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Thieno[3,2-b] Pyridine-6-Carbonitriles and Thieno[2,3-b] Pyridine-5-Carbonitriles as Protein Kinase Inhibitors

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.

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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)].

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-asparte) 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)].

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)].

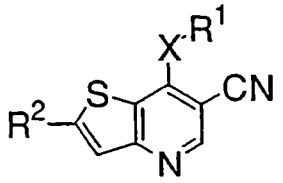
The cyclin-dependent kinases (cdks), including cdc2/cyclin B, cdk2/cyclin A, cdk2/cyclin E and cdk4/cyclin D, and others, are serine/threonine kinases that regulate mammalian cell division. Increased activity or activation of these kinases is associated with the development of human tumors [Garrett, M. D., *Current Opin. Genetics Devel., 9*, 104 (1999); Webster, K. R., *Exp. Opin. Invest. Drugs, 7*, 865 (1998)]. Additional serine/threonine kinases include the protein kinases A, B, and C. These kinases are known as PKA or cyclic AMP-dependent protein kinase, PKB (Akt), and PKC, and 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, 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.

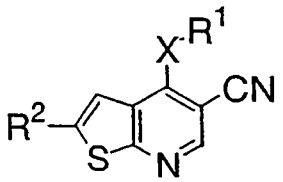
Thieno[3,2-b]pyridines, thieno[2,3-b]pyridines and certain pyridine and pyrimidine derivatives have been noted as kinase inhibitors. These compounds differ both in nature and placement of substituents at various positions when compared to the compounds of this invention.

SUMMARY OF THE INVENTION

This invention relates to thieno[3,2-b]pyridine-6-carbonitrile and thieno[2,3-b]pyridine-5-carbonitrile compounds as well as their pharmaceutically acceptable salts of Formula **Ia** and **Ib**:



Ia



Ib

wherein:

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

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 –H, $-R^3$, -J, $-C(O)XR^3$, -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, $-R^8$, $-(C(R^9)_2)_qXR^8$, $-(C(R^9)_2)_qQ$, $-X(C(R^9)_2)_nXR^8$, $-X(C(R^9)_2)_nQ$, or $-X(C(R^9)_2)_q R^8$;

R^3 is alkyl of 1 to 6 carbon atoms, *cis*-alkenyl of 2-6 carbon atoms, *trans*-alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, aryl or heteroaryl;

R^4 is H, alkyl of 1-6 carbon atoms, *cis*-alkenyl of 2-6 carbon atoms, a *trans*- alkenyl of 2-6 carbon atoms, or an 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, and 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 heteroaryl ring, a aryl or heteroaryl fused to one to three aryl or heteroaryl rings, wherein any of the aryl, cycloalkyl, or heteroaryl 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, *cis*-alkenyl of 2-6 carbon atoms, *trans*-alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, aryl or heteroaryl;

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-, *cis*- and *trans*- -CH=CH- and 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 heteroaryl, and

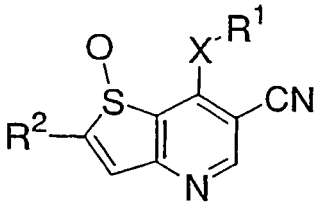
Z and Z' taken together with the nitrogen to which they are attached may form a heterocyclic ring which may have an additional heteroatom selected from nitrogen, oxygen, and sulfur, and may comprise morpholine, piperazine, piperidine, optionally substituted with $-R^4$ on a carbon or a nitrogen, or on nitrogen by a group -$(C(R^9)_2)_nXR^3$, -$C(R^9)_2)_nNZ''Z'''$, or on carbon by a group -$(C(R^9)_2)_qXR^3$, -$(C(R^9)_2)_qNZ''Z'''$,

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;

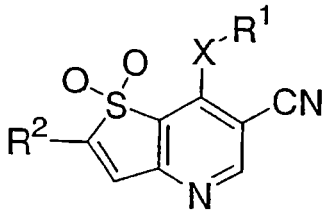
Z"' and Z" may be H, alkyl of 1 to 6 carbon atoms alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, aryl, or heteroaryl; and

J is fluoro, chloro, bromo, and iodo.

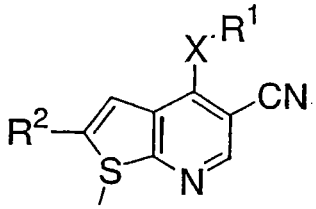
This invention also relates to compounds of Formulas **Ic**, **Id**, **Ie**, and **If**:



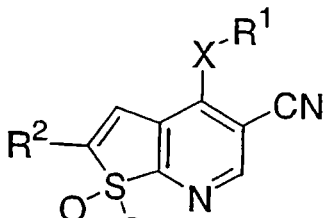
Ic



Id



Ie



If

wherein:

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

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 –H, -R^3, -J, -$C(O)XR^3$, -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, -$(C(R^9)_2)_qXR^8$, -$(C(R^9)_2)_qQ$, -$X(C(R^9)_2)_nXR^8$, -$X(C(R^9)_2)_nQ$, or - $X(C(R^9)_2)_q$ R^8;

R^3 is alkyl of 1 to 6 carbon atoms, *cis*-alkenyl of 2-6 carbon atoms, *trans*-alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, aryl or heteroaryl;

R^4 is H, alkyl of 1-6 carbon atoms, *cis*-alkenyl of 2-6 carbon atoms, a *trans*- alkenyl of 2-6 carbon atoms, or an 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, and 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 heteroaryl ring, a aryl or heteroaryl fused to one to three aryl or heteroaryl rings, wherein any of the aryl, cycloalkyl, or heteroaryl 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, *cis*-alkenyl of 2-6 carbon atoms, *trans*-alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, aryl or heteroaryl;

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-, *cis*- and *trans*- -CH=CH- and 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 heteroaryl, and

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 $-R^4$ on a carbon or a nitrogen, or on nitrogen by a group $-(C(R^9)_2)_nXR^3$, $-C(R^9)_2)_nNZ''Z'''$, or on carbon by a group $-(C(R^9)_2)_qXR^3$, $-(C(R^9)_2)_qNZ''Z'''$,

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; 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 heteroaryl; and

J is fluoro, chloro, bromo, and iodo.

R^1 may be for example a phenyl ring optionally substituted with one to four substituents selected from the group consisting of -J, $-CF_3$, $-OCF_3$, $-R^4$, $-OR^4$ and YR^7; and R^7 is an aryl or heteroaryl ring, optionally substituted with one to four substituents selected from the group consisting of –H, -J, $-CF_3$, $-OCF_3$, $-R^4$ and OR^4.

In particular R^1 may be a phenyl ring optionally substituted with one to four substituents selected from the group consisting of -Cl, $-R^4$ and $-OR^4$.

An example of X is NH.

R^4 may be for example alkyl of 1-6 carbon atoms.

An example of R^2 is substituted aryl or heteroaryl, wherein the substituent may be one or more groups selected from $-(C(R^9)_2)_qQ$; e.g., wherein q is 1 to 3 and/or wherein R^9 is H. Q may be for example 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 or carbon by R^4 or on carbon by $(CH_2)_2OH$.

In some embodiments an example of R^2 is R^3 where R^3 is alkynyl of 2-6 carbon atoms, aryl or heteroaryl; which groups may be substituted by one or more groups selected from

$-R^8$, $-(CH_2)_qOR^8$, $-(CH_2)_qNHR^8$, $-(CH_2)_q\ NR^4R^8$, $-(CH_2)_qQ$,

$-O(CH_2)_nOR^8$, $-\ NH(CH_2)_nOR^8$, $-\ NR^4(CH_2)_nOR^8$,

$-O(CH_2)_nNHR^8$, $-\ NH(CH_2)_nNHR^8$, $-\ NR^4(CH_2)_nNHR^8$,

$-O(CH_2)_nNR^4R^8$, $-\ NH(CH_2)_nCR^8$, $-\ NR^4(CH_2)_nNR^4R^8$,

$-O(CH_2)_nQ$, $-NH(CH_2)_nQ$, $-\ NR^4(CH_2)_nQ$,

$-\ O(CH_2)_qR^8$; $-\ NH(CH_2)_qR^8$; or $-\ NR^4(CH_2)_qR^8$;

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

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

Y is -C(O)-, -C(O)O-, -OC(O)-, -C(O)NH-, -NHC(O)-, $-NHSO_2$-, -S-, -O-, $-NR^4$-;

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

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 $-R^4$ on a carbon or a nitrogen, or on nitrogen by a group $-(CH_2)_nOR^3$, $-(CH_2)_nNHR^3$, $-(CH_2)_nNR^4R^3$, $-(CH_2)_nNZ''Z'''$, or on carbon by a group $-(CH_2)_qOR^3$, $-(CH_2)_qNHR^3$, $-(CH_2)_q\ NR^4R^3$, $-(CH_2)_qNZ''Z'''$,

Z''' and Z'' may be the same or different and are selected from H, alkyl of 1 to 6 carbon atoms

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.

Preferred compounds of the invention or a pharmaceutically acceptable salt thereof include:

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

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

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

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

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

4-({3-Chloro-4-[(1-methyl-1H-imidazol-2-yl)thio]phenyl}amino)thieno[2,3-b]pyridine-5-carbonitrile;

4-[(2,4-Dichloro-5-methoxyphenyl)amino]-2-iodothieno[2,3-b]pyridine-5-carbonitrile;

4-[(2,4-Dichloro-5-methoxyphenyl)amino]-2-methylthieno[2,3-b]pyridine-5-carbonitrile;

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

7-[(2,4-Dichlorophenyl)amino]thieno[3,2-b]pyridine-6-carbonitrile;

7-[(2,4-Dichlorophenoxy)]thieno[3,2-b]pyridine-6-carbonitrile;

7-[(2,4-Dichlorophenyl)thio]thieno[3,2-b]pyridine -6-carbonitrile;

7-[(2,4-Dichlorobenzyl) amino]thieno[3,2-b]pyridine-6-carbonitrile;

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

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

7-[(2,4-Dichloro-5-methoxyphenyl)amino]-2-[4-(4-methylpiperazin-1-ylmethyl)phenyl]thieno[3,2-b]pyridine-6-carbonitrile;

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

7-[(2,4-Dichloro-5-methoxyphenyl)amino]-2-[4-(piperidin-1-ylmethyl)phenyl]thieno[3,2-b]pyridine-6-carbonitrile;

4-{6-Cyano-7-[(2,4-dichloro-5-methoxyphenyl)amino]thieno[3,2-b]pyridine-2-yl]benzoic acid;

4-{6-Cyano-7-[(2,4-dichloro-5-methoxyphenyl)amino]thieno[3,2-b]pyridine-2-yl]benzamide;

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

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

7-[(2,4-Dichloro-5-methoxyphenyl)amino]-2-[3-(dimethylamino)prop-1-ynyl]thieno[3,2-b]pyridine-6-carbonitrile;

2-(1-Benzofuran-2-yl)-7-[(2,4-dichloro-5-methoxyphenyl)amino]thieno[3,2-b]pyridine-6-carbonitrile;

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

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

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

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

4-[5-Cyano-4-(3,4,5-trimethoxy-phenylamino)-thieno[2,3-b]pyridin-2-yl]-butyric acid methyl ester;

2-(4-Hydroxybutyl)-4-[(3,4,5-trimethoxyphenyl)amino]-thieno[2,3-b]pyridine-5-carbonitrile;

2-[4-(4-Morpholinyl)butyl]-4-[(3,4,5-trimethoxyphenyl)amino]-thieno[2,3-b]pyridine-5-carbonitrile;

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

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

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

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

7-[(2,4-Dichloro-5-methoxyphenyl)amino]-2-[5-(1,3-dioxolan-2-yl)thien-3-yl]thieno[3,2-b]pyridine-6-carbonitrile;

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

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

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

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

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

2-Iodo-7-[(4-phenoxyphenyl)amino]thieno[3,2-b]pyridine-6-carbonitrile;

2-(4-Formylphenyl)-7-[(4-phenoxyphenyl)amino]thieno[3,2-b]pyridine-6-carbonitrile;

2-[4-(4-Methylpiperazin-1-ylmethyl)phenyl]-7-[(4-phenoxyphenyl)amino]thieno[3,2-b]pyridine-6-carbonitrile;

2-[4-(Morpholin-4-ylmethyl)phenyl]-7-[(4-phenoxyphenyl)amino]thieno[3,2-b]pyridine-6-carbonitrile;

2-[4-(Hydroxymethyl)phenyl]-7-[(4-phenoxyphenyl)amino]thieno[3,2-b]pyridine-6-carbonitrile;

2-Iodo-7-[(3,4,5-trimethoxyphenyl)amino]thieno[3,2-b]pyridine-6-carbonitrile;

2-Bromo-7-[(4-phenoxyphenyl)amino]thieno[3,2-b]pyridine-6-carbonitrile;

7-[(4-Phenoxyphenyl)amino]-2-[(E)-2-pyridin-4-ylethenyl]thieno[3,2-b]pyridine-6-carbonitrile;

tert-Butyl (2E)-3-{6-cyano-7-[(2,4-dichloro-5-methoxyphenyl)amino]thieno[3,2-b]pyridin-2-yl}prop-2-enoate;

4-[(2,4-Dichloro-5-methoxyphenyl)amino]-2-[3-(4-methylpiperazin-1-yl)prop-1-ynyl]thieno[2,3-b]pyridine-5-carbonitrile;

4-[(2,4-Dichloro-5-methoxyphenyl)amino]-2-(pyridin-3-ylethynyl)thieno[2,3-b]pyridine-5-carbonitrile;

(2E)-3-(6-Cyano-7-[(2,4-dichloro-5-methoxyphenyl)amino]thieno[3,2-b]pyridin-2-yl)prop-2-enoate;

7-[(2,4-Dichloro-5-methoxyphenyl)amino]-2-(2-formyl-1-methyl-1H-imidazol-5-yl)thieno[3,2-b]pyridine-6-carbonitrile;

2-(4-Formylphenyl)-7-[(3,4,5-trimethoxyphenyl)amino]thieno[3,2-b]pyridine-6-carbonitrile;

7-[(2,4-Dichloro-5-methoxyphenyl)amino]-2-[(1E)-3-(4-methylpiperazin-1-yl)-3-oxoprop-1-enyl]thieno[3,2-b]pyridine-6-carbonitrile;

2-[3-(4-Methylpiperazin-1-yl)prop-1-ynyl]-7-[(3,4,5-trimethoxyphenyl)amino]thieno[3,2-b]pyridine-6-carbonitrile;

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

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

7-[(2,4-Dichloro-5-methoxyphenyl)amino]-2-[3-(4-methylpiperazin-1-yl)prop-1-ynyl] thieno[3,2-b]pyridine-6-carbonitrile;

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

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

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

7-[(2,4-Dichloro-5-methoxyphenyl)amino]-2-[4-(4-ethylpiperazin-1-ylmethyl)phenyl] thieno [3,2-b]pyridine-6-carbonitrile;

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

7-[(2-Chloro-5-methoxyphenyl)amino]-2-[4-(4-methylpiperazin-1-ylmethyl)phenyl]thieno [3,2-b]pyridine-6-carbonitrile;

2-{4-[(Dimethylamino)methyl]phenyl}7-[(5-methoxy-2-methylphenyl)amino]-thieno[3,2-b]pyridine-6-carbonitrile;

7-[(5-Methoxy-2-methylphenyl)amino]-2-[4-(4-methylpiperazin-1-ylmethyl) phenyl] thieno [3,2-b]pyridine-6-carbonitrile;

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

7-[(2,4-Dichlorophenyl)amino]-2-[4-(4-methylpiperazin-1-ylmethyl) phenyl] thieno [3,2-b]pyridine-6-carbonitrile;

7-[(2,4-Dichloro-5-methoxyphenyl)amino]-2-[6-(4-methylpiperazin-1-ylmethyl)pyridin-3-yl] thieno [3,2-b]pyridine-6-carbonitrile;

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

7-[(2,4-Dichloro-5-methoxyphenyl)amino]-2-[5-(4-methylpiperazin-1-ylmethyl)furan-3-yl] thieno [3,2-b]pyridine-6-carbonitrile;

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

7-[(2,4-Dichloro-5-methoxyphenyl)amino]-2-[4-(4-methylpiperazin-1-ylmethyl)phenyl]-1-oxo-1H-thieno [3,2-b]pyridine-6-carbonitrile;

7-[(2,4-Dichloro-5-methoxyphenyl)amino]-2-[4-(4-methylpiperazin-1-ylmethyl)phenyl]-1,1-dioxo-1H-thieno [3,2-b]pyridine-6-carbonitrile;

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

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

2-{4-[(Dimethylamino)methyl]phenyl}-1-oxo-7-[(3,4,5-trimethoxyphenyl)amino]-1H-thieno[3,2-b]pyridine-6-carbonitrile; and

2-{4-[(Dimethylamino)methyl]phenyl}-1,1-dioxo-7-[(3,4,5-trimethoxyphenyl)amino]-1H-thieno[3,2-b]pyridine-6-carbonitrile.

7-({3-chloro-4-[(1-methyl-1H-imidazol-2-yl)thio]phenyl}amino)-2-iodothieno[3,2-b]pyridine-6-carbonitrile;

7-({3-chloro-4-[(1-methyl-1H-imidazol-2-yl)thio]phenyl}amino)-2-[4-(morpholin-4-ylmethyl)phenyl]thieno[3,2-b]pyridine-6-carbonitrile;

7-({3-chloro-4-[(1-methyl-1H-imidazol-2-yl)thio]phenyl}amino)-2-[4-(morpholin-4-ylbut-1-ynyl)thieno[3,2-b]pyridine-6-carbonitrile;

7-({3-chloro-4-[(1-methyl-1H-imidazol-2-yl)thio]phenyl}amino)-2-[3-(dimethylamino)prop-1-ynyl]thieno[3,2-b]pyridine-6-carbonitrile;

7-({3-chloro-4-[(1-methyl-1H-imidazol-2-yl)thio]phenyl}amino)-2-(4-formylphenyl)thieno[3,2-b]pyridine-6-carbonitrile;

7-({3-chloro-4-[(1-methyl-1H-imidazol-2-yl)thio]phenyl}amino)-2-{4-[(4-methylpiperazin-1-yl)methyl]phenyl}thieno[3,2-b]pyridine-6-carbonitrile;

7-({3-chloro-4-[(1-methyl-1H-imidazol-2-yl)thio]phenyl}amino)-2-[3-(diethylamino)prop-1-ynyl]thieno[3,2-b]pyridine-6-carbonitrile;

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

7-[(2,4-dichloro-5-methoxyphenyl)amino]-2-[5-(1,3-dioxolan-2-yl)-2-furyl]thieno[3,2-b]pyridine-6-carbonitrile;

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

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

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

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

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

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

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

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

7-[(2,4-dichloro-5-methoxyphenyl)amino]-2-[5-(1,3-dioxolan-2-yl)thien-2-yl]thieno[3,2-b]pyridine-6-carbonitrile;

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

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

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

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

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

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

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

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

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

7-[(2,4-dichloro-5-methoxyphenyl)amino]-2-(1H-pyrrol-3-yl)thieno[3,2-b]pyridine-6-carbonitrile;

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

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

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

7-[(2,4-dichloro-5-methoxyphenyl)amino]-2-[4-(piperazin-1-ylmethyl)phenyl]thieno[3,2-b]pyridine-6-carbonitrile;

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

7-({3-chloro-4-[(1-methyl-1H-imidazol-2-yl)thio]phenyl}amino)-2-(4-formylphenyl)thieno[3,2-b] pyridine-6-carbonitrile;

7-({3-chloro-4-[(1-methyl-1H-imidazol-2-yl)thio]phenyl}amino)-2-{4-[(diethylamino)methyl]phenyl}thieno[3,2-b]pyridine-6-carbonitrile;

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

7-[(2,4-dichloro-5-methoxyphenyl)amino]-2-(1H-pyrazol-4-ylethynyl)thieno[3,2-b]pyridine-6-carbonitrile;

7-[(2,4-dichlorophenyl)amino]-2-iodothieno[3,2-b]pyridine-6-carbonitrile;

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

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

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

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

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

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

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

7-[(2,4-dichloro-5-ethoxyphenyl)amino]-2-iodothieno[3,2-b]pyridine-6-carbonitrile;

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

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

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

7-[(2,4-dichloro-5-methoxyphenyl)amino]-2-(4{[(2R,5S)-2,5-dimethylpiperazin-1-l]methyl}phenyl)thieno[3,2-b]pyridine-6-carbonitrile;

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

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

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

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

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

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

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

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

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

7-[(2,4-dichloro-5-methoxyphenyl)amino]-2-{1-[2-(dimethylamino)ethyl]-1H-pyrrol-3-yl}thieno[3,2-b]pyridine-6-carbonitrile;

7-[(2,4-dichlorophenyl)amino]-2-[4-(dimethylamino)phenyl]thieno[3,2-b]pyridine-6-carbonitrile;

7-[(2,4-dichloro-5-methoxyphenyl)amino]-2-[(1-methyl-1H-imidazol-5-yl)ethynyl]thieno[3,2-b]pyridine-6-carbonitrile;

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

7-[(2,4-dichloro-5-methoxyphenyl)amino]-2-(1H-pyrazol-4-yl)thieno[3,2-b]pyridine-6-carbonitrile;

7-[(2,4-dichloro-5-methoxyphenyl)amino]-2-{[1-(2-hydroxyethyl)-1H-pyrazol-4-yl]ethynyl}thieno[3,2-b]pyridine-6-carbonitrile;

7-[(2,4-dichloro-5-methoxyphenyl)amino]-2-[1-(2-morpholin-4-ylethyl)-1H-pyrazol-4-yl]thieno[3,2-b]pyridine-6-carbonitrile;

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

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

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

7-[(2,4-dichloro-5-methoxyphenyl)amino]-2-[1-(2-hydroxyethyl)-1H-pyrazol-4-yl]thieno[3,2-b]pyridine-6-carbonitrile;

4-{6-cyano-7-[(2,4-dichloro-5-methoxyphenyl)amino]thieno[3,2-b]pyridin-2-yl}-N,N-dimethylbenzamide;

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

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

For purposes of this invention a heteroaryl is an aromatic heterocyclic ring system of one to three fused rings. The heteroaryl moieties are five or six membered rings containing 1 to 4 heteroatoms selected from the group consisting of S, N, and O; e.g., heteroaryl may have 5 to 14 ring members. One ring of the ring system may be fully unsaturated, partially saturated, or fully saturated. The heteroaryl 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, naphthalene, 1,2,3,4-tetrahydronaphthalene, indan, indene, 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 heteroaryl may be oxidized on a nitrogen atom to provide the corresponding N-oxide, such as pyridine-N-oxide or quinoline -N-oxide. The heteroaryl may also be oxidized on a tri-substitued nitrogen atom to provide the corresponding N-oxide, such as N-ethylpiperazine-N-oxide. In another embodiment the heteroaryl may contain a carbonyl group on one of the carbon atoms, such as pyrrolidinone, 1,3,4-oxadiazol-2-one, or 2-indanone.

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 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. An aryl may be selected from but not limited to, the group: phenyl 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 "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, alkenyl and alkynyl groups can be substituted with such substituents as phenyl, substituted phenyl, 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 $-O-(CH_2)_2OCH_3$. 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.

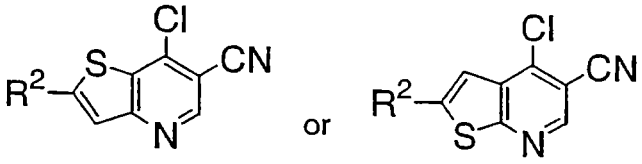
The compounds of this invention may contain one or more asymmetric carbon atoms and may thus give rise to stereoisomers, such as enantiomers and diastereomers. While shown without respect to stereochemistry in Formulas (Ia) - (If), the present invention includes all the individual possible stereoisomers; 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 Formulas (Ia) - (If) with an acidic moiety can be formed from organic and inorganic bases. For example alkali metal salts: sodium, lithium, or potassium and N- tetraalkylammonium salts such as N-tetrabutylammonium salts. 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, naphthalenesulfonic, benzenesulfonic, toluenesulfonic, camphorsulfonic, and similarly known acceptable acids.

This invention also provides a process for preparing a compound of formula (1a) or (1b) as defined herein or a pharmaceutically acceptable salt thereof, which comprises one of the following:

a) reacting a compound of formula:



or an S-oxide or S-dioxide thereof; wherein R^2 is as defined herein with a compound of formula R^1XH where R^1 and X are as defined herein to give a compound of formula I(a) or (Ib);

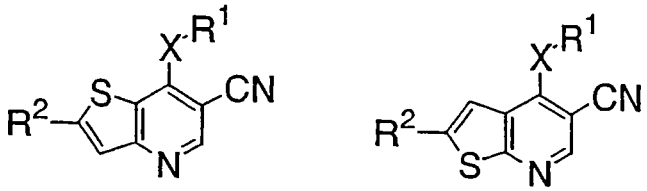
or

b) reacting a compound of formula 1a or 1b or an S-oxide or S-dioxide thereof in which R^2 is a reactive substituent group to give a compound of formula 1a or 1b in which R^2 is a different substituent group as defined herein;

or

c) converting a compound of formula (1a) or (1b) to a pharmaceutically acceptable salt thereof.

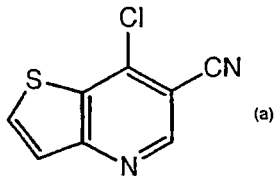
This invention also provides a process of producing a compound of Formula (Ia) and Formula (Ib) ,



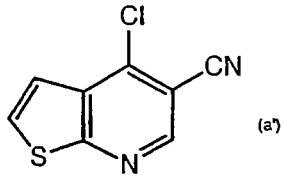
Ia **Ib**

wherein R^2 is iodine, comprising:

a. treating with a base, in an inert solvent at reduced temperature a compound of Formula (a) or (a');

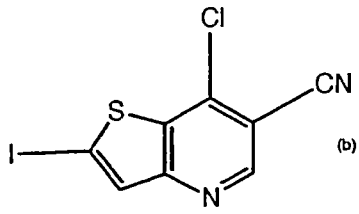


(a)

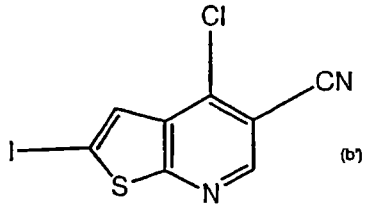


(a')

b. adding iodine to the compound in step (a) to form a compound of Formula (b) or (b'); and



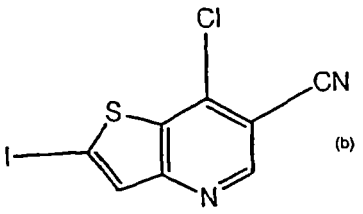
(b)



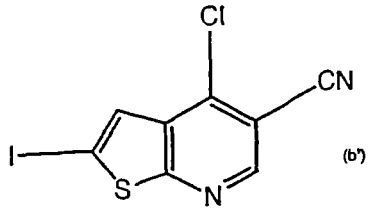
(b')

c. adding a compound of formula R^1XH to the compound in step (b) to form a compound of Formula (Ia) or (Ib), wherein R^2 is iodine.

This invention includes a compound of Formula (b) or (b')

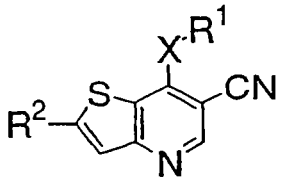


(b)

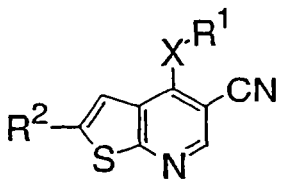


(b')

This invention also provides a process of producing a compound of Formula (Ia) or (Ib)



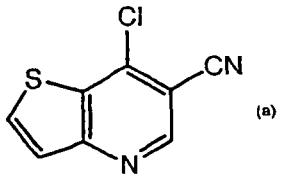
Ia



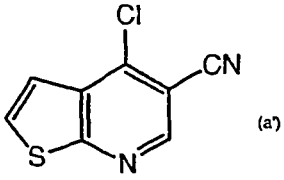
Ib

wherein R^2 is bromine, comprising:

a. treating with a base, in an inert solvent at reduced temperature a compound of Formula (a) or (a');

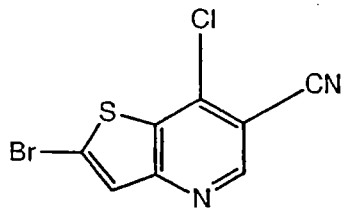


(a)

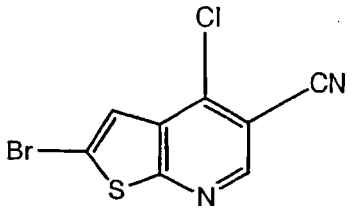


(a')

b. adding bromine or 1,1-dibromo-1,1,2,2-tetrafluoroethane to the compound in step (a) to form a compound of Formula (z) or (z'); and



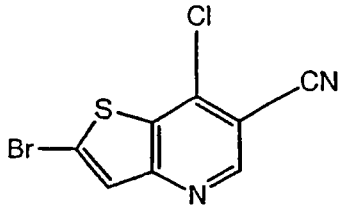
(z)



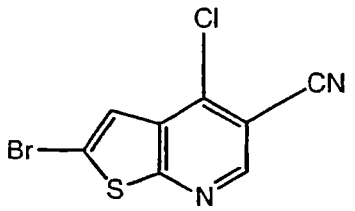
(z')

c. adding a compound of formula R^1XH to the compound in step (b) to form a compound of Formula (Ia) or (Ib), wherein R^2 is bromine.

This invention includes a compound of Formula (z) or (z')



(z)



(z')

The above-identified processes are explained in greater detail under the "Detailed Description of the Invention".

In a preferred embodiment of this invention an inert solvent is a compound that does not react chemically with the compounds of this invention. A preferred inert solvent includes for example tetrahydro furan (THF).

For purposes of this invention a reduced temperature is a temperature ≤-78°C. In a preferred embodiment this temperature is -78°C.

For purposes of this invention an elevated temperature is a temperature of about 50° C to about 150° C.

In another embodiment, the present invention provides a method for the treatment or inhibition of a pathological condition or disorder in a mammal. The present invention accordingly provides to a mammal, a pharmaceutical composition that comprises a compound of this invention in combination or association with a pharmaceutically acceptable carrier. The compound of this invention may be provided alone or in combination with other therapeutically effective compounds or therapies for the treatment or prevention of a pathological condition or disorder in a mammal.

The compounds are preferably provided orally or subcutaneously. The compounds may be provided by intralesional, intraperitoneal, intramuscular or intravenous injection; infusion; liposome-mediated delivery; topical; nasal; anal; vaginal; sublingual; uretheral; transdermal; intrathecal; ocular; or otic delivery. In order to obtain consistency in providing the compound of this invention it is preferred that a compound of the invention is in the form of a unit dose. Suitable unit dose forms include tablets, capsules and powders in sachets or vials. Such unit dose forms may contain from 0.1 to 100 mg of a compound of the invention and preferably from 2 to 50 mg. Still further preferred unit dosage forms contain 5 to 25 mg of a compound of the present invention. The compounds of the present invention can be administered orally at a dose range of about 0.01 to 100 mg/kg or preferably at a dose range of 0.1 to 10 mg/kg. Such compounds may be administered from 1 to 6 times a day, more usually from 1 to 4 times a day. The effective amount will be known to one of skill in the art; it will also be dependent upon the form of the compound. One of skill in the art could routinely perform empirical activity tests to determine the bioactivity of the compound in bioassays and thus determine what dosage is the effective amount to administer.

The compounds of the invention may be formulated with conventional excipients, such as a filler, a disintegrating agent, a binder, a lubricant, a flavoring agent, a color additive, or a carrier. The carrier may be for example a diluent, an aerosol, a topical carrier, an aqueous solution, a nonaqueous solution or a solid carrier. The carrier may be a polymer or a toothpaste. A carrier in this invention encompasses any of the standard pharmaceutically accepted carriers, such as phosphate buffered saline solution, acetate buffered saline solution, water, emulsions such as an oil/water emulsion or a triglyceride emulsion, various types of wetting agents, tablets, coated tablets and capsules.

When provided orally or topically, such compounds would be provided to a subject by delivery in different pharmaceutical carriers. Typically, such carriers contain excipients such as starch, milk, sugar, certain types of clay, gelatin, stearic acid, talc, vegetable fats or oils, gums, or glycols. The specific carrier would need to be selected based upon the desired method of delivery, for example, phosphate buffered saline (PBS) could be used for intravenous or systemic delivery and vegetable fats, creams, salves, ointments or gels may be used for topical delivery.

The compounds of the present invention may be delivered together with suitable diluents, preservatives, solubilizers, emulsifiers, adjuvants and/or carriers. Such compositions are liquids or lyophilized or otherwise dried formulations and include diluents of various buffer content (for example, Tris-HCl, acetate, phosphate), pH and ionic strength, additives such as albumins or gelatin to prevent absorption to surfaces, detergents (for example, TWEEN 20, TWEEN 80, PLURONIC F68, bile acid salts), solubilizing agents (for example, glycerol, polyethylene glycerol), anti-oxidants (for example ascorbic acid, sodium metabisulfate), preservatives (for example, thimerosal, benzyl alcohol, parabens), bulking substances or tonicity modifiers (for example, lactose, mannitol), covalent attachment of polymers such as polyethylene glycol, complexation with metal ions, or incorporation of the compound into or onto particulate preparations of hydrogels or liposomes, micro-emulsions, micelles, unilamellar or multilamellar vesicles, erythrocyte ghosts, or spheroplasts. Such compositions will influence the physical state, solubility, stability, rate of *in vivo*

release, and rate of *in vivo* clearance of the compound or composition. The choice of compositions will depend on the physical and chemical properties of the compound capable of treating or inhibiting a pathological condition or disorder.

The compound of the present invention may be delivered locally via a capsule that allows a sustained release of the compound over a period of time. Controlled or sustained release compositions include formulation in lipophilic depots (for example, fatty acids, waxes, oils).

For purposes of this invention a pathological condition or disorder is linked to kinase molecules and inhibition of the signals generated by these molecules. Generated signals regulate a number of cellular functions such as cell growth, differentiation and cell death. The signals generated by these molecules have been implicated in initiation of tissue level responses, discussed in detail in the "Background of the Invention". The tissue level response triggers cellular damage or deregulated cellular growth. Deregulated cell growth occurs as a result of perturbed signals that moderate or alter cellular behaviour or function. One method of treating a pathological condition or disorder would be to intercept the generated signal before it reachs the tissue. As described in detail previously specific kinases are associated with cellular events that have been implicated in pathological conditions or disorders including, but not limited to, cancer, stroke, osteoporosis, polycystic kidney disease, autoimmune disease, rheumatoid arthritis, neuropathic pain, and transplant rejection.

A pathological condition or disorder is mediated in a mammal when it is linked to kinase molecules as described above. For purpose of this invention a condition or disorder mediated in a mammal is one that effects or acts to alter the mammal's normal state.

For purposes of this invention cancer is a cellular tumor. The natural course of the cancer is fatal. Metastasis develops as a result of adhesion of tumor cells to the vascular endothelium. As the tumor grows, cells are shed in the circulation and spawn an independent tumor nodule known as a metastasis.

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 are conveniently prepared according to the following schemes: (1) from commercially available starting materials or: (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.

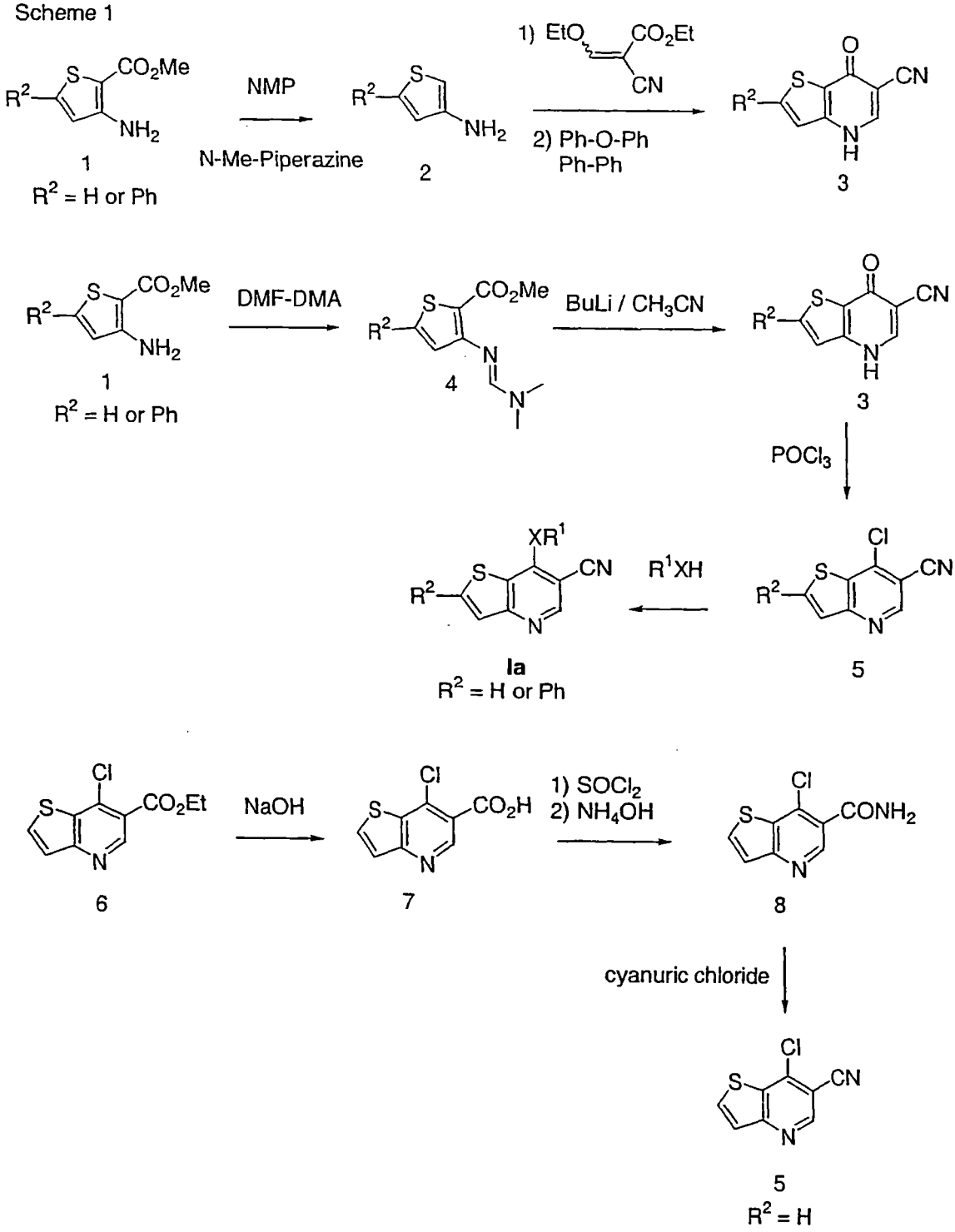
The preparation of the compounds and intermediates of this invention encompassed by formulas **Ia** and **Ib** is described as follows.

As shown in Scheme 1, 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 1. 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 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 **Ia** of the invention. 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 key intermediate 7-chlorothieno[3,2-b]pyridine-6-carbonitrile 5, where R^2 is H.

Scheme 1


1
R2 = H or Ph
NMP
N-Me-Piperazine
2
1) EtO CO2Et CN
2) Ph-O-Ph
Ph-Ph
3
DMF-DMA
4
BuLi / CH3CN
POCl3
5
R1XH
Ia
R2 = H or Ph
6
NaOH
7
1) SOCl2
2) NH4OH
8
cyanuric chloride
5
R2 = H

Compounds of formula **Ia** of the invention can also be prepared according to the routes depicted in Scheme 2. Ethyl 2-bromo-7-chlorothieno[3,2-b]pyridine-6-carboxylate, 9, [Elliott, R.; O'Hanlon, P. J.; Rodgers, N. B. *Tetrahedron,* 43(14), 3295 (1987)] is converted to the corresponding acid 10 by treatment with aqueous sodium hydroxide in a cosolvent such as ethanol at elevated temperatures of 60-70°C. The corresponding 6-carboxamide analog 11 is prepared by treatment of 10 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. Treatment of 11 with a reagent such as phosphorous oxychloride provides the key intermediate 2-bromo-7-chlorothieno[3,2-b]pyridine-6-carbonitrile 12. Addition of a compound of formula R^1XH to compounds of formula 12, optionally 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 **Ia** of the invention where R^2 is Br.

Scheme 2 also depicts an alternate route for the preparation of the key intermediate 12.

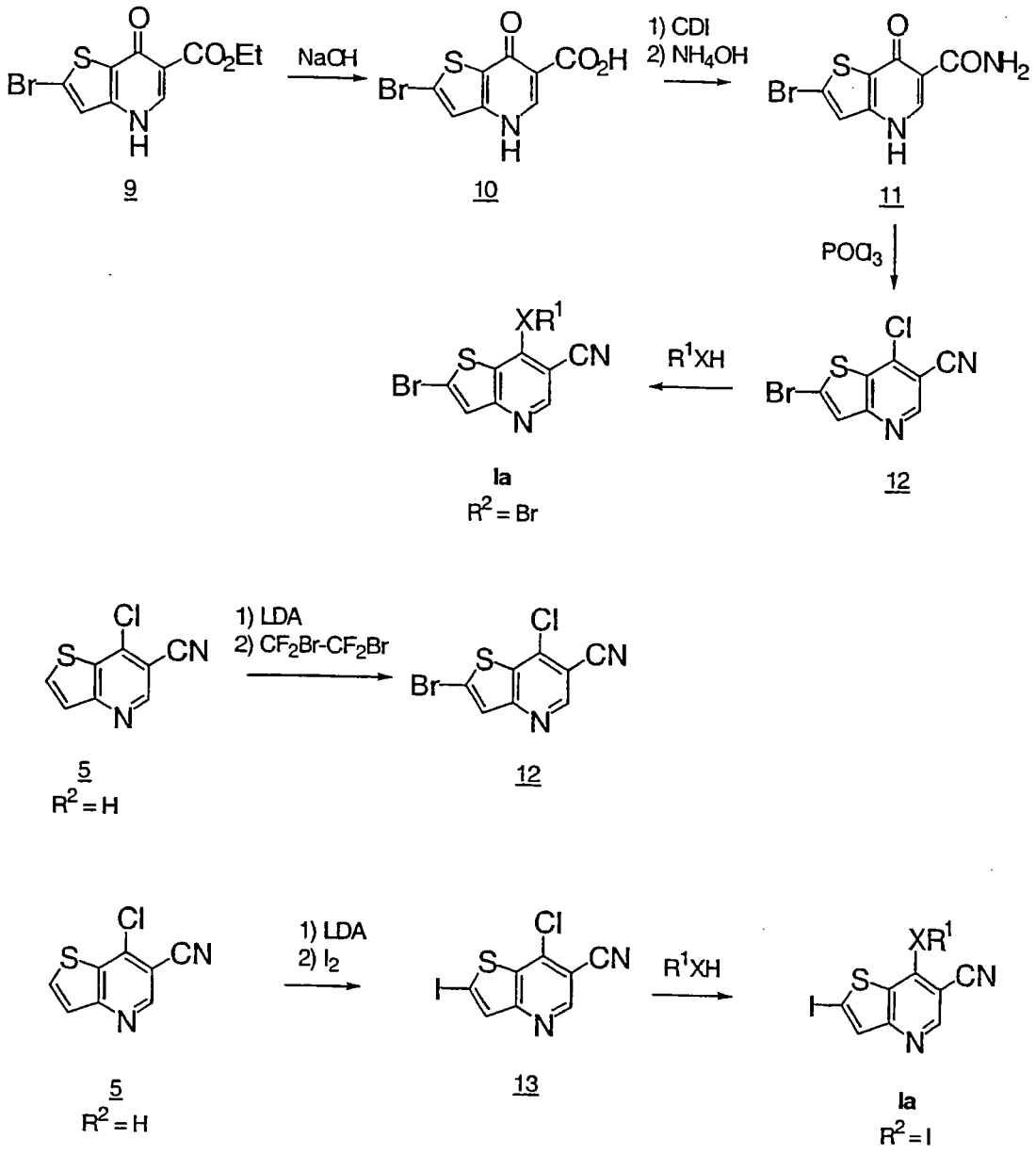
Addition of a compound of formula R^1XH to compound 13, optionally in the presence of pyridine hydrochloride in a solvent such as 2-ethoxyethanol at elevated temperatures of 110-130°C, or in the presence of sodium hydride in a solvent such as tetrahydrofuran at elevated temperatures of 60-70°C, provides compounds of formula **Ia** of the invention where R^2 is I.

Treatment of thiophene 5 with a base, preferentially lithium diisopropylamine (LDA) but also including n-butyl lithium, t-butyl lithium or sodium hydride in an inert solvent, preferably tetrahydrofuran, but also including diethyl ether, in the optional presence of TMEDA (N, N, N', N'-tetramethylethylenediamine), at reduced temperature, preferably at about -78°C, followed by the addition of 1,2-dibromo-1,1,2,2,-tetrafluoroethane or bromine, followed by warming to room temperature provides 12.

Treatment of thiophene 5 with a base, preferentially lithium diisopropylamine (LDA) but also including n-butyl lithium, t-butyl lithium or sodium hydride in an inert

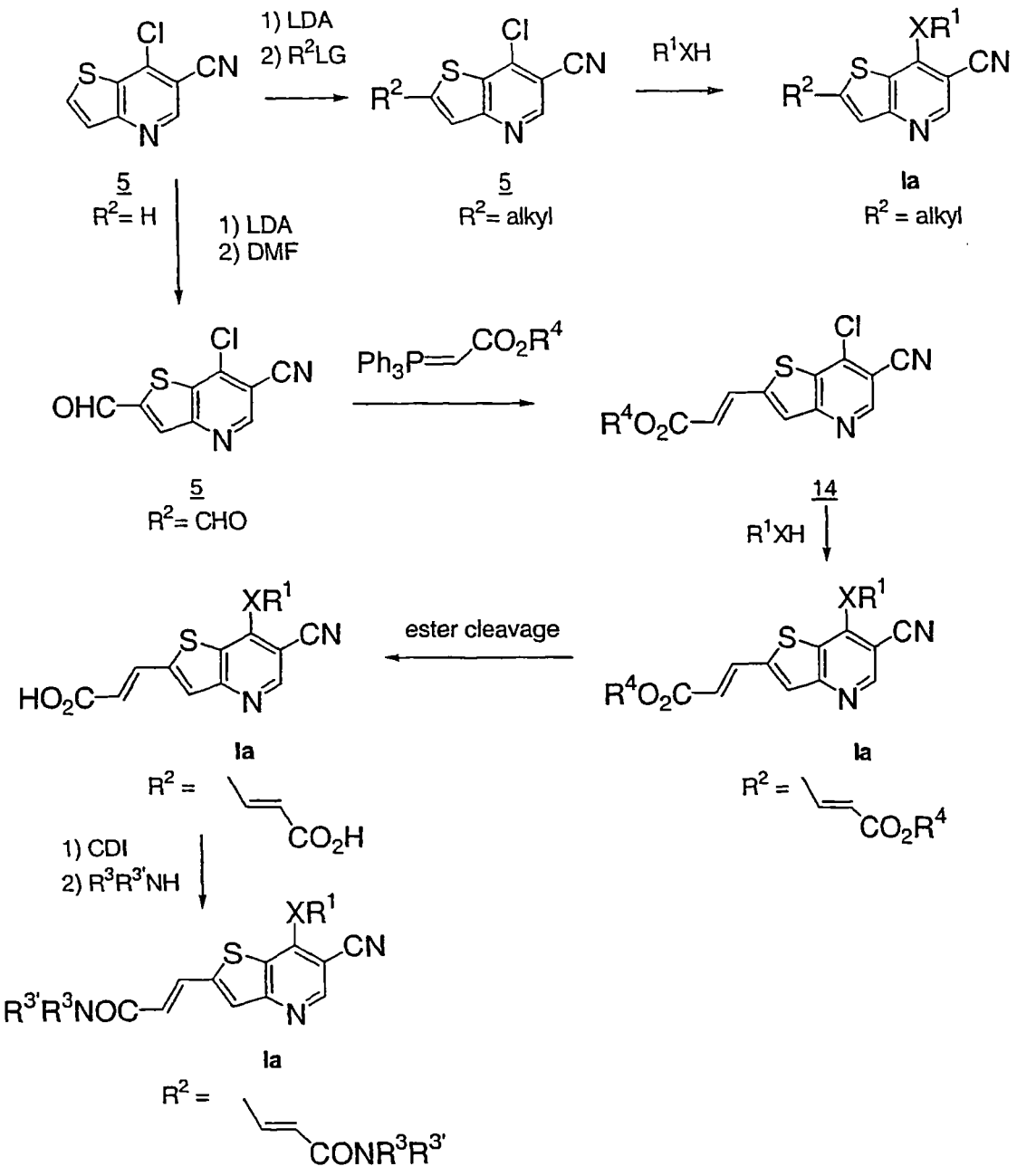
solvent, preferably tetrahydrofuran, but also including diethyl ether, in the optional presence of TMEDA (N, N, N', N'-tetramethylethylenediamine), at reduced temperature, preferably at about -78°C, followed by the addition of iodine, followed by warming to room temperature provides 13.

Scheme 2



Scheme 3 depicts the preparation of compounds of formula **Ia** of the invention with additional R^2 groups. Treatment of thiophene 5 with a base, preferentially lithium diisopropylamine (LDA), in an inert solvent such as tetrahydrofuran at reduced temperature, preferably –78°C, followed by the addition of a compound of formula R^2LG, where LG is a leaving group, preferably iodo, and R^2 is preferably an alkyl group, provides compounds of formula 5, where R^2 is alkyl. Addition of a compound of formula R^1XH to compounds of formula 5, 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, provides compounds of formula **Ia** of the invention where R^2 is alkyl. Alternatively, treatment of thiophene 5 with a base, preferentially lithium diisopropylamine (LDA), in an inert solvent such as tetrahydrofuran at reduced temperature, preferably –78°C, followed by the addition of a formylating agent, preferably N,N-dimethylformamide (DMF) provides compounds of formula 5, where R^2 is formyl. Reaction of the formyl group of 5 with a Wittig reagent, such as (tert-butoxycarbonylmethylene)-triphenylphosphorane in an inert solvent, preferably dichloromethane, provides α,β-unsaturated esters of formula 14. Addition of a compound of formula R^1XH to compounds of formula 14, preferentially 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 **Ia** of the invention where R^2 is an unsaturated ester. Compounds of formula **Ia** of the where R^2 is an unsaturated ester can be converted into compounds of formula **Ia** of the invention where R^2 is an unsaturated acid, by treatment with aqueous base in the presence of an optional cosolvent such as ethanol or methanol. Compounds of formula **Ia** of the invention where R^2 is an α,β-unsaturated amide can be obtained by treatment of compounds of formula **Ia** of the invention where R^2 is an α,β-unsaturated acid with an agent such as N,N-carbonyldiimidazole followed by the addition of an amine of formula $R^3R^{3'}NH$, where $R^3R^{3'}N$ or $NR^3R^{3'}$ = Q.

Scheme 3



Additional compounds of the invention of formula **Ia** where R^2 is an alkenyl, alkynyl, heteroaryl or aryl group can be prepared as depicted in Scheme 4 from

compounds of formula **Ia** where R^2 is either I or Br. Treatment of compounds of formula **Ia** where R^2 is either I or Br with an alkenyl or alkynyl of formula R^9-H in the presence of a palladium catalyst provides compounds of formula **Ia** where R^2 is either an alkenyl or alkynyl group. This alkenyl or alkynyl group can be substituted by groups including aryl and heteroaryl and also alkyl and alkylamino among others.

For the addition of alkenyls of formula R^9-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^9-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.

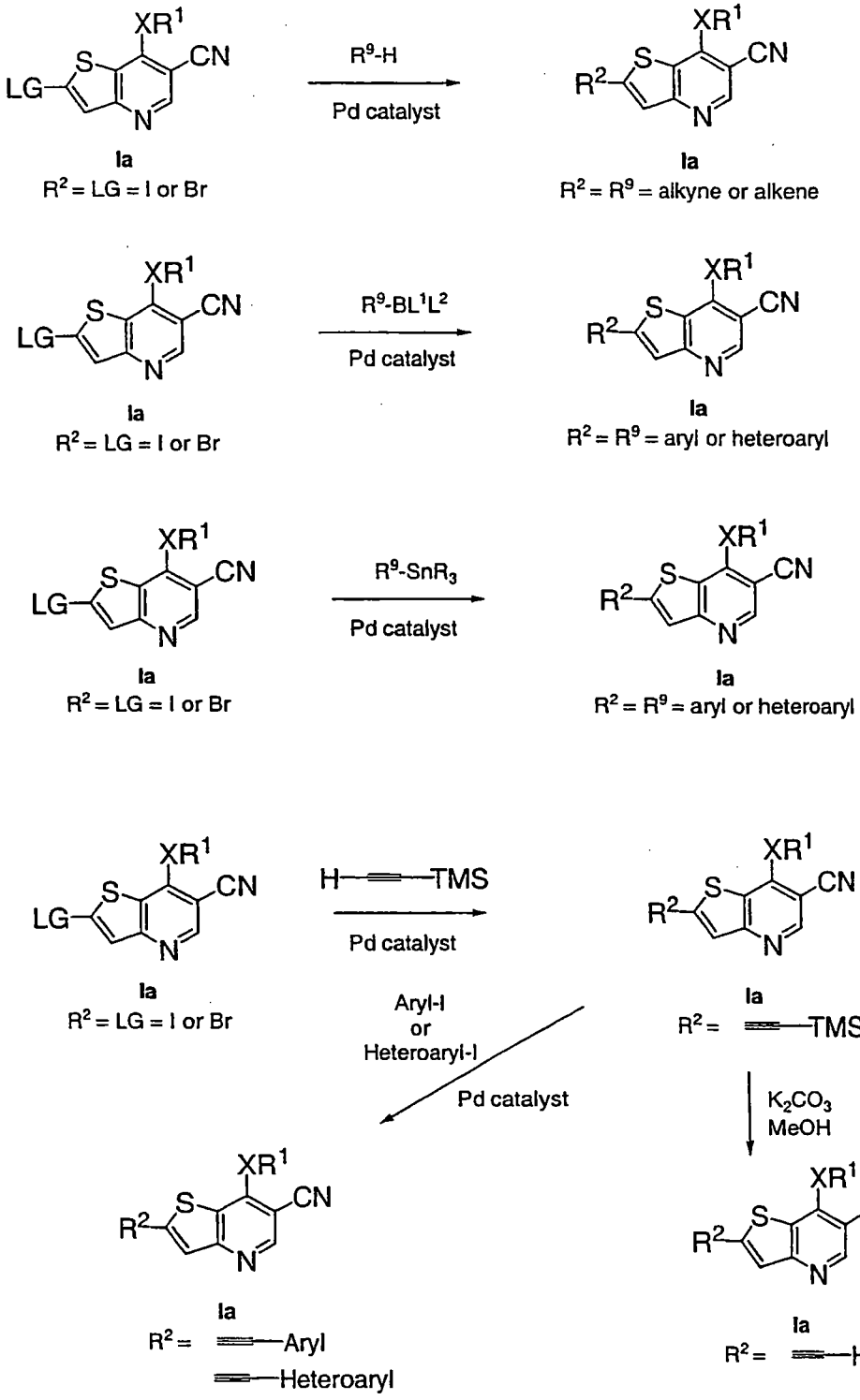
Treatment of compounds of formula **Ia** where R^2 is either I or Br with an aryl or heteroaryl organoboron compound of formula R^9-BL^1L^2 in the presence of a palladium catalyst provides compounds of formula **Ia** where R^2 is either an aryl or heteroaryl group. In compounds of formula R^9-BL^1L^2, the L^1L^2 groups represent ligands and include such groups as lower alkoxy or preferably hydroxy. The aryl or heteroaryl group of compound R^9-BL^1L^2 can be substituted by groups including aryl and heteroaryl and also formyl, carboxylate, alkyl and alkylamino among others. The aryl or heteroaryl group of compound R^9-BL^1L^2 can also be fused to a second aryl or heteroaryl group. For the addition of compounds of formula R^9-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 **Ia** where R^2 is either aryl or heteroaryl can also be prepared by reaction of a compound of formula **Ia** where R^2 is either I or Br with an aryl or heteroaryl stannane compound of formula R^9-SnR_3 in the presence of a palladium catalyst. In compounds of formula R^9-SnR_3 the R group is a lower alkyl group such as butyl or methyl. The aryl or heteroaryl group of compound R^9-SnR_3 can be substituted by groups including aryl and heteroaryl and also formyl, carboxylate, acetal, alkyl and alkylamino among others. The aryl or heteroaryl group

of compound R^9-SnR_3 can also be fused to a second aryl or heteroaryl group. For the addition of compounds of formula R^9-SnR_3 the preferred palladium catalyst is bis(triphenylphosphine)palladium (II) chloride in a solvent such as dioxane.

Compounds of formula **Ia** where R^2 is an alkynyl group can be prepared by the alternative route shown in Scheme 4. Treatment of a compound of formula **Ia**, where R^2 is either Br or I 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 **Ia** where R^2 is a 2-(trimethylsilyl)ethynyl group. Reaction of compounds of formula **Ia** where R^2 is a 2-(trimethylsilyl)ethynyl group with aryliodines or heteroaryliodines 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 **Ia** where R^2 is a 2-(aryl)ethynyl or a 2-(heteroaryl)ethynyl group. In addition the 2-(trimethylsilyl)ethynyl group can be cleaved by treatment with potassium carbonate in methanol to provide compounds of formula **Ia** where R^2 is an ethynyl group.

Scheme 4



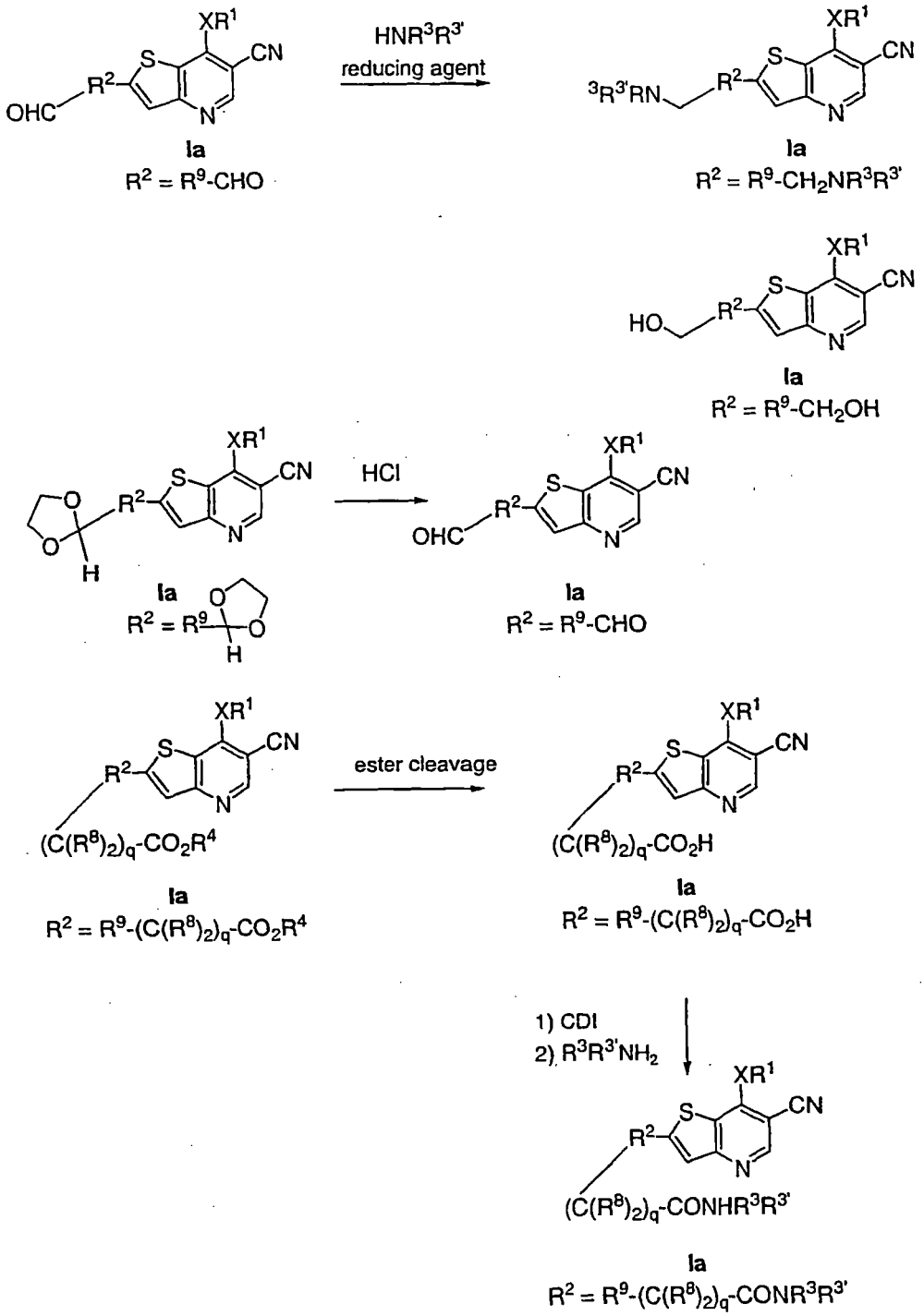
Some additional routes to the compounds of the invention of formula **Ia** are shown in Scheme 5. Compounds of formula **Ia** where the group R^2 is R^9-CHO can be

converted to compounds of formula **Ia** where the group R^2 is R^9-$CH_2NR^3R^{3'}$ via reductive amination. Treatment of compounds of formula **Ia** where the group R^2 is R^9-CHO with an amine of formula $HNR^3R^{3'}$ in the presence of a reducing agent, preferably sodium triacetoxyborohydride, in a solvent system that includes dichloromethane and N,N-dimethylformamide, optionally in the presence of acetic acid, provides compounds of formula **Ia** where the group R^2 is R^9-$CH_2NR^3R^{3'}$. Compounds of formula **Ia** where the group R^2 is R^9-CH_2OH may be obtained as a by-product of this reaction, via reduction of the formyl group of compounds of formula **Ia** where the group R^2 is R^9-CHO.

Compounds of formula **Ia** where the group R^2 is R^9-CHO can be prepared by hydrolysis of the acetal group of compounds of formula **Ia** where the group R^2 is R^9-acetal, preferably with aqueous hydrochloric acid in the presence of a cosolvent such as tetrahydrofuran.

Scheme 5 also depicts the preparation of compounds of formula **Ia** where the group R^2 is $(C(R^8)_2)_q$-CO_2H, and $(C(R^8)_2)_q$-$CONR^3R^{3'}$ from compounds of formula **Ia** where the group R^2 is $(C(R^8)_2)_q$-CO_2R^4. Compounds of formula **Ia** where the group R^2 is $(C(R^8)_2)_q$-$CO_2R^4$are converted to the corresponding acids of formula **Ia** where the group R^2 is $(C(R^8)_2)_q$-CO_2H by treatment with aqueous sodium hydroxide in a cosolvent such as ethanol at elevated temperatures. The corresponding amides of formula **Ia** where the group R^2 is $(C(R^8)_2)_q$-$CONR^3R^{3'}$ 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 $HNR^3R^{3'}$.

Scheme 5



Scheme 6 depicts preparation of compounds of the invention of formula **Ib**. Addition of a compound of formula R^1XH to a compound of formula 15 [Khan, M. A.; Guarconi, A. E., *J. Heterocyclic Chem.*, 14, 807 (1977)], optionally 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 **Ib** of the invention where R^2 is H. Alternatively addition of a compound of formula R^1XH to a compound of formula 15 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 **Ib** of the invention where R^2 is H.

Scheme 6 also depicts a route for the preparation of key intermediates of formula 16. Treatment of thiophene 15 with a base, preferentially lithium diisopropylamine (LDA) but also including n-butyl lithium, t-butyl lithium or sodium hydride in an inert solvent, preferably tetrahydrofuran, but also including diethyl ether, in the optional presence of TMEDA (N, N, N', N'-tetramethylethylenediamine), at reduced temperature, preferably at about -78°C, followed by the addition of 1,2-dibromo-1,1,2,2,-tetrafluoroethane or bromine, followed by warming to room temperature provides 12.

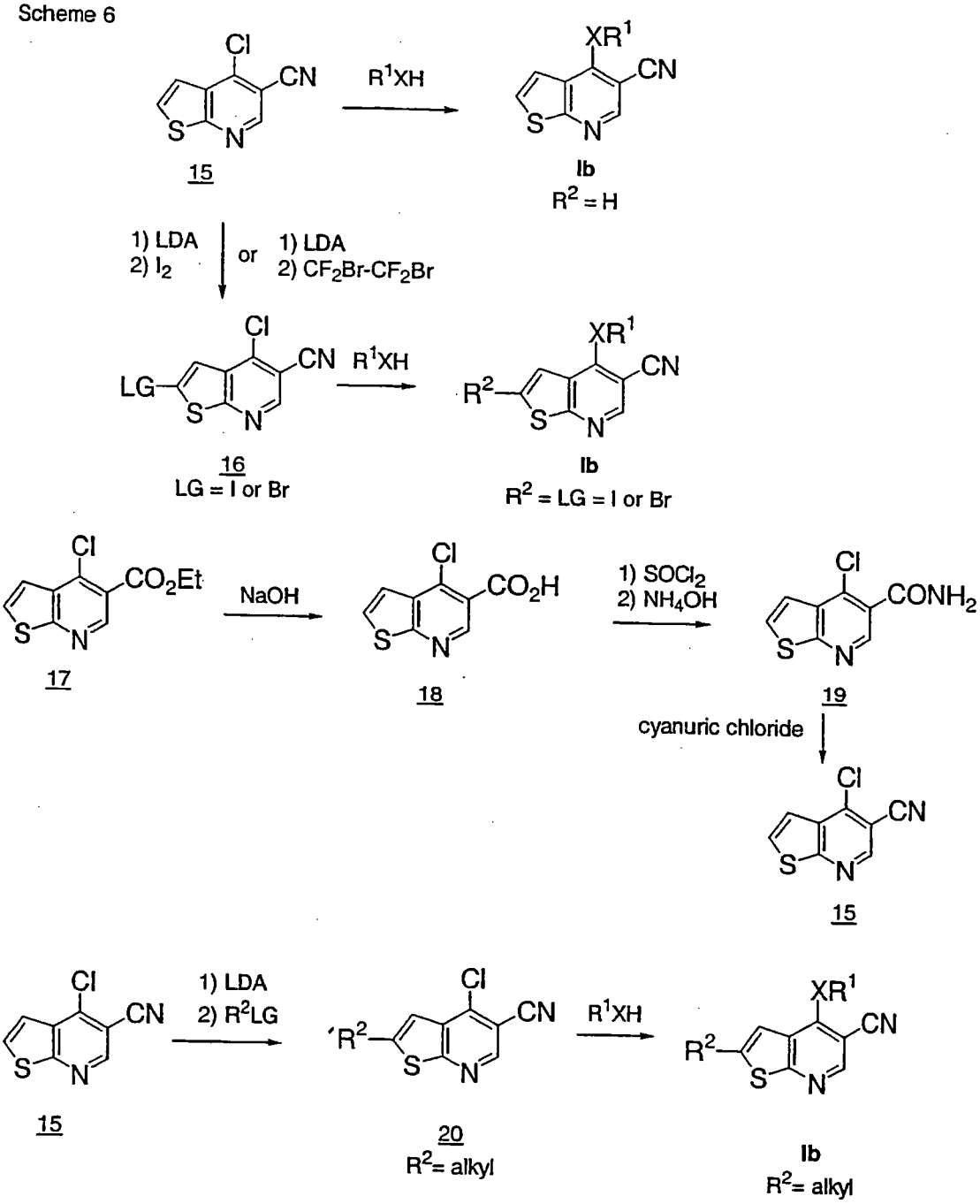
Treatment of thiophene 5 with a base, preferentially lithium diisopropylamine (LDA) but also including n-butyl lithium, t-butyl lithium or sodium hydride in an inert solvent, preferably tetrahydrofuran, but also including diethyl ether, in the optional presence of TMEDA (N, N, N', N'-tetramethylethylenediamine), at reduced temperature, preferably at about -78°C, followed by the addition of iodine, followed by warming to room temperature provides 1b.

Addition of a compound of formula R^1XH to compounds of formula 16, optionally 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 **Ib** of the invention where R^2 is Br or I. Scheme 6 also depicts an alternate route for the preparation of key intermediate 15, starting from compound 17 [Khan, M. A.; Guarconi, A. E., *J. Heterocyclic Chem.*, 14, 807 (1977)]. The ethyl group of ethyl 4-chlorothieno[2,3-b]pyridine-5-carboxylate, 17, is

hydrolyzed to the corresponding 5-carboxylic acid 18 with aqueous sodium hydroxide in a cosolvent such as ethanol at elevated temperature. The corresponding 5-carboxamide analog 19 is prepared by treatment of 18 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 19 with a reagent such as cyanuric chloride provides the key intermediate 4-chlorothieno[3,2-b]pyridine-5-carbonitrile 15.

Scheme 6 also depicts the preparation of compounds of the invention of formula **Ib** where R^2 is alkyl. Treatment of 15 with a base, preferentially lithium diisopropylamine (LDA), in an inert solvent such as tetrahydrofuran at reduced temperature, preferably –78°C, followed by the addition of a R^2LG, where LG is a leaving group, preferably iodo, provides the key intermediate 20 where R^2 is alkyl. Addition of a compound of formula R^1XH to compounds of formula 20, optionally 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 **Ib** of the invention where R^2 is alkyl. Alternatively addition of a compound of formula R^1XH to a compound of formula 20 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 **Ib** of the invention where R^2 is alkyl.

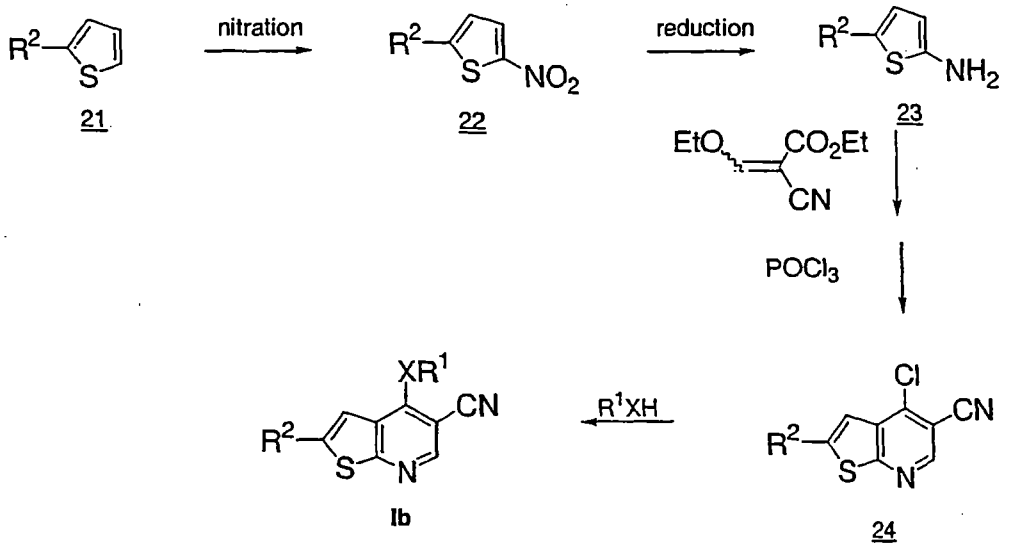
Scheme 6



Scheme 7 depicts an alternate route for the preparation of compounds of the invention of formula **Ib**. A suitably substituted thiophene of formula 21 is nitrated, preferably with nitric acid in acetic anhydride at reduced temperature to provide 2-nitrothiophenes of formula 22. Reduction of the nitro group of compounds of formula 22 with a reducing agent, preferably hydrogen gas in the presence of a catalyst, preferably palladium hydroxide in a solvent, which includes methanol, provides

compounds of formula 23. Addition of ethyl (ethoxymethylene)cyanoacetate in a solvent such as toluene followed by cyclization at high temperatures, preferably in a solvent system of biphenyl and diphenyl ether at reflux, and subsequent chlorination with phosphorous oxychloride, preferably with a catalytic amount of N,N-dimethylformamide, results in compounds of formula 24. Addition of a compound of formula R^1XH to compounds of formula 24, optionally 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 **Ib** of the invention. Alternatively addition of a compound of formula R^1XH to a compound of formula 24 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 **Ib** of the invention.

Scheme 7



Additional compounds of the invention of formula **Ib** where R^2 is an alkenyl, alkynyl, heteroaryl or aryl group from compounds of formula **1b** where R^2 is either I or Br can be prepared as depicted in Scheme 8. Treatment of compounds of formula **1b** where R^2 is either I or Br with an alkenyl or alkynyl of formula R^9-H in the presence of a palladium catalyst provides compounds of formula **1b** where R^2 is

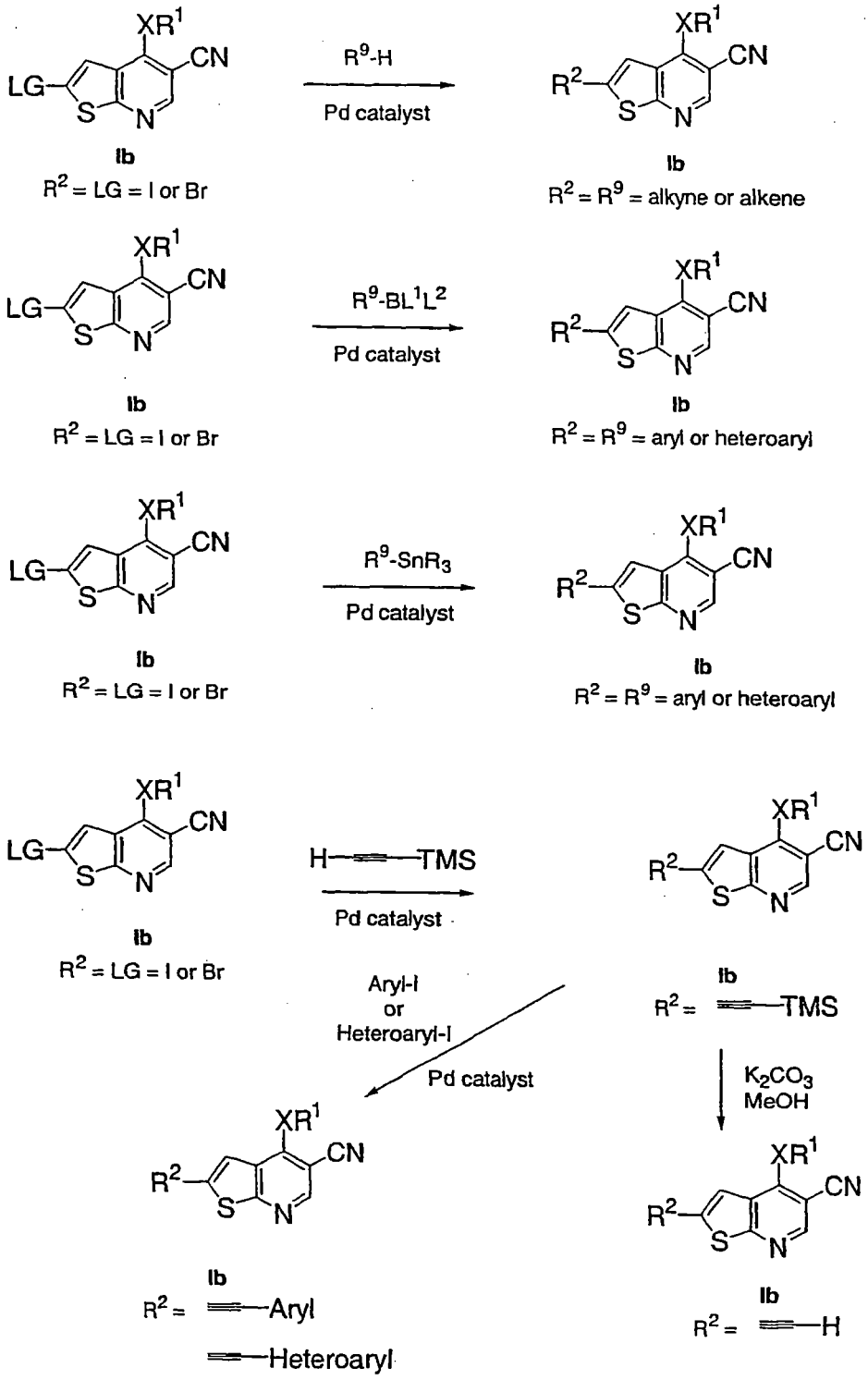
either an alkenyl or alkynyl group. This alkenyl or alkynyl group can be substituted by groups including aryl and heteroaryl and also alkyl and alkyl amino among others. This aryl or heteroaryl group can also be substituted by groups such as alkoxy, alkylamino and others. For the addition of alkenyls of formula R^9-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^9-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 **1b** where R^2 is either I or Br with an aryl or heteroaryl organoboron compound of formula R^9-BL^1L^2 in the presence of a palladium catalyst provides compounds of formula **1b** where R^2 is either an aryl or heteroaryl group. In compounds of formula R^9-BL^1L^2, the L^1L^2 groups represent ligands and include such groups as lower alkoxy or preferably hydroxy. The aryl or heteroaryl group of compound R^9-BL^1L^2 can be substituted by groups including aryl and heteroaryl and also formyl, carboxylate, alkyl and alkylamino among others. The aryl or heteroaryl group of compound R^9-BL^1L^2 can also be fused to a second aryl or heteroaryl group. For the addition of compounds of formula R^9-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 **1b** where R^2 is either aryl or heteroaryl can also be prepared by reaction of a compound of formula **1b** where R^2 is either I or Br with an aryl or heteroaryl stannane compound of formula R^9-SnR_3 in the presence of a palladium catalyst. In compounds of formula R^9-SnR_3 the R group is a lower alkyl group such as butyl or methyl. The aryl or heteroaryl group of compound R^9-SnR_3 can be substituted by groups including aryl and heteroaryl and also formyl, carboxylate, acetal, alkyl and alkylamino among others. The aryl or heteroaryl group of compound R^9-SnR_3 can also be fused to a second aryl or heteroaryl group. For the addition of compounds of formula R^9-SnR_3 the preferred palladium catalyst is bis(triphenylphosphine)palladium (II) chloride in a solvent such as dioxane.

Compounds of formula **Ib** where R^2 is an alkynyl group can be prepared by the alternative route shown in Scheme 8. Treatment of a compound of formula **1b**, where R^2 is either Br or I 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 **Ib** where R^2 is a 2-(trimethylsilyl)ethynyl group. Reaction of compounds of formula **Ib** where R^2 is a 2-(trimethylsilyl)ethynyl group with aryliodines or heteroaryliodines 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 **Ib** where R^2 is a 2-(aryl)ethynyl or a 2-(heteroaryl)ethynyl group. In addition the 2-(trimethylsilyl)ethynyl group can be cleaved by treatment with potassium carbonate in methanol to provide compounds of formula **Ib** where R^2 is an ethynyl group.

Scheme 8



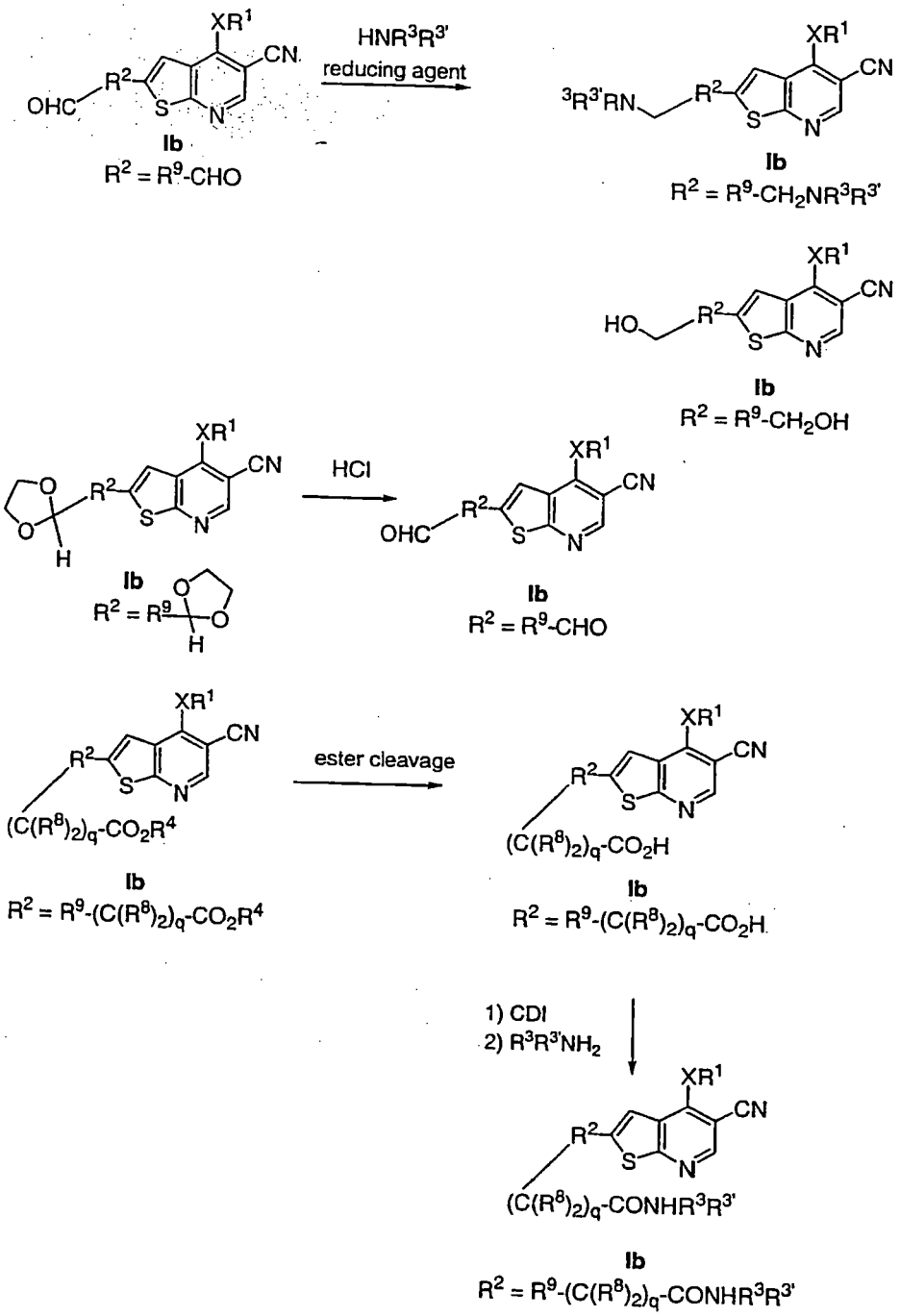
Some additional routes to the compounds of the invention of formula **Ib** are shown in Scheme 9. Compounds of formula **Ib** where the group R^2 is R^9-CHO can be

converted to compounds of formula **Ib** where the group R^2 is R^9-$CH_2NR^3R^{3'}$ via reductive amination. Treatment of compounds of formula **Ib** where the group R^2 is R^9-CHO with an amine of formula $HNR^3R^{3'}$ in the presence of a reducing agent, preferably sodium triacetoxyborohydride, in a solvent system that includes dichloromethane and N,N-dimethylformamide, provides compounds of formula **Ib** where the group R^2 is R^9-$CH_2NR^3R^{3'}$. Compounds of formula **Ib** where the group R^2 is R^9-CH_2OH may be obtained as a by-product of this reaction, via reduction of the formyl group of compounds of formula **Ib** where the group R^2 is R^9-CHO.

Compounds of formula **Ib** where the group R^2 is R^9-CHO can be prepared by hydrolysis of the acetal group of compounds of formula **Ib** where the group R^2 is R^9-acetal, preferably with aqueous hydrochloric acid in the presence of a cosolvent such as tetrahydrofuran.

Scheme 9 also depicts the preparation of compounds of formula **Ib** where the group R^2 is $(C(R^8)_2)_q$-CO_2H, and $(C(R^8)_2)_q$-$CONR^3R^{3'}$ from compounds of formula **Ib** where the group R^2 is $(C(R^8)_2)_q$-CO_2R^4. Compounds of formula **Ib** where the group R^2 is $(C(R^8)_2)_q$-$CO_2R^4$are converted to the corresponding acids of formula **Ib** where the group R^2 is $(C(R^8)_2)_q$-CO_2H by treatment with aqueous sodium hydroxide in a cosolvent such as ethanol at elevated temperatures. The corresponding amides of formula **Ib** where the group R^2 is $(C(R^8)_2)_q$-$CONR^3R^{3'}$ are prepared by treatment of the acids with N,N-carbonyldiimidazole or alternatively thionyl chloride or the like, followed by the addition of an amine of formula $HNR^3R^{3'}$.

Scheme 9


XR1
CN
R2
OHC
S
N
Ib
R2 = R9-CHO
HNR3R3'
reducing agent
3R3'RN
R2 = R9-CH2NR3R3'
HO
R2 = R9-CH2OH
HCl
O
O
H
R2 = R9
R2 = R9-CHO
ester cleavage
(C(R8)2)q-CO2R4
R2 = R9-(C(R8)2)q-CO2R4
(C(R8)2)q-CO2H
R2 = R9-(C(R8)2)q-CO2H
1) CDI
2) R3R3'NH2
(C(R8)2)q-CONHR3R3'
R2 = R9-(C(R8)2)q-CONHR3R3'

Scheme 10 depicts the preparation of key sulfoxide intermediate 25. Oxidation of 12 or 13 with an oxidizing agent such as m-chloroperbenzoic acid, peracetic acid or an oxaziridine provides the sulfoxide derivative 25. The reaction conditions must be controlled to prevent overoxidation to the sulfone. If both the sulfoxide and sulfone are obtained in the reaction, they can be separated by standard laboratory techniques. Addition of a compound of formula R^1XH to compound 25, optionally 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 **Ic** of the invention where R^2 is Br or I.

Compounds of the invention of formula **Ic** where R^2 is an alkene, alkyne, heteroaryl or aryl group can be prepared as depicted in Scheme 10 from compounds of formula **Ic** where R^2 is either I or Br. Treatment of compounds of formula **Ic** where R^2 is either I or Br with an alkene or alkyne of formula R^9-H in the presence of a palladium catalyst provides compounds of formula **Ic** where R^2 is either an alkene or alkyne group. This alkene or alkyne group can be substituted by groups including aryl and heteroaryl and also alkyl and alkylamino among others.

For the addition of alkenes of formula R^9-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 alkynes of formula R^9-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.

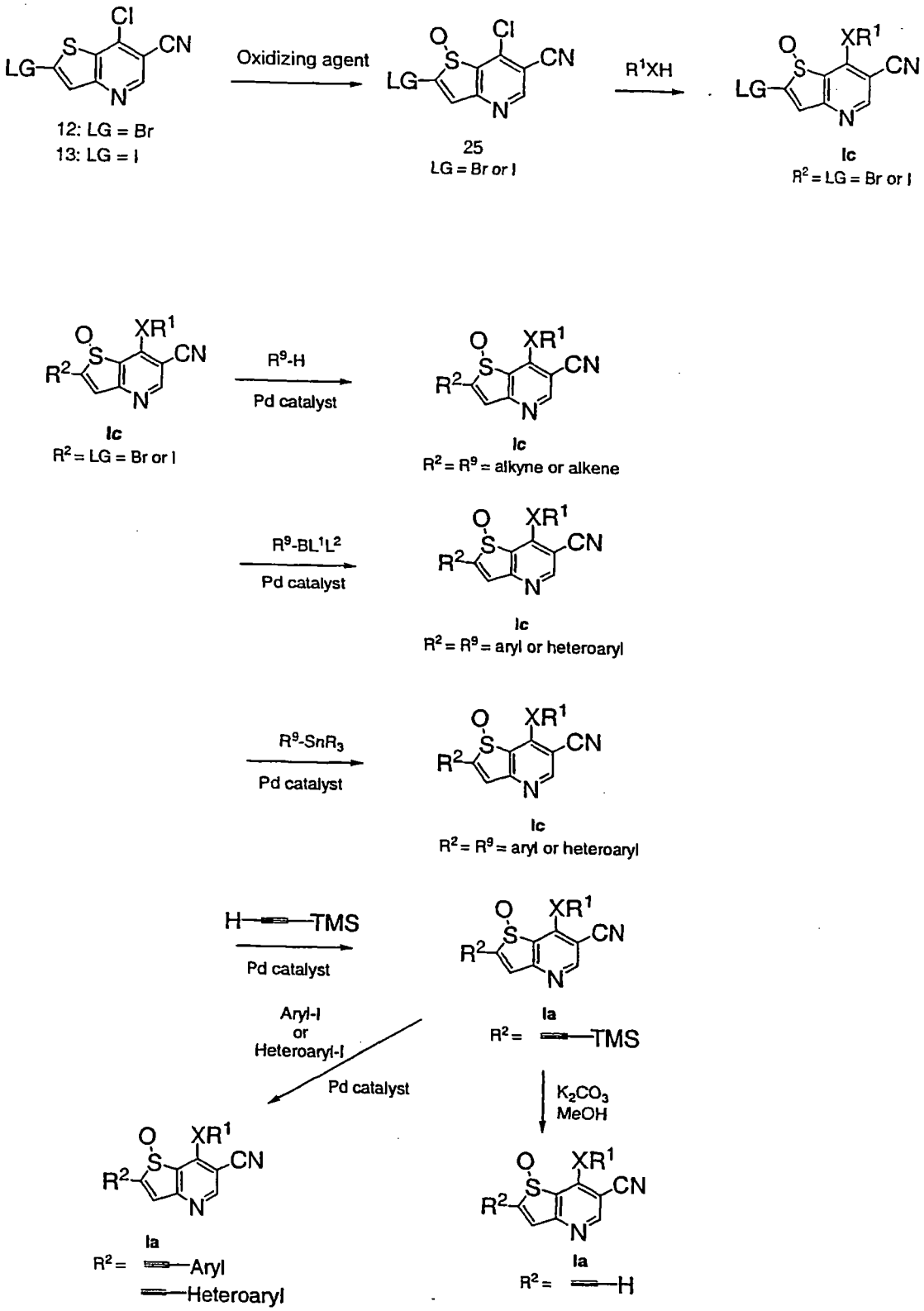
Treatment of compounds of formula **Ic** where R^2 is either I or Br with an aryl or heteroaryl organoboron compound of formula R^9-BL^1L^2 in the presence of a palladium catalyst provides compounds of formula **Ic** where R^2 is either an aryl or heteroaryl group. In compounds of formula R^9-BL^1L^2, the L^1L^2 groups represent ligands and include such groups as lower alkoxy or preferably hydroxy. The aryl or heteroaryl group of compound R^9-BL^1L^2 can be substituted by groups including aryl and heteroaryl and also formyl, carboxylate, alkyl and alkylamino among others. The

aryl or heteroaryl group of compound R^9-BL^1L^2 can also be fused to a second aryl or heteroaryl group. For the addition of compounds of formula R^9-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 **Ic** where R^2 is either aryl or heteroaryl can also be prepared by reaction of a compound of formula **Ic** where R^2 is either I or Br with an aryl or heteroaryl stannane compound of formula R^9-SnR_3 in the presence of a palladium catalyst. In compounds of formula R^9-SnR_3 the R group is a lower alkyl group such as butyl or methyl. The aryl or heteroaryl group of compound R^9-SnR_3 can be substituted by groups including aryl and heteroaryl and also formyl, carboxylate, acetal, alkyl and alkylamino among others. The aryl or heteroaryl group of compound R^9-SnR_3 can also be fused to a second aryl or heteroaryl group. For the addition of compounds of formula R^9-SnR_3 the preferred palladium catalyst is bis(triphenylphosphine)palladium (II) chloride in a solvent such as dioxane.

Compounds of formula **Ic** where R^2 is an alkyne group can also be prepared by the route shown in Scheme 10. Treatment of a compound of formula **Ic**, where R^2 is either Br or I 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 **Ic** where R^2 is a 2-(trimethylsilyl)ethynyl group. Reaction of compounds of formula **Ic** where R^2 is a 2-(trimethylsilyl)ethynyl group with aryliodines or heteroaryliodines 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 **Ic** where R^2 is a 2-(aryl)ethynyl or a 2-(heteroaryl)ethynyl group. In addition the 2-(trimethylsilyl)ethynyl group can be cleaved by treatment with potassium carbonate in methanol to provide compounds of formula **Ic** where R^2 is an ethynyl group.

Scheme 10


Cl
CN
LG
S
N
12: LG = Br
13: LG = I
Oxidizing agent
O
25
LG = Br or I
R1XH
XR1
Ic
R2 = LG = Br or I
R9-H
Pd catalyst
R2 = R9 = alkyne or alkene
R9-BL1L2
R2 = R9 = aryl or heteroaryl
R9-SnR3
H—TMS
Aryl-I
or
Heteroaryl-I
Ia
R2 = TMS
K2CO3
MeOH
R2 = Aryl
Heteroaryl
R2 = H

Scheme 11 depicts the preparation of key sulfone intermediate 26. Oxidation of 12 or 13 with an excess of an oxidizing agent such as m-chloroperbenzoic acid, peracetic acid or an oxiziridine provides the sulfone derivative 26. If both the sulfoxide and sulfone are obtained in the reaction, they can be separated by standard laboratory techniques. Addition of a compound of formula R^1XH to compound 26, optionally 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 **Id** of the invention where R^2 is Br or I.

Compounds of the invention of formula **Id** where R^2 is an alkene, alkyne, heteroaryl or aryl group can be prepared as depicted in Scheme 11 from compounds of formula **Id** where R^2 is either I or Br. Treatment of compounds of formula **Id** where R^2 is either I or Br with an alkene or alkyne of formula R^9-H in the presence of a palladium catalyst provides compounds of formula **Id** where R^2 is either an alkene or alkyne group. This alkene or alkyne group can be substituted by groups including aryl and heteroaryl and also alkyl and alkylamino among others.

For the addition of alkenes of formula R^9-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 alkynes of formula R^9-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.

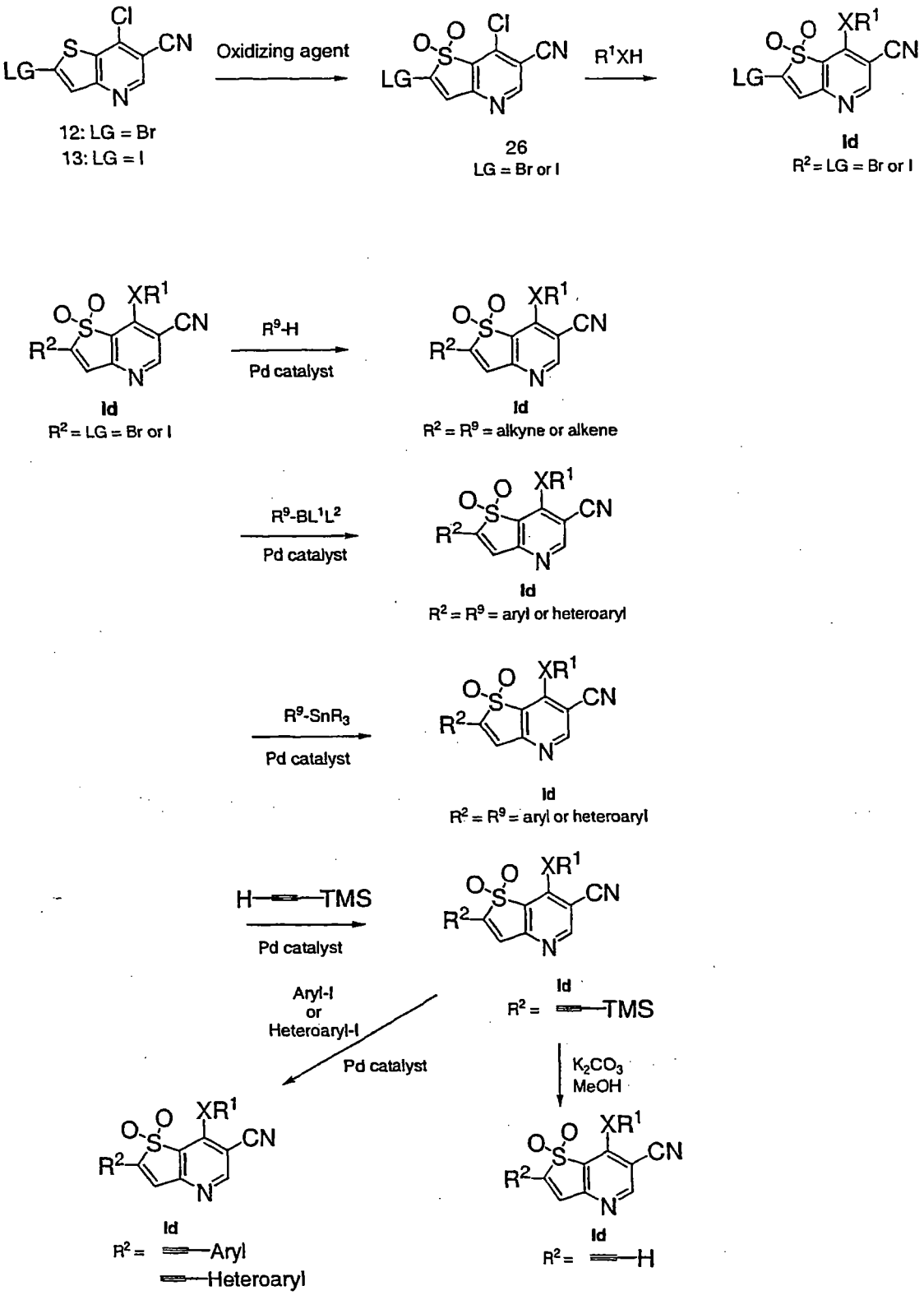
Treatment of compounds of formula **Id** where R^2 is either I or Br with an aryl or heteroaryl organoboron compound of formula R^9-BL^1L^2 in the presence of a palladium catalyst provides compounds of formula **Id** where R^2 is either an aryl or heteroaryl group. In compounds of formula R^9-BL^1L^2, the L^1L^2 groups represent ligands and include such groups as lower alkoxy or preferably hydroxy. The aryl or heteroaryl group of compound R^9-BL^1L^2 can be substituted by groups including aryl and heteroaryl and also formyl, carboxylate, alkyl and alkylamino among others. The aryl or heteroaryl group of compound R^9-BL^1L^2 can also be fused to a second aryl or

heteroaryl group. For the addition of compounds of formula R^9-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 **Id** where R^2 is either aryl or heteroaryl can also be prepared by reaction of a compound of formula **Id** where R^2 is either I or Br with an aryl or heteroaryl stannane compound of formula R^9-SnR_3 in the presence of a palladium catalyst. In compounds of formula R^9-SnR_3 the R group is a lower alkyl group such as butyl or methyl. The aryl or heteroaryl group of compound R^9-SnR_3 can be substituted by groups including aryl and heteroaryl and also formyl, carboxylate, acetal, alkyl and alkylamino among others. The aryl or heteroaryl group of compound R^9-SnR_3 can also be fused to a second aryl or heteroaryl group. For the addition of compounds of formula R^9-SnR_3 the preferred palladium catalyst is bis(triphenylphosphine)palladium (II) chloride in a solvent such as dioxane.

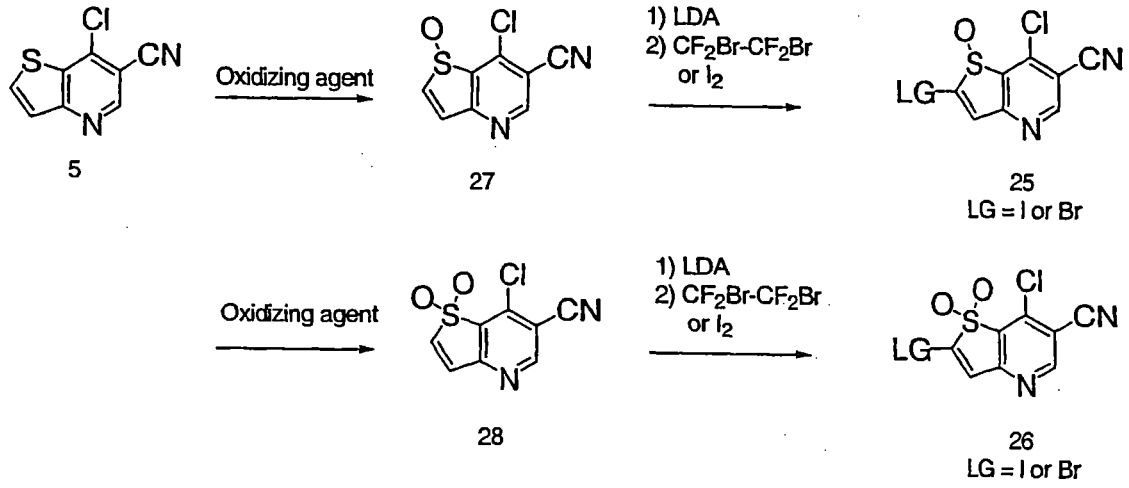
Compounds of formula **Id** where R^2 is an alkyne group can also be prepared by the route shown in Scheme 11. Treatment of a compound of formula **Id**, where R^2 is either Br or I with (trimethylsilyl)acetylene in the presence of a palladium catalyst, preferably tetrakis(triphenylphosphine)palladium(0), with a catalytic amount of copper(I) iodine in a solvent system such as triethylamine and benzene, provides compounds of formula **Id** where R^2 is a 2-(trimethylsilyl)ethynyl group. Reaction of compounds of formula **Id** where R^2 is a 2-(trimethylsilyl)ethynyl group with aryliodines or heteroaryliodines 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 **Id** where R^2 is a 2-(aryl)ethynyl or a 2-(heteroaryl)ethynyl group. In addition the 2-(trimethylsilyl)ethynyl group can be cleaved by treatment with potassium carbonate in methanol to provide compounds of formula **Id** where R^2 is an ethynyl group.

Scheme 11


Cl
CN
LG
S
N
Oxidizing agent
O
O
R1XH
XR1
12: LG = Br
13: LG = I
26
LG = Br or I
Id
R2 = LG = Br or I
R9-H
Pd catalyst
R2 = R9 = alkyne or alkene
R9-BL1L2
R2 = R9 = aryl or heteroaryl
R9-SnR3
H—≡—TMS
Aryl-I
or
Heteroaryl-I
R2 = —≡—TMS
K2CO3
MeOH
R2 = —≡—Aryl
—≡—Heteroaryl
R2 = —≡—H

Alternate routes for the preparation of the key intermediate 25 and 26 are shown in Scheme 12. Oxidation of 5 with an oxidizing agent provides the sulfoxide 27 or the sulfone 28. Excess amounts of oxidizing agent would be expected to provide the sulfone via an intermediate sulfoxide. Treatment of sulfoxide 27 with a base, preferentially lithium diisopropylamine (LDA), in an inert solvent such as tetrahydrofuran at reduced temperature, preferably –78°C, followed by the addition of 1,2-dibromo-1,1,2,2,-tetrafluoroethane or bromine provides 25 where LG = Br. Analogously, treatment of 27 with a base, preferentially lithium diisopropylamine (LDA), in an inert solvent such as tetrahydrofuran at reduced temperature, preferably –78°C, followed by the addition of iodine provides 25 where LG = I. In a similar fashion, treatment of sulfone 28 with a base, preferentially lithium diisopropylamine (LDA), in an inert solvent such as tetrahydrofuran at reduced temperature, preferably –78°C, followed by the addition of 1,2-dibromo-1,1,2,2,-tetrafluoroethane or bromine provides 26 where LG = Br. Analogously, treatment of 28 with a base, preferentially lithium diisopropylamine (LDA), in an inert solvent such as tetrahydrofuran at reduced temperature, preferably –78°C, followed by the addition of iodine provides 26 where LG = I.

Scheme 12



5 27 25 LG = I or Br

28 26 LG = I or Br

Scheme 13 depicts the preparation of key sulfoxide intermediate 29. Oxidation of 16 with an oxidizing agent such as m-chloroperbenzoic acid, peracetic acid or an oxiziridine provides the sulfoxide derivative 29. The reaction conditions are controlled to prevent over oxidation to the sulfone. If both the sulfoxide and sulfone are obtained in the reaction, they can be separated by standard laboratory techniques. Addition of a compound of formula R^1XH to compound 29, optionally 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 **Ie** of the invention where R^2 is Br or I.

Compounds of the invention of formula **Ie** where R^2 is an alkene, alkyne, heteroaryl or aryl group can be prepared as depicted in Scheme 13 from compounds of formula **Ie** where R^2 is either I or Br. Treatment of compounds of formula **Ie** where R^2 is either I or Br with an alkene or alkyne of formula R^9-H in the presence of a palladium catalyst provides compounds of formula **Ie** where R^2 is either an alkene or alkyne group. This alkene or alkyne group can be substituted by groups including aryl and heteroaryl and also alkyl and alkylamino among others.

For the addition of alkenes of formula R^9-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 alkynes of formula R^9-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.

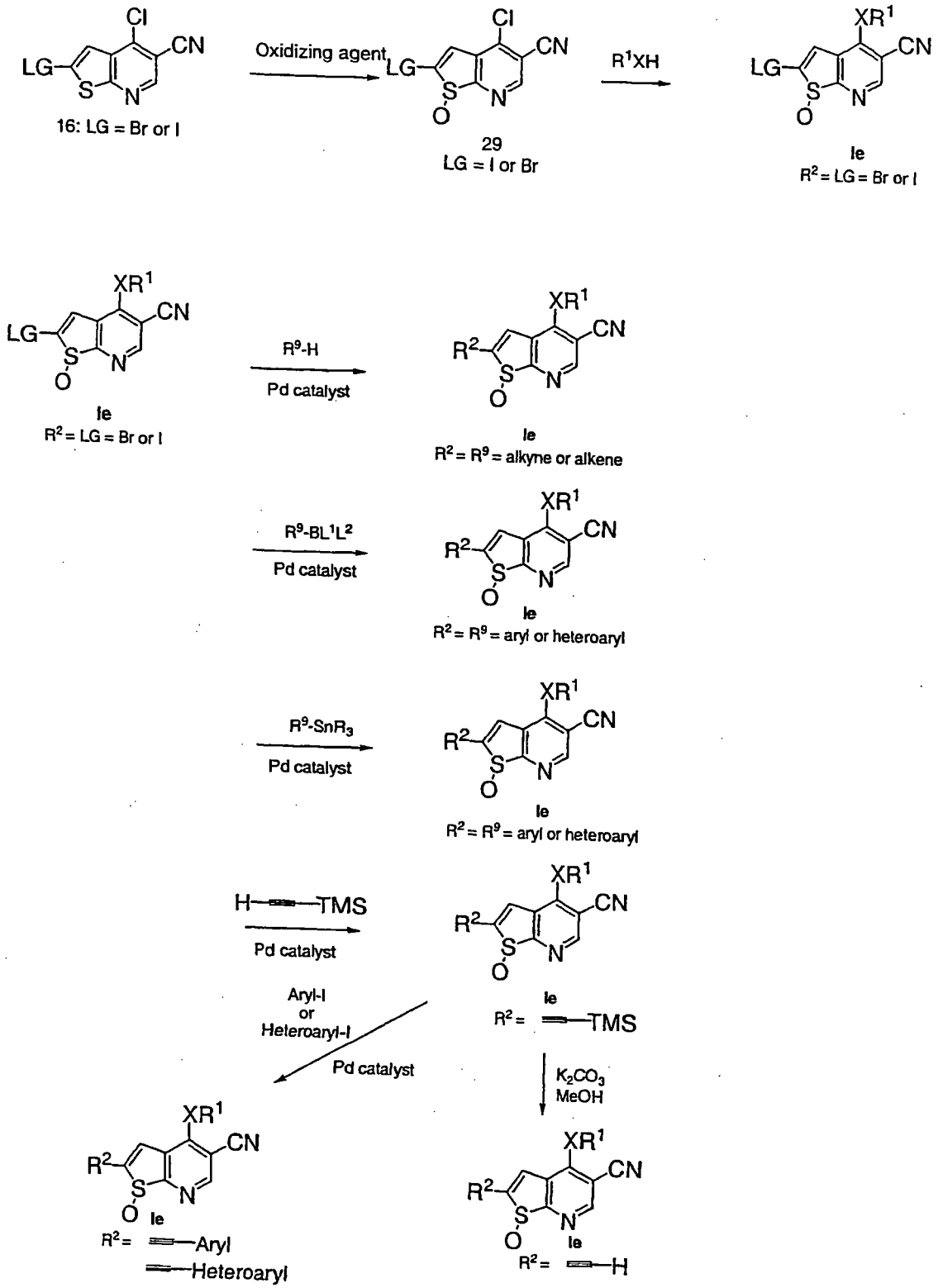
Treatment of compounds of formula **Ie** where R^2 is either I or Br with an aryl or heteroaryl organoboron compound of formula R^9-BL^1L^2 in the presence of a palladium catalyst provides compounds of formula **Ie** where R^2 is either an aryl or heteroaryl group. In compounds of formula R^9-BL^1L^2, the L^1L^2 groups represent ligands and include such groups as lower alkoxy or preferably hydroxy. The aryl or heteroaryl group of compound R^9-BL^1L^2 can be substituted by groups including aryl and heteroaryl and also formyl, carboxylate, alkyl and alkylamino among others. The

aryl or heteroaryl group of compound R^9-BL^1L^2 can also be fused to a second aryl or heteroaryl group. For the addition of compounds of formula R^9-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 **Ie** where R^2 is either aryl or heteroaryl can also be prepared by reaction of a compound of formula **Ie** where R^2 is either I or Br with an aryl or heteroaryl stannane compound of formula R^9-SnR_3 in the presence of a palladium catalyst. In compounds of formula R^9-SnR_3 the R group is a lower alkyl group such as butyl or methyl. The aryl or heteroaryl group of compound R^9-SnR_3 can be substituted by groups including aryl and heteroaryl and also formyl, carboxylate, acetal, alkyl and alkylamino among others. The aryl or heteroaryl group of compound R^9-SnR_3 can also be fused to a second aryl or heteroaryl group. For the addition of compounds of formula R^9-SnR_3 the preferred palladium catalyst is bis(triphenylphosphine)palladium (II) chloride in a solvent such as dioxane.

Compounds of formula **Ie** where R^2 is an alkyne group can also be prepared by the route shown in Scheme 13. Treatment of a compound of formula **Ie**, where R^2 is either Br or I 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 **Ie** where R^2 is a 2-(trimethylsilyl)ethynyl group. Reaction of compounds of formula **Ie** where R^2 is a 2-(trimethylsilyl)ethynyl group with aryliodines or heteroaryliodines 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 **Ie** where R^2 is a 2-(aryl)ethynyl or a 2-(heteroaryl)ethynyl group. In addition the 2-(trimethylsilyl)ethynyl group can be cleaved by treatment with potassium carbonate in methanol to provide compounds of formula **Ie** where R^2 is an ethynyl group.

Scheme 13


Cl
CN
LG
S
N
16: LG = Br or I
Oxidizing agent
O
29
LG = I or Br
R1XH
XR1
Ie
R2 = LG = Br or I
R9-H
Pd catalyst
R2 = R9 = alkyne or alkene
R9-BL1L2
R2 = R9 = aryl or heteroaryl
R9-SnR3
H—TMS
Aryl-I
or
Heteroaryl-I
R2 = TMS
K2CO3
MeOH
R2 = Aryl
Heteroaryl
R2 = H

Scheme 14 depicts the preparation of key sulfone intermediate 30. Oxidation of 16 with an excess of an oxidizing agent such as m-chloroperbenzoic acid, peracetic acid or an oxaziridine provides the sulfone derivative 30. If both the sulfoxide and sulfone are obtained in the reaction, they can be separated by standard laboratory techniques. Addition of a compound of formula R^1XH to compound 30, optionally 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 **If** of the invention where R^2 is Br or I.

Compounds of the invention of formula **If** where R^2 is an alkene, alkyne, heteroaryl or aryl group can be prepared as depicted in Scheme 14 from compounds of formula **If** where R^2 is either I or Br. Treatment of compounds of formula **If** where R^2 is either I or Br with an alkene or alkyne of formula R^9-H in the presence of a palladium catalyst provides compounds of formula **If** where R^2 is either an alkene or alkyne group. This alkene or alkyne group can be substituted by groups including aryl and heteroaryl and also alkyl and alkylamino among others.

For the addition of alkenes of formula R^9-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 alkynes of formula R^9-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.

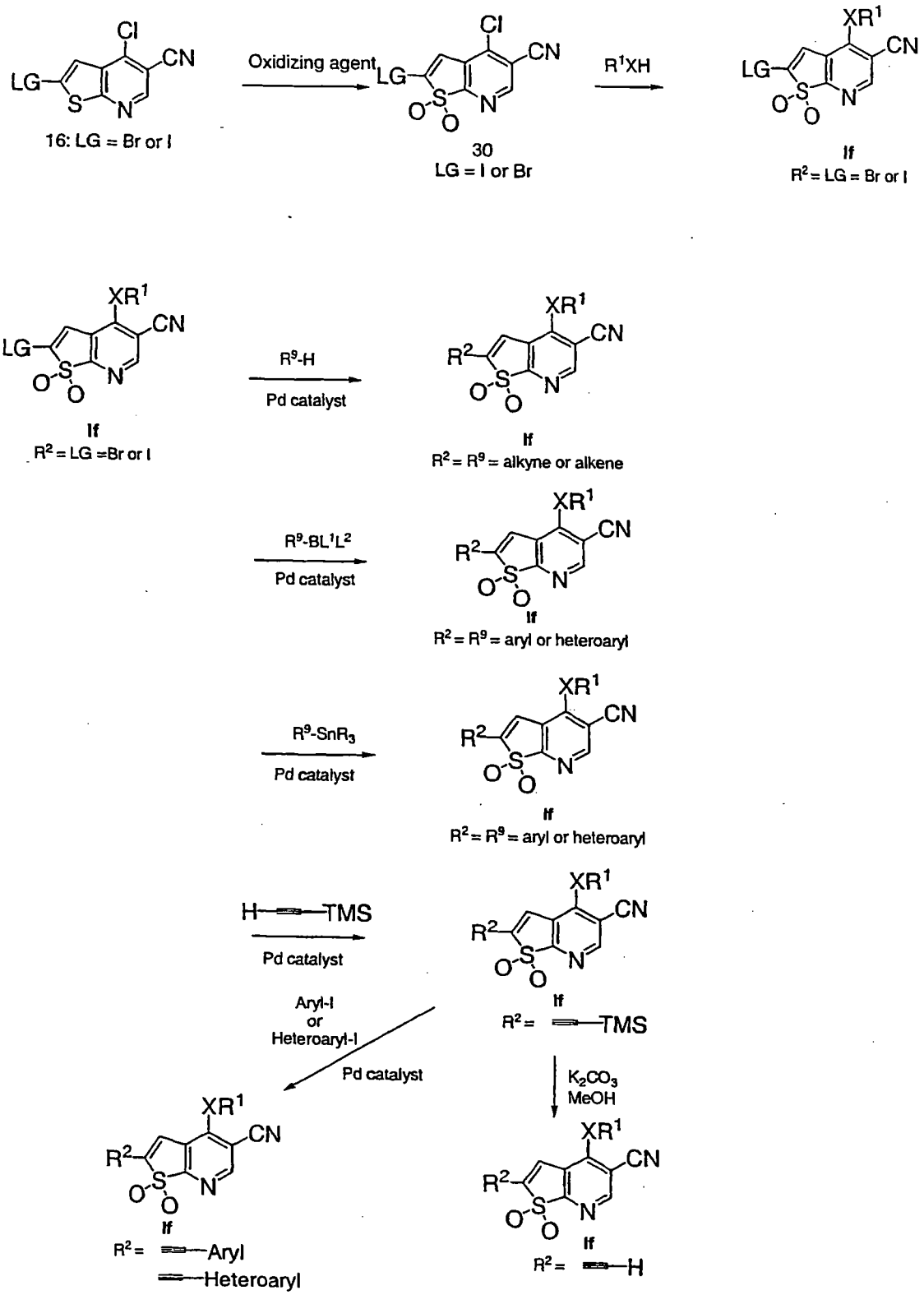
Treatment of compounds of formula **If** where R^2 is either I or Br with an aryl or heteroaryl organoboron compound of formula R^9-BL^1L^2 in the presence of a palladium catalyst provides compounds of formula **If** where R^2 is either an aryl or heteroaryl group. In compounds of formula R^9-BL^1L^2, the L^1L^2 groups represent ligands and include such groups as lower alkoxy or preferably hydroxy. The aryl or heteroaryl group of compound R^9-BL^1L^2 can be substituted by groups including aryl and heteroaryl and also formyl, carboxylate, alkyl and alkylamino among others. The aryl or heteroaryl group of compound R^9-BL^1L^2 can also be fused to a second aryl or

heteroaryl group. For the addition of compounds of formula R^9-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 **If** where R^2 is either aryl or heteroaryl can also be prepared by reaction of a compound of formula **If** where R^2 is either I or Br with an aryl or heteroaryl stannane compound of formula R^9-SnR_3 in the presence of a palladium catalyst. In compounds of formula R^9-SnR_3 the R group is a lower alkyl group such as butyl or methyl. The aryl or heteroaryl group of compound R^9-SnR_3 can be substituted by groups including aryl and heteroaryl and also formyl, carboxylate, acetal, alkyl and alkylamino among others. The aryl or heteroaryl group of compound R^9-SnR_3 can also be fused to a second aryl or heteroaryl group. For the addition of compounds of formula R^9-SnR_3 the preferred palladium catalyst is bis(triphenylphosphine)palladium (II) chloride in a solvent such as dioxane.

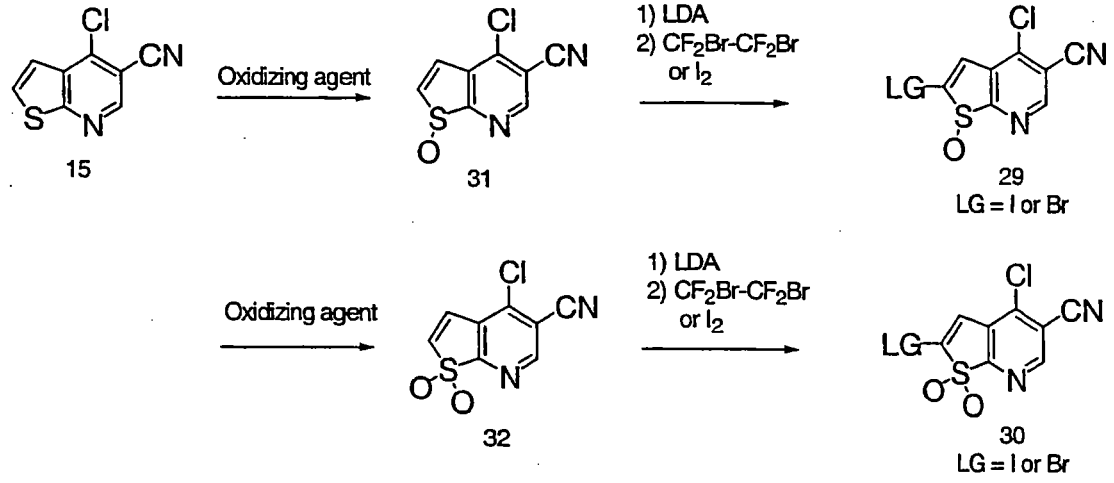
Compounds of formula **If** where R^2 is an alkyne group can also be prepared by the route shown in Scheme 14. Treatment of a compound of formula **If**, where R^2 is either Br or I with (trimethylsilyl)acetylene in the presence of a palladium catalyst, preferably tetrakis(triphenylphosphine)palladium(0), with a catalytic amount of copper(I) iodine in a solvent system such as triethylamine and benzene, provides compounds of formula **If** where R^2 is a 2-(trimethylsilyl)ethynyl group. Reaction of compounds of formula **If** where R^2 is a 2-(trimethylsilyl)ethynyl group with aryliodines or heteroaryliodines 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 **If** where R^2 is a 2-(aryl)ethynyl or a 2-(heteroaryl)ethynyl group. In addition the 2-(trimethylsilyl)ethynyl group can be cleaved by treatment with potassium carbonate in methanol to provide compounds of formula **If** where R^2 is an ethynyl group.

Scheme 14


16: LG = Br or I
Oxidizing agent
30
LG = I or Br
R1XH
If
R2 = LG = Br or I
R9-H
Pd catalyst
If
R2 = R9 = alkyne or alkene
R9-BL1L2
Pd catalyst
If
R2 = R9 = aryl or heteroaryl
R9-SnR3
Pd catalyst
If
R2 = R9 = aryl or heteroaryl
H—≡—TMS
Pd catalyst
If
R2 = ≡—TMS
Aryl-I
or
Heteroaryl-I
Pd catalyst
If
R2 = ≡—Aryl
≡—Heteroaryl
K2CO3
MeOH
If
R2 = ≡—H

Alternate routes for the preparation of the key intermediate 29 and 30 are shown in Scheme 15. Oxidation of 15 with an oxidizing agent provides the sulfoxide 31 or the sulfone 32. Excess amounts of oxidizing agent would be expected to provide the sulfone via an intermediate sulfoxide. Treatment of sulfoxide 31 with a base, preferentially lithium diisopropylamine (LDA), in an inert solvent such as tetrahydrofuran at reduced temperature, preferably –78°C, followed by the addition of 1,2-dibromo-1,1,2,2,-tetrafluoroethane provides 29 where LG = Br. Analogously, treatment of 31 with a base, preferentially lithium diisopropylamine (LDA), in an inert solvent such as tetrahydrofuran at reduced temperature, preferably –78°C, followed by the addition of iodine provides 29 where LG = I. In a similar fashion, treatment of sulfone 32 with a base, preferentially lithium diisopropylamine (LDA), in an inert solvent such as tetrahydrofuran at reduced temperature, preferably –78°C, followed by the addition of 1,2-dibromo-1,1,2,2,-tetrafluoroethane provides 30 where LG = Br. Analogously, treatment of 32 with a base, preferentially lithium diisopropylamine (LDA), in an inert solvent such as tetrahydrofuran at reduced temperature, preferably –78°C, followed by the addition of iodine provides 30 where LG = I.

Scheme 15



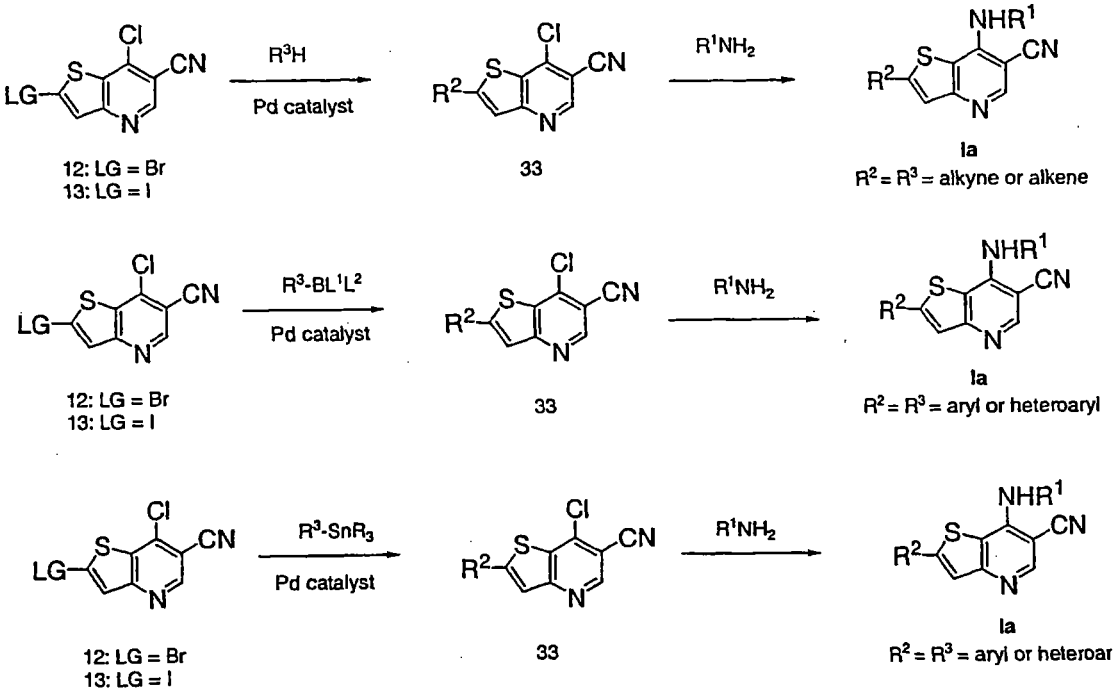
Additional compounds of the invention of formula **Ia** where R^2 is an alkenyl or alkynyl group can be prepared as depicted in Scheme 16. Treatment of intermediates 12 or 13 with an alkenyl or alkynyl reagent of formula R^3-H in the presence of a palladium catalyst provides intermediates of **33** where R^3 is either an alkenyl or alkynyl group. This alkenyl or alkynyl group can be substituted by groups including aryl and heteroaryl and also alkyl and alkyl amino among others. This aryl or heteroaryl 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 **33**, 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 **Ia.**

Treatment of intermediates of formula **12** or **13** with an aryl or heteroaryl organoboron compound of formula R^3-BL^1L^2 in the presence of a palladium catalyst provides intermediates of formula **33** where R^3 is either an aryl or heteroaryl 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 heteroaryl group of compound R^3-BL^1L^2 can be substituted by groups including aryl and heteroaryl and also formyl, carboxylate, alkyl and alkylamino among others. The aryl or heteroaryl group of compound R^3-BL^1L^2 can also be fused to a second aryl or heteroaryl 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 **33**, 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 **Ia.**

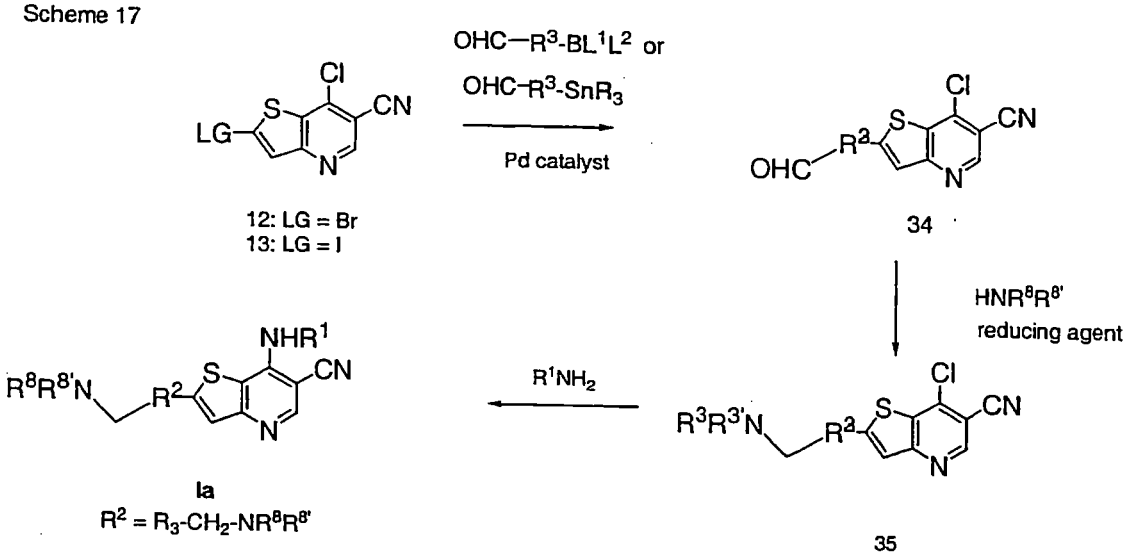
Compounds of formula **1a** where R^2 is either aryl or heteroaryl can also be prepared by reaction of intermediates of formula **12** or **13** with an aryl or heteroaryl stannane compound of formula R^3-SnR_3 in the presence of a palladium catalyst. In compounds of formula R^3-SnR_3 the R group is a lower alkyl group such as butyl or methyl. The aryl or heteroaryl group of compound R^3-SnR_3 can be substituted by groups including aryl and heteroaryl and also formyl, carboxylate, acetal, alkyl and alkylamino among others. The aryl or heteroaryl group of compound R^3-SnR_3 can also be fused to a second aryl or heteroaryl 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 **33**, 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 **Ia.**

Scheme 16



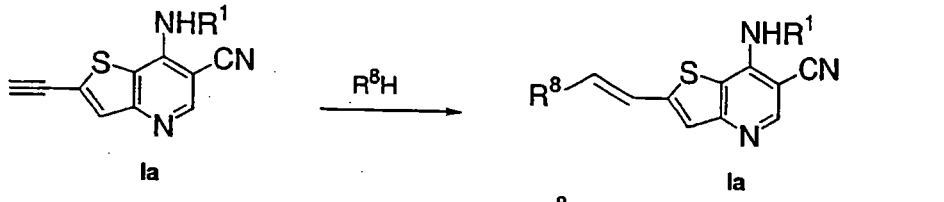
Some additional routes to the compounds of the invention of formula **Ia** are shown in Scheme 17. Intermediates of formula **34** can be converted to intermediates of formula **35** via reductive amination with an amine of formula $HNR^8R^{8'}$ and a reducing agent, preferably sodium triacetoxyborohydride, 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 **35**, 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 **Ia.**

Scheme 17



Additional compounds of the invention of formula **Ia** where R^2 is an alkenyl group can be prepared as depicted in Scheme 18 from reaction of compounds of formula **Ia** where R^2 is an alkynyl group with a heteroaryl compound containing an NH group in the ring. Such heteroaryl compounds include 1,2,3-triazole, imidazole, pyrrole and the like. The reaction is carrried out in the presence of cesium hydroxide in a solvent such as 1-methyl-2-pyrrolidinone.

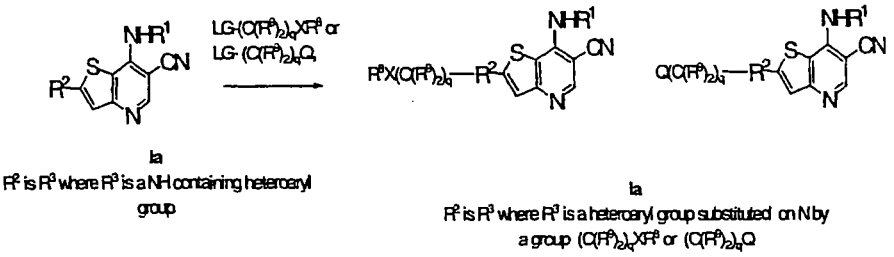
Scheme 18



Additional compounds of the invention of formula **Ia** where R^2 is a substituted heteroaryl group can be prepared as depicted in Scheme 19 from reaction of compounds of formula **Ia** where R^3 is heteroaryl group containing an NH group with a reagent of formula LG-$(C(R^9)_2)_q$-X-R^8 or LG-$(C(R^9)_2)_q$-Q, wherein LG is a leaving group such as Cl, Br, I, mesylate or tosylate. Such reagents include 4-(2-chloroethyl)morpholine, 2-chloroethanol, 2-(dimethylamino)ethyl chloride and the like.

The heteroaryl group containing an NH group includes pyrazole, pyrrole and the like. The reaction is carried out in the presence of a base such as cesium carbonate in a solvent such as dimethylformamide at a slightly elevated temperature such as 50°C.

Scheme 19



Ia
R^2 is R^3 where R^3 is a NH containing heteroaryl group

Ia
R^2 is R^3 where R^3 is a heteroaryl group substituted on N by a group $(C(R^8)_2)_qXR^8$ or $(C(R^8)_2)_qQ$

Reference Example 1

7-Oxo-4,7-dihydrothieno[3,2-b]pyridine-6-carbonitrile

A mixture of methyl 3-amino-2-thiophenecarboxylate (18.3 g, 116.5 mmol) and 80 mL of N,N-dimethylformamide dimethyl acetal is heated at reflux for 90 minutes. The reaction mixture is concentrated in vacuo resulting in a dark brown oil. This material is stirred with diethyl ether. Addition of hexane results in the formation of a small amount of brown solid, which is removed by filtration. Concentration of the filtrate provides 10.65 g of the intermediate amidine as a bright yellow oil.

To a solution of 40 mL of 2.5 M n-butyl lithium in tetrahydrofuran at –78°C is added acetonitrile (6.3 mL). After stirring for 10 min, a solution of the amidine in 100 mL of tetrahydrofuran is added dropwise over 40 minutes. The reaction mixture is stirred at -78°C for 2 hours, then 6.3 mL of acetic acid is added. The mixture is allowed to come to room temperature and stirring is continued overnight. The reaction mixture is concentrated in vacuo and the residue is partitioned between water and ethyl acetate. The organic layer is washed with water, dried over magnesium sulfate, filtered and concentrated in vacuo. The residue is heated at reflux in 60 mL of acetic acid for 3 hours then stirred at room temperature overnight. The reaction mixture is concentrated in vacuo and the crude product is purified by flash column chromatography eluting with a gradient of ethyl acetate to 10% methanol in ethyl acetate. A portion of the product is stirred with methanol and

filtered to provide 7-oxo-4,7-dihydrothieno[3,2-b]pyridine-6-carbonitrile as an orange solid, mp 265-275°C (dec.); ^{1}H NMR (DMSO-d_6) δ7.32 (d, J = 6 Hz, 1H), 8.16 (d, J = 6 Hz, 1H), 8.67 (s, 1H); MS 177.0 (M+H)+.

Analysis for $C_8H_4N_2OS$-0.10 H_2O:

Calcd: C, 53.98; H, 2.38; N, 15.74.

Found: C, 54.04; H, 2.38; N, 15.85.

Reference Example 2

7-Chlorothieno[3,2-b]pyridine-6-carbonitrile

A mixture of 7-oxo-4,7-dihydrothieno[3,2-b]pyridine-6-carbonitrile (3.00 g, 17.0 mmol) and 25 mL of phosphorous oxychloride is heated at reflux for 10 minutes. The reaction mixture is cooled to room temperature and the dark solids are removed by filtration. The filtrate is poured into hexane and allowed to stand at room temperature. The solvent is decanted off and the residual oil is dissolved in ethyl acetate and the solution is washed with water. The organic layer is dried over magnesium sulfate, filtered and passed through silica gel. The filtrate is concentrated in vacuo to give 770 mg of the desired product as a dark orange solid. A portion of this material is purified by flash column chromatography eluting with 1: 1 ethyl acetate : hexane to provide 7-chlorothieno[3,2-b]pyridine-6-carbonitrile as tan crystals, mp 110-111°C; ^{1}H NMR (DMSO-d_6) δ7.81 (d, J = 5 Hz, 1H), 8.59 (d, J = 5 Hz, 1H), 9.12 (s, 1H); MS 194.9 (M+H)+.

Analysis for $C_8H_3ClN_2S$:

Calcd: C, 49.37; H, 1.55; N, 14.39

Found: C, 49.57; H, 1.44; N, 14.48.

Alternate Preparation of Reference Example 2

7-Chlorothieno[3,2-b]pyridine-6-carbonitrile

To a solution of 7-chlorothieno[3,2-b]pyridine-6-carboxamide (10.8 g, 51 mmol) in 80.0 mL of N,N-dimethylformamide is added cyanuric chloride (5.72 g, 31 mmol). After 30 minutes the suspension is poured into ice water. The solid is filtered, washed with ice water and dried in vacuo to give 9.0 g of 7-chlorothieno[3,2-

b]pyridine-6-carbonitrile as an off white solid, mp 105-107°C; ^{1}H NMR (DMSO-d_6) δ7.83 (s, 1H), 8.61 (s, 1H), 9.12 (s, 1H); MS 195.0, 197.0 (M+H)+.

Analysis for $C_8H_3ClN_2S$:
Calcd: C, 49.37; H, 1.55; N, 14.39.

Reference Example 3

5-Phenyl-3-thienylamine

A mixture of methyl 3-amino-5-phenylthiophene-2-carboxylate (2.50 g, 10.7 mmol), 3.5 mL of N-methylpiperazine and 12 mL of N-methylpyrrolidinone is heated at 160°C for 4 hours. The reaction mixture is cooled to room temperature and poured into 100 mL of water. The solids are collected by filtration washing with 50 mL of water. Ethyl acetate and hexane are added and the filtrate is decanted off from the gummy black residue. The filtrate is concentrated to provide 850 mg of 5-phenyl-3-thienylamine as a yellow solid, mp 76-78°C; ^{1}H NMR (DMSO-d_6) δ4.87 (s, 2H), 5.98 (d, J = 1.5 Hz, 1H), 6.95 (d, J = 1.5 Hz, 1H), 7.28 (m, 1H), 7.37 (t, J = 7 Hz, 2H), 7.53 (d, J = 7 Hz, 2H); MS 176.2 (M+H)+.

Analysis for $C_8H_3ClN_2S$:

Calcd: C, 68.53; H, 5.18; N, 7.99

Found: C, 68.73; H, 4.79; N, 7.86.

Reference Example 4

Ethyl-2-cyano-3-[(5-phenyl-3-thienyl)amino]-2-propenoate

A mixture of 5-phenyl-3-thienylamine (1.00 g, 5.7 mmol) and ethyl (ethoxymethylene)cyanoacetate (950 mg, 5.7 mmol) in 20 mL of toluene is heated at reflux for 45 minutes. The reaction mixture is filtered while warm and the collected solid is washed with diethyl ether to provide 198 mg of ethyl 2-cyano-3-[(5-phenyl-3-thienyl)amino]-2-propenoate as white crystals, mp 190-193°C; MS 296.9 (M-H)-.

Analysis for $C_{16}H_{14}N_2O_2S$:

Calcd: C, 64.41; H, 4.73; N, 9.39

Found: C, 64.32; H, 4.67; N, 9.21.

Upon cooling an additional 705 mg of ethyl 2-cyano-3-[(5-phenyl-3-thienyl)amino]-2-propenoate is collected from the filtrate.

Reference Example 5

7-Oxo-2-phenyl-4,7-dihydrothieno[3,2-b]pyridine-6-carbonitrile

A mixture of ethyl 2-cyano-3-[(5-phenyl-3-thienyl)amino]-2-propenoate (696 mg, 2.33 mmol) in 15 mL of Dowtherm-A is heated at reflux for 3 hours. The reaction mixture is cooled to room temperature and the solids are collected by filtration washing with hexane to give 170 mg of a light brown solid. The solid is suspended in hot methanol and ethyl acetate and the mixture is filtered while warm to give 7-oxo-2-phenyl-4,7-dihydrothieno[3,2-b]pyridine-6-carbonitrile as a brown solid, mp >300°C; ^{1}H NMR (DMSO-d_6) δ7.43-7.55 (m, 3H), 7.63 (s, 1H), 7.83 (d, J = 7 Hz, 2H), 8.67 (s, 1H), 13.3 (s, 1H); MS 253.1 (M+H)+.
Analysis for $C_{14}H_8N_2OS - 0.1\ H_2O$:
Calcd: C, 66.17; H, 3.23; N, 11.02
Found: C, 66.14; H, 3.42; N, 11.00.

Reference Example 6

2-Bromo-7-chlorothieno[3,2-b]pyridine-6-carbonitrile

A mixture of ethyl 2-bromo-7-hydroxythieno[3,2-b]pyridine-6-carboxylate (1.3 g, 4.3 mmol) [Elliott, R.; O'Hanlon, P. J.; Rodgers, N. B. *Tetrahedron,* 43(14), 3295 (1987)] in 20 mL of ethanol and 6 mL of 2.5 N sodium hydroxide is heated at reflux for 4 hours. The mixture is poured into ice water and the pH is adjusted to 5-6 by the addition of acetic acid. The mixture is stirred at room temperature and the resulting precipitate is collected by filtration washing with water to provide 840 mg of 2-bromo-7-hydroxythieno[3,2-b]pyridine-6-carboxylic acid. A mixture of 2-bromo-7-hydroxythieno[2,3-b]pyridine-6-carboxylic acid (810 mg, 2.95 mmol) and N,N-

carbonyldiimidazole (1.0 g, 6.17 mmol) in 15 mL of *N,N'*-dimethylformamide is heated at 65°C for 2 hours. The mixture is poured into 50 mL of ice cold aqueous ammonium hydroxide and stirred for 14 hours. The resultant solids are collected by filtration washing with water to provide 800 mg of 2-bromo-7-hydroxythieno[3,2-b]pyridine-6-carboxamide. A mixture of 2-bromo-7-hydroxythieno[3,2-b]pyridine-6-carboxamide (273 mg, 1.0 mmol) and 3 mL of phosphorous oxychloride is heated at reflux for 1 hour. The solvent is removed in vacuo and the residue is poured into ice water and treated with sodium bicarbonate. The resultant solids are collected by filtration washing with water. The solids are purified by flash column chromatography eluting with chloroform to provide 240 mg of 2-bromo-7-chlorothieno[3,2-b]pyridine-6-carbonitrile as yellow crystals, mp 198-199°C; ^{1}H NMR (DMSO-d_6) δ8.12 (s, 1H), 9.11 (s, 1H); MS 273.1, 275.1, 277.1 (M+H)+

Analysis for $C_8H_2BrClN_2S$:

Calcd: C, 35.13; H, 0.74; N, 10.24

Found: C, 34.98; H, 0.80; N, 10.24.

Alternate Preparation of Reference Example 6

2-Bromo-7-chlorothieno[3,2-b]pyridine-6-carbonitrile

To a solution of 7-chlorothieno[3,2-b]pyridine-6-carbonitrile (200 mg, 1.03 mmol) in tetrahydrofuran (5.0 mL) is slowly added lithium diisopropylamine (0.7 mL, 1.40 mmol, 2M in tetrahydrofuran) at –78°C over 5 minutes. After 30 minutes, 1,2-dibromo-1,1,2,2,-tetrafluoroethane (0.16 mL, 1.3 mmol) is added slowly to the solution of the anion. The temperature is maintained at –78°C for 4 hours then warmed to room temperature for 1 hour. The reaction mixture is poured into ice water, extracted with dichloromethane, dried over sodium sulfate, and concentrated in vacuo to afford a dark solid residue. The residue is purified by flash column chromatography eluting with a gradient of 2% ethyl acetate in hexane to 8% ethyl acetate in hexane to provide 103 mg of 2-bromo-7-chlorothieno[3,2-b]pyridine-6-carbonitrile as an off white solid, mp 190-191°C; ^{1}H NMR (DMSO-d_6) δ8.13 (s, 1H), 9.12 (s, 1H); MS 272.8, 274.8, 276.9 (M+H)+.

Analysis for $C_8H_2BrClN_2S$-0.3 H_2O:

Calcd: C, 34.45; H, 0.94; N, 10.04

Found: C, 34.51; H, 1.01; N, 10.04.

Second Alternate Preparation of Reference Example 6

2-Bromo-7-chlorothieno[3,2-b]pyridine-6-carbonitrile

To a solution of 7-chlorothieno[3,2-b]pyridine-6-carbonitrile (200 mg, 1.03 mmol) in tetrahydrofuran (9.0 mL) at –78°C is slowly added lithium diisopropylamine (0.62 mL, 1.24 mmol, 2M in tetrahydrofuran) over 10 minutes. After 40 minutes, a solution of bromine (198 mg, 1.24 mmol) in 1.5 mL of tetrahydrofuran is added slowly to the solution of the anion. The temperature is maintained at –78°C for 5 hours then warmed to room temperature for 1 hour. The reaction mixture is poured into ice water, extracted with dichloromethane, washed with brine, dried over sodium sulfate, and concentrated in vacuo. The residue is purified by preparative thin layer chromatography developing with 90% dichloromethane in hexane to provide 48 mg of 2-bromo-7-chlorothieno[3,2-b]pyridine-6-carbonitrile as a pink solid, ^{1}H NMR (DMSO-d_6) δ8.13 (s, 1H), 9.12 (s, 1H); MS 272.8, 274.8, 276.8 (M+H)+.

Reference Example 7

7-Chlorothieno[3,2-b]pyridine-6-carboxylic acid

A mixture of ethyl 7-chlorothieno[3,2-b]pyridine-6-carboxylate (2.98 g, 12.3 mmol) [Thompson, M.; Forbes, I. F. EP 126970] in 40 mL of ethanol and 15 mL of 2.5 N sodium hydroxide is heated at reflux for 1 hour. The mixture is cooled to 0°C and the pH is adjusted to 4 by the addition of 4 N hydrochloric acid. The mixture is stirred at room temperature and the resulting precipitate is collected by filtration washing with water to provide 2.47 g of 7-chlorothieno[3,2-b]pyridine-6-carboxylic acid as a white solid, ^{1}H NMR (DMSO-d_6) δ7.73 (d, J = 6 Hz, 1H), 8.44 (d, J = 6 Hz, 1H), 9.07 (s, 1H).

Reference Example 8

7-Chlorothieno[3,2-b]pyridine-6-carboxamide

A mixture of 7-chlorothieno[3,2-b]pyridine-6-carboxylic acid (13.8 g, 65 mmol) and thionyl chloride (234 mL) is heated at reflux for 2 hours. After cooling the excess thionyl chloride is removed by rotary evaporation. The residue is suspended in acetone (350 mL) and the resulting suspension cooled in an ice-bath. Aqueous ammonia (S.G. 0.880, 62 mL) is added gradually, keeping the temperature below 10° C. After concentration of the mixture, the resulting suspension is filtered off, washed with water and air-dried to give 10.9 g of 7-chlorothieno[3,2-b]pyridine-6-carboxamide as a beige solid, mp 180-182°C; ^{1}H NMR (DMSO-d_6) δ7.71 (s, 1H), 7.89 (s, 1H), 8.14 (s, 1H), 8.35 (s, 1H), 8.73 (s, 1H); MS 213.0, 215.0 (M+H)+.

Analysis for $C_8H_5ClN_2OS$:
Calcd: C, 45.18; H, 2.37; N, 13.17.
Found: C, 45.38; H, 2.26; N, 13.11.
Found: C, 49.32; H, 1.50; N, 14.41.

Reference Example 9

7-Chloro-2-iodothieno[3,2-b]pyridine-6-carbonitrile

To a solution of 7-chlorothieno[3,2-b]pyridine-6-carbonitrile (735 mg, 3.78 mmol) in 20 mL of tetrahydrofuran at -78°C is added dropwise 2.0 M lithium diisopropylamide in heptane/tetrahydrofuran/ethylbenzene (2.2 mL, 4.40 mmol). After stirring for 20 minutes, a solution of iodine (1.15 g, 4.53 mmol) in 4 mL of tetrahydrofuran is added dropwise over 20 minutes. The reaction mixture is stirred at -78°C for 5 hours, then 20 mL of chloroform and 10 mL of water are added. The mixture is stirred at room temperature overnight, then partitioned between water and chloroform. The organic layer is washed with a solution of sodium thiosulfate, followed by water, then dried over magnesium sulfate, filtered and concentrated in vacuo. The residue is purified by flash column chromatography eluting with 5% methanol in dichloromethane to provide 750 mg of 6-chloro-2-iodothieno[3,2-

b]pyridine-7-carbonitrile as yellow crystals, mp 209-211°C; ^{1}H NMR (DMSO-d_6) δ8.17 (s, 1H), 9.05 (s, 1H).

Analysis for $C_8H_2ClIN_2S$:

Calcd: C, 29.98; H, 0.63; N, 8.74

Found: C, 29.61; H, 0.87; N, 8.68.

Reference Example 10

4-Chloro-2-iodothieno[2,3-b]pyridine-5-carbonitrile

To a solution of 4-chlorothieno[2,3-b]pyridine-5-carbonitrile (1.2 g, 6.16 mmol) [Khan, M. A.; Guarconi, A. E., *J. Heterocyclic Chem.*, 14, 807 (1977)] in 72 mL of tetrahydrofuran at -78°C is added dropwise 2.0 M lithium diisopropylamide in heptane/tetrahydrofuran/ethylbenzene (3.7 mL, 7.40 mmol). After stirring for 35 minutes, a solution of iodine (1.9 g, 7.40 mmol) in 8 mL of tetrahydrofuran is added dropwise over 20 minutes. The reaction mixture is stirred at -78°C for 4 hours, then 85 mL of dichloromethane and 20 mL of water are added. The mixture is allowed to warm to room temperature. The reaction mixture is partitioned between water and dichloromethane. The organic layer is washed with a solution of sodium thiosulfate, dried over magnesium sulfate, filtered and concentrated in vacuo. The residue is purified by flash column chromatography eluting with dichloromethane to provide 1.0 g of 4-chloro-2-iodothieno[2,3-b]pyridine-5-carbonitrile as colorless crystals, mp 181-182°C; ^{1}H NMR (DMSO-d_6) δ 8.00 (s, 1H), 8.88 (s, 1H); MS 320.8 (M+H)+.

Analysis for $C_8H_2ClIN_2S$:

Calcd: C, 29.98; H, 0.63; N, 8.74

Found: C, 30.12; H, 0.83; N, 8.35.

Reference Example 11

4-Chlorothieno[2,3-b]pyridine-5-carboxylic acid

A mixture of ethyl 4-chlorothieno[2,3-b]pyridine-5-carboxylate (800 mg, 3.31 mmol) [Khan, M. A.; Guarconi, A. E., *J. Heterocyclic Chem.*, 14, 807 (1977)] in 15 mL of ethanol and 5 mL of 2.5 N sodium hydroxide is heated at reflux for 90 minutes. The mixture is cooled to 0°C and the pH is adjusted to 4 by the addition of 2 N

hydrochloric acid. The mixture is stirred at room temperature and the resulting precipitate is collected by filtration and washed with water to provide 250 mg of 4-chlorothieno[2,3-b]pyridine-5-carboxylic acid as a white solid, mp 172-174°C; ^{1}H NMR (DMSO-d_6) δ7.62 (d, J = 6 Hz, 1H), 8.14 (d, J = 6 Hz, 1H), 8.94 (s, 1H); MS 212.0 (M-H)-.

Analysis for $C_8H_4ClNO_2S$:

Calcd: C, 44.98; H, 1.89; N, 6.56

Found: C, 44.99; H, 2.14; N, 6.43.

An additional 230 mg of 4-chlorothieno[2,3-b]pyridine-5-carboxylic acid is obtained from the filtrate.

Reference Example 12

4-Chlorothieno[2,3-b]pyridine-5-carboxamide

A mixture of 4-chlorothieno[2,3-b]pyridine-5-carboxylic acid (250 mg, 1.16 mmol) and 5 mL of thionyl chloride is heated at reflux for 2 hours. The mixture is concentrated in vacuo and dried. Acetone is added to the residue and the solution is cooled to 0°C. Aqueous ammonium hydroxide (15 mL) is slowly added and the reaction mixture is stirred at 0°C for 2 hours. The reaction mixture is concentrated in vacuo and water is added to the residue. The resultant solids are collected by filtration washing with water to provide 175 mg of 4-chlorothieno[2,3-b]pyridine-5-carboxamide as a white solid, mp 159-160°C; ^{1}H NMR (DMSO-d_6) δ7.57 (d, J = 6 Hz, 1H), 7.84 (s, 1H), 8.11 (s, 1H), 8.12 (d, J = 6 Hz, 1H), 8.61 (s, 1H);

MS 213.0, 214.9 (M+H)+.

Analysis for $C_8H_5ClN_2OS$:

Calcd: C, 45.18; H, 2,37; N, 13.17

Found: C, 44.88; H, 2.35; N, 12.77.

Reference Example 13

4-Chlorothieno[2,3-b]pyridine-5-carbonitrile

A mixture of 4-chlorothieno[2,3-b]pyridine-5-carboxamide (145 mg, 0.68 mmol) and cyanuric chloride (200 mg, 1.08 mmol) in 5 mL of N,N-dimethylformamide is stirred at room temperature for 30 minutes. Ice is added to the reaction mixture and the resultant solids are collected by filtration washing with water to provide 84 mg of 4-chlorothieno[2,3-b]pyridine-5-carbonitrile as a white solid, mp 100-103°C; ^{1}H NMR (DMSO-d_6) δ7.66 (d, J = 6 Hz, 1H), 8.26 (d, J = 6 Hz, 1H), 9.03 (s, 1H); MS 195.0 (M+H)+.

Analysis for $C_8H_3ClN_2S$ - 0.4 H_2O:

Calcd: C, 47.60; H, 1.90; N, 13.88

Found: C, 47.65; H, 1.55; N, 13.90.

Reference Example 14

4-Chloro-2-methylthieno[2,3-b]pyridine-5-carbonitrile

To a solution of 4-chlorothieno[2,3-b]pyridine-5-carbonitrile (0.3 g, 1.54 mmol) in 15 mL of tetrahydrofuran at –78°C is added dropwise 2.0 M lithium diisopropylamide in heptane/tetrahydrofuran/ethylbenzene (0.93 mL, 1.85 mmol). After stirring for 45 min, a solution of iodomethane (0.115 mL, 1.85 mmol) in 1 mL of tetrahydrofuran is added dropwise. The reaction mixture is stirred at -78°C for 4 hours, then dichloromethane and water are added. The mixture is allowed to warm to room temperature, then partitioned between water and dichloromethane. The organic layer is washed with a solution of sodium thiosulfate, dried over magnesium sulfate, filtered and concentrated in vacuo. The residue is purified by flash column chromatography eluting with 1: 9 ethyl acetate : hexane to provide 0.1 g of 4-chloro-2-methylthieno[2,3-b]pyridine-5-carbonitrile as colorless crystals, mp 101-102°C; ^{1}H NMR (DMSO-d_6) δ 2.68 (s, 3H), 7.39 (s, 1H), 8.92 (s, 1H); MS 209.0 (M+H)+.

Analysis for $C_9H_5ClN_2S$:

Calcd: C, 51.80; H, 2.42; N, 13.42

Found: C, 52.11; H, 2.14; N, 13.08.

Reference Example 15

7-Chloro-2-methylthieno[3,2-b]pyridine-6-carbonitrile

To a solution of 7-chlorothieno[3,2-b]pyridine-6-carbonitrile (500 mg, 2.57 mmol) in 15 mL of tetrahydrofuran at -78°C is added dropwise 2.0 M lithium diisopropylamide in heptane/tetrahydrofuran/ethylbenzene (1.6 mL, 3.21 mmol). After stirring for 40 minutes, iodomethane (616 mg, 0.27 mL, 4.34 mmol) is added dropwise over 7 minutes. The reaction mixture is stirred at -78°C for 5 hours, then the mixture is partitioned between 20 mL of dichloromethane and 10 mL of water. The organic layer is washed with a saturated aqueous ammonium chloride solution, followed by saturated aqueous sodium chloride, then dried over sodium sulfate, filtered and concentrated in vacuo. The residue is purified by flash column chromatography eluting with a gradient of 5% ethyl acetate in hexane to 20% ethyl acetate in hexane to provide 274 mg of 7-chloro-2-methylthieno[3,2-b]pyridine-6-carbonitrile as a white solid, mp 163-164°C; ^{1}H NMR (DMSO-d_6) δ2.73 (s, 3H), 7.55 (s, 1H), 9.03 (s, 1H); MS 209.0, 211.1 (M+H)+.

Analysis for $C_9H_5ClN_2S$:

Calcd: C, 51.80; H, 2.42; N, 13.42

Found: C, 51.56; H, 2.25; N, 13.43.

Reference Example 16

4-Thiophen-2-yl-butyric acid methyl ester

A mixture of 4-(2-thienyl)butyric acid (4.25 g, 25.0 mmol) and 3 mL of concentrated sulfuric acid in 25 mL of methanol is heated at reflux for 2 hours. The reaction mixture is cooled to room temperature and partitioned between ethyl acetate and saturated aqueous sodium carbonate solution. The organic layer is separated and passed through a short pad of silica gel. The filtrate is concentrated and purified by flash column chromatography eluting with 1: 5 ethyl acetate : hexane to provide 4.02 g of 4-thiophen-2-yl-butyric acid methyl ester as a yellow oil, ^{1}H NMR (DMSO-d_6) δ1.85 (quintet, J = 7 Hz, 2H), 2.35 (t, J = 7 Hz, 2H), 2.81 (t, J = 7 Hz, 2H), 3.59 (s, 3H), 6.84 (m, 1H), 6.95 (m, 1H), 7.32 (dd, J = 5, 1 Hz, 1H); MS 185.0 (M+H)+

Analysis for $C_9H_{12}O_2S$:
Calcd: C, 58.67; H, 6.56; N, 0.00
Found: C, 58.87; H, 6.57; N, 0.02.

Reference Example 17

4-(5-Nitro-thiophen-2-yl)-butyric acid methyl ester

To 8 mL of acetic anhydride at -20°C is added 1.2 mL of nitric acid (d = 1.5). The mixture is kept at -20°C, and a solution of 4-thiophen-2-yl-butyric acid methyl ester (1.84 g, 10.0 mmol) in 12 mL of acetic anhydride is added dropwise. The reaction mixture is stirred for 10 minutes after completion of addition, and poured into an ice-water mixture. The product is extracted with ethyl acetate and the organic layer is washed with 10 N aqueous sodium hydroxide solution, dried and concentrated. The residue is purified by flash column chromatography eluting with 1: 4 ethyl acetate : hexane to provide 1.32 g of 4-(5-nitro-thiophen-2-yl)-butyric acid methyl ester as a yellow oil; ^{1}H NMR (DMSO-d_6) δ1.93 (quintet, J = 7 Hz, 2H), 2.41 (t, J = 7 Hz, 2H), 2.88 (t, J = 7 Hz, 2H), 3.59 (s, 3H), 7.04 (d, J = 5 Hz, 1H), 8.01 (d, J = 5 Hz, 1H); MS 229.0 (M)+
Analysis for $C_9H_{11}NO_4S$:
Calcd: C, 47.15; H, 4.84; N, 6.11
Found: C, 47.17; H, 4.91; N, 6.36.

Reference Example 18

4-(5-Amino-thiophen-2-yl)-butyric acid methyl ester

A mixture of 4-(5-nitro-thiophen-2-yl)-butyric acid methyl ester (2.29 g, 10.0 mmol) and palladium hydroxide (500 mg, 20% on carbon) in 30 mL of ethyl acetate and 30 mL of methanol is hydrogenated at 50 psi for 48 hours. The reaction mixture is filtered and concentrated. The residue is purified by flash column chromatography eluting with 1: 3 ethyl acetate: hexane to provide 1.32 g of 4-(5-amino-thiophen-2-yl)-butyric acid methyl ester as a dark oil; ^{1}H NMR (DMSO-d_6) δ1.74 (m, 2H), 2.38 (m, 2H), 2.54 (m, 2H), 3.59 (s, 3H), 5.66 (d, J = 3 Hz, 1H), 6.24 (d, J = 3 Hz, 1H); MS 200.2 (M+H)+.

Reference Example 19

4-(4-Chloro-5-cyano-thieno[2,3-b]pyridin-2-yl)-butyric acid methyl ester

A mixture of 4-(5-amino-thiophen-2-yl)-butyric acid methyl ester (1.00 g, 5.0 mmol) and ethyl (ethoxymethylene)cyanoacetate (930 mg, 5.5 mmol) in 50 mL of toluene is heated at reflux for 1 hour. The reaction mixture is concentrated and 50 mL of Dowtherm-A is added. The mixture is heated at reflux for 3 hours and cooled to room temperature. The crude reaction mixture is passed through a short pad of silica gel, eluting with dichloromethane followed by 10% methanol in dichloromethane. The crude product is further purified by flash column chromatography eluting with 10% methanol in dichloromethane followed by another flash column chromatography eluting with 10% methanol in ethyl acetate to provide 136 mg of methyl 4-(5-cyano-4-oxo-4,7-dihydrothieno[2,3-b]pyridin-2-yl)butanoate as a tan solid.

A mixture of methyl 4-(5-cyano-4-oxo-4,7-dihydrothieno[2,3-b]pyridin-2-yl)butanoate (136 mg) and 2 drops of N,N-dimethylformamide in 5 mL of phosphorous oxychloride is heated at reflux for 10 minutes and concentrated. To the residue is added dichloromethane and the solution is washed with 1% aqueous sodium bicarbonate solution. The organic layer is dried and concentrated. The residue is purified by flash column chromatography eluting with dichloromethane to provide 126 mg of 4-(4-chloro-5-cyano-thieno[2,3-b]pyridin-2-yl)-butyric acid methyl ester as a tan solid, mp 55-57°C; ^{1}H NMR (DMSO-d_6) δ1.98 (quintet, J = 7 Hz, 2H), 2.42 (t, J = 7 Hz, 2H), 3.04 (t, J = 7 Hz, 2H), 3.59 (s, 3H), 7.42 (s, 1H), 8.94 (s, 1H); MS 295.1 (M+H)+

Analysis for $C_{13}H_{11}ClN_2O_2S$:

Calcd: C, 52.97; H, 3.76; N, 9.50

Found: C, 52.80; H, 3.90; N, 9.25.

Reference Example 20

7-Chloro-2-formylthieno[3,2-b]pyridine-6-carbonitrile

To a solution of 7-chlorothieno[3,2-b]pyridine-6-carbonitrile (200 mg, 1.03 mmol) in 6 mL of tetrahydrofuran at -78°C is added dropwise 2.0 M lithium diisopropylamide in heptane/tetrahydrofuran/ethylbenzene (0.645 mL, 1.29 mmol). After stirring for 40 minutes, N,N-dimethylformamide (99 mg, 1.35 mmol) is added dropwise over 5 minutes. The reaction mixture is stirred at -78°C for 4 hours, then dichloromethane is added and the reaction mixture is allowed to warm to room temperature. Water is added and the organic phase is separated and the aqueous phase is extracted with dichloromethane. The organic phases are combined and washed with saturated aqueous sodium chloride, dried over sodium sulfate, filtered and concentrated in vacuo. The residue is purified by preparative thin layer chromatography developing with 30% ethyl acetate in hexane to provide 62 mg of 7-chloro-2-formylthieno[3,2-b]pyridine-6-carbonitrile as a white solid, mp 188-189°C; ^{1}H NMR (DMSO-d_6) δ 8.72 (s, 1H), 9.26 (s, 1H), 10.28 (s, 1H); MS 221.9, 223.9 (M-H)-

Analysis for $C_9H_3ClN_2OS$:

Calcd: C, 48.55; H, 1.36; N, 12.58

Found: C, 48.69; H, 1.48; N, 12.30.

Reference Example 21

tert-Butyl (2E)-3-(7-chloro-6-cyanothieno[3,2-b]pyridin-2-yl)prop-2-enoate

To a solution of 7-chlorothieno[3,2-b]pyridine-6-carbonitrile (100 mg, 0.45 mmol) in 5 mL of dichloromethane is added, in portions, (tert-butoxycarbonylmethylene)triphenylphosphorane (0.645 mL, 1.29 mmol). After stirring for 2.5 hours, the reaction mixture is allowed to stand at room temperature overnight. The mixture is concentrated to ½ its volume and is purified by flash column chromatography eluting with dichloromethane to provide 126 mg of *tert*-butyl (2E)-3-(7-chloro-6-cyanothieno[3,2-b]pyridin-2-yl)prop-2-enoate as a white solid, mp 193-

194°C; ^{1}H NMR ($CDCl_3$) δ 1.55 (s, 9H), 6.46 (d, J = 16 Hz, 1H), 7.26 (s, 1H), 7.70 (s, 1H), 7.77 (d, J = 16 Hz, 1H), 8.84 (s, 1H); MS 321.1, 323.2 (M+H)+

Analysis for $C_{15}H_{13}ClN_2O_2S$:

Calcd: C, 56.16; H, 4.08; N, 8.73

Found: C, 55.76; H, 3.76; N, 8.50.

Reference Example 22

7-Chloro-2-[4-(dimethylamino)phenyl]thieno[3,2-b]pyridine-6-carbonitrile

A mixture of 7-chloro-2-iodothieno[3,2-b]pyridine-6-carbonitrile (321 mg, 1.0 mmol), 4-(dimethylamino)phenylboronic acid (248 mg, 1.5 mmol) and 58 mgs of tetrakis(triphenylphosphine)palladium (0) in 13 mL of ethylene glycol dimethyl ether and 11 mL of aqueous saturated sodium bicarbonate is heated at reflux for 6 hours. 4-(dimethylamino)phenylboronic acid (105 mg) and tetrakis(triphenylphosphine)palladium (0) (29 mg) are added and the reaction mixture is heated at reflux for 6 hours. The mixture is treated with water and extracted into dichloromethane and the organic phase is washed with brine and dried over sodium sulfate, filtered and concentrated in vacuo. The residue is purified by flash column chromatography eluting with a gradient of dichloromethane to 2% ethyl acetate in dichloromethane to provide 187 mg (60%) of 7-chloro-2-[4-(dimethylamino)phenyl]thieno[3,2-b]pyridine-6-carbonitrile as an orange solid, mp 270-272°C; ^{1}H NMR ($CDCl_3$) δ 3.07 (s, 6H), 6.73 (d, J = 5 Hz, 2H), 7.58 (s, 1H), 7.63 (d, J = 5 Hz, 2H), 8.74 (s, 1H); HRMS found: 314.05127.

Reference Example 23

7-Chloro-2-(4-formylphenyl)thieno[3,2-b]pyridine-6-carbonitrile

A mixture of 7-chloro-2-iodo-thieno[3,2-b]pyridine-6-carbonitrile (1.00 g, 3.12 mmol), 4-formylphenylboronic acid (936 mg, 6.24 mmol) and 108 mgs of tetrakis(triphenylphosphine)palladium (0) in 30 mL of ethylene glycol dimethyl ether and 25 mL of aqueous saturated sodium bicarbonate is heated at reflux for 4 hours. The mixture is cooled and the precipitate is collected by filtration washing with ethyl acetate and diethyl ether to provide 818 mg of 7-chloro-2-(4-formylphenyl)thieno[3,2-

b]pyridine-6-carbonitrile as a yellow solid, mp 300-305°C; ^{1}H NMR ($CDCl_3$) δ 7.93 (d, J = 8 Hz, 2H), 7.96 (s, 1H), 8.03 (d, J = 8 Hz, 2H), 8.87 (s, 1H), 10.1 (s, 1H), MS 298.0, 300.0 (M-H)-H.

Reference Example 24

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

A mixture of 7-chloro-2-(4-formylphenyl)thieno[3,2-b]pyridine-6-carbonitrile (700 mg, 2.34 mmol) and 6.0 mL of 2.0 M dimethylamine in tetrahydrofuran in 30 mL of dichloromethane and 5 mL of dimethylformamide is cooled to 0-5°C. Sodium triacetoxyborohydride (2.5 g, 11.7 mmol) is added in portions and after 5 minutes 0.10 mL of acetic acid is added. The mixture is stirred at room temperature for 2 hours then quenched by the addition of ice water and partitioned between dichloromethane and saturated aqueous sodium bicarbonate. The organic phase is dried over sodium sulfate, filtered and concentrated in vacuo. The residue is purified by flash column chromatography eluting with a gradient of dichloromethane to 10% methanol in dichloromethane to provide 496 mg (65%) of 7-chloro-2-{4-[(dimethylamino)methyl]phenyl}thieno[3,2-b]pyridine-6-carbonitrile as a yellow solid, mp 166-168°C; ^{1}H NMR (DMSO-d_6) δ 2.21 (s, 6H), 3.52 (s, 2H), 7.48 (d, J = 8 Hz, 2H), 7.95 (d, J = 8 Hz, 2H), 8.28 (s, 1H), 9.11 (s, 1H); MS 328.1, 330.1(M+H)+; HRMS found: 328.06622

Analysis for $C_{17}H_{14}ClN_3S$-0.3 H_2O:

Calcd: C, 61.27; H, 4.42; N, 12.61

Found: C, 61.22; H, 4.13; N, 12.50.

Example 1

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

A mixture of 2,4-dichloro-5-methoxyaniline (336 mg, 1.75 mmol) and 60% sodium hydride (70 mg, 1.75 mmol) in 10 mL of tetrahydrofuran is heated at reflux for 30 minutes. The solution is cooled and 7-chlorothieno[3,2-b]pyridine-6-carbonitrile (200 mg, 1.02 mmol) is added. The reaction mixture is heated at reflux for 3.5 hours then allowed to stir at room temperature overnight. The resultant black solution is partitioned between ethyl acetate and water. The organic layer is washed with water, dried over magnesium sulfate, filtered and concentrated in vacuo. The residue is purified by flash column chromatography eluting with 1: 1 ethyl acetate:hexane. The fractions containing product are combined and concentrated. Diethyl ether is added and the insoluble material collected by filtration to provide 131 mg of 7-[(2,4-dichloro-5-methoxyphenyl)amino]thieno[3,2-b]pyridine-6-carbonitrile as a tan solid, mp 216-220°C; ^{1}H NMR (DMSO-d_6) δ3.85 (s, 3H), 7.40 (3, 1H), 7.46 (d, J = 5 Hz, 1H), 7.76 (s, 1H), 8.11 (d, J = 5 Hz, 1H), 8.61 (s, 1H), 9.71 (s, 1H); MS 350.2 (M+H)+.

Analysis for $C_{15}H_9Cl_2N_3OS$ - 0.25 H_2O:

Calcd: C, 50.79; H, 2.70; N, 11.85.

Found: C, 50.79; H, 2.48; N, 11.56.

Example 2

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

A mixture of 7-oxo-2-phenyl-4,7-dihydrothieno[3,2-b]pyridine-6-carbonitrile (878 mg, 3.48 mmol) and 10 mL of phosphorous oxychloride is heated at reflux for 1 hour. The reaction mixture is cooled to room temperature and hexane is added. The solids are collected by filtration and stirred with saturated aqueous sodium bicarbonate. The solids are collected by filtration washing with water, ethyl acetate and methanol to provide 751 mg of 7-chloro-2-phenylthieno[3,2-b]pyridine-6-carbonitrile that is not purified.

A mixture of 2,4-dichloro-5-methoxyaniline (336 mg, 1.75 mmol) and 60% sodium hydride (69 mg, 1.73 mmol) in 10 mL of tetrahydrofuran is heated at reflux for 40 minutes. The solution is cooled and 7-chloro-2-phenylthieno[3,2-b]pyridine-6-carbonitrile (270 mg, 1.0 mmol) is added. The reaction mixture is heated at reflux for 5.5 hours then allowed to stir at room temperature overnight. The resultant black

solution is partitioned between ethyl acetate and water. The aqueous layer is acidified with 1 N hydrochloric acid and extracted with ethyl acetate. The organic layer is dried over magnesium sulfate, filtered and concentrated in vacuo. The residue is treated with ethyl acetate and hexane and the insoluble material is collected by filtration. The solid is suspended in hot methanol and ethyl acetate and the mixture is filtered while warm to provide 50 mg of 7-[(2,4-dichloro-5-methoxyphenyl)amino]-2-phenylthieno[3,2-b]pyridine-6-carbonitrile as a light brown solid, mp 274-276°C; ^{1}H NMR (DMSO-d_6) δ3.86 (s, 3H), 7.40 (s, 1H), 7.44-7.53 (m, 3H), 7.73 (d, J = 7 Hz, 2H), 7.78 (s, 1H), 7.94 (s, 1H), 8.63 (s, 1H), 9.78 (s, 1H); MS 426.1 (M+H)+.

Analysis for $C_{21}H_{13}Cl_2N_3OS$ - 0.25 H_2O:

Calcd: C, 58.54; H, 3.16; N, 9.75.

Found: C, 58.50; H, 3.07; N, 9.49.

Example 3

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

A mixture of 2,4-dichloro-5-methoxyaniline (221.8 mg, 1.16 mmol) and 60% sodium hydride (46.2 mg, 1.16 mmol) in 6 mL of tetrahydrofuran is heated at reflux for 1 hour. The solution is cooled and 2-bromo-7-chlorothieno[3,2-b]pyridine-6-carbonitrile (150 mg, 0.55 mmol) is added. The resulting reaction mixture is heated at reflux for 5 hours, cooled to room temperature, and then partitioned between dichloromethane and water. The organic layer is washed with saturated aqueous sodium chloride, dried over sodium sulfate, filtered and concentrated in vacuo. The residue is purified by preparative thin layer chromatography developing with 40 % ethyl acetate in hexane to provide 114.6 mg of 2-bromo-7-[(2,4-dichloro-5-methoxyphenyl)amino]-thieno[3,2-b]pyridine-6-carbonitrile as a white solid, mp 228-229°C; ^{1}H NMR (DMSO-d_6) δ3.86 (s, 3H), 7.40 (s, 1H), 7.71 (s, 1H), 7.80 (s, 1H), 8.61 (s, 1H), 9.80 (s, 1H); MS 426.0, 428.0 (M-H)-.

Analysis for $C_{15}H_8BrCl_2N_3OS$:

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

Found: C, 42.08; H, 2.09; N, 9.62.

Example 4

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

A mixture of 2,4-dichloro-5-methoxyaniline (380 mg, 2.0 mmol) and 60% sodium hydride (80 mg, 2.0 mmol) in 20 mL of tetrahydrofuran is heated at reflux for 1 hour. The solution is cooled and 7-chloro-2-iodothieno[3,2-b]pyridine-6-carbonitrile (320 mg, 1.0 mmol) is added and the reaction mixture is heated at reflux overnight. The reaction mixture is cooled to room temperature and partitioned between ethyl acetate and water. The organic layer is washed with water, dried over magnesium sulfate, filtered and concentrated in vacuo. The residue is purified by flash column chromatography eluting with 2% methanol in chloroform to provide 240 mg of 7-[(2,4-dichloro-5-methoxyphenyl)amino]-2-iodothieno[3,2-b]pyridine-6-carbonitrile as yellow crystals, mp 233-234°C; ^{1}H NMR (DMSO-d_6) δ3.85 (s, 3H), 7.38 (s, 1H), 7.77 (s, 1H), 7.79 (s, 1H), 8.56 (s, 1H), 9.74 (s, 1H); MS 475.9 (M+H)+.

Analysis for $C_{15}H_8Cl_2N_3OS$:

Calcd: C, 37.84; H, 1.69; N, 8.83.

Found: C, 37.44; H, 1.75; N, 8.80.

Example 5

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

A mixture of 2,4-dichloro-5-methoxyaniline (300 mg, 1.57 mmol) and 60% sodium hydride (70 mg, 1.75 mmol) in 10 mL of tetrahydrofuran is heated at reflux for 30 minutes The solution is cooled and 4-chlorothieno[2,3-b]pyridine-5-carbonitrile (150 mg, 0.8 mmol) [Khan, M. A.; Guarconi, A. E., *J. Heterocyclic Chem.,* 14, 807 (1977)] is added. The reaction mixture is heated at reflux for 3.5 hours. The resultant black solution is partitioned between ethyl acetate and water. The organic layer is washed with water, dried over magnesium sulfate, filtered and concentrated in vacuo. The residue is purified by flash column chromatography eluting with 2:3 ethyl acetate:hexane. The fractions containing product are combined and concentrated. Diethyl ether is added and the insoluble material is collected by filtration to provide 60 mg of 4-[(2,4-dichloro-5-methoxyphenyl)amino]thieno[2,3-b]pyridine-5-carbonitrile as a tan solid, mp 197-199°C; ^{1}H NMR (DMSO-d_6) δ 3.85 (s, 3H), 7.38 (s, 1H), 7.68 (d, J = 5.7 Hz, 1H), 7.76 (s, 1H), 7.81 (d, J = 5.7 Hz, 1H), 8.43 (s, 1H), 9.80 (s, 1H); MS 348.2 (M-H)-.

Analysis for $C_{15}H_9Cl_2IN_3OS$:

Calcd: C, 51.44; H, 2.59; N, 12.00.

Found: C, 51.57; H, 2.99; N, 11.60.

Example 6

4-[(3-Chloro-4-[(1-methyl-1H-imidazol-2-yl)thio]phenyl)amino]thieno[2,3-b]pyridine-5-carbonitrile

A mixture of (3-chloro-4-[(1-methyl-1H-imidazol-2-yl)sulfanyl]aniline (135 mg, 0.57 mmol), pyridine hydrochloride (66 mg, 0.57 mmol) and 4-chlorothieno[2,3-b]pyridine-5-carbonitrile (0.1 g, 0.52 mmol) in 4 mL of 2-ethoxyethanol is heated at reflux for 24 hours. The solution is cooled and the solvent is evaporated. The resultant residue is treated with a minimum amount of methanol and the product is purified by flash column chromatography eluting with 3% methanol in dichloromethane. The fractions containing product are combined and concentrated. Ethyl acetate is added and the insoluble material collected by filtration to provide 55 mg of 4-[(3-chloro-4-[(1-methyl-1H-imidazol-2-yl)thio]phenyl)amino]thieno[2,3-b]pyridine-5-carbonitrile as a tan solid, mp >240°C; ^{1}H NMR (DMSO-d_6) δ 3.61 (s, 3H), 6.53 (d, J = 9 Hz, 1H), 7.15 (m, 1H), 7.17 (s, 1H), 7.44 (m, 1H), 7.52 (s, 1H), 7.54 (s, 1H), 7.81 (d, J = 6 Hz, 1H), 8.53 (s, 1H), 9.76 (s, 1H); MS 396.2 (M-H)-.

Analysis for $C_{18}H_{12}ClN_5S_2$ - 0.05 H_2O:

Calcd: C, 54.33; H, 3.04; N, 17.60.

Found: C, 54.21; H, 3.06; N, 17.56.

Example 7

4-[(2,4-Dichloro-5-methoxyphenyl)amino]-2-iodothieno[2,3-b]pyridine-5-carbonitrile

A mixture of 2,4-dichloro-5-methoxyaniline (1.1 g, 5.7 mmol) and 60% sodium hydride (285 mg, 9.9 mmol) in 30 mL of tetrahydrofuran is heated at reflux for 1 hour. The solution is cooled and 4-chloro-2-iodothieno[2,3-b]pyridine-5-carbonitrile (1.0 g, 3.12 mmol) is added. The reaction mixture is heated at reflux for 5 hours then allowed to stir at room temperature overnight. The resultant dark solution is partitioned between ethyl acetate and water. The organic layer is washed with water, dried over magnesium sulfate, filtered and concentrated in vacuo. The residue is purified by flash column chromatography eluting with 0.5: 9.5 methanol : dichloromethane to provide 0.28 g of 4-[(2,4-dichloro-5-methoxyphenyl)amino]-2-iodothieno[2,3-b]pyridine-5-carbonitrile as an off white solid, mp 231-233°C. An additional 0.09 g is obtained by chromatography of a mixture of unreacted starting material and product using a gradient of 9 : 1 to 1 : 1 hexane: ethyl acetate. ^{1}H NMR

(DMSO-d_6) δ 3.87 (s, 3H), 7.36 (s, 1H), 7.76 (s, 1H), 8.11 (s, 1H), 8.39 (s, 1H), 9.76 (s, 1H); MS 473.8 (M-H)-.

Analysis for $C_{15}H_8Cl_2IN_3OS - 0.05\ H_2O$:

Calcd: C, 37.84; H, 1.69; N, 8.83.

Found: C, 37.77; H, 1.71; N, 8.81.

Example 8

4-[(2,4-Dichloro-5-methoxyphenyl)amino]-2-methylthieno[2,3-b]pyridine-5-carbonitrile

A mixture of 2,4-dichloro-5-methoxyaniline (0.15 g, 0.73 mmol) and 60% sodium hydride (50 mg, 1.25 mmol) in 15 mL of tetrahydrofuran is heated at reflux for 1 hour. The solution is cooled and 4-chloro-2-methylthieno[2,3-b]pyridine-5-carbonitrile (0.06 g, 0.29 mmol) is added. The reaction mixture is heated at reflux for 3 hours then allowed to stir at room temperature overnight. The resultant black solution is partitioned between ethyl acetate and water. The organic layer is washed with water, dried over magnesium sulfate, filtered and concentrated in vacuo. The residue is purified by flash column chromatography eluting with 3: 7 ethyl acetate : hexane. The fractions containing product are combined and concentrated. Diethyl ether is added and the insoluble material collected by filtration to provide 79 mg of 4-[(2,4-dichloro-5-methoxyphenyl)amino]-2-methylthieno[2,3-b]pyridine-5-carbonitrile as a tan solid, mp 179-181°C; ^{1}H NMR (DMSO-d_6) δ2.57 (s, 3H), 3.85 (s, 3H), 7.32 (s, 1H), 7.39 (s, 1H), 7.74 (s, 1H), 8.35 (s, 1H), 9.61 (s, 1H); MS 362.1 (M-H)-

Analysis for $C_{16}H_{11}Cl_2N_3OS$

Calcd: C, 52.76; H, 3.04; N, 11.54.

Found: C, 52.46; H, 3.22; N, 11.14.

Example 9

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

A mixture of 2,4-dichloro-5-methoxyaniline (507 mg, 2.64 mmol) and 60% sodium hydride (105.6 mg, 2.64 mmol) in 15 mL of tetrahydrofuran is heated at reflux for 1 hour. The solution is cooled and 7-chloro-2-methylthieno[3,2-b]pyridine-6-carbonitrile (275.3 mg, 1.32 mmol) is added. The reaction mixture is heated at reflux for 6 hours, cooled to room temperature and partitioned between dichloromethane and water. The organic layer 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 5% ethyl acetate in hexane to 20% ethyl acetate in hexane followed by preparative thin layer chromatography developing with 20% ethyl acetate in dichloromethane, to provide 108 mg of 7-[(2,4-dichloro-5-methoxyphenyl)amino]-2-methylthieno[3,2-b]pyridine-6-carbonitrile as an off white solid, mp 213-214°C; ^{1}H NMR (DMSO-d_6) δ2.51 (s, 3H), 3.85 (s, 3H), 7.20 (s, 1H), 7.35 (s, 1H), 7.75 (s, 1H), 8.55 (s, 1H), 9.56 (s, 1H); MS 362.1, 364.3 (M+H)+.

Analysis for $C_{16}H_{11}Cl_2N_3OS$:

Calcd: C, 52.76; H, 3.04; N, 11.54.

Found: C, 52.86; H, 2.95; N, 11.56.

Example 10

7-[(2,4-Dichlorophenyl)amino]thieno[3,2-b]pyridine-6-carbonitrile

A mixture of 2,4-dichloroaniline (333.8 mg, 2.06 mmol) and 60% sodium hydride (82.4 mg, 2.06 mmol) in 10 mL of tetrahydrofuran is heated at reflux for 1 hour. The solution is cooled and 7-chlorothieno[3.2-b]pyridine-6-carbonitrile (200 mg, 1.03 mmol) is added. The resulting reaction mixture is heated at reflux for 7 hours, cooled to room temperature, and concentrated in vacuo. The residue is treated with water for 1 hour. The precipitate is filtered, washed with water, and air dried. The resultant solid is purified by flash column chromatography eluting with a gradient of 1% ethyl acetate in hexane to 8% ethyl acetate in hexane to provide 173.1 mg of 7-[(2,4-dichlorophenyl)amino]thieno[3,2-b]pyridine-6-carbonitrile as a white solid, mp 198-200°C; ^{1}H NMR (DMSO-d_6) δ7.47 (d, J = 4 Hz, 1H), 7.54 (dd, J = 6, 2 Hz, 1H), 7.59

(d, J = 6 Hz, 1H), 7.81 (d, J = 2 Hz, 1H), 8.12 (d, J = 4 Hz, 1H), 8.61 (s, 1H), 9.67 (s, 1H); MS 318.1, 320.2 (M+H)+.

Analysis for $C_{14}H_7Cl_2N_3S$-0.3 H_2O:

Calcd: C, 51.64; H, 2.35; N, 12.91.

Found: C, 51.64; H, 2.08; N, 12.86.

Example 11

7-[(2,4-Dichlorophenoxy)]thieno[3,2-b]pyridine-6-carbonitrile

A mixture of 7-chlorothieno[3,2-b]pyridine-6-carbonitrile (200 mg, 1.03 mmol), potassium carbonate (194.9 mg,1.41 mmol) and 2,4-dichlorophenol (218.3 mg, 1.34 mmol) in 3 mL of N,N-dimethylformamide is stirred at 110° C for 4 hours and allowed to cool to ambient temperature. The reaction mixture is treated with water and stirred at ambient temperature for 10 minutes. The crude solid is collected by filtration washing with water, dried in vacuo, then purified by flash column chromatography eluting with a gradient of 5 % ethyl acetate in hexane to 20% ethyl acetate in hexane to provide 244 mg of 7-[(2,4-dichlorophenoxy)]thieno[3,2-b]pyridine-6-carbonitrile as a white solid, mp 158-160°C; ^{1}H NMR (DMSO-d_6) δ7.63 (dd, J = 6, 2 Hz, 1H), 7.68 (d, J = 4 Hz, 1H), 7.74 (d, J = 6 Hz, 1H), 7.80 (d, J = 2 Hz, 1H), 8.33 (d, J = 4 Hz, 1H), 9.03 (s, 1H); MS 320.9, 322.9 (M+H)+.

Analysis for $C_{14}H_6Cl_2N_2OS$:

Calcd: C, 52.35; H, 1.88; N, 8.72.

Found: C, 52.28; H, 1.69; N, 8.49.

Example 12

7-[(2,4-Dichlorophenyl)thio]thieno[3,2-b]pyridine -6-carbonitrile

A mixture of 7-chlorothieno[3,2-b]pyridine-6-carbonitrile (200 mg, 1.03 mmol) and 2,4-dichlorothiophenol (202.9 mg, 1.13 mmol) in 5 mL of N,N-dimethylformamide is stirred at room temperature for 1 hour, and then concentrated in vacuo. The resulting residue is treated with water and stirred for 1 hour. The precipitate is filtered, washed with water, air dried, and then purified by flash column chromatography eluting with a gradient of 5% ethyl acetate in hexane to 20% ethyl acetate in hexane to provide 249.0 mg of 7-[(2,4-dichlorophenyl)thio]thieno[3,2-b]pyridine-6-carbonitrile as a white solid, mp 126-128°C; ^{1}H NMR (DMSO-d_6) δ7.47

(dd, J = 6, 2 Hz, 1H), 7.54 (d, J = 6 Hz, 1H), 7.73 (d, J = 4 Hz, 1H), 7.88 (d, J = 2 Hz, 1H), 8.43 (d, J = 4 Hz, 1H), 9.09 (s, 1H); MS 336.9, 339.0 (M+H)+.

Analysis for $C_{14}H_6Cl_2N_2S_2$:

Calcd: C, 49.86; H, 1.79; N, 8.31.

Found: C, 49.87; H, 1.67; N, 8.18.

Example 13

7-[(2,4-Dichlorobenzyl) amino]thieno[3,2-b]pyridine-6-carbonitrile

A mixture of 7-chlorothieno[3,2-b]pyridine-6-carbonitrile (200 mg, 1.03 mmol), 2,4-dichlorobenzylamine (217.6 mg, 0.17 mL, 1.24 mmol), N,N-diisopropylethylamine in 5 mL of 2-ethoxyethanol is heated at reflux for 4 hours. After cooling the mixture is concentrated in vacuo and the residue is treated with a saturated aqueous sodium bicarbonate solution for 1 hour. The precipitate is collected by filtration, washed with water, dried in vacuo, and then purified by flash column chromatography eluting with a gradient of 2% methanol in dichloromethane to 4% methanol in dichloromethane to provide 261.2 mg of 7-[(2,4-dichlorobenzyl)amino]thieno[3,2-b]pyridine-6-carbonitrile as a white solid, mp 215-216°C; ^{1}H NMR (DMSO-d_6) δ4.95 (d, J = 5 Hz, 2H), 7.28 (d, J = 6 Hz, 1H), 7.40 (dd, J = 6, 2 Hz, 1H), 7.46 (dd, J = 4, 2 Hz, 1H), 7.69 (d, J = 2 Hz, 1H), 8.12 (d, J = 5 Hz, 1H), 8.16 (m, 1H) 8.47 (d, J = 6 Hz, 1H); MS 334.0, 335.8 (M+H)+.

Analysis for $C_{15}H_9Cl_2N_3S$:

Calcd: C, 53.90; H, 2.71; N, 12.57.

Found: C, 53.58; H, 2.43; N, 12.49.

Example 14

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

A mixture of 7-[(2,4-dichloro-5-methoxyphenyl)amino]-2-iodothieno[3,2-b]pyridine-6-carbonitrile (240 mg, 0.50 mmol), 4-formylphenylboronic acid (150 mg, 1.0 mmol) and 4 mg of tetrakis(triphenylphosphine)palladium(0) in 20 mL of ethylene glycol dimethyl ether and 16 mL of saturated aqueous sodium bicarbonate is heated at reflux for 2 hours. The reaction mixture is cooled to room temperature and

partitioned between water and ethyl acetate. The organic layer is dried over sodium sulfate, filtered and concentrated in vacuo. The residue is purified by flash column chromatography eluting with chloroform to provide 160 mg of 7-[(2,4-dichloro-5-methoxyphenyl)amino]-2-(4-formylphenyl)thieno[3,2-b]pyridine-6-carbonitrile as yellow crystals, mp 261-262°C; ^{1}H NMR (DMSO-d_6) δ3.87 (s, 3H), 7.41 (s, 1H), 7.63 (s, 1H), 7.90-8.03 (m, 4H), 8.15 (s, 1H), 8.65 (s, 1H), 9.83 (s, 1H), 10.05 (s, 1H); MS 454.0 (M+H)+.

Analysis for $C_{22}H_{13}Cl_2N_3O_2S$ – 1.0 H_2O:

Calcd: C, 55.94; H, 3.20; N, 8.90.

Found: C, 56.24; H, 2.87; N, 9.02.

Example 15

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

Morpholine (16 mg, 0.18 mmol) is added to a suspension of 7-[(2,4-dichloro-5-methoxyphenyl)amino]-2-(4-formylphenyl)thieno[3,2-b]pyridine-6-carbonitrile (66 mg, 0.15 mmol) in 5 mL of dichloromethane and 0.5 mL of N,N-dimethylformamide. The reaction mixture is cooled to 0°C and sodium triacetoxyborohydride (85 mg, 0.40 mmol) is added. After stirring at 0°C for 1.5 hours, acetic acid (0.02 mL) is added and the reaction mixture is allowed to warm to room temperature and stirred overnight. The reaction is quenched by the addition of water and then partitioned between water and dichloromethane. The organic layer is dried over sodium sulfate, filtered and concentrated in vacuo. The residue is purified by flash column chromatography to provide 48 mg of 7-[(2,4-dichloro-5-methoxyphenyl)amino]-2-[4-(4-morpholinylmethyl)phenyl]thieno[3,2-b]pyridine-6-carbonitrile as yellow crystals, mp 244-245°C; ^{1}H NMR (DMSO-d_6) δ2.36 (m, 4H), 3.50 (s, 2H), 3.57 (m, 4H), 3.85 (s, 3H), 7.31 (s, 1H), 7.42 (d, J = 8 Hz, 2H), 7.68 (d, J = 8 Hz, 2H), 7.76 (s, 1H), 7.89 (s, 1H), 8.60 (s, 1H), 9.73 (s, 1H); MS 525.2 (M+H)+.

Example 16

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

N-methylpiperazine (177 μL, 1.6 mmol) is added to a suspension of 7-[(2,4-dichloro-5-methoxyphenyl)amino]-2-(4-formylphenyl)thieno[3,2-b]pyridine-6-carbonitrile (560 mg, 1.23 mmol) in 12 mL of dichloromethane and 3 mL of N,N-dimethylformamide. The reaction mixture is cooled to 0°C and sodium triacetoxyborohydride (1.3 g, 6.13 mmol) is added. After stirring at 0°C for 10 minutes, 3 drops of acetic acid are added and the reaction mixture is allowed to warm to room temperature and stirred for 5.5 hours. The reaction is quenched by the addition of water and then partitioned between saturated aqueous sodium bicarbonate and dichloromethane. The organic layer is washed with water, dried over sodium sulfate, filtered and concentrated in vacuo. The residue is purified by flash column chromatography eluting with 5% methanol in dichloromethane. The fractions containing product are combined and concentrated in vacuo. The residue is washed with diethyl ether to provide 215 mg of 7-[(2,4-dichloro-5-methoxyphenyl)amino]-2-[4-(4-methylpiperazin-1-ylmethyl)phenyl]thieno[3,2-b]pyridine-6-carbonitrile as white crystals, mp 226-228°C; ^{1}H NMR (DMSO-d_6) δ2.17 (s, 3H), 2.37 (br s, 8H), 3.49 (s, 2H), 3.85 (s, 3H), 7.37 (s, 1H), 7.40 (d, J = 8 Hz, 2H), 7.67(d, J = 8 Hz, 2H), 7.76 (s, 1H), 7.89 (s, 1H), 8.60 (s, 1H), 9.73 (s, 1H); MS 538.2 (M+H)+.

Analysis for $C_{27}H_{25}Cl_2N_5OS$- 0.25 H_2O:

Calcd: C, 59.72; H, 4.73; N, 12.90.

Found: C, 59.60; H, 4.51; N, 12.88.

Example 17

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

4-(2-Hydroxyethyl)piperazine (104 mg, 0.80 mmol) is added to a suspension of 7-[(2,4-dichloro-5-methoxyphenyl)amino]-2-(4-formylphenyl)thieno[3,2-b]pyridine-6-carbonitrile (227 mg, 0.50 mmol) in 15 mL of dichloromethane and 1 mL of N,N-dimethylformamide. The reaction mixture is cooled to 0°C and sodium triacetoxyborohydride (800 mg, 3.8 mmol) is added. After stirring at 0°C for 1.5

hours, 2 drops of acetic acid are added and the reaction mixture is allowed to warm to room temperature and stirred overnight. The reaction is quenched by the addition of water and then partitioned between aqueous sodium bicarbonate and dichloromethane. The organic layer is dried over sodium sulfate, filtered and concentrated in vacuo. The residue is purified by flash column chromatography eluting with 10% methanol in dichloromethane to provide 100 mg of 7-[(2,4-dichloro-5-methoxyphenyl)amino]-2-(4-{[4-(2-hydroxyethyl)piperazin-1-yl]methyl}phenyl)thieno[3,2-b]pyridine-6-carbonitrile as white crystals, mp 189-190°C; ^{1}H NMR (DMSO-d_6) δ2.27-2.44 (m, 10H), 3.41-3.50 (m, 4H), 3.85 (s, 3H), 4.36 (s, 1H), 7.37 (s, 1H), 7.40 (d, J = 8 Hz, 2H), 7.67 (d, J = 8 Hz, 2H), 7.76 (s, 1H), 7.89 (s, 1H), 8.60 (s, 1H), 9.74 (s, 1H); MS 566.3 (M-H)-.

Example 18

7-[(2,4-Dichloro-5-methoxyphenyl)amino]-2-[4-(piperidin-1-ylmethyl)phenyl]thieno[3,2-b]pyridine-6-carbonitrile

Piperidine (50 mg, 0.59 mmol) is added to a suspension of 7-[(2,4-dichloro-5-methoxyphenyl)amino]-2-(4-formylphenyl)thieno[3,2-b]pyridine-6-carbonitrile (200 mg, 0.44 mmol) in 4 mL of dichloromethane and 1 mL of N,N-dimethylformamide. The reaction mixture is cooled to 0°C and sodium triacetoxyborohydride (500 mg, 2.4 mmol) is added. After stirring at 0°C for 1.5 hours, a few drops of acetic acid are added and the reaction mixture is allowed to warm to room temperature and stirred overnight. The reaction is quenched by the addition of water and then partitioned between aqueous sodium bicarbonate and dichloromethane. The organic layer is dried over sodium sulfate, filtered and concentrated in vacuo. The residue is purified by flash column chromatography eluting with a gradient of 1 : 1 hexane : ethyl acetate to 5% methanol in ethyl acetate to provide 41 mg of 7-[(2,4-dichloro-5-methoxyphenyl)amino]-2-[4-(piperidin-1-ylmethyl)phenyl]thieno[3,2-b]pyridine-6-carbonitrile as yellow crystals, mp 218-220°C; ^{1}H NMR (DMSO-d_6) δ1.38 (m, 2H), 1.50 (m, 4H), 2.33 (m, 4H), 3.46 (m, 2H), 3.85 (s, 3H), 7.38 (s, 1H), 7.40 (d, J = 8 Hz, 2H), 7.67 (d, J = 8 Hz, 2H), 7.76 (s, 1H), 7.89 (s, 1H), 8.60 (s, 1H), 9.72 (s, 1H); MS 521.3 (M-H)-.

Example 19

4-{6-Cyano-7-[(2,4-dichloro-5-methoxyphenyl)amino]thieno[3,2-b]pyridine-2-yl]benzoic acid

A mixture of 7-[(2,4-dichloro-5-methoxyphenyl)amino]-2-iodothieno[3,2-b]pyridine-6-carbonitrile (500 mg, 1.05 mmol), 4-carboxylphenylboronic acid (350 mg, 2.12 mmol) and 100 mg of tetrakis(triphenylphosphine)palladium(0) in 50 mL of ethylene glycol dimethyl ether and 35 mL of saturated aqueous sodium bicarbonate is heated at reflux for 1 hour. The reaction mixture is cooled to room temperature and partitioned between water and ethyl acetate. The organic layer 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 chloroform to 10% methanol in chloroform to provide 4-{6-cyano-7-[(2,4-dichloro-5-methoxyphenyl)amino]thieno[3,2-b]pyridine-2-yl]benzoic acid as yellow crystals, mp >300°C; ^{1}H NMR (DMSO-d_6) δ3.86 (s, 3H), 7.40 (s, 1H), 7.78 (s, 1H), 7.86 (d, J = 8 Hz, 2H), 8.03 (d, J = 8 Hz, 2H), 8.03 (s, 1H), 8.08 (s, 1H), 8.64 (s, 1H), 9.80 (s, 1H), 13.14 (s, 1H); MS 470.2 (M+H)+.

Example 20

4-{6-Cyano-7-[(2,4-dichloro-5-methoxyphenyl)amino]thieno[3,2-b]pyridine-2-yl}benzamide

1,1'-Carbonyldiimidazole (100 mg, 0.61 mmol) is added to a suspension of 4-{6-cyano-7-[(2,4-dichloro-5-methoxyphenyl)amino]thieno[3,2-b]pyridine-2-yl]benzoic acid (130 mg, 0.28 mmol) in 10 mL of N,N-dimethylformamide. After stirring at 60°C for 2 hours the reaction mixture is allowed to cool to room temperature and ammonia gas is bubbled through the mixture for 15 minutes. The mixture is stirred at room temperature for an additional 60 minutes and poured into 50 g of ice and stirred for 30 minutes. The mixture is adjusted to pH 4 with concentrated hydrochloric acid and stirred for 60 minutes. The resulting precipitate is collected by filtration washing with water and dried under reduced pressure. The resulting solid is purified by flash column chromatography eluting with a gradient of ethyl acetate to 20% methanol in ethyl acetate to provide 12.3 mg of 4-{6-cyano-7-[(2,4-dichloro-5-methoxyphenyl)amino]thieno[3,2-b]pyridine-2-yl}benzamide as a gray solid, mp >300°C; ^{1}H NMR (DMSO-d_6) δ3.86 (s, 3H), 7.40 (s, 1H), 7.48 (s, 1H), 7.78 (s, 1H),

7.82 (d, J = 8Hz, 2H), 7.97 (d, J = 8 Hz, 2H), 8.06 (s, 2H), 8.08 (s, 1H), 8.63 (s, 1H), 9.78 (s, 1H); MS 468.9, 471.1 (M+H)+.

Example 21

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

A mixture of 7-[(2,4-dichloro-5-methoxyphenyl)amino]-2-iodothieno[3,2-b]pyridine-6-carbonitrile (134 mg, 0.28 mmol), 1-ethynyl-4-methoxybenzene (50 μL, 0.39 mmol), 3 mg of tetrakis(triphenylphosphine)palladium(0) and 5 mg of copper(I) iodide in 2 mL of triethylamine and 7 mL of benzene is heated at reflux for 24 hours. An additional 1 mL of triethylamine and 4 mL of benzene are added and the reaction is heated at reflux for 6 hours. The mixture is cooled to room temperature and 2 mL of methanol are added. The solvents are removed in vacuo and the residue is treated with 10 mL of ethyl acetate. The insoluble material is removed by filtration, washing with ethyl acetate. The filtrate is washed with 10% aqueous hydrochloric acid, water, and saturated aqueous sodium chloride, dried over magnesium sulfate, filtered and concentrated in vacuo. The residue is purified by flash column chromatography eluting with 4 : 1 hexane : ethyl acetate to provide 92 mg of 7-[(2,4-dichloro-5-methoxyphenyl)amino]-2-[(4-methoxyphenyl)ethynyl]thieno[3,2-b]pyridine-6-carbonitrile as yellow crystals, mp 249-250°C; ^{1}H NMR (DMSO-d_6) δ3.81 (s, 3H), 3.86 (s, 3H), 7.01 (d, J = 7 Hz, 2H), 7.40 (s, 1H), 7.55 (d, J = 7 Hz, 2H), 7.70 (s, 1H), 7.79 (s, 1H), 8.65 (s, 1H), 9.81 (s, 1H); MS 477.9, 479.9 (M-H)-.

Analysis for $C_{24}H_{15}Cl_2N_3O_2S$ –0.1 $(C_2H_4)_2O$- 0.2 C_6H_{14}:

Calcd: C, 60.71; H, 3.70; N, 8.30.

Found: C, 60.60; H, 3.45; N, 8.08.

Example 22

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

A mixture of 7-[(2,4-dichloro-5-methoxyphenyl)amino]-2-iodothieno[3,2-b]pyridine-6-carbonitrile (300 mg, 0.63 mmol), 2-ethynylpyridine (90 μL, 0.82 mmol), 7.3 mg of tetrakis(triphenylphosphine)palladium(0) and 3 mg of copper(I) iodide in 2 mL of triethylamine and 7 mL of benzene is heated at reflux overnight. The mixture

is cooled to room temperature and 5 mL of methanol are added. The solvents are removed in vacuo and the residue is treated with 10 mL of ethyl acetate. The insoluble material is removed by filtration, washing with ethyl acetate. The filtrate is washed with 10% aqueous hydrochloric acid, water, and saturated aqueous sodium chloride. The combined aqueous layers are extracted with dichloromethane. The organic layer is washed with saturated aqueous sodium chloride, dried over magnesium sulfate, filtered and concentrated in vacuo. The aqueous layer is adjusted to pH 6 and extracted with chloroform. The organic layer is washed with water, dried over magnesium sulfate, filtered and concentrated in vacuo. The residues are combined and purified by flash column chromatography eluting with 5% methanol in dichloromethane. The fractions containing product are combined and concentrated. The resultant solid is recrystallized from ethyl acetate and hexane to provide 92 mg of 7-[(2,4-dichloro-5-methoxyphenyl)amino]-2-(pyridin-2-ylethynyl)thieno[3,2-b]pyridine-6-carbonitrile as light brown crystals, mp 237-239°C; ^{1}H NMR (DMSO-d_6) δ3.86 (s, 3H), 7.35-7.52 (m, 2H), 7.73 (d, J = 8 Hz, 1H), 7.80 (s, 1H), 7.83-7.92 (m, 2H), 8.60-8.72 (m, 2H), 9.89 (s, 1H); MS 449.1, 450.9 (M-H)-.

Example 23

7-[(2,4-Dichloro-5-methoxyphenyl)amino]-2-[3-(dimethylamino)prop-1-ynyl]thieno[3,2-b]pyridine-6-carbonitrile

A mixture of 7-[(2,4-dichloro-5-methoxyphenyl)amino]-2-iodothieno[3,2-b]pyridine-6-carbonitrile (300 mg, 0.63 mmol), 1-dimethylamino-2-propyne (90 μL, 0.84 mmol), 7.5 mg of tetrakis(triphenylphosphine)palladium(0) and 3 mg of copper(I) iodide in 2 mL of triethylamine and 7 mL of benzene is heated at reflux overnight. The mixture is cooled to room temperature and 2 mL of methanol are added. The solvents are removed in vacuo and the residue is treated with 10 mL of chloroform. The insoluble material is removed by filtration, washing with chloroform. The filtrate is washed with 10% aqueous hydrochloric acid, water, and saturated aqueous sodium chloride. The combined aqueous layers are brought to pH 8 by adding 2 N sodium hydroxide. The aqueous layer is extracted with chloroform, dried over magnesium sulfate, filtered and concentrated in vacuo. The residue is purified by flash column chromatography eluting with 5% methanol in dichloromethane to provide 225 mg of 7-[(2,4-dichloro-5-methoxyphenyl)amino]-2-[3-(dimethylamino)prop-1-ynyl]thieno[3,2-

b]pyridine-6-carbonitrile as red crystals, mp 164-166°C; ^{1}H NMR (DMSO-d_6) δ2.21 (s, 6H), 3.53 (s, 2H), 3.85 (s, 3H), 7.37 (s, 1H), 7.62 (s, 1H), 7.78 (s, 1H), 8.62 (s, 1H), 9.77 (s, 1H); MS 429.3, 431.2 (M-H)-.

Example 24

2-(1-Benzofuran-2-yl)-7-[(2,4-dichloro-5-methoxyphenyl)amino]thieno[3,2-b]pyridine-6-carbonitrile

A mixture of 7-[(2,4-dichloro-5-methoxyphenyl)amino]-2-iodothieno[3,2-b]pyridine-6-carbonitrile (500 mg, 1.05 mmol), 2-benzofuranboronic acid (340 mg, 2.10 mmol) and 65 mg of tetrakis(triphenylphosphine)palladium(0) in 70 mL of ethylene glycol dimethyl ether and 40 mL of saturated aqueous sodium bicarbonate is heated at reflux for 2.5 hours. An additional 50 mg of tetrakis(triphenylphosphine)palladium(0) is added and the reaction is heated at reflux for 1 hour. The reaction mixture is cooled to room temperature and partitioned between water and ethyl acetate. The organic layer is washed with water, dried over sodium sulfate, filtered and concentrated in vacuo. The residue is purified by flash column chromatography eluting with 2 : 1 hexane : ethyl acetate. The fractions containing product are combined and concentrated in vacuo. The residue is washed with diethyl ether to provide 160 mg of 2-(1-benzofuran-2-yl)-7-[(2,4-dichloro-5-methoxyphenyl)amino]thieno[3,2-b]pyridine-6-carbonitrile as yellow crystals, mp 281-282°C; ^{1}H NMR (DMSO-d_6) δ3.87 (s, 3H), 7.29-7.45 (m, 3H), 7.61 (s, 1H), 7.69-7.73 (m, 2H), 7.81 (s, 1H), 8.02 (s, 1H), 8.65 (s, 1H), 9.82 (s, 1H); MS 464.2, 465.9 (M-H)-.

Analysis for $C_{23}H_{13}Cl_2N_3O_2S$- 0.25 H_2O:

Calcd: C, 58.67; H, 2.89; N, 8.92.

Found: C, 58.56; H, 2.82; N, 8.69.

Example 25

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

A mixture of 7-[(2,4-dichloro-5-methoxyphenyl)amino]-2-iodothieno[3,2-b]pyridine-6-carbonitrile (500 mg, 1.05 mmol), 3-formylphenylboronic acid (330 mg, 2.2 mmol) and 65 mg of tetrakis(triphenylphosphine)palladium(0) in 70 mL of ethylene glycol dimethyl ether and 40 mL of saturated aqueous sodium bicarbonate is heated at reflux for 1.5 hours. The reaction mixture is cooled to room temperature and partitioned between water and ethyl acetate. The organic layer is washed with water, dried over sodium sulfate, filtered and concentrated in vacuo. The residue is purified by flash column chromatography eluting with 1 : 1 hexane : ethyl acetate. The fractions containing product are combined and concentrated in vacuo. The residue is recrystallized from ethyl acetate to provide 62 mg of 7-[(2,4-dichloro-5-methoxyphenyl)amino]-2-(3-formylphenyl)thieno[3,2-b]pyridine-6-carbonitrile as yellow crystals, mp 262-263°C; ^{1}H NMR (DMSO-d_6) δ3.86 (s, 3H), 7.39 (s, 1H), 7.69-7.82 (m, 2H), 7.98 (s, 1H), 8.03-8.14 (m, 2H), 8.23 (s, 1H), 8.64 (s, 1H), 9.80 (s, 1H), 10.08 (s, 1H); MS 452.0, 453.9 (M-H)-.

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

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

Found: C, 57.80; H, 2.85; N, 9.16.

Example 26

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

Morpholine (100 μL, 1.15 mmol) is added to a suspension of 7-[(2,4-dichloro-5-methoxyphenyl)amino]-2-(3-formylphenyl)thieno[3,2-b]pyridine-6-carbonitrile (400 mg, 0.88 mmol) in 8 mL of dichloromethane and 2 mL of N,N-dimethylformamide. The reaction mixture is cooled to 0°C and sodium triacetoxyborohydride (1.0 g, 4.73 mmol) is added. After stirring at 0°C for 1 hour, 2 drops of acetic acid are added and the reaction mixture is allowed to warm to room temperature and stirred for 2 hours. The reaction is quenched by the addition of water and then partitioned between saturated aqueous sodium bicarbonate and dichloromethane. The organic layer is washed with water, dried over sodium sulfate, filtered and concentrated in vacuo. The residue is purified by flash column chromatography eluting with a gradient of 1 :

1 hexane : ethyl acetate to 5% methanol in ethyl acetate to provide 154 mg of 7-[(2,4-dichloro-5-methoxyphenyl)amino]-2-[3-(morpholin-4-ylmethyl)phenyl]thieno[3,2-b]pyridine-6-carbonitrile as yellow crystals, mp 205-207°C; ^{1}H NMR (DMSO-d_6) δ2.38 (m, 4H), 3.51 (s, 2H), 3.59 (m, 4H), 3.86 (s, 3H), 7.32-7.48 (m, 3H), 7.64-7.70 (m, 2H), 7.77 (s, 1H), 7.91 (s, 1H), 8.61 (s, 1H), 9.74 (s, 1H); MS 523.1, 525.0 (M-H)-.

Analysis for $C_{26}H_{22}Cl_2N_4O_2S$- 0.50 H_2O:

Calcd: C, 58.43; H, 4.34; N, 10.48.

Found: C, 58.49; H, 4.10; N, 10.39.

Example 27

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

A mixture of 4-[(2,4-dichloro-5-methoxyphenyl)amino]-2-iodothieno[2,3-b]pyridine-5-carbonitrile (0.25 g, 0.52 mmol), 4-formylphenylboronic acid (0.16 mg, 1.05 mmol), and 30 mg of tetrakis(triphenylphosphine)palladium(0) in 45 mL of ethylene glycol dimethyl ether is prepared. To the mixture is added 20 mL of a saturated sodium carbonate solution and the reaction mixture is heated at reflux for 1 hour. The mixture is allowed to warm to room temperature and partitioned between water and dichloromethane. The organic layer is dried over magnesium sulfate, filtered and concentrated in vacuo. The residue is triturated with ethyl acetate and the resulting solid is filtered and washed with diethyl ether to provide 0.16 g of 4-[(2,4-dichloro-5-methoxyphenyl)amino]-2-(4-formylphenyl)thieno[2,3-b]pyridine-5-carbonitrile as an off white solid, mp >240°C; ^{1}H NMR (DMSO-d_6) δ 3.87 (s, 3H), 7.42 (s, 1H), 7.79 (s, 1H), 7.94 (d, J = 8.3 Hz, 2H), 8.07 (d, J = 8.3 Hz, 2H), 8.46 (s, 1H), 8.47 (s, 1H), 9.92 (s, 1H), 10.06 (s, 1H); MS 452.0 (M-H)-.

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

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

Found: C, 58.09; H, 2.53; N, 9.00.

Example 28

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

A suspension of 4-[(2,4-dichloro-5-methoxyphenyl)amino]-2-(4-formylphenyl)thieno[2,3-b]pyridine-5-carbonitrile (0.1 g, 0.24 mmol) in 1 mL of N,N-dimethylformamide and 4 mL of dichloromethane is prepared. To the mixture is added morpholine (0.03 mL, 0.32 mmol). The reaction mixture is cooled to 0°C and sodium triacetoxyborohydride (0.26 g, 1.2 mmol) is added. After stirring at 0°C for 30 minutes a drop of acetic acid is added and the mixture is stirred at 0°C for an additional 4 hours. Additional morpholine (0.01 mL, 0.1 mmol) and sodium triacetoxyborohydride are added and the reaction mixture is allowed to warm to room temperature and stirred overnight. The resultant light brown solution is partitioned between dichloromethane and water. The organic layer is washed with saturated aqueous sodium chloride and water, dried over magnesium sulfate, filtered and concentrated in vacuo. The resulting residue is triturated with acetone and water to provide 86 mg of 4-[(2,4-dichloro-5-methoxyphenyl)amino]-2-[4-(morpholin-4-ylmethyl)phenyl]thieno[2,3-b]pyridine-5-carbonitrile as a white solid, mp 106-108°C; ^{1}H NMR (DMSO-d_6) δ 2.38 (br s, 4H), 3.51 (br s, 2H), 3.59 (br s, 4H), 3.86 (s, 3H), 7.40 (s, 1H), 7.46 (d, J = 8.0 Hz, 2H), 7.67 (d, J = 8.0 Hz, 2H), 7.77 (s, 1H), 8.19 (s, 1H), 8.42 (s, 1H), 9.80 (s, 1H); MS 525.0 (M+H)+.

Analysis for $C_{26}H_{22}Cl_2N_4O_2S$

Calcd: C, 59.43; H, 4.22; N, 10.66.

Found: C, 59.34; H, 4.02; N, 10.26.

Example 29

4-[5-Cyano-4-(3,4,5-trimethoxyphenylamino)-thieno[2,3-b]pyridin-2-yl]-butyric acid methyl ester

A mixture of 4-(4-chloro-5-cyano-thieno[2,3-b]pyridin-2-yl)-butyric acid methyl ester (60 mg, 0.20 mmol), 3,4,5-trimethoxyaniline (92 mg, 0.50 mmol), and pyridine hydrochloride (10 mg, 0.09 mmol) in 10 mL of 2-ethoxyethanol is heated at reflux for 24 hours. The solution is cooled and the solvent is evaporated. The residue is purified by flash column chromatography eluting with 1: 1 ethyl acetate : hexane to provide 62 mg of 4-[5-cyano-4-(3,4,5-trimethoxy-phenylamino)-thieno[2,3-b]pyridin-2-

yl]-butyric acid methyl ester as a tan solid, mp 101-103°C; ^{1}H NMR (DMSO-d_6) δ1.94 (quintet, J = 7 Hz, 2H), 2.41 (t, J = 7 Hz, 2H), 2.88 (t, J = 7 Hz, 2H), 3.60 (s, 3H), 3.67 (s, 3H), 3.75 (s, 6H), 6.60 (s, 2H), 7.28 (s, 1H), 8.40 (s, 1H), 9.62 (s, 1H); MS 442.1 (M+H)+.

Analysis for $C_{22}H_{23}N_3O_5S$:

Calcd: C, 59.85; H, 5.25; N, 9.52.

Found: C, 59.72; H, 5.41; N, 9.40.

Example 30

2-(4-Hydroxybutyl)-4-[(3,4,5-trimethoxyphenyl)amino]-thieno[2,3-b]pyridine-5-carbonitrile

To a solution of 4-[5-cyano-4-(3,4,5-trimethoxyphenylamino)-thieno[2,3-b]pyridin-2-yl]-butyric acid methyl ester (1.10 g, 2.5 mmol) in 15 mL of tetrahydrofuran at room temperature is added dropwise lithium borohydride in tetrahydrofuran (10 mL, 2.0 M, 20 mmol). The mixture is heated at reflux for 1 hour, and cooled to room temperature. Methanol (20 mL) is added, and stirring is continued at room temperature overnight. The reaction mixture is partitioned between saturated aqueous sodium chloride and ethyl acetate. The organic layer is dried, and concentrated. The residue is purified by flash column chromatography eluting with with 2: 1 ethyl acetate : hexane to provide 563 mg of 2-(4-hydroxybutyl)-4-[(3,4,5-trimethoxyphenyl)amino]-thieno[2,3-b]pyridine-5-carbonitrile as a white solid, mp 125-127°C; ^{1}H NMR (DMSO-d_6) δ1.50 (m, 2H), 1.72 (m, 2H), 2.91 (t, J = 7 Hz, 2H), 3.42 (m, 2H), 3.68 (s, 3H), 3.76 (s, 6H), 4.42 (t, J = 5 Hz, 1H), 6.75 (s, 2H), 7.44 (s, 1H), 8.45 (s, 1H), 10.23 (s, 1H); MS 414.4 (M+H)+.

Example 31

2-[4-(4-Morpholinyl)butyl]-4-[(3,4,5-trimethoxyphenyl)amino]-thieno[2,3-b]pyridine-5-carbonitrile

To a solution of 2-(4-hydroxybutyl)-4-[(3,4,5-trimethoxyphenyl)amino]-thieno[2,3-b]pyridine-5-carbonitrile (413 mg, 1.0 mmol) and carbon tetrabromide (464 mg, 1.4 mmol) in 10 mL of dichloromethane is added a solution of triphenylphosphine (314 mg, 1.2 mmol) in 5 mL of dichloromethane with stirring. The mixture is stirred at room temperature for 2 hours and concentrated. The residue is purified by flash

column chromatography eluting with a gradient of 9 : 1 hexane : ethyl acetate to 1 : 2 hexane : ethyl acetate to provide crude 2-(4-bromobutyl)-4-[(3,4,5-trimethoxyphenyl)amino]-thieno[2,3-b]pyridine-5-carbonitrile. The crude 2-(4-bromobutyl)-4-[(3,4,5-trimethoxyphenyl)amino]-thieno[2,3-b]pyridine-5-carbonitrile is heated 70°C in 2 mL of morpholine in the presence of sodium iodide (100 mg, 0.67 mmol) for 1 hour. The mixture is concentrated, and the residue is purified by flash column chromatography eluting with a gradient of ethyl acetate to 10% methanol in ethyl acetate to provide 2-[4-(4-morpholinyl)butyl]-4-[(3,4,5-trimethoxyphenyl)amino]-thieno[2,3-b]pyridine-5-carbonitrile as a yellow oil; ^{1}H NMR (DMSO-d_6) δ1.49 (quintet, J = 7 Hz, 2H), 1.68 (quintet, J = 7 Hz, 2H), 2.31 (m, 6H), 2.87 (t, J = 7 Hz, 2H), 3.55 (m, 4H), 3.67 (s, 3H), 3.74 (s, 6H), 6.59 (s, 2H), 7.23 (s, 1H), 8.37 (s, 1H), 9.46 (s, 1H); MS 483.5 (M+H)+.

Example 32

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

A mixture of 7-[(2,4-dichloro-5-methoxyphenyl)amino]-2-iodothieno[3,2-b]pyridine-6-carbonitrile (500 mg, 1.05 mmol), (trimethylsilyl)acetylene (237 μL, 1.67 mmol), 12.5 mg of tetrakis(triphenylphosphine)palladium(0) and 5 mg of copper(I) iodide in 3.5 mL of triethylamine and 12 mL of benzene is heated at reflux for 20 hours. The mixture is cooled to room temperature and 50 mL of chloroform are added. The mixture is washed with saturated aqueous sodium chloride, dried over sodium sulfate, filtered through a celite pad and concentrated in vacuo. The resulting brown solid is suspended in diethyl ether. The solids are collected by filtration and washed with diethyl ether to yield 7-[(2,4-dichloro-5-methoxyphenyl)amino]-2-[(trimethylsilyl)ethynyl]thieno[3,2-b]pyridine-6-carbonitrile as yellow crystals, mp 169-171°C; ^{1}H NMR ($CDCl_3$) δ0.26 (s, 9H), 3.88 (s, 3H), 6.79 (s, 1H), 6.89 (s, 1H), 7.51 (s, 1H), 7.56 (s, 1H), 8.65 (s, 1H); MS 444.1, 446.1 (M-H)-.

Analysis for $C_{20}H_{17}Cl_2N_3OSSi$- 0.15 $CHCl_3$:

Calcd: C, 52.12; H, 3.72; N, 9.05.

Found: C, 52.23; H, 3.41; N, 9.12.

Example 33

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

To the suspension of 7-[(2,4-dichloro-5-methoxyphenyl)amino]-2-[(trimethylsilyl)ethynyl] thieno[3,2-b]pyridine-6-carbonitrile (97 mg, 0.22 mmol) in 10 mL of methanol is added potassium carbonate (46 mg, 0.33 mmol) The mixture is stirred at room temperature for 30 minutes, concentrated in vacuo and then partitioned between water and ethyl acetate. The organic layer is dried over magnesium sulfate, filtered and concentrated in vacuo. The residue is purified by flash column chromatography eluting with 1: 1 ethyl acetate: hexane to provide 38 mg of 7-[(2,4-dichloro-5-methoxyphenyl)amino]-2-ethynylthieno[3,2-b]pyridine-6-carbonitrile as white crystals, mp 198-200°C; ^{1}H NMR (DMSO-d_6) δ 3.85 (s, 3H), 5.01 (s, 1H), 7.38 (s, 1H), 7.72 (s, 1H), 7.79 (s, 1H), 8.63 (s, 1H), 9.85 (s, 1H); MS 372.0 (M-H)-.

Analysis for $C_{17}H_9Cl_2N_3OS$- 0.60 $C_4H_{10}O$:

Calcd: C, 55.64; H, 3.61; N, 10.03.

Found: C, 55.34; H, 3.45; N, 9.64.

Example 34

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

A mixture of 7-[(2,4-dichloro-5-methoxyphenyl)amino]-2-[(trimethylsilyl)ethynyl] thieno[3,2-b]pyridine-6-carbonitrile (365 mg, 0.82 mmol), 4-iodopyridine (252 mg, 1.23 mmol), potassium carbonate (565 mg, 4.09 mmol), 30 mg of bis(triphenylphosphine)palladium(II) chloride, 43 mg of triphenylphosphine and 8 mg of copper(I) iodide in 10 mL of tetrahydrofuran and 2 mL of methanol is heated at reflux overnight. The mixture is cooled to room temperature and 50 mL of chloroform are added. The mixture is washed with water and saturated aqueous sodium chloride, dried over magnesium sulfate, filtered and concentrated in vacuo. The residue is purified by two flash column chromatographies, first eluting with 5% methanol in dichloromethane and then eluting with 1: 1 ethyl acetate : hexane to provide 174 mg of 7-[(2,4-dichloro-5-methoxyphenyl)amino]-2-(pyridin-4-

ylethynyl)thieno[3,2-b]pyridine-6-carbonitrile as orange crystals, mp 221-223°C; ^{1}H NMR ($CDCl_3$) δ 3.86 (s, 3H), 7.43 (s, 1H), 7.59 (d, J = 5 Hz, 2H), 7.81 (s, 1H), 7.89 (s, 1H), 8.61-8.71 (m, 3H), 9.89 (s, 1H); MS 451.2 (M-H)+.

Analysis for $C_{22}H_{12}Cl_2N_4OS$- 0.11 $CHCl_3$:

Calcd: C, 57.17; H, 2.62; N, 12.06.

Found: C, 57.42; H, 2.65; N, 11.68.

Example 35

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

A mixture of 7-[(2,4-dichloro-5-methoxyphenyl)amino]-2-iodothieno[3,2-b]pyridine-6-carbonitrile (160 mg, 0.33 mmol), 3-ethynylpyridine (45 mg, 0.43 mmol), 5 mg of tetrakis(triphenylphosphine)palladium(0) and 20 mg of copper(I) iodide in 2 mL of triethylamine and 7 mL of benzene is heated at reflux overnight. The mixture is cooled to room temperature and 5 mL of methanol is added. The solvents are removed in vacuo and the residue is treated with 50 mL of chloroform. The insoluble material is removed by filtration, washing with chloroform. The filtrate is washed with water. The residue is suspended in acetone, combined with the chloroform phase and concentrated in vacuo. The residue is purified by flash column chromatography eluting with a gradient of 5% methanol in dichloromethane to 10% methanol and 1% ammonium hydroxide in dichloromethane. The fractions containing product are combined and concentrated to provide 99 mg of 7-[(2,4-dichloro-5-methoxyphenyl)amino]-2-(pyridin-3-ylethynyl)thieno[3,2-b]pyridine-6-carbonitrile as light brown crystals, mp 249-250°C; MS 451.0(M+H)+.

Analysis for $C_{22}H_{12}Cl_2N_4OS$:

Calcd: C, 58.55; H, 2.68; N, 12.41.

Found: C, 58.49; H, 2.65; N, 12.11.

Example 36

7-[(2,4-Dichloro-5-methoxyphenyl)amino]-2-[5-(1,3-dioxolan-2-yl)thien-3-yl]thieno[3,2-b]pyridine-6-carbonitrile

A mixture of 7-[(2,4-dichloro-5-methoxyphenyl)amino]-2-iodothieno[3,2-b]pyridine-6-carbonitrile (564 mg, 1.18 mmol), tributyl-(5-[1,3]dioxolan-2-yl-thiophen-3-yl)-stannane (680 mg, 1.52 mmol) and a pinch of bis(triphenylphosphine)palladium(II) chloride in 15 mL of dioxane is heated at reflux for 5 hours. Additional bis(triphenylphosphine)palladium(II) chloride is added and the reaction is heated at reflux overnight. Additional bis(triphenylphosphine)palladium(II) chloride and 10 mL of dioxane are added and the reaction is heated at reflux for 5 hours. The reaction mixture is concentrated in vacuo and partitioned between water and chloroform. The organic layer is dried over sodium sulfate, filtered and concentrated in vacuo. The residue is purified by flash column chromatography eluting with 1 : 1 hexane : ethyl acetate. The fractions containing product are combined and concentrated in vacuo to provide 447 mg of 7-[(2,4-dichloro-5-methoxyphenyl)amino]-2-[5-(1,3-dioxolan-2-yl)thien-3-yl]thieno[3,2-b]pyridine-6-carbonitrile as white crystals, mp 219-221°C; ^{1}H NMR (DMSO-d_6) δ3.85 (s, 3H), 3.92-4.10 (m, 4H), 6.08 (s, 1H), 7.36 (s, 1H), 7.63 (s, 1H), 7.75 (s, 1H), 7.80 (s, 1H), 7.97 (s, 1H), 8.60 (s, 1H), 9.69 (s, 1H); MS 502.1 (M-H)-.

Analysis for $C_{22}H_{15}Cl_2N_3O_3S_2$:

Calcd: C, 52.39; H, 3.00; N, 8.33.

Found: C, 52.58; H, 3.21; N, 7.93.

Example 37

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

To the suspension of 7-[(2,4-dichloro-5-methoxyphenyl)amino]-2-[5-(1,3-dioxolan-2-yl)thien-3-yl]thieno[3,2-b]pyridine-6-carbonitrile (337 mg, 0.67 mmol) in 10 mL of tetrahydrofuran is added 5 mL of 2N hydrochloric acid. The mixture is stirred at room temperature, overnight. The mixture is slowly poured into 30 mL of saturated aqueous sodium bicarbonate and extracted with chloroform. The organic layer is

washed with saturated aqueous sodium chloride, dried over magnesium sulfate, filtered and concentrated in vacuo. The residue is purified by flash column chromatography eluting with 5% methanol in dichloromethane to provide 271 mg of 7-[(2,4-dichloro-5-methoxyphenyl)amino]-2-(5-formylthien-3-yl)thieno[3,2-b]pyridine-6-carbonitrile as yellow crystals, mp 259-261°C; ^{1}H NMR (DMSO-d_6) δ 3.85 (s, 3H), 7.38 (s, 1H), 7.76 (s, 1H), 7.93 (s, 1H), 8.42 (s, 1H), 8.50 (s, 1H), 8.63 (s, 1H), 9.76 (s, 1H), 9.98 (s, 1H); MS 458.1 (M-H)-.

Analysis for $C_{20}H_{11}Cl_2N_3O_2S_2$+ 0.05 CH_2Cl_2+ 0.10 $CHCl_3$:
Calcd: C, 50.78; H, 2.37; N, 8.82.
Found: C, 50.59; H, 2.21; N, 8.74.

Example 38

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

1-Methylpiperazine (70 μL, 0.63 mmol) is added to a suspension of 7-[(2,4-dichloro-5-methoxyphenyl)amino]-2-(5-formylthien-3-yl)thieno[3,2-b]pyridine-6-carbonitrile (225 mg, 0.49 mmol) in 4 mL of dichloromethane and 1 mL of N,N-dimethylformamide. The reaction mixture is cooled to 0°C and sodium triacetoxyborohydride (520 mg, 2.45 mmol) is added. After stirring at 0°C for 10 minutes, 2 drops of acetic acid are added and the reaction mixture is allowed to warm to room temperature and stirred for 4 hours. The reaction is quenched by the addition of water and then partitioned between saturated aqueous sodium bicarbonate and dichloromethane. The organic layer is washed with water, dried over sodium sulfate, filtered and concentrated in vacuo. The residue is purified by flash column chromatography eluting with 5% methanol in dichloromethane. The fractions containing product are combined and concentrated in vacuo. The residue is washed with diethyl ether to provide 133 mg of 7-[(2,4-dichloro-5-methoxyphenyl)amino]-2{5-[(4-methylpiperazin-1-yl)methyl]thien-3-y}thieno[3,2-b]pyridine-6-carbonitrile as white crystals, mp 224-226°C; ^{1}H NMR (DMSO-d_6) δ2.18 (s, 3H), 2.25-2.55 (m, 8H), 3.68 (s, 2H), 3.85 (s, 3H), 7.35 (s, 1H), 7.37 (s, 1H), 7.74 (s, 1H), 7.75 (s, 1H), 7.82 (s, 1H), 8.58 (s, 1H), 9.68 (s, 1H); MS 523.1, 544.2 (M+H)+.

Analysis for $C_{25}H_{23}Cl_2N_5OS_2$- 0.50 H_2O:
Calcd: C, 54.24; H, 4.37; N, 12.65.
Found: C, 54.57; H, 4.34; N, 12.30.

Example 39

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

Morpholine (50 μL, 0.57 mmol) is added to a suspension of 7-[(2,4-dichloro-5-methoxyphenyl)amino]-2-(5-formylthien-3-yl)thieno[3,2-b]pyridine-6-carbonitrile (200 mg, 0.43 mmol) in 4 mL of dichloromethane and 1 mL of N,N-dimethylformamide. The reaction mixture is cooled to 0°C and sodium triacetoxyborohydride (460 mg, 2.17 mmol) is added. After stirring at 0°C for 10 minutes, 2 drops of acetic acid are added and the reaction mixture is allowed to warm to room temperature and stirred for 4 hours. The reaction is quenched by the addition of water and then partitioned between saturated aqueous sodium bicarbonate and dichloromethane. The organic layer is washed with water, dried over sodium sulfate, filtered and concentrated in vacuo. The crude residue is purified by flash column chromatography eluting with 5% methanol in dichloromethane to provide 169 mg of 7-[(2,4-dichloro-5-methoxyphenyl)amino]-2-[5-(morpholin-4-ylmethyl)thien-3-yl]thieno[3,2-b]pyridine-6-carbonitrile as a white solid, mp 209-212°C; MS 531.0(M+H)+.
Analysis for $C_{24}H_{20}Cl_2N_4O_2S_2$:
Calcd: C, 54.24; H, 3.79; N, 10.54.
Found: C, 54.16; H, 3.43; N, 10.40.

Examples 40 & 41

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

4-Hydroxypiperidine (100 mg, 0.99 mmol) is added to a suspension of 7-[(2,4-dichloro-5-methoxyphenyl)amino]-2-(4-formylphenyl)thieno[3,2-b]pyridine-6-carbonitrile (165 mg, 0.36 mmol) in 5 mL of dichloromethane and 2 mL of N,N-dimethylformamide. The reaction mixture is cooled to 0°C and sodium

triacetoxyborohydride (0.55 g, 2.60 mmol) is added. After stirring at 0°C for 4 hours, 3 drops of acetic acid are added and the reaction mixture is allowed to warm to room temperature and stirred for 1.5 hours. The reaction is quenched by the addition of water and then partitioned between saturated aqueous sodium bicarbonate and dichloromethane. The organic layer is washed with water, dried over sodium sulfate, filtered and concentrated in vacuo. The residue is purified by flash column chromatography eluting with a gradient of ethyl acetate to 5% methanol in ethyl acetate to provide 98 mg of 7-[(2,4-dichloro-5-methoxyphenyl)amino]-2-{4-[(4-hydroxypiperidin-1-yl)methyl]phenyl}thieno[3,2-b]pyridine-6-carbonitrile as yellow crystals, mp 149-150°C; ^{1}H NMR (DMSO-d_6) δ1.35-1.45 (m, 2H), 1.65-1.75 (m, 2H), 2.00-2.10 (m, 2H), 2.62-2.70 (m, 2H), 3.47 (s, 3H), 3.85 (s, 3H), 4.54 (d, J = 4 Hz, 1H), 7.37 (s, 1H), 7.40 (d, J = 8 Hz, 2H), 7.67 (d, J = 8 Hz, 2H), 7.76 (s, 1H), 7.89 (s, 1H), 8.59 (s, 1H), 9.72 (s, 1H); MS 536.9 (M-H)-.

Analysis for $C_{27}H_{24}Cl_2N_4O_2S$- 2.00 H_2O+ 0.1 $C_4H_8O_2$ + 0.15 C_6H_{14}:

Calcd: C, 56.90; H, 5.21; N, 9.38.

Found: C, 56.61; H, 4.85; N, 8.99.

From the above flash column chromatography is also isolated 61 mg of 7-[(2,4-dichloro-5-methoxyphenyl)amino]-2-[4-(hydroxymethyl)phenyl]thieno[3,2-b]pyridine-6-carbonitrile as yellow crystals, mp 239-240°C; ^{1}H NMR (DMSO-d_6) δ3.86 (s, 3H), 4.54 (d, J = 6 Hz, 2H), 5.29 (t, J = 6 Hz, 1H), 7.38 (s, 1H), 7.43 (d, J = 8 Hz, 2H), 7.69(d, J = 8 Hz, 2H), 7.77 (s, 1H), 7.90 (s, 1H), 8.61 (s, 1H), 9.72 (s, 1H); MS 456.1 (M+H)+.

Analysis for $C_{22}H_{15}Cl_2N_3O_2S$- 0.70 H_2O:

Calcd: C, 56.34; H, 3.52; N, 8.96.

Found: C, 56.73; H, 3.65; N, 8.55.

Example 42

2-Iodo-7-[(4-phenoxyphenyl)amino]thieno[3,2-b]pyridine-6-carbonitrile

A mixture of 4-phenoxyaniline (1.05 g, 5.67 mmol), pyridine hydrochloride (100 mg, 0.76 mmol) and 4-chloro-2-iodothieno[3,2-b]pyridine-6-carbonitrile (1 g, 3.12 mmol) in 50 mL of 2-ethoxyethanol is heated at reflux for 1.5 hours. The solution is poured into saturated aqueous sodium bicarbonate and the resulting solid is collected by filtration, washed with water and dried under reduced pressure. The

solid is purified by flash column chromatography eluting with chloroform. The fractions containing product are combined and concentrated. Diethyl ether is added and the insoluble material collected by filtration to provide 1.38 g of 2-iodo-7-[(4-phenoxyphenyl)amino]thieno[2,3-b]pyridine-6-carbonitrile as white crystals, mp 260-262°C; ^{1}H NMR (DMSO-d_6) δ 7.09 (t, J = 8 Hz, 4H), 7.17 (t, J = 8 Hz, 1H), 7.36 (d, J = 8 Hz, 2H), 7.43 (t, J = 8 Hz, 2H), 7.73 (s, 1H), 8.53 (s, 1H), 9.56 (s, 1H); MS 468.0 (M-H)-.

Analysis for $C_{20}H_{12}IN_3OS$ - 0.10 $CHCl_3$:

Calcd: C, 50.16; H, 2.54; N, 8.73.

Found: C, 50.15; H, 2.31; N, 8.55.

Example 43

2-(4-Formylphenyl)-7-[(4-phenoxyphenyl)amino]thieno[3,2-b]pyridine-6-carbonitrile

A mixture of 2-iodo-7-[(4-phenoxyphenyl)amino]thieno[2,3-b]pyridine-5-carbonitrile (600 mg, 1.28 mmol), 4-formylphenylboronic acid (380 mg, 2.53 mmol) and 75 mg of tetrakis(triphenylphosphine)palladium(0) in 53 mL of ethylene glycol dimethyl ether and 40 mL of saturated aqueous sodium bicarbonate is heated at reflux for 1 hour. The reaction mixture is cooled to room temperature and partitioned between water and ethyl acetate. The organic layer is washed with water, dried over sodium sulfate, filtered and concentrated in vacuo. The residue is purified by flash column chromatography eluting with 2 : 1 hexane : ethyl acetate to provide 2-(4-formylphenyl)-7-[(4-phenoxyphenyl)amino]thieno[3,2-b]pyridine-6-carbonitrile as yellow crystals, mp 230-232°C; ^{1}H NMR (DMSO-d_6) δ 7.06-7.20 (m, 5H), 7.36-7.45 (m, 4H), 7.92-8.05 (m, 4H), 8.11 (s, 1H), 8.63 (s, 1H), 9.67 (s, 1H), 10.05 (s, 1H); MS 446.2 (M-H)-.

Analysis for $C_{27}H_{17}N_3O_2S$- 0.40 H_2O:

Calcd: C, 71.31; H, 3.95; N, 9.24.

Found: C, 70.97; H, 3.48; N, 9.16.

Example 44

2-[4-(4-Methylpiperazin-1-ylmethyl)phenyl]-7-[(4-phenoxyphenyl)amino]thieno[3,2-b]pyridine-6-carbonitrile

1-Methylpiperazine (65 μL, 0.59 mmol) is added to a suspension of 2-(4-formylphenyl)-7-[(4-phenoxyphenyl)amino]thieno[3,2-b]pyridine-6-carbonitrile (200 mg, 0.45 mmol) in 4 mL of dichloromethane and 1 mL of N,N-dimethylformamide. The reaction mixture is cooled to 0°C and sodium triacetoxyborohydride (474 mg, 2.24 mmol) is added. After stirring at 0°C for 10 minutes, 3 drops of acetic acid are added and the reaction mixture is allowed to warm to room temperature and stirred for 4 hours. The reaction is quenched by the addition of water and then partitioned between saturated aqueous sodium bicarbonate and dichloromethane. The organic layer is washed with water, dried over sodium sulfate, filtered and concentrated in vacuo. The residue is purified by flash column chromatography eluting with 5% methanol in dichloromethane to provide 138 mg of 2-[4-(4-methylpiperazin-1-ylmethyl)phenyl]-7-[(4-phenoxyphenyl)amino]thieno[3,2-b]pyridine-6-carbonitrile as white crystals, mp 199-201°C; ^{1}H NMR (DMSO-d_6) δ2.17 (s, 3H), 2.37 (br s, 8H), 3.50 (s, 2H), 7.05-7.18 (m, 5H), 7.35-7.44 (m, 6H), 7.66 (d, J = 8 Hz, 2H), 7.86 (s, 1H), 8.59 (s, 1H), 9.58 (s, 1H); MS 532.3 (M+H)+.

Analysis for $C_{32}H_{29}N_5OS$:

Calcd: C, 72.29; H, 5.50; N, 13.17.

Found: C, 72.14; H, 5.61; N, 13.11.

Examples 45 & 46

2-[4-(Morpholin-4-ylmethyl)phenyl]-7-[(4-phenoxyphenyl)amino]thieno[3,2-b]pyridine-6-carbonitrile

2-[4-(Hydroxymethyl)phenyl]-7-[(4-phenoxyphenyl)amino]thieno[3,2-b]pyridine-6-carbonitrile

Morpholine (51 μL, 0.58 mmol) is added to a suspension of 2-(4-formylphenyl)-7-[(4-phenoxyphenyl)amino]thieno[3,2-b]pyridine-6-carbonitrile (200 mg, 0.45 mmol) in 8 mL of dichloromethane and 2 mL of N,N-dimethylformamide. The reaction mixture is cooled to 0°C and sodium triacetoxyborohydride (474 mg, 2.24 mmol) is added. After stirring at 0°C for 10 minutes, 2 drops of acetic acid are added and the reaction mixture is allowed to warm to room temperature and stirred for 4 hours. The reaction is quenched by the addition of water and then partitioned between saturated aqueous sodium bicarbonate and dichloromethane. The organic layer is washed with water, dried over sodium sulfate, filtered and concentrated in vacuo. The residue is purified by flash column chromatography eluting with ethyl acetate to provide 79 mg of 2-[4-(morpholin-4-ylmethyl)phenyl]-7-[(4-phenoxyphenyl)amino]thieno[3,2-b]pyridine-6-carbonitrile as white crystals, mp 254-256°C; ^{1}H NMR (DMSO-d_6) δ2.36 (s, 4H), 3.51 (s, 2H), 3.58 (s, 4H), 7.04-7.18 (m, 5H), 7.34-7.45 (m, 6H), 7.67 (d, J =8 Hz, 2H), 7.86 (s, 1H), 8.59 (s, 1H), 9.58 (s, 1H); MS 519.2 (M+H)+.

Analysis for $C_{31}H_{26}N_4O_2S$:

Calcd: C, 71.79; H, 5.05; N, 10.80.

Found: C, 71.96; H, 4.97; N, 10.60.

From the above flash column chromatography, is also isolated 37 mg of 2-[4-(hydroxymethyl)phenyl]-7-[(4-phenoxyphenyl)amino]thieno[3,2-b]pyridine-6-carbonitrile as yellow crystals, mp 225-228°C; ^{1}H NMR (DMSO-d_6) δ4.54 (d, J = 6 Hz, 2H), 5.31 (t, J = 6 Hz, 1H), 7.06-7.19 (m, 5H), 7.35-7.43 (m, 6H), 7.67 (d, J = 8 Hz, 2H), 7.86 (s, 1H), 8.59 (s, 1H), 9.58 (s, 1H); MS 450.3 (M+H)+.

Analysis for $C_{27}H_{19}N_3O_2S$- 0.50 H_2O:

Calcd: C, 70.71; H, 4.39; N, 9.16.

Found: C, 70.53; H, 4.02; N, 9.03.

Example 47

2-Iodo-7-[(3,4,5-trimethoxyphenyl)amino]thieno[3,2-b]pyridine-6-carbonitrile

A mixture of 3,4,5-trimethoxyaniline (964 mg, 5.26 mmol), pyridine hydrochloride (100 mg, 0.76 mmol) and 4-chloro-2-iodothieno[3,2-b]pyridine-6-carbonitrile (937 mg, 2.92 mmol) in 50 mL of 2-ethoxyethanol is heated at reflux overnight. The solution is poured into saturated aqueous sodium bicarbonate and the resulting solid is collected by filtration, washed with water and dried under reduced pressure. The resultant solid is purified by flash column chromatography eluting with 2% methanol in dichloromethane. The fractions containing product are combined and concentrated to provide 1.17 g of 2-iodo-7-[(3,4,5-trimethoxyphenyl)amino]thieno[3,2-b]pyridine-6-carbonitrile as white crystals, mp 254-256°C; ^{1}H NMR (DMSO-d_6) δ 3.70-3.78 (m, 9H), 6.66 (s, 2H), 7.72 (s, 1H), 8.53 (s, 1H), 9.56 (s, 1H); MS 468.1 (M+H)+.

Analysis for $C_{17}H_{14}IN_3O_3S$:

Calcd: C, 43.70; H, 3.02; N, 8.99.

Found: C, 43.96; H, 2.91; N, 8.98.

Example 48

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

A mixture of 4-phenoxyaniline (430 mg, 2.32 mmol), pyridine hydrochloride (244 mg, 2.11 mmol) and 2-bromo-4-chlorothieno[3,2-b]pyridine-6-carbonitrile (578 mg, 2.11 mmol) in 10 mL of 2-ethoxyethanol is heated at 125°C for 4 hours. The mixture is poured into diethyl ether and the solids are collected by filtration. The solids are stirred with saturated aqueous sodium bicarbonate for 1 hour. The solids are collected by filtration, washed with water and diethyl ether to give 717 mg of 2-bromo-7-[(4-phenoxyphenyl)amino]thieno[3,2-b]pyridine-6-carbonitrile as a tan solid, mp 248-250°C; ^{1}H NMR (DMSO-d_6) δ7.01-7.19 (m, 5H), 7.23-7.47 (m, 4H), 7.66 (s, 1H), 8.57 (s, 1H), 9.62 (s, 1H); MS 422.1, 424.1 (M+H)+.

Analysis for $C_{20}H_{12}BrN_3OS$-0.2 H_2O:

Calcd: C, 56.40; H, 2.93; N, 9.87.

Found: C, 56.34; H, 2.66; N, 9.91.

Example 49

7-[(4-Phenoxyphenyl)amino]-2-[(E)-2-pyridin-4-ylethenyl]thieno[3,2-b]pyridine-6-carbonitrile

A mixture of 2-bromo-7-[(4-phenoxyphenyl)amino]thieno[3,2-b]pyridine-6-carbonitrile (200 mg, 0.47 mmol), 4-vinylpyridine (79.7 mg, 0.75 mmol), palladium acetate (21.1 mg, 0.094 mmol) and tri-o-tolylphosphine (7.2 mg, 0.024 mmol) in 4 mL of N,N-dimethylformamide and 2.3 mL of triethylamine is heated at 125°C for 4 hours. After cooling to room temperature the reaction mixture is concentrated in vacuo and the residue is diluted with dichloromethane. The organic phase is washed with water and saturated aqueous sodium chloride, then dried over sodium sulfate, filtered and concentrated in vacuo.

The reaction is repeated a second time with the modification that the reaction mixture is now heated at 125°C for only 60 minutes. The crude products are combined and purified by thin layer preparative chromatography developing with 7% methanol in dichloromethane. A second thin layer preparative chromatography developing with 5% methanol in dichloromethane gives 16 mg of 7-[(4-phenoxyphenyl)amino]-2-[(E)-2-pyridin-4-ylethenyl]thieno[3,2-b]pyridine-6-carbonitrile as a yellow solid, mp 240-241°C; ^{1}H NMR (DMSO-d_6) δ 7.02-7.21 (m, 6H), 7.32-7.47 (m, 4H), 7.57-7.62 (m, 2H), 7.67 (s, 1H), 7.83 (d, J = 16 Hz, 1H), 8.56-8.62 (m, 3H), 9.60 (s, 1H); MS 446.9 (M+H)+.

Analysis for $C_{27}H_{18}N_4OS$-0.5 H_2O:

Calcd: C, 71.19; H, 4.20; N, 12.30.

Found: C, 71.06; H, 3.85; N, 12.09.

Example 50

tert-Butyl (2E)-3-{6-cyano-7-[(2,4-dichloro-5-methoxyphenyl)amino]thieno[3,2-b]pyridin-2-yl}prop-2-enoate

A mixture of tert-butyl (2E)-3-(7-chloro-6-cyanothieno[3,2-b]pyridin-2-yl)prop-2-enoate (1.29 g , 3.74 mmol), 2,4-dichloro-5-methoxyaniline (862 mg, 4.49 mmol), Tris(dibenzylideneacetone)-dipalladium(0) (343 mg, 0.37 mmol), potassium phosphate (1.29 g, 5.61 mmol) and 2-dicyclohexylphosphino-2'-(N,N-dimethylamino)biphenyl (456 mg, 1.16 mmol) in 36 mL of ethylene glycol dimethyl

ether is heated at 90°C for 3 hours. The reaction mixture is cooled to room temperature and partitioned between water and ethyl acetate. The aqueous layer is extracted with additional ethyl acetate and the organic layers are combined, dried over sodium sulfate, filtered and concentrated in vacuo. The residue is purified by flash column chromatography eluting with a gradient of hexane to 40% ethyl acetate in hexane to provide 974 mg of *tert*-butyl (2E)-3-{6-cyano-7-[(2,4-dichloro-5-methoxyphenyl)amino]thieno[3,2-b]pyridin-2-yl}prop-2-enoate as a light tan solid, mp 224°C dec; ^{1}H NMR (DMSO-d_6) δ 1.48 (s, 9H), 3.85 (s, 3H), 6.26 (d, J = 16 Hz, 1H), 7.37 (s, 1H), 7.75 (d, J = 16 Hz, 1H), 7.78 (s, 1H), 7.91 (s, 1H), 8.62 (s, 1H), 9.80 (s, 1H); MS 476.0, 478.0 (M+H)+.

Analysis for $C_{22}H_{19}Cl_2N_3O_3S$-0.4 H_2O:

Calcd: C, 54.64; H, 4.13; N, 8.69.

Found: C, 54.51; H, 3.96; N, 8.50.

Example 51

4-[(2,4-Dichloro-5-methoxyphenyl)amino]-2-[3-(4-methylpiperazin-1-yl)prop-1-ynyl]thieno[2,3-b]pyridine-5-carbonitrile

A mixture of 4-[(2,4-dichloro-5-methoxyphenyl)amino]-2-iodothieno[2,3-b]pyridine-5-carbonitrile (160 mg, 0.34 mmol), 1-methyl-4-prop-2-ynyl-piperazine (70 mg, 0.5 mmol), 15 mg of tetrakis(triphenylphosphine)palladium(0) and copper iodide (8 mg, 0.016 mmol) in 7 mL of benzene and 2 mL of triethylamine is heated at reflux for 7 hours. The reaction mixture is cooled to room temperature and partitioned between water and dichloromethane. The organic layer is dried over magnesium sulfate, filtered and concentrated in vacuo. The residue is triturated with ether and hexanes to provide 110 mg of 4-[(2,4-dichloro-5-methoxyphenyl)amino]-2-[3-(4-methylpiperazin-1-yl)prop-1-ynyl]thieno[2,3-b]pyridine-5-carbonitrile as an off white solid, mp 175°C (decomposition); ^{1}H NMR (DMSO-d_6) δ2.17 (s, 3H), 2.37 (bs, 4H), 2.54 (bs, 4H), 3.62 (s, 2H), 3.85 (s, 3H), 7.38 (s, 1H), 7.76 (s, 1H), 7.91 (s, 1H), 8.47 (bs, 1H), 9.83 (bs, 1H); MS 486.2 (M+H)+.

Analysis for $C_{23}H_{21}Cl_2N_5OS$:

Calcd: C, 56.79; H, 4.35; N, 14.40.

Found: C, 56.39; H, 4.33; N, 14.06.

Example 52

4-[(2,4-Dichloro-5-methoxyphenyl)amino]-2-(pyridin-3-ylethynyl)thieno[2,3-b]pyridine-5-carbonitrile

A mixture of 4-[(2,4-dichloro-5-methoxyphenyl)amino]-2-iodothieno[2,3-b]pyridine-5-carbonitrile (220 mg, 0.50 mmol), 3-ethynylpyridine (72 mg, 0.7 mmol), 20 mg of tetrakis(triphenylphosphine)palladium(0) and copper iodide (6 mg, 0.22 mmol) in 7 mL of benzene and 2 mL of triethylamine is heated at reflux for 5 hours. The reaction mixture is cooled to room temperature and a solid appears. The solid is triturated with hot ethyl acetate, filtered, washed with hexanes and dried under vacuum to provide 100 mg of 4-[(2,4-dichloro-5-methoxyphenyl)amino]-2-(pyridin-3-ylethynyl)thieno[2,3-b]pyridine-5-carbonitrile as a tan solid, mp 191°C (decomposition); ^{1}H NMR (DMSO-d_6 + TFA) δ3.88 (s, 3H), 7.37 (s, 1H), 7.43 (s, 1H), 7.78 (s, 1H), 7.85 (bs, 1H), 8.16 (s, 1H), 8.39 (bs, 1H), 8.54 (s, 1H), 10.02 (bs, 1H); MS 451.0 (M+H)+.

Analysis for $C_{22}H_{12}Cl_2N_4OS - 0.1\ H_2O$:

Calcd: C, 58.55; H, 2.68; N, 12.41.

Found: C, 58.31; H, 2.71; N, 12.36.

Example 53

(2E)-3-(6-Cyano-7-[(2,4-dichloro-5-methoxyphenyl)amino]thieno[3,2-b]pyridin-2-yl)prop-2-enoate

A solution of *tert*-butyl (2E)-3-{6-cyano-7-[(2,4-dichloro-5-methoxyphenyl)amino]thieno[3,2-b]pyridine-2yl)prop-2-enoate (910.8 mg, 1.91 mmol), trifluoroacetic acid (2.18 g, 19.1 mmol) in 27 mL of dichloromethane is stirred at room temparature for 3 days, then concentrated in vacuo. The residue is triturated with ether to provide 741 mg of (2E)-3-(6-cyano-7-[(2,4-dichloro-5-methoxyphenyl)amino]thieno[3,2-b]pyridin-2-yl)prop-2-enoic acid as a beige solid, mp >250°C; ^{1}H NMR (DMSO-d_6) δ 3.84 (s, 3H), 6.28 (d, J = 16 Hz, 1H), 7.38 (s, 1H), 7.70 - 7.88 (m, 2H), 7.90 (s, 1H), 8.62 (s, 1H), 9.81 (s, 1H), 12.50 (s, 1H); MS 420.1, 422.0 (M+H)+.

Analysis for $C_{18}H_{11}Cl_2N_3O_3S$:

Calcd: C, 51.44; H, 2.64; N, 10.00

Found: C, 51.52; H, 2.81; N, 9,68.

Example 54

7-[(2,4-Dichloro-5-methoxyphenyl)amino]-2-(2-formyl-1-methyl-1H-imidazol-5-yl)thieno[3,2-b]pyridine-6-carbonitrile

A mixture of 7-[(2,4-dichloro-5-methoxyphenyl)amino]-2-iodothieno[3,2-b]pyridine-6-carbonitrile (443.2 mg, 0.93 mmol), 1-methyl-5-(tributylstannyl)-1H-imidazole-2-carbaldehyde (743.1 mg, 1.86 mmol), dichlorobis(triphenylphosphine)palladium(II) (33.0 mg, 0.047 mmol) and triethylamine (103.2 mg, 1.02 mmol) in 8.0 mL of 1,4-dioxane is heated at 110°C for 3 hours. After cooling, the mixture is treated with saturated aqueous sodium bicarbonate and extracted with ethyl acetate. The organic phases 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 5% ethyl acetate in dichloromethane to 50% ethyl acetate in dichloromethane to provide 222.7 mg of 7-(2,4-dichloro-5-methoxyphenyl)amino]-2-(2-formyl-1-methyl-1H-imidazol-5-yl)thieno[3,2-b]pyridine-6-carbonitrile as a yellow solid, mp 225-227°C; ^{1}H NMR (DMSO-d_6) δ 3.86 (s, 3H), 4.08 (d, 3H), 7.41 (s, 1H), 7.63 (s, 1H), 7.77 (s, 1H), 7.90 (s, 1H), 8.67 (s, 1H), 9.77 (s, 1H), 9.87 (s, 1H); MS 458.1, 460.1 (M+H)+.

Analysis for $C_{20}H_{13}Cl_2N_5O_2S$ - 0.5 H_2O:

Calcd: C, 51.40; H, 3.02; N, 14.98

Found: C, 51.43; H, 2.88; N, 14.60.

Example 55

2-(4-Formylphenyl)-7-[(3,4,5-trimethoxyphenyl)amino]thieno[3,2-b]pyridine-6-carbonitrile

A mixture of 2-iodo-7-[(3,4,5-trimethoxyphenyl)amino]thieno[3,2-b]pyridine-6-carbonitrile (500 mg, 1.07 mmol), 4-formylphenylboronic acid (240.7 mg, 1.61 mmol), tetrakis(triphenylphosphine)palladium(0) (61.8 mg, 0.054 mmol) in 16 mL of saturated aqueous sodium bicarbonate and 20 mL of ethylene glycol dimethyl ether is heated at reflux for 3 h. After cooling, the mixture is treated with water. The precipitate is filtered, washed with water, ethyl acetate, and ether, then dried in vacuo to provide 447.2 mg of 2-(4-formylphenyl)-7-[(3,4,5-trimethoxyphenyl)amino]thieno[3,2-b]pyridine-6-carbonitrile as a yellow solid, mp

268-270°C; ^{1}H NMR (DMSO-d_6) δ 3.73 (s, 3H), 3.75 (s, 6H), 6.69 (s, 2H), 7.94 (d, J = 8 Hz, 2H), 8.00 (d, J = 8 Hz, 2H), 8.10 (s, 1H), 8.64 (s, 1H), 9.64 (s, 1H), 10.00 (s, 1H); HRMS 446.11691 (M+H)+.

Example 56

7-[(2,4-Dichloro-5-methoxyphenyl)amino]-2-[(1E)-3-(4-methylpiperazin-1-yl)-3-oxoprop-1-enyl]thieno[3,2-b]pyridine-6-carbonitrile

A mixture of (2E)-3-{6-cyano-7-[2,4-dichloro-5-methoxyphenyl)amino]thieno[3,2-b]pyridine-2-yl}prop-2-enoic acid (68.8 mg, 0.16 mmol), benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate (109.3 mg, 0.21 mmol), diisopropylethylamine (103.4 mg, 0.80 mmol), 1-methylpiperazine (16 mg, 0.1 mmol) in 2.5 mL of dichloromethane is stirred at room temperature under nitrogen for 18 hours, and then quenched with saturated aqueous sodium bicarbonate. The organic phase is separated and the aqueous phase is extracted with dichloromethane. The organic phases are combined and washed with brine, dried over sodium sulfate, filtered and concentrated in vacuo. The residue is purified by preparative thin layer chromatography developing with 7% methanol in dichloromethane to provide 43.8 mg of 7-[(2,4-dichloro-5-methoxyphenyl)amino]-2-[(1E)-3-(4-methylpiperazin-1-yl)-3-oxoprop-1-enyl]thieno[3,2-b]pyridine-6-carbonitrile as an off white solid, mp 218-220°C; ^{1}H NMR (DMSO-d_6) δ2.19 s, 3H), 2.31 (s, 4H), 3.55 (s, 2H), 3.62 (s, 2H), 3.84 (s, 3H), 7.16 (d, J= 15 Hz, 1H), 7.31 (s, 1H),7.62 (d, J= 15 Hz, 1H), 7.73 (s, 1H), 7.92 (s, 1H), 8.58 (s, 1H), 9.77 (s, 1H); MS 502.2, 504.2 (M+H)+.

Analysis for $C_{23}H_{21}Cl_2N_5O_2S$:

Calcd: C, 54.98; H, 4.21; N, 13.94.

Found: C, 54.67; H, 4.28; N, 13.55.

Example 57

2-[3-(4-Methylpiperazin-1-yl)prop-1-ynyl]-7-[(3,4,5-trimethoxyphenyl)amino]thieno[3,2-b]pyridine-6-carbonitrile

A mixture of 2-iodo-7-[(3,4,5-methoxyphenyl)amino]thieno[3,2-b]pyridine-6-carbonitrile (200 mg, 0.43 mmol), 1-methyl-4-prop-2-ynyl-piperazine (89.1 mg, 0.65 mmol), 9.9 mg of tetrakis(triphenylphosphine)palladium(0) and 2.1 mg of copper(I)

iodide in 2 mL of triethylamine and 7 mL of benzene is heated at reflux for 7 hours. The mixture is cooled to room temperature and 2 mL of methanol are added. The solvents are removed in vacuo and the residue is treated with 10 mL of chloroform. The insoluble material is removed by filtration, washing with chloroform. The filtrate is concentrated in vacuo and the residue is purified by preparative thin layer chromatography developing with 10% methanol in dichloromethane to provide 112.1 mg of 2-[3-(4-methylpiperazin-1-yl)prop-1-ynyl]-7-[(3,4,5-trimethoxyphenyl)amino]thieno[3,2-b]pyridine-6-carbonitrile as a beige solid, mp 180-182°C; ^{1}H NMR (DMSO-d_6) δ2.35 (s, 3H), 2.50 (s, 2H), 2.56 (s, 6H), 3.62 (s, 2H), 3.71 (s, 3H), 3.74 (s, 6H), 6.68 (s, 2H), 7.59 (s, 1H), 8.61 (s, 1H), 9.62 (s, 1H); MS 478.2, (M+H)+.

Analysis for $C_{25}H_{27}N_5O_3S$ - $0.5H_2O$:

Calcd: C, 61.71; H, 5.80; N, 14.39.

Found: C, 61.84; H, 5.58; N, 14.53.

Example 58

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

1-Methylpiperazine (135.2 mg, 1.35 mmol) is added to a suspension of 2-(4-formylphenyl)-7-[3,4,5-trimethoxyphenyl)amino]thieno[3,2-b]pyridine-6-carbonitrile (200 mg, 0.45 mmol) in 8 mL of dichloromethane and 1.1 mL of N,N-dimethylformamide The reaction mixture is cooled to 0°C and sodium triacetoxyborohydride (572.2 mg, 2.70 mmol) is added. After stirring at 0°C for 10 minutes, 0.13 mL of acetic acid are added and the reaction mixture is allowed to warm to room temperature and stirred for 2 hours. The reaction is quenched by the addition of water and then partitioned between saturated aqueous sodium bicarbonate and dichloromethane. The organic layer is washed with brine, dried over sodium sulfate, filtered and concentrated in vacuo. The residue is purified by preparative thin layer chromatography developing with 12% methanol in dichloromethane to give a solid which is triturated with ether and ethyl acetate (1: 1), to provide 125.2 mg of 2-{4-[(4-methylpiperazin-1-yl)methyl]phenyl}-7-[(3,4,5-trimethoxyphenyl)amino]thieno[3,2-b]pyridine-6-carbonitrile as a beige solid, mp 189-191°C; ^{1}H NMR (DMSO-d_6) δ2.15 (s, 3H), 2.35 (s, 8H), 3.47 (s, 2H), 3.72 (s, 3H),

3.75 (s, 6H), 6.67 (s, 2H), 7.39 (d, J= 8 Hz, 2H), 7.66 (d, J= 8 Hz, 2H), 7.86 (s, 1H), 8.60 (s, 1H), 9.55 (s, 1H); MS 530.2 (M+H)+.

Analysis for $C_{29}H_{31}N_5O_3S$ -1.0 H_2O:

Calcd: C, 63.60; H, 6.07; N, 12.79.

Example 59

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

To a solution of 7-[(2,4-dichloro-5-methoxyphenyl)amino]-2-(2-formyl-1-methyl-1H-imidazole-5-yl)thieno[3,2-b]pyridine-6-carbonitrile (200.6 mg, 0.44 mmol) 1-methylpiperazine (132.2 mg, 1.32 mmol) in 4.3 mL of dichloromethane and 1.1 mL of N,N-dimethylformamide is added sodium triacetoxyborohydride (559.5 mg, 2.64 mmol) in portions at 0-5°C followed by 0.13 mL of acetic acid. The resulting reaction mixture is stirred for 30 minutes, allowed to warm to room temperature and stirred for 5 hours. The reaction is quenched by the addition of water and then partitioned between saturated aqueous sodium bicarbonate and dichloromethane. The organic layer is 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 5% methanol in dichloromethane to 20% methanol in dichloromethane to provide 145.2 mg of 7-[(2,4-dichloro-5-methoxyphenyl)amino]-2-{1-methyl-2-[(4-methylpiperazine-1-yl)methyl]-1H-imidazole-5-yl}thieno[3,2-b]pyridine-6-carbonitrile as an off white solid, mp 234-235°C; ^{1}H NMR (DMSO-d_6) δ2.18 (s, 3H), 2.41 (s, 8H), 3.59 (s, 2H), 3.77 (s, 3H), 3.85 (s, 3H), 7.14 (s,1H), 7.37 (s, 1H), 7.63 (s, 1H), 7.75 (s, 1H), 8.60 (s, 1H), 9.74 (s, 1H); MS 542.2, 544.1 (M+H)+.

Analysis for $C_{25}H_{25}Cl_2N_7OS$ - 0.9 H_2O:

Calcd: C, 53.74; H, 4.83; N, 17.55.

Found: C, 53.39; H, 4.61; N, 17.45.

Example 60

7-[(2,4-Dichloro-5-methoxyphenyl)amino]-2-[3-(4-methylpiperazin-1-yl)prop-1-ynyl] thieno[3,2-b]pyridine-6-carbonitrile

A mixture of 7-[(2,4-dichloro-5-methoxyphenyl)amino]-2-iodothieno[3,2-b]pyridine-6-carbonitrile (200 mg, 0.42 mmol), 1-methyl-4-prop-2-ynyl-piperazine (87.0 mg, 0.65 mmol), 9.7 mg of tetrakis(triphenylphosphine)palladium(0) and 2.0 mg of copper(I) iodide in 2 mL of triethylamine and 7 mL of benzene is heated at reflux for 5 hours. The mixture is cooled to room temperature and 2 mL of methanol are added. The solvents are removed in vacuo and the residue is purified by preparative thin layer chromatography developing with 12% methanol in dichloromethane to give a solid which is triturated with ether containing several drops of dichloromethane, to provide 89.6 mg of 7-[(2,4-dichloro-5-methoxyphenyl)amino]-2-[3-(4-methylpiperazin-1-yl)prop-1-ynyl]thieno[3,2-b]pyridine-6-carbonitrile as a yellow solid, mp 172-173°C; ^{1}H NMR (DMSO-d_6) δ2.18 (s, 3H), 2.37 (s, 4H), 2.49 (s, 4H), 3.59 (s, 2H), 3.85 (s, 3H), 7.37 (s, 1H), 7.62 (s, 1H), 7.78 (s, 1H), 8.62 (s, 1H), 9.82 (s 1H); MS 486.1, 488.1 (M+H)+.

Analysis for $C_{23}H_{21}Cl_2N_5OS$:

Calcd: C, 56.79; H, 4.35; N, 14.40.

Found: C, 56.39; H, 4.28; N, 14.19.

Example 61

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

A suspension of 2 M dimethylamine in tetrahydrofuran (1.13 mL, 2.25 mmol) and 2-(4-formylphenyl)-7-[3,4,5-trimethoxyphenyl)amino]thieno[3,2-b]pyridine-6-carbonitrile (200 mg, 0.45 mmol) in 4.5 mL of dichloromethane and 1.1 mL of N,N-dimethylformamide is cooled to 0°C and sodium triacetoxyborohydride (572.2 mg, 2.70 mmol) is added. After stirring at 0°C for 5 minutes, 0.13 mL of acetic acid are added and the reaction mixture is allowed to warm to room temperature and stirred for 17 hours. The reaction is quenched by the addition of water and then partitioned between saturated aqueous sodium bicarbonate and dichloromethane. The organic layer is dried over sodium sulfate, filtered and concentrated in vacuo. The residue is purified by flash column chromatography eluting with a gradient of 1% methanol in

ichloromethane to 10% methanol in dichloromethane to provide 147.2 mg 2-{4-dimethylamino)methyl]phenyl}-7-[(3,4,5-trimethoxyphenyl)amino]thieno[3,2-]pyridine-6-carbonitrile as a yellow solid, mp 199-201°C; ^{1}H NMR (DMSO-d_6) δ2.15 s, 6H), 3.41 (s, 2H), 3.72 (s, 3H), 3.75 (s, 6H), 6.67 (s, 2H), 7.39 (d, J = 8 Hz, 2H), .66 (d, J = 8 Hz, 2H), 7.87 (s, 1H), 8.60 (s, 1H), 9.54 (s, 1H); MS 475.2 (M+H)+.

nalysis for $C_{26}H_{26}N_4O_3S$ – 0.6 H_2O:

alcd: C, 64.34; H, 5.65; N, 11.54.

ound: C, 64.19; H, 5.68; N, 11.49.

Example 62

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

To a suspension of 2-(4-formylphenyl)-7-[2,4-dichloro-5-ethoxyphenyl)amino]thieno[3,2-b]pyridine-6-carbonitrile (312 mg, 0.69 mmol) and .73 mL of 2 M dimethylamine in tetrahydrofuran (3.45 mmol) in 6.9 mL of ichloromethane and 1.7 mL of N,N-dimethylformamide at 0°C is added sodium iacetoxyborohydride (877 mg, 4.14 mmol). After stirring at 0°C for 5 minutes, 0.20 nL of acetic acid are added and the reaction mixture is allowed to warm to room emperature and stirred for 17 hours. The reaction is quenched by the addition of vater and then partitioned between saturated aqueous sodium bicarbonate and ichloromethane. The organic layer is dried over sodium sulfate, filtered and oncentrated in vacuo. The residue is purified by flash column chromatography eveloping with a gradient of from 1% to 10% methanol in dichloromethane to give a olid which is washed with hexane to provide 222 mg of 7-[(2,4-dichloro-5-ethoxyphenyl)amino]-2-{4-[(dimethylamino)methyl]phenyl}thieno[3,2-b]pyridine-6 arbonitrile as a tan solid, mp 224-225°C; ^{1}H NMR (DMSO-d_6) δ2.17 (s, 6H), 3.44 (s, H), 3.86 (s, 3H), 7.37 (s, 1H), 7.40 (d, J= 8 Hz, 2H), 7.68 (d, J= 8 Hz, 2H), 7.76 (s, H), 7.90 (s, 1H), 8.60 (s, 1H), 9.73 (s, 1H); MS 483.1, 485.1 (M+H)+.

nalysis for $C_{24}H_{20}Cl_2N_4OS$ – 0.5 H_2O:

alcd: C, 58.54; H, 4.30; N, 11.38.

ound: C, 58.45; H, 4.20; N, 11.27.

Evaluation of representative compounds of this invention in several standard harmacological 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 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 eczema.

Example 63

N-(6-Cyanothieno[3,2-b]pyridin-7-yl)-N-(2,4-dichloro-5-methoxyphenyl)acetamide

A mixture of 7-[(2,4-dichloro-5-methoxyanilino)amino]thieno[3,2-b]pyridine-6-carbonitrile (332 mg, 0.95 mmol), acetic anhydride (976 mg, 9.5 mmol), and 4-(dimethylamino)pyridine (140 mg, 1.14 mmol) in 3 mL of pyridine are heated at reflux for 2 hours. The mixture is cooled to room temperature and concentrated in vacuo. Dichloromethane and water are added and the organic layer is extracted, dried over magnesium sulfate and filtered. The filtrate is concentrated in vacuo and the residue is purified by chromatography eluting with 2% methanol in dichloromethane to provide 280 mg of N-(6-cyanothieno[3,2-b]pyridin-7-yl)-N-(2,4-

lichloro-5-methoxyphenyl)acetamide as a white solid, mp 202-204°C; ^{1}H NMR DMSO-d_6) δ 2.23 (s, 3H), 3.95 (s, 3H), 7.69 (d, J = 6 Hz, 1H), 7.84 (s, 2H), 8.35 (d, = 6 Hz, 1H), 9.11 (s, 1H); MS 392.0 (M+H)+.

\nalysis for $C_{17}H_{11}Cl_2N_3O_2S$:

Calcd: C, 52.05; H, 2.83; N, 10.71.

Found: C, 52.44; H, 2.93; N, 10.45.

Example 64

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

A mixture of 4-[(2,4-dichloro-5-methoxyphenyl)amino]-2-iodothieno[3,2-b]pyridine-5-carbonitrile (250 mg, 0.53 mmol), E-styrylboronic acid (90 mg, 0.60 mmol), 20 mg of tetrakis(triphenylphosphine)palladium(0), 390 mg of potassium phosphate, and 0.1 mL of water in 3 mL of toluene is heated at 110°C overnight. The mixture is cooled to room temperature and ethyl acetate and water are added. The solid is collected by filtration, dissolved in a hot mixture of methanol and dichloromethane and passed through celite. The filtrate is concentrated in vacuo and dried to give 48 mg of 7-[(2,4-dichloro-5-methoxyphenyl)amino]-2-[(E)-2-phenylvinyl]thieno[3,2-b]pyridine-6-carbonitrile as a light yellow solid. The ethyl acetate layer is separated, dried over magnesium sulfate and filtered. The filtrate is concentrated in vacuo and the residue is purified by chromatography eluting with a gradient of 0 to 5% methanol in dichloromethane. The fractions are concentrated and the solid is triturated with hot ether, filtered and dried to provide an additional 49 mg of product, mp 236-238°C; ^{1}H NMR (DMSO-d_6) δ 3.85 (s, 3H), 7.15 (d, J = 16 Hz, 1H), 7.31-7.42 (m, 4H), 7.54 (d, J = 16 Hz, 1H), 7.56-7.65 (m, 3H), 7.77 (s, 1H), 8.58 (s, 1H), 9.66 (s, 1H); HRMS 452.0.3872 (M+H)+.

Example 65

7-[(2,4-Dichloro-5-methoxyphenyl)amino]-2-{[1-(2-morpholin-4-ylethyl)-1H-pyrazol-4-yl]ethynyl}thieno[3,2-b]pyridine-6-carbonitrile

A mixture of 7-[(2,4-dichloro-5-methoxyphenyl)amino]-2-(1H-pyrazol-4-ylethynyl)thieno[3,2-b]pyridine-6-carbonitrile (57 mg, 0.13 mmol), 4-(2-chloroethyl)morpholine hydrochloride (24 mg, 0.13 mmol), and cesium carbonate (42 mg, 0.13 mmol) in 1 mL of dimethylformamide is heated at 50°C overnight. The mixture is cooled to room temperature and then added to water. The resulting precipitate is collected by filtration. The collected solid is purified by flash column chromatography, eluting with 1:7 methanol : ethyl acetate to provide 50 mg of 7-[(2,4-dichloro-5-methoxyphenyl)amino]-2-{[1-(2-morpholin-4-ylethyl)-1H-pyrazol-4-yl]ethynyl}thieno[3,2-b]pyridine-6-carbonitrile as a yellow solid, mp greater than 200°C; ^{1}H NMR (DMSO-d6) δ 2.44 (br s, 4H), 2.62 (t, 2H), 3.53 (br s, 4H), 3.81 (s, 3H), 4.23 (br s, 2H), 6.77 (s, 1H), 7.57 (s, 1H), 7.71 (s, 1H), 7.80 (br, 1H), 8.24 (br, 1H), 8.37 (s, 1H), 13.36 (br s, 1H); MS 553.1 (M+H)+.

Example 66

7-[(2,4-Dichloro-5-methoxyphenyl)amino]-2-[(E)-2-(2H-1,2,3-triazol-2-yl)vinyl]thieno[3,2-b]pyridine-6-carbonitrile

To a mixture of 1,2,3-triazole (50 □L, 0.81 mmol) and cesium hydroxide monohydrate (18 mg, 0.11 mmol) in 1-methyl-2-pyrrolidinone (5 mL) is added slowly 7-[(2,4-dichloro-5-methoxyphenyl)amino]-2-ethynylthieno[3,2-b]pyridine-6-carbonitrile (200 mg, 0.54 mmol). The mixture is heated to 120°C for 12 hours, cooled to room temperature and partitioned between water and ethyl acetate. The organic layer is washed with water, dried over sodium sulfate, and concentrated *in vacuo*. The residue is purified by flash column chromatography eluting with a gradient of methanol in dichloromethane (0-2%) to provide 90 mg (38%) of 7-[(2,4-dichloro-5-methoxyphenyl)amino]-2-[(E)-2-(2H-1,2,3-triazol-2-yl)vinyl]thieno[3,2-b]pyridine-6-carbonitrile as a yelllow solid, mp 315-316°C; ^{1}H NMR (DMSO-d_6-TFA) δ 3.88 (s, 3H), 7.50 (s, 1H), 7.65 (d, J = 14 Hz, 1H), 7.85 (s, 1H), 7.88 (s, 1H), 8.15 (s, 2H), 8.32 (d, J = 14 Hz, 1H), 9.01 (s, 1H); MS 443.0 (M+H)+.

Analysis for $C_{19}H_{12}Cl_2N_6OS - 0.1\ CH_2Cl_2$:

Calcd: C, 50.77; H, 2.72; N, 18.60

Found: C, 50.54; H, 2.32; N, 18.25.

Example 67

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

Prepared as for example 37, MS 441.1,446.1 (M+H)+, mp > 250.

Example 68

7-[(2,4-dichloro-5-methoxyphenyl)amino]-2-[5-(1,3-dioxolan-2-yl)-2-furyl]thieno[3,2-b]pyridine-6-carbonitrile

Prepared as for ecample 36, MS 488.1, 490.1, mp 187-189.

Example 69

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

Prepared as for example 15, MS 527.9, 529.9 (M+H)+, mp 215-217.

Example 70

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

Prepare as for example 15, MS 552.0 (M+H)+, mp 198-200.

Example 71

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

Prepared as for example 15, HRMS 452.0387, mp 230 decomposition.

Example 72

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

Prepared as for example 15, MS 540 (M+H)+, mp > 245.

Example 73

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

Prepared as for example 14, MS 469.0, 471.1 (M+H)+, mp 255-258.

Example 74

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

Prepared as for example 15, MS 538.0, 540.0 (M+H)+, mp 178-180.

Example 75

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

Prepared as for example 15, MS 483.0, 485.0 (M+H)+, mp 204-206.

Example 76

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

Prepared as for example 15, MS 473.0, 475.0 (M+H)+, mp 200-202.

Example 77

7-[(2,4-dichloro-5-methoxyphenyl)amino]-2-[5-(1,3-dioxolan-2-yl)thien-2-yl]thieno[3,2-b]pyridine-6-carbonitrile

Prepared as for example 36, MS 503.8, 505.8 (M+H)+, mp 213-217.

Example 78

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

Prepared as for example 14, MS 459.9 (M+H)+, mp 128-130.

Example 79

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

Prepared as for example 37, MS 459.9, 461.8 (M+H)+, mp > 245.

Example 80

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

Prepared as for example 15, MS 488.9, 490.9 (M+H)+, mp 184-186.

Example 81

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

Prepared as for example 15, MS 544.0, 546.0 (M+H)+, softens 182, mp 200-202.

Example 82

7-({3-chloro-4-[(1-methyl-1H-imidazol-2-yl)thio]phenyl}amino)-2-iodothieno[3,2-b]pyridine-6-carbonitrile

Prepared as for example 47. MS 523.8(M+H)+, mp 290-291.

Example 83

7-({3-chloro-4-[(1-methyl-1H-imidazol-2-yl)thio]phenyl}amino)-2-[4-(morpholin-4-ylmethyl)phenyl]thieno[3,2-b]pyridine-6-carbonitrile

Prepared as for example 14, MS 573.3(M+H)+, mp 150-152.

Example 84

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

Prepared as for example 15, MS 544.2 (M+H)+, mp 218-219.

Example 85

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

Prepared as for example 15, MS 554.3 (M+H)+, mp 205 decomp.

Example 86

7-({3-chloro-4-[(1-methyl-1H-imidazol-2-yl)thio]phenyl}amino)-2-[4-(morpholin-4-ylbut-1-ynyl)thieno[3,2-b]pyridine-6-carbonitrile

Prepared as for example 21, MS 535.3, 537.2 (M+H)+, mp 195-200.

Example 87

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

Prepared as for example 21, MS 508.2, 510.2 (M+H)+, mp 190-191.

Example 88

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

Prepared as for example 15, MS 486.8, 488.8 (M+H)+, mp 210-212.

Example 89

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

Prepared as for example 15, MS 546.1 (M+H)+, mp 128-130.

Example 90

7-[(2,4-dichloro-5-methoxyphenyl)amino]-2-(1H-pyrrol-3-yl)thieno[3,2-b]pyridine-'6-carbonitrile

Prepared as for example 14, MS 415.0 (M+H)+, mp > 245.

Example 91

7-({3-chloro-4-[(1-methyl-1H-imidazol-2-yl)thio]phenyl}amino)-2-[3-(dimethylamino)prop-1-ynyl]thieno[3,2-b]pyridine-6-carbonitrile

Prepared as for example 21, MS 479.0, 481.1 (M+H)+, mp 204-207.

Example 92

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

Prepared as for example 15, MS 513.0 (M+H)+, mp 162-164.

Example 93

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

Prepared as for example 15, MS 527.0 (M-H)-, mp 154-156.

Example 94

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

Prepared as for example 15, MS 541.0 (M+H)+, mp 198-201.

Example 95

7-[(2,4-dichloro-5-methoxyphenyl)amino]-2-[4-(piperazin-1-ylmethyl)phenyl]thieno[3,2-b]pyridine-6-carbonitrile

Prepared as for example 15, MS 524.1 (M+H)+, mp 218-220.

Example 96

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

Prepared as for example 36, MS 511.0, 513.0 (M+H)+, mp > 250.

Example 97

7-({3-chloro-4-[(1-methyl-1H-imidazol-2-yl)thio]phenyl}amino)-2-(4-formylphenyl)thieno[3,2-b]pyridine-6-carbonitrile

Prepared as for example 14, MS 502.0 (M+H)+, mp 279-281.

Example 98

7-({3-chloro-4-[(1-methyl-1H-imidazol-2-yl)thio]phenyl}amino)-2-{4-[(diethylamino)methyl]phenyl}thieno[3,2-b]pyridine-6-carbonitrile

Prepared as for example 15, MS 559.0 (M+H)+, mp 200-203.

Example 99

7-({3-chloro-4-[(1-methyl-1H-imidazol-2-yl)thio]phenyl}amino)-2-{4-[(4-methylpiperazin-1-yl)methyl]phenyl}thieno[3,2-b]pyridine-6-carbonitrile

Prepared as for example 15, MS 585.0 (M+H)+, mp 221-224.

Example 100

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

Prepared as for example 21, MS 508.0 (M+H)+, mp 215-217.

Example 101

7-[(2,4-dichloro-5-methoxyphenyl)amino]-2-(1H-pyrazol-4-ylethynyl)thieno[3,2-b]pyridine-6-carbonitrile

Prepared as for example 34, MS 440.0 (M+H)+, mp +200 decomposition.

Example 102

7-[(2,4-dichlorophenyl)amino]-2-iodothieno[3,2-b]pyridine-6-carbonitrile

Prepared as for example 1, MS 445.8, 447.8 (M+H)+, mp 230-233.

Example 103

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

Prepared as for example 36, MS 539.0 (M+H)+, mp 229-232.

Example 104

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

Prepared as for example 15, MS 511.0 (M+H)+, mp 167-169.

Example 105

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

Prepared as for example 15, MS 557.0 (M+H)+, mp 242-245.

Example 106

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

Prepared as for example 15, MS 511.0 (M+H)+, mp 160-162.

Example 107

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

Prepared as for example 15, MS 513.1 (M+H)+, mp 141-143.

Example 108

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

Prepared as for example 36, MS 526.0, 528.0 (M+H)+, mp 227-229.

Example 109

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

Prepared as for example 36, MS 512.1, 514.1 (M+H)+, mp 225-227.

Example 110

7-[(2,4-dichloro-5-ethoxyphenyl)amino]-2-iodothieno[3,2-b]pyridine-6-carbonitrile

Prepared as for example 1, MS 489.9, 491.9 (M+H)+, mp 232-233.

Example 111

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

Prepared as for example 15, MS 573.1 (M+H)+, mp > 245.

Example 112

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

Prepared as for example 15, MS 601.2 (M+H)+, mp 245-247.

Example 113

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

Prepared as for example 15, MS 600.2 (M+H)+, mp 238-240.

Example 114

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

Prepared as for example 15, MS 552.2 (M+H)+, mp 165-168.

Example 115

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

Prepared as for example 14, MS 424.0, 426.1 (M+H)+, mp 170-171.

Example 116

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

Prepared as for example 14, MS 468.1, 470.1 (M+H)+, mp > 245.

Example 117

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

Prepared as for example 20, MS 552.1, 554.1 (M+H)+, mp 240-243 dec.

Example 118

7-({3-chloro-4-[(1-methyl-1H-imidazol-2-yl)thio]phenyl}amino)-2-[3-(diethylamino)prop-1-ynyl]thieno[3,2-b]pyridine-6-carbonitrile

Prepared as for example 21, MS 507.1, 509.2(M+H)+, mp 190-194.

Example 119

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

Prepared as for example 15, MS 508.1, 510.1 (M+H)+, mp 245-247.

Example 120

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

Prepared as for example 15, MS 630.1 (M+H)+, mp 176-179.

Example 121

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

Prepared as for example 15, MS 525.1 (M+H)+, mp 195-197.

Example 122

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

Prepared as for example 15, MS 602.1 (M+H)+, mp 211-213.

Example 123

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

Prepared as for example 15, MS 552.2, 554.2 (M+H)+, mp 227-229.

Example 124

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

Prepared as for example 15, MS 615.1 (M+H)+, mp 105-107.

Example 125

7-[(2,4-dichloro-5-methoxyphenyl)amino]-2-{1-[2-(dimethylamino)ethyl]-1H-pyrrol-3-yl}thieno[3,2-b]pyridine-6-carbonitrile

Prepared as for example 65, MS 486.2 (M+H)+, mp 230 decomposition.

Example 126

7-[(2,4-dichlorophenyl)amino]-2-[4-(dimethylamino)phenyl]thieno[3,2-b]pyridine-6-carbonitrile

Prepared as for example 50, MS 439.2, 441.1 (M+H)+, mp 239-241.

Example 127

7-[(2,4-dichloro-5-methoxyphenyl)amino]-2-[(1-methyl-1H-imidazol-5-yl)ethynyl]thieno[3,2-b]pyridine-6-carbonitrile

Prepared as for example 21, MS 454.1 (M+H)+, mp >260.

Example 128

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

Prepared as for example 36, MS 484.1, 486.1 (M+H)+, mp 221-223.

Example 129

7-[(2,4-dichloro-5-methoxyphenyl)amino]-2-(1H-pyrazol-4-yl)thieno[3,2-b]pyridine-6-carbonitrile

Prepared as for example 14, MS 416.0 (M+H)+, mp +250 decomposition.

Example 130

7-[(2,4-dichloro-5-methoxyphenyl)amino]-2-{[1-(2-hydroxyethyl)-1H-pyrazol-4-yl]ethynyl}thieno[3,2-b]pyridine-6-carbonitrile

Prepared as for example 65, MS 484.0 (M+H)+, mp 172.5.

Example 131

7-[(2,4-dichloro-5-methoxyphenyl)amino]-2-[1-(2-morpholin-4-ylethyl)-1H-pyrazol-4-yl]thieno[3,2-b]pyridine-6-carbonitrile

Prepared as for example 65, MS 529.1 (M+H)+, mp 155.2.

Example 132

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

Prepared as for example 36, MS 484.0, 486.0 (M+H)+, mp 229-231.

Example 133

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

Prepared as for example 36, MS 512.0, 514.0 (M+H)+, mp 192-193.

Example 134

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

Prepared as for example 14, MS 497.0, 499.0 (M+H)+, mp 196-197.

Example 135

7-[(2,4-dichloro-5-methoxyphenyl)amino]-2-[1-(2-hydroxyethyl)-1H-pyrazol-4-yl]thieno[3,2-b]pyridine-6-carbonitrile

Prepared as for example 60, MS 460.0 (M+H)+, mp +250 decomposition.

Example 136

4-{6-cyano-7-[(2,4-dichloro-5-methoxyphenyl)amino]thieno[3,2-b]pyridin-2-yl}-N,N-dimethylbenzamide

Prepared as for example 14, MS 497.1, 499.0 (M+H)+, mp 246-249.

Example 137

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

Prepared as for example 15, MS 528.1, 530.1 (M+H)+, mp 189-192.

Example 138

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

Prepared as for example 14, MS 444.0, 446.0 (M+H)+, mp 223-224.

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 1. Multiple entries for a given compound indicate that it was tested multiple times.

Table 1

Example	Src cells IC_{50} μM	Src cells % inh at 10μM	Src cells % inh at 100μM
1	nt		
2	>10		
3	37		
4	3.1		

Table 1

Example	Src cells IC_{50} μM	Src cells % inh at 10μM	Src cells % inh at 100μM
5	5.6		
6			3
7		31	
8		33	
9	20		
10	39		
11	23, 23		
12		23	
13		34	
14	0.66		
15	0.56, 0.26		
16	0.67		
17	0.37		
18	1.0		

Table 1

Example	Src cells IC_{50} μM	Src cells % inh at 10μM	Src cells % inh at 100μM
19	>10		
20	1.0		
21	32, 32		
22	1.0		
23	5.6		
24	3.8		
25	1.1		
26	1.0		
27			19, 28
28	5.9		
29	17, 50		
30	23, 25		
31	35, 35		
32	1.5		
33	0.88		

Table 1

Example	Src cells IC_{50} μM	Src cells % inh at 10μM	Src cells % inh at 100μM
34	8.6		
35	0.98		
36	1.6		
37	1.1		
38	0.36, 0.49, 0.45		
39	0.85		
40	0.71, 0.43		
41	0.56		
42			5
43			4
44	2.4		
45			2
46			26
47			74

Table 1

Example	Src cells IC_{50} μM	Src cells % inh at 10μM	Src cells % inh at 100μM
48			30
49			14
50	7.4		
51	9.9		
52			61
53			45
54	1.51, 1.01		
55			97
56	3.93, 2.20		
57			70
58	0.165, 0.245		
59	1.21, 2.29		
60	10.1		
61	0.217, 0.279		
62	0.183, 0.402		

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 2. Multiple entries for a given compound indicate that it was tested multiple times.

Table 2

Example	Lck cells IC_{50} μM
3	32
15	0.35
16	0.22, 0.089, 0.048
17	0.14
38	0.17, 0.18, 0.13
39	0.68
58	0.048
59	0.27, 0.32
61	0.017, 0.015, 0.014
62	0.079

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.

Table 3

EX	Src Enzyme IC_{50} nM	Src Cells IC_{50} μM or % inhib at 10μM	Lck Cells IC_{50} μM
64	not tested	6.4, 5.6	7.4, 7.9
65	not tested	0.7	>10
66	not tested	26%, 26%	>10 (n = 2)
67	not tested	3.7, 3.7	1.5 , 1.7
68	not tested	6.1, 6.0	2.8, 3.0
69	54, 50	2.8, 3.4	1.9, 2.2
70	7.3, 9.2	0.68, 0.58	0.12, 0.11
71	not tested	1.6, 0.90	0.20, 0.11
72	9.4, 15	1.3, 0.70	0.12, 0.077
73	120, 94	1.4, 1.1	1.2, 1.1
74	26, 16	1.5, 0.98	0.6, 0.51
75	26.3, 34.7	1.5, 0.97	0.32, 0.27
76	not tested	4.9, 2.6	0.91, 0.99
77	not tested	2.4, 1.5	1.9, 1.7

79	not tested	2.4, 2.8	1.5, 1.6
80	13, 14	0.79, 0.58	0.074, 0.073
81	23, 26	2.3, 2.4	0.18, 0.22
84	320, 580, 347	3.3	3.4
85	not tested	3.3, 3.16	0.5
87	not tested	4.95, 2.35	1, 1.85
88	not tested	2.4, 2.3	0.16, 0.25
89	not tested	1.5, 1.21	1, 1.0, 1.06
90	not tested	2.6, 3.1	2.7, 2.4
92	8.8, 11	0.829, 0.486	0.145, 0.103
93	15, 16	1.22, 0.638	0.341, 0.276
94	58, 46	5.52, 2.92, 3.17	0.932, 0.907, 1.17
95	8.4, 8.3, 6.9, 5.3	0.614, 0.185, 0.221	0.193, 0.133, 0.168
96	not tested	>10 (n =2)	5.88, 1.80
100	not tested	>10 (n=2)	3.34, 1.93
101	not tested	0.804, 0.810	0.938, 0.804
103	11, 9.6	0.401, 0.445	0.058, 0.071
104	10, 12	0.837, 0.939	0.252, 0.235
105	8.5, 7.0	0.473, 0.550	0.222, 0.235
106	10, 6.6	0.495, 0.561, 0.313, 0.210	0.103, 0.095, 0.058, 0.071
107	9, 11	0.531, 0.543	0.063, 0.065
108	13, 12	0.474, 0.319	0.201, 0.240
109	not tested	>10	4.5
111	16, 16	0.572, 0.411	0.283, 0.428
112	not tested	>10, 5.78	>10 (n =2)
113	not tested	62, 18%	>10, >10
114	not tested	0.598, 0.245	0.156, 0.174
117	15, 11	0.388, 0.274	0.129, 0.171
119	51, 48	3.51, 1.75	1.22, 1.34
120	not tested	5.6, 2.24	8.9, >10
121	not tested	1, 2.19, 2.16	0.525, 0.576, 0.951
122	18, 23	0.733, 1.68, 2.01	0.897, 1.08, 1.56

123	943, 1020	>10 (n=2)	3.23, 4.69
124	not tested	0.914, 0.576	0.803, 1.88
125	not tested	>10 (n =2)	>10, 5.8
127	not tested	0%, 9%	>10
128	66, 69	2.1, 0.79	0.539, 0.557
129	not tested	3.23, 2.19	1.46, 1.40
130	not tested	5.59, 3.20	3.64, 4.07
131	not tested	16%, 17%	>10 (n=2)
132	11, 15	0.777, 0.515	0.112, 0.096
133	not tested	0.436, 0.289	0.082, 0.097
134	7.6, 10	0.505, 0.337	0.13, 0.17
136	not tested	5.53, 1.51, 1.69	0.463, .331, 0.341
137	not tested	0.303, 0.211	0.067, 0.053

Raf/Mek Kinase Cascade Assay

Raf-1 (c-Raf) is used to phosphorylate and activate inactive GST-MEK1 which then can phosphorylate and activate inactive p42 GST-MAPK, which subsequently is measured for phosphorylation of the TEY sequence (aa's 202-204) by a phospho-specific antibody from Sigma (cat. # 77439219041) Reagents: Sf9 insect cell lysate containing full length 6his-tagged recombinant human c-Raf. (Specific Activity: ~200U/ml). Human Non-active Mek-1-GST and human GST-MAP kinase (recombinant proteins produced in *E. coli*).

Stock Solutions Raf/Mek cascade Assay:

1. Assay Dilution Buffer (ADB): 20mM MOPS, pH 7.2, 25mM ß-glycerol phosphate, 5mM EGTA, 1mM sodium orthovanadate, 1mM dithiothreitol.
2. Magnesium/ATP Cocktail: 500μM cold ATP and 75 mM magnesium chloride in ADB.
4. Active Kinase: Human Active c-Raf: Use at 0.4U per assay point.
5. Non-active GST-MEK1: Use at 0.1μg per assay point.
6. Non-active GST-p42 MAP Kinase: Use at 1.0 μg per assay point.

Stock Solutions ELISA:

1. TBST - Tris (50 mM, pH 7.5), NaCl (150 mM), Tween-20 (0.05 %)
2. Superblock (Pierce)
3. Anti-GST Ab (Pharmacia)
4. Anti-Phospho MAPK (Sigma)
5. Anti-Mouse Ab / Europium conjugate (Wallac)

Assay Procedure:

First Stage: c-Raf Dependent Activation of GST-MEK and GST-MAPK

1. Add 20 ml of ADB per assay (i.e. per well of a 96 well plate)
2. Add 10 ml of 0.5 mM cold ATP and 75 mM magnesium chloride in ADB.
3. Add 2 ml of c-Raf (0.4U/assay), in conjunction with 1.6ml non-active MEK1 (0.4 mg/assay).
4. Add 4 ml of non-active GST-p42 MAP Kinase (1.0 mg/assay).

5. Incubate for 60 minutes at 30°C in a shaking incubator.
6. Transfer this mixture to an anti-GST Ab coated 96 well plate (Nunc Immunosorb plates coated o/n with a-GST, then blocked with Pierce Superblock).
7. Incubate for 60 minutes at 30°C in a shaking incubator

Wash 3X with TBST, add Anti-Phospho MAPK (Sigma) (1:3000)

6. Incubate for 60 minutes at 30°C in a shaking incubator
7. Wash 3X with TBST, add Anti-Mouse Ab / Europium conjugate (Wallac) (1:500)
8. Incubate for 60 minutes at 30°C in a shaking incubator
9. Wash 3X with TBST, Read plates in Wallac Victor model Plate Reader.
10. Collect data analyze in Excel for single point and IC50 determinations.

Single point assay - % inhibition at 10 mg/ml (% Inhibition = 1 - cpd.treated sample/untreated control). IC_{50} determinations - done on compounds from single point assays with >80% inhibition. Typically, the Raf/Mek assay is run at compound concentrations from 10 □M to 1 nM in half log dilutions. (% inhibition is determined for each compound concentration). . Multiple entries for a given compound indicate that it was tested multiple times. The results obtained measure Raf and/or Mek kinase I nhibition, and for representative compounds of this invention are listed in Table 4.

Cell Based Screen for Inhibitors of Raf and/or Mek Kinase.

Materials

Cell Lines: Human tumor cell lines LoVo which are known to be growth inhibited by low nM concentrations of a reference standard inhibitor of *Ras* and human adenocarcinoma cell line CaCo-2, which is known to be growth resistant to the same reference compound.

Cell Media : RPMI 1640 with 10% Fetal Bovine Serum supplemented with L-glutamine and Pennicilin/Streptomycin.

Compounds: Supplied usually as a 10 mM stock in 100% DMSO.

Normal Saline: 150 mM NaCl+V

Trichloroacetic Acid (TCA): 50% (w/v) in water

Sulforhodamine B (SRB): 0.4% (w/v) in 1% Acetic Acid

Tris Base: 10 mM in water

Methods

Cells are plated at 2000 cells per well for cell line LoVo, 1,750 cells for cell line BXPC3, 1,000 cells for cell line WM266-4 and 1500 cells for cell line CaCo-2 in 96 well plates. Cells are plated in media (200 μl) and allowed to adhere overnight at 37°C. At 24 hours post plating, compounds are added directly at a volume of 0.5 μl. For the qualitative screen (compounds screened at 25 μM) compound is added directly to cells. For the quantitative screen, compound is first diluted in DMSO to generate concentrations of compound or reference standard of: 1, 5, 10 and 25 μM. It is advisable to make the dilutions in an identical 96 well plate so that compounds can be added using a multichannel micropipettor set at 0.5 μl. The cells are then incubated for four days after which the media is removed using a 12 well manifold by first tipping the plate forward at a 45 degree angle and then inserting the manifold in an upright orientation to prevent the tips of the manifold from disturbing cells at the bottom of the plate. 200 μl of normal saline is then added to each well using an 8 well multichannel pipettor, followed by the careful addition of 50μl of 50% TCA. The plates are then incubated for 2 hours at 4°C, after which the supernatant is removed using the same technique as above and the plated washed twice with 200 μl water. The plates are then air dried and 50 μl of SRB stock solution is carefully added so that the entire bottom of each well is covered. This again can be used using an 8 well multichannel pipettor. The SRB is incubated with fixed cells for 15 minutes at room temperature after which the SRB is removed with the manifold as described above and the plates washed twice with 350 μl of 1% acetic acid per well each time. The plates are then air dried after which the bound SRB is released from protein by the addition of 200 μl of Tris base. Resolubilizing the SRB is aided by placing the plates on a rotator for 15-30 minutes. The absorbance of each well is determined at 550 or 562 nm using a microtiter plate reader.

Each compound or dilution thereof is performed in triplicate. Outliers are identified by visual inspection of the data. Each plate should have a "0" control (vehicle only).

Qualitative screen: To calculate % inhibition of a compound at 25 μM, the following formula is used: 1- (experimental absorbance @ 25 μM compound/

"0" control absorbance) x 100= % inhibition at 25 μM. Compounds having >50% inhibition at 25 μM are placed in the quantitative assay.

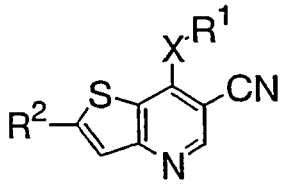
Quantitative Assay: A standard curve is constructed by plotting the concentration of compound against the average absorbance calculated at that concentration. A curve is plotted and the concentration at which the curve passes through the 50% the absorbance mark seen in the "0" control well is the IC_{50} calculated for that compound. 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 4.

Table 4

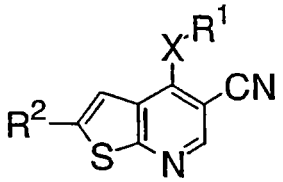
EX	Raf/MEK enzyme IC_{50} nM	Lovo cells IC_{50} μM	BXPC3 cells IC_{50} μM	WM266-4 cells IC_{50} μM
83	41	0.036, 0.038	>1	>1
86	221, 332	0.094, 0.160	0.35	0.35
91	475	0.064	0.092	0.095, 0.085
98	5.6	0.033	0.038	0.04
99	4.5	0.039	0.041	>1
118	not tested	0.073	0.071	not tested

What is claimed is:

1. A compound of Formula (1a) or Formula (1b)



Ia



Ib

or an S-oxide or S-dioxide thereof

wherein:

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

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 –H, $-R^3$, -J, $-C(O)XR^3$, -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, $-R^8$, $-(C(R^9)_2)_qXR^8$, $-(C(R^9)_2)_qQ$, $-X(C(R^9)_2)_nXR^8$, $-X(C(R^9)_2)_nQ$, or $-X(C(R^9)_2)_q R^8$;

R^3 is alkyl of 1 to 6 carbon atoms, *cis*-alkenyl of 2-6 carbon atoms, *trans*-alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, aryl or heteroaryl;

R^4 is H, alkyl of 1-6 carbon atoms, *cis*-alkenyl of 2-6 carbon atoms, a *trans*- alkenyl of 2-6 carbon atoms, or an 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, and 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 heteroaryl ring, a aryl or heteroaryl fused to one to three aryl or heteroaryl rings, wherein any of the aryl, cycloalkyl, or heteroaryl 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, *cis*-alkenyl of 2-6 carbon atoms, *trans*-alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, aryl or heteroaryl;

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-, *cis*- and *trans*- -CH=CH- and cycloalkyl of 3-10 carbon atoms;

Q is NZZ' wherein Z and Z' may be the same or different and 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 heteroaryl;

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^4 on a carbon or a nitrogen, or on

nitrogen by a group $-(C(R^9)_2)_nXR^3$, $-C(R^9)_2)_nNZ''Z'''$, or on carbon by a group $-(C(R^9)_2)_qXR^3$, $-(C(R^9)_2)_qNZ''Z'''$,

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;

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

J is fluoro, chloro, bromo, and iodo; or

a pharmaceutically acceptable salt thereof.

2. A compound of formula Ia or Ib according to claim 1 wherein X is NH.

3. A compound of formula Ia or Ib 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, $-CF_3$, $-OCF_3$, $-R^4$, $-OR^4$ and YR^7; and R^7 is an aryl or heteroaryl ring, optionally substituted with one to four substituents selected from the group consisting of –H, -J, $-CF_3$, $-OCF_3$, $-R^4$ and OR^4.

4. A compound of formula Ia or Ib 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 -Cl, $-R^4$ and $-OR^4$.

5. A compound of formula Ia or Ib according to claim 4 wherein R^4 is alkyl of 1-6 carbon atoms.

6. A compound of formula Ia or Ib according to claim 1 wherein R^2 is substituted aryl or heteroaryl, wherein the substituent may be one or more groups selected from $-(C(R^9)_2)_qQ$.

7. A compound of formula Ia or Ib according to claim 6 wherein q is 1 to 3.

8. A compound of formula Ia or Ib according to claim 6 or claim 7 wherein R^9 is H.

9. A compound of formula Ia or Ib according to any one of claims 6 to 8 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 or carbon by R^4 or on carbon by $(CH_2)_2OH$.

10. A compound of formula Ia or Ib according to claim 1 or claim 2 wherein R^2 is R^3 where R^3 is alkynyl of 2-6 carbon atoms, aryl or heteroaryl; which groups may be substituted by one or more groups selected from

$-R^8$, $-(CH_2)_qOR^8$, $-(CH_2)_qNHR^8$, $-(CH_2)_q\ NR^4R^8$, $-(CH_2)_qQ$,

$-O(CH_2)_nOR^8$, $-\ NH(CH_2)_nOR^8$, $-\ NR^4(CH_2)_nOR^8$,

$-O(CH_2)_nNHR^8$, $-\ NH(CH_2)_nNHR^8$, $-\ NR^4(CH_2)_nNHR^8$,

$-O(CH_2)_nNR^4R^8$, $-\ NH(CH_2)_nCR^8$, $-\ NR^4(CH_2)_nNR^4R^8$,

$-O(CH_2)_nQ$, $-NH(CH_2)_nQ$, $-\ NR^4(CH_2)_nQ$,

- $O(CH_2)_qR^8$; - $NH(CH_2)_qR^8$; or - $NR^4(CH_2)_qR^8$;

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

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

Y is -C(O)-, -C(O)O-, -OC(O)-, -C(O)NH-, -NHC(O)-, -$NHSO_2$-, -S-, -O-, -NR^4-;

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

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^4 on a carbon or a nitrogen, or on nitrogen by a group -$(CH_2)_nOR^3$, -$(CH_2)_nNHR^3$, -$(CH_2)_nNR^4R^3$, -$(CH_2)_nNZ''Z'''$, or on carbon by a group -$(CH_2)_qOR^3$, -$(CH_2)_qNHR^3$, -$(CH_2)_q$ NR^4R^3, -$(CH_2)_qNZ''Z'''$,

Z''' and Z'' may be the same or different and are selected from H, alkyl of 1 to 6 carbon atoms

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.

11. A compound of claim 1 which is one of the following:

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

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

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

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

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

4-[(3-Chloro-4-[(1-methyl-1H-imidazol-2-yl)thio]phenyl)amino]thieno[2,3-b]pyridine-5-carbonitrile;

4-[(2,4-Dichloro-5-methoxyphenyl)amino]-2-iodothieno[2,3-b]pyridine-5-carbonitrile;

4-[(2,4-Dichloro-5-methoxyphenyl)amino]-2-methylthieno[2,3-b]pyridine-5-carbonitrile;

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

7-[(2,4-Dichlorophenyl)amino]thieno[3,2-b]pyridine-6-carbonitrile;

7-[(2,4-Dichlorophenoxy)]thieno[3,2-b]pyridine-6-carbonitrile;

7-[(2,4-Dichlorophenyl)thio]thieno[3,2-b]pyridine -6-carbonitrile;

7-[(2,4-Dichlorobenzyl) amino]thieno[3,2-b]pyridine-6-carbonitrile;

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

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

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

7-[(2,4-Dichloro-5-methoxyphenyl)amino]-2-[4-(4-methylpiperazin-1-ylmethyl)phenyl] thieno [3,2-b] pyridine-6-carbonitrile;

7-[(2,4-Dichloro-5-methoxyphenyl)amino]-2-[4-(piperidin-1-ylmethyl)phenyl] thieno [3,2-b]pyridine-6-carbonitrile;

4-{6-Cyano-7-[(2,4-dichloro-5-methoxyphenyl)amino]thieno[3,2-b]pyridine-2-yl} benzoic acid;

4-{6-Cyano-7-[(2,4-dichloro-5-methoxyphenyl)amino]thieno[3,2-b]pyridine-2-yl} benzamide;

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

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

7-[(2,4-Dichloro-5-methoxyphenyl)amino]-2-[3-(dimethylamino)prop-1-ynyl] thieno [3,2-b]pyridine-6-carbonitrile;

2-(1-Benzofuran-2-yl)-7-[(2,4-dichloro-5-methoxyphenyl)amino]thieno[3,2-b] pyridine-6-carbonitrile;

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

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

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

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

4-[5-Cyano-4-(3,4,5-trimethoxy-phenylamino)-thieno[2,3-b]pyridin-2-yl]-butyric acid methyl ester;

2-(4-Hydroxybutyl)-4-[(3,4,5-trimethoxyphenyl)amino]-thieno[2,3-b]pyridine-5-carbonitrile;

2-[4-(4-Morpholinyl)butyl]-4-[(3,4,5-trimethoxyphenyl)amino]-thieno[2,3-b]pyridine-5-carbonitrile;

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

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

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

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

7-[(2,4-Dichloro-5-methoxyphenyl)amino]-2-[5-(1,3-dioxolan-2-yl)thien-3-yl]thieno [3,2-b]pyridine-6-carbonitrile;

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

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

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

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

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

2-Iodo-7-[(4-phenoxyphenyl)amino]thieno[3,2-b]pyridine-6-carbonitrile;

2-(4-Formylphenyl)-7-[(4-phenoxyphenyl)amino]thieno[3,2-b]pyridine-6-carbonitrile;

2-[4-(4-Methylpiperazin-1-ylmethyl)phenyl]-7-[(4-phenoxyphenyl)amino]thieno[3,2-b] pyridine-6-carbonitrile;

2-[4-(Morpholin-4-ylmethyl)phenyl]-7-[(4-phenoxyphenyl)amino]thieno[3,2-b] pyridine-6-carbonitrile;

2-[4-(Hydroxymethyl)phenyl]-7-[(4-phenoxyphenyl)amino]thieno[3,2-b]pyridine-6-carbonitrile;

2-Iodo-7-[(3,4,5-trimethoxyphenyl)amino]thieno[3,2-b]pyridine-6-carbonitrile;

2-Bromo-7-[(4-phenoxyphenyl)amino]thieno[3,2-b]pyridine-6-carbonitrile;

7-[(4-Phenoxyphenyl)amino]-2-[(E)-2-pyridin-4-ylethenyl]thieno[3,2-b]pyridine-6-carbonitrile;

tert-Butyl(2E)-3-{6-cyano-7-[(2,4-dichloro-5-methoxyphenyl)amino]thieno[3,2-b] pyridin-2-yl}prop-2-enoate;

4-[(2,4-Dichloro-5-methoxyphenyl)amino]-2-[3-(4-methylpiperazin-1-yl)prop-1-ynyl] thieno [2,3-b]pyridine-5-carbonitrile;

4-[(2,4-Dichloro-5-methoxyphenyl)amino]-2-(pyridin-3-ylethynyl)thieno[2,3-b] pyridine-5-carbonitrile;

(2E)-3-(6-Cyano-7-[(2,4-dichloro-5-methoxyphenyl)amino]thieno[3,2-b]pyridin-2-yl) prop-2-enoate;

7-[(2,4-Dichloro-5-methoxyphenyl)amino]-2-(2-formyl-1-methyl-1H-imidazol-5-yl) thieno [3,2-b]pyridine-6-carbonitrile;

2-(4-Formylphenyl)-7-[(3,4,5-trimethoxyphenyl)amino]thieno[3,2-b]pyridine-6-carbonitrile;

7-[(2,4-Dichloro-5-methoxyphenyl)amino]-2-[(1E)-3-(4-methylpiperazin-1-yl)-3-oxoprop-1-enyl]thieno[3,2-b]pyridine-6-carbonitrile;

2-[3-(4-Methylpiperazin-1-yl)prop-1-ynyl]-7-[(3,4,5-trimethoxyphenyl)amino] thieno [3,2-b]pyridine]-6-carbonitrile;

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

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

7-[(2,4-Dichloro-5-methoxyphenyl)amino]-2-[3-(4-methylpiperazin-1-yl)prop-1-ynyl] thieno[3,2-b]pyridine]-6-carbonitrile;

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

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

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

7-[(2,4-Dichloro-5-methoxyphenyl)amino]-2-[4-(4-ethylpiperazin-1-ylmethyl)phenyl] thieno [3,2-b]pyridine-6-carbonitrile;

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

7-[(2-Chloro-5-methoxyphenyl)amino]-2-[4-(4-methylpiperazin-1-ylmethyl)phenyl]thieno [3,2-b]pyridine-6-carbonitrile;

2-{4-[(Dimethylamino)methyl]phenyl}7-[(5-methoxy-2-methylphenyl)amino]-thieno[3,2-b]pyridine-6-carbonitrile;

7-[(5-methoxy-2-methylphenyl)amino]-2-[4-(4-methylpiperazin-1-ylmethyl) phenyl] thieno [3,2-b]pyridine-6-carbonitrile;

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

7-[(2,4-Dichlorophenyl)amino]-2-[4-(4-methylpiperazin-1-ylmethyl)phenyl] thieno [3,2-b]pyridine-6-carbonitrile;

7-[(2,4-Dichloro-5-methoxyphenyl)amino]-2-[6-(4-methylpiperazin-1-ylmethyl)pyridin-3-yl] thieno [3,2-b]pyridine-6-carbonitrile;

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

7-[(2,4-Dichloro-5-methoxyphenyl)amino]-2-[5-(4-methylpiperazin-1-ylmethyl)furan-3-yl] thieno [3,2-b]pyridine-6-carbonitrile; or

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

12. A compound of claim 1 which is one of the following:

7-[(2,4-Dichloro-5-methoxyphenyl)amino]-2-[4-(4-methylpiperazin-1-ylmethyl)phenyl] thieno [3,2-b]pyridine-6-carbonitrile;

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

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

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

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

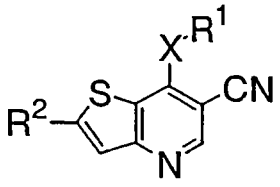
7-[(2,4-Dichloro-5-methoxyphenyl)amino]-2-[4-(piperidin-1-ylmethyl)phenyl]thieno[3,2-b]pyridine-6-carbonitrile;

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

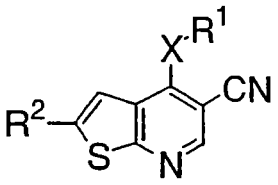
7-[(2,4-Dichloro-5-methoxyphenyl)amino]-2-[5-(morpholin-4-ylmethyl)thien-3-yl]thieno[3,2-b]pyridine-6-carbonitrile; or

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

13. A compound as claimed in claim 1 of Formula (1a) or Formula (1b)



Ia



Ib

wherein:

X is -NH-

n = 2-5

q = 1-3

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

R^2 is substituted aryl or heteroaryl, wherein the substituent may be one or more groups selected from $-(C(R^9)_2)_qQ$;

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

R^9 is H;

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

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 or carbon by R^4 or on carbon by $(CH_2)_2OH$; or

a pharmaceutically acceptable salt thereof.

14. A compound according to claim 13 which is one of the following:

7-[(2,4-Dichloro-5-methoxyphenyl)amino]-2-[4-(4-methylpiperazin-1-ylmethyl) phenyl] thieno [3,2-b]pyridine-6-carbonitrile;

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

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

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

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

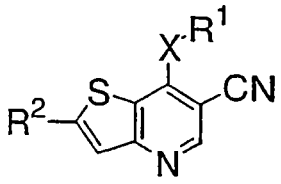
7-[(2,4-Dichloro-5-methoxyphenyl)amino]-2-[4-(piperidin-1-ylmethyl)phenyl]thieno[3,2-b]pyridine-6-carbonitrile;

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

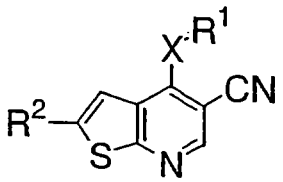
7-[(2,4-Dichloro-5-methoxyphenyl)amino]-2-[5-(morpholin-4-ylmethyl)thien-3-yl]thieno[3,2-b]pyridine-6-carbonitrile; or

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

15. A compound according to claim 1 of Formula (1a) and Formula (1b)



Ia



Ib

wherein:

X is –NH-,

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, $-CF_3$, $-OCF_3$, $-R^4$, $-OR^4$, or YR^7;

R^2 is alkynyl of 2-6 carbon atoms, aryl or heteroaryl;

and may be substituted by one or more groups selected from

$-R^8$, $-(CH_2)_qOR^8$, $-(CH_2)_qNHR^8$, $-(CH_2)_q NR^4R^8$, $-(CH_2)_qQ$,

$-O(CH_2)_nOR^8$, $- NH(CH_2)_nOR^8$, $- NR^4(CH_2)_nOR^8$,

$-O(CH_2)_nNHR^8$, $- NH(CH_2)_nNHR^8$, $- NR^4(CH_2)_nNHR^8$,

$-O(CH_2)_nNR^4R^8$, $- NH(CH_2)_nCR^8$, $- NR^4(CH_2)_nNR^4R^8$,

$-O(CH_2)_nQ$, $-NH(CH_2)_nQ$, $- NR^4(CH_2)_nQ$,

$- O(CH_2)_qR^8$; $- NH(CH_2)_qR^8$; or $- NR^4(CH_2)_qR^8$;

R^3 is alkyl of 1 to 6 carbon atoms;

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

R^7 is an aryl or heteroaryl ring, optionally substituted with one to four substituents selected from the group consisting of –H, -J, $-CF_3$, $-OCF_3$, $-R^4$, $-OR^4$;

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

Y is -C(O)-, -C(O)O-, -OC(O)-, -C(O)NH-, -NHC(O)-, -$NHSO_2$-, -S-, -O-, -NR^4-;

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

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^4 on a carbon or a nitrogen, or on nitrogen by a group -$(CH_2)_nOR^3$, -$(CH_2)_nNHR^3$, -$(CH_2)_nNR^4R^3$, -$(CH_2)_nNZ''Z'''$, or on carbon by a group -$(CH_2)_qOR^3$, -$(CH_2)_qNHR^3$, -$(CH_2)_q$ NR^4R^3, -$(CH_2)_qNZ''Z'''$,

Z''' and Z'' may be the same or different and are selected from H, alkyl of 1 to 6 carbon atoms

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 and iodo

16. A compound according to claim 15 which is one of the following:

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

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

7-[(2,4-Dichloro-5-methoxyphenyl)amino]-2-[4-(4-methylpiperazin-1-ylmethyl)phenyl]thieno[3,2-b]pyridine-6-carbonitrile;

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

7-[(2,4-Dichloro-5-methoxyphenyl)amino]-2-[4-(piperidin-1-ylmethyl)phenyl]thieno[3,2-b]pyridine-6-carbonitrile;

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

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

7-[(2,4-Dichloro-5-methoxyphenyl)amino]-2-[3-(dimethylamino)prop-1-ynyl]thieno[3,2-b]pyridine-6-carbonitrile;

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

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

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

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

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

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

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

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

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

2-[4-(4-Methylpiperazin-1-ylmethyl)phenyl]-7-[(4-phenoxyphenyl)amino]thieno[3,2-b]pyridine-6-carbonitrile;

2-[4-(Morpholin-4-ylmethyl)phenyl]-7-[(4-phenoxyphenyl)amino]thieno[3,2-b]pyridine-6-carbonitrile;

2-[4-(Hydroxymethyl)phenyl]-7-[(4-phenoxyphenyl)amino]thieno[3,2-b]pyridine-6-carbonitrile;

7-[(4-Phenoxyphenyl)amino]-2-[(E)-2-pyridin-4-ylethenyl]thieno[3,2-b]pyridine-6-carbonitrile;

4-[(2,4-Dichloro-5-methoxyphenyl)amino]-2-[3-(4-methylpiperazin-1-yl)prop-1-ynyl]thieno[2,3-b]pyridine-5-carbonitrile;

4-[(2,4-Dichloro-5-methoxyphenyl)amino]-2-(pyridin-3-ylethynyl)thieno[2,3-b]pyridine-5-carbonitrile;

7-[(2,4-Dichloro-5-methoxyphenyl)amino]-2-(2-formyl-1-methyl-1H-imidazol-5-yl)thieno[3,2-b]pyridine-6-carbonitrile;

2-[3-(4-Methylpiperazin-1-yl)prop-1-ynyl]-7-[(3,4,5-trimethoxyphenyl)-amino]thieno[3,2-b]pyridine-6-carbonitrile;

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

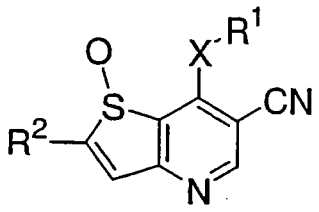
7-[(2,4-Dichloro-5-methoxyphenyl)amino]-2-{1-methyl-2-[(4-methylpiperazin-1-yl)methyl]-1H-imidazol-5-yl} thieno[3,2-b]pyridine-6-carbonitrile;

7-[(2,4-Dichloro-5-methoxyphenyl)amino]-2-[3-(4-methylpiperazin-1-yl)prop-1-ynyl] thieno[3,2-b]pyridine-6-carbonitrile;

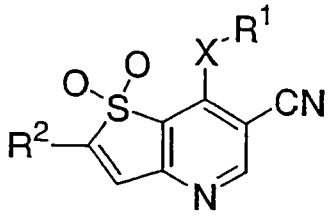
2-{4-[(Dimethylamino)methyl]phenyl}-7-[(3,4,5-trimethoxyphenyl)amino]thieno[3,2-b]pyridine-6-carbonitrile; or

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

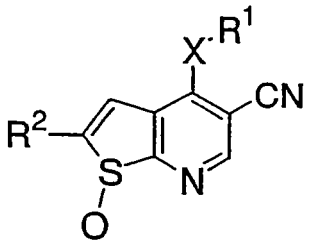
17. A compound as claimed in claim 1 which is an S-oxide or S-dioxide of Formula (1c), Formula (1d), (1e) or (1f):



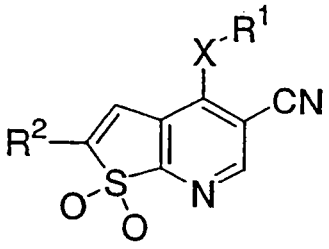
Ic



Id



Ie



If

wherein: X, R^1 and $R^2$are as defined in claim 1.

18. A compound according to claim 17 which is one of the following:

7-[(2,4-Dichloro-5-methoxyphenyl)amino]-2-[4-(4-methylpiperazin-1-ylmethyl)phenyl]-1-oxo-1H-thieno [3,2-b]pyridine-6-carbonitrile;

7-[(2,4-Dichloro-5-methoxyphenyl)amino]-2-[4-(4-methylpiperazin-1-ylmethyl)phenyl]-1,1-dioxo-1H-thieno [3,2-b]pyridine-6-carbonitrile;

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

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

2-{4-[(Dimethylamino)methyl]phenyl}-1-oxo-7-[(3,4,5-trimethoxyphenyl)amino]-1H-thieno[3,2-b]pyridine-6-carbonitrile; or

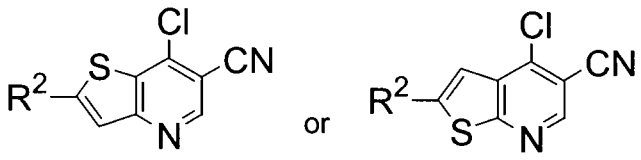
2-{4-[(Dimethylamino)methyl]phenyl}-1,1-dioxo-7-[(3,4,5-trimethoxyphenyl)amino]-1H-thieno[3,2-b]pyridine-6-carbonitrile.

19. Use of a compound of Formula (Ia) and (Ib) or an S-oxide or S-dioxide thereof as claimed in any one of claims 1 to 18 or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating or inhibiting a pathological condition or disorder in a mammal, the pathological condition or disorder selected from cancer, stroke, osteoporosis, polycystic kidney disease, autoimmune disease, rheumatoid arthritis, transplant rejection or neuropathic pain.

20. A pharmaceutical composition comprising a compound of Formula (Ia) and (Ib) or an S-oxide or S-dioxide thereof as claimed in any one of claims 1 to 18 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

21. A process for preparing a compound of formula (1a) or (1b) as defined in claim 1 or a pharmaceutically acceptable salt thereof, which comprises one of the following:

a) reacting a compound of formula:



or an S-oxide or S-dioxide thereof; wherein R^2 is as defined in Claim 1 with a compound of formula R^1XH where R^1 and X are as defined in Claim 1 to give a compound of formula I(a) or (Ib);

or

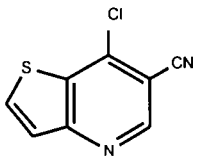
b) reacting a compound of formula 1a or 1b or an S-oxide or S-dioxide thereof in which R^2 is a reactive substituent group to give a compound of formula 1a or 1b in which R^2 is a different substituent group as defined in claim 1;

or

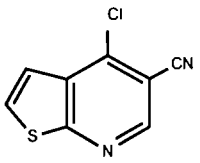
c) converting a comppund of formula (1a) or (1b) to a pharmaceutically acceptable salt thereof.

22. A process of producing a compound of Formula (Ia) and Formula (Ib) of claim 1, wherein R^2 is iodine, comprising:

a) treating with a base, in an inert solvent at reduced temperature compound of Formula (a) or (a');a

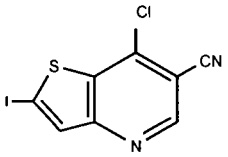


(a)

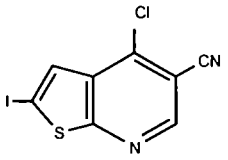


(a')

b) adding iodine to the compound in step (a) to form a compound of Formula (b) or (b'); and



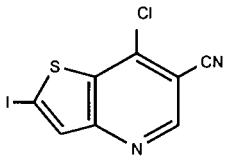
(b)



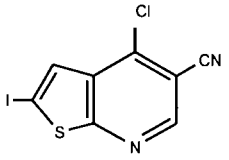
(b")

c) adding a compound of formula R^1XH to the compound in step (b) to form a compound of Formula (Ia) or (Ib), wherein R^2 is iodine.

23. A compound of Formula (b) or (b')



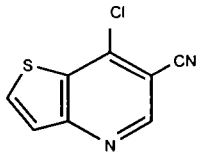
(b)



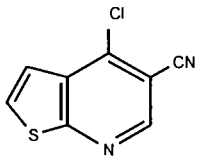
(b'')

24. A process of producing a compound of Formula (Ia) or (Ib) of claim 1, wherein R^2 is bromine, comprising:

a) treating with a base, in an inert solvent at reduced temperature a compound of Formula (a) or (a');

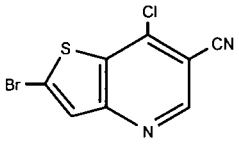


(a)

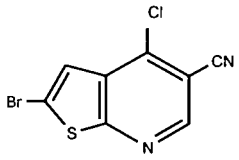


(a')

b) adding 1,1-dibromo-1,1,2,2-tetrafluoroethane to the compound in step (a) to form a compound of Formula (z) or (z'); and



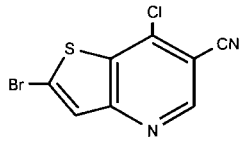
(z)



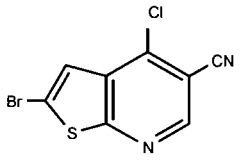
(z')

c) adding a compound of formula R^1XH to the compound in step (b) to form a compound of Formula (Ia) or (Ib), wherein R^2 is bromine.

25. A compound of Formula (z) or (z')



(z)



(z')

26. A compound of claim 1 which is one of the following:

7-({3-chloro-4-[(1-methyl-1H-imidazol-2-yl)thio]phenyl}amino)-2-iodothieno[3,2-b]pyridine-6-carbonitrile;

7-({3-chloro-4-[(1-methyl-1H-imidazol-2-yl)thio]phenyl}amino)-2-[4-(morpholin-4-ylmethyl)phenyl]thieno[3,2-b]pyridine-6-carbonitrile;

7-({3-chloro-4-[(1-methyl-1H-imidazol-2-yl)thio]phenyl}amino)-2-[4-(morpholin-4-ylbut-1-ynyl)thieno[3,2-b]pyridine-6-carbonitrile;

7-({3-chloro-4-[(1-methyl-1H-imidazol-2-yl)thio]phenyl}amino)-2-[3-(dimethylamino)prop-1-ynyl]thieno[3,2-b]pyridine-6-carbonitrile;

7-({3-chloro-4-[(1-methyl-1H-imidazol-2-yl)thio]phenyl}amino)-2-(4-formylphenyl)thieno[3,2-b]pyridine-6-carbonitrile;

7-({3-chloro-4-[(1-methyl-1H-imidazol-2-yl)thio]phenyl}amino)-2-{4-[(4-methylpiperazin-1-yl)methyl]phenyl}thieno[3,2-b]pyridine-6-carbonitrile;

7-({3-chloro-4-[(1-methyl-1H-imidazol-2-yl)thio]phenyl}amino)-2-[3-(diethylamino)prop-1-ynyl]thieno[3,2-b]pyridine-6-carbonitrile;

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

7-[(2,4-dichloro-5-methoxyphenyl)amino]-2-[5-(1,3-dioxolan-2-yl)-2-furyl]thieno[3,2-b]pyridine-6-carbonitrile;

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

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

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

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

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

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

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

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

7-[(2,4-dichloro-5-methoxyphenyl)amino]-2-[5-(1,3-dioxolan-2-yl)thien-2-yl]thieno[3,2-b]pyridine-6-carbonitrile;

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

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

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

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

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

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

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

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

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

7-[(2,4-dichloro-5-methoxyphenyl)amino]-2-(1H-pyrrol-3-yl)thieno[3,2-b]pyridine-6-carbonitrile;

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

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

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

7-[(2,4-dichloro-5-methoxyphenyl)amino]-2-[4-(piperazin-1-ylmethyl)phenyl]thieno[3,2-b]pyridine-6-carbonitrile;

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

7-({3-chloro-4-[(1-methyl-1H-imidazol-2-yl)thio]phenyl}amino)-2-(4-formylphenyl)thieno[3,2-b] pyridine-6-carbonitrile;

7-({3-chloro-4-[(1-methyl-1H-imidazol-2-yl)thio]phenyl}amino)-2-{4-[(diethylamino)methyl]phenyl}thieno[3,2-b]pyridine-6-carbonitrile;

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

7-[(2,4-dichloro-5-methoxyphenyl)amino]-2-(1H-pyrazol-4-ylethynyl)thieno[3,2-b]pyridine-6-carbonitrile;

7-[(2,4-dichlorophenyl)amino]-2-iodothieno[3,2-b]pyridine-6-carbonitrile;

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

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

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

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

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

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

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

7-[(2,4-dichloro-5-ethoxyphenyl)amino]-2-iodothieno[3,2-b]pyridine-6-carbonitrile;

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

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

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

7-[(2,4-dichloro-5-methoxyphenyl)amino]-2-(4{[(2R,5S)-2,5-dimethylpiperazin-1-l]methyl}phenyl)thieno[3,2-b]pyridine-6-carbonitrile;

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

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

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

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

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

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

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

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

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

7-[(2,4-dichloro-5-methoxyphenyl)amino]-2-{1-[2-(dimethylamino)ethyl]-1H-pyrrol-3-yl}thieno[3,2-b]pyridine-6-carbonitrile;

7-[(2,4-dichlorophenyl)amino]-2-[4-(dimethylamino)phenyl]thieno[3,2-b]pyridine-6-carbonitrile;

7-[(2,4-dichloro-5-methoxyphenyl)amino]-2-[(1-methyl-1H-imidazol-5-yl)ethynyl]thieno[3,2-b]pyridine-6-carbonitrile;

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

7-[(2,4-dichloro-5-methoxyphenyl)amino]-2-(1H-pyrazol-4-yl)thieno[3,2-b]pyridine-6-carbonitrile;

7-[(2,4-dichloro-5-methoxyphenyl)amino]-2-{[1-(2-hydroxyethyl)-1H-pyrazol-4-yl]ethynyl}thieno[3,2-b]pyridine-6-carbonitrile;

7-[(2,4-dichloro-5-methoxyphenyl)amino]-2-[1-(2-morpholin-4-ylethyl)-1H-pyrazol-4-yl]thieno[3,2-b]pyridine-6-carbonitrile;

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

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

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

7-[(2,4-dichloro-5-methoxyphenyl)amino]-2-[1-(2-hydroxyethyl)-1H-pyrazol-4-yl]thieno[3,2-b]pyridine-6-carbonitrile;

4-{6-cyano-7-[(2,4-dichloro-5-methoxyphenyl)amino]thieno[3,2-b]pyridin-2-yl}-N,N-dimethylbenzamide;

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

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