95			
	17	--	--		136	65.8	
30	2	742	5540		742	228	8.42
	8	--	--	7.37			
	15	--	--	23.7			
	17	--	--		416	123	
100	2	1560	18500		1560	1050	97.8
	8	--	--	135			
	15	--	--	54.7			
	22	1550	21200		1550	1330	47.7
200	2	2500	47200		2370	2500	1270
	8	--	--	454			
	15	--	--	434			
	22	1940	3 1600		1940	1400	1050
300	2	3450	61300		3450	2900	1950
	8	--	--	911			
	15	--	--	1220			
	18	2980	58400		2440	2250	2980

[1] AUC calculated from 3 concentration-time data pairs
-- Not determined

* Predose concentrations

[0905] Tissue concentrations of compound **1** on Day 22 were higher than those in plasma in the 100 and 200 mg/kg dose groups at each of the two sampling times (8 and 24 hours postdose) (Table 16). Brain or heart concentrations of compound **1** were 13- to 34-fold higher than those in plasma; whereas liver, lung, and kidney concentrations were 40- to 126-fold higher than those in plasma at 8 or 24 hours postdose in these two dose groups. In general, the ratio of tissue-to-plasma concentrations at 8 hours

was comparable to that at 24 hours. Furthermore, tissue concentrations at 24 hours were consistently lower compared to those at 8 hours. Taken together, these results suggest that tissue concentrations of compound **1** appeared to decline in parallel with those in plasma. Therefore, compound **1** appears to be widely distributed into tissues (including brain) relative to plasma but does not accumulate in tissues following multiple oral dosing.

Table 16. Mean Tissue, Tumor and Plasma Concentrations on Day 22 Following Once-Daily Oral Administration of 100 or 200 mg/kg/day compound **1** to KM12L4a Tumor-Bearing Mice

Dose	Time	Tissue Concentrations (ng/g)						Plasma Conc
(mg/kg)	(hr)	Brain	Heart	Kidney	Liver	Lung	Tumor	(ng/mL)
100	8	16900	24700	83700	107000	87500	48500	1330
	24	675	1630	3900	5080	3170	16900	47.7
200	8	24200	40400	143000	176000	277000	107000	1400
	24	9160	18700	82800	109000	41600	87900	1050

N=2/timepoint/dose group, except in the 200 mg/kg at 24 hr, where N=1

[0906] Tumor compound **1** concentrations on Day 22 were 37- to 354-fold higher than those in plasma in the 100 and 200 mg/kg dose groups at each of the two sampling times (8 and 24 hours postdose). However, tumor concentrations at 24 hours were only 17 to 65% lower than those at 8 hours postdose in these two dose groups suggesting a somewhat slower elimination rate from tumors compared to that from other normal tissues (such as, brain, heart, liver, lung, and kidneys). Therefore, compound **1** appears to be extensively distributed to tumors relative to plasma but may exhibit preferential retention in tumor relative to plasma or normal tissues.

[0907] In summary, the efficacy and tolerability of compound **1** was dose related, with significant inhibitions after 4 to 7 days of treatment. Tumor regressions were observed at 300 and 200 mg/kg; these doses were tolerated daily for approximately 14 and 21 days, respectively. Weight loss was the

clinical sign associated with toxicity. Doses of 100 mg/kg were tolerated for 37 days with no adverse clinical signs, with tumor growth inhibition of 80% compared to control. 30 mg/kg inhibited growth by 60%. Compound **1** demonstrated dose- and time-independent pharmacokinetics in tumor-bearing mice. Plasma compound **1** C_{max}, AUC, and C_{min} values associated with 35-60% tumor growth inhibition ranged from 163-742 ng/mL, 1420-5540 ng*hr/mL, and 2-135 ng/mL, respectively. Compound **1** was distributed widely to tissues, however did not appear to accumulate in tissues following multiple oral dosing. There was a trend towards preferential retention of compound **1** in tumors relative to other tissues following oral dosing.

Intermittent Oral Dosing in the PC3 Human Prostate Tumor Model

[0908] This single agent study evaluated intermittent oral dosing of compound **1** in the PC3 human prostate tumor model.

[0909] SCID mice were implanted with PC3 human prostate cells subcutaneously. Treatment began when tumors reached 150 mm^3. This was designated as study day 1. Compound **1** was formulated as a solution in water and administered by oral gavage.

[0910] Five treatment groups were included in the study, (n = 10/group): Vehicle (water) *p.o., q.d.*; and four groups of compound **1** doses of 100 mg/kg q.d., q.2.d., q.3.d., q.4.d.

[0911] As shown in Table 17, significant and similar tumor inhibition results were observed in all treatment groups. The study was suspended for the daily dosing group on day 11. The study was terminated on study day 25 for the remaining groups and mean tumor volume was measured and compared to vehicle. As a clinical indication of toxicity percentage weight loss was measured for each group.

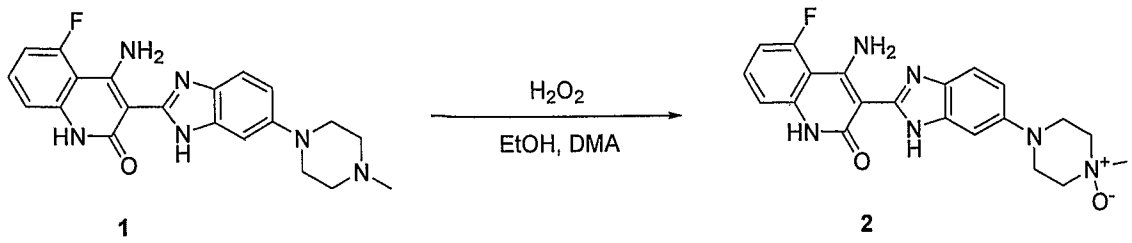
Table 17

Group	n	Total doses compound **1**	Mean Tumor Volume day 25	% TGI vs. vehicle	Mean % Wt. loss (range)
Vehicle	10		2011		13 (1-24%)
100mpk qd, days 1-11	8	11	790	60%	12 (3-35%)
100 mpk q 2 days	10	13	507	75%	4 (0-13%)
100mpk q 3 days	10	9	645	68%	4 (0-11%)
100mpk q 4 days	9	7	686	66%	10 (5-17%)

Synthesis of 4-Amino-5-fluoro-3-[5-(4-methyl-4-oxidopiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one (Compound 2) and 4-Amino-5-fluoro-3-(5-piperazin-1-yl-1H-benzimidazol-2-yl)quinolin-2(1H)-one (Compound 3)

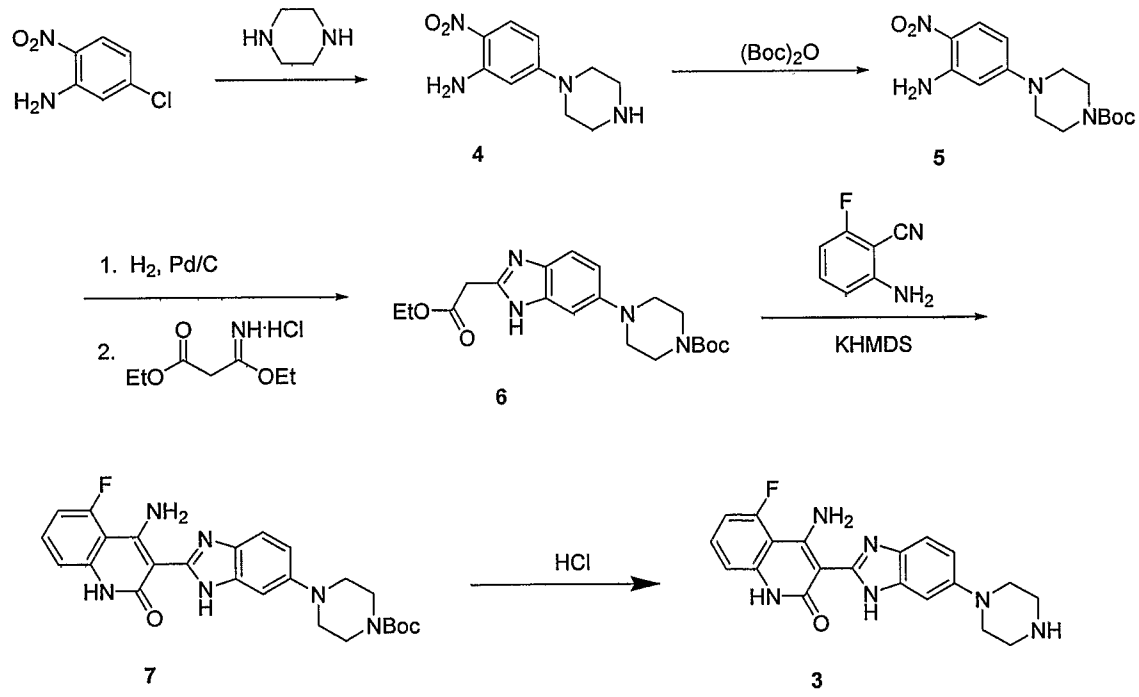
[0912] To confirm the structures of the identified metabolites of compound **1**, the metabolites were independently synthesized.

[0913] Compound **2**, the N-oxide metabolite of compound **1**, was synthesized as shown in the scheme below. Compound **1** was heated in a mixture of ethanol, dimethylacetamide and hydrogen peroxide. Upon completion of the reaction, compound **2** was isolated by filtration and washed with ethanol. If necessary, the product could be further purified by column chromatography.



1 2

[0914] Compound **3**, the N-desmethyl metabolite of compound **1**, was synthesized as shown in the scheme below. 5-Chloro-2-nitroaniline was treated with piperazine to yield **4** which was subsequently protected with a butyloxycarbonyl (Boc) group to yield **5**. Reduction of the nitro group followed by condensation with 3-ethoxy-3-iminopropionic acid ethyl ester gave **6**. Condensation of **6** with 6-fluoroanthranilonitrile using potassium hexamethyldisilazide as the base yielded **7**. Crude **7** was treated with aqueous HCl to yield the desired metabolite as a yellow/brown solid after purification.



Model Evaluation

[0915] This study evaluated the antiangiogenic potential of compound **1** in the FGF supplemented Matrigel model.

[0916] Female BDF1 mice, aged 11-12 weeks (Charles River, Wilmington, MA), were subcutaneously implanted with 0.5 mL Matrigel (BD Biosciences, Bedford, MA) supplemented with 2μg FGF-2. The FGF-2 supplemented blood vessel formation (neovascularization or angiogenesis) was quantified by measuring hemoglobin levels in the Matrigel plugs following their removal from the animals.

[0917] Oral administration of test article began one day prior to Matrigel implantation and continued once daily for eight doses. Compound **1** was formulated as a solution in 10 mM H_3PO_4. Twelve treatment groups were included: vehicle (10 mM H_3PO_4) *p.o., q.d.*x 8 days (2 control groups; mice implanted with unsupplemented Matrigel (baseline hemoglobin level) or FGF-supplemented Matrigel (positive control); compound **1** dosed at 3, 10, 30, 100, 200, 300 mg/kg *p.o., q.d.* x 8 days. There were 8 mice per group, except for mice dosed at 200 and 300 mg/kg, which were 4 per group.

[0918] Percent inhibition of hemoglobin levels in compound-treated mice compared to mice treated with vehicle indicates the antiangiogenic potency of the compound. Results are expressed as total hemoglobin (mg/dL) per Matrigel plug. The ED_{50} is defined as the dose that effectively inhibits angiogenesis by approximately 50%. Hemoglobin concentrations were determined in homogenized Matrigel plugs removed from mice and flash frozen, using absorbance spectroscopy with Drabkin's reagent (Sigma Diagnostics, St. Louis MO).

[0919] To evaluate plasma exposures of compound **1**, blood was collected 2 and 24 hours after 8 consecutive doses (Day 8). In the 200 and 300 mg/kg dose groups, blood was collected only at the 2 hour timepoint. Plasma concentrations of **1** were determined by a non-validated LC/MS/MS assay with a calibration range of 1 to 8000 ng/mL and a lower limit of quantitation (LLOQ) of 1 ng/mL (Charles River Laboratories, Worcester, MA).

[0920] On Day 8, hemoglobin levels in Matrigel plugs and plasma concentrations of compound **1** were measured. Animals were observed and body weights were measured throughout the study.

[0921] Compound **1** resulted in significant inhibition of hemoglobin concentration in Matrigel plugs at each dose evaluated compared to plugs from vehicle treated animals (Table 18). The calculated ED_{50} was 2.6 mg/kg. The 3 and 10 mg/kg doses resulted in 54% and 57% inhibition, respectively, whereas the 30, 100, 200 and 300 mg/kg doses reduced hemoglobin to the level of unsupplemented Matrigel, resulting in 70-92% inhibition vs. FGF-supplemented controls. The plasma concentrations of compound **1** at 2 hours post dose on day 8, showed a dose proportional increase with concentrations ranging from 44 ng/mL at 3 mg/kg to 3920 ng/mL at 300 mg/kg (Table 19). All doses were well tolerated and no weight loss was observed.

Table 18. Hemoglobin Concentrations and Dose Dependent Reduction in Hb Concentrations in Matrigel Plugs Inhibition in Matrigel Following Oral Administration of Compound 1

Treatment	n	Mean Hb ±SD mg/dL	% Hb inhibition vs. Vehicle treatment of Matrigel + FGF	p value t-test vs. vehicle treatment Matrigel FGF
Matrigel alone	8	26 ± 15		
Matrigel FGF + Vehicle	8	69 ± 34		
300mg/kg **1**	4	6 ± 0.8	91 %	0.005
200mg/kg **1**	4	8 ± 0.3	89 %	0.004
100mg/kg **1**	8	14 ± 7	80 %	<0.0005
30mg/kg **1**	8	20 ± 8	71 %	<0.0005
10mg/kg **1**	8	29 ± 16	58 %	0.010
3mg/kg **1**	8	32 ± 14	54 %	0.012

Table 19 Plasma Concentrations of Compound 1 Measured After 8 Consecutive Doses

Compound 1 Dose (mg/kg/day)	Mean Plasma Conc @ 2 hr# (ng/mL)	Mean Plasma Conc @ 24 hr# (ng/mL)
3	44	0[a]
10	123	0[a]
30	339	1.4
100	954	24
200	1910	NS
300	3920	NS

[a] Plasma concentrations below lower limit of quantitation (≤ 1 ng/mL)
NS = No samples were collected
#samples collected 2 hours and 24 hours after dosing

[0922] Plasma concentrations of **1** (2 hr postdose) increased proportionally with dose. A dose and plasma concentration dependent reduction in hemoglobin content of Matrigel plugs was observed. Plasma concentrations (2 hr postdose, Day 8) of 44 ng/mL appear to be associated with antiangiogenic activity in this model.

[0923] In summary, the hemoglobin inhibition of compound **1** was dose-dependent , with significant inhibition after 8 days of treatment. Statistically significant hemoglobin inhibition was observed with all doses of compound **1**. All doses were well tolerated with no weight loss or adverse clinical signs observed. Compound **1** plasma concentrations (2 hr postdose) of 44 ng/mL were associated with antiangiogenic activity in this model.

Monkey Multiple Oral Dose Experiment

[0924] The metabolite profile of compound **1** in monkey plasma from a 5 mg/kg BID multiple oral dose study was determined in dose day 1 and 14 samples. One metabolite was identified and characterized by LC/UV and LD/MS/MS resulting from demethylation (compound **3**). Parent (P) compound **1** produced an $M+H^+$ ion at m/z = 393.3 with a chromatographic retention time of 18.3 minutes. The demethylated metabolite ($P-CH_3$) was identified with an m/z = 379.3 ($M+H^+$) and a chromatographic retention time of 18.1 min. The

mass difference of 14 daltons between the metabolite and compound **1** is consistent with a demethylated compound **1**. The mass and chromatographic retention of the metabolite was identical to independently synthesized compound **3**. The metabolite corresponding to the piperazine N-oxide of compound **1** (N-oxide compound **2**) was not detected in plasma at this dose level. The components producing a UV signal at 17.7 and 18.5 minutes in the absorbance chromatogram at 356 nm were determined to be matrix components and not metabolites based on the UV spectral comparisons to compound 1 and due to their presence in blank plasma (time 0 dose day 1).

[0925] The estimated levels of the demethylated metabolite are given in Table 20. The estimated levels of metabolites (in compound **1** equivalents) are based on UV absorbance peak height ratios of metabolite to that of compound 1 obtained in this analysis and extrapolated by factoring the absorbance ratio to the known levels of compound **1** determined in the same samples in a previous quantitative analytical study. It was found that parent compound was in greater abundance than the metabolite at all pooled time points. The levels of compound **1** were found to be substantially lower in the day 14 samples in parallel with the N-desmethyl metabolite which was essentially undetectable. No other metabolites including conjugated Phase II type metabolites (glucuronide or sulphate) were detected in these plasma samples on day 1 or 14 of dose administration.

Table 10: compound 1 levels and estimated compound 1 metabolite levels in rat plasma (N=2) with multiple oral doses of compound 1 (5 mg/kg, BID).

Dose (mg/kg/day)[a]	Day	Pooled Sample Time (hr)	(P-CH_3) (ng/ml)[b]	compound 1 (ng/ml)[c]
10	1	0	0	0
10	1	1, 2	8.5	28
10	1	4, 8	31	62
10	1	12, 13, 14, 16, 20, 24	10	21
10	14	0	ND	2
10	14	1, 2	ND	4.2
10	14	4, 8	ND	2.2
10	14	12, 13, 14, 16, 20, 24	ND	3.2

a. Rats were dosed with 5/mg/kg compound 1 BID in 12 hour intervals (T=0 and T=12 hours).
b. Metabolite levels estimated based on metabolite/compound 1 UV response ratios obtained in this study and factored by the known compound **1** levels previously determined in a separate quantitative study.
c. Compound **1** levels presented in this table are averaged values of previously quantified levels from a separate study.
ND: Non detectable

Pharmacodynamic Enpoint Analysis

[0926] Studies with plasma and tumors collected from mice following treatment with compound **1** were performed to evaluate potential pharmacodynamic endpoints. Analysis of target modulation in KM12L4a tumors after compound **1** treatment indicated that phosphorylation of VEGFR1, VEGFR2, PDGFRβ, and FGFR1 were inhibited in a time- and dose-dependent manner. For example, HMVEC cells showed inhibition of VEGF mediated VEGFR2 phosphorylation with an IC_{50} of about 0.1 μM. In addition, treatment of endothelial cells with compound **1** inhibited MAPK and Akt phosphorylation mediated by VEGF.

[0927] Furthermore, a time- and dose- dependent inhibition of ERK (MAPK) activation, a downstream target of receptor tyrosine kinases, was observed with IC_{50}s ranging from 0.1 to 0.5 μM in KM12L4A cells. (KM12L4A cells express PDGFRβ and VEGFR1/2 on their surfaces.) KM12L4A cells were incubated 3 hours with compound **1** in serum-free DMEM. After the

harvest, lysates were separated by SDS-Page and probed with the phosphor-ERK1/2 and ERK1/2 antibodies. For detection, ECL reagents (Amersham) were used. The inhibitory effects of compound **1** on receptor phosphorylation and ERK activation were maintained for 24 hours after treatment. Phosphorylation of ERK1/2 in MV4-11 cells was inhibited by **1** at IC_{50}s of 0.01 to 0.1 μM in a dose-dependent manner.

[0928] Significant activity was observed *in vivo* in the HCT116 human colon tumor model. In HCT116 tumors, compound **1** inhibited the phosphorylation of ERK (MAPK) in a dose- and time-dependent manner and significant changes in histology analyses of the tumors was observed.

[0929] These PK/PD evaluations in preclinical models indicate that compound **1** showed a dose- and time-dependent inhibition of both the target receptors and the downstream signaling molecule, ERK (MAPK). These studies will aid in the identification of potential biomarkers to support the monitoring of biological activity of compound **1** in clinical trials.

Tissue Distribution

[0930] The distribution of radioactivity in tissues after administration of a single oral (PO) dose (5 mg/kg) of ^{14}C-labeled compound **1** to male and female Sprague Dawley (SD) rats was determined by whole-body autoradiography (WBA). Blood and carcasses for WBA were collected at specified time points through 24 hours postdose. Plasma was analyzed for concentration of radioactivity by liquid scintillation counting (LSC).

[0931] Following oral administration of ^{14}C-**1**, radioactivity derived from ^{14}C-**1** was widely distributed throughout all tissues by 1 hour postdose, and had reached C_{max} in most tissues by 4 hours postdose. Overall distribution of radioactivity in the tissues of males and females was similar. ^{14}C-**1**-derived radioactivity was cleared more slowly from tissues than from plasma. In males and females, the highest tissue concentrations of ^{14}C-**1**, excluding the gastrointestinal tract through 24 hours were detected in the harderian gland,

adrenal gland, renal medulla, intra-orbital lacrimal gland, and exorbital lacrimal gland. ^{14}C-**1**-derived radioacitivity crossed the blood/brain barrier after oral dose administration.

[0932] Each of the following compounds was synthesized and was assayed using the procedures described herein: 3-{5-[2-(ethylanilino)ethoxy]-1H-benzimidazol-2-yl}-4-hydroxy-2(1H)-quinolinone; 3-[5-(4-aminophenoxy)-1H-benzimidazol-2-yl]-4-hydroxy-2(1H)-quinolinone; 3-{6-[[2-(dimethylamino)ethyl](methyl)amino]-1H-benzimidazol-2-yl}-4-hydroxy-2(1H)-quinolinone; 4-hydroxy-3-[5-(4-morpholinyl)-1H-benzimidazol-2-yl]-2(1H)-quinolinone; 3-[5-(3-amino-1-pyrrolidinyl)-1H-benzimidazol-2-yl]-4-hydroxy-2(1H)-quinolinone; N,N-dimethyl-2-(2-oxo-1,2-dihydro-3-quinolinyl)-1H-benzimidazole-5-carboxamide; 3-{5-[2-(4-morpholinyl)ethoxy]-1H-benzimidazol-2-yl}-2(1H)-quinolinone; 3-{5-[3-(dimethylamino)-1-pyrrolidinyl]-1H-benzimidazol-2-yl}-2(1H)-quinolinone; 3-(1H-benzimidazol-2-yl)-2-oxo-1,2-dihydro-4-quinolinecarbonitrile; 4-amino-3-{5-[2-(4-morpholinyl)ethoxy]-1H-benzimidazol-2-yl}-2(1H)-quinolinone; 4-amino-3-[6-(4-morpholinyl)-1H-benzimidazol-2-yl]-2(1H)-quinolinone; 4-amino-3-[6-(3-amino-1-pyrrolidinyl)-1H-benzimidazol-2-yl]-2(1H)-quinolinone; 2-(4-amino-2-oxo-1,2-dihydro-3-quinolinyl)-1H-benzimidazole-5-carbonitrile; 2-(4-amino-2-oxo-1,2-dihydro-3-quinolinyl)-N,N-dimethyl-1H-benzimidazole-5-carboxamide; 4-amino-3-{5-[3-(dimethylamino)-1-pyrrolidinyl]-1H-benzimidazol-2-yl}-2(1H)-quinolinone; 2-(4-amino-2-oxo-1,2-dihydro-3-quinolinyl)-1H-benzimidazole-6-carboximidamide; 4-amino-3-[5-(4-morpholinylcarbonyl)-1H-benzimidazol-2-yl]-2(1H)-quinolinone; 4-amino-3-[5-(1H-1,2,4-triazol-1-yl)-1H-benzimidazol-2-yl]-2(1H)-quinolinone; 4-amino-3-[5-(dimethylamino)-1H-benzimidazol-2-yl]-2(1H)-quinolinone; 4-amino-3-[5-(1-piperidinyl)-1H-benzimidazol-2-yl]-2(1H)-quinolinone; 4-amino-3-[5-(2-thienyl)-1H-benzimidazol-2-yl]-2(1H)-quinolinone; 4-amino-3-{5-[3-(1-pyrrolidinyl)propoxy]-1H-benzimidazol-2-yl}-2(1H)-quinolinone; 4-amino-3-{5-[3-(4-morpholinyl)propoxy]-1H-benzimidazol-2-yl}-2(1H)-quinolinone; 4-amino-3-[5-(3,5-dimethyl-1-piperazinyl)-1H-benzimidazol-2-yl]-2(1H)-quinolinone; 4-

amino-3-[5-(2,6-dimethyl-4-morpholinyl)-1H-benzimidazol-2-yl]-2(1H)-quinolinone; 4-amino-3-[5-(4-methyl-1-piperazinyl)-1H-benzimidazol-2-yl]-2(1H)-quinolinone; 4-amino-3-(1H-benzimidazol-2-yl)-6-[hydroxy(oxido)amino]-2(1H)-quinolinone; 4-amino-3-(1H-benzimidazol-2-yl)-5-[2-(4-morpholinyl)ethoxy]-2(1H)-quinolinone; 4-amino-3-(1H-benzimidazol-2-yl)-6-(4-methyl-1-piperazinyl)-2(1H)-quinolinone; 4-amino-3-(1H-benzimidazol-2-yl)-5-[(1-methyl-3-piperidinyl)oxy]-2(1H)-quinolinone; 4-amino-6-chloro-3-[5-(4-morpholinyl)-1H-benzimidazol-2-yl]-2(1H)-quinolinone; 4-amino-6-chloro-3-{5-[3-(dimethylamino)-1-pyrrolidinyl]-1H-benzimidazol-2-yl}-2(1H)-quinolinone; 4-amino-6-[hydroxy(oxido)amino]-3-{5-[2-(4-morpholinyl)ethoxy]-1H-benzimidazol-2-yl}-2(1H)-quinolinone; 4-amino-5-[2-(4-morpholinyl)ethoxy]-3-{5-[2-(4-morpholinyl)ethoxy]-1H-benzimidazol-2-yl}-2(1H)-quinolinone; 4-amino-3-(1H-benzimidazol-2-yl)-6-(2-pyridinylmethoxy)-2(1H)-quinolinone; 4-amino-6-fluoro-3-[5-(4-morpholinyl)-1H-benzimidazol-2-yl]-2(1H)-quinolinone; 4-amino-3-{5-[3-(dimethylamino)-1-pyrrolidinyl]-1H-benzimidazol-2-yl}-6-fluoro-2(1H)-quinolinone; 3-(1H-benzimidazol-2-yl)-4-[(tetrahydro-2-furanylmethyl)amino]-2(1H)-quinolinone; 3-(1H-benzimidazol-2-yl)-4-(methylamino)-2(1H)-quinolinone; 3-(1H-benzimidazol-2-yl)-4-(ethylamino)-2(1H)-quinolinone; 3-(1H-benzimidazol-2-yl)-4-{[2-(1-methyl-2-pyrrolidinyl)ethyl]amino}-2(1H)-quinolinone; 3-(1H-benzimidazol-2-yl)-4-[(4-piperidinylmethyl)amino]-2(1H)-quinolinone; 3-(1H-benzimidazol-2-yl)-4-(4-fluoroanilino)-2(1H)-quinolinone; 4-(1-azabicyclo[2.2.2]oct-3-ylamino)-3-(1H-benzimidazol-2-yl)-2(1H)-quinolinone; 3-(1H-benzimidazol-2-yl)-4-(1H-benzimidazol-6-ylamino)-2(1H)-quinolinone; 4-anilino-3-(1H-benzimidazol-2-yl)-2(1H)-quinolinone; 3-(1H-benzimidazol-2-yl)-4-(methoxyamino)-2(1H)-quinolinone; 3-(1H-benzimidazol-2-yl)-4-[(1H-imidazol-5-ylmethyl)amino]-2(1H)-quinolinone; 3-(1H-benzimidazol-2-yl)-4-(4-morpholinylamino)-2(1H)-quinolinone; 3-(1H-benzimidazol-2-yl)-4-hydrazino-2(1H)-quinolinone; 4-(1-azabicyclo[2.2.2]oct-3-ylamino)-3-(1H-benzimidazol-2-yl)-2(1H)-quinolinone; 4-(1-azabicyclo[2.2.2]oct-3-ylamino)-3-(1H-benzimidazol-2-yl)-2(1H)-quinolinone; 4-[(2-methoxyethyl)amino]-3-[6-(4-morpholinyl)-1H-benzimidazol-2-yl]-2(1H)-quinolinone; 4-[(2-hydroxyethyl)amino]-3-[5-(4-morpholinyl)-1H-

benzimidazol-2-yl]-2(1H)-quinolinone; 4-(methoxyamino)-3-[5-(4-morpholinyl)-1H-benzimidazol-2-yl]-2(1H)-quinolinone; 3-[5-(4-morpholinyl)-1H-benzimidazol-2-yl]-4-(3-piperidinylamino)-2(1H)-quinolinone; 3-[5-(4-morpholinyl)-1H-benzimidazol-2-yl]-4-[(3-piperidinylmethyl)amino]-2(1H)-quinolinone; 4-{[2-(dimethylamino)ethyl]amino}-3-[5-(4-morpholinyl)-1H-benzimidazol-2-yl]-2(1H)-quinolinone; 3-[5-(4-morpholinyl)-1H-benzimidazol-2-yl]-4-[(tetrahydro-2-furanylmethyl)amino]-2(1H)-quinolinone; 4-{[2-(methylamino)ethyl]amino}-3-[5-(4-morpholinyl)-1H-benzimidazol-2-yl]-2(1H)-quinolinone; 3-[5-(4-morpholinyl)-1H-benzimidazol-2-yl]-4-(3-pyrrolidinylamino)-2(1H)-quinolinone; 4-[(2-amino-4-methylpentyl)amino]-3-[5-(4-morpholinyl)-1H-benzimidazol-2-yl]-2(1H)-quinolinone; 4-[(2-amino-3-methylbutyl)amino]-3-[5-(4-morpholinyl)-1H-benzimidazol-2-yl]-2(1H)-quinolinone; 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-4-(3-piperidinylamino)-2(1H)-quinolinone; 4-[(2-aminocyclohexyl)amino]-3-[5-(4-morpholinyl)-1H-benzimidazol-2-yl]-2(1H)-quinolinone; 4-[(2-aminocyclohexyl)amino]-3-[5-(4-morpholinyl)-1H-benzimidazol-2-yl]-2(1H)-quinolinone; 3-(1H-benzimidazol-2-yl)-4-hydroxybenzo[g]quinolin-2(1H)-one; 4-amino-3-(3H-imidazo[4,5-b]pyridin-2-yl)quinolin-2(1H)-one; 4-amino-3-(5-morpholin-4-yl-3H-imidazo[4,5-b]pyridin-2-yl)quinolin-2(1H)-one; 4-amino-5-[(2R,6S)-2,6-dimethylmorpholin-4-yl]-3-(3H-imidazo[4,5-b]pyridin-2-yl)quinolin-2(1H)-one; 4-amino-3-{5-[3-(dimethylamino)pyrrolidin-1-yl]-3H-imidazo[4,5-b]pyridin-2-yl}quinolin-2(1H)-one; 4-amino-3-{5-[(3S)-3-(dimethylamino)pyrrolidin-1-yl]-1H-benzimidazol-2-yl}quinolin-2(1H)-one; 4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-chloroquinolin-2(1H)-one; 4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-chloroquinolin-2(1H)-one; 3-(1H-benzimidazol-2-yl)-4-[(3R)-3-(dimethylamino)pyrrolidin-1-yl]quinolin-2(1H)-one; 3-(1H-benzimidazol-2-yl)-6-chloro-4-[(3R)-3-(dimethylamino)pyrrolidin-1-yl]quinolin-2(1H)-one; 4-amino-3-[5-(4-ethylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1-methylquinolin-2(1H)-one; 4-amino-3-(6-piperazin-1-yl-1H-benzimidazol-2-yl)quinolin-2(1H)-one; 4-amino-3-[6-(pyridin-4-ylmethyl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one; 4-amino-3-{5-[(3R,5S)-3,5-dimethylpiperazin-1-yl]-1H-benzimidazol-2-yl}quinolin-2(1H)-

one; 4-amino-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one; 4-amino-3-(6-methyl-5-morpholin-4-yl-1H-benzimidazol-2-yl)quinolin-2(1H)-one; 4-amino-3-{5-[(1-methylpiperidin-3-yl)oxy]-1H-benzimidazol-2-yl}quinolin-2(1H)-one; 4-amino-3-{5-[(2R,6S)-2,6-dimethylmorpholin-4-yl]-6-fluoro-1H-benzimidazol-2-yl}quinolin-2(1H)-one; 4-amino-3-{5-[(1-methylpyrrolidin-3-yl)oxy]-1H-benzimidazol-2-yl}quinolin-2(1H)-one; 4-amino-3-[5-(4-methyl-1,4-diazepan-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one; 4-amino-3-{5-[(3R)-3-(dimethylamino)pyrrolidin-1-yl]-1H-benzimidazol-2-yl}quinolin-2(1H)-one; 4-amino-6-chloro-3-{5-[(3R)-3-(dimethylamino)pyrrolidin-1-yl]-1H-benzimidazol-2-yl}quinolin-2(1H)-one; ethyl {4-[2-(4-amino-2-oxo-1,2-dihydroquinolin-3-yl)-1H-benzimidazol-6-yl]piperazin-1-yl}acetate; 4-amino-3-{6-[methyl(1-methylpiperidin-4-yl)amino]-1H-benzimidazol-2-yl}quinolin-2(1H)-one; 3-[6-(4-acetylpiperazin-1-yl)-1H-benzimidazol-2-yl]-4-aminoquinolin-2(1H)-one; 4-amino-3-[6-(1,4'-bipiperidin-1'-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one; 2-(4-amino-2-oxo-1,2-dihydroquinolin-3-yl)-1H-benzimidazole-6-carboxylic acid; 4-amino-5-(methyloxy)-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one; 4-amino-3-{6-[4-(1-methylethyl)piperazin-1-yl]-1H-benzimidazol-2-yl}quinolin-2(1H)-one; {4-[2-(4-amino-2-oxo-1,2-dihydroquinolin-3-yl)-1H-benzimidazol-6-yl]piperazin-1-yl}acetic acid; 4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)quinolin-2(1H)-one; 4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)quinolin-2(1H)-one; 4-amino-3-[5-(4-ethylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one; 4-amino-3-(5-{(2S,5S)-2-[(dimethylamino)methyl]-5-methylmorpholin-4-yl}-1H-benzimidazol-2-yl)quinolin-2(1H)-one; 4-amino-6-chloro-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one; 4-amino-6-chloro-3-{5-[(3S)-3-(dimethylamino)pyrrolidin-1-yl]-1H-benzimidazol-2-yl}quinolin-2(1H)-one; 4-amino-5,6-dichloro-3-{5-[(3S)-3-(dimethylamino)pyrrolidin-1-yl]-1H-benzimidazol-2-yl}quinolin-2(1H)-one; 4-amino-5,6-dichloro-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one; 4-amino-3-(1H-benzimidazol-2-yl)-6-[(pyridin-2-ylmethyl)oxy]quinolin-2(1H)-one; 4-amino-3-(1H-benzimidazol-2-yl)-6-

[(2R,6S)-2,6-dimethylmorpholin-4-yl]quinolin-2(1H)-one; 4-amino-3-(1H-benzimidazol-2-yl)-6-morpholin-4-ylquinolin-2(1H)-one; 4-amino-3-(1H-benzimidazol-2-yl)-5-[(1-methylpiperidin-3-yl)oxy]quinolin-2(1H)-one; 4-amino-3-(1H-benzimidazol-2-yl)-5-[(pyridin-2-ylmethyl)oxy]quinolin-2(1H)-one; 4-amino-3-(5-morpholin-4-yl-1H-benzimidazol-2-yl)-5-[(pyridin-4-ylmethyl)oxy]quinolin-2(1H)-one; 4-amino-3-(1H-benzimidazol-2-yl)-5-(methyloxy)quinolin-2(1H)-one; 4-amino-3-(5-methyl-1H-benzimidazol-2-yl)-5-(methyloxy)quinolin-2(1H)-one; 4-amino-3-{5-[(2R,6S)-2,6-dimethylmorpholin-4-yl]-1H-benzimidazol-2-yl}-5-(methyloxy)quinolin-2(1H)-one; 4-amino-3-(1H-benzimidazol-2-yl)-5-morpholin-4-ylquinolin-2(1H)-one; 4-amino-3-(1H-benzimidazol-2-yl)-5-[(2R,6S)-2,6-dimethylmorpholin-4-yl]quinolin-2(1H)-one; 4-amino-3-(1H-benzimidazol-2-yl)-5-(4-methylpiperazin-1-yl)quinolin-2(1H)-one; 4-amino-5,6-dichloro-3-(5-morpholin-4-yl-1H-benzimidazol-2-yl)quinolin-2(1H)-one; 3-{5-[(2-morpholin-4-ylethyl)oxy]-1H-benzimidazol-2-yl}quinolin-2(1H)-one; 4-amino-3-{5-[(3-pyrrolidin-1-ylpropyl)oxy]-1H-benzimidazol-2-yl}quinolin-2(1H)-one; 4-amino-3-{5-[(3-morpholin-4-ylpropyl)oxy]-1H-benzimidazol-2-yl}quinolin-2(1H)-one; 4-amino-6-fluoro-3-(5-morpholin-4-yl-1H-benzimidazol-2-yl)quinolin-2(1H)-one; 4-amino-3-{5-[3-(dimethylamino)pyrrolidin-1-yl]-1H-benzimidazol-2-yl}-6-fluoroquinolin-2(1H)-one; 4-amino-3-(1H-benzimidazol-2-yl)-6-fluoroquinolin-2(1H)-one; 4-amino-3-(6-fluoro-5-morpholin-4-yl-1H-benzimidazol-2-yl)quinolin-2(1H)-one; 4-amino-3-{5-[(tetrahydrofuran-2-ylmethyl)oxy]-1H-benzimidazol-2-yl}quinolin-2(1H)-one; 4-amino-6-fluoro-3-(6-fluoro-5-morpholin-4-yl-1H-benzimidazol-2-yl)quinolin-2(1H)-one; 4-amino-3-[6-fluoro-5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one; 4-amino-3-(5-{[2-(methyloxy)ethyl]oxy}-1H-benzimidazol-2-yl)quinolin-2(1H)-one; 4-amino-3-[4,6-difluoro-5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one; 4-amino-3-{5-[3-(dimethylamino)pyrrolidin-1-yl]-1H-benzimidazol-2-yl}-5-fluoroquinolin-2(1H)-one; 4-amino-5-fluoro-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one; 4-amino-5-chloro-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one; 4-amino-3-{5-[3-(dimethylamino)pyrrolidin-1-yl]-6-fluoro-1H-benzimidazol-2-yl}quinolin-2(1H)-

one; 4-amino-5-chloro-3-{5-[3-(dimethylamino)pyrrolidin-1-yl]-1H-benzimidazol-2-yl}quinolin-2(1H)-one; 4-amino-6-chloro-3-{5-[3-(dimethylamino)pyrrolidin-1-yl]-6-fluoro-1H-benzimidazol-2-yl}quinolin-2(1H)-one; 4-amino-5-[(2R,6S)-2,6-dimethylmorpholin-4-yl]-3-(3H-imidazo[4,5-b]pyridin-2-yl)quinolin-2(1H)-one; 4-amino-3-(6-thiomorpholin-4-yl-1H-benzimidazol-2-yl)quinolin-2(1H)-one; 4-amino-3-[5-(4-cyclohexylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one; 4-amino-3-{6-[3-(diethylamino)pyrrolidin-1-yl]-1H-benzimidazol-2-yl}quinolin-2(1H)-one; 4-amino-3-[6-(4-pyridin-2-ylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one; 4-amino-3-[5-(4-methylpiperazin-1-yl)-3H-imidazo[4,5-b]pyridin-2-yl]quinolin-2(1H)-one; 4-amino-6-chloro-3-[5-(4-methylpiperazin-1-yl)-1H-imidazo[4,5-b]pyridin-2-yl]quinolin-2(1H)-one; 2-(4-amino-2-oxo-1,2-dihydroquinolin-3-yl)-N-methyl-N-(1-methylpiperidin-4-yl)-1H-benzimidazole-5-carboxamide; 4-amino-3-(5-{[4-(1-methylethyl)piperazin-1-yl]carbonyl}-1H-benzimidazol-2-yl)quinolin-2(1H)-one; 4-amino-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-6-nitroquinolin-2(1H)-one; 4-amino-3-[5-(1,4'-bipiperidin-1'-ylcarbonyl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one; 4-amino-3-{5-[(4-methylpiperazin-1-yl)carbonyl]-1H-benzimidazol-2-yl}quinolin-2(1H)-one; 4-amino-3-[5-(1-oxidothiomorpholin-4-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one; 3-{5-[(4-acetylpiperazin-1-yl)carbonyl]-1H-benzimidazol-2-yl}-4-aminoquinolin-2(1H)-one; 4-amino-3-(5-{[(3R)-3-(dimethylamino)pyrrolidin-1-yl]carbonyl}-1H-benzimidazol-2-yl)quinolin-2(1H)-one; 4-amino-3-(5-{[(3S)-3-(dimethylamino)pyrrolidin-1-yl]carbonyl}-1H-benzimidazol-2-yl)quinolin-2(1H)-one; 4-amino-3-(5-{[4-(dimethylamino)piperidin-1-yl]carbonyl}-1H-benzimidazol-2-yl)quinolin-2(1H)-one; methyl 2-(4-amino-5-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)-1H-benzimidazole-6-carboxylate; 4-amino-3-[5-(1,3'-bipyrrolidin-1'-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one; 4-amino-3-[5-(pyridin-3-yloxy)-1H-benzimidazol-2-yl]quinolin-2(1H)-one; 4-amino-5,6-bis(methyloxy)-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one; 2-(4-amino-2-oxo-1,2-dihydroquinolin-3-yl)-N-[2-(dimethylamino)ethyl]-N-methyl-1H-benzimidazole-5-carboxamide; 2-(4-amino-2-oxo-1,2-dihydroquinolin-3-yl)-N-methyl-N-(1-methylpyrrolidin-3-yl)-

1H-benzimidazole-5-carboxamide; 4-amino-3-{5-[(5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl)carbonyl]-1H-benzimidazol-2-yl}quinolin-2(1H)-one; 4-amino-3-{5-[(4-cyclohexylpiperazin-1-yl)carbonyl]-1H-benzimidazol-2-yl}quinolin-2(1H)-one; 4-amino-3-{5-[(2-piperidin-1-ylethyl)amino]-1H-benzimidazol-2-yl}quinolin-2(1H)-one; ethyl 4-{[2-(4-amino-2-oxo-1,2-dihydroquinolin-3-yl)-1H-benzimidazol-5-yl]amino}piperidine-1-carboxylate; 4-amino-3-[5-({(5R)-5-[(methyloxy)methyl]pyrrolidin-3-yl}amino)-1H-benzimidazol-2-yl]quinolin-2(1H)-one; 4-amino-3-{5-[(pyridin-2-ylmethyl)amino]-1H-benzimidazol-2-yl}quinolin-2(1H)-one; 4-amino-3-[5-(piperidin-3-ylamino)-1H-benzimidazol-2-yl]quinolin-2(1H)-one; 4-amino-5-fluoro-3-{5-[(pyridin-2-ylmethyl)amino]-1H-benzimidazol-2-yl}quinolin-2(1H)-one; ethyl 4-{[2-(4-amino-5-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)-1H-benzimidazol-5-yl]amino}piperidine-1-carboxylate; 4-amino-5-fluoro-3-[5-(piperidin-3-ylamino)-1H-benzimidazol-2-yl]quinolin-2(1H)-one; 4-amino-3-(1H-benzimidazol-2-yl)-6-bromoquinolin-2(1H)-one; 4-amino-3-(1H-benzimidazol-2-yl)-7-bromoquinolin-2(1H)-one; 4-amino-3-(5-bromo-1H-benzimidazol-2-yl)quinolin-2(1H)-one; N,N-dimethyl-2-(2-oxo-1,2-dihydroquinolin-3-yl)-1H-benzimidazole-5-carboxamide; 4-amino-3-(5-thien-2-yl-1H-benzimidazol-2-yl)quinolin-2(1H)-one; 2-(4-amino-2-oxo-1,2-dihydroquinolin-3-yl)-N,N-dimethyl-1H-benzimidazole-5-sulfonamide; 4-amino-6-iodo-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one; 4-amino-3-(5-{2-[(dimethylamino)methyl]morpholin-4-yl}-1H-benzimidazol-2-yl)quinolin-2(1H)-one; 4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-chloro-6-iodoquinolin-2(1H)-one; 4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-nitroquinolin-2(1H)-one; 4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-methylquinolin-2(1H)-one; 4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6,7-difluoroquinolin-2(1H)-one; 4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-chloroquinolin-2(1H)-one; 4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-bromoquinolin-2(1H)-one; 4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-2-oxo-1,2-dihydroquinoline-6-carbonitrile; 4-[(3R)-1-

azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-fluoroquinolin-2(1H)-one; 4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6,7-bis(methyloxy)quinolin-2(1H)-one; 4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6,7-dichloroquinolin-2(1H)-one; 1-[4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-fluoro-2-oxo-1,2-dihydroquinolin-7-yl]piperidine-4-carboxamide; 4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-fluoro-7-[(3-hydroxypropyl)amino]quinolin-2(1H)-one; 4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-(dimethylamino)-6-fluoroquinolin-2(1H)-one; 4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-5-fluoroquinolin-2(1H)-one; 4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-(4-nitrophenyl)quinolin-2(1H)-one; 4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-{[2-(dimethylamino)ethyl]amino}-6-fluoroquinolin-2(1H)-one; 4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-fluoro-7-(1H-imidazol-1-yl)quinolin-2(1H)-one; 4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-[4-(methyloxy)phenyl]quinolin-2(1H)-one; 4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-fluoro-7-morpholin-4-ylquinolin-2(1H)-one; 4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-6,7-difluoro-3-(3H-imidazo[4,5-b]pyridin-2-yl)quinolin-2(1H)-one; 4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-(3-nitrophenyl)quinolin-2(1H)-one; 1-[4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-fluoro-2-oxo-1,2-dihydroquinolin-7-yl]piperidine-3-carboxamide; 4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-5-methylquinolin-2(1H)-one; 6-(3-acetylphenyl)-4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(3H-imidazo[4,5-b]pyridin-2-yl)quinolin-2(1H)-one; 4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-5-chloroquinolin-2(1H)-one; 4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-6-fluoro-3-(3H-imidazo[4,5-b]pyridin-2-yl)-7-morpholin-4-ylquinolin-2(1H)-one; 4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-(cyclopropylamino)-6-fluoroquinolin-2(1H)-one; N-{3-[4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(3H-imidazo[4,5-b]pyridin-2-yl)-2-oxo-1,2-

dihydroquinolin-6-yl]phenyl}acetamide; 4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-fluoro-7-(4-methylpiperazin-1-yl)quinolin-2(1H)-one; 4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-6-fluoro-7-(1H-imidazol-1-yl)-3-(3H-imidazo[4,5-b]pyridin-2-yl)quinolin-2(1H)-one; 4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-fluoro-7-[(2-pyridin-2-ylethyl)amino]quinolin-2(1H)-one; 4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-fluoro-7-piperidin-1-ylquinolin-2(1H)-one; 6-chloro-3-(3H-imidazo[4,5-b]pyridin-2-yl)quinolin-2(1H)-one; ethyl 1-[4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-fluoro-2-oxo-1,2-dihydroquinolin-7-yl]piperidine-4-carboxylate; 4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-(1-benzothien-2-yl)quinolin-2(1H)-one; 4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-fluoro-7-pyrrolidin-1-ylquinolin-2(1H)-one; 4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(3H-imidazo[4,5-b]pyridin-2-yl)-6-[2-(trifluoromethyl)phenyl]quinolin-2(1H)-one; 4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(3H-imidazo[4,5-b]pyridin-2-yl)-6-[2-(methyloxy)phenyl]quinolin-2(1H)-one; ethyl 1-[4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-fluoro-2-oxo-1,2-dihydroquinolin-7-yl]piperidine-3-carboxylate; 4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-(4-ethylphenyl)quinolin-2(1H)-one; 4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-fluoro-7-[(2-methylpropyl)amino]quinolin-2(1H)-one; 4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-5-methylquinolin-2(1H)-one; 4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-6-(2,4-dichlorophenyl)-3-(3H-imidazo[4,5-b]pyridin-2-yl)quinolin-2(1H)-one; 4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-[3-(trifluoromethyl)phenyl]quinolin-2(1H)-one; 3-(1H-benzimidazol-2-yl)-4-(dimethylamino)quinolin-2(1H)-one; 4-hydroxy-3-(1H-imidazo[4,5-f]quinolin-2-yl)quinolin-2(1H)-one; 4-hydroxy-3-(1H-imidazo[4,5-b]pyridin-2-yl)quinolin-2(1H)-one; 4-[4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-5-fluoro-2-oxo-1,2-dihydroquinolin-6-yl]benzoic acid; 4-[4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-5-fluoro-2-oxo-1,2-dihydroquinolin-6-yl]benzamide; N-{3-[4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-5-fluoro-2-oxo-1,2-

dihydroquinolin-6-yl]phenyl}acetamide; 3-[4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-5-fluoro-2-oxo-1,2-dihydroquinolin-6-yl]benzoic acid; 4-[4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-fluoro-2-oxo-1,2-dihydroquinolin-6-yl]benzoic acid; N-{3-[4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-fluoro-2-oxo-1,2-dihydroquinolin-6-yl]phenyl}acetamide; 4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-chloro-6-(2-methylphenyl)quinolin-2(1H)-one; 4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-2-oxo-1,2-dihydroquinoline-7-carbonitrile; 4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-(methyloxy)quinolin-2(1H)-one; 4-[4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-2-oxo-1,2-dihydroquinolin-7-yl]benzamide; 4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-fluoro-7-(methyloxy)quinolin-2(1H)-one; 4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-chloro-7-(dimethylamino)quinolin-2(1H)-one; 4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-(dimethylamino)-6-iodoquinolin-2(1H)-one; 3-[4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-(1H-imidazol-1-yl)-2-oxo-1,2-dihydroquinolin-6-yl]benzoic acid; 4-[4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-2-oxo-7-piperidin-1-yl-1,2-dihydroquinolin-6-yl]benzoic acid; 4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-(methyloxy)-6-[4-(methylsulfonyl)phenyl]quinolin-2(1H)-one; 4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-8-methylquinolin-2(1H)-one; 4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6,7-difluoroquinolin-2(1H)-one; 3-(1H-benzimidazol-2-yl)-6-methyl-4-(piperidin-3-ylamino)quinolin-2(1H)-one; 4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-[2-(methyloxy)phenyl]quinolin-2(1H)-one; 4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-[3-(methyloxy)phenyl]quinolin-2(1H)-one; 3-(1H-benzimidazol-2-yl)-6,7-difluoro-4-(piperidin-4-ylamino)quinolin-2(1H)-one; 3-(1H-benzimidazol-2-yl)-6,7-difluoro-4-(pyrrolidin-3-ylamino)quinolin-2(1H)-one; 3-(1H-benzimidazol-2-yl)-6-chloro-4-[(3-morpholin-4-ylpropyl)amino]quinolin-2(1H)-one; 6-chloro-3-(5-morpholin-4-yl-

1H-benzimidazol-2-yl)-4-(piperidin-4-ylamino)quinolin-2(1H)-one; 6-chloro-3-(5-morpholin-4-yl-1H-benzimidazol-2-yl)-4-[(piperidin-2-ylmethyl)amino]quinolin-2(1H)-one; 4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-6-chloro-3-(5-morpholin-4-yl-1H-benzimidazol-2-yl)quinolin-2(1H)-one; 6-chloro-3-(5-morpholin-4-yl-1H-benzimidazol-2-yl)-4-(piperidin-3-ylamino)quinolin-2(1H)-one; 6-chloro-4-{[2-(dimethylamino)ethyl]amino}-3-(5-morpholin-4-yl-1H-benzimidazol-2-yl)quinolin-2(1H)-one; 4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-6-chloro-3-(5-morpholin-4-yl-1H-benzimidazol-2-yl)quinolin-2(1H)-one; 6-chloro-3-(5-morpholin-4-yl-1H-benzimidazol-2-yl)-4-[(piperidin-3-ylmethyl)amino]quinolin-2(1H)-one; 6-chloro-3-(5-morpholin-4-yl-1H-benzimidazol-2-yl)-4-[(piperidin-4-ylmethyl)amino]quinolin-2(1H)-one; 4-{[(1R,2R)-2-aminocyclohexyl]amino}-6-chloro-3-(5-morpholin-4-yl-1H-benzimidazol-2-yl)quinolin-2(1H)-one; 4-[(4-aminocyclohexyl)amino]-6-chloro-3-(5-morpholin-4-yl-1H-benzimidazol-2-yl)quinolin-2(1H)-one; 4-{[(2S)-2-amino-3-methylbutyl]amino}-6-chloro-3-(5-morpholin-4-yl-1H-benzimidazol-2-yl)quinolin-2(1H)-one; 4-({[4-(aminomethyl)phenyl]methyl}amino)-6-chloro-3-(5-morpholin-4-yl-1H-benzimidazol-2-yl)quinolin-2(1H)-one; 6-chloro-3-(5-morpholin-4-yl-1H-benzimidazol-2-yl)-4-[(pyrrolidin-2-ylmethyl)amino]quinolin-2(1H)-one; 4-{[(1R)-1-(aminomethyl)propyl]amino}-6-chloro-3-(5-morpholin-4-yl-1H-benzimidazol-2-yl)quinolin-2(1H)-one; 4-{[(1S)-2-amino-1-(phenylmethyl)ethyl]amino}-6-chloro-3-(5-morpholin-4-yl-1H-benzimidazol-2-yl)quinolin-2(1H)-one; 6-chloro-4-{[3-(4-methylpiperazin-1-yl)propyl]amino}-3-(5-morpholin-4-yl-1H-benzimidazol-2-yl)quinolin-2(1H)-one; 6-chloro-3-(5-morpholin-4-yl-1H-benzimidazol-2-yl)-4-{[1-(phenylmethyl)piperidin-4-yl]amino}quinolin-2(1H)-one; 6-chloro-3-(5-morpholin-4-yl-1H-benzimidazol-2-yl)-4-[(3-morpholin-4-ylpropyl)amino]quinolin-2(1H)-one; 6-chloro-3-(5-morpholin-4-yl-1H-benzimidazol-2-yl)-4-[(2-piperidin-1-ylethyl)amino]quinolin-2(1H)-one; 6-chloro-3-(5-morpholin-4-yl-1H-benzimidazol-2-yl)-4-[(pyridin-3-ylmethyl)amino]quinolin-2(1H)-one; 6-chloro-4-{[3-(1H-imidazol-1-yl)propyl]amino}-3-(5-morpholin-4-yl-1H-benzimidazol-2-yl)quinolin-2(1H)-one; 6-chloro-3-(5-morpholin-4-yl-1H-benzimidazol-2-yl)-4-[(pyridin-4-ylmethyl)amino]quinolin-2(1H)-one; 6-chloro-4-{[2-(methylamino)ethyl]amino}-

3-(5-morpholin-4-yl-1H-benzimidazol-2-yl)quinolin-2(1H)-one; 6-chloro-4-{[(2-methyl-1-piperidin-4-yl-1H-benzimidazol-5-yl)methyl]amino}-3-(5-morpholin-4-yl-1H-benzimidazol-2-yl)quinolin-2(1H)-one; 6-chloro-3-(5-morpholin-4-yl-1H-benzimidazol-2-yl)-4-[(2-pyrrolidin-1-ylethyl)amino]quinolin-2(1H)-one; 6-chloro-3-(5-morpholin-4-yl-1H-benzimidazol-2-yl)-4-(pyrrolidin-3-ylamino)quinolin-2(1H)-one; 4-{[(1R,2R)-2-aminocyclohexyl]amino}-6-chloro-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one; 4-[(4-aminocyclohexyl)amino]-6-chloro-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one; 4-({[4-(aminomethyl)phenyl]methyl}amino)-6-chloro-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one; 6-chloro-4-{[2-(methylamino)ethyl]amino}-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one; 6-chloro-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-4-{[3-(4-methylpiperazin-1-yl)propyl]amino}quinolin-2(1H)-one; 6-chloro-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-4-{[1-(phenylmethyl)piperidin-4-yl]amino}quinolin-2(1H)-one; 6-chloro-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-4-[(2-pyrrolidin-1-ylethyl)amino]quinolin-2(1H)-one; 6-chloro-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-4-(pyrrolidin-3-ylamino)quinolin-2(1H)-one; 6-chloro-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-4-(piperidin-4-ylamino)quinolin-2(1H)-one; 6-chloro-3-(5-morpholin-4-yl-1H-benzimidazol-2-yl)-4-[(2-piperidin-2-ylethyl)amino]quinolin-2(1H)-one; 4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-7-chloro-3-(5-morpholin-4-yl-1H-benzimidazol-2-yl)quinolin-2(1H)-one; 7-chloro-3-(5-morpholin-4-yl-1H-benzimidazol-2-yl)-4-(piperidin-3-ylamino)quinolin-2(1H)-one; 6-chloro-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-4-[(piperidin-2-ylmethyl)amino]quinolin-2(1H)-one; 6-chloro-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-4-{[(2S)-pyrrolidin-2-ylmethyl]amino}quinolin-2(1H)-one; 6-chloro-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-4-{[(2R)-pyrrolidin-2-ylmethyl]amino}quinolin-2(1H)-one; 6-chloro-4-({[(2S)-1-ethylpyrrolidin-2-yl]methyl}amino)-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one; 6-chloro-4-({[(2R)-1-ethylpyrrolidin-2-yl]methyl}amino)-3-[5-(4-

methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one; 4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-[4-(methyloxy)phenyl]quinolin-2(1H)-one; and 6-(3-aminophenyl)-4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)quinolin-2(1H)-one. In some embodiments, the invention provides: a method of inhibiting a serine/threonine kinase or a tyrosine kinase, the tyrosine kinase selected from Fyn, Lck, c-Kit, c-ABL, p60src, FGFR3, VEGFR3, PDGFRα, PDGFRβ, FLT-3, or Tie-2; a method of treating a biological condition mediated by a serine/threonine kinase or a tyrosine kinase, the tyrosine kinase selected from Fyn, Lck, c-Kit, c-ABL, p60src, FGFR3, VEGFR3, PDGFRα, PDGFRβ, FLT-3, or Tie-2; and the use in the manufacture of a medicament for inhibiting, or treating a biological condition mediated by, a serine/threonine kinase or a tyrosine kinase, the tyrosine kinase selected from Fyn, Lck, c-Kit, c-ABL, p60src, FGFR3, VEGFR3, PDGFRα, PDGFRβ, FLT-3, or Tie-2. In such embodiments, the compound is selected from one of the above-listed compounds, a tautomer of the compound, a pharmaceutically acceptable salt of the compound, a pharmaceutically acceptable salt of the tautomer, an enantiomer or diastereomer of the compound, an enantiomer or diastereomer of the tautomer, an enantiomer or diastereomer of the pharmaceutically acceptable salt of the compound, an enantiomer or diastereomer of the pharmaceutically acceptable salt of the tautomer, or a mixture of the compounds, enantiomers, tautomers, or salts. In some such embodiments, the invention provides the compound, the tautomer of the compound, the pharmaceutically acceptable salt of the compound, or the pharmaceutically acceptable salt of the tautomer, or mixtures thereof. The invention further provides methods for inhibiting any of the serine/threonine kinases described herein utilizing these compounds and methods of treating biological conditions mediated by any of the serine/threonine kinases utilizing these compounds.

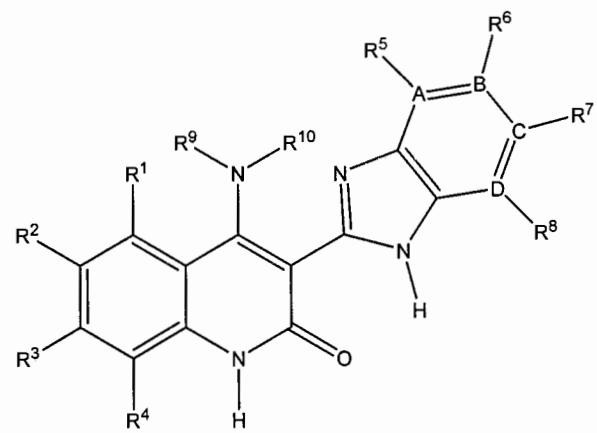
[0933] All documents or references cited herein are hereby incorporated by reference in their entireties and for all purposes as if fully set forth herein.

[0934] It is understood that the invention is not limited to the embodiments set forth herein for illustration, but embraces all such forms thereof as come within the scope of the following claims.

CLAIMS

What is claimed is:

1. Use of a compound, a pharmaceutically acceptable salt of the compound, a pharmaceutically acceptable salt of the tautomer, or a mixture thereof in the preparation of a medicament for inhibiting fibroblast growth factor receptor 3 in a subject or treating a biological condition mediated by fibroblast growth factor receptor 3 in a subject wherein the biological condition is multiple myeloma, the subject is a multiple myeloma patient, and the multiple myeloma expresses fibroblast growth factor receptor 3 and further wherein Structure I has the following formula and fibroblast growth factor receptor 3 is inhibited in the subject after administration of the compound of Structure I, the tautomer of the compound, the pharmaceutically acceptable salt of the compound, the pharmaceutically acceptable salt of the tautomer, or the mixture thereof



I

wherein,

A, B, C, and D are independently selected from the group consisting of carbon and nitrogen;

R^1 is selected from the group consisting of -H, -F, -Cl, -Br, -I, -CN, $-NO_2$, substituted and unsubstituted alkyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted alkenyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted aryl groups, substituted and unsubstituted aralkyl groups,

substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted heterocyclylalkyl groups, -SH, substituted and unsubstituted -S-alkyl groups, substituted and unsubstituted -S-heterocyclyl groups, -OH, substituted and unsubstituted alkoxy groups, substituted and unsubstituted heterocyclyloxy groups, substituted and unsubstituted heterocyclylalkoxy groups, $-NH_2$, substituted and unsubstituted -N(H)(alkyl) groups, substituted and unsubstituted $-N(alkyl)_2$ groups, substituted and unsubstituted -N(H)(heterocyclyl) groups, substituted and unsubstituted -N(alkyl)(heterocyclyl) groups, substituted and unsubstituted $-N(heterocyclyl)_2$ groups, substituted and unsubstituted -N(H)(heterocyclylalkyl) groups, substituted and unsubstituted -N(alkyl)(heterocyclylalkyl) groups, substituted and unsubstituted $-N(heterocyclylalkyl)_2$ groups, substituted and unsubstituted -N(H)-C(=O)-alkyl groups, substituted and unsubstituted -N(H)-C(=O)-heterocyclyl groups, substituted and unsubstituted -N(H)-C(=O)-heterocyclylalkyl groups, substituted and unsubstituted $-N(alkyl)-S(=O)_2$-alkyl groups, substituted and unsubstituted $-N(alkyl)-S(=O)_2$-heterocyclyl groups, substituted and unsubstituted $-N(alkyl)-S(=O)_2$-heterocyclylalkyl groups, substituted and unsubstituted -C(=O)-alkyl groups, substituted and unsubstituted -C(=O)-heterocyclyl groups, substituted and unsubstituted -C(=O)-heterocyclylalkyl groups, $-C(=O)-NH_2$, substituted and unsubstituted -C(=O)-N(H)(alkyl) groups, substituted and unsubstituted $-C(=O)-N(alkyl)_2$ groups, substituted and unsubstituted -C(=O)-N(H)(heterocyclyl) groups, substituted and unsubstituted -C(=O)-N(alkyl)(heterocyclyl) groups, substituted and unsubstituted $-C(=O)-N(heterocyclyl)_2$ groups, substituted and

unsubstituted -C(=O)-N(H)(heterocyclylalkyl) groups, substituted and
unsubstituted -C(=O)-N(alkyl)(heterocyclylalkyl) groups, substituted and unsubstituted -C(=O)-N(heterocyclylalkyl)$_2$ groups, -CO_2H, substituted and unsubstituted -C(=O)-O-alkyl groups, substituted and unsubstituted -C(=O)-O-heterocyclyl groups, and substituted and
unsubstituted -C(=O)-O-heterocyclylalkyl groups;

R^2 and R^3 are independently selected from the group consisting of -H, -F, -Cl, -Br, -I, -NO_2, -CN, substituted and unsubstituted alkyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted alkenyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted aryl groups, substituted and unsubstituted aralkyl groups, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted heterocyclylalkyl groups, -SH, substituted and unsubstituted -S-alkyl groups, substituted and unsubstituted -S(=O)$_2$-O-alkyl groups, substituted and unsubstituted -S(=O)$_2$-alkyl groups, substituted and unsubstituted -S(=O)$_2$-heterocyclyl groups, -S(=O)$_2$-NH_2, substituted and unsubstituted -S(=O)$_2$-N(H)(alkyl) groups, substituted and unsubstituted -S(=O)$_2$-N(alkyl)$_2$ groups, substituted and unsubstituted -S(=O)-alkyl groups, substituted and unsubstituted -S(=O)-heterocyclyl groups, -OH, substituted and unsubstituted alkoxy groups, substituted and unsubstituted aryloxy groups, substituted and unsubstituted heterocyclyloxy groups, substituted and unsubstituted heterocyclylalkoxy groups, -NH_2, substituted and unsubstituted -N(H)(alkyl) groups, substituted and unsubstituted -N(alkyl)$_2$ groups, substituted and unsubstituted -N(H)(aryl) groups, substituted and unsubstituted -N(alkyl)(aryl) groups, substituted and unsubstituted -N(aryl)$_2$ groups, substituted and

unsubstituted -N(H)(aralkyl) groups, substituted and unsubstituted -N(alkyl)(aralkyl) groups, substituted and unsubstituted -N(aralkyl)$_2$ groups, substituted and unsubstituted -N(H)(heterocyclyl) groups, substituted and unsubstituted -N(alkyl)(heterocyclyl) groups, substituted and unsubstituted -N(heterocyclyl)$_2$ groups, substituted and unsubstituted -N(H)(heterocyclylalkyl) groups, substituted and unsubstituted -N(alkyl)(heterocyclylalkyl) groups, substituted and unsubstituted -N(heterocyclylalkyl)$_2$ groups, substituted and unsubstituted -N(H)-C(=O)-alkyl groups, substituted and unsubstituted -N(alkyl)-C(=O)-alkyl groups, substituted and unsubstituted -N(H)-C(=O)-aryl groups, substituted and unsubstituted -N(alkyl)-C(=O)-aryl groups, substituted and unsubstituted -N(H)-C(=O)-aralkyl groups, substituted and unsubstituted -N(alkyl)-C(=O)-aralkyl groups, substituted and unsubstituted -N(H)-C(=O)-heterocyclyl groups, substituted and unsubstituted -N(alkyl)-C(=O)-heterocyclyl groups, substituted and unsubstituted -N(H)-C(=O)-heterocyclylalkyl groups, substituted and unsubstituted -N(alkyl)-C(=O)-heterocyclylalkyl groups, substituted and unsubstituted -N(H)-S(=O)$_2$-alkyl groups, substituted and unsubstituted -N(H)-S(=O)$_2$-aryl, substituted and unsubstituted -N(H)-S(=O)$_2$-heterocyclyl groups, substituted and unsubstituted -C(=O)-alkyl groups, substituted and unsubstituted -C(=O)-aryl, substituted and unsubstituted -C(=O)-aralkyl, substituted and unsubstituted -C(=O)-heterocyclyl groups, substituted and unsubstituted -C(=O)-heterocyclylalkyl groups, -C(=O)-NH$_2$, substituted and unsubstituted -C(=O)-N(H)(alkyl) groups, substituted and unsubstituted -C(=O)-N(alkyl)$_2$ groups, substituted and unsubstituted -C(=O)-N(H)(aryl) groups, substituted and unsubstituted -C(=O)-N(alkyl)(aryl) groups,

substituted and unsubstituted -C(=O)-N(aryl)$_2$ groups, substituted and unsubstituted -C(=O)-N(H)(aralkyl) groups, substituted and unsubstituted -C(=O)-N(alkyl)(aralkyl) groups, substituted and unsubstituted -C(=O)-N(aralkyl)$_2$ groups, substituted and unsubstituted -C(=O)-N(H)(heterocyclyl) groups, substituted and unsubstituted -C(=O)-N(alkyl)(heterocyclyl) groups, substituted and unsubstituted -C(=O)-N(heterocyclyl)$_2$ groups, substituted and unsubstituted -C(=O)-N(H)(heterocyclylalkyl) groups, substituted and unsubstituted -C(=O)-N(alkyl)(heterocyclylalkyl) groups, substituted and unsubstituted -C(=O)-N(heterocyclylalkyl)$_2$ groups, -CO_2H, substituted and unsubstituted -C(=O)-O-alkyl groups, C(=O)-O-aryl groups -C(=O)-O-aralkyl groups, substituted and unsubstituted -C(=O)-O-heterocyclyl groups, and substituted and unsubstituted -C(=O)-O-heterocyclylalkyl groups;

R^4 is selected from the group consisting of –H and substituted and unsubstituted alkyl groups having from 1 to 12 carbon atoms;

R^5 and R^8 are independently selected from the group consisting of -H, -F, -Cl, -Br, -I, -CN, -NO_2, substituted and unsubstituted alkyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted alkenyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted heterocyclylalkyl groups, -OH, substituted and unsubstituted alkoxy groups, substituted and unsubstituted heterocyclyloxy groups, substituted and unsubstituted heterocyclylalkoxy groups; or R^5 may be absent if A is nitrogen; or R^8 may be absent if D is nitrogen;

R^6 and R^7 are independently selected from the group consisting of -H, -F, -Cl, -Br, -I, -CN, -NO_2, substituted and unsubstituted alkyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted alkenyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted aryl groups, substituted and unsubstituted arylakyl groups, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted heterocyclylalkyl groups, -SH, substituted and unsubstituted -S-alkyl groups, substituted and unsubstituted -S-heterocyclyl groups, -$S(=O)_2$-NH_2, substituted and unsubstituted -$S(=O)_2$-N(H)(alkyl) groups, substituted and unsubstituted -$S(=O)_2$-$N(alkyl)_2$ groups, -OH, substituted and unsubstituted alkoxy groups, substituted and unsubstituted heterocyclyloxy groups, substituted and unsubstituted heterocyclylalkoxy groups, -NH_2, substituted and unsubstituted -N(H)(alkyl) groups, substituted and unsubstituted -$N(alkyl)_2$ groups, substituted and unsubstituted -N(H)(heterocyclyl) groups, substituted and unsubstituted -N(alkyl)(heterocyclyl) groups, substituted and unsubstituted -$N(heterocyclyl)_2$ groups, substituted and unsubstituted -N(H)(heterocyclylalkyl) groups, substituted and unsubstituted -N(alkyl)(heterocyclylalkyl) groups, substituted and unsubstituted -$N(heterocyclylalkyl)_2$ groups, substituted and unsubstituted -N(H)-C(=O)-alkyl groups, substituted and unsubstituted -N(H)-C(=O)-heterocyclyl groups, substituted and unsubstituted -N(H)-C(=O)-heterocyclylalkyl groups, substituted and unsubstituted -N(alkyl)-C(=O)-alkyl groups, substituted and unsubstituted -N(alkyl)-C(=O)-heterocyclyl groups, substituted and unsubstituted -N(alkyl)-C(=O)-heterocyclylalkyl, substituted and unsubstituted -N(H)-$S(=O)_2$-alkyl groups, substituted and unsubstituted -N(H)-$S(=O)_2$-heterocyclyl groups, substituted

and unsubstituted -N(H)-S(=O)$_2$-heterocyclylalkyl groups, substituted and unsubstituted -C(=O)-alkyl groups, substituted and unsubstituted -C(=O)-heterocyclyl groups, substituted and unsubstituted -C(=O)-heterocyclylalkyl groups, -C(=O)-NH$_2$, substituted and unsubstituted -C(=O)-N(H)(alkyl) groups, substituted and unsubstituted -C(=O)-N(alkyl)$_2$ groups, substituted and unsubstituted -C(=O)-N(H)(heterocyclyl) groups, substituted and unsubstituted -C(=O)-N(alkyl)(heterocyclyl) groups, substituted and unsubstituted -C(=O)-N(heterocyclyl)$_2$ groups, substituted and unsubstituted -C(=O)-N(H)(heterocyclylalkyl) groups, substituted and unsubstituted -C(=O)-N(alkyl)(heterocyclylalkyl) groups, substituted and unsubstituted -C(=O)-N(heterocyclylalkyl)$_2$ groups, -CO$_2$H, substituted and unsubstituted -C(=O)-O-alkyl groups, substituted and unsubstituted -C(=O)-O-heterocyclyl groups, and substituted and unsubstituted -C(=O)-O-heterocyclylalkyl groups; or R^6 is absent if B is nitrogen; or R^7 is absent if C is nitrogen;

R^9 is selected from the group consisting of -H, substituted and unsubstituted alkyl groups having from 1 to 12 carbon atoms, substituted and unsubstituted alkenyl groups having from 1 to 12 carbons, substituted and unsubstituted aryl groups, substituted and unsubstituted aralkyl groups, substituted and unsubstituted heterocyclyl groups, substituted and unsubstituted heterocyclylalkyl groups, -OH, substituted and unsubstituted alkoxy groups, substituted and unsubstituted heterocyclyloxy groups, -NH$_2$, and substituted and unsubstituted heterocyclylaminoalkyl; and

R^{10} is -H.

2. The use of claim 1, wherein A, B, C, and D are all carbon.

3. The use of claim 2, wherein R^9 is H.

4. The use of claim 3, wherein R^1 is selected from -H, -F, -Cl, -Br, -I, substituted or unsubstituted straight or branched chain alkyl groups having from 1 to 8 carbon atoms, substituted or unsubstituted cycloalkyl groups, substituted or unsubstituted heterocyclyl groups, substituted or unsubstituted heterocyclylalkyl groups, substituted or unsubstituted alkoxy groups, substituted or unsubstituted heterocyclyloxy groups, or substituted or unsubstituted heterocyclylalkoxy groups.

5. The use of claim 3, wherein R^1 is F.

6. The use of claim 3, wherein R^2 is selected from –H, -Cl, -F, -Br, -I, $-NO_2$, -CN, substituted or unsubstituted straight or branched chain alkyl having from 1 to 8 carbons, substituted or unsubstituted phenyl groups, substituted or unsubstituted thiophene groups, substituted or unsubstituted 1,2,3,6-tetrahydropyridinyl groups, substituted or unsubstituted pyridinyl groups, substituted or unsubstituted straight or branched chain alkoxy groups, substituted or unsubstituted pyridinylalkoxy groups, substituted or unsubstituted dialkylamino groups, or $-CO_2H$.

7. The use of claim 3, wherein R^2 is H.

8. The use of claim 3, wherein R^3 is selected from -H, -F, -Cl, -Br, methoxy, or dimethylamino groups.

9. The use of claim 3, wherein R^3 is H or R^4 is H.

10. The use of claim 3, wherein R^5 is H and R^8 is H.

11. The use of claim 3, wherein at least one of R^6 or R^7 is a substituted or unsubstituted heterocyclyl group.

12. The use of claim 11, wherein one of R^6 or R^7 is a substituted or unsubstituted heterocyclyl group and the heterocyclyl group is selected from morpholine, piperazine, piperidine, pyrrolidine, thiomorpholine, homopiperazine, tetrahydrothiophene, tetrahydrofuran, or tetrahydropyran.

13. The use of claim 11, wherein one of R^6 or R^7 is selected from substituted or unsubstituted morpholine groups, or substituted or unsubstituted piperazine groups.

14. The use of claim 11, wherein one of R^6 or R^7 is an N-alkyl substituted piperazine.

15. The use of claim 11, wherein one of R^6 or R^7 is N-methyl piperazine.

16. The use of claim 3, wherein one of R^6 or R^7 is an N-alkyl substituted piperazine and the other of R^6 or R^7 is H, and further wherein R^5 and R^8 are both H.

17. The use of claim 1, wherein the biological condition is multiple myeloma and the subject is a multiple myeloma patient with a t(4;14) chromosomal translocation.

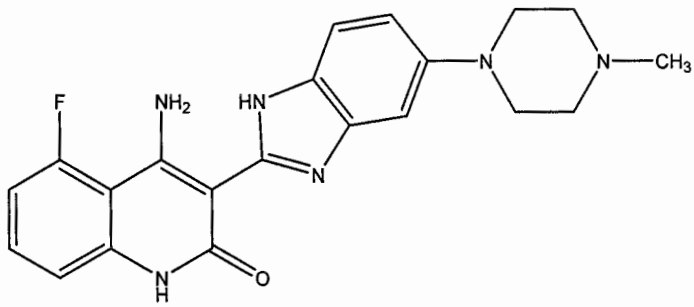
18. The use of claim 1, wherein the subject is a multiple myeloma patient having multiple myeloma cells, and further wherein apoptotic cell death is induced in the multiple myeloma cells after administration of the compound of Structure I, the tautomer of the compound, the pharmaceutically acceptable salt of the compound, the

pharmaceutically acceptable salt of the tautomer, or the mixture thereof to the subject.

19. The use of claim 1, wherein osteolytic bone loss is reduced in the subject after administration of the compound of Structure I, the tautomer of the compound, the pharmaceutically acceptable salt of the compound, the pharmaceutically acceptable salt of the tautomer, or the mixture thereof to the subject.

20. The use of claim 1, wherein the lactate salt of the compound of Structure I or the tautomer thereof is administered to the subject.

21. The use of claim 1, wherein the compound of Structure I has the following formula



22. The use of claim 21, wherein the biological condition is multiple myeloma and the subject is a multiple myeloma patient with a t(4;14) chromosomal translocation.

23. The use of claim 21, wherein the subject is a multiple myeloma patient having multiple myeloma cells, and further wherein apoptotic cell death is induced in the multiple myeloma cells after administration of the compound of Structure I, the tautomer of the compound, the pharmaceutically acceptable salt of the compound, the pharmaceutically acceptable salt of the tautomer, or the mixture thereof to the subject.

24. The use of claim 21, wherein osteolytic bone loss is reduced in the subject after administration of the compound of Structure I, the tautomer of the compound, the pharmaceutically acceptable salt of the compound, the pharmaceutically acceptable salt of the tautomer, or the mixture thereof to the subject.

25. The use of claim 22, wherein the lactate salt of the compound of Structure I or the tautomer thereof is administered to the subject.