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(54) Benævnelse: **6-O-Substituerede benzoxazol og benzothiazolforbindelser og fremgangsmåder til en inhibering af CSF-1R-signalering**

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DESCRIPTION

Field of the Invention

[0001] The present invention relates to 6-O-substituted benzoxazole and benzothiazole compounds, as defined herein, their tautomers, stereoisomers, solvates, oxides, and to the pharmaceutically acceptable salts thereof. This invention also relates to compositions of the compounds together with pharmaceutically acceptable carriers. In another aspect, this invention relates to uses of the compounds, either alone or in combination with at least one additional therapeutic agent, in the prophylaxis or treatment of cancer.

State of the Art

[0002] CSF-1R is the receptor for M-CSF (macrophage colony stimulating factor, also called CSF-1) and mediates the biological effects of this cytokine (Sherr 1985). The cloning of the colony stimulating factor-1 receptor (also called c-fms) was described for the first time in Roussel et al., Nature 325:549-552 (1987). In that publication, it was shown that CSF-1R had transforming potential dependent on changes in the C-terminal tail of the protein including the loss of the inhibitory tyrosine 969 phosphorylation which binds Cbl and thereby regulates receptor down regulation (Lee1999).

[0003] CSF-1R is a single chain, transmembrane receptor tyrosine kinase (RTK) and a member of the family of immunoglobulin (Ig) motif containing RTKs characterized by repeated Ig domains in the extracellular portion of the receptor. The intracellular protein tyrosine kinase domain is interrupted by a unique insert domain that is also present in the other related RTK class III family members that include the platelet derived growth factor receptors (PDGFR), stem cell growth factor receptor (c-Kit) and fins-like cytokine receptor (FLT3). In spite of the structural homology among this family of growth factor receptors, they have distinct tissue-specific functions. CSF-1R is mainly expressed on cells of the monocytic lineage and in the female reproductive tract and placenta. In addition expression of CSF-1R has been reported in Langerhans cells in skin, a subset of smooth muscle cells (Inaba 1992), B cells (Baker 1993) and microglia (Sawada 1990).

[0004] The main biological effects of CSF-1R signaling are the differentiation, proliferation, migration, and survival of the precursor macrophages and osteoclasts from the monocytic lineage. Activation of CSF-1R is mediated by its only ligand, M-CSF. Binding of M-CSF to CSF-1R induces the formation of homodimers and activation of the kinase by tyrosine phosphorylation (Stanley 1997). Further signaling is mediated by the p85 subunit of PI3K and Grb2 connecting to the PI3K/AKT and Ras/MAPK pathways, respectively. These two important signaling pathways can regulate proliferation, survival and apoptosis. Other signaling molecules that bind the phosphorylated intracellular domain of CSF-1R include STAT1, STAT3, PLCγ, and Cbl (Bourette 2000).

[0005] CSF-1R signaling has a physiological role in immune responses, in bone remodeling and in the reproductive system. The knockout animals for either M-CSF-1 (op/op mouse; Pollard 1996) or CSF-1R (Dai 2002) have been shown to have osteopetrotic, hematopoietic, tissue macrophage, and reproductive phenotypes consistent with a role for CSF-1R in the respective cell types.

[0006] The recent success of targeted therapeutics, such as Herceptin® and Avastin®, has underscored the importance in developing "cleaner" less promiscuous drugs with a more specific mechanism of action. These drugs can minimize adverse events, have greater predictability, give physicians greater flexibility in their treatments, and provide researchers with a better understanding of a particular target. Additionally, targeted therapy may allow treatment of multiple indications affected by the same signaling pathway with fewer and potentially easier to manage toxicities. (BioCentury, V. 14(10) Feb, 2006) Inhibition of an individual kinase, such as CSF-1R, which is integrated within a pathway associated with cancer or other diseases, can effectively modulate downstream kinases as well, thereby affecting the entire pathway. However, the active sites of 491 human protein kinase domains are highly conserved, which makes the design of selective inhibitors a formidable challenge (Cohen 2005). For example (WO2005/073224) discloses compounds that are effective for prophylaxis and treatment of HGF mediated diseases, for example diseases and other maladies or conditions involving, cancer and the like.

SUMMARY OF THE INVENTION

[0007] A continuing need exists for compounds that inhibit cellular proliferation, inhibit the growth of tumors, treat cancer, modulate cell cycle arrest, and/or specifically inhibit molecules such as CSF-1R, and for pharmaceutical formulations and medicaments that contain such compounds. A need also exists for selective CSF-1R inhibitory compounds. A need also exists for compounds for use in methods of administering such compounds, pharmaceutical formulations, and medicaments to patients or subjects in need thereof.

[0008] One embodiment is directed to compounds selected from the group defined in claim 1, stereoisomers, tautomers, solvates, oxides, or pharmaceutically acceptable salts thereof.

[0009] Another embodiment is directed to the compound defined in claim 2 or a solvate, oxide, or pharmaceutically acceptable salts thereof.

[0010] Another embodiment is directed to the compound defined in claim 3 or a solvate, oxide, or pharmaceutically acceptable salts thereof.

[0011] Another embodiment is directed to the compound defined in claim 4 or a solvate, oxide, or pharmaceutically acceptable salts thereof.

[0012] Also disclosed is a CSR-1R inhibitory compound selected from the group defined in claim 1 or a stereoisomer, tautomer, solvate, or oxide, or pharmaceutically acceptable salt thereof for use in the treatment of a a CSF-1R mediated disorder as herein defined.

[0013] In a more particular embodiment said compound does not substantially inhibit Raf kinase. In a more particular embodiment said compound preferentially inhibits CSF-1R over Raf kinase. In a more particular embodiment said compound inhibits Raf kinase at an IC_{50} of greater than about 1 µM. In a more particular embodiment said compound inhibits CSF-1R at an IC_{50} of at less than about 1 µM. More particular still, said compound inhibits CSF-1R at an IC_{50} of at less than about 0.1 µM.

DETAILED DESCRIPTION

[0014] Throughout this application, the text refers to various embodiments of the present compounds, compositions and uses.

Definitions

[0015] Unless specifically defined otherwise, the terms used herein are defined below.

[0016] "Oxide" refers to products resulting from the oxidation of one or more heteroatoms. Examples include N-oxides, sulfoxides, and sulfones."Solvate" or "solvates" refer compounds or a salt thereof that are bound to a stoichiometric or non-stoichiometric amount of a solvent. Preferred solvents are volatile, non-toxic, and/or acceptable for administration to humans in trace amounts. Suitable solvates include water.

[0017] "Stereoisomer" or "stereoisomers" refer to compounds that differ in the chirality of one or more stereocenters. Stereoisomers include enantiomers and diastereomers.

[0018] "Tautomer" refer to alternate forms of a compound that differ in the position of a proton, such as enol-keto and imine-enamine tautomers, or the tautomeric forms of heteroaryl groups containing a ring atom attached to both a ring -NH- moiety and a ring =N-moeity such as pyrazoles, imidazoles, benzimidazoles, triazoles, and tetrazoles.

[0019] "Pharmaceutically acceptable salt" refers to pharmaceutically acceptable salts of a compound, which salts are derived from a variety of organic and inorganic counter ions well known in the art and include, by way of example only, sodium, potassium, calcium, magnesium, ammonium, and tetraalkylammonium; and when the molecule contains a basic functionality, salts of organic or inorganic acids, such as hydrochloride, hydrobromide, tartrate, mesylate, acetate, maleate, and oxalate. The term also includes pharmaceutically acceptable salts of stereoisomers, tautomers, of the compound.

[0020] "Patient" refers to mammals and includes humans and non-human mammals.

[0021] "Treating" or "treatment" of a disease in a patient refers to 1) preventing the disease from occurring in a patient that is predisposed or does not yet display symptoms of the disease; 2) inhibiting the disease or arresting its development; or 3) ameliorating or causing regression of the disease.

[0022] "Selective" inhibition, refers to a compound, composition, or chemotype that preferentially inhibits a particular target or class of targets. Reference to "selective inhibition of CSF-1R" indicates the preferential inhibition of CSF-1R and optionally like kinase receptors such as PDGFR. In some embodiments, selective inhibition of CSF-1R refers to preferential inhibition of CSF-1R over Raf kinase. "Selective," "targeted," "specific," or "preferential" inhibition is not intended to mean complete absence of inhibitory activity with respect to all other kinases or receptors.

[0023] "CSF-1R inhibitor" refers to a compound that can inhibit CSF-1R. Preferably, a CSF-1R inhibitor is selective of CSF-IR over other targets. In an embodiment, a CSF-1R inhibitor has selective inhibition of CSF-1R over Raf kinase. In a preferred embodiment, such selective inhibition refers to at least a 2:1 binding preference of a compound of this invention to CSF-1R relative to Raf kinase, more preferably at least 5:1, and even more preferably at least 10:1.

[0024] One embodiment is directed to the compounds selected from the group defined in claim 1 stereoisomers, tautomers, solvates, or oxides, or pharmaceutically acceptable salts thereof.

[0025] Another embodiment is directed to the compound defined in claim 2 or a solvate, oxide, or pharmaceutically acceptable salts thereof.

[0026] Another embodiment is directed to the compound defined in claim 3 or asolvate, oxide, or pharmaceutically acceptable salts thereof.

[0027] Another embodiment is directed to the compound defined in claim 4 or a solvate, oxide, or pharmaceutically acceptable salts thereof.

[0028] In other embodiments, provided is a compound of Table 2 or 3 or a stereoisomer, tautomer, solvate, oxide, or pharmaceutically acceptable salt thereof.

[0029] It will also be apparent to those skilled in the art that the compounds of the invention according to any one of claims 1 to 4 or their stereoisomers, as well as the pharmaceutically acceptable salts, may be subject to tautomerization and may therefore exist in various tautomeric forms wherein a proton of one atom of a molecule shifts to another atom and the chemical bonds between the atoms of the molecules are consequently rearranged. See, e.g., March, Advanced Organic Chemistry: Reactions, Mechanisms and Structures, Fourth Edition, John Wiley & Sons, pages 69-74 (1992).

[0030] Preferred embodiments, including the compounds according to any one of claims 1 to 4 or their tautomers, as well as the pharmaceutically acceptable salts, may comprise asymmetrically substituted carbon atoms. Such asymmetrically substituted carbon atoms can result in the compounds of preferred embodiments existing in enantiomers, diastereomers, and other stereoisomeric forms that may be defined, in terms of absolute stereochemistry, such as in (R)- or (S)- forms. As a result, all such possible isomers, individual stereoisomers in their optically pure forms, mixtures thereof, racemic mixtures (or "racemates"), mixtures of diastereomers, as well as single diastereomers of the compounds of the preferred embodiments are contemplated. The terms "S" and "R" configuration, as used herein, are as defined by the IUPAC 1974 RECOMMENDATIONS FOR SECTION E, FUNDAMENTAL STEREOCHEMISTRY, Pure Appl. Chem. 45:13-30 (1976). The terms α and β are employed for ring positions of cyclic compounds. The α-side of the reference plane is that side on which the preferred substituent lies at the lower numbered position. Those substituents lying on the opposite side of the reference plane are assigned β descriptor. It should be noted that this usage differs from that for cyclic stereoparents, in which "α" means "below the plane" and denotes absolute configuration. The terms α and β configuration, as used herein, are as defined by the CHEMICAL ABSTRACTS INDEX GUIDE-APPENDIX IV (1987) paragraph 203.

[0031] There are 3 distinct mechanisms by which CSF-1R signaling is likely involved in tumor growth and metastasis. The first is that expression of CSF-ligand and receptor has been found in tumor cells originating in the female reproductive system (breast, ovarian, endometrium, cervical) (Scholl 1994; Kacinski 1997; Nagan 199; Kirma 2007) and the expression has been associated with breast cancer xenograft growth as well as poor prognosis in breast cancer patients. Two point mutations were seen in CSF-1R in about 10-20% of acute myelocytic leukemia, chronic myelocytic leukemia and myelodysplasia patients tested in one study, and one of mutations was found to disrupt receptor turnover (Ridge 1990). However the incidence of the mutations could not be confirmed in later studies (Abu-Duhier 2003). Mutations were also found in some cases of hepatocellular cancer (Yang 2004) and idiopathic myelofibrosis (Abu-Duhier 2003).

[0032] Pigmented villonodular synovitis (PVNS) and Tenosynovial Giant cell tumors (TGCT) can occur as a result of a translocation that fuses the M-CSF gene to a collagen gene COL6A3 and results in overexpression of M-CSF (West 2006). A landscape effect is proposed to be responsible for the resulting tumor mass that consists of monocytic cells attracted by cells that express M-CSF. TGCTs are smaller tumors that can be relatively easily removed from fingers where they mostly occur. PVNS is more aggressive as it can recur in large joints and is not as easily controlled surgically.

[0033] The second mechanism is based on blocking signaling through M-CSF/CSF-1R at metastatic sites in bone which induces osteoclastogenesis, bone resorption and osteolytic bone lesions. Breast, kidney, and lung cancers are examples of cancers that have been found to metastasize to the bone and cause osteolytic bone disease resulting in skeletal complications. M-CSF released by tumor cells and stroma induces the differentiation of hematopoietic myeloid monocyte progenitors to mature osteoclasts in collaboration with the receptor activator of nuclear factor kappa-B ligand-RANKL. During this process, M-CSF acts as a permissive factor by giving the survival signal to osteoclasts (Tanaka 1993). Inhibition of CSF-1R kinase activity during osteoclast differentiation and maturation with a small molecule inhibitor is likely to prevent unbalanced activity of osteoclasts that cause osteolytic disease and the associated skeletal related events in metastatic disease. Whereas breast, lung cancer and multiple myeloma typically result in osteolytic lesions, metastasis to the bone in prostate cancer initially has an osteoblastic appearance in which increased bone forming activity results in 'woven bone' which is different from typical lamellar structure of normal bone. During disease progression bone lesions display a significant osteolytic component as well as high serum levels of bone resorption and suggests that anti-resorptive therapy may be useful. Bisphosphonates have been shown to inhibit the formation of osteolytic lesions and reduced the number of skeletal-related events only in men with hormone-refractory metastatic prostate cancer but at this point their effect on osteoblastic lesions is controversial and bisphosphonates have not been beneficial in preventing bone metastasis or hormone responsive prostate cancer to date. The effect of anti-resorptive agents in mixed osteolytic/osteoblastic prostate cancer is still being studied in the clinic (Choueiri 2006; Vessella 2006).

[0034] The third mechanism is based on the recent observation that tumor associated macrophages (TAM) found in solid tumors of the breast, prostate, ovarian and cervical cancers correlated with poor prognosis (Bingle 2002; Pollard 2004). Macrophages are recruited to the tumor by M-CSF and other chemokines. The macrophages can then contribute to tumor progression through the secretion of angiogenic factors, proteases and other growth factors and cytokines and may be blocked by inhibition of CSF-1R signaling. Recently it was shown by Zins et al (Zins 2007) that expression of siRNA of Tumor necrosis factor alpha (TNFα), M-CSF or the combination of both would reduce tumor growth in a mouse xenograft model between 34% and 50% after intratumoral injection of the respective siRNA the xenograft. SiRNA targeting the TNFalpha secreted by the human SW620 cells reduced the mouse M-CSF and led to reduction of macrophages in the tumor. In addition treatment of MCF7 tumor xenografts with an antigen binding fragment directed against M-CSF antibody did result in 40% tumor growth inhibition, reversed the resistance to chemotherapeutics and improved survival of the mice when given in combination with chemotherapeutics (Paulus 2006).

[0035] TAMs are only one example of an emerging link between chronic inflammation and cancer. There is additional evidence for a link between inflammation and cancer as many chronic diseases are associated with an increased risk of cancer, cancers arise at sites of chronic inflammation, chemical mediators of inflammation are found in many cancers; deletion of the cellular or chemical mediators of inflammation inhibits development of experimental cancers and long-term use of anti-inflammatory agents reduce the risk of some cancers. A link to cancer exists for a number of inflammatory conditions among those *H.pylori* induced gastritis for gastric cancer, Schistosomiasis for bladder cancer, HHV8 for Kaposi's sarcoma, endometriosis for ovarian cancer and prostatitis for prostate cancer (Balkwill 2005).

Macrophages are key cells in chronic inflammation and respond differentially to their microenvironment. There are two types of macrophages that are considered extremes in a continuum of functional states: M1 macrophages are involved in Type 1 reactions. These reactions involve the activation by microbial products and consequent killing of pathogenic microorganisms that result in reactive oxygen intermediates. On the other end of the extreme are M2 macrophages involved in Type 2 reactions that promote cell proliferation, tune inflammation and adaptive immunity and promote tissue remodeling, angiogenesis and repair (Mantovani 2004). Chronic inflammation resulting in established neoplasia is usually associated with M2 macrophages. A pivotal cytokine that mediates inflammatory reactions is TNF-α that true to its name can stimulate anti-tumor immunity and hemorrhagic necrosis at high doses but has also recently been found to be expressed by tumor cells and acting as a tumor promoter (Zins 2007; Balkwill 2006). The specific role of macrophages with respect to the tumor still needs to be better understood including the potential spatial and temporal dependence on their function and the relevance to specific tumor types.

[0036] Also disclosed is a compound as defined in any one of claims 1 to 4 for use in the treatment of periodontitis, histiocytosis X, osteoporosis, Paget's disease of bone (PDB), bone loss due to cancer therapy, periprosthetic osteolysis, glucocorticoid-induced osteoporosis, rheumatoid arthritis, psiratic arthritis, osteoarthritis, inflammatory arthridities, and inflammation.

[0037] Rabello 2006 has demonstrated that SNPs in the CSF1 gene exhibited a positive association with aggressive periodontitis: an inflammatory disease of the periodontal tissues that causes tooth loss due to resorption of the alveolar bone.

[0038] Histiocytosis X (also called Langerhans cell histiocytosis, LCH) is a proliferative disease of Langerhans dendritic cells that appear to differentiate into osteoclasts in bone and extraosseous LCH lesions. Langerhans cells are derived from circulating monocytes (Ginoux 2006). Increased levels of M-CSF that have been measured in sera and lesions where found to correlate with disease severity (da Costa 2005). The disease occurs primarily in a pediatric patient population and has to be treated with chemotherapy when the disease becomes systemic or is recurrent.

[0039] The pathophysiology of osteoporosis is mediated by loss of bone forming osteoblasts and increased osteoclast dependent bone resorption. Supporting data has been described by Cenci et al showing that an anti-M-CSF antibody injection preserves bone density and inhibits bone resorption in ovarectomized mice (Cenci 2000). Recently a potential link between postmenopausal bone loss due to estrogen deficiency was identified and found that the presence of TNF alpha producing T-cell affected bone metabolism (Roggia 2004). A possible mechanism could be the induction of M-CSF by TNF alpha *in vivo*. An important role for M-CSF in TNF-alpha-induced osteoclastogenesis was confirmed by the effect of an antibody directed against the M-CSF-inhibitor that blocked the TNF alpha induced osteolysis in mice and thereby making inhibitors of CSF-1R signaling potential targets for inflammatory arthritis (Kitaura 2005).

[0040] Paget's disease of bone (PDB) is the 2nd most common bone metabolism disorder after osteoporosis in which focal abnormalities of increased bone turnover lead to complications such as bone pain, deformity, pathological fractures, and deafness. Mutations in four genes have been identified that regulate normal osteoclast function and predispose individuals to PDB and related disorders: insertion mutations in TNFRSF11A, which encodes receptor activator of nuclear factor (NF) kappaB (RANK)-a critical regulator of osteoclast function, inactivating mutations of TNFRSF11B which encodes osteoprotegerin (a decoy receptor for RANK ligand), mutations of the sequestosome 1 gene (SQSTM1), which encodes an important scaffold protein in the NFkappaB pathway and mutations in the valosin-containing protein (VCP) gene. This gene encodes VCP, which has a role in targeting the inhibitor of NFkappaB for degradation by the proteasome (Daroszewska, 2006). Targeted CSF-1R inhibitors provide an opportunity to block the deregulation of the RANKL signaling indirectly and add an additional treatment option to the currently used bisphosphonates.

[0041] Cancer therapy induced bone loss especially in breast and prostate cancer patients is an additional indication where a targeted CSF-1R inhibitor could prevent bone loss (Lester 2006).With the improved prognosis for early breast cancer the long-term consequences of the adjuvant therapies become more important as some of the therapies including chemotherapy, irradiation, aromatase inhibitors and ovary ablation affect bone metabolism by decreasing the bone mineral density, resulting in increased risk for osteoporosis and associated fractures (Lester 2006). The equivalent to adjuvant aromatase inhibitor therapy in breast cancer is androgen ablation therapy in prostate cancer which leads to loss of bone mineral density and significantly increases the risk of osteoporosis-related fractures (Stoch 2001).

[0042] Targeted inhibition of CSF-1R signaling is likely to be beneficial in other indications as well when targeted cell types include osteoclasts and macrophages e.g. treatment of specific complications in response to joint replacement as a consequence of rheumatoid arthritis. Implant failure due to periprosthetic bone loss and consequent loosing of protheses is a major complication of joint replacement and requires repeated surgery with high socioeconomic burdens for the individual patient and the health-care system. To date, there is no approved drug therapy to prevent or inhibit periprosthetic osteolysis (Drees 2007).

[0043] Glucocorticoid-induced osteoporosis (GIOP) is another indication in which a CSF-1R inhibitor could prevent bone loss after longterm glucocorticocosteroid use that is given as a result of various conditions among those chronic obstructive pulmonary disease, asthma and rheumatoid arthritis (Guzman-Clark 2007; Feldstein 2005).

[0044] Rheumatoid arthritis, psiratic arthritis and inflammatory arthridities are in itself potential indications for CSF-1R signaling inhibitors in that they consist of a macrophage component a to a varying degree bone destruction (Ritchlin 2003). Osteoarthritis and rheumatoid arthritis are inflammatory autoimmune disease caused by the accumulation of macrophages in the connective tissue and infiltration of macrophages into the synovial fluid, which is at least partially mediated by M-CSF. Campbell et al. (2000) demonstrated that M-CSF is produced by human-joint tissue cells (chondrocytes, synovial fibroblasts) *in vitro* and is found in synovial fluid of patients with rheumatoid arthritis, suggesting that it contributes to the synovial tissue proliferation and macrophage infiltration which is associated with the pathogenesis of the disease. Inhibition of CSF-1R signaling is likely to control the number of macrophages in the joint and alleviate the pain from the associated bone destruction. In order to minimize adverse affects and to further understand the impact of the CSF-1R signaling in these indications, one method is to specifically inhibit CSF-1R without targeting a myriad other kinases, such as Raf kinase.

[0045] Recent literature reports correlate increased circulating M-CSF with poor prognosis and atherosclerotic progression in chronic coronary artery disease (Saitoh 2000; Ikonomidis 2005); M-CSF influences the atherosclerotic process by aiding the formation of foam cells (macrophages with ingested oxidized LDL) that express CSF-1R and represent the initial plaque (Murayama 1999).

[0046] Expression and signaling of M-CSF and CSF-1R is found in activated microglia. Microglia, which are resident macrophages of the central nervous system, can be activated by various insults, including infection and traumatic injury. M-CSF is considered a key regulator of inflammatory responses in the brain and M-CSF levels increase in HIV-1 encephalitis, Alzheimer's disease (AD) and brain tumors. Microgliosis as a consequence of autocrine signaling by M-CSF/CSF-1R results in induction of inflammatory cytokines and nitric oxides being released as demonstrated by e.g. using an experimental neuronal damage model (Hao 2002; Murphy 1998). Microglia that have increased expression of CSF-1R are found to surround plaques in AD and in the amyloid precursor protein V717F transgenic mouse model of AD (Murphy 2000). On the other hand op/op mice with fewer microglia in the brain resulted in fibrilar deposition of Aβ and neuronal loss compared to normal control suggesting that microglia do have a neuroprotective function in the development of AD lacking in the op/op mice (Kaku 2003).

[0047] In one aspect, the disclosure provides a compound according to any one of claims 1 to 4 for the use in the treatment of CSF-1R related disorders in an amount effective to reduce or prevent the disorder. In a preferred embodiment, the disorder is tumor growth and/or metathesis in the subject.

[0048] In other aspects, the disclosure provides a compound according to anyone of claims 1 to 4 for use in the treatment of CSF-1R related disorders in an amount effective to reduce or prevent osteoclastogenesis, bone resorption and/or bone lesions in the subject.

[0049] In yet other aspects, the disclosure provides a compound according to anyone of claims 1 to 4 for use in the treatment of CSF-1R related disorders in an amount effective to treat the disorder in the subject in combination with at least one additional agent. In a more particular embodiment the additional agent is a bisphosphonate. In one embodiment the disorder is tumor growth and/or metastasis, osteoclastogenesis, bone resorption and/or bone lesions

[0050] In yet other aspects, the disclosure provides compounds according to any one of claims 1 to 4 that are capable of selectively or preferentially inhibiting CSF-1R. In preferred embodiments the selective inhibitors of CSF-1R are capable of inhibiting CSF-1R at greater than about 5-fold, or about 10 fold, or about 20 fold, or about 30 fold, or about 50 fold, or about 100 fold, or about 250 fold, or about 500 fold, or about 750 fold, or about 1,000 fold, or about 2,000 the inhibitory activity (with respect to IC_{50} values, for example) in Raf kinase.

[0051] In other aspects the disclosure provides a compound according to anyone of claims 1 to 4 for use in the inhibition of CSF-1R comprising contacting a cell with said compound.

[0052] In one aspect, the inhibitory effect of compounds on Raf is determined using the following biotinylated assay. The Raf kinase activity is measured by providing ATP, a recombinant kinase inactive MEK substrate and assaying the transfer of phosphate moiety to the MEK residue. Recombinant full length MEK with an inactivating K97R ATP binding site mutation (rendering kinase inactive) is expressed in *E. coli* and labelled with biotin post purification. The MEK cDNA is subcloned with an N-terminal $(His)_6$ tag and expressed in E. coli and the recombinant MEK substrate is purified from *E. coli* lysate by nickel affinity chromatography followed by anion exchange. The final MEK substrate preparation is biotinylated (Pierce EZ-Link Sulfo-NHS-LC-Biotin) and concentrated to about 11.25μM. Recombinant Raf (including c-Raf and mutant B-Raf isoforms) is obtained by purification from sf9 insect cells infected with the corresponding human Raf recombinant expression vectors. The recombinant Raf isoforms are purified via a Glu antibody interaction or by Metal Ion Chromatography.

[0053] For each assay, the compound is serially diluted, for instance, starting at 25 μM with 3-fold dilutions, in DMSO and then mixed with various Raf isoforms (about 0.50 nM each). The kinase inactive biotin-MEK substrate (50 nM) is added in reaction buffer plus ATP (1 μM). The reaction buffer contains 30 mM Tris-HCl_2 pH 7.5, 10 mM $MgCl_2$, 2 mM DTT, 4mM EDTA, 25 mM beta-glycerophosphate, 5 mM $MnCl_2$, and 0.01% BSA/PBS. Reactions are subsequently incubated for about 2 hours at room temperature and stopped by the addition of 0.5 M EDTA. Stopped reaction mixture is transferred to a neutradavin-coated plate and incubated for about 1 hour. Phosphorylated product is measured with the DELFIA time-resolved fluorescence system, using a rabbit anti-p-MEK (Cell Signaling) as the primary antibody and europium labeled anti-rabbit as the secondary antibody. Time resolved fluorescence can be read on a Wallac 1232 DELFIA fluorometer. The concentration of the compound for 50% inhibition (IC_{50}) is calculated by non-linear regression using XL Fit data analysis software.

[0054] In yet other aspects, the preferred embodiments provide a compound, tautomer, solvate, oxide, or pharmaceutically acceptable salt thereof according to any one of claims 1 to 4 in an amount effective to reduce or prevent tumor growth in the subject in combination with at least one additional agent for the treatment of cancer. In a more particular embodiment the additional agent is a bisphosphonate.

[0055] A number of suitable anticancer agents to be used as combination therapeutics are contemplated for use as defined herein. Indeed, the preferred embodiments include administration of numerous additional anticancer agents such as, but not limited to, agents that induce apoptosis; polynucleotides (e.g., ribozymes); polypeptides (e.g., enzymes); drugs; biological mimetics; alkaloids; alkylating agents; antitumor antibiotics; antimetabolites; hormones; platinum compounds; monoclonal antibodies conjugated with anticancer drugs, toxins, and/or radionuclides; biological response modifiers (e.g. interferons [e.g. IFN-α, etc.] and interleukins [e.g. IL-2, etc.], etc.); adoptive immunotherapy agents; hematopoietic growth factors; agents that induce tumor cell differentiation (e.g. all-trans-retinoic acid, etc.); gene therapy reagents; antisense therapy reagents and nucleotides; tumor vaccines; inhibitors of angiogenesis, and the like. Numerous other examples of chemotherapeutic compounds and anticancer therapies suitable for coadministration with the disclosed compounds according to any one of claims 1 to 4 are known to those skilled in the art.

[0056] In preferred embodiments, additional anticancer agents to be used in combination with compounds as defined in any one of claims 1 to 4 comprise agents that induce or stimulate apoptosis. Agents that induce apoptosis include, but are not limited to, radiation (e.g., ω); kinase inhibitors (e.g., Epidermal Growth Factor Receptor [EGFR] kinase inhibitor, Vascular Endothelial Growth Factor Receptor [VEGFR] kinase inhibitor, Fibroblast Growth Factor Receptor [FGFR] kinase inhibitor, Platelet-derived Growth Factor Receptor [PDGFR] I kinase inhibitor, and Bcr-Abl kinase inhibitors such as STI-571, Gleevec, and Glivec]); antisense molecules; antibodies [e.g., Herceptin and Rituxan]; antiestrogens [e.g., raloxifene and tamoxifen]; anti-androgens [e.g., flutamide, bicalutamide, finasteride, aminoglutethamide, ketoconazole, and corticosteroids]; cyclooxygenase 2 (COX-2) inhibitors [e.g., Celecoxib, meloxicam, NS-398, and non-steroidal antiinflammatory drugs (NSAIDs)]; and cancer chemotherapeutic drugs [e.g., irinotecan (Camptosar), CPT-11, fludarabine (Fludara), dacarbazine (DTIC), dexamethasone, mitoxantrone, Mylotarg, VP-16, cisplatinum, 5-FU, Doxrubicin, Taxotere or taxol; cellular signaling molecules; ceramides and cytokines; and staurosprine, and the like.

[0057] The compounds of the preferred embodiments are useful *in vitro* or *in vivo* in inhibiting the growth of cancer cells. The compounds may be used alone or in compositions together with a pharmaceutically acceptable carrier or excipient.

[0058] In other aspects, the disclosure provides a pharmaceutical compositions comprising at least one compound according to any one of claims 1 to 4 together with a pharmaceutically acceptable carrier suitable for administration to a human or animal subject, either alone or together with other anticancer agents.

[0059] In other aspects, the disclosure provides methods of manufacture of compounds of the invention as described herein.

[0060] In other aspects provided is a pharmaceutical composition comprising an effective amount of a compound, stereoisomer, tautomer, solvate, or oxide, or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 4 and a pharmaceutically acceptable carrier. In some aspects the compound preferentially inhibits CSF-1R over Raf kinase. More particularly said compound inhibits Raf kinase at greater than about 1 µM.

[0061] Other aspects further comprise an additional agent. More particularly, said additional agent is a bisphosphonate.

[0062] Other aspects provide compounds as defined in any one of claims 1 to 4 effective to inhibit CSF-1R activity in a human or animal subject when administered thereto. More particularly, said compound exhibits an IC_{50} value with respect to CSF-1R inhibition of less than about 1 µM. More particularly, said compound exhibits an IC_{50} value with respect to Raf inhibition of greater than about 1 µM.

[0063] The disclosure provides the use of a compound as defined herein to inhibit CSF-1R, wherein said compound selectively inhibits CSF-1R.

[0064] The compounds of the embodiments are useful *in vitro* or *in vivo* in inhibiting the growth of cancer cells. The compounds may be used alone or in compositions together with a pharmaceutically acceptable carrier or excipient. Suitable pharmaceutically acceptable carriers or excipients include, for example, processing agents and drug delivery modifiers and enhancers, such as, for example, calcium phosphate, magnesium stearate, talc, monosaccharides, disaccharides, starch, gelatin, cellulose, methyl cellulose, sodium carboxymethyl cellulose, dextrose, hydroxypropyl-β-cyclodextrin, polyvinylpyrrolidinone, low melting waxes, ion exchange resins, and the like, as well as combinations of any two or more thereof. Other suitable pharmaceutically acceptable excipients are described in "Remington's Pharmaceutical Sciences," Mack Pub. Co., New Jersey (1991).

Administration and Pharmaceutical Composition

[0065] In general, the compounds of the disclosurewill be administered in a therapeutically effective amount by any of the accepted modes of administration for agents that serve similar utilities. The actual amount of the compound of preferred embodiments, i.e., the active ingredient, will depend upon numerous factors such as the severity of the disease to be treated, the age and relative health of the subject, the potency of the compound used, the route and form of administration, and other factors. The drug can be administered more than once a day, preferably once or twice a day. All of these factors are within the skill of the attending clinician.

[0066] Effective amounts of the compounds of the disclosure generally include any amount sufficient to detectably inhibit CSF-1R activity by any of the assays described herein, by other CSF-1R kinase activity assays known to those having ordinary skill in the art or by detecting an inhibition or alleviation of symptoms of cancer.

[0067] The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination, and the severity of the particular disease undergoing therapy. The therapeutically effective amount for a given situation can be readily determined by routine experimentation and is within the skill and judgment of the ordinary clinician.

[0068] For purposes of the disclosure, a therapeutically effective dose generally can be a total daily dose administered to a host in single or divided doses may be in amounts, for example, of from about 0.001 to about 1000 mg/kg body weight daily and more preferred from about 1.0 to about 30 mg/kg body weight daily. Dosage unit compositions may contain such amounts of submultiples thereof to make up the daily dose.

[0069] The choice of formulation depends on various factors such as the mode of drug administration and bioavailability of the drug substance. In general, compounds of the disclosure can be administered as pharmaceutical compositions by any one of the following routes: oral, systemic (e.g., transdermal, intranasal or by suppository), or parenteral (e.g., intramuscular, intravenous or subcutaneous) administration. The preferred manner of administration is oral using a convenient daily dosage regimen that can be adjusted according to the degree of affliction. Compositions can take the form of tablets, pills, capsules, semisolids, powders, sustained release formulations, solutions, suspensions, elixirs, aerosols, or any other appropriate compositions. Another preferred manner for administering compounds of preferred embodiments is inhalation. This is an effective method for delivering a therapeutic agent directly to the respiratory tract (see U.S. Patent 5,607,915).

[0070] Suitable pharmaceutically acceptable carriers or excipients include, for example, processing agents and drug delivery modifiers and enhancers, such as, for example, calcium phosphate, magnesium stearate, talc, monosaccharides, disaccharides, starch, gelatin, cellulose, methyl cellulose, sodium carboxymethyl cellulose, dextrose, hydroxypropyl-β-cyclodextrin, polyvinylpyrrolidinone, low melting waxes, ion exchange resins, and the like, as well as combinations of any two or more thereof. Liquid and semisolid excipients can be selected from glycerol, propylene glycol, water, ethanol and various oils, including those of petroleum, animal, vegetable or synthetic origin, e.g., peanut oil, soybean oil, mineral oil, sesame oil, etc. Preferred liquid carriers, particularly for injectable solutions, include water, saline, aqueous dextrose, and glycols. Other suitable pharmaceutically acceptable excipients are described in "Remington's Pharmaceutical Sciences," Mack Pub. Co., New Jersey (1991).

[0071] As used herein, the term "pharmaceutically acceptable salts" refers to the nontoxic acid or alkaline earth metal salts of the compounds as defined in any one of claims 1 to 4. These salts can be prepared *in situ* during the final isolation and purification of the compounds as defined in any one of claims 1 to 4, or by separately reacting the base or acid functions with a suitable organic or inorganic acid or base, respectively. Representative salts include, but are not limited to, the following: acetate, adipate, alginate, citrate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate, digluconate, cyclopentanepropionate, dodecylsulfate, ethanesulfonate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, fumarate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, methanesulfonate, nicotinate, 2-naphthalenesulfonate, oxalate, pamoate, pectinate, persulfate, 3-phenylproionate, picrate, pivalate, propionate, succinate, sulfate, tartrate, thiocyanate, p-toluenesulfonate and undecanoate. Also, the basic nitrogen-containing groups can be quaternized with agents such as alkyl halides, such as methyl, ethyl, propyl, and butyl chloride, bromides, and iodides; dialkyl sulfates like dimethyl, diethyl, dibutyl, and diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides, aralkyl halides like benzyl and phenethyl bromides, and others. Water or oil-soluble or dispersible products are thereby obtained.

[0072] Examples of acids which may be employed to form pharmaceutically acceptable acid addition salts include such inorganic acids as hydrochloric acid, sulfuric acid and phosphoric acid and such organic acids as oxalic acid, maleic acid, methanesulfonic acid, succinic acid and citric acid. Basic addition salts can be prepared *in situ* during the final isolation and purification of the compounds as defined in any one of claims 1 to 4, or separately by reacting carboxylic acid moieties with a suitable base such as the hydroxide, carbonate or bicarbonate of a pharmaceutically acceptable metal cation or with ammonia, or an organic primary, secondary or tertiary amine. Pharmaceutically acceptable salts include, but are not limited to, cations based on the alkali and alkaline earth metals, such as sodium, lithium, potassium, calcium, magnesium, aluminum salts and the like, as well as nontoxic ammonium, quaternary ammonium, and amine cations, including, but not limited to ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, ethylamine, and the like. Other representative organic amines useful for the formation of base addition salts include diethylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine and the like.

[0073] The compounds of the disclosure may be administered orally, parenterally, sublingually, by aerosolization or inhalation spray, rectally, or topically in dosage unit formulations containing conventional nontoxic pharmaceutically acceptable carriers, adjuvants, and vehicles as desired. Topical administration may also involve the use of transdermal administration such as transdermal patches or ionophoresis devices. The term parenteral as used herein includes subcutaneous injections, intravenous, intrathecal, intramuscular, intrasternal injection, or infusion techniques.

[0074] Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-propanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or di-glycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

[0075] Suppositories for rectal administration of the drug can be prepared by mixing the drug with a suitable nonirritating excipient such as cocoa butter and polyethylene glycols, which are solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum and release the drug.

[0076] Solid dosage forms for oral administration may include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound may be admixed with at least one inert diluent such as sucrose lactose or starch. Such dosage forms may also comprise, as is normal practice, additional substances other than inert diluents, e.g., lubricating agents such as magnesium stearate. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents. Tablets and pills can additionally be prepared with enteric coatings.

[0077] Liquid dosage forms for oral administration may include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art, such as water. Such compositions may also comprise adjuvants, such as wetting agents, emulsifying and suspending agents, cyclodextrins, and sweetening, flavoring, and perfuming agents.

[0078] The compounds of the disclosure can also be administered in the form of liposomes. As is known in the art, liposomes are generally derived from phospholipids or other lipid substances. Liposomes are formed by mono- or multi-lamellar hydrated liquid crystals that are dispersed in an aqueous medium. Any non-toxic, physiologically acceptable and metabolizable lipid capable of forming liposomes can be used. The present compositions in liposome form can contain, in addition to a compound of the preferred embodiments, stabilizers, preservatives, excipients, and the like. The preferred lipids are the phospholipids and phosphatidyl cholines (lecithins), both natural and synthetic. Methods to form liposomes are known in the art. See, for example, Prescott, Ed., Methods in Cell Biology, Volume XIV, Academic Press, New York, N.W., p. 33 et seq. (1976).

[0079] Compressed gases may be used to disperse a compound of the disclosure in aerosol form. Inert gases suitable for this purpose are nitrogen, carbon dioxide, etc. Other suitable pharmaceutical excipients and their formulations are described in Remington's Pharmaceutical Sciences, edited by E. W. Martin (Mack Publishing Company, 18th ed., 1990).

[0080] For delivery via inhalation the compound can be formulated as liquid solution, suspensions, aerosol propellants or dry powder and loaded into a suitable dispenser for administration. There are several types of pharmaceutical inhalation devices-nebulizer inhalers, metered dose inhalers (MDI) and dry powder inhalers (DPI). Nebulizer devices produce a stream of high velocity air that causes the therapeutic agents (which are formulated in a liquid form) to spray as a mist that is carried into the patient's respiratory tract. MDI's typically are formulation packaged with a compressed gas. Upon actuation, the device discharges a measured amount of therapeutic agent by compressed gas, thus affording a reliable method of administering a set amount of agent. DPI dispenses therapeutic agents in the form of a free flowing powder that can be dispersed in the patient's inspiratory air-stream during breathing by the device. In order to achieve a free flowing powder, the therapeutic agent is formulated with an excipient such as lactose. A measured amount of the therapeutic agent is stored in a capsule form and is dispensed with each actuation.

[0081] Recently, pharmaceutical formulations have been developed especially for drugs that show poor bioavailability based upon the principle that bioavailability can be increased by increasing the surface area i.e., decreasing particle size. For example, U.S. Pat. No. 4,107,288 describes a pharmaceutical formulation having particles in the size range from about 10 to about 1,000 nm in which the active material is supported on a crosslinked matrix of macromolecules. U.S. Patent No. 5,145,684 describes the production of a pharmaceutical formulation in which the drug substance is pulverized to nanoparticles (average particle size of about 400 nm) in the presence of a surface modifier and then dispersed in a liquid medium to give a pharmaceutical formulation that exhibits remarkably high bioavailability.

Combination Therapies

[0082] Disclosed is that the compounds of the preferred embodiments can be administered as the sole active pharmaceutical agent, and they can also be used in combination with one or more other agents used in the treatment of cancer. The compounds of the preferred embodiments are also useful in combination with known therapeutic agents and anti-cancer agents, and combinations of the presently disclosed compounds with other anti-cancer or chemotherapeutic agents are disclosed. Examples of such agents can be found in Cancer Principles and Practice of Oncology, V. T. Devita and S. Hellman (editors), 6th edition (Feb. 15, 2001), Lippincott Williams & Wilkins Publishers. A person of ordinary skill in the art would be able to discern which combinations of agents would be useful based on the particular characteristics of the drugs and the cancer involved. Such anti-cancer agents include, but are not limited to, the following: estrogen receptor modulators, androgen receptor modulators, retinoid receptor modulators, cytotoxic/cytostatic agents, antiproliferative agents, prenyl-protein transferase inhibitors, HMG-CoA reductase inhibitors and other angiogenesis inhibitors, inhibitors of cell proliferation and survival signaling, apoptosis inducing agents and agents that interfere with cell cycle checkpoints. The compounds of the preferred embodiments are also useful when co-administered with radiation therapy.

[0083] Therefore, in one embodiment, the compounds are also used in combination with known anticancer agents including, for example, estrogen receptor modulators, androgen receptor modulators, retinoid receptor modulators, cytotoxic agents, antiproliferative agents, prenyl-protein transferase inhibitors, HMG-CoA reductase inhibitors, HIV protease inhibitors, reverse transcriptase inhibitors, and other angiogenesis inhibitors.

[0084] Estrogen receptor modulators are compounds that can interfere with or inhibit the binding of estrogen to the receptor, regardless of mechanism. Examples of estrogen receptor modulators include, but are not limited to, tamoxifen, raloxifene, idoxifene, LY353381, LY117081, toremifene, fulvestrant, 4-[7-(2,2-dimethyl-1-oxopropoxy-4-methyl-2-[4-[2-(1-piperidinyl)ethoxy]phenyl]-2H-1-benzopyran-3-yl]-phenyl-2,2-dimethyl-propanoate, 4,4'-dihydroxybenzophenone-2,4-dinitrophenyl-hydrazone, and SH646.

[0085] Androgen receptor modulators are compounds which can interfere with or inhibit the binding of androgens to an androgen receptor. Representative examples of androgen receptor modulators include finasteride and other 5α-reductase inhibitors, nilutamide, flutamide, bicalutamide, liarozole, and abiraterone acetate. Retinoid receptor modulators are compounds which interfere or inhibit the binding of retinoids to a retinoid receptor. Examples of retinoid receptor modulators include bexarotene, tretinoin, 13-cis-retinoic acid, 9-cis-retinoic acid, α-difluoromethylornithine, LX23-7553, trans-N-(4'-hydroxyphenyl) retinamide, and N4-carboxyphenyl retinamide.

[0086] Cytotoxic and/or cytostatic agents are compounds which can cause cell death or inhibit cell proliferation primarily by interfering directly with the cell's functioning or inhibit or interfere with cell mytosis, including alkylating agents, tumor necrosis factors, intercalators, hypoxia activatable compounds, microtubule inhibitors/microtubule-stabilizing agents, inhibitors of mitotic kinesins, inhibitors of kinases involved in mitotic progression, antimetabolites; biological response modifiers; hormonal/anti-hormonal therapeutic agents, haematopoietic growth factors, monoclonal antibody targeted therapeutic agents, topoisomerase inhibitors, proteasome inhibitors and ubiquitin ligase inhibitors. Examples of cytotoxic agents include, but are not limited to, sertenef, cachectin, ifosfamide, tasonermin, lonidamine, carboplatin, altretamine, prednimustine, dibromodulcitol, ranimustine, fotemustine, nedaplatin, oxaliplatin, temozolomide, heptaplatin, estramustine, improsulfan tosilate, trofosfamide, nimustine, dibrospidium chloride, pumitepa, lobaplatin, satraplatin, profiromycin, cisplatin, irofulven, dexifosfamide, cis-aminedichloro(2-methyl-pyridine)platinum, benzylguanine, glufosfamide, GPX100, (trans, trans, trans)-bis-mu-(hexane-1,6-diamine)-mu-[diamine-platinum(II)]bis[diamine(chloro)platinum (II)]tetrachloride, diarizidinylspermine, arsenic trioxide, 1-(11-dodecylamino-10-hydroxyundecyl)-3,7-dimethylxanthine, zorubicin, idarubicin, daunorubicin, bisantrene, mitoxantrone, pirarubicin, pinafide, valrubicin, amrubicin, antineoplaston, 3'-deamino-3'-morpholino-13-deoxo-10-hydroxycarminomycin, annamycin, galarubicin, elinafide, MEN10755, and 4-demethoxy-3-deamino-3-aziridinyl-4-methylsulphonyl-daunorubicin (see WO 00/50032). A representative example of a hypoxia activatable compound is tirapazamine. Proteasome inhibitors include, but are not limited to, lactacystin and bortezomib. Examples of microtubule inhibitors/microtubule-stabilizing agents include paclitaxel, vindesine sulfate, 3',4'-didehydro-4'-deoxy-8'-norvincaleukoblastine, docetaxol, rhizoxin, dolastatin, mivobulin isethionate, auristatin, cemadotin, RPR109881, BMS184476, vinflunine, cryptophycin, 2,3,4,5,6-pentafluoro-N-(3-fluoro4-methoxyphenyl) benzene sulfonamide, anhydrovinblastine, N,N-dimethyl-L-valyl-L-valyl-N-methyl-L-valyl-L-prolyl-Lproline-t-butylamide, TDX258, the epothilones (see for example U.S. Pat. Nos. 6,284,781 and 6,288,237) and BMS188797. Representative examples of topoisomerase inhibitors include topotecan, hycaptamine, irinotecan, rubitecan, 6-ethoxypropionyl-3',4'-O-exo-benzylidene-chartreusin, 9-methoxy-N,N-dimethyl-5-nitropyrazolo[3,4,5-kl]acridine-2-(6H) propanamine, 1-amino-9-ethyl-5-fluoro-2,3-dihydro-9-hydroxy-4-methyl-1H,12H-benzo[de]pyrano[3',4':b,7]-indolizino[1,2b]quinoline-10,13(9H,15H)dione, lurtotecan, 7-[2-(N-isopropylamino)ethyl]-(20S)camptothecin, BNP1350, BNPI1100, BN80915, BN80942, etoposide phosphate, teniposide, sobuzoxane, 2'-dimethylamino-2'-deoxy-etoposide, GL331, N-[2-(dimethylamino)ethyl]-9-hydroxy-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carboxamide, asulacrine, (5a, 5aB, 8aa, 9b)-9-[2-[N-[2-(dimethylamino)ethyl]-N-methylamino]ethyl]-5-[4-hydroOxy-3,5-dimethoxyphenyl]-5,5a,6,8,8a,9-hexahydrofuro(3',4':6,7)naphtho(2,3-d)-1,3-dioxol-6-one, 2,3-(methylene-dioxy)-5-methyl-7-hydroxy-8-methoxybenzo[c]-phenanthridinium, 6,9-bis [(2-aminoethyl)amino]benzo[g]isoguinoline-5,10-dione, 5-(3-aminopropylamino)-7,10-dihydroxy-2-(2-hydroxyethylaminomethyl)-6H-pyrazolo[4,5,1'-de]acridin-6-one, N-[1-[2(diethylamino)-ethylamino]-7-methoxy-9-oxo-9H-thioxanthen-4-ylmethyl]formamide, N-(2-(dimethylamino)ethyl)acridine-4-carboxamide, 6-[[2-(dimethylamino)ethyl]amino]-3-hydroxy-7H-indeno[2,1-c]quinolin-7-one, and dimesna. Examples of inhibitors of mitotic kinesins, such as the human mitotic kinesin KSP, are described in PCT Publications WO 01/30768 and WO 01/98278, WO 03/050,064 (Jun. 19, 2003), WO 03/050,122 (Jun. 19, 2003), WO 03/049,527 (Jun. 19, 2003), WO 03/049,679 (Jun. 19, 2003), WO 03/049,678 (Jun. 19, 2003) and WO 03/39460 (May 15, 2003) and pending PCT Appl. Nos. US03/06403 (filed Mar. 4, 2003), US03/15861 (filed May 19, 2003), US03/15810 (filed May 19, 2003), US03/18482 (filed Jun. 12, 2003) and US03/18694 (filed Jun. 12, 2003). Inhibitors of mitotic kinesins include, but are not limited to inhibitors of KSP, inhibitors of MKLP1, inhibitors of CENP-E, inhibitors of MCAK, inhibitors of Kif14, inhibitors of Mphosph1 and inhibitors of Rab6-KIFL.

[0087] Inhibitors of kinases involved in mitotic progression include, but are not limited to, inhibitors of aurora kinase, inhibitors of Polo-like kinases (PLK) (e.g., inhibitors of PLK-1), inhibitors of bub-1 and inhibitors of bub-1R. Antiproliferative agents include antisense RNA and DNA oligonucleotides such as G3139, ODN698, RVASKRAS, GEM231, and INX3001, and antimetabolites such as enocitabine, carmofur, tegafur, pentostatin, doxifluridine, trimetrexate, fludarabine, capecitabine, galocitabine, cytarabine ocfosfate, fosteabine sodium hydrate, raltitrexed, paltitrexid, emitefur, tiazofurin, decitabine, nolatrexed, pemetrexed, nelzarabine, 2'-deoxy-2'-methylidenecytidine, 2'-fluoromethylene-2'-deoxycytidine, N-[5-(2,3-dihydro-benzofuryl)sulfonyl]-N'-(3,4-dichlorophenyl)urea, N6-[4-deoxy-4-[N2-[2(E),4(E)-tetradecadienoyl]glycylamino]-L-glycero-B-L-manno-heptopyranosyl]adenine, aplidine, ecteinascidin, troxacitabine, 4-[2-amino-4-oxo4,6,7,8-tetrahydro-3H-pyrimidino[5,4-b][1,4]thiazin-6-yl-(S)-ethyl]-2,5-thienoyl-L-glutamic acid, aminopterin, 5-flurouracil, alanosine, 11-acetyl-8-(carbamoyloxymethyl)-4-formyl-6-methoxy-14-oxa-1,1-diazatetracyclo(7.4.1.0.0)-tetradeca-2,4,6-trien-9-yl acetic acid ester, swainsonine, lometrexol, dexrazoxane, methioninase, 2'-cyano-2'-deoxy-N4-palmitoyl-1-B-D-arabino furanosyl cytosine and 3-aminopyridine-2-carboxaldehyde thiosemicarbazone. Examples of monoclonal antibody targeted therapeutic agents include those therapeutic agents which have cytotoxic agents or radioisotopes attached to a cancer cell specific or target cell specific monoclonal antibody.

Examples include, for example, Bexxar. HMG-CoA reductase inhibitors are inhibitors of 3-hydroxy-3-methylglutaryl-CoA reductase. Compounds which have inhibitory activity for HMG-CoA reductase can be readily identified by using assays well-known in the art such as those described or cited in U.S. Pat. No. 4,231,938 and WO 84/02131. Examples of HMG-CoA reductase inhibitors that may be used include, but are not limited to, lovastatin (MEVACOR®; see U.S. Pat. Nos. 4,231,938, 4,294,926 and 4,319,039), simvastatin (ZOCOR®; see U.S. Pat. Nos. 4,444,784, 4,820,850 and 4,916,239), pravastatin (PRAVACHOL®.; see U.S. Pat. Nos. 4,346,227, 4,537,859, 4,410,629, 5,030,447 and 5,180,589), fluvastatin (LESCOL®; see U.S. Pat. Nos. 5,354,772, 4,911,165, 4,929,437, 5,189,164, 5,118,853, 5,290,946 and 5,356,896) and atorvastatin (LIPITOR®; see U.S. Pat. Nos. 5,273,995, 4,681,893, 5,489,691 and 5,342,952). Disclosed is that the structural formulas of these and additional HMG-CoA reductase inhibitors that may be used in the instant methods are described at page 87 of M. Yalpani, "Cholesterol Lowering Drugs", Chemistry & Industry, pp. 85-89 (5 Feb. 1996) and U.S. Pat. Nos. 4,782,084 and 4,885,314. In an embodiment, the HMG-CoA reductase inhibitor is selected from lovastatin or simvastatin.

[0088] Prenyl-protein transferase inhibitors are compounds which inhibit any one or any combination of the prenyl-protein transferase enzymes, including farnesyl-protein transferase (FPTase), geranylgeranyl-protein transferase type I (GGPTase-I), and geranylgeranyl-protein transferase type-II (GGPTase-II, also called Rab GGPTase). Examples of prenyl-protein transferase inhibiting compounds include (±)-6-[amine(4-chlorophenyl)(1-methyl-1H-imidazol-5-yl)methyl]-4-(3-chlorophenyl)-1-methyl-2(1H)-quinolinone, (-)-6-[amino(4-chlorophenyl)(1-methyl-1H-imidazol-5-yl)methyl]-4-(3-chlorophenyl)-1-methyl-2(1H)-quinolinone, (+)-6-[amino(4-chlorophenyl)(1-methyl-1H-imidazol-5-yl) methyl]-4-(3-chlorophenyl)-1-methyl-2(1H)-quinolinone, 5(S)-n-butyl-1-(2,3-dimethylphenyl)-4-[1-(4-cyanobenzyl)-5-imnidazolylmethyl-2-piperazinone, (S)-1-(3-chlorophenyl)-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-5-[2-(ethanesulfonyl) methyl)-2-piperazinone, 5(S)-n-butyl-1-(2-methylphenyl)-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-2-piperazinone, 1-(3-chlorophenyl)-4-[1-(4-cyanobenzyl)-2-methyl-5-imidazolylmethyl]-2-piperazinone, 1-(2,2-diphenylethyl)-3-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl]piperidine, 4-{-[4-hydroxymethyl-4-(4-chloropyridin-2-ylmethyl)-piperidine-1-ylmethyl]-2-methylimidazol-1-ylmethyl}benzonitrile, 4-{-5-[4-hydroxymethyl-4-(3-chlorobenzyl)-piperidine-1-ylmethyl]-2-methylimnidazol-1-ylmethyl}-benzonitrile, 4-{3-[4-(2-oxo-2H-pyridin-1-yl)benzyl]-3H-imidazol-4-ylmethyl}benzonitrile, 4-{3-[4-(5-chloro-2-oxo-2H-[1,2']bipyridin-5'-ylmethyl]-3H-imidazol-4-yl-methyl}benzonitrile, 4-{3-[4-(2-oxo-2H-[1,2']bipyridin-5'-ylmethyl]-3H-imidazol4-yl-methyl}benzonitrile, 4-[3-(2-oxo-1-phenyl-1,2-dihydropyridin-4-ylmethyl)-3H-midazol-4-ylmethyl}benzonitrile, 18,19-dihydro-19-oxo-5H,17H-6,10:12,16-dimetheno-1H-imidazo[4,3-c][1,11,4]dioxaazacyclo-nonadecine-9-carbonitrile, (±)-19,20-dihydro-19-oxo-5H-18,21-ethano-12,14-etheno-6,10-metheno-22H-benzo[d]imidazo[4,3-k]-[1,6,9,12]oxatriaza-cyclooctadecine-9-carbonitrile, 19,20-dihydro-19-oxo-5H,17H-18,21-ethano-6,10:12,16-dimetheno-22H-imidazo[3,4-h] [1,8,11,14]oxatriazacycloeicosine-9-carbonitrile, and (.+-.)-19,20-dihydro-3-methyl-19-oxo-5H-18,21-ethano-12,14-etheno-6,10-metheno-22H-benzo[d]imidazo[4,3-k][1,6,9,12]oxa-triazacyclooctadecine-9-carbonitrile. Other examples of prenyl-protein transferase inhibitors can be found in the following publications and patents: WO 96/30343, WO 97/18813, WO 97/21701, WO 97/23478, WO 97/38665, WO 98/28980, WO 98/29119, WO 95/32987, U.S. Pat. No. 5,420,245, U.S. Pat. No. 5,523,430, U.S. Pat. No. 5,532,359, U.S. Pat. No. 5,510,510, U.S. Pat. No. 5,589,485, U.S. Pat. No. 5,602,098, European Patent Publ. 0 618 221, European Patent Publ. 0 675 112, European Patent Publ. 0 604 181, European Patent Publ. 0 696 593, WO 94/19357, WO 95/08542, WO 95/11917, WO 95/12612, WO 95/12572, WO 95/10514, U.S. Pat. No. 5,661,152, WO 95/10515, WO 95/10516, WO 95/24612, WO 95/34535, WO 95/25086, WO 96/05529, WO 96/06138, WO 96/06193, WO 96/16443, WO 96/21701, WO 96/21456, WO 96/22278, WO 96/24611, WO 96/24612, WO 96/05168, WO 96/05169, WO 96/00736, U.S. Pat. No. 5,571,792, WO 96/17861, WO 96/33159, WO 96/34850, WO 96/34851, WO 96/30017, WO 96/30018, WO 96/30362, WO 96/30363, WO 96/31111, WO 96/31477, WO 96/31478, WO 96/31501, WO 97/00252, WO 97/03047, WO 97/03050, WO 97/04785, WO 97/02920, WO 97/17070, WO 97/23478, WO 97/26246, WO 97/30053, WO 97/44350, WO 98/02436, and U.S. Patent No. 5,532,359. For an example of the role of a prenyl-protein transferase inhibitor on angiogenesis see European J. of Cancer 35(9):1394-1401 (1999).

[0089] Angiogenesis inhibitors refers to compounds that can inhibit the formation of new blood vessels, regardless of mechanism. Examples of angiogenesis inhibitors include, but are not limited to, tyrosine kinase inhibitors, such as inhibitors of the tyrosine kinase receptors Flt-1 (VEGFR1) and Flk-1/KDR (VEGFR2), inhibitors of epidermal-derived, fibroblast-derived, or platelet derived growth factors, MMP (matrix metalloprotease) inhibitors, integrin blockers, interferon-.alpha., interleukin-12, pentosan polysulfate, cyclooxygenase inhibitors, including nonsteroidal anti-inflammatories (NSAIDs) like aspirin and ibuprofen as well as selective cyclooxy-genase-2 inhibitors like celecoxib and rofecoxib (PNAS 89:7384 (1992); JNCI 69:475 (1982); Arch. Ophthalmol. 108:573 (1990); Anat. Rec., (238):68 (1994); FEBS Letters 372:83 (1995);Clin, Orthop. 313:76 (1995); J. Mol. Endocrinol. 16:107 (1996); Jpn. J. Pharmacol. 75:105 (1997); Cancer Res. 57:1625 (1997); Cell 93:705 (1998); Intl. J. Mol. Med. 2:715 (1998); J. Biol. Chem. 274:9116 (1999)), steroidal anti-inflammatories (such as corticosteroids, mineralocorticoids, dexamethasone, prednisone, prednisolone, methylpred, betamethasone), carboxyamidotriazole, combretastatin A4, squalamine, 6-O-chloroacetyl-carbonyl)-fumagillol, thalidomide, angiostatin, troponin-1, angiotensin II antagonists (see Fernandez et al., J. Lab. Clin. Med. 105:141-145 (1985)), and antibodies to VEGF (see, Nature Biotechnology, 17:963-968 (October 1999); Kim et al., Nature, 362:841-844 (1993); WO 00/44777; and WO 00/61186). Other therapeutic agents that modulate or inhibit angiogenesis and may also be used in combination with the compounds of the preferred embodiments include agents that modulate or inhibit the coagulation and fibrinolysis systems (see review in Clin. Chem. La. Med. 38:679-692 (2000)). Examples of such agents that modulate or inhibit the coagulation and fibrinolysis pathways include, but are not limited to, heparin (see Thromb. Haemost. 80:10-23 (1998)), low molecular weight heparins and carboxypeptidase U inhibitors (also known as inhibitors of active thrombin activatable fibrinolysis inhibitor [TAFIa]) (see Thrombosis Res. 101:329-354 (2001)). TAFIa inhibitors have been described in PCT Publication WO 03/013,526 and U.S. Ser. No. 60/349,925 (filed Jan. 18, 2002). The disclosure also encompass combinations of the compounds of the preferred embodiments with NSAIDs which are selective

COX-2 inhibitors (generally defined as those which possess a specificity for inhibiting COX-2 over COX-1 of at least about 100 fold as measured by the ratio of IC_{50} for COX-2 over IC_{50} for COX-1 evaluated by cell or microsomal assays). Such compounds include, but are not limited to those disclosed in U.S. Pat. No. 5,474,995, issued Dec. 12, 1995, U.S. Pat. No. 5,861,419, issued Jan. 19, 1999, U.S. Pat. No. 6,001,843, issued Dec. 14, 1999, U.S. Pat. No. 6,020,343, issued Feb. 1, 2000, U.S. Pat. No. 5,409,944, issued Apr. 25, 1995, U.S. Pat. No. 5,436,265, issued Jul. 25, 1995, U.S. Pat. No. 5,536,752, issued Jul. 16, 1996, U.S. Pat. No. 5,550,142, issued Aug. 27, 1996, U.S. Pat. No. 5,604,260, issued Feb. 18, 1997, U.S. Pat. No. 5,698,584, issued Dec. 16, 1997, U.S. Pat. No. 5,710,140, issued Jan. 20, 1998, WO 94/15932, published Jul. 21, 1994, U.S. Pat. No. 5,344,991, issued Jun. 6, 1994, U.S. Pat. No. 5,134,142, issued Jul. 28, 1992, U.S. Pat. No. 5,380,738, issued Jan. 10, 1995, U.S. Pat. No. 5,393,790, issued Feb. 20, 1995, U.S. Pat. No. 5,466,823, issued Nov. 14, 1995, U.S. Pat. No. 5,633,272, issued May 27, 1997, and U.S. Pat. No. 5,932,598, issued Aug. 3, 1999. Representative inhibitors of COX-2 that are useful include 3-phenyl-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone; and 5-chloro-3-(4-methylsulfonyl)phenyl-2-(2-methyl-5-pyridinyl)pyridine. Compounds which are described as specific inhibitors of COX-2 and are therefore useful in the preferred embodiments, and synthesis thereof, can be found in the following patents, pending applications and publications: WO 94/15932, published Jul. 21, 1994, U.S. Pat. No. 5,344,991, issued Jun. 6, 1994, U.S. Pat. No. 5,134,142, issued Jul. 28, 1992, U.S. Pat. No. 5,380,738, issued Jan. 10, 1995, U.S. Pat. No. 5,393,790, issued Feb. 20, 1995, U.S. Pat. No. 5,466,823, issued Nov. 14, 1995, U.S. Pat. No. 5,633,272, issued May 27, 1997, U.S. Pat. No. 5,932,598, issued Aug. 3, 1999, U.S. Pat. No. 5,474,995, issued Dec. 12, 1995, U.S. Pat. No. 5,861,419, issued Jan. 19, 1999, U.S. Pat. No. 6,001,843, issued Dec. 14, 1999, U.S. Pat. No. 6,020,343, issued Feb. 1, 2000, U.S. Pat. No. 5,409,944, issued Apr. 25, 1995, U.S. Pat. No. 5,436,265, issued Jul. 25, 1995, U.S. Pat. No. 5,536,752, issued Jul. 16, 1996, U.S. Pat. No. 5,550,142, issued Aug. 27, 1996, U.S. Pat. No. 5,604,260, issued Feb. 18, 1997, U.S. Pat. No. 5,698,584, issued Dec. 16, 1997, and U.S. Pat. No. 5,710,140, issued Jan. 20,1998. Other examples of angiogenesis inhibitors include, but are not limited to, endostatin, ukrain, ranpirnase, IM862, 5-methoxy-4-[2-methyl-3-(3-methyl-2-butenyl)oxiranyl]-1-oxaspiro[2,5]oct-6-yl(chloroacetyl)carbamate, acetyldinanaline, 5-amino-1-[[3,5-dichloro-4-(4-chlorobenzoyl)phenyl]methyl]-1H-1,2,3-triazole-4-carboxamide, CM101, squalamine, combretastatin, RPI4610, NX31838, sulfated mannopentaose phosphate, 7,7-(carbonyl-bis[imino-N-methyl-4,2-pyrrolocarbonylimino[N-methyl-4,2-pyrrole]-carbonylimino]-bis-(1,3-naphthalene disulfonate), and 3-[(2,4-dimethylpyrrol-5-yl)methylene]-2-indolinone (SU5416).

[0090] Agents that interfere with cell cycle checkpoints are compounds that can inhibit protein kinases that transduce cell cycle checkpoint signals, thereby sensitizing the cancer cell to DNA damaging agents. Such agents include inhibitors of ATR, ATM, the Chk1 and Chk2 kinases and cdk and cdc kinase inhibitors and are specifically exemplified by 7-hydroxystaurosporin, flavopiridol, CYC202 (Cyclacel) and BMS-387032.

[0091] Inhibitors of cell proliferation and survival signaling pathway can be pharmaceutical agents that can inhibit cell surface receptors and signal transduction cascades downstream of those surface receptors. Such agents include inhibitors of EGFR (for example gefitinib and erlotinib), inhibitors of ERB-2 (for example trastuzumab), inhibitors of IGFR, inhibitors of cytokine receptors, inhibitors of MET, inhibitors of PI3K (for example LY294002), serine/threonine kinases (including but not limited to inhibitors of Akt such as described in WO 02/083064, WO 02/083139, WO 02/083140 and WO 02/083138), inhibitors of Raf kinase (for example BAY-43-9006), inhibitors of MEK (for example CI-1040 and PD-098059) and inhibitors of mTOR (for example Wyeth CCI-779). Such agents include small molecule inhibitor compounds and antibody antagonists.

[0092] Apoptosis inducing agents include activators of TNF receptor family members (including the TRAIL receptors).

[0093] The disclosure provides representative agents useful in combination with the compounds of the preferred embodiments for the treatment of cancer include, for example, irinotecan, topotecan, gemcitabine, 5-fluorouracil, leucovorin carboplatin, cisplatin, taxanes, tezacitabine, cyclophosphamide, vinca alkaloids, imatinib (Gleevec), anthracyclines, rituximab, trastuzumab, as well as other cancer chemotherapeutic agents.

[0094] The above compounds to be employed in combination with the compounds of the preferred embodiments can be used in therapeutic amounts as indicated in the Physicians' Desk Reference (PDR) 47th Edition (1993), or such therapeutically useful amounts as would be known to one of ordinary skill in the art.

[0095] The compounds of the preferred embodiments and the other anticancer agents can be administered at the recommended maximum clinical dosage or at lower doses. Dosage levels of the active compounds in the compositions of the preferred embodiments may be varied so as to obtain a desired therapeutic response depending on the route of administration, severity of the disease and the response of the patient. The combination can be administered as separate compositions or as a single dosage form containing both agents. When administered as a combination, the therapeutic agents can be formulated as separate compositions, which are given at the same time or different times, or the therapeutic agents, can be given as a single composition.

General Synthetic Methods

[0096] The compounds of preferred embodiments can be prepared from readily available starting materials using the following general methods and procedures. It will be appreciated that where typical or preferred process conditions (i.e., reaction temperatures, times, mole ratios of reactants, solvents, pressures, etc.) are given, other process conditions can also be used unless otherwise stated. Optimum reaction conditions may vary with the particular reactants or solvent used, but such conditions can be determined by one skilled in the art by routine optimization procedures.

[0097] Additionally, as will be apparent to those skilled in the art, conventional protecting groups may be necessary to prevent certain functional groups from undergoing undesired reactions. Suitable protecting groups for various functional groups as well as suitable conditions for protecting and deprotecting particular functional groups are well known in the art. For example, numerous protecting groups are described in T. W. Greene and G. M. Wuts, Protecting Groups in Organic Synthesis, Third Edition, Wiley, New York, 1999, and references cited therein.

[0098] Furthermore, the compounds of preferred embodiments contain one or more chiral centers. Accordingly, if desired, such compounds can be prepared or isolated as pure stereoisomers, i.e., as individual enantiomers or diastereomers, or as stereoisomer-enriched mixtures. All such stereoisomers (and enriched mixtures) are included within the scope of the embodiments, unless otherwise indicated. Pure stereoisomers (or enriched mixtures) may be prepared using, for example, optically active starting materials or stereoselective reagents well-known in the art. Alternatively, racemic mixtures of such compounds can be separated using, for example, chiral column chromatography, chiral resolving agents and the like.

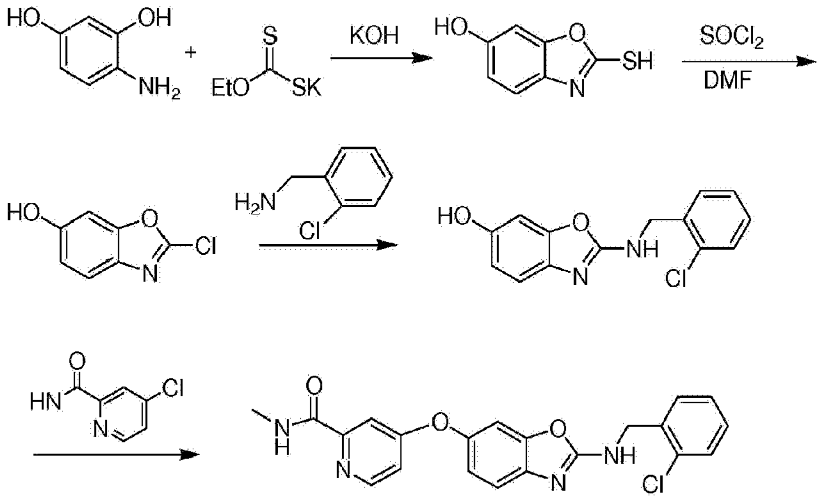
[0099] The starting materials for the following reactions are generally known compounds or can be prepared by known procedures or obvious modifications thereof. For example, many of the starting materials are available from commercial suppliers such as Aldrich Chemical Co. (Milwaukee, Wisconsin, USA), Bachem (Torrance, California, USA), Emka-Chemce or Sigma (St. Louis, Missouri, USA). Others may be prepared by procedures, or obvious modifications thereof, described in standard reference texts such as Fieser and Fieser's Reagents for Organic Synthesis, Volumes 1-15 (John Wiley and Sons, 1991), Rodd's Chemistry of Carbon Compounds, Volumes 1-5 and Supplementals (Elsevier Science Publishers, 1989), Organic Reactions, Volumes 1-40 (John Wiley and Sons, 1991), March's Advanced Organic Chemistry, (John Wiley and Sons, 4th Edition), and Larock's Comprehensive Organic Transformations (VCH Publishers Inc., 1989).

[0100] The various starting materials, intermediates, and compounds of the preferred embodiments may be isolated and purified where appropriate using conventional techniques such as precipitation, filtration, crystallization, evaporation, distillation, and chromatography. Characterization of these compounds may be performed using conventional methods such as by melting point, mass spectrum, nuclear magnetic resonance, and various other spectroscopic analyses.

[0101] Compounds of the embodiments may generally be prepared using a number of methods familiar to one of skill in the art, such as, for example, the methods disclosed in U.S. patent application Publication Nos. US20040087626 A1 and US20040122237 A1. The compounds of the embodiments may be generally made in accordance with the following reaction Reference Schemes 1-8, which are described in detail in the Examples and Reference Examples, below.

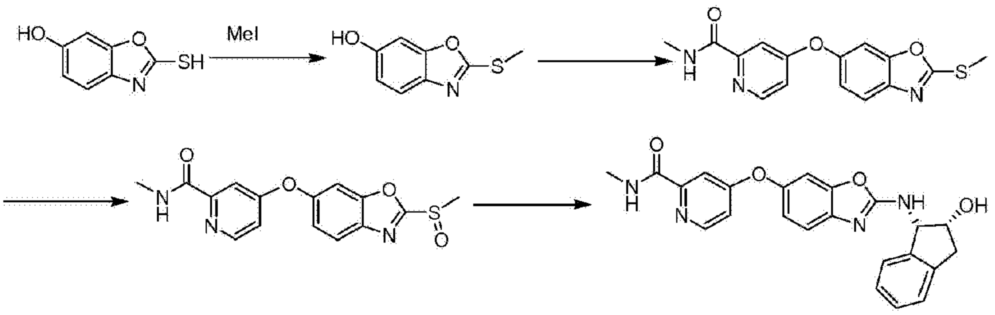
[0102] Reference Schemes 1-8 illustrate general methods for the preparation of intermediates and compounds of the Examples and Reference Examples. These compounds are prepared from starting materials either known in the art or are commercially available. The specific compounds are for illustrative purposes only.

Reference Scheme 1



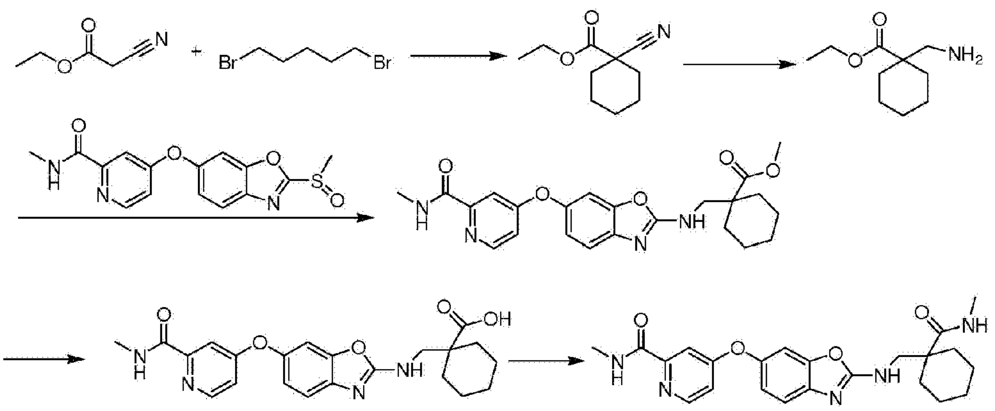
[0103] In Reference Scheme 1, 2-hydroxyaniline or a derivative thereof reacts with ethylxanthic acid to give a thiol-benzoxazole. The thiol-benzoxazole is converted to a chloro-benzoxazole with reaction with thionyl chloride. Alternatively, the thiol benzoxazole can be converted to halogenated benzoxazole with a array of halogenating agents, such as, but not limited to phosphorus trichloride, phosphorus tribromide, phosgene, or oxalyl chloride. The chloro-benzoxazole is then reacted with a benzylamine such as 2-chlorobenzylamine to give a benzylamino-benzoxazole. The benzylamino-benzoxazole is coupled with chloro-pyridine in the presence of a base such as, cesium carbonate to give a compound of the Examples or Reference Examples. Alternatively, a halogenated pyridine can be used for the coupling.

Reference Scheme 2



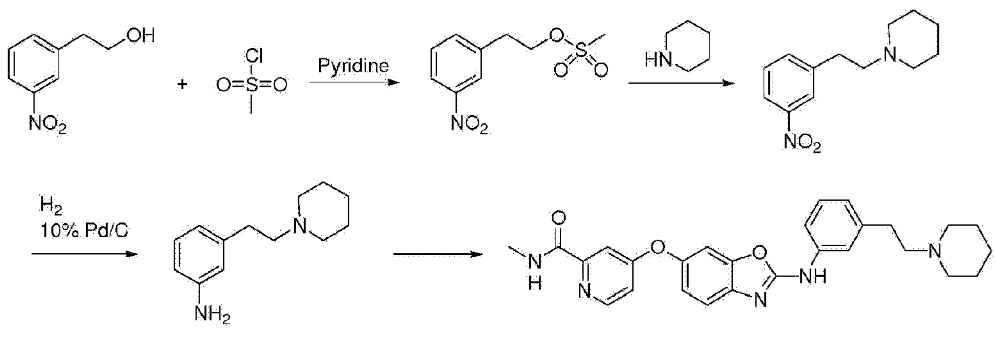
[0104] In Reference Scheme 2, a thiol-benzoxazole or derivative thereof is alkylated at the thiol moiety. The alkylated thiol-benzoxazole is coupled with the corresponding halo pyridine such as chloro-pyridine in the presence of a base such as cesium carbonate to give a compound of the Examples or Reference Examples. The resulting benzoxazolyloxy-pyridine is oxidized, for instance, with mCPBA. Other oxidizing agents can be used to oxidize the thiol to a sulfoxide. Other oxidizing agents include, but are not limited to, hydrogen peroxide, sodium periodate, pyridinium chlorochromate or chromium trioxide. The sulfoxide of the benzoxazolyloxy-pyridine is subjected to nucleophilic attack with an amine to give a compound of the Examples or Reference Examples.

Reference Scheme 3



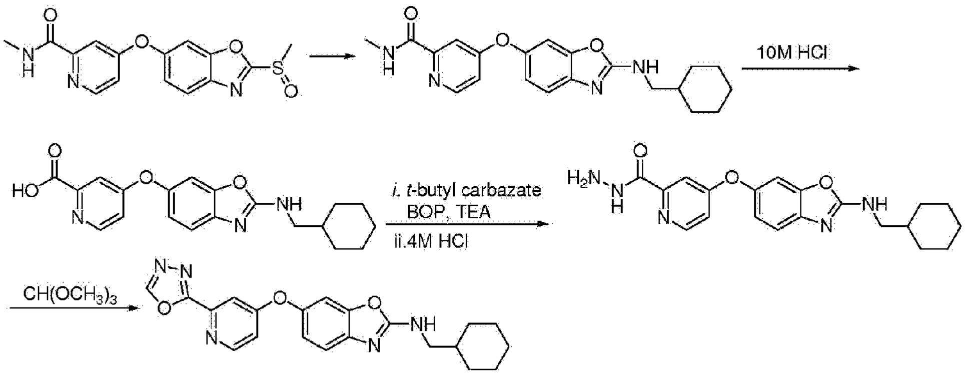
[0105] In Reference Scheme 3, cyanoacetate and 1,5-dibromopentane are coupled to form 1-cyano-cyclohexanecarboxylic acid ethyl ester after cyclization. This product is reduced with hydrogen and Raney nickel. Other reducing agents can be used to reduce the nitrile group to an amine. Other reducing agents include, but are not limited to, catalytic hydrogenation using platinum oxide or Raney nickel or lithium aluminum hydride, diisobutyl aluminum hydride, sodium borohydride, or lithium triethylborohydride. The reduced product is coupled with sulfoxo-benzoxazolyloxy-pyridine. The resulting product from the coupling reaction can be further functionalized or derivatized. For example, in Reference Scheme 3, an ester group can be converted to a carboxylic acid group from hydrolysis and then converted to an amide from reaction with an amine. These reactions are well-known conversions to one skilled in the art.

Reference Scheme 4



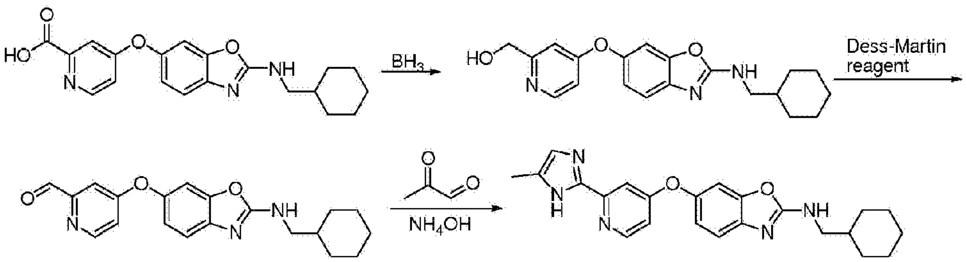
[0106] In Scheme Reference 4, 3-(2-piperidin-1-yl-ethyl)-phenylamine is an example of an amine that can be used to form a compound of the Examples or Reference Examples. 3-(2-Piperidin-1-yl-ethyl)-phenylamine is formed from sulfonation of 2-(3-nitrophenyl)-ethanol, then aminating the resulting methanesulfonic acid 2-(3-nitrophenyl)-ethyl ester, and subsequently reducing the resulting 1-[2-(3-nitrophenyl)-ethyl]-piperidine.

Reference Scheme 5



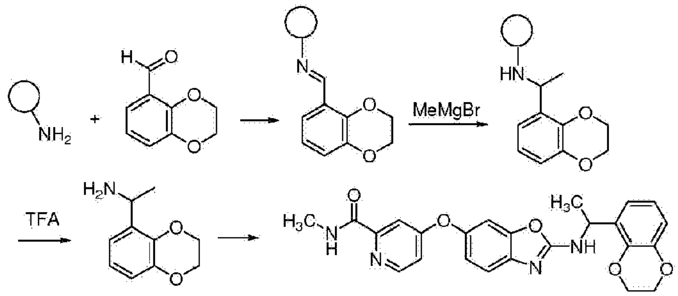
[0107] In Reference Scheme 5, 4-(2-(methylsulfinyl)benzo[d]oxazol-6-yloxy)-*N*-methylpyridine-2-carboxamide is aminated with cyclohexylmethanamine. The resulting 4-(2-(cyclohexylmethylamino)benzo[d]oxazol-6-yloxy)-N-methylpyridine-2-carboxamide is then hydrolyzed to form 4-[2-(cyclohexylmethyl-amino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid. 4-[2-(Cyclohexylmethyl-amino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid then reacts with benzotriazol-1-yloxytris(dimethylamino)-phosphonium hexafluorophosphate, *tert*-butyl carbazate, and triethyl amine to form 4-(2-(cyclohexylmethylamino)benzo[d]oxazol-6-yloxy)pyridine-2-carbohydrazide. 4-(2-(Cyclohexylmethylamino)benzo[d]oxazol-6-yloxy)pyridine-2-carbohydrazide then reacts with trimethyl orthoformate to form a compound of the Examples or Reference Examples.

Reference Scheme 6



[0108] In Reference Scheme 6, a compound of the Examples or Reference Examples can be further functionalized. For instance, 4-(2-(cyclohexylmethylamino)benzo[d]oxazol-6-yloxy)pyridine-2-carboxylic acid is reduced to {4-(2-(cyclohexylmethylamino)benzo[d]oxazol-6-yloxy)pyridine-2-yl}-methanol with borane. Other suitable reducing agents include, but are not limited to, lithium aluminum hydride, aluminum hydride, diisobultyl aluminum hydride, sodium borohydride, or lithium triethylborohydride. {4-(2-(Cyclohexylmethylamino)benzo[d]oxazol-6-yloxy)pyridine-2-yl}-methanol is then oxidized to 4-(2-(cyclohexylmethylamino)benzo[d]oxazol-6-yloxy)pyridine-2-carbaldehyde with Dess-Martin reagent. Other suitable oxidizing agents include, but are not limited to, pyridinium chlorochromate, SO_3 pyridine in DMSO, or conditions commonly refered to as a Swern or Moffet oxidation. 4-(2-(Cyclohexylmethylamino)benzo[d]oxazol-6-yloxy)pyridine-2-carbaldehyde is then converted to cyclohexylmethyl-{6-[2-(5-methyl-1H-imidazol-2-yl)-pyridin-4-yloxy]-benzooxazol-2-yl}-amine by reaction with pyruvic aldehyde.

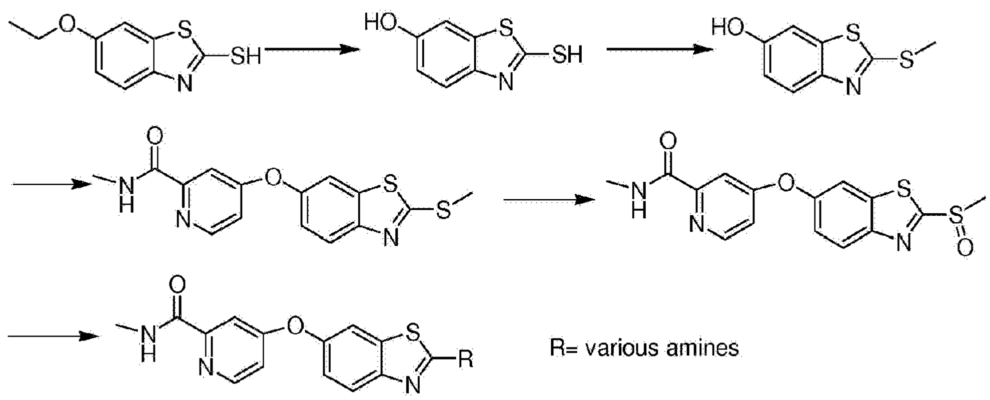
Reference Scheme 7



[0109] In Reference Scheme 7, a compound of the Examples or Reference Examples is synthesized from reaction of 4-(2-methanesulfinyl-benzooxazol-6-yloxy)-pyridine-2-carboxylic acid methylamide (from Example 2) with 1-(2,3-dihydro-benzo[1,4]dioxin-5-yl)-ethylamine. In one instance, 1-(2,3-dihydro-benzo[1,4]dioxin-5-yl)-ethylamine is synthesized via a resin.

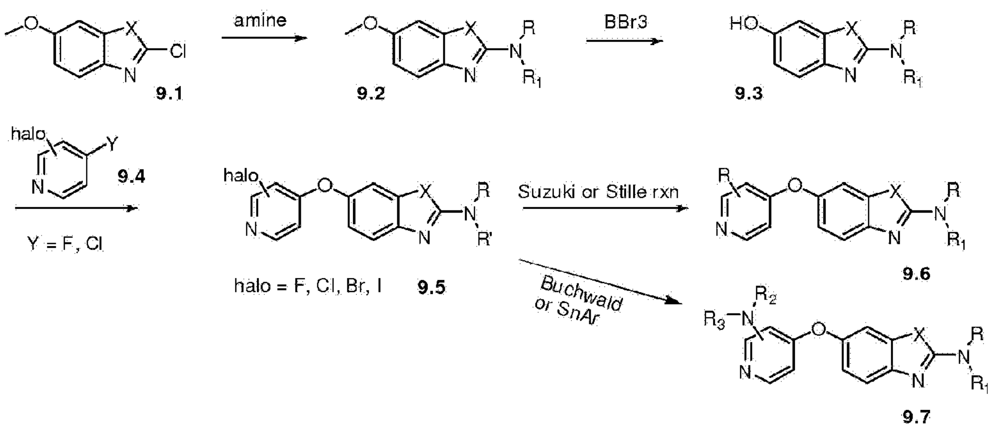
[0110] An amine linked to a resin is reacted with 2,3-dihydro-benzo[1,4]dioxine-5-carbaldehyde, thus giving C-(2,3-dihydro-benzo[1,4]dioxin-5-yl)-methyleneamine. C-(2,3-dihydro-benzo[1,4]dioxin-5-yl)-methyleneamine is derivatized with alkylation at the imino site, such as with methyl magnesium bromide. Other alkylating agents can be used according to the desired molecule. The resulting 1-(2,3-dihydro-benzo[1,4]dioxin-5-yl)-ethylamine is cleaved from the resin. An example of a resin-cleaving agent is trifluoroacetic acid (TFA). The resulting 1-(2,3-dihydro-benzo[1,4]dioxin-5-yl)-ethylamine can be used for synthesis of a compound of the Examples or Reference Examples. For instance, 1-(2,3-dihydro-benzo[1,4]dioxin-5-yl)-ethylamine can be used to react with 4-(2-methanesulfinyl-benzooxazol-6-yloxy)-pyridine-2-carboxylic acid methylamide to form 4-{2-[1-(2,3-dihydro-benzo[1,4]dioxin-5-yl)-ethylamino]-benzooxazol-6-yloxy}-pyridine-2-carboxylic acid methylamide.

Reference Scheme 8



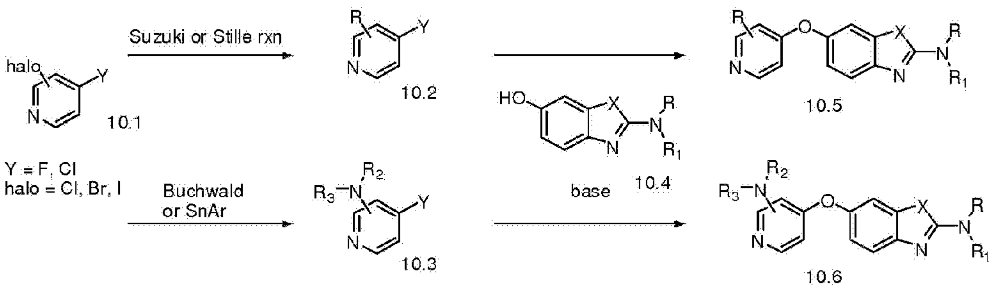
[0111] In Reference Scheme 8, 2-mercapto-benzothiazol-6-ol was prepared as per United States Patent No. 4,873,346. 2-Mercapto-benzothiazol-6-ol is then converted to 2-methylsulfanyl-benzothiazol-6-ol *via* conventional procedures to remove an ethereal protecting group. Reaction of 2-methylsulfanyl-benzothiazol-6-ol with methyl iodide provides alkylation at the thiol position. Reaction of 2-methylsulfanyl-benzothiazol-6-ol with 4-chloro-pyridine-2-carboxylic acid methylamide gives 4-(2-methylsulfanyl-benzothiazol-6-yloxy)-pyridine-2-carboxylic acid methylamide. Subsequent oxidation of 4-(2-methylsulfanyl-benzothiazol-6-yloxy)-pyridine-2-carboxylic acid methylamide gives 4-(2-methanesulfinyl-benzothiazol-6-yloxy)-pyridine-2-carboxylic acid methylamide. 4-(2-Methanesulfinyl-benzothiazol-6-yloxy)-pyridine-2-carboxylic acid methylamide can be a substrate for reaction with various amines. For instance, 4-(2-methanesulfinyl-benzothiazol-6-yloxy)-pyridine-2-carboxylic acid methylamide can react with cyclohexylmethylamine to give 4-[2-(cyclohexylmethyl-amino)-benzothiazol-6-yloxy]-pyridine-2-carboxylic acid methylamide.

Reference Scheme 9



[0112] In Reference Scheme 9 benzoxazoles or benzothiazoles of formula 9.1 can be reacted with a substituted amine to provide intermediates of the formula 9.2. Treatement of intermediates of formula 9.2 with a reagent such as, for example, BBr_3 provides phenols of the formula 9.3. Subsequent treatment of intermediates of formula 9.3 with 4-halo pyridines of formula 9.4 at temperatures generally ranging from, but not limited to, room temperature to 130°C provides in the presence of a base such as, for example, potassium or cesium carbonate provides compounds for formula 9.5. Further treatment with boronic acids or stannanes under conditions known to those practiced in the art as Suzuki or Stille reactions provides compounds of formula 9.6. In addition, treatment of a compound of formula 9.5 with a substituted amine under conditions known to those practiced in the art for a Buchwald reaction or SnAr reaction provides compounds of formula 9.7.

Reference Scheme 10



[0113] In Reference Scheme 10 benzoxazoles or benzothiazoles of formula 10.5 and 10.6 can be prepared starting with a 4-halopyridine for formula 10.1 which can be (1) treated with boronic acids or stannanes under conditions known to those practiced in the art as Suzuki or Stille reactions provides intermediates of formula 10.2 or (2) reacted with a substituted amine under conditions known to those practiced in the art for a Buchwald reaction or SnAr reaction to provide intermediates of formula 10.3. Subsequent reaction of intermediates of formula 10.2 or 10.3 with a phenolic intermediate of formula 10.4 in the presence of a base such as, for example, potassium or cesium carbonate in a solvent such as, for example, dimethyl formamide, acetonitrile or dioxane provides compounds of formula 10.5 and 10.6.

EXAMPLES

[0114] Referring to the examples and reference examples that follow, compounds of the preferred embodiments were synthesized using the methods described herein, or other methods, which are known in the art.

[0115] The compounds and/or intermediates were characterized by high performance liquid chromatography (HPLC) using a Waters Millenium chromatography system with a 2695 Separation Module (Milford, MA). The analytical columns were reversed phase Phenomenex Luna C18 -5 µ, 4.6 x 50 mm, from Alltech (Deerfield, IL). A gradient elution was used (flow 2.5 mL/min), typically starting with 5% acetonitrile/95% water and progressing to 100% acetonitrile over a period of 10 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, MI), or Fisher Scientific (Pittsburgh, PA).

[0116] 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.

[0117] 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; gradient: 5-95% (or 35-95%, or 65-95% or 95-95%) acetonitrile in water with 0.05% TFA over a 4 min period ; flow rate 0.8 mL/min; molecular weight range 200-1500; 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; gradient: 5-95% acetonitrile in water with 0.05% TFA over a 4 min period ; flow rate 0.8 mL/min; molecular weight range 150-850; cone Voltage 50 V; column temperature 30°C). All masses were reported as those of the protonated parent ions.

[0118] GCMS analysis is performed on a Hewlett 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/min; column: 5% phenyl methyl siloxane, Model No. HP 190915-443, dimensions: 30.0 m x 25 m x 0.25 m).

[0119] Nuclear magnetic resonance (NMR) analysis was performed on some of the compounds with a Varian 300 MHz NMR (Palo Alto, CA). The spectral reference was either TMS or the known chemical shift of the solvent. Some compound samples were run at elevated temperatures (e.g., 75°C) to promote increased sample solubility.

[0120] The purity of some of the compounds is assessed by elemental analysis (Desert Analytics, Tucson, AZ).

[0121] Melting points are determined on a Laboratory Devices Mel-Temp apparatus (Holliston, MA).

[0122] Preparative separations are carried out using a Flash 40 chromatography system and KP-Sil, 60A (Biotage, Charlottesville, VA), or by flash column chromatography using silica gel (230-400 mesh) packing material, or by HPLC using a Waters 2767 Sample Manager, C-18 reversed phase column, 30X50 mm, flow 75 mL/min. Typical solvents employed for the Flash 40 Biotage system and flash column chromatography are dichloromethane, methanol, ethyl acetate, hexane, acetone, aqueous ammonia (or ammonium hydroxide), and triethyl amine. Typical solvents employed for the reverse phase HPLC are varying concentrations of acetonitrile and water with 0.1% trifluoroacetic acid.

[0123] It should be understood that the organic compounds according to the preferred embodiments 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 preferred embodiments encompasses any tautomeric form of the drawn structure.

[0124] The examples below as well as throughout the application, the following abbreviations have the following meanings. If not defined, the terms have their generally accepted meanings.

Abbreviations

[0125]

ACN
: Acetonitrile

BINAP
: 2,2'-bis(diphenylphosphino)-1,1'-binapthyl

DCM
: Dichloromethane

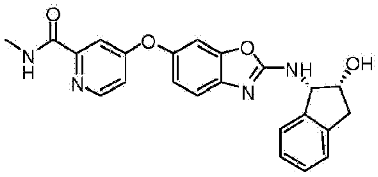
DIEA
diisopropylethylamine
DIPEA
N,N-diisopropylethylamine
DME
1,2-dimethoxyethane
DMF
N,N-dimethylformamide
DMSO
dimethyl sulfoxide
DPPF
1,1'-bis(diphenylphosphino)ferrocene
EtOAc
ethyl acetate
EtOH
ethanol
HATU
2-(7-Aza-1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HPLC
high performance liquid chromatography
MCPBA
meta-chloroperoxybenzoic acid
MeOH
methanol
NBS
N-bromosuccinimide
NMP
N-methyl-2-pyrrolidone
RT
room temperature
THF
tetrahydrofuran

COMPOUNDS ACCORDING TO ANY ONE OF CLAIMS 1 TO 4

Reference example 2

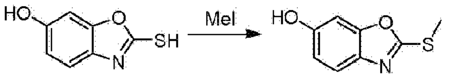
4-[2-((1S,2R)-2-Hydroxy-indan-1-ylamino)-benzoxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide (Table 2, Compound 50)

[0126]



Step 1. Synthesis of 2-(methylthio)benzo[d]oxazol-6-ol

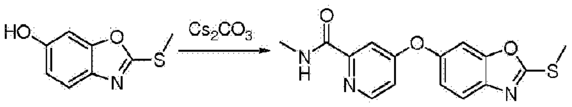
[0127]



[0128] To a solution of the 2-mercaptobenzo[d]oxazol-6-ol (1.55 g, 9.28 mmol, 1.0 eq) in 20 mL of methylene chloride was added triethylamine (1.87 g, 18.56 mmol, 2.0 eq) and methyl iodide (1.77 g, 13.92 mmol, 1.5 eq) at room temperature. The reaction mixture was stirred at rt for 3 hours. The mixture was diluted with 100 mL of methylene chloride. The resulting mixture was washed with water (10 mL), brine (10mL), then dried over $MgSO_4$, filtered, and evaporated under reduced pressure to give crude product, which was purified by silica gel column eluted with ethyl acetate and hexane to give the titled compound. MH+ = 182.

Step 2. Synthesis of 4-(2-(methylthio)benzo[d]oxazol-6-yloxy)-N-methylpyridine-2-carboxamide

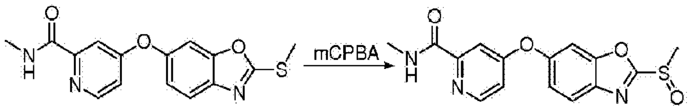
[0129]



[0130] To a solution of 2-(methylthio)benzo[d]oxazol-6-ol (8.5 g, 46.7 mmol, 1 eq) in 80 mL of *N*,*N*-dimethylformamide was added 4-chloro-*N*-methylpyridine-2-carboxamide (16.0 g, 93.4 mmol, 2.0 eq) and cesium carbonate (45.7 g, 140.1 mmol, 3.0 eq). The reaction mixture was stirred at 75°C for 6 hours. After the mixture was cooled to room temperature, the mixture was added 120 mL of water. After filtration, the solid was purified by silica gel column eluted with ethyl acetate and hexane to give the titled compound. MH+ = 316.

Step 3. Synthesis of 4-(2-(methylsulfinyl)benzo[d]oxazol-6-yloxy)-N-methylpyridine-2-carboxamide

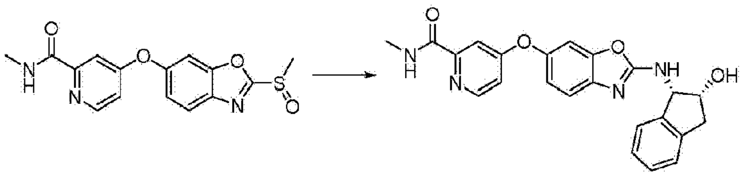
[0131]



[0132] To a solution of the 4-(2-(methylthio)benzo[d]oxazol-6-yloxy)-N-methylpyridine-2-carboxamide (1.26 g, 4.0 mmol, 1.0 eq) in 40 mL of methylene chloride was added 3-chloroperoxybenzoic acid (70%, 989 mg, 4.4 mmol, 1.1 eq). The reaction mixture was stirred at room temperature for 5 hours and then was diluted with 200 mL of methylene chloride. The resulting mixture was washed with aqueous sodium bicarbonate and brine then dried over $MgSO_4$, filtered, and evaporated under reduced pressure to give crude product, which was used to next step without further purification. MH+ = 332.

Step 4. 4-[2-((1S,2R)-2-Hydroxy-indan-1-ylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide

[0133]

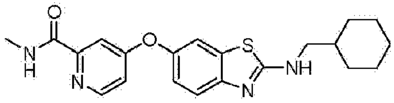


A solution of 4-(2-(methylsulfinyl)benzo[d]oxazol-6-yloxy)-N-methylpyridine-2-carboxamide (17 mg, 0.05 mmol, 1.0 eq) and (1*S*,2*R*)-1-amino-2,3-dihydro-1H-inden-2-ol (30 mg, 0.2 mml, 4.0 eq) in 1 mL of *N,N*-dimethylacetamide was heated in the microwave at 90°C for 600 seconds. The crude product was purified by reverse phase prep HPLC to give the title compound. MH= = 417.0.

Reference example 15 (Reference Scheme 8)

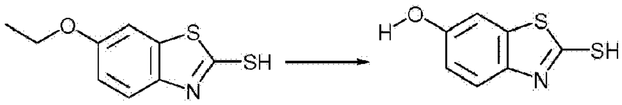
Preparation of 4-[2-(Cyclohexylmethyl-amino)-benzothiazol-6-yloxy]-pyridine-2-carboxylic acid methylamide (Table 2, Compound 128)

[0134]



Step 1. Preparation of 2-Mercapto-benzothiazol-6-ol

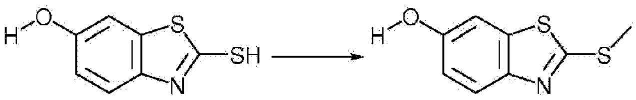
[0135]



[0136] As per the United States Patent 4,873,346 - Substituted Benzothiazoles, Benzimidazoles and benzoxazoles; Anderson, David J.; The Upjohn Company, Kalamazoo, Michigan; Oct. 10th, 1989. M+H = 184.0

Step 2. Preparation of 2-Methylsulfanyl-benzothiazol-6-ol

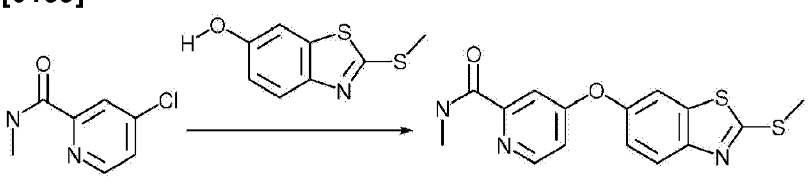
[0137]



[0138] To the ice cooled solution of 2-mercapto-benzothiazol-6-ol from step 1 (3.80g, 20.76 mmol, 1.0 eq) in DCM (40mL, 0.5M) at 0°C, was added triethylamine (7.29mL, 51.91 mmol, 2.5 eq) followed by iodomethane (1.93mL, 31.14mmol, 1.5eq). The reaction was stirred from 0°C to -10°C for 3 hours. The solvent was removed *in vacuo.* Water (ca.200mL) was added and the aqueous layer was extracted with ethyl acetate (3X150mL). The organic layer was dried over sodium sulfate, filtered, and evaporated *in vacuo* to yield 2-methylsulfanyl-benzothiazol-6-ol as light green powder (3.76g, 92%). The crude product was used in the next step without purification. M+H = 198.0

Step 3. Preparation of 4-(2-Methylsulfanyl-benzothiazol-6-yloxy)-pyridine-2-carboxylic acid methylamide

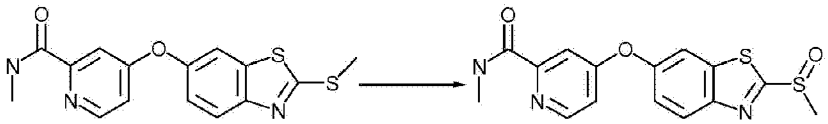
[0139]



[0140] To the solution of 2-methylsulfanyl-benzothiazol-6-ol (3.76g, 19.08mmol, 1.0eq) in DMF (25mL), was added $CsCO_3$ (15.54g, 47.70 mmol, 2.5 eq) at room temperature. After stirring for a while, 4-chloro-pyridine-2-carboxylic acid methylamide (4.86g, 28.62mmol, 1.5eq) was added to the mixture and the mixture was stirred at 70°C under reflux condenser overnight. After cooling the reaction mixture in ice bath, water (100mL) was added and the aqueous layer was extracted with ethyl acetate (3X150mL). The organic layer was dried over sodium sulfate, filtered, and evaporated *in vacuo.* The crude product was purified using 20g of ISCO Silica Gel column (0%-50%-80%-100% ethyl acetate-hexane mixture over 45 min 40mL/min run) to yield 4-(2-methylsulfanyl-benzothiazol-6-yloxy)-pyridine-2-carboxylic acid methylamide (3.88g, 62%) as a white solid. M+H = 332.1

Step 4. Preparation of 4-(2-Methanesulfinyl-benzothiazol-6-yloxy)-pyridine-2-carboxylic acid methylamide

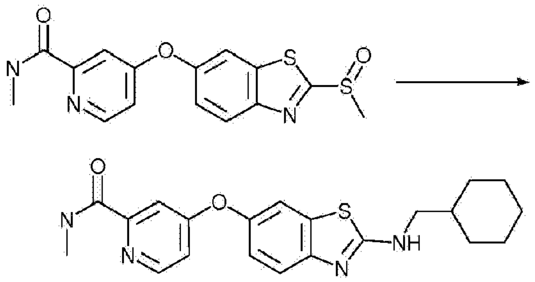
[0141]



[0142] To the solution of 4-(2-methylsulfanyl-benzothiazol-6-yloxy)-pyridine-2-carboxylic acid methylamide from step 3 (3.88g, 11.72mmol, 1.0eq) in DCM (20mL) at 0°C, was added MCPBA (77%, 2.88g, 1.1eq). The mixture was stirred at this temperature for one hour. Saturated sodium bicarbonate solution (100mL) was added. The aqueous layer was extracted with DCM (3X150mL). The organic layer was dried over sodium sulfate, filtered, and evaporated *in vacuo* to yield 4-(2-methanesulfinyl-benzothiazol-6-yloxy)-pyridine-2-carboxylic acid methylamide as white powder in quantitative yields. The crude product was used in the next step without purification. M+H = 348.0.

Step 5. Preparation of 4-[2-(Cyclohexylmethyl-amino)-benzothiazol-6-yloxy]-pyridine-2-carboxylic acid methylamide

[0143]

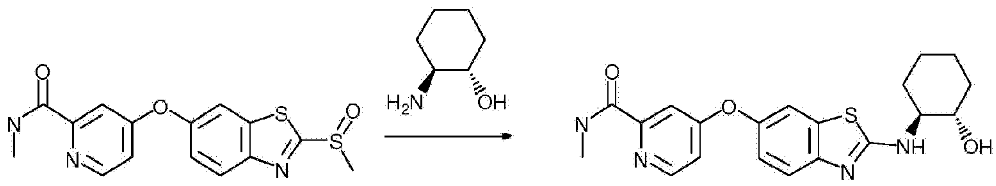


[0144] To the solution of 4-(2-methanesulfinyl-benzothiazol-6-yloxy)-pyridine-2-carboxylic acid methylamide (25mg, 0.072 mmol, 1.0eq) in DMF (500µL), was added cyclohexylmethylamine (18.7µL, 0.144 mmol, 2.0eq) and reaction was stirred at 70°C overnight. The neat reaction mixture was purified on reverse phase preparatory HPLC. Pure fractions were lyophilized as TFA salts. M+H = 397.1

Example 16

Preparation of 4-(2-((1S,2S)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide (Table 2, Compound 137)

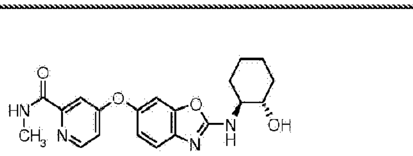
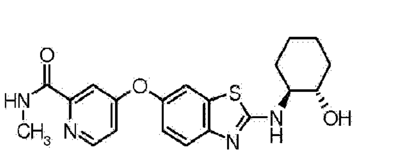
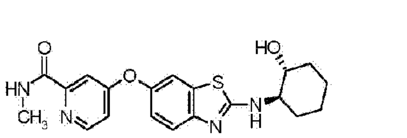
[0145]



[0146] To the solution of 4-(2-methanesulfinyl-benzothiazol-6-yloxy)-pyridine-2-carboxylic acid methylamide (70mg, 0.202 mmol, 1.0eq; Reference Example 15-step 4) in DMA (600μL), was added (1S,2S)-2-aminocyclohexanol hydrochloride (92 mg, 0.606 mmol, 3.0eq) followed by diisopropylethylamine (0.21 mL, 1.21 mmol). The reaction was heated at 110 °C for 24-hours. The neat reaction mixture was purified on reverse phase preparatory HPLC. Pure fractions were lyophilized as TFA salts. M+H = 398

[0147] The compounds in the following Table 2 were made by the general procedures described above.

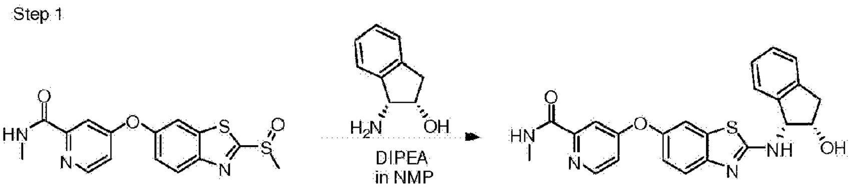
Table 2

Compound	Structure	M+H; Rt(min)	Compound Name
52		383.0; 1.94	4-[2-((1S,2S)-2-Hydroxy-cyclohexylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide
137		399.1; 1.94	4-[2-((1S,2S)-2-Hydroxy-cyclohexylamino)-benzothiazol-6-yloxy]-pyridine-2-carboxylic acid methylamide
157		399.1; 1.94	4-[2-((1R,2R)-2-Hydroxy-cyclohexylamino)-benzothiazol-6-yloxy]-pyridine-2-carboxylic acid methylamide

Reference example 162

Preparation of 4-(2-((1R,2S)-2-hydroxy-2,3-dihydro-1H-inden-1-ylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide

[0148] The subject compound was prepared according to the general Scheme below

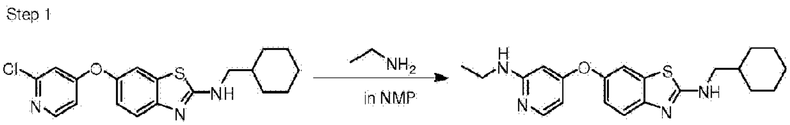


[0149] To the solution of N-methyl-4-(2-(methylsulfinyl)benzo[d]thiazol-6-yloxy)picolinamide (300 mg, 0.86 mmol) in 5 ml of NMP was added (1R,2S)-1-amino-2,3-dihydro-1H-inden-2-ol (597 mg, 4 mmol) and DIPEA (300 µL, 1.73 mmol). The reaction solution was stirred at 105°c for 24 hours. The crude reaction solution was purified on prep HPLC and evaporated *in vaccuo* to give 4-(2-((1R,2S)-2-hydroxy-2,3-dihydro-1H-inden-1-ylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide (347 mg, 0.63 mmol) as TFA salt. ES/MS *m*/*z* 433.1(MH$^+$).

Reference example 170

Preparation of N-(cyclohexylmethyl)-6-(2-(ethylamino)pyridin-4-yloxy)benzo[d]thiazol-2-amine

[0150]

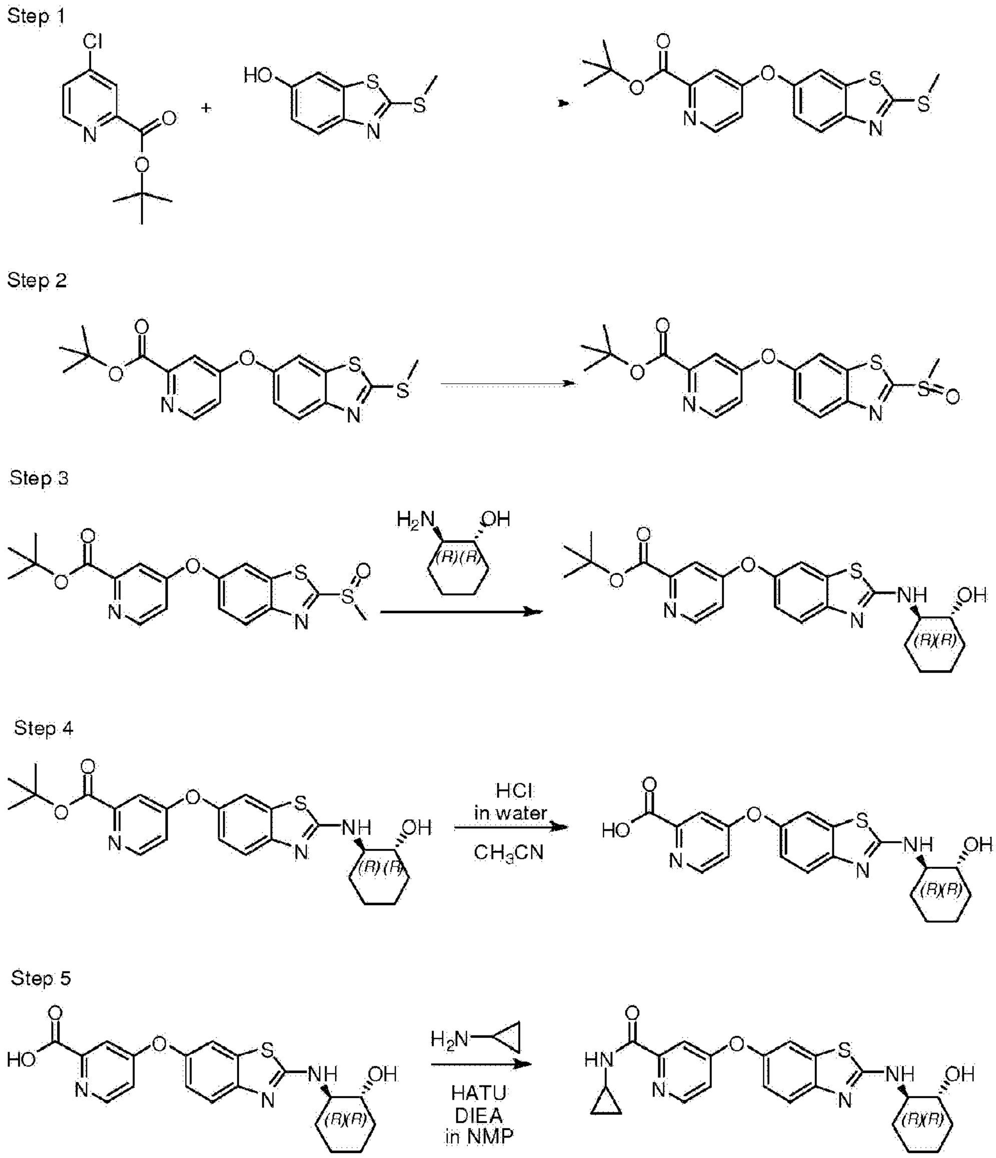


[0151] To the reaction solution of 6-(2-chloropyridin-4-yloxy)-N-(cyclohexylmethyl) benzo[d]thiazol-2-amine (12 mg, 0.03 mmol) in 400 µL of NMP was added DIPEA (9 µL, 0.05 mmol) and 70% ethylamine in water (200 µL, 2.51 mmol). The reaction mixture was stirred at 110 °C for 96 hours or until done by LC. The crude reaction mixture was filtered, purified on prep HPLC and evaporated *in vaccuo* to give N-(cyclohexylmethyl)-6-(2-(ethylamino)pyridin-4-yloxy)benzo[d]thiazol-2-amine as TFA salt (1.8 mg). ES/MS *m*/*z* 383.1 (MH$^+$).

Example 171

N-cyclopropyl-4-(2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-yloxy)picolinamide

[0152] The subject compound was prepared according to the general Scheme below:



Step 1 . Synthesis of tert-butyl 4-(2-(methylthio)benzo[d]thiazol-6-yloxy)picolinate

[0153] To a solution of 2-(methylthio)benzo[d]thiazol-6-ol (5.0 g, 25.38 mmol, 1.0 eq) in 25 mL of *N,N*-dimethylformamide was added tert-butyl 4-chloropicolinate (8.13 g, 38.07 mmol, 1.5 eq) and cesium carbonate (20.67 g, 63.45 mmol, 2.5 eq). The reaction mixture was stirred at 75°C for 6 hours. After the mixture was cooled to room temperature, the mixture was added 120 mL of water and aqueous phase extracted with ethyl acetate (3X150mL), combined organic layers were dried over sodium sulfate. After filtration, the solid was purified by silica gel column eluted with ethyl acetate-hexane 0%-50% mixture to give 5.84g of the titled compound as brown powder (62%). MH+ = 375.

[0154] Step 2. Synthesis of tert-butyl 4-(2-(methylsulfinyl)benzo[d]thiazol-6-yloxy) picoli- nate

[0155] To a solution of the tert-butyl 4-(2-(methylthio)benzo[d]thiazol-6-yloxy)picolinate (5.84 g, 15.61 mmol, 1.0 eq) in 25 mL of methylene chloride was added 3-chloroperoxybenzoic acid (77%, 3.84 g, 17.17 mmol, 1.1 eq). The reaction mixture was stirred at room temperature for 1.5 hours and then was diluted with 200 mL of methylene chloride. The resulting mixture was washed with aqueous sodium bicarbonate and brine then dried over $MgSO_4$, filtered, and evaporated under reduced pressure to give crude product, which was used to next step without further purification. MH+ = 391.0.

Step 3. Preparation of tert-butyl 4-(2-((1R,2R)-2 hydroxycyclohexylamino)-benzo[d]thiazol-6-yloxy)picolinate

[0156] To the solution of tert-butyl 4-(2-(methylsulfinyl)benzo[d]thiazol-6-yloxy)picolinate (500 mg, 1.25 mmol) in 10 ml ofNMP was added (1R,2R)-cyclohexane-1,2-diamine (581 mg, 3.84 mmol) and DIPEA (0.995 ml, 5.76 mmol). The reaction solution was stirred at 100°c for 3 days. The crude reaction solution was purified on prep HPLC and evaporated *in vaccuo* to give tert-butyl 4-(2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-yloxy)picolinate (240 mg, 0.544 mmol) as white powder. ES/MS *m/z* 442.5(MH^+).

Step 4. Preparation of 4-(2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-yloxy)picolinic acid

[0157] To the solution of tert-butyl 4-(2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-yloxy)picolinate (250 mg, 0566 mmol) in 10 ml of acetonitrile was added 6 M of hydrochloric acid (1 ml, 6 mmol). The reaction solution was stirred at room temperature for 1 hour and then at 60°c for 2 hours. The crude reaction solution was concentrated and re-dissolved with 10 ml of acetonitrile. The resulting solution was evaporated *in vaccuo* to give light brown oily product 4-(2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-yloxy)picolinic acid (215 mg, 0.56 mmol). ES/MS *m/z* 386.5(MH^+).

Step 5. Preparation of N-cyclopropyl-4-(2-((1R,2R)-2-hydroxycyclohexylamino)-benzo[d]thiazol-6-yloxy)picolinamide

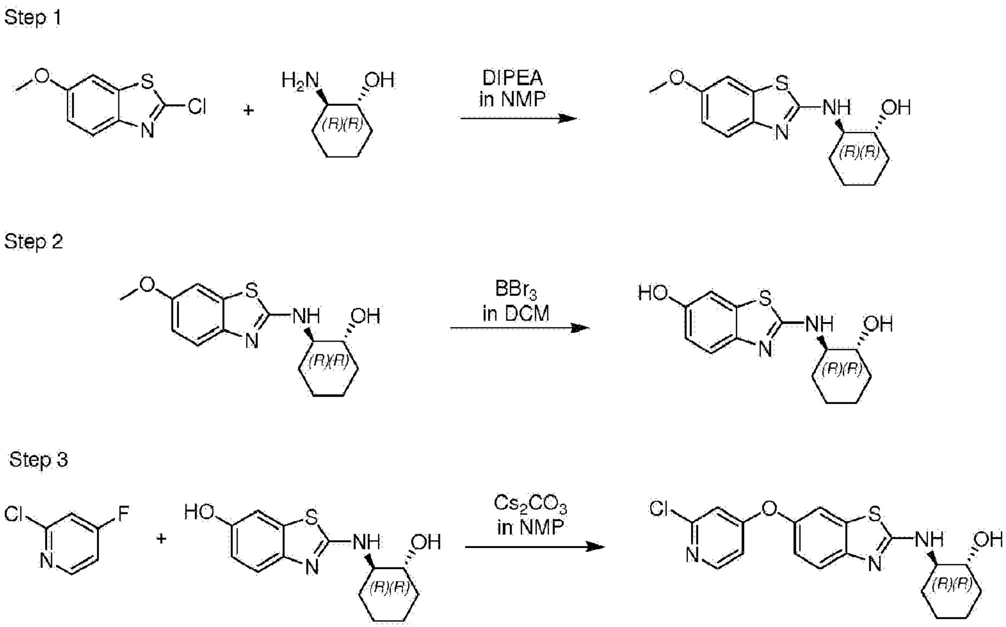
[0158] To the reaction solution of 4-(2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-

yloxy)picolinic acid (5 mg, 39 µmol), HATU (15 mg, 39 µmol) and DIPEA (14 µL, 78 µmol) in 1 ml ofNMP was added cyclopropylamine (7ul mg, 30 µmol). The reaction solution was stirred at room temperature for 12 hours. The crude reaction solution was purified on prep HPLC and evaporated *in vaccuo* to give N-cyclopropyl-4-(2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-yloxy)picolinamide (1 mg, 2.3 µmol) as white powder. ES/MS *m*/*z* 425.2(MH^+).

Example 173

Preparation of (1R,2R)-2-(6-(2-chloropyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol

[0159] The subject compound was prepared according to the general Scheme below:



Step 1. Preparation of (1R,2R)-2-(6-methoxybenzo[d]thiazol-2-ylamino)cyclohexanol.

[0160] To the solution of 2-chloro-6-methoxybenzo[d]thiazole (1.0 g, 5 mmol) in 5.5 ml of NMP was added (1R, 2R)-2-aminocyclohexanol hydrochloride (910 mg, 6 mmol) and DIPEA (2.44 ml, 14 mmol). The reaction solution was stirred at 115°c for 96 hours. The crude reaction solution was purified by prep HPLC to give purified fractions that was combined and neutralized with solid $NaHCO_3$. The resulting solution was extracted with ethyl acetate (2x300ml). The combined organic layers were washed with water (60 ml) and brine (60 ml), then dried over Na_2SO_4 and evaporated *in vaccuo* to give (1R,2R)-2-(6-methoxybenzo[d]thiazol-2-ylamino)cyclohexanol (1.06 g, 3.81 mmol) as an ivory solid. ES/MS *m/z* 279.1(MH$^+$).

Step 2. Preparation of 2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-ol.

[0161] To the solution of (1R, 2R)-2-(6-methoxybenzo[d]thiazol-2-ylamino)cyclohexanol (1.06 g, 3.81 mmol) in 16 ml of DCM was added 1 M boron tribromide in DCM (8 ml, 8 mmol) slowly at 0°c. The reaction solution was stirred at room temperature for 2 hours. Removal of all solvent *in vaccuo,* followed by quenching with water (ca. 30ml) and diluted $NaHCO_3$ solution, and extraction of aqueous phase with ethyl acetate (3x100ml) and drying of combined organic extracts over Na_2SO_4 and subsequent removal of ethyl acetate *in vaccuo* yielded the desired product (1.16 g) as pink solid. The residue was purified by flash column chromatography to give 2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-ol (1.0 g, 3.78 mmol) as brown solid. ES/MS *m/z* 265.1(MH$^+$).

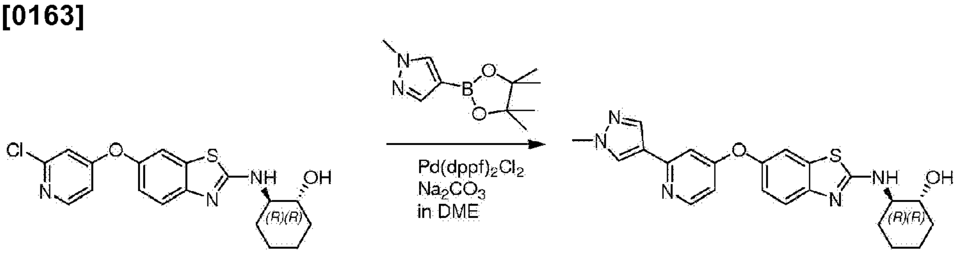
Step 3. Preparation of (1R,2R)-2-(6-(2-chloropyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol.

[0162] To the mixture of 2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-ol (265 mg, 1 mmol) and cesium carbonate (651 mg, 2 mmol) in 3 ml ofNMP was added 2-chloro-4-fluoropyridine(263 mg, 2 mmol). The reaction mixture was stirred at 60°c for 20 hours. The crude reaction mixture was filtered and then purified on prep HPLC to give (1R,2R)-2-(6-(2-chloropyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol as powder (341 mg, 0.9 mmol). ES/MS *m/z* 376.0(MH$^+$).

Example 174

Preparation of (1R,2R)-2-(6-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol

[0163]



Step 4. Preparation of (1R,2R)-2-(6-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-

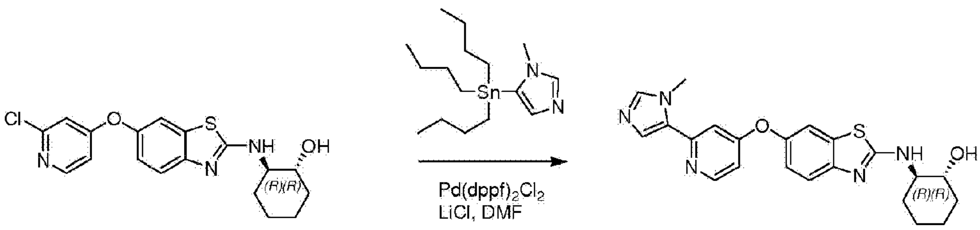
yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol.

[0164] To the reaction mixture of (1R,2R)-2-(6-(2-chloropyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol (20 mg, 40 µmol) in 400 µL of DME, 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (21 mg, 100 µmol), $Pd(dppf)_2Cl_2$ (4 mg, 5 µmol) and 2M Na_2CO_3 (100 µL, 200 µmol) were added. The reaction mixture was stirred at 90°c for 24hours. The reaction mixture was poured into 10 ml of saturated $NaHCO_3$ solution and extracted with ethyl acetate (2x30ml). The combined organic layers were washed with water (2x10ml) and brine (20 ml), then dried over Na_2SO_4 and evaporated *in vaccuo* to give a brown solid (65 mg) that was purified on prep HPLC to give (1R,2R)-2-(6-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol as powder (6.4 mg). ES/MS *m*/*z* 422.2(MH^+).

Example 175

Preparation of (1R,2R)-2-(6-(2-(1-methyl-1H-imidazol-5-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol

[0165] The subject compound was prepared according to the general Scheme below:



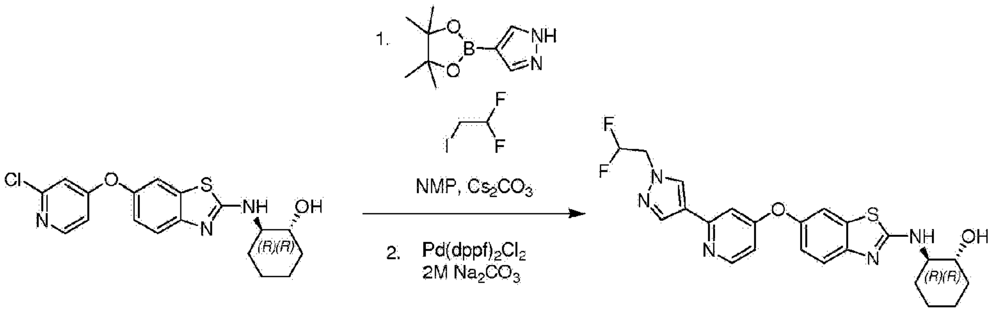
Preparation of (1R,2R)-2-(6-(2-(1-methyl-1H-imidazol-5-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol.

[0166] To the reaction mixture of (1R,2R)-2-(6-(2-chloropyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol (11 mg, 0.029 mmol) in 0.5 ml of DMF was added $Pd(dppf)_2Cl_2$ (7.2 mg, 0.0088 mmol), LiCl (19 mg, 0.44 mmol) and then 1-methyl-5-(tributylstannyl)-1H-imidazole (44 mg, 0.117 mmol). The reaction solution was stirred at 105-110 °C for 18 hours or done by LC. The crude reaction mixture was filtered, purified on prep HPLC and lyophilized to give (1R,2R)-2-(6-(2-(1-methyl-1H-imidazol-5-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol as TFA salt (3.5 mg). ES/MS *m*/*z* 422.1(MH^+).

Example 176

Preparation of (1R,2R)-2-(6-(2-(1-(2,2-difluoroethyl)-1H-pyrazol-4-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol

[0167] The subject compound was prepared according to the general Scheme below:



Preparation of (1R,2R)-2-(6-(2-(1-(2,2-difluoroethyl)-1H-pyrazol-4-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol.

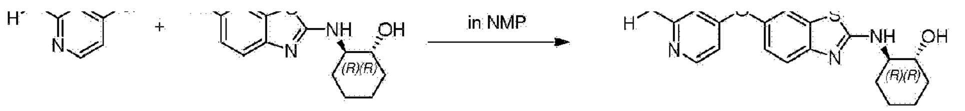
[0168] To the reaction mixture of 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (210 mg, 1.08 mmol) in 2.0 ml of NMP was added Cesium Carbonate (672 mg, 2.06mmol). The reaction mixture was stirred for 5 minutes and then 1,1-difluoro-2-iodoethane (197 mg, 1.03 mmol) was added and stirred at RT for 40hours. From the above crude reaction mixture remove (0.8 ml, 0.432 mol) and use. (The remaining 1.2 ml was stored in freezer). To the 0.8 ml reaction mixture add (1R,2R)-2-(6-(2-chloropyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol (20 mg, 0.053 mmol), Pd(dppf)$_2$Cl$_2$(15.2 mg, 0.019 mmol) and 2M Na_2CO_3 (0.150 ml, 0.3 mmol). The reaction mixture was microwaved at 140 °C for 720 seconds. The crude reaction mixture was filtered, purified on prep HPLC and lyophilized to give (1R,2R)-2-(6-(2-(1-(2,2-difluoroethyl)-1H-pyrazol-4-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol as TFA salt (4.6 mg). ES/MS *m/z* 472.0 (MH^+).

Example 177

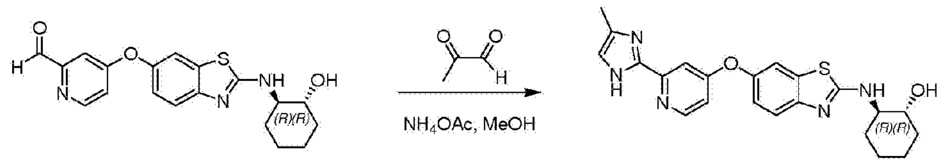
Preparation of (1R,2R)-2-(6-(2-(4-methyl-1H-imidazol-2-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol

[0169] The subject compound was prepared according to the general Scheme below:

Step 1



Step 2



Step 1. Preparation of 4-(2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-yloxy)picolinaldehyde.

[0170] To the reaction mixture of 2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-ol (90 mg, 0.34 mmol) in 1.9 ml ofNMP was added Cesium Carbonate (232 mg, 0.71mmol) and 4-chloropicolinaldehyde (125 mg, 0.883 mmol). The reaction mixture was stirred at RT for 10 minutes and then microwaved at 150 °C for 750 seconds. The crude reaction mixture was filtered, purified on prep HPLC and lyophilized to give 4-(2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-yloxy)picolinaldehyde as TFA salt (88 mg). ES/MS *m*/*z* 388.1(MH^+) as the hydrate (+18).

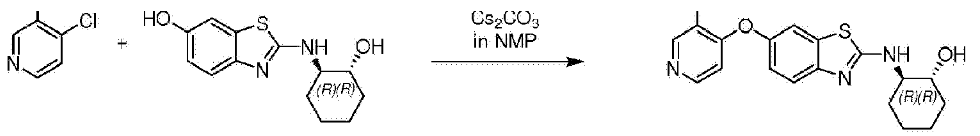
Step 2. Preparation of (1R,2R)-2-(6-(2-(4-methyl-1H-imidazol-2-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol.

[0171] To the reaction mixture of 4-(2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-yloxy)picolinaldehyde (16 mg, 0.041 mmol) in 0.75 ml of MeOH was added ammonium acetate (32 mg, 0.41 mmol) and 2-oxopropanal 40% wt solution of in water (0.037 ml, 0.21 mmol). The reaction mixture was stirred at 70 °C for 2 hours. The crude reaction mixture was concentrated, re-dissolved in 0.8 ml DMF, filtered, purified on prep HPLC and lyophilized to give (1R,2R)-2-(6-(2-(4-methyl-1H-imidazol-2-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol as TFA salt (3.2 mg). ES/MS *m*/*z* 422.1 (MH^+).

EXAMPLE 178

Preparation of (1R,2R)-2-(6-(3-bromopyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol

[0172] The subject compound was prepared according to the general Scheme below:



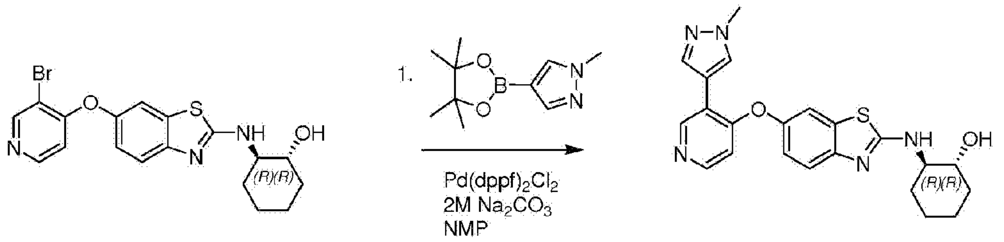
Preparation of (1R,2R)-2-(6-(3-bromopyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol.

[0173] To the reaction mixture of 2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-ol (12.5 mg, 0.047 mmol) in 0.4 ml of NMP was added Cesium Carbonate (39 mg, 0.118mmol) and stirred at RT for 1-3 minutes. To this mixture was added 3-bromo-4-chloropyridine (18.2 mg, 0.094 mmol). The reaction mixture was stirred at 90 °C for 4 hours or until done by LC. The crude reaction mixture was filtered, purified on prep HPLC and lyophilized to (1R,2R)-2-(6-(3-bromopyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol as TFA salt (9.2 mg). ES/MS *m/z* 420.1/422.0 (MH^+).

EXAMPLE 179

Preparation of (1R,2R)-2-(6-(3-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol

[0174] The subject compound was prepared according to the general Scheme below:



Preparation of (1R,2R)-2-(6-(3-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol.

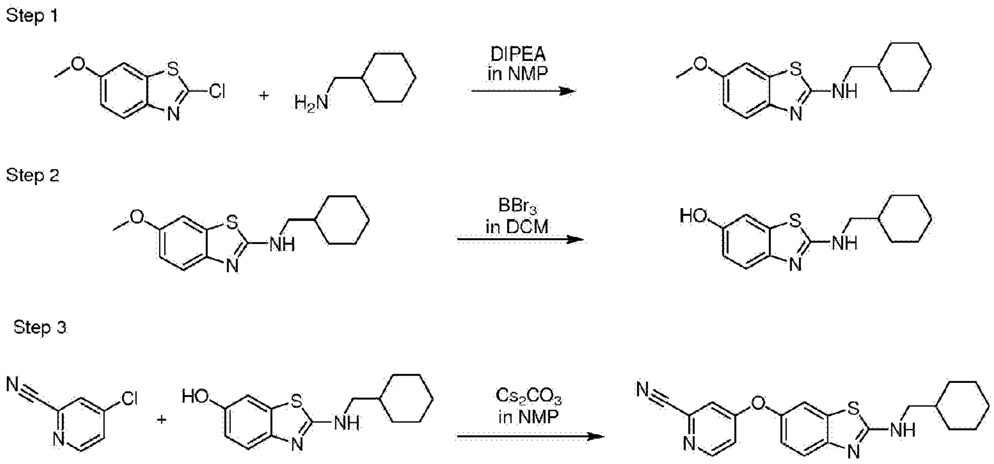
[0175] To the reaction mixture of (1R,2R)-2-(6-(3-bromopyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol (15 mg, 0.036 mmol) in 0.5 ml of NMP was added $Pd(dppf)_2Cl_2$ (8.8 mg, 0.0107 mmol), 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (30 mg, 0.143 mmol) and 2M Na_2CO_3 (0.12 ml, 0.24 mmol). The reaction solution was stirred at 105-110 °C for 2 hours or until done by LC. The crude reaction mixture was filtered, purified on prep HPLC and lyophilized to give (1R,2R)-2-(6-(3-(1-methyl-1H-pyrazol-4-yl)pyridin-4-

yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol as TFA salt (5.5 mg). ES/MS *m/z* 422.1(MH^+).

Reference example 180

Preparation of 4-(2-(cyclohexylmethylamino)benzo[d]thiazol-6-yloxy)picolinonitrile

[0176] The subject compound was prepared according to the general Scheme below:



Step 1. Preparation of N-(cyclohexylmethyl)-6-methoxybenzo[d]thiazol-2-amine.

[0177] To the solution of 2-chloro-6-methoxybenzo[d]thiazole (900 mg, 4.5 mmol) in 4.5 ml ofNMP was added cyclohexylmethanamine (865 mg, 7.65 mmol) and DIPEA (1.57 ml, 9.0 mmol). The reaction solution was stirred at 105-110 °C for 66 hours. The reaction was worked up by adding 250 ml ethyl acetate and washed with 2 x 60 ml of saturated $NaHCO_3$, 3 x 60 ml water, 1 x 60 ml saturated NaCl, dried with sodium sulfate, filtered and concentrated *in vaccuo* to give N-(cyclohexylmethyl)-6-methoxybenzo[d]thiazol-2-amine as solid (1.18 grams). ES/MS *m/z* 277.1(MH^+).

Step 2. Preparation of 2-(cyclohexylmethylamino)benzo[d]thiazol-6-ol.

[0178] To the solution of N-(cyclohexylmethyl)-6-methoxybenzo[d]thiazol-2-amine (1.40 g, 5.05 mmol) in 12 ml of DCM was added 1 M boron tribromide in DCM (10.6 ml, 10.6 mmol) slowly over about 3 minutes at 0 °C. The reaction solution was stirred at 0 °C for 20 min and then at RT for 2 hr. The reaction mixture was concentrated to a solid. To the residual solids add 200 ml of ethyl acetate and 50 ml of water and stir at RT for 10 minutes. With stirring, carefully add excess solid $NaHCO_3$ until basic. Stir at RT about 1 hour to dissolve the solids.

Remove the aqueous layer and extract with 100 ml of ethyl acetate. Combine organic layers and wash with 1 x 30 ml water, 1 x 25 ml saturated NaCl solution and dry with sodium sulfate. This mixture was filter through a silica gel plug (1.25 in. x 3 in.) and flushed with ethyl acetate. The filtrate was concentrated under reduced pressure to give 2-(cyclohexylmethylamino)benzo[d]thiazol-6-ol as solid (1.32 grams). ES/MS *m/z* 263.1(MH^+).

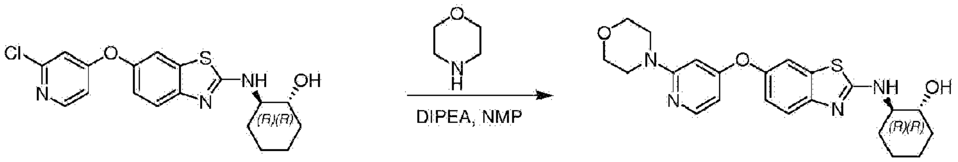
Step 3. Preparation of 4-(2-(cyclohexylmethylamino)benzo[d]thiazol-6-yloxy)picolinonitrile.

[0179] To the reaction mixture of 2-(cyclohexylmethylamino)benzo[d]thiazol-6-ol (18 mg, 0.068 mmol) in 0.4 ml of NMP was added Cesium Carbonate (56 mg, 0.171mmol) and stirred at RT for 1-3 minutes. To this mixture was added 4-chloropicolinonitrile (19 mg, 0.136 mmol). The reaction mixture was stirred at 60 °C for 5 hours or until done by LC. The crude reaction mixture was filtered, purified on prep HPLC and lyophilized to give 4-(2-(cyclohexylmethylamino)benzo[d]thiazol-6-yloxy)picolinonitrile as TFA salt (9.8 mg). ES/MS *m/z* 365.1(MH^+).

EXAMPLE 183

Preparation of (1R,2R)-2-(6-(2-morpholinopyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol

[0180]



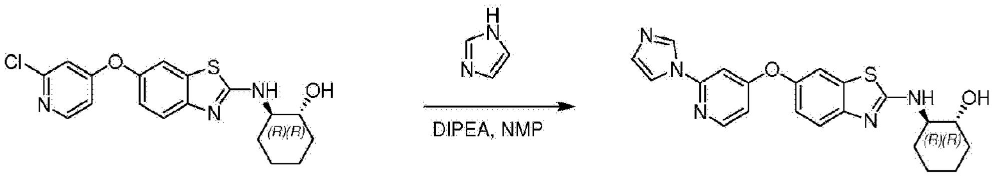
Preparation of (1R,2R)-2-(6-(2-morpholinopyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol.

[0181] To the reaction mixture of (1R,2R)-2-(6-(2-chloropyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol (14 mg, 0.037 mmol) in 0.4 ml of NMP was added (DIPEA) diisopropylethylamine (13ul, 0.074 mmol) and morpholine (49 mg , 0.558 mmol). The reaction mixture was stirred at 110 °C for 48 hours or until done by LC. The crude reaction mixture was filtered, purified on prep HPLC and lyophilized to give (1R,2R)-2-(6-(2-morpholinopyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol as TFA salt (3.7 mg). ES/MS *m/z* 427.1(MH^+).

EXAMPLE 187

Preparation of (1R,2R)-2-(6-(2-(1H-imidazol-1-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol

[0182]



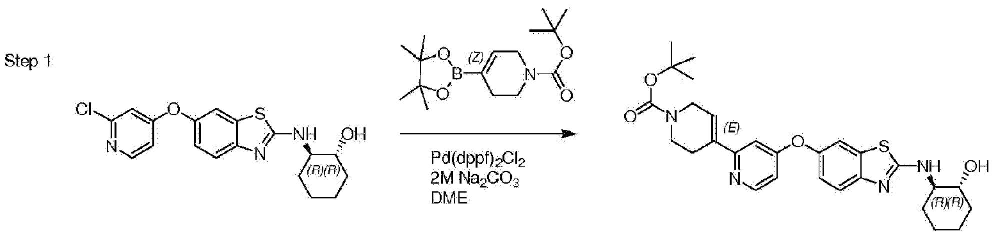
Preparation of (1R,2R)-2-(6-(2-(1H-imidazol-1-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol.

[0183] To the reaction mixture of (1R,2R)-2-(6-(2-chloropyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol (12 mg, 0.032 mmol) in 0.55 ml of NMP was added (DIPEA) diisopropylethylamine (17ul, 0.096 mmol) and 1H-imidazole (180 mg , 2.64 mmol). The reaction mixture was followed by LC, LCMS and microwaved as follows: (150 °C for 750 seconds, 230 °C for 750 seconds, 250 °C for 1000 seconds, again at 250 °C for 1000 seconds). The crude reaction mixture was filtered, purified on prep HPLC and lyophilized to give (1R,2R)-2-(6-(2-(1H-imidazol-1-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol as TFA salt (1.4 mg). ES/MS *m/z* 408.2(MH^+).

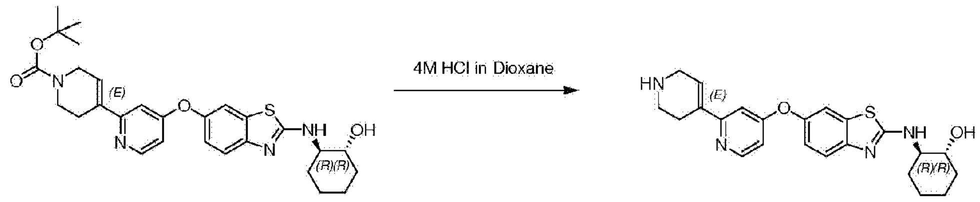
Example 188

Preparation of (1R,2R)-2-(6-(2-(1,2,3,6-tetrahydropyridin-4-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol

[0184]



Step 2



Step 1. Preparation of tert-butyl 4-(4-(2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-yloxy)pyridin-2-yl)-5,6-dihydropyridine-1(2H)-carboxylate.

[0185] To the reaction mixture of (1R,2R)-2-(6-(2-chloropyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol (11 mg, 0.029 mmol) in 0.5 ml of DME, tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-dihydropyridine-1(2H)-carboxylate (36 mg, 0.117 mmol), $Pd(dppf)_2Cl_2$ (7.2 mg, 0.0088 mmol) and 2M Na_2CO_3 (0.125 ml, 0.25 mmol) were added. The reaction solution was stirred at 105-110 °C for 24 hours or until done by LC. The crude reaction mixture was concentrated to solid re-dissolved in 0.8 ml DMF, filtered, purified on prep HPLC and lyophilized to give tert-butyl 4-(4-(2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-yloxy)pyridin-2-yl)-5,6-dihydropyridine-1(2H)-carboxylate as TFA salt (2.5 mg). ES/MS *m/z* 523.1(MH^+).

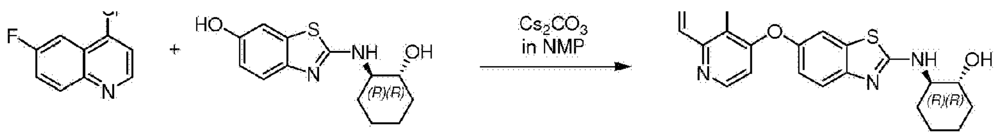
Step 2. Preparation of (1R,2R)-2-(6-(2-(1,2,3,6-tetrahydropyridin-4-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol.

[0186] To the solid of tert-butyl 4-(4-(2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-yloxy)pyridin-2-yl)-5,6-dihydropyridine-1(2H)-carboxylate (2.5 mg, 0.0039 mmol) was added 4M HCL in Dioxane (1 ml, 4.0 mmol). The reaction mixture was stirred at RT for 45 minutes. The crude reaction mixture was concentrated to solid and lyophilized to give (1R,2R)-2-(6-(2-(1,2,3,6-tetrahydropyridin-4-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol as HCl salt (1.4 mg). ES/MS *m/z* 423.1(MH^+).

Reference example 192

Preparation of (1R,2R)-2-(6-(6-fluoroquinolin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol

[0187] The subject compound was prepared according to the general Scheme below:



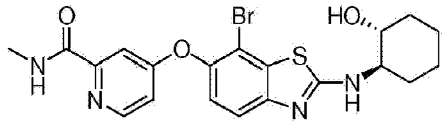
Preparation of (1R,2R)-2-(6-(6-fluoroquinolin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol.

[0188] To the reaction mixture of 2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-ol (15.1 mg, 0.057 mmol) in 0.4 ml ofNMP was added Cesium Carbonate (47 mg, 0.143 mmol) and stirred at RT for 1-3 minutes. To this mixture was added 4-chloro-6-fluoroquinoline (21 mg, 0.114 mmol). The reaction mixture was stirred at 105-110 °C for 18 hours or until done by LC. The crude reaction mixture was filtered, purified on prep HPLC and lyophilized to give (1R,2R)-2-(6-(6-fluoroquinolin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol as TFA salt (9.2 mg). ES/MS *m/z* 410.1(MH^+).

Example 195

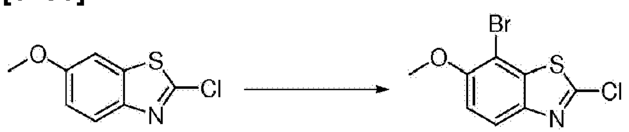
4-(7-bromo-2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide

[0189]



Step 1. Synthesis of 7-bromo-2-chloro-6-methoxybenzo[d]thiazole

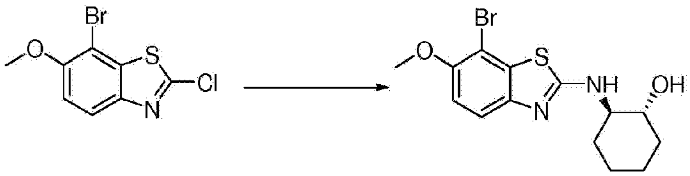
[0190]



[0191] To the solution of 2-chloro-6-methoxy-benzothiazole (200mg, 1.0mmol, 1.0eq) in 5mL ofNMP was added N-bromosuccinimide (213mg, 1.20mmol, 1.2eq) at room temperature. The reaction mixture was stirred at 75°C for >24 hours with subsequent addition of NBS in small batches for reaction progress, thereafter the mixture was diluted with water (ca. 100mL) and aqueous layer extracted with ethyl acetate (ca. 150mLX3). Combined organic layers were dried over sodium sulfate, filtered and condensed under reduced pressure. Purification on ISCO using gradient 0%-50% ethyl acetate-hexane gave 336 mg of product as off white fluffy powder in 60% yields structure of which was confirmed by H^+NMR. LC/MS (m/z) [279.9] (MH^+)

Step 2. Synthesis of (1R,2R)-2-(7-bromo-6-methoxybenzo[d]thiazol-2ylamino)cyclohexanol

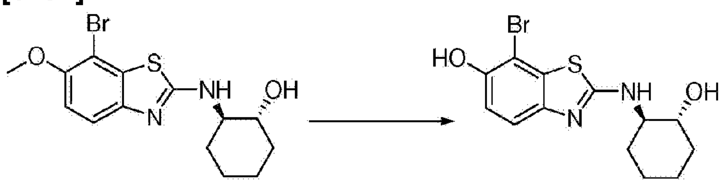
[0192]



[0193] To the solution of 7-bromo-2-chloro-6-methoxybenzo[d]thiazole (150mg, 0.539mmol, 1.0eq) in 1mL ofNMP was added (1R,2R)-2-aminocyclohexanol hydrochloride (0.123mg, 0.809mmol, 1.5eq) and DIPEA (263µL, 1.503 mmol, 2.8 eq) at room temperature. The reaction mixture was stirred at 125°C for 12 hours, thereafter the mixture was diluted with saturated sodium bicarbonate solution (ca. 100mL) and aqueous layer extracted with ethyl acetate (ca. 200mLX3). Combined organic layers were dried over sodium sulfate, filtered and condensed under reduced pressure to give crude product as brown oil which was sufficiently pure and was carried to next step without further purification. LC/MS (m/z) [359.0] (MH^+)

Step 3. Synthesis of 7-bromo-2-((1R,2R)-2-hydroxycyclohexylamino)-benzo[d]thiazol-6-ol

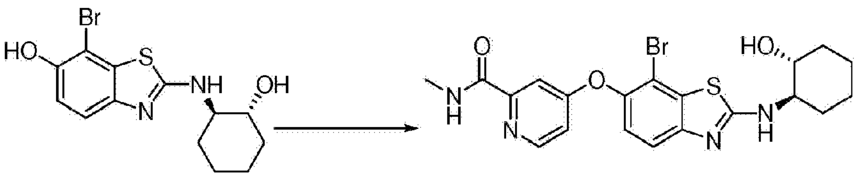
[0194]



[0195] To the solution of (1R,2R)-2-(7-bromo-6-methoxybenzo[d]thiazol-2-ylamino) cyclohexanol (191mg, 0.537mmol, 1.0eq) in 10mL of DCM was added 1 M solution of boron tribromide (ca.3.0mL, 2.68 mmol, 5.0eq) at room temperature. The reaction mixture was refluxed for 12 hours, thereafter the mixture was diluted with saturated sodium bicarbonate (ca. 100mL) till PH=7 and aqueous layer extracted with ethyl acetate (ca. 150mLX3). Combined organic layers were dried over sodium sulfate, filtered and condensed under reduced pressure to give sufficiently pure crude product which was carried to next step without further purification LC/MS (m/z) [345.0] (MH^+).

Step 4. Synthesis of 4-(7-bromo-2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide

[0196]

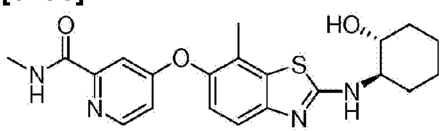


[0197] To the solution of 7-bromo-2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-ol (50mg, 0.145mmol, 1.0eq) in 1mL of NMP was added 4-chloro-N-methylpicolinamide (29mg, 0.174mmol), 1.2eq) and cesium carbonate (165mg, 0.507mmol, 3.5eq) at room temperature. The reaction mixture was stirred at 80°C for ca.12 hours, thereafter the mixture was purified on the reverse phase HPLC. LC/MS (m/z) [479.0] (MH^+)

Example 196

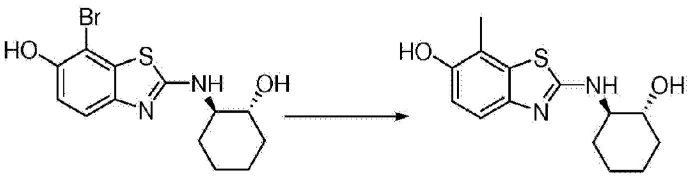
4-(2-((1R,2R)-2-hydroxycyclohexylamino)-7-methylbenzo[d]thiazol-6-yloxy)-N-methylpicolinamide

[0198]



Step 1. Synthesis of 2-((1R,2R)-2-hydroxycyclohexylamino)-7-methylbenzo[d]thiazol-6-ol

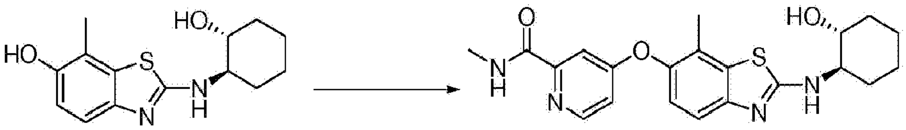
[0199]



[0200] To the solution of 7-bromo-2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-ol (117mg, 0.34 mmol, 1.0eq) in 1mL DMF in a microwave vial was added trimethylboraxine (128mg, 1.02 mmol, 3.0eq), Pd(Cl_2)dPPf(27mg, 0.034mmol, 0.1eq) and 1mL of 2M Na_2CO_3 solution at room temperature. Thereafter, the reaction mixture was heated in the microwave at 120°C for 15 minutes. The reaction was quenched with saturated $NaHCO_3$ solution (25ml) and the aqueous phase extracted with ethyl acetate (50mLX3), combined organic layers dried over Na_2SO_4, filtered and condensed under reduced pressure. Purification over ISCO using a gradient of 0%-18% methanol-DCM gave 17 mg of product as brownish powder in 17% yield. LC/MS (m/z) [279.1] (MH^+)

Step 2. Synthesis of 4-(2-((1R,2R)-2-hydroxycyclohexylamino)-7-methylbenzo-[d]thiazol-6-yloxy)-N-methylpicolinamide

[0201]

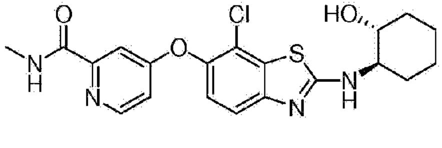


Prepared following the procedure in example 543 step 4. LC/MS (m/z) [413.1] (MH^+)

Example 197

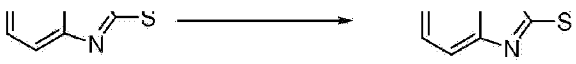
4-(7-chloro-2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide

[0202]



Step 1. Synthesis of 7-chloro-2-(methylthio)benzo[d]thiazol-6-ol

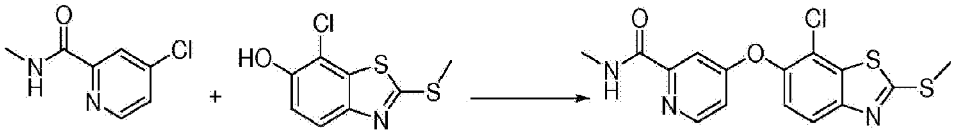
[0203]



[0204] To the solution of 2-(methylthio)benzo[d]thiazol-6-ol (500mg, 2.53mmol, 1.0eq) in 10mL of NMP was added N-chlorosuccinimide (507mg, 3.80mmol, 1.5eq) at room temperature. The reaction mixture was stirred at room temperature for 1 hour thereafter the mixture was diluted with saturated sodium bicarbonate solution (ca. 100mL) and aqueous layer extracted with DCM (ca. 150mLX3). Combined organic layers were dried over sodium sulfate, filtered and condensed under reduced pressure. Purification on ISCO using gradient 0%-100% ethyl acetate-hexane gave 283.39 mg of product in 48% yields structure of which was confirmed by H^+NMR. LC/MS (m/z) [232.0] (MH^+)

Step 2. Synthesis of 4-(7-chloro-2-(methylthio)benzo[d]thiazol-6-yloxy)-N methyl picolinamide

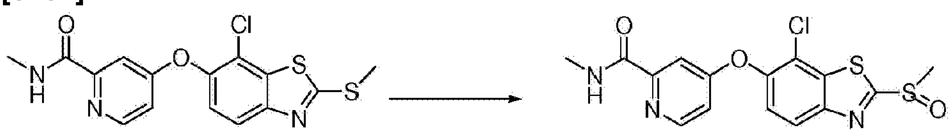
[0205]



[0206] To the solution of 7-chloro-2-(methylthio)benzo[d]thiazol-6-ol (80mg, 0.346mmol, 1.0eq) in 1mL of NMP was added 4-chloro-N-methylpicolinamide (88mg, 0.519mmol, 1.5eq) and cesium carbonate (281mg, 0.865mmol, 2.5eq) at room temperature. The reaction mixture was stirred at 85°C for >48 hours till ca. 75%-80% completion, thereafter the mixture was diluted with water (ca. 50mL) and aqueous layer extracted with ethyl acetate (ca. 50mLX3). Combined organic layers were dried over sodium sulfate, filtered and condensed under reduced pressure to give crude product which was purified on ISCO using gradient 0%-100% ethyl acetate-hexane mixture to give 64 mg of product in 50% yield. LC/MS (m/z) [366.0] (MH^+)

Step 3. Synthesis of 4-(7-chloro-2-(methylsulfinyl)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide

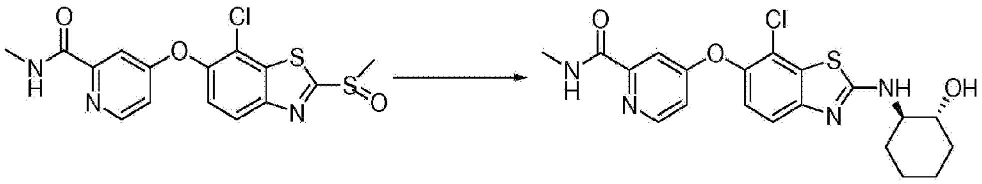
[0207]



[0208] To the solution of 4-(7-chloro-2-(methylthio)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide (64mg, 0.175mmol, 1.0eq) in 5 mL of DCM was added MCPBA (33mg, 0.192 mmol, 1.1 eq) at 0°C and reaction stirred for 30-45min. Thereafter, it was quenched with water (10mL) and aqueous phase extracted with ethyl acetate (25mLX5), combined organic layers dried over sodium sulfate, filtered and condensed under reduced pressure to yield crude product which was sufficiently pure and was carried to next step without further purification. LC/MS (m/z) [382.0] (MH^+)

Step 4. Synthesis of 4-(7-chloro-2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide

[0209]

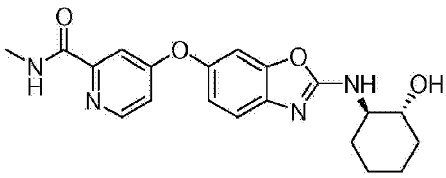


[0210] To the solution of 4-(7-chloro-2-(methylsulfinyl)benzo[d]thiazol-6-yloxy)-Nmethylpicolinamide (10mg, 0.026mmol), 1.0eq) in NMP was added (1R,2R)-2-aminocyclohexanol hydrochloride (6mg, 0.039mmol, 1.5eq) and DIPEA (13µL, 0.078mmol, 3.0eq) and reaction mixture heated at 160°C in microwave for 15 min. Thereafter, the product was purified via reverse phase HPLC. LC/MS (m/z) [433.1] (MH^+)

Example 201

4-(2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]oxazol-6-yloxy)-N-methylpicolinamide

[0211]

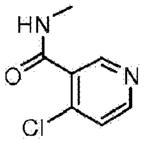


[0212] To the solution of N-methyl-4-(2-(methylsulfinyl)benzo[d]oxazol-6-yloxy)picolinamide (25mg, 0.075 mmol, 1.0eq, described in step 3 reference exemple 2) in 1 mL ofNMP was added (1R,2R)-2-aminocyclohexanol hydrochloride (17mg, 0.112mmol, 1.5eq) and DIPEA (40µL, 0.225mmol, 3.0eq) and reaction mixture stirred at room temperature for 48 hours. Thereafter, the product was purified via reverse phase HPLC. LC/MS (m/z) [383.1] (MH^+)

Intermediates

Synthesis of 4-chloro-*N*-methylpyridine-3-carboxamide

[0213]

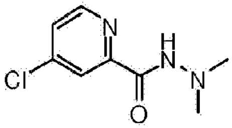


[0214] Step 1. To a suspension of 4-chloronicotinic acid (1.57 g, 10.0 mmol, 1.0 eq) in 25 mL of toluene was added thionyl chloride (1.8 mL, 25.0 mmol, 2.5 eq) at room temperature. The reaction mixture was stirred at 100°C for 3 hours. The mixture was concentrated under reduced pressure, dissolved in 25mL of toluene and concentrated again to give crude 4-chloronicotinoyl chloride hydrochloride salt, which was used in the next step without further purification.

[0215] Step 2. To a suspension of crude 4-chloronicotinoyl chloride hydrochloride in 25 mL of THF was added methylamine solution (2M in THF, 20 mL, 40 mmol, 4.0 eq) at 0°C. The reaction mixture was stirred at room temperature for 1 hour and concentrated under reduced pressure. The crude material was dissolved in ethylacetate (75 mL) and water/brine/saturated sodium bicarbonate solution (1/1/1, 75 mL). The separated aqueous layer was extracted with EtOAc. The combined organic layers were washed with water/brine/saturated sodium bicarbonate solution (1/1/1, 25 mL) and brine (25 mL) and dried over sodium sulfate. Removal of the solvent under reduced pressure afforded the title compound as orange solid (400 mg, 24%), which was used without further purification. MH+ = 171.0, Rt = 0.55min.

Synthesis of 4-chloro-*N'*,*N'*-dimethylpyridine-2-carboxhydrazide

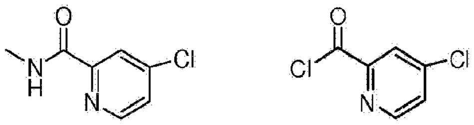
[0216]



[0217] To a suspension of 4-chloropicolinoyl chloride hydrochloride (352 mg, 2.0 mmol, 1,0 eq) in 10 mL of THF were added *N*,*N*-dimethylhydrazine (120 mg, 2.0 mmol, 1.0 eq) and *N*,*N*-diisopropylethylamine (383 µL, 2.2 mmol, 1.1 eq) at room temperature. The reaction mixture was stirred for 15 min and diluted with water (25 mL) and EtOAc (50 mL). The separated organic layer was washed with brine (25mL), saturated sodium bicarbonate solution (25 mL) and dried over sodium sulfate. Concentration under reduced pressure gave the title compound as colorless solid (223 mg, 56%), which was used without further purification. MH+ = 200, Rt = 1.42min.

Synthesis of 4-chloro-N-methylpicolinamide and 4-chloropicolinoyl chloride

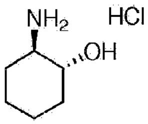
[0218]



[0219] Prepared following the method described in "A Scaleable Synthesis of BAY 43-9006: A Potent Raf Kinase Inhibitor for the treatment of cancer". Donald Bankston, Jacques Dumas, Reina Natero, Bernd Riedl, Mary-Katherine Monahan, Robert Sibley.; Bayer Research Center. Pharmaceutical Division. Organic Process Research and Development 2002 (6) 777-781.

Synthesis of (1R,2R)-2-aminocyclohexanol hydrochloride

[0220]



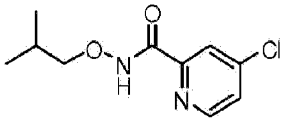
[0221] To an ice bath cooled solution of amine (1R,2R)-(-)-2-Benzyloxycyclohexylamine (20 g, 97.4 mmol) in dry MeOH (390 mL) was added 4.0 M HCl solution in dioxane (49 mL, 195 mmol) slowly via syringe. The ice bath was removed and resulting solution was sparged with N_2 for 10 min. 10 % Pd/C (3 g, 28 mmol) was added to the solution and the reaction was purged with H_2 and maintained under a H_2 atmosphere. After 4 h, an additional 10 mL of 4.0 M HCl solution in dioxane was added[2] and the reaction was maintained under a H_2 atmosphere overnight. Upon completion (followed by LCMS), the reaction was filtered through a thin, tightly packed pad of Celite and the collected solids were washed successively with MeOH and EtOAc. The combined organic filtrates were evaporated and dried under vacuum gave (1R,2R)-2-aminocyclohexanol hydrochloride as a pale-colored solid, (13.8 g, 91 mmol, 93%). LCMS *m/z* 116.0 (MH^+), t_R = 0.37 min.

[0222] (1S,2S)-2-aminocyclohexanol hydrochloride was prepared in the same manner.

Reference example 202

4-chloro-*N*-isobutoxypicolinamide

[0223]

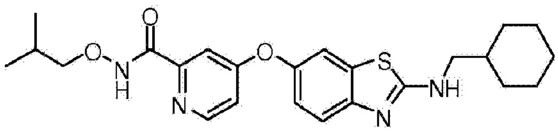


[0224] To a suspension of 4-chloropicolinoyl chloride hydrochloride (1.0 g, 5.68 mmol, 1.0 eq) in 25 ml of THF were added *O*-isobutylhydroxylamin hydrochloride (785 mg, 6.25 mmol, 1.1 eq) and *N*,*N*-diisopropylethylamine (2.97 ml, 17.0 mmol, 3.0 eq) at room temperature. The reaction mixture was stirred for 30 min and diluted with water (25 mL) and EtOAc (50 mL). The separated organic layer was washed with brine (25mL), saturated sodium bicarbonate solution (2x 25 mL) and dried over sodium sulfate. Concentration under reduced pressure gave the title compound as colorless solid (870 mg, 67%), which was used without further purification. ES/MS *m*/*z* 229.0 (MH^+), Rt = 2.61 min.

Reference example 203

4-(2-(cyclohexylmethylamino)benzo[d]thiazol-6-yloxy)-N-isobutoxypicolinamide

[0225]

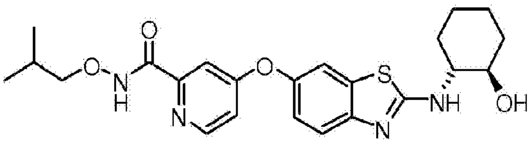


[0226] To the reaction mixture 2-(cyclohexylmethylamino)benzo[d]thiazol-6-ol (30 mg, 0.114 mmol; Reference Example 180-step 2) and cesium carbonate (326 mg, 0.228 mmol) in 1.2 ml of DMF was added 4-chloro-*N*-isobutoxypicolinamide (40 mg, 0.171 mmol). The reaction mixture was stirred at rt for 10 min and then microwaved at 130 °C for 3x 20min. The crude reaction mixture was filtered, purified on preparative HPLC and lyophilized to give the title compound as its TFA salt as a white solid (15 mg, 23%). ES/MS *m*/*z* 455.1 (MH^+), Rt = 2.90 min.

Example 204

4-(2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-yloxy)-N-isobutoxypicolinamide

[0227]

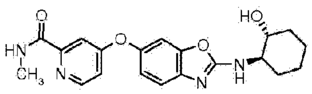
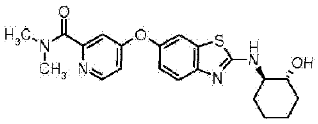
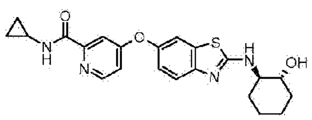
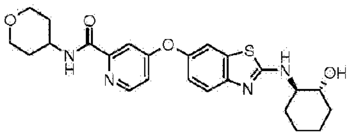
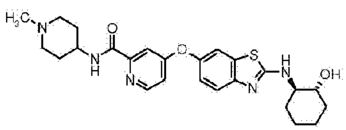
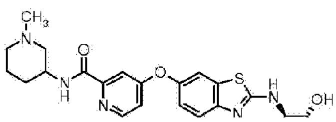


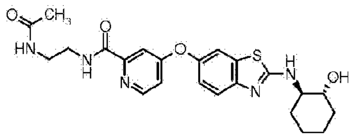
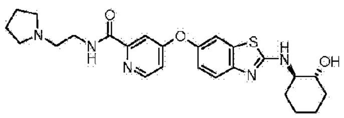
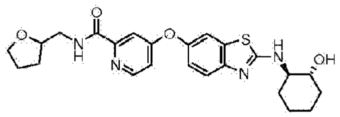
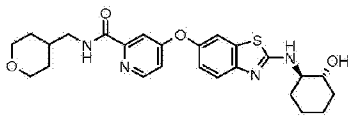
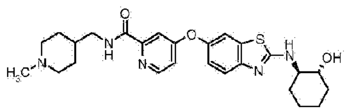
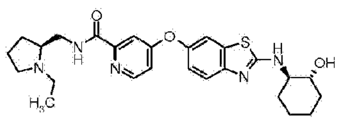
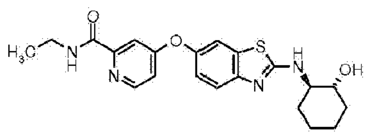
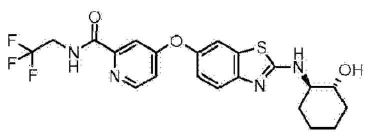
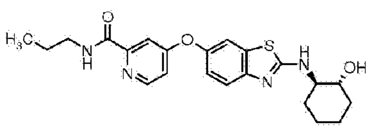
[0228] Prepared as in the preceeding example. ES/MS *m/z* 457.0 (MH^+), Rt = 2.35 min.

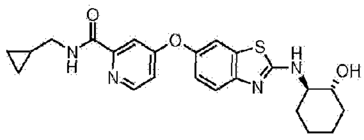
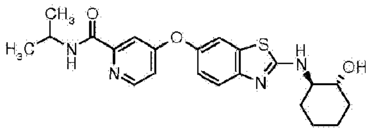
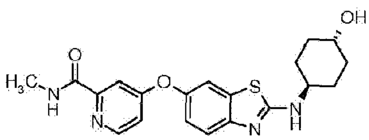
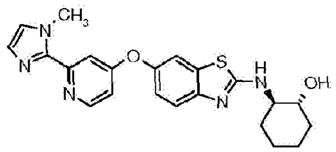
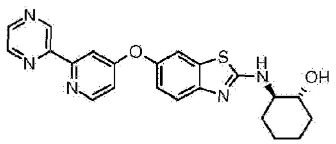
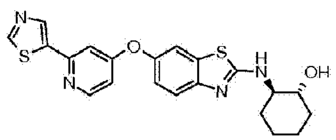
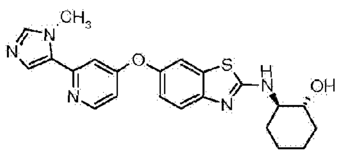
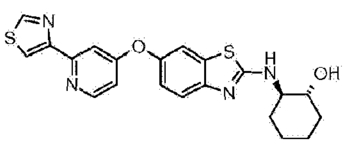
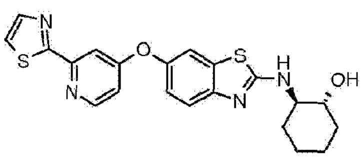
yloxy)benzo[d]thiazol-2-amine as TFA salt (3.0mg). ES/MS *m/z* 434.2 (MH^+).

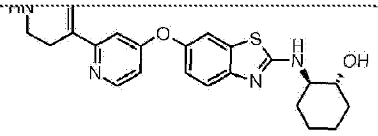
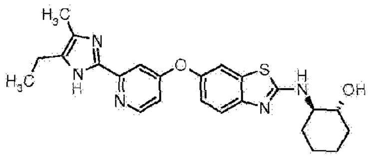
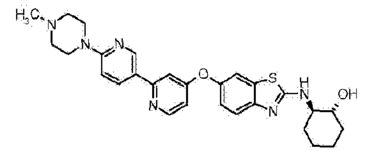
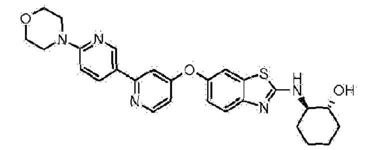
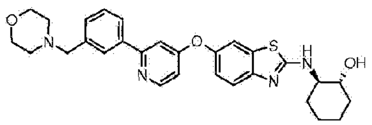
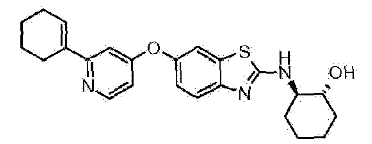
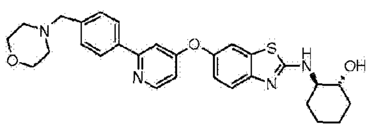
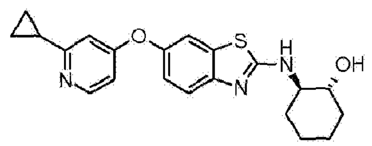
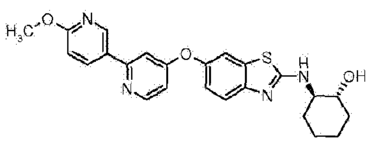
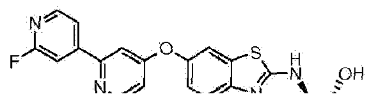
[0229] Compounds in Table 3 were made according to the examples above, and in particular according to the example noted in the Ex Prep (Example Preparation) column.

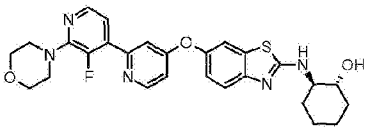
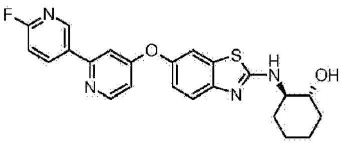
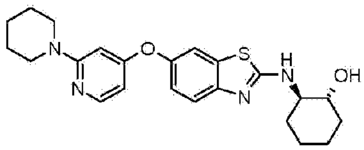
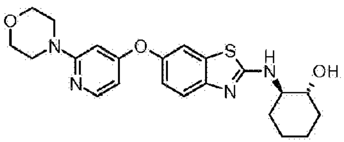
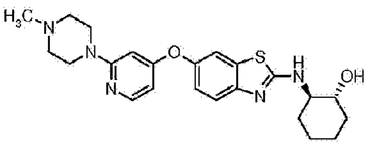
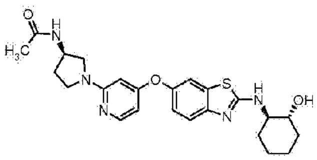
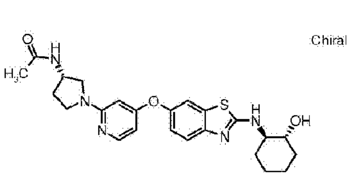
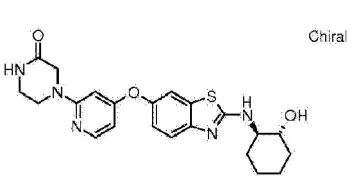
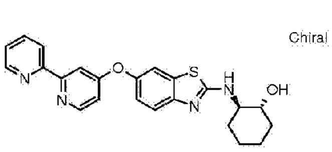
Table 3

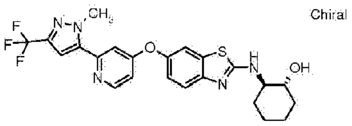
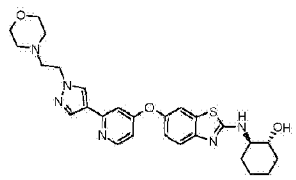
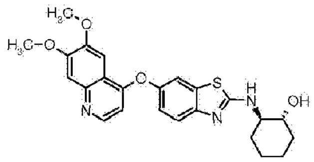
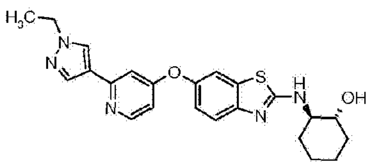
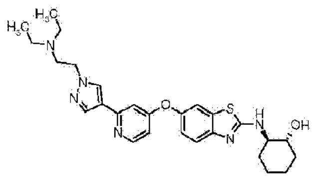
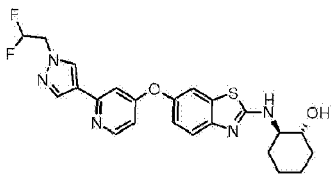
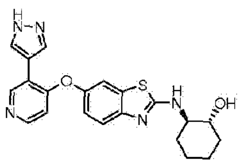
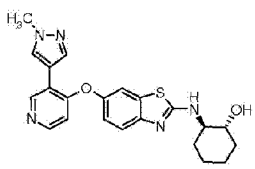
Cmpd	Ex Prep	Structure	Name	(M+H)+, Rt(min.)
7	201		4-(2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]oxazol-6-yloxy)-N-methylpicolinamide	383, 1.96
10	171		4-(2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-yloxy)-N,N-dimethylpicolinamide	413.1, 1.87
11	171		N-cyclopropyl-4-(2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-yloxy)picolinamide	425.2, 2.13
12	171		4-(2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-yloxy)-N-(tetrahydro-2H-pyran-4-yl)picolinamide	469.2, 2.09
13	171		4-(2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-yloxy)-N-(1-methylpiperidin-4-yl)picolinamide	482.2, 1.85
14	171		4-(2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-yloxy)-N-(1-methylpiperidin-3-	482.2, 1.87

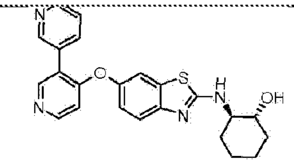
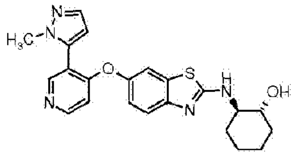
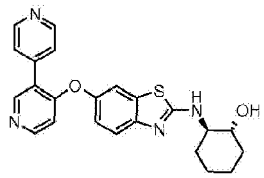
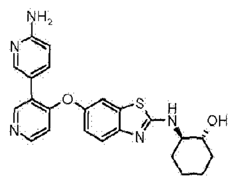
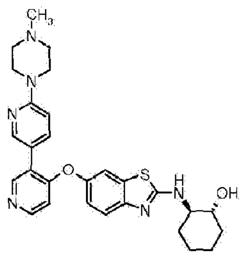
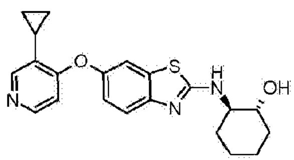
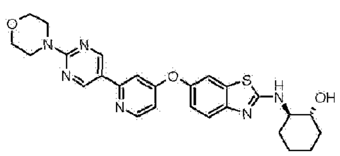
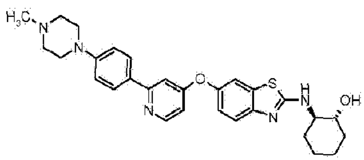
Cmpd	Ex Prep	Structure	Name	(M+H)+, Rt(min.)
			yl)picolinamide	
15	171		N-(2-acetamidoethyl)-4-(2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-yloxy)picolinamide	470.2, 1.86
16	171		4-(2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-yloxy)-N-(2-(pyrrolidin-1-yl)ethyl)picolinamide	482.2, 1.84
17	171		4-(2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-yloxy)-N-((tetrahydrofuran-2-yl)methyl)picolinamide	469.2, 2.16
18	171		4-(2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-yloxy)-N-((tetrahydro-2H-pyran-4-yl)methyl)picolinamide	483.2, 2.12
19	171		4-(2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-yloxy)-N-((1-methylpiperidin-4-yl)methyl)picolinamide	496.2, 1.84
20	171		N-(((S)-1-ethylpyrrolidin-2-yl)methyl)-4-(2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-yloxy)picolinamide	496.2, 1.88
47	171		N-ethyl-4-(2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-yloxy)picolinamide	413.2, 2.09
48	171		4-(2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-yloxy)-N-(2,2,2-trifluoroethyl)picolinamide	467.1, 2.37
49	171		4-(2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-yloxy)-N-propylpicolinamide	427.1, 2.25

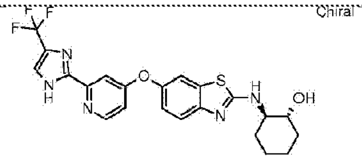
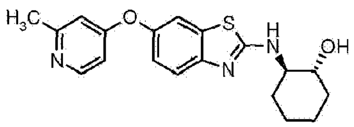
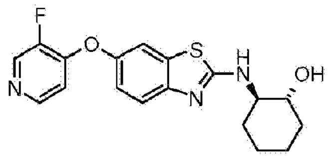
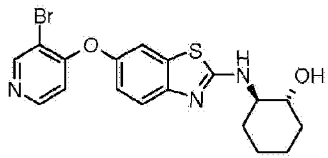
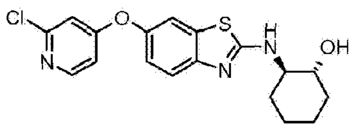
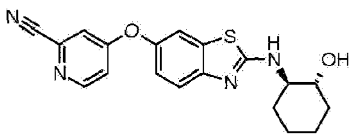
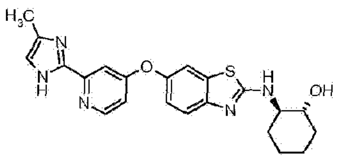
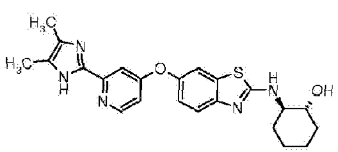
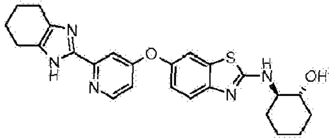
Cmpd	Ex Prep	Structure	Name	(M+H)+, Rt(min.)
50	171		N-(cyclopropylmethyl)-4-(2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-yloxy)picolinamide	439.2, 2.32
51	171		4-(2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-yloxy)-N-isopropylpicolinamide	427.2, 2.24
125	162		4-(2-((1r,4r)-4-hydroxycyclohexylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	399.1, 1.83
155	175		(1R,2R)-2-(6-(2-(1-methyl-1H-imidazol-2-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	422.1, 1.83
156	175		(1R,2R)-2-(6-(2-(pyrazin-2-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	420.1, 1.91
157	175		(1R,2R)-2-(6-(2-(thiazol-5-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	425.0, 2.05
158	175		(1R,2R)-2-(6-(2-(1-methyl-1H-imidazol-5-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	422.1, 1.84
159	175		(1R,2R)-2-(6-(2-(thiazol-4-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	425.0, 1.85
160	175		(1R,2R)-2-(6-(2-(thiazol-2-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	425.0, 2.28
			(1R,2R)-2-(6-(2-(1,2,3,6-	

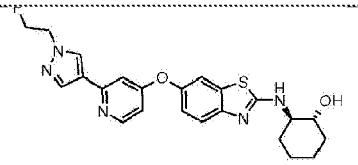
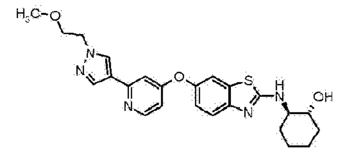
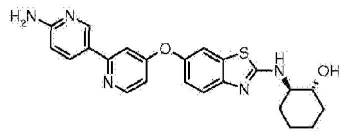
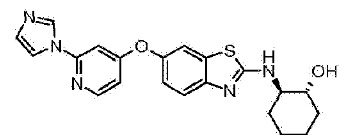
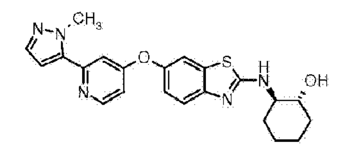
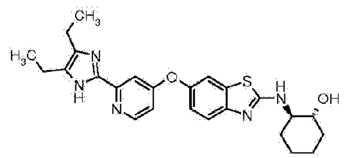
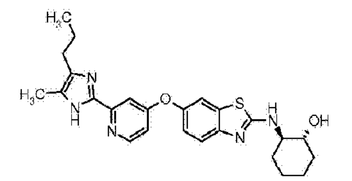
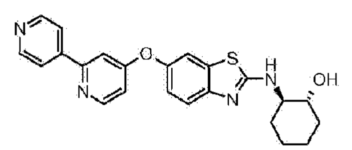
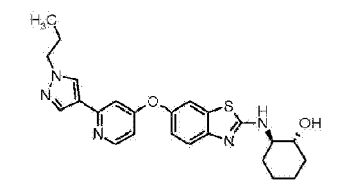
Cmpd	Ex Prep	Structure	Name	(M+H)+, Rt(min.)
161	188		tetrahydropyridin-4-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	423.1, 1.38
162	177		(1R,2R)-2-(6-(2-(5-ethyl-4-methyl-1H-imidazol-2-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	450.1, 1.82
164	174		(1R,2R)-2-(6-(6'-(4-methylpiperazin-1-yl)-2,3'-bipyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	517.2, 1.75
165	174		(1R,2R)-2-(6-(6'-morpholino-2,3'-bipyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	504.1, 1.93
166	174		(1R,2R)-2-(6-(2-(3-(morpholinomethyl)phenyl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	517.1, 1.78
167	174		(1R,2R)-2-(6-(2-cyclohexenylpyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	422.1, 2.07
168	174		(1R,2R)-2-(6-(2-(4-(morpholinomethyl)phenyl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	517.2, 1.76
169	174		(1R,2R)-2-(6-(2-cyclopropylpyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	382.1, 1.84
170	174		(1R,2R)-2-(6-(6'-methoxy-2,3'-bipyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	449.1, 1.98
171	174		(1R,2R)-2-(6-(2'-fluoro-2,4'-bipyridin-4-yloxy)benzo[d]thiazol-2-	437.1, 2.22

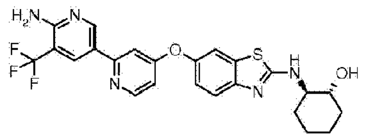
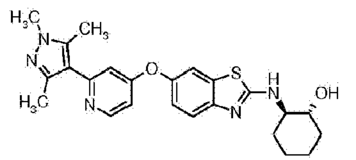
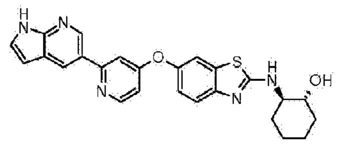
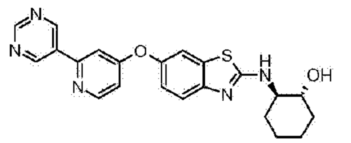
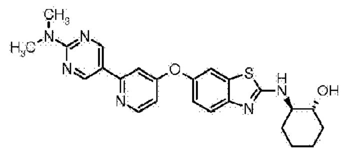
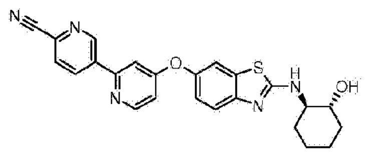
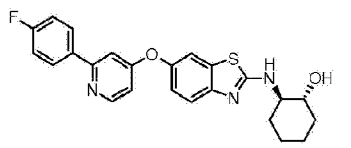
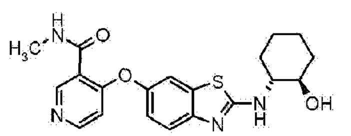
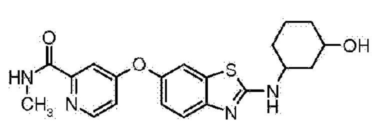
Cmpd	Ex Prep	Structure	Name	(M+H)+, Rt(min.)
			ylamino)cyclohexanol	
172	174		(1R,2R)-2-(6-(3'-fluoro-2'-morpholino-2,4'-bipyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	522.2, 2.17
173	174		(1R,2R)-2-(6-(6'-fluoro-2,3'-bipyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	437.1, 2.04
174	183		(1R,2R)-2-(6-(2-(piperidin-1-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	425.1, 1.98
175	183		(1R,2R)-2-(6-(2-morpholinopyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	427.1, 1.80
176	183		(1R,2R)-2-(6-(2-(4-methylpiperazin-1-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	440.1, 1.66
177	183		N-((R)-1-(4-(2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-yloxy)pyridin-2-yl)pyrrolidin-3-yl)acetamide	468.1, 1.78
178	183		N-((S)-1-(4-(2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-yloxy)pyridin-2-yl)pyrrolidin-3-yl)acetamide	468.1, 1.77
179	183		4-(4-(2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-yloxy)pyridin-2-yl)piperazin-2-one	440.1, 1.70
180	175		(1R,2R)-2-(6-(2,2'-bipyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	419.0, 1.87

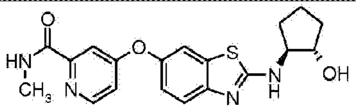
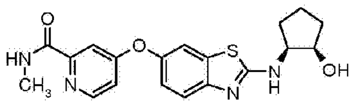
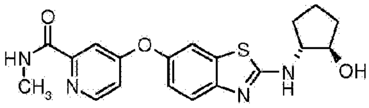
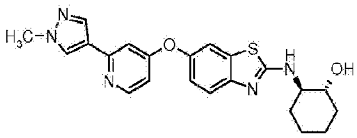
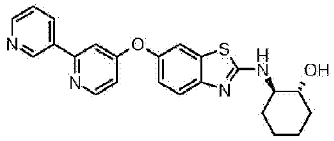
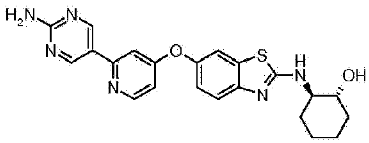
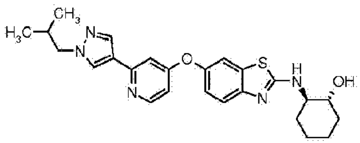
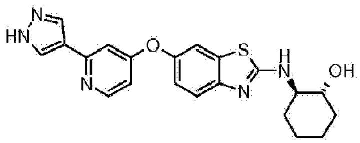
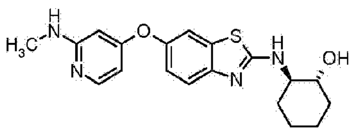
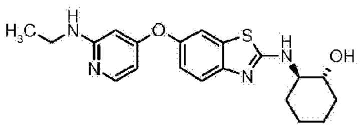
Cmpd	Ex Prep	Structure	Name	(M+H)+, Rt(min.)
181	175		(1R,2R)-2-(6-(2-(1-methyl-3-(trifluoromethyl)-1H-pyrazol-5-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	490.1, 2.60
182	174		(1R,2R)-2-(6-(2-(1-(2-morpholinoethyl)-1H-pyrazol-4-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	521.1, 1.71
184	192		(1R,2R)-2-(6-(6,7-dimethoxyquinolin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	452.1, 2.00
185	176		(1R,2R)-2-(6-(2-(1-ethyl-1H-pyrazol-4-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	436.0, 1.89
186	176		(1R,2R)-2-(6-(2-(1-(2-(diethylamino)ethyl)-1H-pyrazol-4-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	507.1, 1.75
187	176		(1R,2R)-2-(6-(2-(1-(2,2-difluoroethyl)-1H-pyrazol-4-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	472.0, 1.90
188	179		(1R,2R)-2-(6-(3-(1H-pyrazol-4-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	408.1, 1.70
189	179		(1R,2R)-2-(6-(3-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	422.1, 1.79

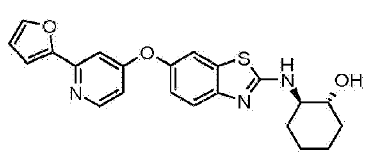
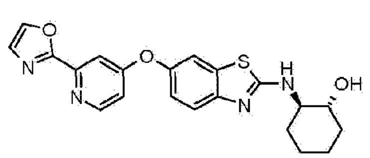
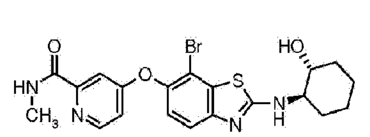
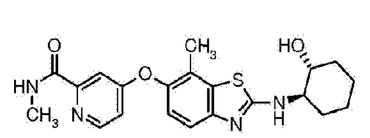
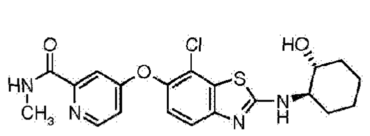
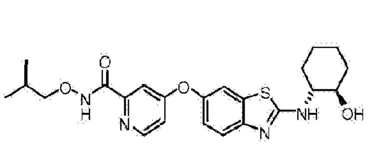
Cmpd	Ex Prep	Structure	Name	(M+H)+, Rt(min.)
190	179		(1R,2R)-2-(6-(3,3'-bipyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	419.1, 1.66
191	179		(1R,2R)-2-(6-(3-(1-methyl-1H-pyrazol-5-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	422.1, 1.83
192	179		(1R,2R)-2-(6-(3,4'-bipyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	419.1, 1.61
193	179		(1R,2R)-2-(6-(6'-amino-3,3'-bipyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	434.1, 1.60
194	179		(1R,2R)-2-(6-(6'-(4-methylpiperazin-1-yl)-3,3'-bipyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	517.2, 1.64
195	179		(1R,2R)-2-(6-(3-cyclopropylpyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	382.1, 1.97
196	174		(1R,2R)-2-(6-(2-(2-morpholinopyrimidin-5-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	505.1, 2.03
197	174		(1R,2R)-2-(6-(2-(4-(4-methylpiperazin-1-yl)phenyl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	516.2, 1.85
			(1R,2R)-2-(6-(2-(4-	

Cmpd	Ex Prep	Structure	Name	(M+H)+, Rt(min.)
200	177		(trifluoromethyl)-1H-imidazol-2-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	476.1, 2.35
203	192		(1R,2R)-2-(6-(2-methylpyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	356.1, 1.73
209	192		(1R,2R)-2-(6-(3-fluoropyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	360.1, 1.83
224	178		(1R,2R)-2-(6-(3-bromopyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	420.1/422.0, 1.81
225	173		(1R,2R)-2-(6-(2-chloropyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	376.1, 2.13
226	173		4-(2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-yloxy)picolinonitrile	367.1, 2.03
231	177		(1R,2R)-2-(6-(2-(4-methyl-1H-imidazol-2-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	422.1, 1.88
232	177		(1R,2R)-2-(6-(2-(4,5-dimethyl-1H-imidazol-2-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	436.1, 1.93
258	177		(1R,2R)-2-(6-(2-(4,5,6,7-tetrahydro-1H-benzo[d]imidazol-2-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	462.2, 2.03
			(1R,2R)-2-(6-(2-(1-(2-	

Cmpd	Ex Prep	Structure	Name	(M+H)+, Rt(min.)
259	176		fluoroethyl)-1H-pyrazol-4-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	454.2, 1.89
260	176		(1R,2R)-2-(6-(2-(1-(2-methoxyethyl)-1H-pyrazol-4-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	466.2, 1.89
261	174		(1R,2R)-2-(6-(6'-amino-2,3'-bipyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	434.2, 1.78
262	187		(1R,2R)-2-(6-(2-(1H-imidazol-1-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	408.2, 1.85
265	174		(1R,2R)-2-(6-(2-(1-methyl-1H-pyrazol-5-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	422.1, 1.93
266	177		(1R,2R)-2-(6-(2-(4,5-diethyl-1H-imidazol-2-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	464.2, 2.10
267	177		(1R,2R)-2-(6-(2-(5-methyl-4-propyl-1H-imidazol-2-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	464.2, 2.10
280	174		(1R,2R)-2-(6-(2,4'-bipyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	419.0, 1.68
281	174		(1R,2R)-2-(6-(2-(1-propyl-1H-pyrazol-4-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	450.0, 2.02

Cmpd	Ex Prep	Structure	Name	(M+H)+, Rt(min.)
282	174		(1R,2R)-2-(6-(6'-amino-5'-(trifluoromethyl)-2,3'-bipyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	502.0, 2.02
283	174		(1R,2R)-2-(6-(2-(1,3,5-trimethyl-1H-pyrazol-4-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	450.0, 1.86
284	174		(1R,2R)-2-(6-(2-(1H-pyrrolo[2,3-b]pyridin-5-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	458.0, 1.91
285	174		(1R,2R)-2-(6-(2-(pyrimidin-5-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	420.1, 1.90
286	174		(1R,2R)-2-(6-(2-(2-(dimethylamino)pyrimidin-5-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	463.1, 1.96
287	174		4-(2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-yloxy)-2,3'-bipyridine-6'-carbonitrile	444.0, 2.18
288	174		(1R,2R)-2-(6-(2-(4-fluorophenyl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	436.0, 2.06
291	195		4-(2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-yloxy)-N-methylnicotinamide	399.1, 1.72
293	162		4-(2-(3-hydroxycyclohexylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	399.1, 1.76
			4-(2-((1S,2S)-2-	

Cmpd	Ex Prep	Structure	Name	(M+H)+, Rt(min.)
320	162		hydroxycyclopentylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	385.1, 1.74
322	162		4-(2-((1S,2R)-2-hydroxycyclopentylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	385.1, 1.75
324	162		4-(2-((1R,2R)-2-hydroxycyclopentylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	385.1, 1.75
344	174		(1R,2R)-2-(6-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	422.2, 1.68
345	174		(1R,2R)-2-(6-(2,3'-bipyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	419.1, 1.69
346	174		(1R,2R)-2-(6-(2-(2-aminopyrimidin-5-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	435.2, 1.61
359	174		(1R,2R)-2-(6-(2-(1-isobutyl-1H-pyrazol-4-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	464.4, 1.95
360	174		(1R,2R)-2-(6-(2-(1H-pyrazol-4-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	408.1, 1.63
368	170		(1R,2R)-2-(6-(2-(methylamino)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	371.1, 1.79
369	170		(1R,2R)-2-(6-(2-(ethylamino)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	385.1, 1.74

Cmpd	Ex Prep	Structure	Name	(M+H)+, Rt(min.)
371	175		(1R,2R)-2-(6-(2-(furan-2-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	408.1, 1.94
372	175		(1R,2R)-2-(6-(2-(oxazol-2-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	409.1, 1.98
376	195		4-(7-bromo-2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	479, 2.37
377	196		4-(2-((1R,2R)-2-hydroxycyclohexylamino)-7-methylbenzo[d]thiazol-6-yloxy)-N-methylpicolinamide	413, 2.09
378	197		4-(7-chloro-2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	433, 2.33
381	204		4-(2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-yloxy)-N-isobutoxypicolinamide	457.0, 2.35

[0230] Each of the compounds of the invention listed in Table 2 were shown to have activity with respect to inhibition of CSF-1R with an IC_{50} of less than about 10 μM. Many of the compounds exhibited activity with an IC_{50} of less than about 1 μM, or less than about 0.1 μM, or less than about 0.01 μM with respect to CSF-1R inhibition. The compounds of the invention in Tables 3 were found to have an activity of less than 1 μM. As such, each of the compounds of Tables 2 and 3 is preferred individually and as a member of a group.

[0231] In addition to CSF-1R inhibitory activity, many of the compounds of Tables 2 and3 were also screened for Raf inhibition (according to biochemical screens described in US 10/405,945), as well as other kinases, and shown to inhibit CSF-1R significantly greater (between about 2 and about 1,000 fold greater) than Raf and other kinases screened. More particularly, many of the compounds screened had activity greater about 1 μM with respect to Raf inhibition, whereas many of the same compounds exhibited activities with respect to CSF-1R at less than about 0.1 μM. As such, many of the compounds of Tables 2 and 3 are potent and selective inhibitors of CSF-1R.

BIOLOGICAL EXAMPLES

Biological Example 1

In Vitro Kinase Assays for Colony Stimulating Factor-1 Receptor (CSF-1R)

[0232] The kinase activity of various protein tyrosine kinases can be measured by providing ATP and a suitable peptide or protein tyrosine-containing substrate, and assaying the transfer of phosphate moiety to the tyrosine residue. Recombinant protein corresponding to the cytoplasmic domain of the human CSF-1R was purchased from Invitrogen Corporation, Carlsbad, CA U.S.A. (#PV3249). For each assay, test compounds were serially diluted, starting at 25 µM with 3 fold dilutions, in DMSO in 384 well plates then mixed with an appropriate kinase reaction buffer consisting of 50 mM Hepes, 5 mM $MgCl_2$, 10 mM $MnCl_2$, 0.1% BSA, pH 7.5, 1.0 mM dithiothreitol, 0.01% Tween 80 plus 1µM ATP. Kinase protein and an appropriate biotinylated peptide substrate at 50 nM were added to give a final volume of 20 µL, reactions were incubated for 2 hours at room temperature and stopped by the addition of 10 µL of 45mM EDTA, 50mM Hepes pH 7.5. Added to the stopped reaction mix was 30 µL of PT66 Alphascreen beads (Perkin Elmer, Boston, MA, U.S.A.). The reaction was incubated overnight and read on the Envision (Perkin Elmer). Phosphorylated peptide product was measured with the AlphaScreen system (Perkin Elmer) using acceptor beads coated with anti-phosphotyrosine antibody PT66 and donor beads coated with streptavidin that emit a fluorescent signal at the 520-620 nM emission wave length if in close proximity. The concentration of each compound for 50% inhibition (IC_{50}) was calculated by non-linear regression using XL Fit data analysis software.

[0233] CSF-1R kinase was assayed in 50 mM Hepes pH 7.0, 5 mM $MgCl_2$, 10 mM $MnCl_2$, 1 mM DTT, 1 mg/ml BSA, 1.0 µM ATP, and 0.05 µM biotin-GGGGRPRAATF-NH_2 (SEQ ID NO:2) peptide substrate. CSF-1R kinase was added at final concentration of 4 nM.

Biological Example 2

In Vitro Inhibition of CSF-1R Receptor Tyrosine Phosphorylation

[0234] To test the inhibition of CSF-1R receptor tyrosine phosphorylation, HEK293H purchased from Invitrogen Cat. # 11631017 cells transfected with the full-length human CSF-1R receptor cloned in house into mammalian episomal transfection vector were incubated for 1 h with serial dilutions of compounds starting at 10μM with 3 fold dilutions and then stimulated for 8 min with 50 ng/ml MCSF. After the supernatant was removed, the cells were lysed on ice with lysis buffer (150 mM NaCl, 20 mM Tris, pH 7.5, 1 mM EDTA, 1 mM EGTA, 1% Triton X-100 and NaF, protease and phosphatase inhibitors) and then shaken for 15-20 min at 4°C. The lysate was then transferred to total CSF-1R antibody coated 96- well plates that had already been blocked with 3% Blocker A from Mesoscale discovery (MSD) for 2 hours and washed afterwards. Lysates were incubated overnight at 4°C and the plates were then washed 4x with MSD Tris Wash Buffer. The SULFO-TAG anti-pTyr antibody from MSD was diluted to 20nM final in 1% Blocker A (MSD) solution and added to the washed plates and incubated for 1.5-2 h before addition of read buffer (MSD). The plates were read on the Sector 6000 instrument (MSD). Raw data was imported in Abase and EC_{50}s calculated with XL-fit data analysis software.

Biological Example 3

CSF-1R Inhibitors in MNFS-60 Pk/Pd Model

[0235] Five million MNFS-60 cells were implanted in HBSS/matrigel solution s.q. in the right flank. Approximately 3 weeks following tumor cell injection tumors were measured and selected mice were randomized (n=3 except for the vehicle group, where n=6) into groups based on their tumor size.

[0236] Compounds that inhibited M-CSF mediated proliferation in MNFS-60 cells and phosphorylation of CSF-1R with EC_{50}s <100 nM were tested in the MNFS-60 syngeneic tumor model (5 X 10^6 where implanted subcutaneously in matrigel and grown 3-4 weeks until they reached approximately 150 mm^2). A single 100 mg/kg dose of representative compounds disclosed herein was administered to MNFS-60 tumored animals; plasma and tumor samples were harvested at various time points after dosing starting at 1h up to 24h.

[0237] Several of the compounds disclosed herein were shown to inhibit Tyr723 phosphorylation of CSF-1R in tumor lysates at ≥ 50% compared to vehicle control 4 hrs after dosing as determined by Western Blot.

[0238] Additionally, several of the compounds disclosed herein were tested in a rapid onset severe arthritis mouse model (Terato, K. et al., Journal of Immunology 148:2103-2108; 1992) and treatment started on day three after injection of the anti-collagen antibody cocktail followed by LPS stimulation. Throughout the 12 days of treatment with CSF-1R inhibitors, the extent of swelling in the paws and bone resorption severity was scored. Significant attenuation of the swelling was not observed in the treated compared to control group; however, there was a trend toward improvement of bone resorption severity. There are no reports to date that CSF-1R inhibitors are effective in this arthritis model. The only successful reduction of disease progression was reported for inhibition by CSF-1R signaling with an Anti-MCSF antibody in a less severe, slower onset arthritis mouse model (Campbell et al J. Leukoc. Biol. 68: 144-150; 2000).

Biological Example 4

Inhibition of Raf Kinase Signaling in an *In Vitro* Biochemical Assay

[0239] The inhibitory effect of compounds on Raf was determined using the following biotinylated assay. The Raf kinase activity was measured by providing ATP, a recombinant kinase inactive MEK substrate and assaying the transfer of phosphate moiety to the MEK residue. Recombinant full length MEK with an inactivating K97R ATP binding site mutation (rendering kinase inactive) was expressed in *E. coli* and labelled with biotin post purification. The MEK cDNA was subcloned with an N-terminal $(His)_6$ tag and expressed in E. coli and the recombinant MEK substrate was purified from *E. coli* lysate by nickel affinity chromatography followed by anion exchange. The final MEK substrate preparation was biotinylated (Pierce EZ-Link Sulfo-NHS-LC-Biotin) and concentrated to 11.25μM. Recombinant Raf (including c-Raf and mutant B-Raf isoforms) was obtained by purification from sf9 insect cells infected with the corresponding human Raf recombinant expression vectors. The recombinant Raf isoforms were purified via a Glu antibody interaction or by Metal Ion Chromatography.

[0240] For each assay, the compound was serially diluted, starting at 25 μM with 3-fold dilutions, in DMSO and then mixed with various Raf isoforms (0.50 nM each). The kinase inactive biotin-MEK substrate (50 nM) was added in reaction buffer plus ATP (1 μM). The reaction buffer contained 30 mM Tris-HCL_2 pH 7.5, 10 mM $MgCl_2$, 2 mM DTT, 4mM EDTA, 25 mM beta-glycerophosphate, 5 mM $MnCl_2$, and 0.01% BSA/PBS. Reactions were subsequently incubated for 2 hours at room temperature and stopped by the addition of 0.5 M EDTA. Stopped reaction mixture was transferred to a neutradavin-coated plate (Pierce) and incubated for 1 hour. Phosphorylated product was measured with the DELFIA time-resolved fluorescence system (Wallac), using a rabbit anti-p-MEK (Cell Signaling) as the primary antibody and europium labeled anti-rabbit as the secondary antibody. Time resolved fluorescence can be read on a Wallac 1232 DELFIA fluorometer. The concentration of the compound for 50% inhibition (IC_{50}) was calculated by non-linear regression using XL Fit data analysis software.

Biological Example 5

Inhibition of cKIT and PDGFRb Kinase Signaling in an *In Vitro* Biochemical Assay

[0241] The IC50 values for the inhibition of RTKs were determined in the alphascreen format measuring the inhibition by compound of phosphate transfer to a substrate by the respective enzyme. Briefly, the respective RTK domain purchased as human recombinant protein (cKIT Upstate #14-559, PDGFRb Invitrogen #P3082) were incubated with serial dilutions of compound in the presence of substrate and ATP concentrations within 3 times the Km of the enzyme.

[0242] The kinase domain of cKIT was assayed in 50mM Hepes, pH=7.5, 5 mM MgCl2, 10 mM MnCl2, 1mM DTT, 0.1% BSA with 0.06 uM biotinylated peptide substrate (GGLFDDPSYVNVQNL-NH2) and 15 uM ATP (ATP KM apparent = 15 uM). The kinase domain of PDGFRβ was assayed in 50mM Hepes, pH=7.5, 20mM MgCl2, 1mM DTT, 0.1 % BSA with 0.1 uM biotinylated peptide substrate (GGLFDDPSYVNVQNL-NH2) and 10 uM ATP (ATP KM apparent = 25 uM). Reactions were incubated at room temperature for 3 to 4 hr and stopped with buffer (20 mM EDTA, 0.01 % Tween-20 for both PDGFRb and cKIT). Alphascreen PY20 beads were added to the stopped cKIT reactions and PY20 Ab / Protein A Alphascreen beads were added to the PDGFRβ stopped reactions. Both reactions were incubated overnight and read on the Alphascreen reader. The concentration of compound for 50% inhibition (IC_{50}) was calculated employing non-linear regression using XL-Fit data analysis software. As a control compou84d, staurosporine is run in every assay and a Z'>0.5 is required to validate results.

Biological Example 6

Cell viability assay in MCSF dependent MNFS60 cells

[0243] Cell viability was assessed by Cell Titer Glo, Promega. MNFS60 (murine AML cells) were seeded in TC treated 96-well plates at a density of 5,000 cells per well in RPMI-1640, 10%FBS, and 1% Penicillin Streptomycin prior to addition of compound. Test compounds were serially diluted (3 fold) in DMSO to 500x the final concentration. For each concentration of test compound, 2 µl (500x) aliquots of compound or 100% DMSO (control) were diluted in 500µl of culture medium that contained 2x final concentration of growth factor MCSF for 2 x concentration and then diluted 1x on the cells. Final concentration of MCSF is 10 ng/ml. Cells were incubated for 72hrs at 37°C, 5% CO_2. After the incubation 100 µl Cell Titer Glo is added to each well to determine viable cells. The assay was performed according to the manufacturer's instruction (Promega Corporation, Madison,WI. USA). Each experimental condition was performed in triplicate. Raw data was imported in Abase and EC_{50}s calculated with XL-fit data analysis software. Relative light units of wells that contained cells without MCSF in the media and as a consequence didn't grow were defined as 100% inhibited.

Biological Example 7

Tumor Induced Osteolysis Model

[0244] Tumor-induced osteolysis (TIO) models have been shown to recapitulate gross bone destruction seen in cancer patients with osteolytic tumor metastasis and have been reported extensively in both the bisphosphonate literature and in conjunction with the testing of novel anti-osteolytic agents. Results from these studies correlate well with human clinical activity (Kim S-J et al., 2005, Canc. Res., 65(9): 3707; Corey, E et al., 2003, Clin. Canc. Res., 9:295; Alvarez, E. et al., 2003, Clin. Canc. Res., 9: 5705). The procedure includes injection of tumor cells directly into the proximal tibia. Once the cells are established, they proliferate and secrete factors that potentiate osteoclast activity, resulting in trabecular and cortical bone resorption. Animals are treated with anti-resorptive agents following tumor cell implantation and bone destruction is measured in a number of ways at the end of the study.

[0245] The tumor cell lines utilized in this protocol are of human origin and represent tumor lines that have been previously modified such that they now express the enzyme Luciferase in order to track tumor cells in the animal using the Xenogen system. The strength of the light signal also gives an indication of approximately how many tumor cells are located at a particular site.

[0246] Mice are injected subcutaneously with either 2.5 mg/kg flunixin meglumine 30 minutes prior to cell inoculation to provide post-procedural analgesia. The mice are then be anesthetized by isoflurane inhalation (ketamine/xylazine injection may be used if isoflurane is not available). Anesthetized animals are placed in the supine position and following tumor cell aspiration into a 50 or 100 µl micro-syringe fitted with a 26- or 27-gauge needle, the needle will be inserted through the cortex of the anterior tuberosity of the right tibia with a rotating "drill-like" movement to minimize the chance for cortical fracture. Successful passage of the needle through the cortex and into the marrow is indicated by loss of resistance against the forward movement of the needle. Once the bone cortex is traversed, 10-20 µl of cell suspension (6X10^5 MDA-MB-231Luc breast carcinoma or 3X10^5 PC-3MLuc prostate carcinoma cells) will be injected into the tibia bone marrow. Animals will be observed to ensure uneventful recovery (warming pad or lamp) until they have recovered from anesthesia.

[0247] Progression of tumor growth in the bone can be divided into five stages (Stages 0-4). The stages are defined as follows and can be monitored by comparison to the uninjected (left) leg of the mouse:

Stage 0: normal, no sign of any change in the bone.

Stage 1: Equivocal or minimal lesion; cortex/architecture normal.

Stage 2: Definite lesion; minimal cortex/architecture disruption.

Stage 3: Large lesion; cortex/architecture disruption.

Stage 4: Gross destruction; no preservation of architecture, "late stage". Animals reaching this stage will be taken off the study and euthanized.

[0248] Photon imaging of the legs are used to assess the tumor growth at the injection and remote sites during study using the Xenogen system to quantitate tumor cells in the tibia and confirm lack of leakage into other areas. Radiograms of the legs are taken up to once a week through the end of the study using Faxitron X-ray Unit to assess cortical bone destruction at the injection site. While using more invasive cell lines such as the PC-3M-Luc, we monitor bone damage one to two weeks after injection and weekly thereafter. For cell lines that form lesions at a slower rate, such as the MDA-MB-231Luc, which does not manifest bone damage until 4-5 weeks post-implantation, first radiographic images are taken approximately 4 weeks after animals have been intratibially implanted with cells to establish baseline controls and then once a week to measure bone damage starting at a time point when lesions begin to develop based on model development pilot studies. For example, in mice injected with MDA-MB-231Luc, an image would be taken approximately 4 weeks post-implantation, with weekly images thereafter.

[0249] Animals may be dosed with small molecules, monoclonal antibodies, or proteins once or twice daily, by any standard routes.

[0250] The endpoint of this study is the time point at which the majority of untreated (negative control) animals have reached late stage disease (Stage 4) and have been euthanized. At that point, the remaining animals in the study are euthanized, regardless of the stage of their tumors. Studies last approximately 5-10 weeks depending on the cell line. After the final x-ray is taken, blood is drawn from the animals by cardiac puncture (for assaying serum bone markers; see below). Endpoint x-ray images are then distributed to 5 volunteers who score each image according to the scoring system detailed above. Scores for each mouse are averaged and expressed as mean osteolytic score or percent of animals with severe osteolysis (animals with scores greater than 2).

Biological Example 8

Mouse Trap5b Assay (IDS Inc., Fountain Hills, AZ)

[0251] This assay is a solid phase immunofixed enzyme activity assay for the determination of osteoclast-derived tartrate-resistant acid phosphatase 5b in mouse serum samples. Trap5b is expressed by bone resorbing osteoclasts and secreted into the circulation. Thus, serum Trap5b is considered to be a useful marker of osteoclast activity, number and bone resorption.

[0252] The mouse Trap5b assay uses a polyclonal antibody prepared using recombinant mouse Trap5b as antigen. In the test, the antibody is incubated in anti-rabbit IgG-coated microtiter wells. After washing, standard, controls and diluted serum samples are incubated in the wells, and bound Trap5b activity is determined with a chromogenic substrate to develop color. The reaction is stopped and the absorbance of the reaction mixture read in a microtiter plate reader at 405 nm. Color intensity is directly proportional to the amount and activity of Trap5b present in the sample. By plotting the mean absorbance for each standard on the ordinate against concentration on the abscissa, values for unknown samples can be read from the standard curve and expressed in U/L Trap5b. Analytical sensitivity of the assay is 0.1 U/L and inter- and intra-assay variation are below 10%. Trap5b levels were found to correlate well with mean osteolytic score (assessed by x-ray).

[0253] While a number of preferred embodiments of the invention and variations thereof have been described in detail, other modifications and methods of use will be readily apparent to those of skill in the art. Accordingly, it should be understood that various applications, modifications and substitutions may be made of equivalents without departing from the spirit of the invention or the scope of the claims.

[0254] The percent inhibition activities of the compounds of Tables 2 and 3 when tested at about 1μM in the indicated assay as described in the Biological Examples are shown respectively in Tables 5, 6, and 7. It is contemplated that compounds having 0 % inhibition at 1μM will exhibit inhibitory activities at a higher concentration. An "N/D" means that the compound was not tested in the particular assay.

Table 5. Activities of the compounds of Table 2

Cmpd	PDGFRβ	CSF-1R	cKit	M-NFS-60 CP	pCSF1R
52	50	100	12	56	71
137	98	100	45	100	98
157	20	100	20	100	99

Table 6. Activities of the compounds of Table 3

Cmpd	PDGFRβ	CSF-1R	cKit	M-NFS-60 CP	pCSF1R
7	9	100	12	35	N/D
10	9	67	0	N/D	N/D
11	60	100	0	69	92
12	1	95	0	N/D	N/D
13	0	93	9	N/D	N/D
14	0	96	3	N/D	N/D
15	7	99	15	4	N/D
16	9	99	12	30	N/D
17	12	99	19	23	N/D
18	23	99	80	22	N/D
19	0	96	8	23	N/D
20	0	76	0	N/D	N/D

Cmpd	PDGFRβ	CSF-1R	cKit	M-NFS-60 CP	pCSF1R
47	4	100	0	55	83
48	16	99	14	26	
49	12	100	21	33	77
50	14	99	13	18	N/D
51	0	95	10	N/D	N/D
125	9	99	2	17	N/D
155	18	99	34	0	N/D
156	3	100	36	33	N/D
157	17	100	43	42	N/D
158	1	99	27	0	N/D
159	23	100	29	98	96
160	19	100	95	30	N/D
161	26	54	20	N/D	N/D
162	30	100	20	100	99
164	87	100	79	100	100
165	83	100	83	100	98
166	0	100	13	49	78
167	0	100	16	24	N/D
168	43	100	40	100	99
169	0	75	12	N/D	N/D
170	23	100	28	100	96
171	18	100	25	96	95
172	18	100	22	100	97
173	8	100	18	52	81
174	3	86	18	N/D	N/D
175	1	100	11	17	N/D
176	0	63	12	N/D	N/D
177	0	67	15	N/D	N/D
178	-3	82	17	N/D	N/D
179	16	98	10	27	N/D
180	12	100	23	96	93
181	17	72	27	N/D	N/D
182	4	100	16	100	98
184	84	100	45	100	95
185	29	100	32	100	94

Cmpd	PDGFRβ	CSF-1R	cKit	M-NFS-60 CP	pCSF1R
186	14	100	13	100	99
187	25	100	32	100	98
188	35	100	55	38	N/D
189	23	100	31	26	N/D
190	19	98	22	5	N/D
191	15	45	19	N/D	N/D
192	22	99	56	14	N/D
193	15	95	27	0	N/D
194	16	77	20	N/D	N/D
195	25	81	90	N/D	N/D
196	23	100	29	100	98
197	89	100	93	100	98
200	19	100	29	69	83
203	15	98	22	20	N/D
209	1	100	17	36	N/D
224	0	100	26	33	N/D
225	0	90	21	N/D	N/D
226	0	80	20	N/D	N/D
231	49	100	9	100	99
232	64	100	34	100	99
258	62	100	44	100	99
259	6	100	24	100	98
260	0	100	25	100	98
261	30	100	25	100	98
262	3	100	20	46	48
265	12	100	9	32	N/D
266	21	100	18	100	94
267	26	100	16	100	96
280	22	100	11	100	65
281	36	100	22	100	96
282	7	99	23	22	N/D
283	20	99	38	0	N/D
284	53	100	61	100	N/D
285	8	99	33	0	N/D

Cmpd	PDGFRβ	CSF-1R	cKit	M-NFS-60 CP	pCSF1R
286	0	100	23	71	94
287	20	100	57	35	N/D
288	24	100	78	70	N/D
291	0	48	4	N/D	N/D
293	0	100	22	67	82
320	20	100	16	25	N/D
322	11	99	18	21	N/D
324	19	99	21	15	N/D
344	65	100	45	100	95
345	13	100	19	97	93
346	0	100	13	67	84
359	19	100	31	95	93
360	16	100	29	100	98
368	8	100	24	12	N/D
369	12	100	26	44	N/D
371	9	100	29	69	79
372	8	100	21	75	88
376	28	100	72	87	77
377	49	100	75	93	N/D
378	43	100	62	90	87
381	20	100	30	100	99

[0255] The following references are cited in the specification.

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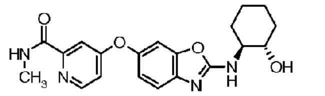
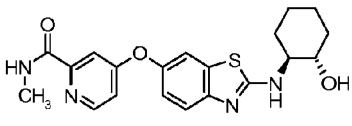
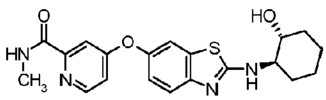
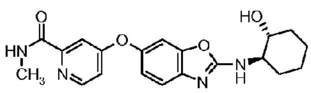
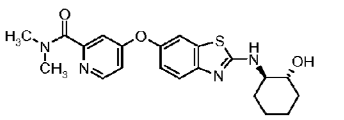
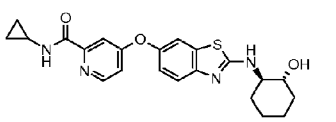
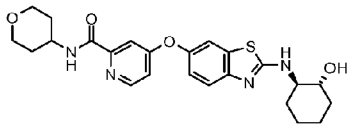
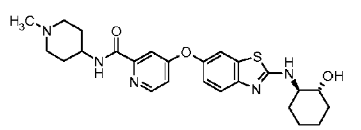
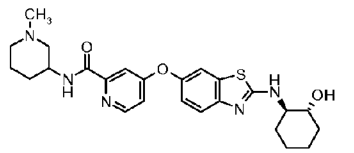
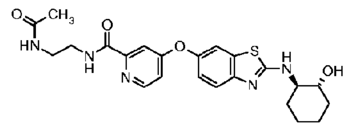
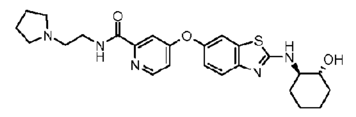
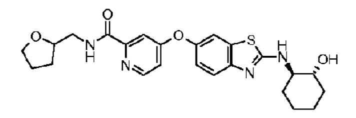
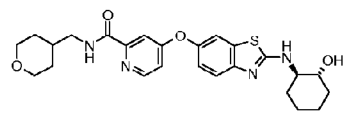
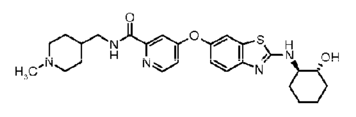
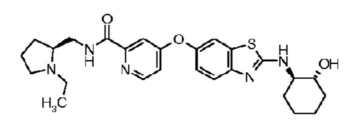
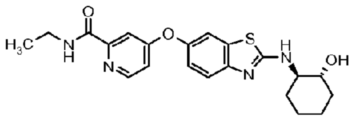
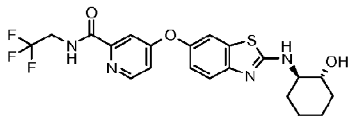
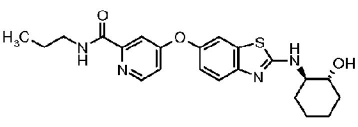
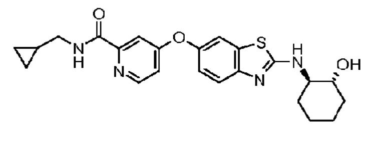
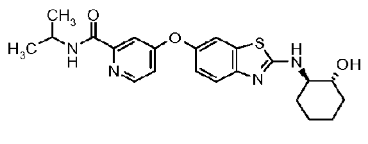
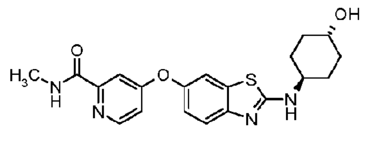
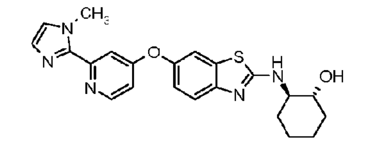
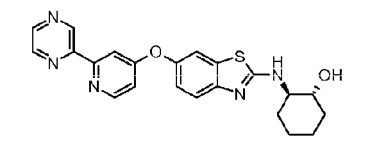
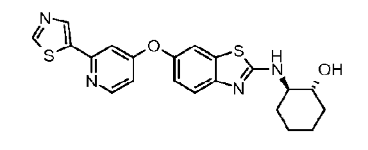
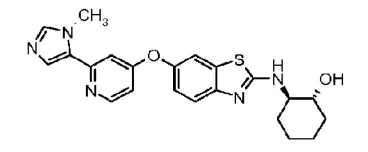
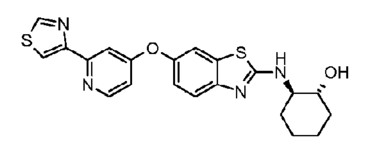
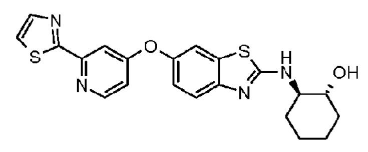
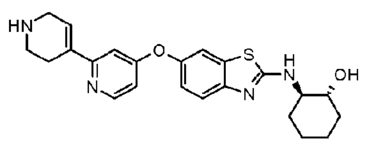
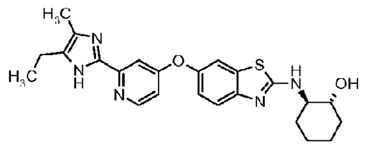
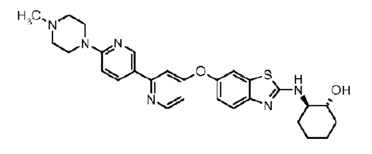










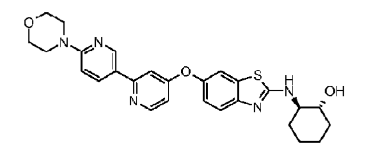










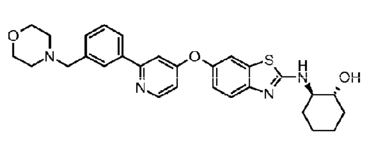










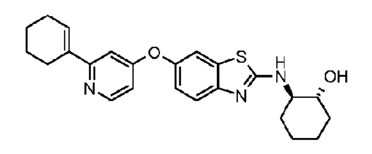


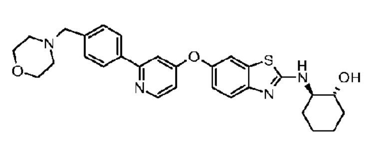


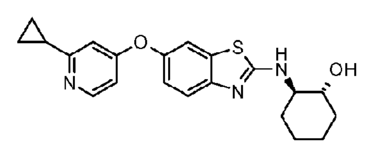


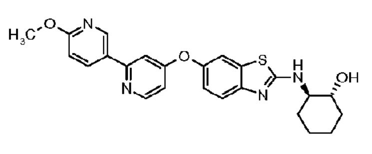


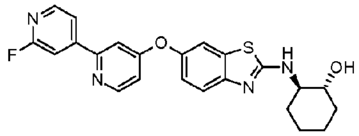
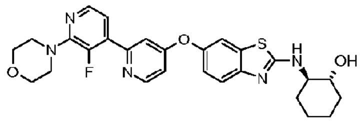
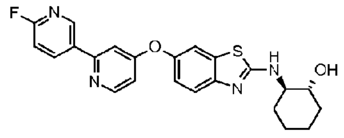
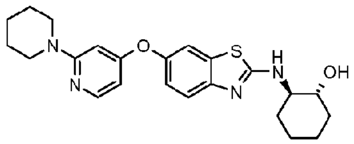
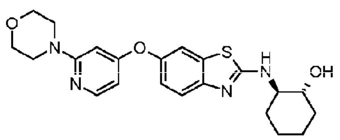
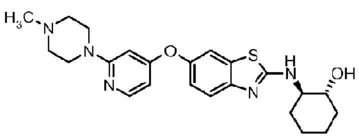
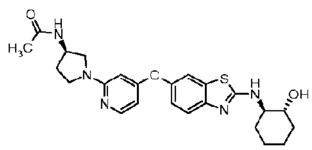
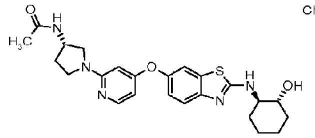
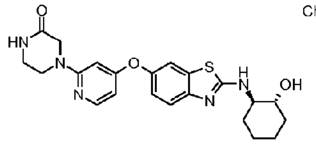


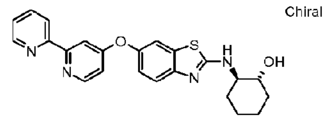
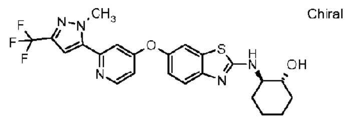
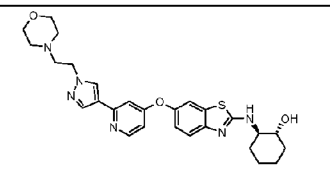
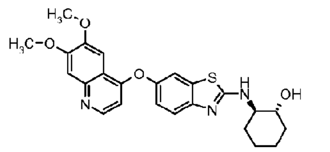
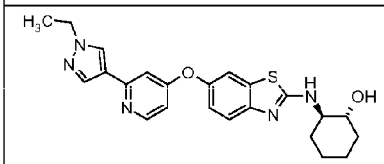
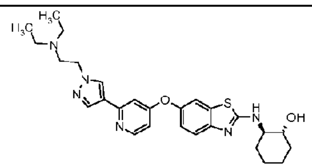
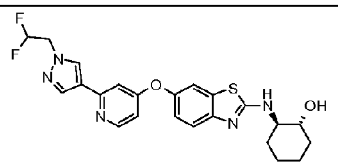
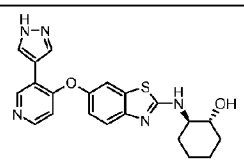
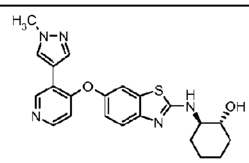


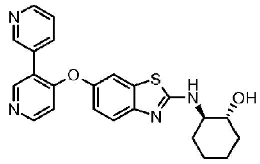
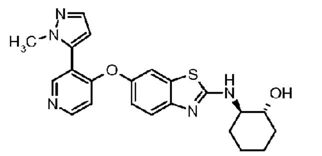
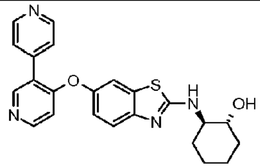
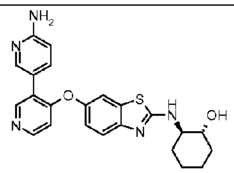
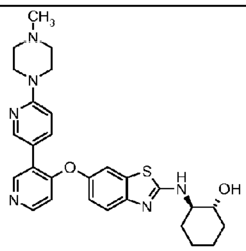
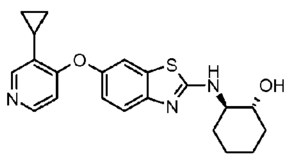
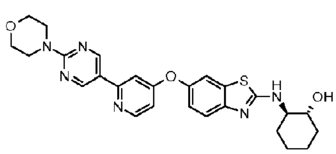
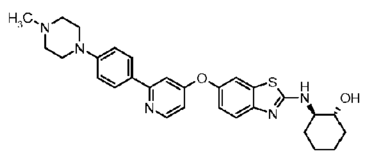


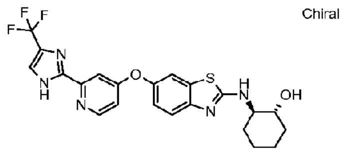
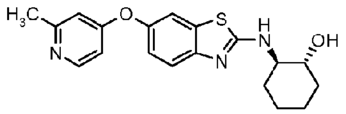
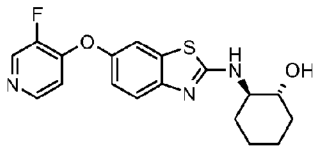
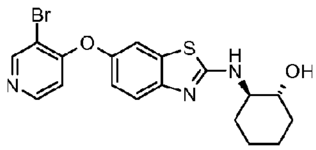
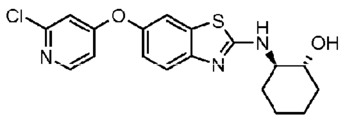
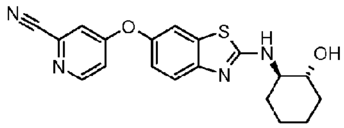
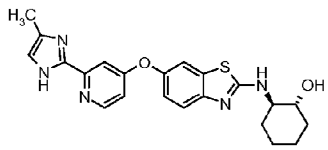
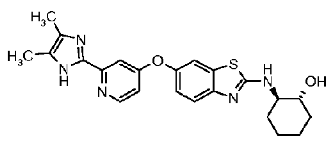
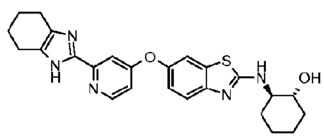


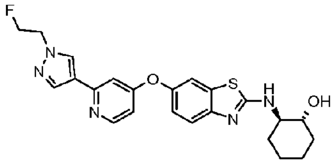
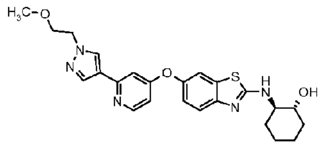
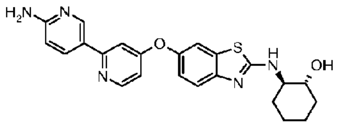
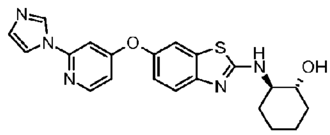
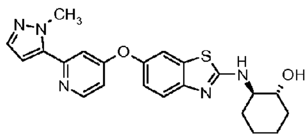
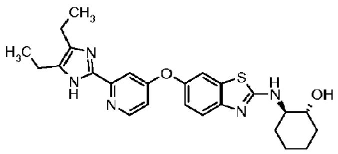
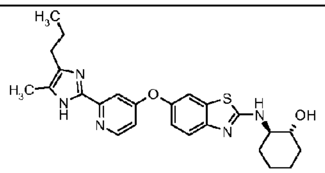
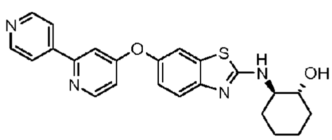


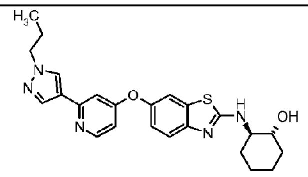
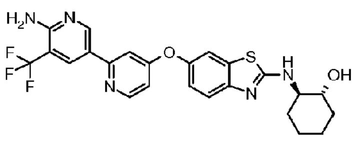
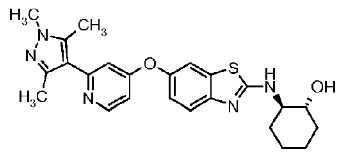
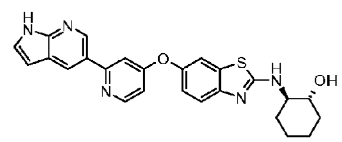
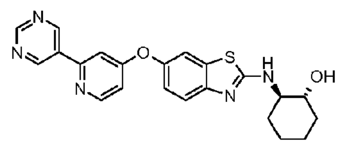
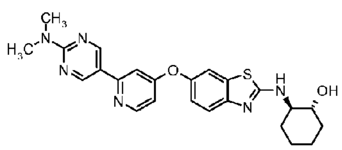
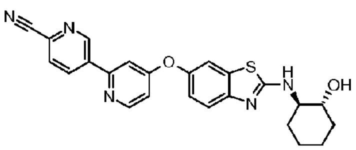
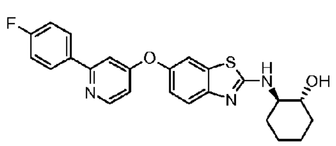







Chiral 
Chiral 

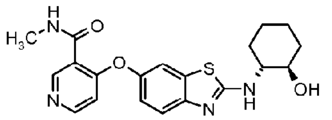
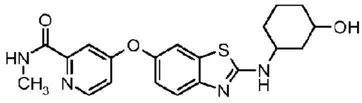
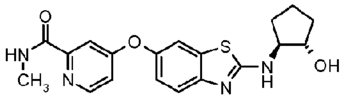
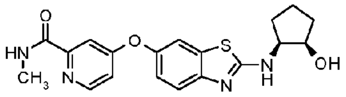
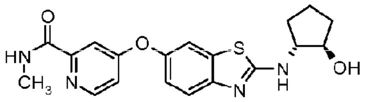
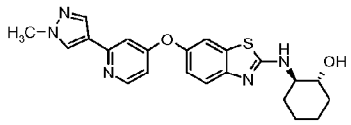
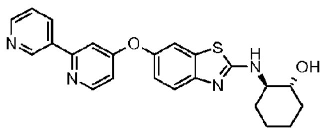
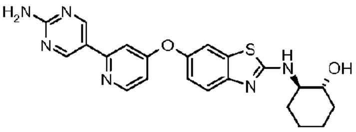
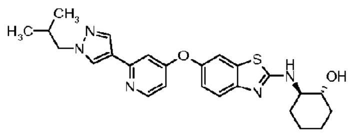
Chiral
Chiral








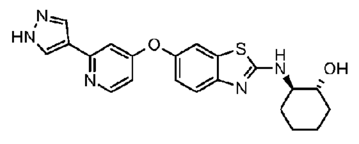
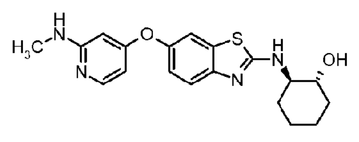
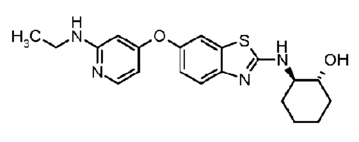
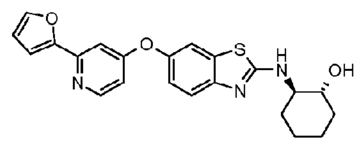
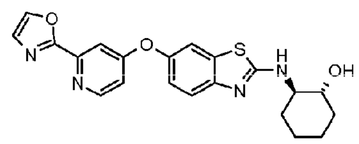
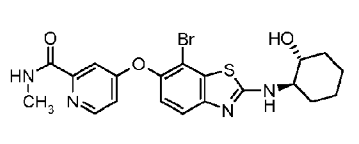
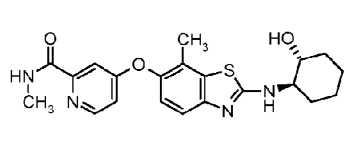
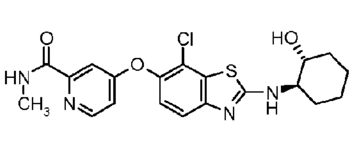
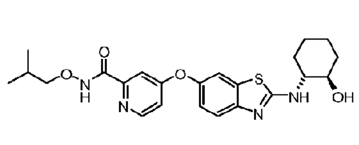









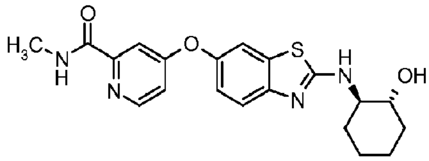









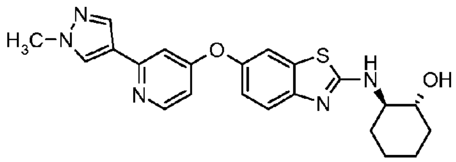
eller en stereoisomer, tautomer, et solvat eller oxid, eller et farmaceutisk acceptabelt salt deraf.

2. Forbindelse ifølge krav 1, som er



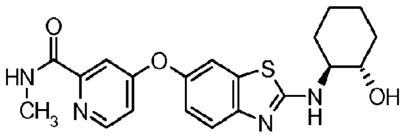
eller et solvat, oxid, eller et farmaceutisk acceptabelt salt deraf.

3. Forbindelse ifølge krav 1, som er



eller et solvat, oxid, eller et farmaceutisk acceptabelt salt deraf.

4. Forbindelse ifølge krav 1, som er



eller et solvat, oxid, eller et farmaceutisk acceptabelt salt deraf.

5. Farmaceutisk sammensætning omfattende en forbindelse, en stereoisomer, en tautomer, et solvat eller et oxid eller et farmaceutisk acceptabelt salt deraf ifølge ethvert af kravene 1 til 4, sammen med farmaceutisk acceptable bærestoffer.

6. Anvendelse af en forbindelse, en stereoisomer, en tautomer, et solvat eller et oxid eller et farmaceutisk acceptabelt salt deraf ifølge ethvert af kravene 1 til 4, til fremstillingen af et medikament til behandlingen af cancer, osteoporose, arthritis, atherosclerose , myelocytisk leukæmi, idiopatisk myelofibrose, brystcancer, cervicalcancer, ovariecancer, endometrialcancer, prostatacancer, hepatocellularcancer, multiple myelomer, lungecancer, knoglecancer og rheumatoid arthritis.

7. Forbindelse, stereoisomer, tautomer, solvat eller oxid eller farmaceutisk acceptabelt salt deraf ifølge ethvert af kravene 1 til 4 i en mængde, som er effektiv til reduktion eller forebyggelse af tumorvækst i et subjekt, i kombination med i det mindste et yderligere middel til behandlingen af cancer.

8. Forbindelse, stereoisomer, tautomer, solvat eller oxid, eller farmaceutisk acceptabelt salt deraf ifølge krav 7, hvor det yderligere middel til behandlingen af cancer er valgt blandt østrogen-receptormodulatorer, androgen-receptormodulatorer, retinoid-receptormodulatorer, cytotoksiske/cytostatiske midler, antiproliferative midler, prenyl-proteintransferaseinhibitorer, HMG-CoA-reduktaseinhibitorer og andre angiogenese-inhibitorer, inhibitorer for celleproliferation og overlevelsessignalering, apoptose inducerende midler og midler som interfererer med cellecykluskontrolpunkter, HIV proteaseinhibitorer og revers transkriptaseinhibitorer.

9. Forbindelse ifølge ethvert af kravene 1 til 4 eller stereoisomer, tautomer, solvat eller oxid eller farmaceutisk acceptabelt salt deraf til anvendelse ved behandlingen af cancer, osteoporose, arthritis, atherosclerose, myelocytisk leukæmi, idiopatisk myelofibrose, brystcancer, cervicalcancer, ovariecancer, endometrialcancer, prostatacancer, hepatocellulær cancer, multiple myelomer, lungecancer, knoglecancer og rheumatoid arthritis.

10. Forbindelse ifølge ethvert af kravene 1 til 4 eller stereoisomer, tautomer, solvat eller oxid eller farmaceutisk acceptabelt salt deraf til anvendelse til samtidig indgivelse med strålingsterapi.

11. Kombination omfattende en forbindelse, stereoisomer, tautomer, solvat eller oxid, eller farmaceutisk acceptabelt salt deraf ifølge ethvert af kravene 1 til 4 og ét eller flere midler, som anvendes ved behandlingen af cancer.

12. Forbindelse, stereoisomer, tautomer, solvat eller oxid eller farmaceutisk acceptabelt salt deraf ifølge ethvert af kravene 1 til 4 og i det mindste ét yderligere terapeutisk middel til anvendelse ved behandlingen af cancer.