THIENO[3,2-b]PYRIDINE-6-CARBONITRILES AS PROTEIN KINASE INHIBITORS

This application relates to thieno[3,2-b]pyridine-6-carbonitriles useful as pharmaceuticals, more particularly to 3-substituted-thieno[3,2-b]pyridine-6-carbonitriles, processes for preparing them and pharmaceutical compositions containing them. The 3-substituted-thieno[3,2-b]pyridine-6-carbonitriles are useful as protein kinase inhibitors particular for the treatment of cancer, stroke, myocardial infarction, neuropathic pain, osteoporosis, polycystic kidney disease, autoimmune disease, rheumatoid arthritis, and transplant rejection.

BACKGROUND OF THE INVENTION

This invention relates to compounds that inhibit the activity of protein kinases. Protein kinases are enzymes that catalyze the transfer of a phosphate group from ATP to an amino acid residue, such as tyrosine, serine, threonine, or histidine on a protein. Regulation of these protein kinases is essential for the control of a wide variety of cellular events including proliferation and migration. Specific protein kinases have been implicated in diverse conditions including cancer [Blume-Jensen, P., *Nature*, *411*, 355 (2001)) Traxler, P. M., *Exp. Opin. Ther. Patents*, *8*, 1599 (1998); Bridges, A. J., *Emerging Drugs*, *3*, 279 (1998)]; restenosis [Mattsson, E., *Trends Cardiovascular Medicine 5*, 200 (1995)]; atherosclerosis [Raines, E. W., *Bioessays, 18,* 271 (1996)]; angiogenesis [Shawver, L. K., *Drug Discovery Today, 2,* 50 (1997); Folkman, J., *Nature Medicine, 1*, 27 (1995)] stroke [Paul, R., *Nature Medicine* 7, 222 (2001)]; and osteoporosis [Boyce, *J. Clin. Invest., 90,* 1622 (1992)].

Tyrosine kinases (TK) are a class of protein kinases. The major family of cytoplasmic protein TKs is the Src family which consists of at least eight members (Src, Fyn, Lyn, Yes, Lck, Fgr, Hck and Blk) that participate in a variety of signaling pathways [Schwartzberg, P. L., *Oncogene, 17*, 1463 (1998)]. The prototypical member of this tyrosine kinase family is Src, which is involved in proliferation and migration responses in many cell types [Sawyer, T., *Expert Opin. Investig. Drugs*, *10*, 1327 (2001)]. Src activity has been shown to be elevated in breast, colon (~90%), pancreatic (>90%) and liver (>90%) tumors. Greatly increased Src activity is also associated with metastasis (>90%) and poor prognosis. Antisense Src message

impedes growth of colon tumor cells in nude mice [Staley, C. A., *Cell Growth Differentiation, 8*, 269 (1997)], suggesting that Src inhibitors could slow tumor growth. In addition to its role in cell proliferation, Src also acts in stress response pathways, including the hypoxia response. Nude mice studies with colon tumor cells expressing antisense Src message have reduced vascularization [Ellis, L. M., *J. Biol. Chem., 273,* 1052 (1998)], which suggests that Src inhibitors could be anti-angiogenic as well as anti-proliferative.

Src disrupts E-cadherin associated cell-cell interactions [E. Avezienyte, *Nature Cell Bio.,* 4, 632 (2002)]. A low molecular weight Src inhibitor prevents this disruption thereby reducing cancer cell metastasis [Nam, J.S., *Clinical Cancer Res.*, 8, 2340 (2002)].

Src inhibitors may prevent the secondary injury that results from a VEGF-mediated increase in vascular permeability such as that seen following stroke [Eliceiri, B. P., Mol. Cell., 4, 915 (1999); Paul, R., *Nat. Med.* 7, 222 (2001)].

Blockade of Src prevents dissociation of the complex involving Flk, VE-cadherin, and β-catenin with the same kinetics with which it prevents VEGF-mediated VP/edema and account for the Src requirement in VEGF-mediated permeability and provide a basis for Src inhibition as a therapeutic option for patients with acute myocardial infarction [Weis, S., J. Clin. Invest., 113, 885 (2004)].

Src also plays a role in osteoporosis. Mice genetically engineered to be deficient in Src production were found to exhibit osteopetrosis, the failure to resorb bone [Soriano, P., *Cell, 64*, 693 (1991); Boyce, B. F., *J. Clin., Invest., 90,* 1622 (1992)]. This defect was characterized by a lack of osteoclast activity. Since osteoclasts normally express high levels of Src, inhibition of Src kinase activity may be useful in the treatment of osteoporosis [Missbach, M., *Bone, 24*, 437 (1999)].

Inhibitors of the NMDA (N-methyl-D-aspartate) receptor could provide treatment of chronic neuropathic pain [Urban, L. *Drug Dev. Res.,* 54, 159 (2002)]. The activity of NMDA receptors is regulated by Src family kinases (SFKs) (Yu, X. M., *Proc. Nat. Acad. Sci.,* U.S.A., 96, 7697 (1999) and a low molecular weight SFK inhibitor, PP2, decreases phosphorylation of the NMDA receptor NR2 subunit [Guo,

W.J. *Neuro.*, 22(14), 6208 (2002)]. SFK inhibitors therefore have potential in the treatment of neuropathic pain.

Tyrosine kinases (TKs) are divided into two classes: the non-transmembrane TKs and transmembrane growth factor receptor TKs (RTKs) [Blume-Jensen, P., *Nature*, *411*, 355 (2001)]. Growth factors, such as epidermal growth factor (EGF), bind to the extracellular domain of their partner RTK on the cell surface which activates the RTK, initiating a signal transduction cascade that controls a wide variety of cellular responses including proliferation and migration. The overexpression of EGF and also of members of the epidermal growth factor receptor (EGFr) family, which includes EGF-r, erbB-2, erbB-3 and erbB-4, is implicated in the development and progression of cancer [Rusch, V., *Cytokine Growth Factor Rev., 7,* 133 (1996), Davies, D. E., *Biochem. Pharmacol., 51,* 1101 (1996) and Modjtahedi, E., *Int. J. Oncol., 4*, 277 (1994)]. Specifically, over expression of the receptor kinase product of the erbB-2 oncogene has been associated with human breast and ovarian cancers [Slamon, D. J., *Science*, *244*, 707 (1989) and Slamon, D. J., *Science*, *235*, 177 (1987)]. Upregulation of EGFr kinase activity has been associated with epidermoid tumors [Reiss, M., *Cancer Res.*, *51*, 6254 (1991)]; breast tumors [Macias, A., *Anticancer Res.*, *7*, 459 (1987)]; and tumors involving other major organs [Gullick, W.J., *Brit. Med. Bull.*, *47*, 87 (1991)].

It is also known that deregulation of EGF receptors is a factor in the growth of epithelial cysts in the disease described as polycystic kidney disease [Du, J., *Amer. J. Physiol., 269* (2 Pt 1), 487 (1995); Nauta, J., *Pediatric Res., 37(6),* 755 (1995); Gattone, V. H., *Developmental Biology, 169(2),* 504 (1995); Wilson, P. D., *Eur. J. Cell Biol., 61(1),* 131, (1993)]. The compounds of this invention, which inhibit the catalytic function of the EGF receptors, are consequently useful for the treatment of this disease.

In addition to EGFr, there are several other RTKs including FGFr, the receptor for fibroblast growth factor (FGF); flk-1, also known as KDR, and flt-1, the receptors for vascular endothelial growth factor (VEGF); and PDGFr, the receptor for platelet derived growth factor (PDGF). The formation of new blood vessels, a process known as angiogenesis, is essential for tumor growth. Two natural

angiogenesis inhibitors, angiostatin and endostatin, dramatically inhibited the growth of a variety of solid tumors. [O'Reilly, M. S., *Cell, 79*, 315 (1994); O'Reilly, M. S., *Nature Medicine, 2,* 689 (1996); O'Reilly, M. S., *Cell, 88*, 277 (1997)]. Since FGF and VEGF are known to stimulate angiogenesis, inhibition of the kinase activity of their receptors should block the angiogenic effects of these growth factors. In addition, the receptor tyrosine kinases tie-1 and tie-2 also play a key role in angiogenesis [Sato, T. N., *Nature, 376*, 70 (1995)]. Compounds of the invention that inhibit the kinase activity of FGFr, flk-1, flt-1, tie-1 or tie-2 may inhibit tumor growth by their effect on angiogenesis.

PDGF is a potent growth factor and chemoattractant for smooth muscle cells (SMCs). The renarrowing of coronary arteries following angioplasty is due in part to the enhanced proliferation of SMCs in response to increased levels of PDGF. Therefore, compounds that inhibit the kinase activity of PDGFr may be useful in the treatment of restenosis. In addition, since PDGF and PDGFr are overexpressed in several types of human gliomas, small molecules capable of suppressing PDGFr activity, have potential utility as anticancer therapeutics [Nister, M., *J. Biol. Chem. 266*, 16755 (1991); Strawn, L. M., *J. Biol. Chem. 269*, 21215 (1994)].

Other RTKs that could potentially be inhibited by compounds of this invention include colony stimulating factor receptor, the nerve growth factor receptors (trka, trkB and trkC), the insulin receptor, the insulin-like growth factor receptor, the hepatocyte growth factor receptor and the erythropoietin-producing hepatic cell receptor (EPH).

In addition to the RTKs there is another family of TKs termed the cytoplasmic protein or non-receptor TKs. The cytoplasmic protein TKs have intrinsic kinase activity, are present in the cytoplasm and nucleus, and participate in diverse signaling pathways. There are a large number of non-receptor TKs including Abl, Jak, Fak, Syk, Zap-70 and Csk. Inhibitors of Abl kinase are useful for the treatment of chronic myeloid leukemia as evidenced by STI-571, marketed as Gleevec [Kantarjian, H., N. Engl. J. Med., 346 (9), 645 (2110)]. Compounds that are dual inhibitors of Src and Ab1 may be useful for the treatment of Gleevec resistant chronic myeloid leukemia (CML) [Warmuth, M., Current Pharm. Design, 9, 2043 (2003)].

Two members of the cytoplasmic protein TKs, lck and ZAP-70 are predominately expressed on T-cells and natural killer (NK) cells. Inhibitors of these kinases can suppress the immune system and therefore have possible therapeutic potential to treat autoimmune diseases such as rheumatoid arthritis, sepsis, and transplant rejection [Kamens, J. S., *Current Opin. Investig. Drugs, 2,* 1213 (2001); Myers, M., *Current Pharm. Design, 3*, 473 (1997)]. A low molecular weight Lck inhibitor is effective in preventing allograft rejection [Waegell, W. *Transplant. Proceed.* 34, 1411 (2002)].

Besides TKs, there are additional kinases including those that phosphorylate serine and/or threonine residues on proteins. A major pathway in the cellular signal transduction cascade is the mitogen-activated protein kinase (MAPK) pathway which consists of the MAP kinase kinases (MAPKK), including mek, and their substrates, the MAP kinases (MAPK), including erk [Seger, R., *FASEB, 9*, 726 (1995)]. When activated by phosphorylation on two serine residues by upstream kinases, such as members of the raf family, mek catalyzes the phosphorylation of threonine and tyrosine residues on erk. The activated erk then phosphorylates and activates both transcription factors in the nucleus and other cellular targets. Over-expression and/or over-activation of mek or erk is associated with various human cancers [Sivaraman, V. S., *J. Clin. Invest., 99*, 1478 (1997)].

As mentioned above, members of the raf family of kinases phosphorylate serine residues on mek. There are three serine/threonine kinase members of the raf family known as a-raf, b-raf and c-raf. While mutations in the raf genes are rare in human cancers, c-raf is activated by the ras oncogene which is mutated in a wide number of human tumors. Therefore inhibition of the kinase activity of c-raf may provide a way to prevent ras mediated tumor growth [Campbell, S. L., *Oncogene, 17*, 1395 (1998)].

The cyclin-dependent kinases (cdks), including cdc2/cyclin B, cdk2/cyclin A, cdk2/cyclin E and cdk4/cyclin D, and others, are serine/threonine kinases that regulate mammalian cell division. Increased activity or activation of these kinases is associated with the development of human tumors [Garrett, M. D., *Current Opin. Genetics Devel., 9*, 104 (1999); Webster, K. R., *Exp. Opin. Invest. Drugs, 7*, 865

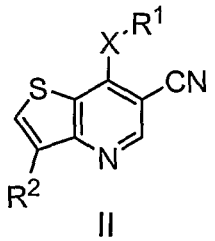
(1998)]. Additional serine/threonine kinases include PDK1, SGK and the protein kinases A, B, and C, known as PKA or cyclic AMP-dependent protein kinase, PKB (Akt), and PKC, of which all three play key roles in signal transduction pathways responsible for oncogenesis [Glazer, R. I., *Current Pharm. Design, 4(3),* 277 (1998)]. Compounds capable of inhibiting the kinase activity of mek, erk, raf, cdc2/cyclin B, cdk2/cyclin A, cdk2/cyclin E, cdk4/cyclin D, PDK1, SGK, PKA, PKB (Akt) or PKC may be useful in the treatment of diseases characterized by abnormal cellular proliferation, such as cancer.

The serine/threonine kinase UL97 is a virion-associated protein kinase which is required for the replication of human cytomegalovirus [Wolf, D.G., *Arch. Virology 143(6),* 1223 (1998) and He, Z., *J. Virology, 71,* 405(1997)]. Compounds capable of inhibiting the kinase activity of UL97 may be useful antiviral therapeutics. Since certain bacteria require the action of a histidine kinase for proliferation [Loomis, W. F., *J. Cell Sci., 110,* 1141 (1997)], compounds capable of inhibiting such histidine kinase activity may be useful antibacterial agents.

Thieno[3,2-b]pyridines, thieno[2,3-b]pyridines and certain pyridine and pyrimidine derivatives have been noted as kinase inhibitors. These compounds differ both in nature and placement of substituents at various positions when compared to the compounds of this invention. Our co-pending WO 2004/048386 published 10 June 2004 (the contents of which are incorporated herein in their entirety) describes 2-substituted-thieno[3,2-b]pyridine-6-carbonitriles and 2-substituted-thieno[2,3-b]pyridine-5-carbonitriles as protein kinase inhibitors.

SUMMARY OF THE INVENTION

This invention is directed to compounds of Formula II



II

wherein:

X is –NH-, $-NR^4-$, -O-, $-S(O)_m-$, or $-NHCH_2-$;

m is an integer of 0-2;

n is an integer of 2-5;

q is an integer of 0-5;

R^1 is a phenyl ring optionally substituted with one to four substituents selected from the group consisting of J, $-NO_2$, -CN, $-N_3$, -CHO, $-CF_3$, $-OCF_3$, R^4, $-OR^4$, $-S(O)mR^4$, $-NR^4R^4$, $-NR^4S(O)_mR^4$, $-OR^6OR^4$, $-OR^6NR^4R^4$, $-N(R^4)R^6OR^4$, $-N(R^4)R^6NR^4R^4$, $-NR^4C(O)R^4$, $-C(O)R^4$, $-C(O)OR^4$, $-C(O)NR^4R^4$, $-OC(O)R^4$, $-OC(O)OR^4$, $-OC(O)NR^4R^4$, $NR^4C(O)R^4$, $-NR^4C(O)OR^4$, $-NR^4C(O)NR^4R^4$, $-R^5OR^4$, $-R^5NR^4R^4$, $-R^5S(O)_mR^4$, $-R^5C(O)R^4$, $-R^5C(O)OR^4$, $-R^5C(O)NR^4R^4$, $-R^5OC(O)R^4$, $-R^5OC(O)OR^4$, $-R^5OC(O)NR^4R^4$, $-R^5NR^4C(O)R^4$, $-R^5NR^4C(O)OR^4$, $-R^5NR^4C(O)NR^4R^4$, or YR^7;

R^2 is R^3, J, $-C(O)XR^3$, or -CHO, wherein the R^3 group may be substituted by one or more groups selected from $-C(O)XR^8$, -CHO, -C(O)Q, 1,3-dioxolane, $-R^8$, $-(C(R^9)_2)_qXR^8$, $-(C(R^9)_2)_qQ$, $-X(C(R^9)_2)_nXR^8$, -X(C(R9)2)nQ, or - X(C(R9)2)qR8;

R^3 is alkyl of 1 to 6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, aryl or heterocycle;

R^4 is H, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, or alkynyl of 2-6 carbon atoms;

R^5 is a divalent group comprising alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, or alkynyl of 2-6 carbon atoms;

R^6 is a divalent alkyl group of 2-6 carbon atoms;

R^7 is a cycloalkyl ring of 3-7 carbons, an aryl or heterocyclic ring, or an aryl or heterocyclic ring fused to one to three aryl or heterocyclic rings, wherein any of the aryl, cycloalkyl, or heterocyclic rings may be optionally substituted with one to four substituents selected from the group consisting of H, -aryl, $-CH_2$-aryl, -NH-aryl,

-O-aryl, -$S(O)_m$-aryl, J, -NO_2, -CN, -N_3, -CHO, -CF_3, -OCF_3, R^4, -OR^4, -$S(O)_mR^4$, -NR^4R^4, -$NR^4S(O)_mR^4$, -OR^6OR^4, -$OR^6NR^4R^4$, -$N(R^4)R^6OR^4$, -$N(R^4)R^6NR^4R^4$, -$NR^4C(O)R^4$, -$C(O)R^4$, -$C(O)OR^4$, -$C(O)NR^4R_4$, -$OC(O)R^4$-, -$OC(O)OR^4$, -$OC(O)NR^4R^4$, -$NR^4C(O)R^4$, -$NR^4C(O)OR^4$, -$NR^4C(O)NR^4R^4$, -R^5OR^4, $R^5NR^4R^4$, -$R^5S(O)_mR^4$, -$R^5C(O)R^4$, -$R^5C(O)OR^4$, -$R^5C(O)NR^4R^4$, -$R^5C(O)R^4$, -$R^5C(O)OR^4$, -$R^5C(O)NR^4R^4$, -$R^5OC(O)R^4$, -$R^5OC(O)OR^4$, -$R^5OC(O)NR^4R^4$, -$R^5NR^4C(O)R^4$, -$R^5NR^4C(O)OR^4$, or –$R^5NR^4C(O)NR^4R^4$;

R^8 is H, alkyl of 1 to 6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, aryl or heterocycle;

R^9 is R^4 or F;

Y is -C(O)-, -C(O)O-, -OC(O)-, -C(O)NH-, -NHC(O)-, -$NHSO_2$-, -SO_2NH-, -C(OH)H-, -$X(C(R^9)_2)_q$-, -$(C(R^9)_2)_q$-, -$(C(R^9)_2)_qX$-, -C□C-, -CH=CH- or cycloalkyl of 3-10 carbon atoms;

Q is NZZ' wherein Z and Z' may be the same or different and may be H, alkyl of 1 to 6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, aryl, or heterocycle, or

Z and Z' taken together with the nitrogen to which they are attached may form a heterocyclic ring which may have an additional heteroatom selected from nitrogen, oxygen, and sulfur, and may comprise morpholine, piperazine, piperidine, optionally substituted with –R^8 on a carbon or a nitrogen, or on nitrogen by a group -$(C(R^9)_2)_nXR^8$, -$C(R^9)_2)_nNZ"Z"'$, or on carbon by a group -$(C(R^9)_2)_qXR^8$, -$(C(R^9)_2)_qNZ"Z"'$;

Z"' and Z" may be H, alkyl of 1 to 6 carbon atoms alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, aryl, or heterocycle, or

Z" and Z"' taken together with the nitrogen to which they are attached may form a heterocyclic ring which may contain an additional heteroatom selected from nitrogen, oxygen and sulfur; and

J is fluoro, chloro, bromo, or iodo;

or a pharmaceutically acceptable salt thereof.

In some embodiments, XR^1 is $-NH-R^1$.

R^1 may be, for example, a phenyl ring optionally substituted with one to four substituents selected from the group consisting of J, or $-OR^4$, wherein R^4 may be, for example, H or alkyl of 1- 4 carbon atoms.

R^2 may be J or R^3 wherein R^3 is aryl or heterocycle and the R^3 group is optionally substituted by at least one group selected from $-C(O)XR^8$, -CHO, -C(O)Q, 1,3-dioxolane, R^8, $-(C(R^9)_2)_qXR^8$, $-(C(R^9)_2)_qQ$, $-X(C(R^9)_2)_nXR^8$, $-X(C(R^9)_2)_nQ$, or $-X(C(R^9)_2)_q R^8$. In some embodiments, R^2 may be J or R^3 wherein R^3 is aryl or heterocycle and the R^3 group is optionally substituted by or at least one group selected from -CHO, $-(C(R^9)_2)_qQ$, or R^8.

Q may be NZZ' wherein Z and Z' may be the same or different and may be H or alkyl of 1 to 6 carbon atoms; or Z and Z' taken together with the nitrogen to which they are attached may form a heterocyclic ring which may have an additional heteroatom selected from nitrogen and oxygen, said ring may be substituted on nitrogen by R^4.

R^8 may be H, alkyl of 1 to 6 carbon atoms, aryl or heterocycle. J may be chloro or bromo. In some embodiments, R^9 is H. Certain embodiments include compounds wherein q is 1.

The compounds of the invention include:

3-bromo-7-[(2,4-dichloro-5-methoxyphenyl)amino]thieno[3,2-b]pyridine-6-carbonitrile,

7-[(2,4-dichloro-5-methoxyphenyl)amino]-3-(4-formylphenyl)thieno[3,2-b]pyridine-6-carbonitrile,

7-[(2,4-dichloro-5-methoxyphenyl)amino]-3-{4-[(dimethylamino)methyl]phenyl} thieno[3,2-b]pyridine-6-carbonitrile,

7-[(2,4-dichloro-5-methoxyphenyl)amino]-3-{4-[(4-methylpiperazin-1-yl)methyl] phenyl}thieno[3,2-b]pyridine-6-carbonitrile,

7-[(2,4-dichloro-5-methoxyphenyl)amino]-3-[4-(morpholin-4-ylmethyl)phenyl] thieno[3,2-b]pyridine-6-carbonitrile,

and pharmaceutically acceptable salts thereof.

For purposes of this invention a heterocycle or heterocyclic ring is a 3-14 membered aromatic or non-aromatic heterocyclic ring system of one to three fused rings containing 1 to 4 heteroatoms selected from the group consisting of S, N, and O. Each ring of the ring system may be fully unsaturated, partially saturated, or fully saturated. The heterocycle moieties include, but are not limited to, thiophene, furan, pyrrole, pyrazole, imidazole, 1,2,3-triazole, 1,2,4-triazole, tetrazole, thiazole, oxazole, isothiazole, isoxazole, 1,3,4-oxadiazole, 1,2,4-oxadiazole, 1,3,4-thiadiazole, pyridine, pyrimidine, pyrazine, pyridazine, 1,3,5-triazine, morpholine, thiomorpholine, thiomorpholine-S-oxide, thiomorpholine-S,S-dioxide, piperidine, piperazine, pyrrolidine, aziridine, oxirane, tetrahydrothiophene, tetrahydrofuran, 1,2-pyran, 1,4-pyran, dioxane, 1,3-dioxolane, tetrahydropyran, isoindene, indole, 2,3-dihydroindole, 2-indazole, isoindazole, quinoline, isoquinoline, tetrahydroquinoline, benzofuran, benzothiophene, benzimidazole, benzotriazole, benzothiazole, benzoxazole, benzisoxazole, 1,2-benzopyran, cinnoline, phthalazine, quinazoline, 1,8-naphthyridine, pyrido[3,2-b]pyridine, pyrido[3,4-b]pyridine, pyrido[4,3-b]pyridine, pyrido[2,3-d]pyrimidine, purine, and pteridine. The heterocycle may be oxidized on a nitrogen atom to provide the corresponding N-oxide, such as pyridine-N-oxide or quinoline -N-oxide. The heterocycle may also be oxidized on a tri-substitued nitrogen atom to provide the corresponding N-oxide, such as N-ethylpiperazine-N-oxide. The heterocycle may contain a carbonyl group on one of the carbon atoms, such as pyrrolidinone, 1,3,4-oxadiazol-2-one, or 2-indanone. The heterocycle may be optionally mono-, di-, tri- or tetra-substituted with substituents selected from, but not limited to, the group consisting of alkyl, acyl, alkoxycarbonyl, alkoxy, alkoxyalkyl, alkoxyalkoxy, cyano, halogen, hydroxy, or nitro.

For purposes of this invention the term "aryl" is defined as an aromatic hydrocarbon moiety and may be substituted or unsubstituted and may contain for example 6-14 carbon atoms and have one to three rings. One or more ring of the ring system may be partially saturated or fully saturated. An aryl may be selected

from but not limited to phenyl, naphthyl, 1,2,3,4-tetrahydronaphthyl, indan, indene or biphenyl and may be optionally mono-, di-, tri- or tetra-substituted with substituents selected from, but not limited to, the group consisting of alkyl, acyl, alkoxycarbonyl, alkoxy, alkoxyalkyl, alkoxyalkoxy, cyano, halogen, hydroxy, or nitro.

For purposes of this invention "alkyl" includes both straight and branched alkyl moieties, preferably of of 1-6 carbon atoms and includes iso-propyl, n-butyl and the like.

For purposes of this invention the term "cycloalkyl" refers to alicyclic hydrocarbon groups of 3-7 carbon atoms and includes a simple carbocycle as well as a carbocycle containing an alkyl substituent, for example, cyclopropyl, cyclohexyl, adamantyl and the like.

For purposes of this invention "alkenyl" is defined as a radical aliphatic hydrocarbon that contains at least one carbon-carbon double bond and includes both straight and branched carbon chains of 2-6 carbon atoms in all possible configurational isomers, for example *cis* and *trans*, and includes ethenyl, 3-hexen-1-yl and the like.

For purposes of this invention "alkynyl" includes both straight or branched carbon chain of 2-6 carbon atoms that contains at least one carbon-carbon triple bond and includes propenyl and the like.

In one embodiment of this invention the alkyl, cycloalkyl, alkenyl and alkynyl groups can be substituted with substituents including, but not limited to, phenyl, substituted phenyl, heterocycle, substituted heterocycle, hydroxy, halogen, alkoxy, thioalkyl, carboxy, alkoxycarbonyl and acyl.

For purposes of this invention "alkoxy" comprises a group of 1-6 carbon atoms having an alkyl group attached to an oxygen atom and includes methoxy, t-butoxy and also includes polyethers such as $-O-(CH_2)_2\ OCH_3$. A thioalkyl group of 1-6 carbon atoms is defined as an alkyl group attached to a sulfur atom and includes methylthio and the like. A carboxy group is defined as –C(O)OH, and an alkoxycarbonyl group is defined as -C(O)OR where R is a group of 1-6 carbon atoms

and includes methoxycarbonyl, allyloxycarbonyl and the like. An acyl group is defined as a group –C(O)R where R is an aliphatic (e.g., alkyl) or aryl radical and includes acetyl, trifluoroacetyl, benzoyl and the like.

The compounds of this invention may include a "divalent group" defined herein as a linking group, for example, $-CH_2CH_2-$.

The compounds of this invention may contain one or more asymmetric carbon atoms and may thus give rise to stereoisomers, such as enantiomers and diastereomers. While shown without respect to stereochemistry in Formula II, the present invention includes all the individual possible stereoisomers; as well as the racemic mixtures and other mixtures of R and S stereoisomers (scalemic mixtures which are mixtures of unequal amounts of enantiomers) and pharmaceutically acceptable salts thereof. It should be noted that stereoisomers of the invention having the same relative configuration at a chiral center may nevertheless have different R and S designations depending on the substitution at the indicated chiral center. Some of the compounds of this invention may contain one or more double bonds; in such cases, the compounds of this invention include each of the possible configurational isomers as well as mixtures of these isomers.

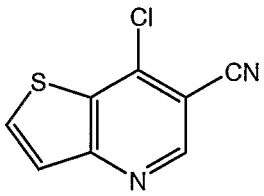
Pharmaceutically acceptable salts of the compounds of Formula II with an acidic moiety can be formed from organic and inorganic bases. Examples include alkali (e.g., N-tetrabutylammonium). Similarly, when a compound of this invention contains a basic moiety, salts can be formed from organic and inorganic acids. For example salts can be formed from acetic, propionic, lactic, citric, tartaric, succinic, fumaric, maleic, malonic, mandelic, malic, phthalic, hydrochloric, hydrobromic, phosphoric, nitric, sulfuric, methanesulfonic, napthalenesulfonic, benzenesulfonic, toluenesulfonic, camphorsulfonic, and similar known acids.

This invention includes a method of treating or inhibiting a pathological condition or disorder in a mammal comprising, providing to said mammal an effective amount of the compound of Formula II or a pharmaceutically acceptable salt thereof. The pathological condition or disorder is indicated by an increase in Src expression. Examples of pathological conditions or disorders include, but are not limited to, cancer, stroke, myocardial infarction, osteoporosis, polycystic kidney disease,

autoimmune disease, rheumatoid arthritis, and transplant rejection, and neuropathic pain. The cancer can be found for example, in the breast, colon, lung, pancrease, and liver.

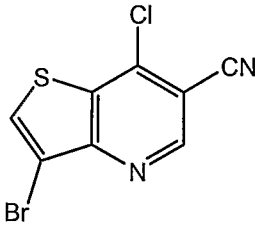
This invention includes a process for preparing a compound of Formula II comprising:

a. treating with N-bromosuccinimide a compound of Formula (a);



(a)

to provide a compound of Formula (b);

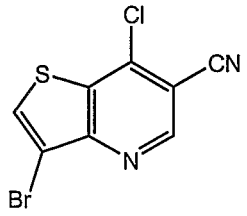


(b)

b. adding a compound of formula R^1XH to the compound of Formula (b) to form a compound of Formula II wherein R^2 is bromine; and

c. treating the compound produced in step (b) with a compound comprising formula R^3-H, R^3-BL^1L^2, or R^3SnR_3, in the presence of a palladium catalyst optionally in a solvent system, to form a compound of Formula II wherein Br is replaced by R^3.

This invention also includes a compound having the structure:



(b)

The terms used in this specification generally have their ordinary meanings in the art, within the context of the invention, and in the specific context where each term is used. Certain terms are discussed below, or elsewhere in the specification, to provide additional guidance to the practitioner in describing the compounds, compositions, and methods of the invention and how to make and use them. Moreover, it will be appreciated that the same thing can be said in more than one way. Consequently, alternative language and synonyms may be used for any one or more of the terms discussed herein, nor is any special significance to be placed upon whether or not a term is elaborated or discussed herein. The use of examples anywhere in this specification, including examples of any terms discussed herein, is illustrative only, and in no way limits the scope and meaning of the invention or of any exemplified term. Likewise, the invention is not limited to the examples presented.

In addition to the utilities, described herein some of the compounds of this invention are intermediates useful for the preparation of other compounds of this invention.

Throughout this application structures are presented with chemical names. Where any question arises as to nomenclature the structure prevails.

The following experimental details are set forth to aid in an understanding of the invention, and are not intended, and should not be construed, to limit in any way the invention set forth in the claims that follow thereafter.

DETAILED DESCRIPTION OF THE INVENTION

The compounds of this invention were prepared according to the following schemes: (1) from commercially available starting materials, (2) from known starting

materials which can be prepared as described in literature procedures, or (3) from new intermediates described in the schemes and experimental procedures. Optically active isomers may be prepared, for example, by resolving racemic derivatives or by asymmetric synthesis. The resolution can be carried out by methods known to those skilled in the art such as in the presence of a resolving agent, by chromatography, or combinations thereof.

Reactions are performed in a solvent appropriate to the reagents and materials employed and suitable for the transformation being effected. It is understood by those skilled in the art of organic synthesis that the various functionalities present on the molecule must be consistent with the chemical transformations proposed. This may necessitate judgement as to the order of synthetic steps, protecting groups, if required, and deprotection conditions. Substituents on the starting materials may be incompatible with some of the reaction conditions. Such restrictions to the substituents which are compatible with the reaction conditions will be apparent to one skilled in the art. Reactions are run under inert atmospheres where appropriate.

The preparation of the compounds and intermediates of this invention encompassed by Formula II are described as follows.

As shown in Scheme 20, decarboxylation of a 3-amino-2-thiophenecarboxylate of formula 1 with N-methylpiperazine in N-methylpyrrolidinone provides 3-aminothiophenes of formula 2. This decarboxylation can also be performed in a base such as aqueous sodium hydroxide at elevated temperatures. Addition of ethyl (ethoxymethylene) cyanoacetate to compounds of formula 2, in a solvent such as toluene, provides the intermediate propenoate. Thermal cyclization of these intermediate propionates in a solvent system such as biphenyl and diphenyl ether results in 7-oxo-4,7-dihydrothieno[3,2-b]pyridine-6-carbonitriles of formula 3. Compounds of formula 3 can also be prepared by the alternate route depicted in Scheme 20. Treatment of 3-amino-2-thiophenecarboxylates of formula 1 with the dimethylacetal of dimethylformamide provides amidines of formula 4. Addition of these amidines to the anion of acetonitrile, generated at low temperature, preferably –78°C by the action of n-butyl lithium on acetonitrile, in a solvent such as

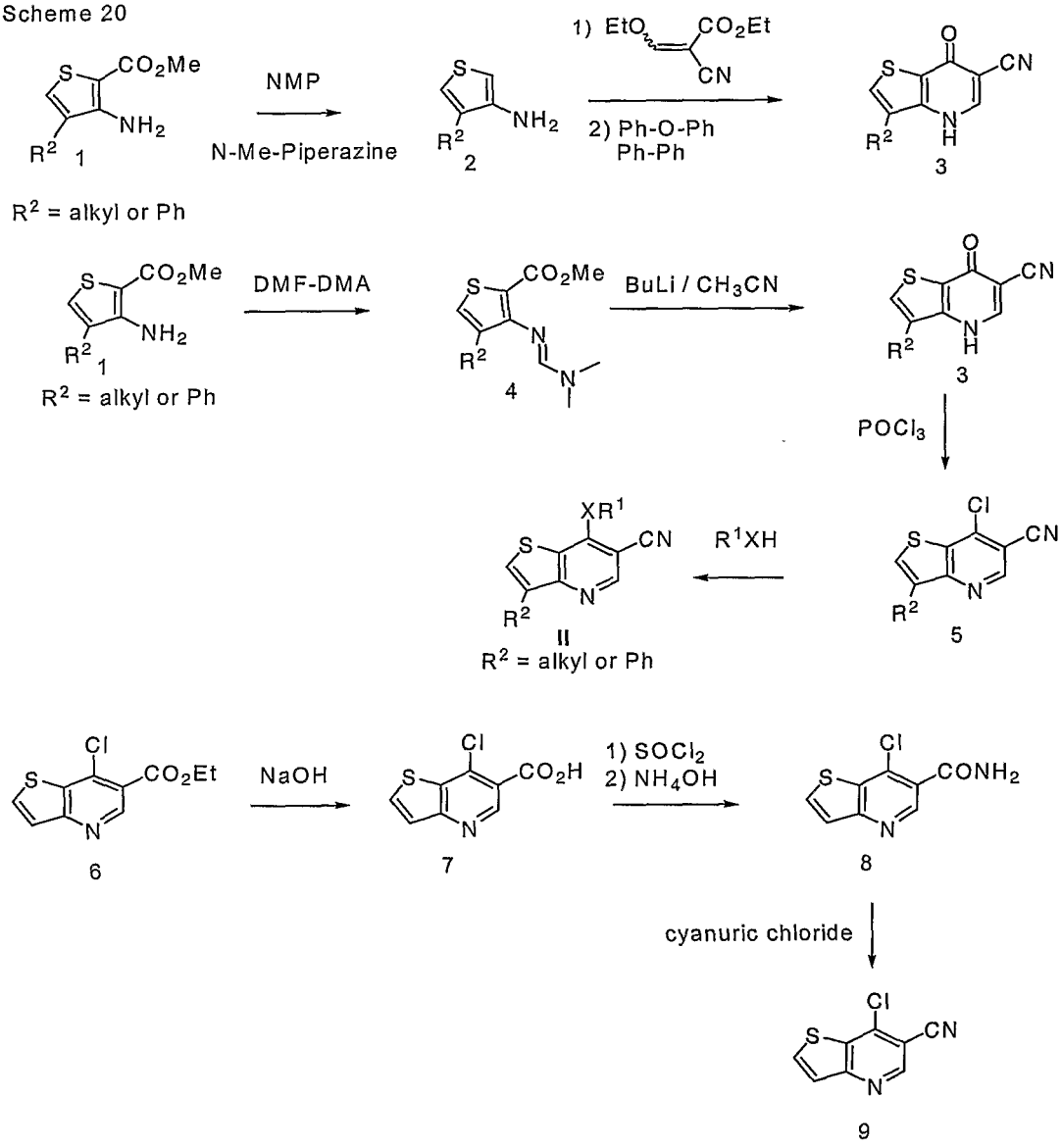
tetrahydrofuran, provides 7-oxo-4,7-dihydrothieno[3,2-b]pyridine-6-carbonitriles of formula 3.

Treatment of compounds of formula 3 with a chlorinating agent, preferably phosphorous oxychloride, provides compounds of formula 5. Addition of a compound of formula R^1XH, where X is NH or NR^4, to compounds of formula 5, in the presence of pyridine hydrochloride in a solvent such as 2-ethoxyethanol at elevated temperatures of 110-130°C, or in the presence of sodium hydride in a solvent such as tetrahydrofuran at elevated temperatures of 60-70°C, provides compounds of Formula II of the invention where X is NH or NR^4. Alternatively addition of a compound of formula R^1XH, where X is NH or NR^4, to a compound of formula 5 in the presence of a palladium catalyst such as tris(dibenzylideneacetone)-dipalladium(0) and a ligand such as 2-dicyclohexylphosphino-2'-(N,N-dimethylamino)biphenyl, and potassium phosphate in a solvent such as ethylene glycol dimethyl ether at elevated temperatures of preferentially 90°C provides compounds of Formula II of the invention where X is NH or NR^4. Addition of a compound of formula R^1XH, where X is O, to compounds of formula 5, optionally with the addition of a base such as potassium carbonate in a solvent such as dimethylformamide at elevated temperature, provides compounds of Formula II of the invention where X is O. Addition of a compound of formula R^1XH, where X is S, to compounds of formula 5, in a solvent such as dimethylformamide, provides compounds of Formula II of the invention where X is S. Addition of a compound of formula R^1XH, where X is $NHCH_2$, to compounds of formula 5, optionally with the addition of a base such as N,N-diisopropylamine in a solvent such as 2-ethoxyethanol at elevated temperature, provides compounds of Formula II of the invention where X is $NHCH_2$.

Alternatively the ethyl group of 6, ethyl 7-chlorothieno[3,2-b]pyridine-6-carboxylate [Thompson, M.; Forbes, I. F. EP 126970] is hydrolyzed to the corresponding 6-carboxylic acid 7 with aqueous sodium hydroxide in a cosolvent such as ethanol at elevated temperature. The corresponding 6-carboxamide analog 8 is prepared by treatment of 7 with a reagent such as thionyl chloride or alternatively N,N-carbonyldiimidazole and the like, followed by the addition of aqueous ammonium hydroxide or alternatively ammonia gas. Dehydration of 8 with a reagent such as

cyanuric chloride provides the intermediate 7-chlorothieno[3,2-b]pyridine-6-carbonitrile 9.

Scheme 20



Scheme 21 depicts a route for the preparation of compounds of the invention of Formula II where R^2 is bromo. Treatment of 9 with N-bromosuccinimide at elevated temperature, preferably at about 40-90°C, in a solvent such as dimethylformamide or acetic acid provides 10. Addition of a compound of formula R^1XH, where X is NH or NR^4, to compounds of formula 10, in the presence of pyridine hydrochloride in a solvent such as 2-ethoxyethanol at elevated temperatures of 110-130°C, or in the presence of sodium hydride in a solvent such as

tetrahydrofuran at elevated temperatures of 60-70°C, provides compounds of Formula II of the invention where X is NH or NR^4 and R^2 is Br. Alternatively addition of a compound of formula R^1XH, where X is NH or NR^4, to a compound of formula 10 in the presence of a palladium catalyst such as tris(dibenzylideneacetone)-dipalladium(0) and a ligand such as 2-dicyclohexylphosphino-2'-(N,N-dimethylamino)biphenyl, and potassium phosphate in a solvent such as ethylene glycol dimethyl ether at elevated temperatures of preferentially 90°C provides compounds of Formula II of the invention where X is NH or NR^4 and R^2 is Br. Addition of a compound of formula R^1XH, where X is O, to compounds of formula 10, optionally with the addition of a base such as potassium carbonate in a solvent such as dimethylformamide at elevated temperature, provides compounds of Formula II of the invention where X is O and R^2 is Br. Addition of a compound of formula R^1XH, where X is S, to compounds of formula 10, in a solvent such as dimethylformamide, provides compounds of Formula II of the invention where X is S and R^2 is Br. Addition of a compound of formula R^1XH, where X is $NHCH_2$, to compounds of formula 10, optionally with the addition of a base such as N,N-diisopropyamine in a solvent such as 2-ethoxyethanol at elevated temperature, provides compounds of Formula II of the invention where X is $NHCH_2$ and R^2 is Br.

Compounds of the invention of Formula II where R^2 is an alkenyl, alkynyl, heterocycle or aryl group can be prepared as depicted in Scheme 21 from compounds of Formula II where R^2 is Br. Treatment of compounds of Formula II where R^2 is Br with an alkenyl or alkynyl of formula R^3-H in the presence of a palladium catalyst provides compounds of Formula II where R^2 is either an alkenyl or alkynyl group. This alkenyl or alkynyl group can be substituted by groups including aryl and heterocycle and also alkyl and alkylamino among others.

For the addition of alkenyls of formula R^3-H the preferred palladium catalyst is palladium acetate in the presence of a ligand, preferably tri-*o*-tolylphosphine, in a solvent system that includes triethylamine or preferably a mixture of triethylamine and N,N-dimethylformamide. For the addition of alkynyls of formula R^3-H the preferred palladium catalyst is tetrakis(triphenylphosphine)palladium (0) along with a catalytic amount of copper(I)iodide in a solvent mixture that includes triethylamine and benzene.

Treatment of compounds of Formula II where R^2 is Br with an aryl or heterocycle organoboron compound of formula R^3-BL^1L^2 in the presence of a palladium catalyst provides compounds of Formula II where R^2 is either an aryl or heterocycle group. In compounds of formula R^3-BL^1L^2, the L^1L^2 groups represent ligands and include such groups as lower alkoxy or preferably hydroxy. The aryl or heterocycle group of compound R^3-BL^1L^2 can be substituted by groups including aryl and heterocycle and also formyl, carboxylate, alkyl and alkylamino among others. The aryl or heterocycle group of compound R^3-BL^1L^2 can also be fused to a second aryl or heterocycle group. For the addition of compounds of formula R^3-BL^1L^2 the preferred palladium catalyst is tetrakis(triphenylphosphine)palladium (0) in a solvent mixture that includes saturated aqueous sodium bicarbonate and ethylene glycol dimethyl ether.

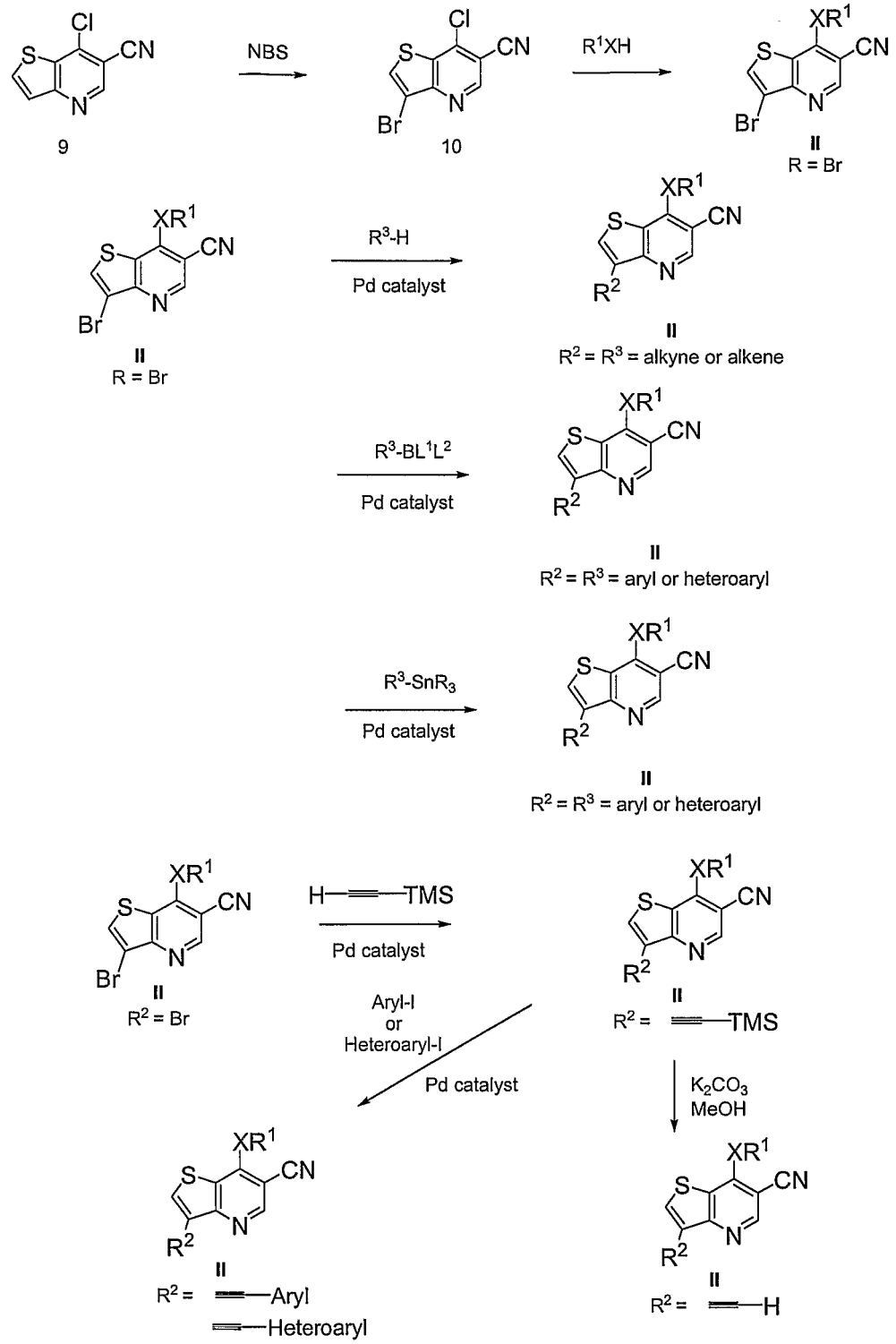
Compounds of Formula II where R^2 is either aryl or heterocycle can also be prepared by reaction of a compound of Formula II where R^2 is Br with an aryl or heterocycle stannane compound of formula R^3-SnR_3 in the presence of a palladium catalyst. In compounds of formula R^3-SnR_3 the R group is a lower alkyl group such as butyl or methyl. The aryl or heterocycle group of compound R^3-SnR_3 can be substituted by groups including aryl and heterocycle and also formyl, carboxylate, acetal, alkyl and alkylamino among others. The aryl or heterocycle group of compound R^3-SnR_3 can also be fused to a second aryl or heterocycle group. For the addition of compounds of formula R^3-SnR_3 the preferred palladium catalyst is bis(triphenylphosphine)palladium (II) chloride in a solvent such as dioxane.

Compounds of Formula II where R^2 is an alkynyl group can be prepared by the alternative route shown in Scheme 21. Treatment of a compound of Formula II, where R^2 is Br with (trimethylsilyl)acetylene in the presence of a palladium catalyst, preferably tetrakis(triphenylphosphine)palladium(0), with a catalytic amount of copper(I) iodine in a solvent system such as triethylamine and benzene, provides compounds of Formula II where R^2 is a 2-(trimethylsilyl)ethynyl group. Reaction of compounds of Formula II where R^2 is a 2-(trimethylsilyl)ethynyl group with aryliodines or heterocycleiodines in the presence of a palladium catalyst, preferably bis(triphenylphosphine)palladium(II)chloride, in the presence of triphenylphosphine, potassium carbonate and copper(I) iodide, in a solvent mixture of tetrahydrofuran

and methanol, provides compounds of Formula II where R^2 is a 2-(aryl)ethynyl or a 2-(heterocycle)ethynyl group. In addition the 2-(trimethylsilyl)ethynyl group can be cleaved by treatment with potassium carbonate in methanol to provide compounds of Formula II where R^2 is an ethynyl group.

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Scheme 21

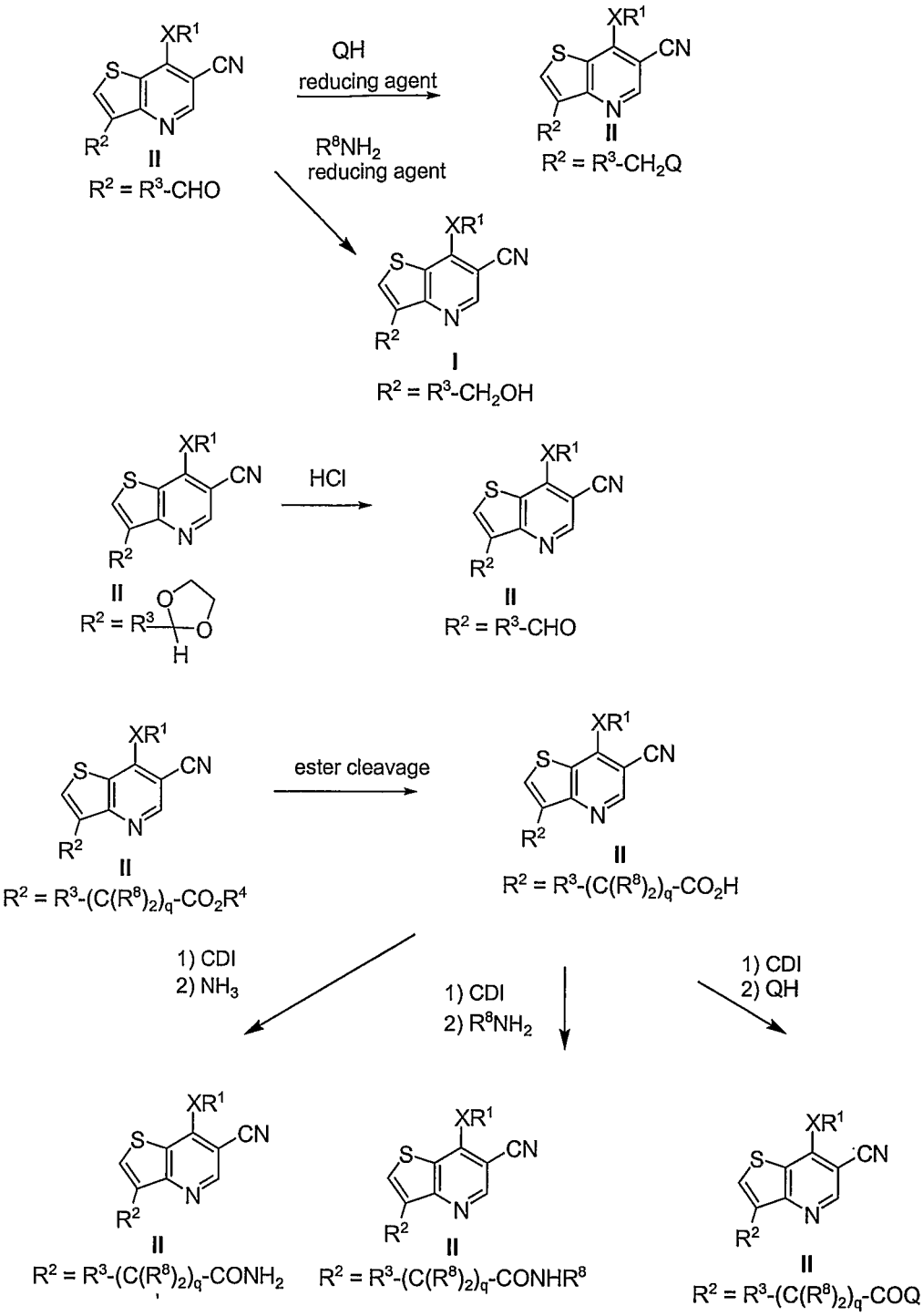

Cl
CN
S
N
NBS
Br
9
10
R1XH
XR1
II
R = Br
R3-H
Pd catalyst
R2
II
R2 = R3 = alkyne or alkene
R3-BL1L2
Pd catalyst
II
R2 = R3 = aryl or heteroaryl
R3-SnR3
Pd catalyst
II
R2 = R3 = aryl or heteroaryl
H—≡—TMS
Pd catalyst
II
R2 = Br
II
R2 = ≡—TMS
Aryl-I
or
Heteroaryl-I
Pd catalyst
K2CO3
MeOH
II
R2 = ≡—Aryl
≡—Heteroaryl
II
R2 = ≡—H

Some additional routes to the compounds of the invention of Formula II are shown in Scheme 22. Compounds of Formula II where the group R^2 is R^3-CHO can be converted to compounds of Formula II where the group R^2 is R^3-CH_2Q via reductive amination. Treatment of compounds of Formula II where the group R^2 is R^3-CHO with an amine of formula QH in the presence of a reducing agent, preferably sodium triacetoxyborohydride, in a solvent system that includes dichloromethane and N,N-dimethylformamide or 1-methyl-2-pyrrolidinone, optionally in the presence of acetic acid, provides compounds of Formula II where the group R^2 is R^3-CH_2Q. Compounds of Formula II where the group R^2 is R^3-CH_2OH may be obtained as a by-product of this reaction, via reduction of the formyl group of compounds of Formula II where the group R^2 is R^3-CHO.

Compounds of Formula II where the group R^2 is R^3-CHO can be prepared by hydrolysis of the acetal group of compounds of Formula II where the group R^2 is R^3-acetal, preferably with aqueous hydrochloric acid in the presence of a cosolvent such as tetrahydrofuran.

Scheme 22 also depicts the preparation of compounds of Formula II where the group R^2 is R^3-$(C(R^8)_2)_q$-CO_2H, and R^3-$(C(R^8)_2)_q$-CONQ from compounds of Formula II where the group R^2 is R^3-$(C(R^8)_2)_q$-CO_2R^4. Compounds of Formula II where the group R^2 is R^3-$(C(R^8)_2)_q$-CO_2R^4 are converted to the corresponding acids of Formula II where the group R^2 is R^3-$(C(R^8)_2)_q$-CO_2H by treatment with aqueous sodium hydroxide in a cosolvent such as ethanol at elevated temperatures. The corresponding amides of Formula II where the group R^2 is $(C(R^8)_2)_q$-CONQ are prepared by treatment of the acid with N,N-carbonyldiimidazole or alternatively thionyl chloride or the like, followed by the addition of an amine of formula QH. In addition, the corresponding amides of Formula II where the group R^2 is R^3-$(C(R^8)_2)_q$-$CONHR^8$ or R^3-$(C(R^8)_2)_q$-$CONH_2$ are prepared by treatment of the acid with N,N-carbonyldiimidazole or alternatively thionyl chloride or the like, followed by the addition of an amine of formula R^8NH_2 or of ammonium hydroxide or ammonia (g).

Scheme 22



Scheme 23 depicts an alternate route for the preparation of compounds of the invention of Formula II. Treatment of intermediate 10 with an alkenyl or alkynyl reagent of formula R^3-H in the presence of a palladium catalyst provides

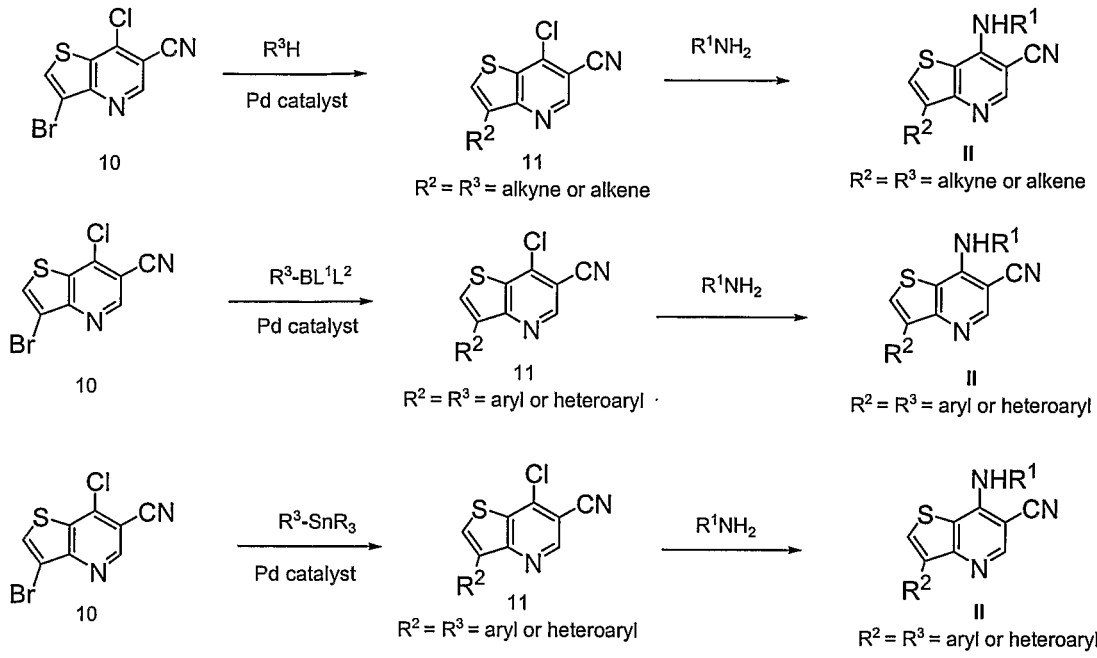
intermediates of formula 11 where R^3 is either an alkenyl or alkynyl group. This alkenyl or alkynyl group can be substituted by groups including aryl and heterocycle and also alkyl and alkyl amino among others. This aryl or heterocycle group can also be substituted by groups such as alkoxy, alkylamino and others. For the addition of alkenyls of formula R^3-H the preferred palladium catalyst is palladium acetate in the presence of a ligand, preferably tri-o-tolylphosphine, in a solvent system that includes triethylamine or preferably a mixture of triethylamine and N,N'-dimethylformamide. For the addition of alkynyls of formula R^3-H the preferred palladium catalyst is tetrakis(triphenylphosphine)palladium (0) along with a catalytic amount of copper(I)iodide in a solvent mixture that includes triethylamine and benzene. Addition of a compound of formula R^1NH_2 to compounds of formula 11, optionally with the addition of pyridine hydrochloride in a solvent such as 2-ethoxyethanol at elevated temperatures of 110-130°C, or in the presence of sodium hydride in a solvent such as tetrahydrofuran at elevated temperatures of 60-70°C, or under palladium catalyzed coupling conditions, including the use of tris(dibenzylideneacetone)-dipalladium(0) and (2-dicyclohexylphosphino-2'-(*N,N*-dimethylamino)biphenyl, in a solvent such as ethylene glycol dimethyl ether at elevated temperatures such as 90°C provides compounds of Formula II.

Treatment of intermediates of formula 10 with an aryl or heterocycle organoboron compound of formula R^3-BL^1L^2 in the presence of a palladium catalyst provides intermediates of formula 11 where R^3 is either an aryl or heterocycle group. In compounds of formula R^3-BL^1L^2, the L^1L^2 groups represent ligands and include such groups as lower alkoxy or preferably hydroxy. The aryl or heterocycle group of compound R^3-BL^1L^2 can be substituted by groups including aryl and heterocycle and also formyl, carboxylate, alkyl and alkylamino among others. The aryl or heterocycle group of compound R^3-BL^1L^2 can also be fused to a second aryl or heterocycle group. For the addition of compounds of formula R^3-BL^1L^2 the preferred palladium catalyst is tetrakis(triphenylphosphine)palladium (0) in a solvent mixture that includes saturated aqueous sodium bicarbonate and ethylene glycol dimethyl ether. Addition of a compound of formula R^1NH_2 to compounds of formula 11, optionally with the addition of pyridine hydrochloride in a solvent such as 2-ethoxyethanol at elevated temperatures of 110-130°C, or in the presence of sodium hydride in a solvent such as tetrahydrofuran at elevated temperatures of 60-70°C, or under palladium

catalyzed coupling conditions, including the use of tris(dibenzylideneacetone)-dipalladium(0) and (2-dicyclohexylphosphino-2'-(*N,N*-dimethylamino)biphenyl, in a solvent such as ethylene glycol dimethyl ether at elevated temperatures such as 90°C provides compounds of Formula II.

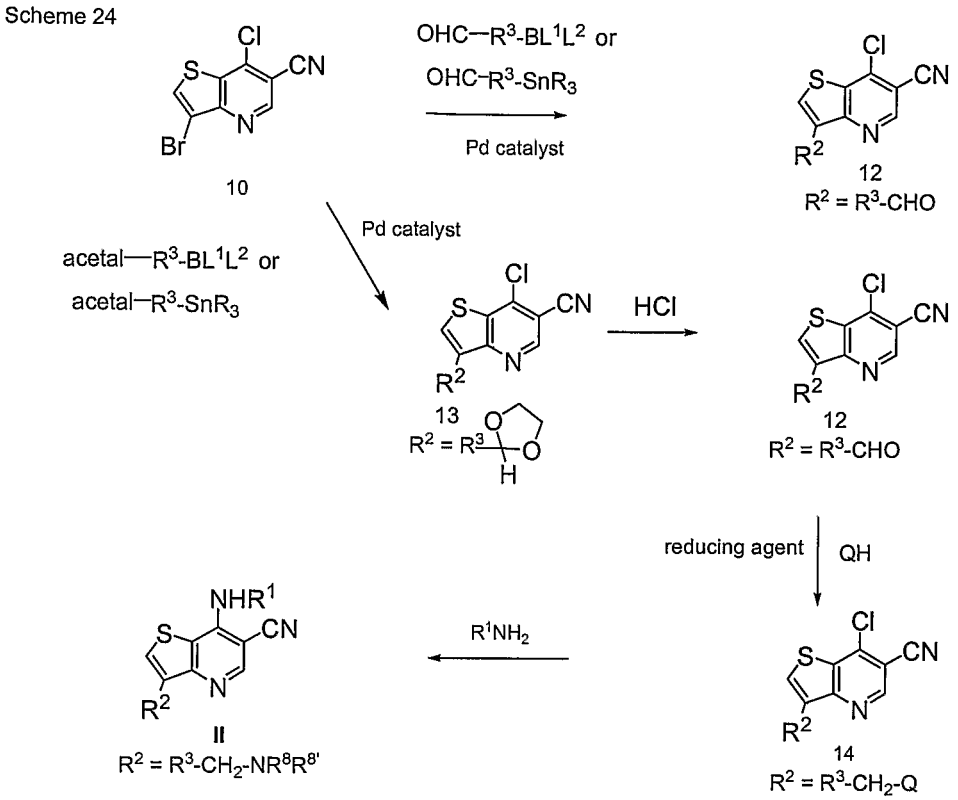
Intermediates of formula 11 where R^2 is either aryl or heterocycle can also be prepared by reaction of intermediates of formula 10 with an aryl or heterocycle stannane compound of formula R^3-SnR_3 in the presence of a palladium catalyst. In compounds of formula R^3-SnR_3 the R group is a lower alkyl group such as butyl or methyl. The aryl or heterocycle group of compound R^3-SnR_3 can be substituted by groups including aryl and heterocycle and also formyl, carboxylate, acetal, alkyl and alkylamino among others. The aryl or heterocycle group of compound R^3-SnR_3 can also be fused to a second aryl or heterocycle group. For the addition of compounds of formula R^3-SnR_3 the preferred palladium catalyst is bis(triphenylphosphine)palladium (II) chloride in a solvent such as dioxane. Addition of a compound of formula R^1NH_2 to compounds of formula 11 optionally with the addition of pyridine hydrochloride in a solvent such as 2-ethoxyethanol at elevated temperatures of 110-130°C, or in the presence of sodium hydride in a solvent such as tetrahydrofuran at elevated temperatures of 60-70°C, or under palladium catalyzed coupling conditions, including the use of tris(dibenzylideneacetone)-dipalladium(0) and (2-dicyclohexylphosphino-2'-(*N,N*-dimethylamino)biphenyl, in a solvent such as ethylene glycol dimethyl ether at elevated temperatures such as 90°C provides compounds of Formula II.

Scheme 23



Some additional routes to the compounds of the invention of Formula II are shown in Scheme 24. Intermediates of formula 12 where the group R^2 is R^3-CHO can be prepared by addition of boron or tin reagents that contain an aldehyde group. They can also be prepared by hydrolysis of the acetal group of intermediates of formula 13 where the group R^2 is R^3-acetal, preferably with aqueous hydrochloric acid in the presence of a cosolvent such as tetrahydrofuran. Intermediates of formula 12 can be converted to intermediates of formula 14 via reductive amination with an amine of formula QH and a reducing agent, preferably sodium triacetoxyborohydride, in a solvent system that includes dichloromethane and N,N-dimethylformamide or 1-methyl-2-pyrrolidinone, optionally in the presence of acetic acid. Addition of a compound of formula R^1NH_2 to compounds of formula 13, optionally with the addition of pyridine hydrochloride in a solvent such as 2-ethoxyethanol at elevated temperatures of 110-130°C, or in the presence of sodium hydride in a solvent such as tetrahydrofuran at elevated temperatures of 60-70°C, or under palladium catalyzed coupling conditions, including the use of tris(dibenzylideneacetone)-dipalladium(0) and (2-dicyclohexylphosphino-2'-(*N,N*-dimethylamino)biphenyl, in a solvent such as ethylene glycol dimethyl ether at elevated temperatures such as 90°C provides compounds of Formula II.

Scheme 24



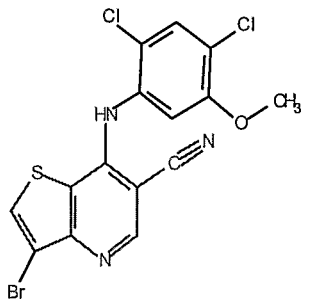
Evaluation of representative compounds of this invention in several standard pharmacological test procedures indicated that the compounds of this invention possess significant antiproliferative activity and are inhibitors of protein tyrosine kinases. Based on the activity shown in the standard pharmacological test procedures, the compounds of this invention are therefore useful as antineoplastic agents. In particular, these compounds are useful in treating, inhibiting the growth of, or eradicating neoplasms such as those of the breast, kidney, bladder, mouth, larynx, esophagus, stomach, colon, ovary, lung, pancreas, liver, prostate and/or skin.

In addition to having antineoplastic properties, the compounds of the present invention are expected to be useful in treating a variety of protein tyrosine kinase associated disorders including, but not limited to, osteoarthritis, restenosis, atherosclerosis, fibroplasia, angiofibromas, hemangiomas, diabetes, acute and chronic nephropathies, Kaposi's sarcoma, atheroma, neovascular glaucoma, neovascularization associated with macular degeneration, rheumatoid arthritis, psoriatic arthritis, transplant rejection, T-cell mediated hypersensitivity diseases, including gluten-sensitive enteropathy (Celiac disease), contact and delayed-type

hypersensitivity, psoriasis, contact dermatitis, protection from ischemic or reperfusion injury such as that incurred during organ transplantation, stroke or myocardial infarction, transplantation tolerance induction, lupus, graft versus host disease, glomerulonephritis, serum sickness, respiratory and skin allergies, autoimmune alopecia, pernicious anemia, Hashimoto's thyroiditis, autoimmune hyperthyroidism, Addison's disease, multiple sclerosis, inflammatory bowel disease, acute inflammatory responses (for example acute respiratory distress syndrome), Behcet's disease, atopic dermatitis, systemic sclerosis and/or eczema.

Example 1

3-Bromo-7-[(2,4-dichloro-5-methoxyphenyl)amino]thieno[3,2-b]pyridine-6-carbonitrile



To a suspension of sodium hydride (438 mg of a 60% dispersion in mineral oil, 10.96 mmol) in 60 mL of tetrahydrofuran is added 2,4-dichloro-5-methoxyaniline (2.10 g, 10.96 mmol). The mixture is heated at reflux for 1 hour and then cooled to room temperature and 1.50 g of a 1 to 2.4 mixture of 3-bromo-7-chlorothieno[3,2-b]pyridine-6-carbonitrile and 3,7-dibromothieno[3,2-b]pyridine-6-carbonitrile is added. The reaction mixture is heated at reflux for 2 hours then cooled to room temperature and treated with saturated aqueous sodium chloride. The organic layer is separated and the aqueous layer is extracted with ethyl acetate. The combined organic layers are washed with brine, dried over sodium sulfate, filtered and concentrated in vacuo. The residue is purified by flash column chromatography eluting with a gradient of ethyl acetate in hexane to provide 1.78 g of 3-bromo-7-[(2,4-dichloro-5-methoxyphenyl)amino]thieno[3,2-b]pyridine-6-carbonitrile as a tan solid, mp 265-266°C; ^{1}H NMR (DMSO-d_6) δ3.85 (s, 3H), 7.44 (s, 1H), 7.79 (s, 1H), 8.31 (s, 1H), 8.72 (s, 1H), 9.93 (s, 1H); MS 427.9, 429.9, 431.8 (M+H)+.

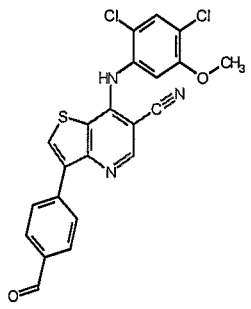
Analysis for $C_{15}H_8BrCl_2N_3OS$:

Calcd: C, 41.98; H, 1.88; N, 9.79.

Found: C, 41.87; H, 1.76; N, 9.64.

Example 2

7-[(2,4-Dichloro-5-methoxyphenyl)amino]-3-(4-formylphenyl)thieno[3,2-b]pyridine-6-carbonitrile



A mixture of 3-bromo-7-[(2,4-dichloro-5-methoxyphenyl)amino]thieno[3,2-b]pyridine-6-carbonitrile (1.67 g, 3.89 mmol), 4-formylphenyl boronic acid (1.17 g, 7.78 mmol), and tetrakis(triphenylphosphine)pallidium (225 mg, 0.20 mmol) in 50 mL of ethylene glycol dimethyl ether and 42 mL of saturated aqueous sodium bicarbonate is heated at reflux for 2 hours and then cooled to room temperature. The precipitate is collected by filtration washing with ethyl acetate and diethyl ether to provide 1.09 g of 7-[(2,4-dichloro-5-methoxyphenyl)amino]-3-(4-formylphenyl) thieno[3,2-b]pyridine-6-carbonitrile as a tan solid, mp 268°C dec; ^{1}H NMR (DMSO-d_6) δ 3.87 (s, 3H), 7.44 (s, 1H), 7.79 (s, 1H), 8.01 (d, J = 8 Hz, 2H), 8.23 (d, J = 8 Hz, 2H), 8.55 (s, 1H), 8.73 (s, 1H), 9.86 (s, 1H), 10.05 (s, 1H); MS 454.0, 456.0 (M+H)+; HRMS found:454.01716 (M+H)+.

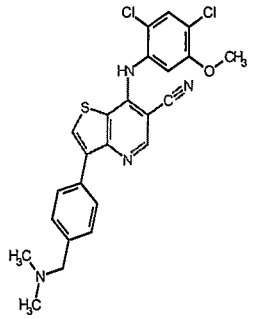
Analysis for $C_{22}H_{13}Cl_2N_3O_2S$:

Calcd: C, 58.16; H, 2.88; N, 9.25.

Found: C, 57.96; H, 2.57; N, 8.85.

Example 3

7-[(2,4-Dichloro-5-methoxyphenyl)amino]-3-{4-[(dimethylamino)methyl]phenyl}thieno[3,2-b]pyridine-6-carbonitrile



A mixture of 7-[(2,4-dichloro-5-methoxyphenyl)amino]-3-(4-formylphenyl)thieno[3,2-b]pyridine-6-carbonitrile (200 mg, 0.44 mmol) and 1.1 mL of a 2 M solution of dimethylamine in tetrahydrofuran (2.20 mmol) in 5 mL of dichloromethane and 1 mL of dimethylformamide is cooled to 0°C. Sodium triacetoxyborohydride (560 mg, 2.64 mmol) is added in portions followed by 3 drops of acetic acid. The resulting mixture is stirred at room temperature for 2.5 hours then quenched by the addition of water. The mixture is partitioned between dichloromethane and saturated aqueous sodium bicarbonate. The organic phase is washed with saturated aqueous sodium chloride, dried over sodium sulfate, filtered and concentrated in vacuo. The residue is purified by flash column chromatography eluting with a gradient of methanol in dichloromethane to provide 147 mg (69%) of 7-[(2,4-dichloro-5-methoxyphenyl)amino]-3-{4-[(dimethylamino)methyl]phenyl}thieno [3,2-b]pyridine-6-carbonitrile as a white solid, mp 201-202°C; ^{1}H NMR (DMSO-d_6) δ2.19 (s, 6H), 3.46 (s, 2H), 3.86 (s, 3H), 7.38 (d, J = 8 Hz, 2H), 7.42 (s, 1H), 7.78 (s, 1H), 7.89 (d, J = 8 Hz, 2H), 8.31 (s, 1H), 8.69 (s, 1H), 9.78 (s, 1H); MS 483.0, 485.0 (M+H)+; HRMS found: 483.08061 (M+H)+.

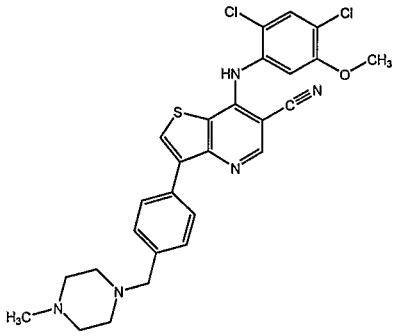
Analysis for $C_{24}H_{20}Cl_2N_4OS$ - 0.8 H_2O:

Calcd: C, 57.90; H, 4.37; N, 11.25.

Found: C, 57.95; H, 3.98; N, 10.85.

Example 4

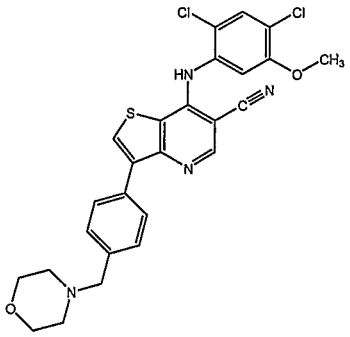
7-[(2,4-Dichloro-5-methoxyphenyl)amino]-3-{4-[(4-methylpiperazin-1-yl)methyl] phenyl}thieno[3,2-b]pyridine-6-carbonitrile



MS 538.0, 540.0 (M+H)+; m.p. 197-198.

Example 5

7-[(2,4-Dichloro-5-methoxyphenyl)amino]-3-[4-(morpholin-4-ylmethyl) phenyl]thieno[3,2-b]pyridine-6-carbonitrile



MS 525.0, 527.0 (M+H)+; m.p. 184-185.

The test procedures used and results obtained are shown below.

Anchorage Independent Src-transformed Fibroblast Proliferation Assay

Rat2 fibroblasts stably transformed with a plasmid containing a CMV promotor controlled v-Src/Hu c-Src fusion gene in which the catalytic domain of human c-Src was inserted in place of the v-Src catalytic domain in the v-Src gene are

used for the measurement of src dependent suspension growth. Ultra-low cluster plates (Costar # 3474) are seeded with 10,000 cells per well on Day 1. Compound is added in serial two-fold dilutions from 10 micromolar to 0.009 micromolar on Day 2 and MTS reagent (Promega) is added on Day 5 (100 microliters of MTS/medium mix + 100 microliters of medium already on the cells and the absorbance is measured at 490nm. The results are analyzed as follows to yield an IC_{50} for proliferation (micromolar units) as follows: %inhibition = (Abs490 nm sample - blank)/(Abs490 nm no cmpd control - blank) X 100%. The results obtained for representative compounds of this invention are listed in Table 3 below.

Anchorage Independent Lck-transformed Fibroblast Proliferation Assay

Rat2 fibroblasts stably transformed with a plasmid containing a CMV promotor controlled v-Src/Hu Lck fusion gene in which the catalytic domain of human Lck was inserted in place of the v-Src catalytic domain in the v-Src gene are used for the measurement of src dependent suspension growth. Ultra-low cluster plates (Costar # 3474) are seeded with 10,000 cells per well on Day 1. Compound is added in serial two-fold dilutions from 10 micromolar to 0.009 micromolar on Day 2 and MTS reagent (Promega) is added on Day 5 (100 microliters of MTS/medium mix + 100 microliters of medium already on the cells and the absorbance is measured at 490nm. The results are analyzed as follows to yield an IC_{50} for proliferation (micromolar units) as follows: %inhibition = (Abs490 nm sample - blank)/(Abs490 nm no cmpd control - blank) X 100%. The results obtained for representative compounds of this invention are listed in Table 3 below.

Src Kinase Assay

Recombinant human Src enzyme was obtained from PanVera (P3044). Biotinylated peptide corresponding to residues 6 – 20 of Cdk1 was used as a substrate (Biotin-KVEKIGEGTYGVVYK-COOH). Homogeneous fluorescence resonance energy transfer kinase assays were performed using the europium/APC detection format (LANCE, Perkin Elmer). Src enzyme (10 ng) was mixed with biotinylated peptide (final concentration 2 μM), 50 mM Hepes (pH 7.5), 10 mM $MgCl_2$, 20 ug/ml BSA, 0.001% Brij-35 (Sigma), 100 μM ATP, 1% DMSO. The kinase reaction

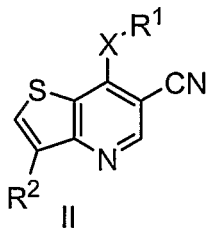
was incubated for 70 min at 37°C. The reaction was stopped with EDTA at a final concentration of 30mM EDTA/25mM Hepes (pH 7.5)/10 μg/ml BSA. The mixture was combined with Eu-labeled anti-phosphotyrosine antibody PT66 (Perkin Elmer, AD0068) and Streptavidin Surelight-APC (Perkin Elmer, CR130-100) in 50 mM Hepes (pH 7.5)/ 20 μg/ml BSA, and incubated for 30 min according to manufacturer's specifications. Fluorescence intensity at 665 nm was used to monitor the extent of the kinase reaction. Multiple entries for a given compound indicate that it was tested multiple times. The results obtained for representative compounds of this invention are listed in Table 3 below.

Table 3

Ex.	Src Enzyme IC_{50} (nM)	Src Cells IC_{50} (μM) or % inhib at 10μM	Lck Cells IC_{50} (μM)
2	not tested	8.46, 8.58	>10 (n=2)
3	4350, 5040	4.52, 4.11	3.18, 4.24
4	>10,000 (n=2)	3.25, 1.99	3.54, 4.35
5	>10,000 (n=2)	61%, 45%	>10

CLAIMS:

1. A compound of Formula II



II

wherein:

X is –NH-, $-NR^4-$, -O-, $-S(O)_m-$, or $-NHCH_2-$;

m is an integer of 0-2;

n is an integer of 1-5;

q is an integer of 0-5;

R^1 is a phenyl ring optionally substituted with one to four substituents selected from the group consisting of J, $-NO_2$, -CN, $-N_3$, -CHO, $-CF_3$, $-OCF_3$, R^4, $-OR^4$, $-S(O)_mR^4$, $-NR^4R^4$, $-NR^4S(O)_mR^4$, $-OR^6OR^4$, $-OR^6NR^4R^4$, $-N(R^4)R^6OR^4$, $-N(R^4)R^6NR^4R^4$, $-NR^4C(O)R^4$, $-C(O)R^4$, $-C(O)OR^4$, $-C(O)NR^4R^4$, $-OC(O)R^4$, $-OC(O)OR^4$, $-OC(O)NR^4R^4$, $NR^4C(O)R^4$, $-NR^4C(O)OR^4$, $-NR^4C(O)NR^4R^4$, $-R^5OR^4$, $-R^5NR^4R^4$, $-R^5S(O)_mR^4$, $-R^5C(O)R^4$, $-R^5C(O)OR^4$, $-R^5C(O)NR^4R^4$, $-R^5OC(O)R^4$, $-R^5OC(O)OR^4$, $-R^5OC(O)NR^4R^4$, $-R^5NR^4C(O)R^4$, $-R^5NR^4C(O)OR^4$, $-R^5NR^4C(O)NR^4R^4$, or YR^7;

R^2 is R^3, J, $-C(O)XR^3$, or -CHO, wherein the R^3 group is optionally substituted by at least one group selected from $-C(O)XR^8$, -CHO, -C(O)Q, 1,3-dioxolane, R^8, $-(C(R^9)_2)_qXR^8$, $-(C(R^9)_2)_qQ$, $-X(C(R^9)_2)_nXR^8$, $-X(C(R^9)_2)_nQ$, or $-X(C(R^9)_2)_qR^8$;

R^3 is alkyl of 1 to 6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, aryl or heterocycle;

R^4 is H, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, or alkynyl of 2-6 carbon atoms;

R^5 is a divalent group comprising alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, or alkynyl of 2-6 carbon atoms;

R^6 is a divalent alkyl group of 2-6 carbon atoms;

R^7 is a cycloalkyl ring of 3-7 carbons, an aryl or heterocyclic ring, or an aryl or heterocyclic ring fused to one to three aryl or heterocyclic rings, wherein any of the aryl, cycloalkyl, or heterocyclic rings may be optionally substituted with one to four substituents selected from the group consisting of H, aryl, $-CH_2$-aryl, -NH-aryl, -O-aryl, $-S(O)_m$-aryl, J, $-NO_2$, -CN, $-N_3$, -CHO, $-CF_3$, $-OCF_3$, R^4, $-OR^4$, $-S(O)_mR^4$, $-NR^4R^4$, $-NR^4S(O)_mR^4$, $-OR^6OR^4$, $-OR^6NR^4R^4$, $-N(R^4)R^6OR^4$, $-N(R^4)R^6NR^4R^4$, $-NR^4C(O)R^4$, $-C(O)R^4$, $-C(O)OR^4$, $-C(O)NR^4R^4$, $-OC(O)R^4$-, $-OC(O)OR^4$, $-OC(O)NR^4R^4$, $-NR^4C(O)R^4$, $-NR^4C(O)OR^4$, $-NR^4C(O)NR^4R^4$, $-R^5OR^4$, $R^5NR^4R^4$, $-R^5S(O)_mR^4$, $-R^5C(O)R^4$, $-R^5C(O)OR^4$, $-R^5C(O)NR^4R^4$, $-R^5C(O)R^4$, $-R^5C(O)OR^4$, $-R^5C(O)NR^4R^4$, $-R^5OC(O)R^4$, $-R^5OC(O)OR^4$, $-R^5OC(O)NR^4R^4$, $-R^5NR^4C(O)R^4$, $-R^5NR^4C(O)OR^4$, or $-R^5NR^4C(O)NR^4R^4$;

R^8 is H, alkyl of 1 to 6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, aryl or heterocycle;

R^9 is R^4 or F;

Y is -C(O)-, -C(O)O-, -OC(O)-, -C(O)NH-, -NHC(O)-, $-NHSO_2$-, $-SO_2NH$-, -C(OH)H-, $-X(C(R^9)_2)_q$-, $-(C(R^9)_2)_q$-, $-(C(R^9)_2)_qX$-, -C≡C-, -CH=CH- or cycloalkyl of 3-10 carbon atoms;

Q is NZZ' wherein Z and Z' may be the same or different and may be H, alkyl of 1 to 6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, aryl, or heterocycle, or

Z and Z' taken together with the nitrogen to which they are attached may form a heterocyclic ring which may have an additional heteroatom selected from nitrogen, oxygen, and sulfur, optionally substituted with R^8 on a carbon or a

nitrogen, or on nitrogen by a group $-(C(R^9)_2)_nXR^8$, $-C(R^9)_2)_nNZ"Z"'$, or on carbon by a group $-(C(R^9)_2)_qXR^8$, $-(C(R^9)_2)_qNZ"Z"'$;

Z"' and Z" may be H, alkyl of 1 to 6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, aryl, or heterocycle, or

Z" and Z"' taken together with the nitrogen to which they are attached may form a heterocyclic ring which may contain an additional heteroatom selected from nitrogen, oxygen and sulfur; and

J is fluoro, chloro, bromo, or iodo;

or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 wherein XR^1 is $-NH-R^1$.

3. A compound according to claim 1 or claim 2 wherein R^1 is a phenyl ring optionally substituted with one to four substituents selected from the group consisting of J, or $-OR^4$.

4. A compound according to any one of claims 1 to 3 wherein R^4 is H or alkyl of 1-4 carbon atoms.

5. A compound according to any one of claims 1 to 4 wherein R^2 is J or R^3 wherein R^3 is aryl or heterocycle and the R^3 group is optionally substituted by at least one group selected from $-C(O)XR^8$, -CHO, -C(O)Q, 1,3-dioxolane, $-R^8$, $-(C(R^9)_2)_qXR^8$, $-(C(R^9)_2)_qQ$, $-X(C(R^9)_2)_nXR^8$, $-X(C(R^9)_2)_nQ$, or $-X(C(R^9)_2)_qR^8$.

6. A compound according to any one of claims 1 to 4 wherein R^2 is J or R^3, wherein R^3 is aryl or heterocycle and the R^3 group is optionally substituted by at least one group selected from -CHO, $-(C(R^9)_2)_qQ$, or R^8.

7. A compound according to any one of claims 1 to 6 wherein Q is NZZ' wherein Z and Z' may be the same or different and may be H, alkyl of 1 to 6 carbon atoms; or Z and Z' taken together with the nitrogen to which they are attached may form a heterocyclic ring which may have an additional heteroatom selected from nitrogen and oxygen, said ring may be substituted on nitrogen by R^4.

8. A compound according to any one of claims 1 to 7 wherein R^8 is H, alkyl of 1 to 6 carbon atoms, or aryl.

9. A compound according to any one of claims 1 to 8 wherein J is chloro or bromo.

10. A compound according to any one of claims 1 to 9 wherein R^9 is H.

11. A compound according to any one of claims 1 to 10 wherein q is 1.

12. A compound according to claim 1 wherein:

XR^1 is $-NH-R^1$;

q is an integer of 0-5;

n is an integer of 1-5;

R^1 is a phenyl ring optionally substituted with one to four substituents selected from the group consisting of J or $-OR^4$;

R^2 is J or R^3 wherein the R^3 group is optionally substituted by at least one group selected from $-C(O)XR^8$, -CHO, -C(O)Q, 1,3-dioxolane, $-R^8$, $-(C(R^9)_2)_qXR^8$, $-(C(R^9)_2)_qQ$, $-X(C(R^9)_2)_nXR^8$, $-X(C(R^9)_2)_nQ$, or $-X(C(R^9)_2)_q R^8$;

R^3 is aryl or heterocycle;

R^4 is H or alkyl of 1-6 carbon atoms;

R^8 is H, alkyl of 1 to 6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, aryl or heterocycle;

R^9 is H;

Q is NZZ' wherein Z and Z' may be the same or different and may be H, or alkyl of 1 to 6 carbon atoms, or

Z and Z' taken together with the nitrogen to which they are attached may form a heterocyclic ring which may have an additional heteroatom selected from nitrogen, oxygen, or sulfur, optionally substituted with R^8 on a carbon or a nitrogen, or on nitrogen by a group $-(C(R^9)_2)_nXR^8$, $-C(R^9)_2)_nNZ"Z"'$, or on carbon by a group $-(C(R^9)_2)_qXR^8$, $-(C(R^9)_2)_qNZ"Z"'$;

Z"' and Z" may be H, alkyl of 1 to 6 carbon atoms alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, aryl, or heterocycle, or

Z" and Z"' taken together with the nitrogen to which they are attached may form a heterocyclic ring which may contain an additional heteroatom selected from nitrogen, oxygen or sulfur; and

J is chloro or bromo;

or a pharmaceutically acceptable salt thereof.

13. The compound according to claim 1 wherein:

XR^1 is –NH-R^1;

q is an integer of 0-5;

n is an integer of 1-5;

R^1 is a phenyl ring optionally substituted with one to four substituents selected from the group consisting of J or -OR^4;

R^2 is J or R^3, wherein the R^3 group is optionally substituted by at least one group selected from -CHO, -$(C(R^9)_2)$qQ, or R^8;

R^3 is aryl or heterocycle;

R^8 is H, alkyl of 1 to 6 carbon atoms, aryl or heterocycle;

R^9 is H;

J is chloro or bromo;

or a pharmaceutically acceptable salt thereof.

14. A compound according to claim 1 which is one of the following;

3-bromo-7-[(2,4-dichloro-5-methoxyphenyl)amino]thieno[3,2-b]pyridine-6-carbonitrile;

7-[(2,4-dichloro-5-methoxyphenyl)amino]-3-(4-formylphenyl)thieno[3,2-b]pyridine-6-carbonitrile;

7-[(2,4-dichloro-5-methoxyphenyl)amino]-3-{4-[(dimethylamino)methyl]phenyl}thieno[3,2-b]pyridine-6-carbonitrile;

7-[(2,4-dichloro-5-methoxyphenyl)amino]-3-{4-[(4-methylpiperazin-1-yl)methyl]phenyl}thieno[3,2-b]pyridine-6-carbonitrile; and

7-[(2,4-dichloro-5-methoxyphenyl)amino]-3-[4-(morpholin-4-ylmethyl)phenyl]thieno[3,2-b]pyridine-6-carbonitrile,

or a pharmaceutically acceptable salt thereof.

15. A method of treating or inhibiting a pathological condition or disorder consisting of an increase or activation in Src expression in a mammal comprising, providing to said mammal an effective amount of the compound of any one of claims 1 to 14, or a pharmaceutically acceptable salt thereof.

16. The method of claim 15 wherein the pathological condition or disorder is cancer.

17. The method of claim 16 wherein the cancer is breast, colon, lung, pancreatic, liver and leukemia.

18. The method of claim 15 wherein the pathological condition or disorder is stroke or myocardial infarction.

19. The method of claim 15 wherein the pathological condition or disorder is osteoporosis.

20. The method of claim 15 wherein the pathological condition or disorder is polycystic kidney disease.

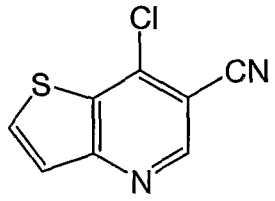
21. The method of claim 15 wherein the pathological condition or disorder comprises autoimmune disease, rheumatoid arthritis, and transplant rejection.

22. The method of claim 15 wherein the pathological condition or disorder is neuropathic pain.

23. A pharmaceutical composition comprising a compound of any one of claims 1 to 14 and a pharmaceutically acceptable carrier.

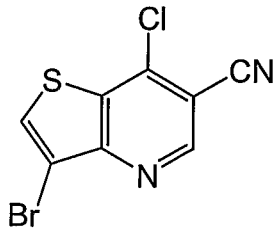
24. A process for preparing a compound of Formula II as claimed in claim 1 comprising one of the following:

a. reacting a compound of Formula (a) ;



(a)

with N-bromosuccinimide to provide a compound of Formula (b);

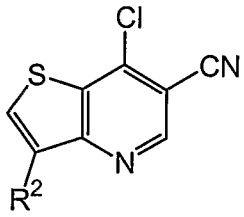


(b)

and reacting the compound of Formula (b) with a compound of formula R^1XH to form a compound of Formula II wherein R^2 is bromine; or

b. reacting a compound of formula II wherein R^2 is Br with a compound of formula R^3-H, R^3-BL^1L^2, or R^3SnR_3, in the presence of a palladium catalyst optionally in a solvent system, to form a compound of formula II wherein Br is replaced by R^3, or

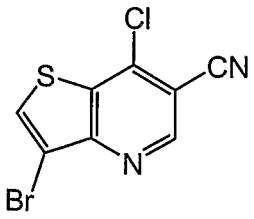
c. reacting a compound of formula



wherein R^2 is as defined in clam 1, with a compound of formula R^1NH_2 to obtain a compound of Formula II; or

d. converting a basic compound of formula II to a pharmaceutically acceptable acid addition salt and vice versa.

25. A compound having the structure:



(b)