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(71) Applicants *(for all designated States except US)*: **THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY** [US/US]; 1705 El Camino Real, Palo Alto, CA 94306 (US). **AUCKLAND UNISERVICES LIMITED** [NZ/NZ]; 70 Symonds Street, Auckland, 1142 (NZ).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **TURCOTTE, Sandra** [CA/CA]; 8382 St-urbain, Montreal, H2P 2P1 (CA). **CHAN, Denise, A.** [US/US]; 411 College Avenue, Apt. C, Palo Alto, CA 94306 (US). **SUTPHIN, Patrick, D.** [US/US]; 130 Bowdoin Street, Apt. 1802, Boston, MA 02108 (US). **GIACCIA, Amato, J.** [US/US]; 856 Esplanada Way, Stanford, CA 94305 (US). **HAY, Michael, P.** [NZ/NZ]; 52 St. Leonards Road, Epsom, Auckland, 1024 (NZ). **DENNY, William, A.** [NZ/NZ]; 165 Gossamer Drive, Pakuranga, Auckland, 1706 (NZ). **BONNET, Muriel, Marie** [FR/NZ]; 2/24 Kakariki Ave, Mt Eden, Auckland, 1024 (NZ).

(74) Agent: **VINCENT, Matthew, P.**; Ropes & Gray Llp, One International Place, Boston, MA 02110 (US).

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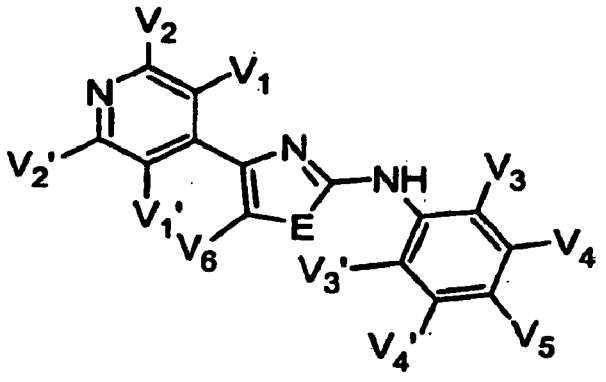
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(54) **Title**: HETEROARYL COMPOUNDS, COMPOSITIONS, AND METHODS OF USE IN CANCER TREATMENT



Formula II

(57) **Abstract**: Provided herein are novel heteroaryl compounds, compositions comprising the compounds, and methods of treatment or prevention comprising administration of the compounds. The compounds are effective in the targeting of cells defective in the von Hippel-Lindau gene and in inducing autophagic cell death. The methods are directed to treating or preventing diseases such as cancer, and in particular cancers resulting from von Hippel-Lindau disease. The compounds of the invention may be administered in combination with another therapeutic agent.

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Heteroaryl Compounds, Compositions, and Methods of Use in Cancer Treatment

Cross-Reference To Related Application

[0001] This application claims the benefit of U. S. Provisional Application No. 61/035,358, filed March 10, 2008, the disclosure of which is incorporated herein by reference in its entirety.

Statement Regarding Federally Sponsored Research or Development

[0002] This invention was made with Government support under contract CA082566, awarded by the National Cancer Institute. The government has certain rights in this invention.

Background of the Invention

[0003] Mutations and/or inactivation of the von Hippel-Lindau (VHL) tumor suppressor gene occur in the majority of clear cell renal carcinoma (CC-RCC) and is associated with metastatic disease (Motzer, R.J.,et al., *N. Engl. J. Med.* **1996**, *335*, 865). The tumor suppressor function of VHL was demonstrated by the restoration of VHL function in VHL-/- RCC that resulted in significant inhibition of these cells to form tumors in nude mice (Iliopoulos, O., et al., *Nat. Med.* **1995**, *1*, 822). Functional studies indicate that pVHL, the protein product of VHL, is an E3 ubiquitin ligase that targets the α-subunit of the hypoxia-inducible factor (HIF) for proteasomal degradation under normoxia. In the presence of oxygen, hydroxylation

on proline residues 564 and 402 by prolyl hydroxylases (PHDs) marks HIF-α for recognition and binding with pVHL, leading to degradation of HIF-α. Under hypoxic conditions, activity of the PHDs decrease, which prevents the recognition of HIF-α by pVHL (Ivan, M., et al. Science, 2001, 292, 464; Jaakkola, P., et al., *Science*, **2001**, *292*, 468; Chan, D.A., et al., *J. Biol. Chem.* **2002**, *277*, 40112). In cells that lack VHL, stabilized HIF-α binds HIF-β to activate the transcription of genes involved in several processes (Staller, P., et al., *Nature*, **2003**, *425*, 307; Gnarra, J.R., et al. *Proc. Natl Acad. Sci. U S A*, **1996**, *93*, 10589; Iliopoulos, O., et al., . *Proc. Natl Acad. Sci. U S A*, **1996**, *93*, 10595; Knebelmann, B., et al., *Cancer Res.,* 1998, *58*, 226). In addition to its role in HIF regulation, pVHL has been implicated in a variety of processes including extracellular matrix assembly, regulation of microtubule stability, polyubiquitination of atypical PKC family members, regulation of fibronectin, and RNA polymerase II subunits (Hergovich, A., *Nat. Cell Biol.* **2003**, *5*, 64; Okuda, H., et al., *J. Biol. Chem.* **2001**, *276*, 43611; Ohh, M., et al., *Mol. Cell* **1998**, *1*, 959; Na, X., et al., *EMBO J.* **2003**, *22*, 4249). It has also been reported that an acidic domain present in the N-terminal region of pVHL contributes to its tumor suppression function in a HIF-independent manner and may be relevant for the development of VHL-associated malignancies (Lolkema, M.P., et al., *J. Biol. Chem.* **2005**, *280*, 22205).

[0004] Defects in apoptosis that are observed in many solid tumor cells, including RCCs, increase the resistance of the tumor cells to chemotherapy, radiotherapy and molecularly targeted therapies. In contrast to apoptosis, autophagy regulates the turnover of organelles and long-lived proteins to ensure homeostasis. Under metabolic stress, autophagy is activated and promotes survival (Mathew, R., et al., *Genes Dev.* **2007**, *21*, 1367). It can also result in cell death if this proceeds to completion under persistent stress or genetic alterations. Studies have reported a deregulated level of autophagy in diverse diseases including neuronal degeneration, infectious disease, and cancer (Kondo, Y., et al., *Nat. Rev. Cancer* **2005**, *5*, 726).

[0005] Autophagy occurs in all eukaryotic cells from yeast to mammals. In response to a diverse number of stimuli, such as starvation, hypoxia, or high temperature, portions of the cytoplasm and organelles are sequestered in a double-

membrane vesicle called an autophagosome. These vesicles undergo maturation by fusion with endosomes and/or lysosomes to become autolysosomes where hydrolases degrade their contents (Klionsky, D.J. and S.D. Emr, *Science* **2000**, *290*, 1717). The induction of autophagy selectively in tumor cells has potential for the treatment of cancer.

[0006] Westphal, G., et al., *J. Praktische Chemie* **1976,** *318*, 875 describe the synthesis of pyridyl thiazoles.

[0007] PCT International Publication No. WO01/64674 A1 describes 2,4-disubstituted thiazolyl derivatives purportedly useful in the prevention or treatment of diseases mediated through cytokines, particularly TNF-α and/or Interleukin-12.

[0008] PCT International Publication No. WO2007/031440 A2 describes 2-aniline-4-aryl substituted thiazole derivatives purportedly useful in the modulation of the α7 nicotinic receptor.

[0009] PCT International Publication No. WO00/33837 describes compounds, including substituted thiazoles, as inhibitors of membrane-associated tyrosine and threonine kinases.

[0010] US Patent Application Publication No. 2005/0176776 A1 relates to substituted thiazole derivatives purportedly useful in inhibiting mitotic kinesins, particularly KSP, and Kin I kinesin-related proteins, particularly MCAK. The compounds are suggested to be useful in treating cellular proliferative diseases.

[0011] US Patent Application Publication No. 2008/0039466 A1 and PCT International Publication Nos. WO2004/014903 A1, WO2004/096225 A2, WO2005/016323 A2, and WO2005/073225 A1 relate to substituted amino-aryl-thiazoles as tyrosine kinase inhibitors, specifically inhibitors of c-kit and c-kit pathway. The compounds are proposed to be candidates for treating diseases such as autoimmune diseases, inflammatory diseases, cancer, mastocytosis, diabetes, and cerebral ischemia.

[0012] PCT International Publication No. WO2005/063709 A1 relates to heterocyclyl moiety-containing amides as BCR-ABL tyrosine kinase inhibitors.

[0013] PCT International Publication No. WO2007/118149 A2 describe substituted thiazoles and thiophenes reportedly useful in targeting transcription factors NF-κB and AP-1 and translation initiation factor eIF-4E.

[0014] PCT International Publication Nos. WO2006/122011 A2, WO2006/135383 A2, and WO2007/103550 A2 and Severson, W.E., et al., *J. Biomol. Screening* **2007**, *12*, 33 describe compounds, including thiazole derivatives, as inhibitors of viral metabolism.

[0015] PCT International Publication No. WO2001/068645 A2 describes thiazole derivatives as cysteine protease inhibitors for the treatment of osteoporosis.

[0016] PCT International Publication No. WO2004/110350 A2 describes the use of aryl compounds, including substituted thiazoles, in the modulation of amyloid β.

[0017] PCT International Publication No. WO2005/012295 A1 relates to substituted thiazoles as inhibitors of phosphotyrosine phosphatase IB in the treatment of diabetes.

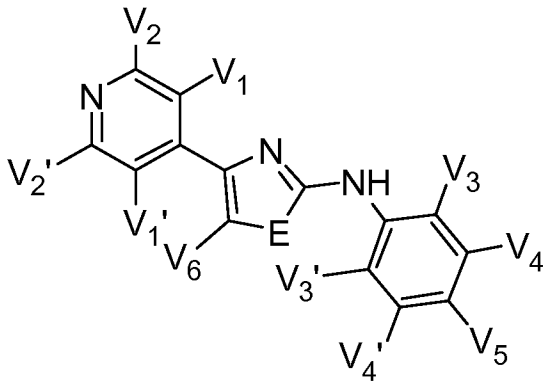
[0018] Narayana, B., et al., *Phosphorus, Sulfur and Silicon and the Related Elements* **2007**, *182*, 7 describe thiazole derivatives as antifungals and antibacterials.

[0019] None of the above publications describes the use of heteroaryl compounds, such as substituted thiazoles, in the targeting of cells defective in the von Hippel-Lindau gene or in the treatment of patients afflicted with diseases associated with such defects. Furthermore, it is known that radiation and standard chemotherapy have been unsuccessful in the treatment of diseases such as renal cell carcinoma. There is therefore a need in the art for the development of novel compounds, compositions, and treatments that target cells defective in the von Hippel-Lindau gene and diseases associated with such defects.

Summary of the Invention

[0020] The present invention addresses these problems by providing novel heteroaryl compounds, compositions, and methods of treatment.

[0021] In one aspect, the invention provides compounds represented by structural formula II:



Formula II

or a pharmaceutically acceptable salt, derivative, or prodrug thereof, wherein:

E is S, O, or N-V_7;

V_3, V_3', V_4', and V_5 are all hydrogen;

V_1, V_1', V_2, V_2', V_4, V_6, and V_7 are independently hydrogen, halo, R, OH, OR, OC(O)H, OC(O)R, $OC(O)NH_2$, OC(O)NHR, OC(O)NRR, $OP(O)(OH)_2$, $OP(O)(OR)_2$, NO_2, NH_2, NHR, NRR, $N^+(-O^-)RR$, NHC(O)H, NHC(O)R, NRC(O)R, $NHC(O)NH_2$, NHC(O)NRR, NRC(O)NHR, $N^2C(O)NHR$, SH, SR, S(O)H, S(O)R, SO_2R, SO_2NH_2, SO_2NHR, SO_2NRR, CF_3, CN, CO_2H, CO_2R, CHO, C(O)R, $C(O)NH_2$, C(O)NHR, C(O)NRR, $CONHSO_2H$, $C(O)NHSO_2R$, $C(O)NRSO_2R$, cyclic C_3-C_7 alkylamino, imidazolyl, piperazinyl, morpholinyl, piperidinyl, azepanyl, pyrrolidinyl or azetidinyl;

wherein each imidazolyl, piperazinyl, morpholinyl, piperidinyl, azepanyl, pyrrolidinyl and azetidinyl is optionally and independently substituted by one or more R^1, halo, OH, OR^1, $OC(O)R^1$, $OC(O)NH_2$, $OC(O)NHR^1$, $OC(O)NR^1R^1$, $OP(O)(OH)_2$, $OP(O)(OR^1)_2$, NO_2, NH_2, NHR^1, NR^1R^1, $N^+(-O^-)R^1R^1$, NHC(O)H, $NHC(O)R^1$, $NR^1C(O)R^1$, $NHC(O)NH_2$, $NHC(O)NR^1R^1$, $NR^1C(O)NHR^1$, SH, SR^1, S(O)H, $S(O)R^1$, SO_2R^1, SO_2NH_2, SO_2NHR^1, $SO_2NR^1R^1$, CF_3, CN, CO_2H, CO_2R^1, CHO, $C(O)R^1$, $C(O)NH_2$, $C(O)NHR^1$, $C(O)NR^1R^1$, $CONHSO_2H$, $C(O)NHSO_2R^1$ or $C(O)NR^1SO_2R^1$;

and wherein V_1 and V_2, taken together with the atoms to which they are attached, optionally form a cyclic structure having from 4 to 8 atoms in the ring;

each R is independently C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cyclic alkyl, aryl, aralkyl, heteroaryl, or heteroaralkyl, and is optionally and independently substituted with halo, OH, R^1, OR^1, $OC(O)R^1$, $OC(O)NH_2$, $OC(O)NHR^1$, $OC(O)NR^1R^1$, $OP(O)(OH)_2$, $OP(O)(OR^1)_2$, NO_2, NH_2, NHR^1, NR^1R^1, $N^+(-O^-)R^1R^1$, $NHC(O)H$, $NHC(O)R^1$, $NR^1C(O)R^1$, $NHC(O)NH_2$, $NHC(O)NR^1R^1$, $NR^1C(O)NHR^1$, SH, SR^1, $S(O)H$, $S(O)R^1$, SO_2R^1, SO_2NH_2, SO_2NHR^1, $SO_2NR^1R^1$, CF_3, CN, CO_2H, CO_2R^1, CHO, $C(O)R^1$, $C(O)NH_2$, $C(O)NHR^1$, $C(O)NR^1R^1$, $C(O)NHSO_2R^1$, $C(O)NR^1SO_2R^1$, cyclic C_3-C_7 alkylamino, imidazolyl, piperazinyl, morpholinyl, piperidinyl, azepanyl, pyrrolidinyl, or azetidinyl;

wherein each imidazolyl, piperazinyl, morpholinyl, piperidinyl, azepanyl, pyrrolidinyl and azetidinyl is optionally and independently substituted with one or more R^1, halo, OH, OR^1, $OC(O)R^1$, $OC(O)NH_2$, $OC(O)NHR^1$, $OC(O)NR^1R^1$, $OP(O)(OH)_2$, $OP(O)(OR^1)_2$, NO_2, NH_2, NHR^1, NR^1R^1, $N^+(-O^-)R^1R^1$, $NHC(O)H$, $NHC(O)R^1$, $NR^1C(O)R^1$, $NHC(O)NH_2$, $NHC(O)NR^1R^1$, $NR^1C(O)NHR^1$, SH, SR^1, $S(O)H$, $S(O)R^1$, SO_2R^1, SO_2NH_2, SO_2NHR^1, $SO_2NR^1R^1$, CF_3, CN, CO_2H, CO_2R^1, CHO, $C(O)R^1$, $C(O)NH_2$, $C(O)NHR^1$, $C(O)NR^1R^1$, $CONHSO_2H$, $C(O)NHSO_2R^1$ or $C(O)NR^1SO_2R^1$;

and wherein each heteroaryl group contains one or more heteroatoms in its ring system, independently selected from O, N or S;

each R^1 is independently C_{1-6} alkyl or C_{2-6} alkenyl, optionally and independently substituted with halo, OH, OR^2, $OC(O)R^2$, $OC(O)NH_2$, $OC(O)NHR^2$, $OC(O)NR^2R^2$, $OP(O)(OH)_2$, $OP(O)(OR^2)_2$, NO_2, NH_2, NHR^2, NR^2R^2, $N^+(-O^-)R^2R^2$, $NHC(O)R^2$, $NR^2C(O)R^2$, $NHC(O)NH_2$, $NHC(O)NR^2R^2$, $NR^2C(O)NHR^2$, SH, SR^2, $S(O)H$, $S(O)R^2$, SO_2R^2, SO_2NH_2, SO_2NHR^2, $SO_2NR^2R^2$, CF_3, CN, CO_2H, CO_2R^2, CHO, $C(O)R^2$, $C(O)NH_2$, $C(O)NHR^2$, $C(O)NR^2R^2$, $C(O)NHSO_2R^2$, $C(O)NR^2SO_2R^2$, cyclic C_3-C_7 alkylamino, imidazolyl, piperazinyl, morpholinyl, piperidinyl, azepanyl, pyrrolidinyl or azetidinyl;

wherein each imidazolyl, piperazinyl, morpholinyl, piperidinyl, azepanyl, pyrrolidinyl and azetidinyl is optionally and independently substituted with one or more R^2, halo, OH, OR^2, $OC(O)R^2$, $OC(O)NH_2$, $OC(O)NHR^2$, $OC(O)NR^2R^2$, $OP(O)(OH)_2$, $OP(O)(OR^2)_2$, NO_2, NH_2, NHR^2, NR^2R^2, $N^+(-O^-)R^2R^2$, $NHC(O)H$,

$NHC(O)R^2$, $NR^2C(O)R^2$, $NHC(O)NH_2$, $NHC(O)NR^2R^2$, $NR^2C(O)NHR^2$, SH, SR^2, S(O)H, $S(O)R^2$, SO_2R^2, SO_2NH_2, SO_2NHR^2, $SO_2NR^2R^2$, CF_3, CN, CO_2H, CO_2R^2, CHO, $C(O)R^2$, $C(O)NH_2$, $C(O)NHR^2$, $C(O)NR^2R^2$, $CONHSO_2H$, $C(O)NHSO_2R^2$ or $C(O)NR^2SO_2R^2$;

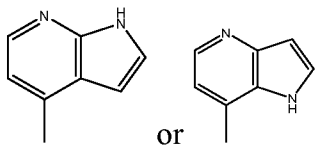
each R^2 is independently C_{1-6} alkyl, C_{2-6} alkenyl, OH, OMe, NO_2, NH_2, CF_3, CN, CO_2H or SH;

provided that V_1, V_1', V_2, V_2', V_4, V_6, and V_7 are not all hydrogen; and

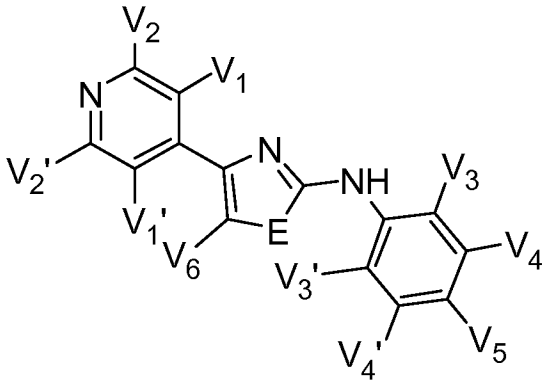
when E is S; V_1, V_1', V_2', and V_6 are all hydrogen; and V_2 is Cl; then V_4 is not Cl; and

when E is S and V_1, V_1', V_2, V_2', and V_6 are all hydrogen; then V_4 is not COOH, $COOCH_3$, $C(O)CH_3$, CF_3, CH_3, OH, OCH_3, SCH_3, CN, O-phenyl, Cl, Br, or NO_2; and

when E is S; V_1', V_2', V_4, and V_6 are all hydrogen; then V_1 and V_2, taken together with the ring to which they are attached, do not form

 or .

[0022] In another aspect, the invention provides compounds represented by structural formula II:



Formula II

or a pharmaceutically acceptable salt, derivative, or prodrug thereof, wherein:

E is S, O, or N-V_7;

V_5 and V_6 are both hydrogen;

V_1, V_1', V_2, V_2', V_3, V_3', V_4, V_4', and V_7 are independently hydrogen, halo, R, OH, OR, OC(O)H, OC(O)R, $OC(O)NH_2$, OC(O)NHR, OC(O)NRR,

$OP(O)(OH)_2$, $OP(O)(OR)_2$, NO_2, NH_2, NHR, NRR, $N^+(-O^-)RR$, NHC(O)H, NHC(O)R, NRC(O)R, $NHC(O)NH_2$, NHC(O)NRR, NRC(O)NHR, $N^2C(O)NHR$, SH, SR, S(O)H, S(O)R, SO_2R, SO_2NH_2, SO_2NHR, SO_2NRR, CF_3, CN, CO_2H, CO_2R, CHO, C(O)R, $C(O)NH_2$, C(O)NHR, C(O)NRR, $CONHSO_2H$, $C(O)NHSO_2R$, $C(O)NRSO_2R$, cyclic C_3-C_7 alkylamino, imidazolyl, piperazinyl, morpholinyl, piperidinyl, azepanyl, pyrrolidinyl or azetidinyl;

wherein each imidazolyl, piperazinyl, morpholinyl, piperidinyl, azepanyl, pyrrolidinyl and azetidinyl is optionally and independently substituted by one or more R^1, halo, OH, OR^1, $OC(O)R^1$, $OC(O)NH_2$, $OC(O)NHR^1$, $OC(O)NR^1R^1$, $OP(O)(OH)_2$, $OP(O)(OR^1)_2$, NO_2, NH_2, NHR^1, NR^1R^1, $N^+(-O^-)R^1R^1$, NHC(O)H, $NHC(O)R^1$, $NR^1C(O)R^1$, $NHC(O)NH_2$, $NHC(O)NR^1R^1$, $NR^1C(O)NHR^1$, SH, SR^1, S(O)H, $S(O)R^1$, SO_2R^1, SO_2NH_2, SO_2NHR^1, $SO_2NR^1R^1$, CF_3, CN, CO_2H, CO_2R^1, CHO, $C(O)R^1$, $C(O)NH_2$, $C(O)NHR^1$, $C(O)NR^1R^1$, $CONHSO_2H$, $C(O)NHSO_2R^1$ or $C(O)NR^1SO_2R^1$;

and wherein groups V_1 and V_2 and groups V_3 and V_4, taken together with the atoms to which they are attached, optionally and independently form a cyclic structure having from 4 to 8 atoms in the ring;

each R is independently C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cyclic alkyl, aryl, aralkyl, heteroaryl, or heteroaralkyl, and is optionally and independently substituted with halo, OH, R^1, OR^1, $OC(O)R^1$, $OC(O)NH_2$, $OC(O)NHR^1$, $OC(O)NR^1R^1$, $OP(O)(OH)_2$, $OP(O)(OR^1)_2$, NO_2, NH_2, NHR^1, NR^1R^1, $N^+(-O^-)R^1R^1$, NHC(O)H, $NHC(O)R^1$, $NR^1C(O)R^1$, $NHC(O)NH_2$, $NHC(O)NR^1R^1$, $NR^1C(O)NHR^1$, SH, SR^1, S(O)H, $S(O)R^1$, SO_2R^1, SO_2NH_2, SO_2NHR^1, $SO_2NR^1R^1$, CF_3, CN, CO_2H, CO_2R^1, CHO, $C(O)R^1$, $C(O)NH_2$, $C(O)NHR^1$, $C(O)NR^1R^1$, $C(O)NHSO_2R^1$, $C(O)NR^1SO_2R^1$, cyclic C_3-C_7 alkylamino, imidazolyl, piperazinyl, morpholinyl, piperidinyl, azepanyl, pyrrolidinyl, or azetidinyl;

wherein each imidazolyl, piperazinyl, morpholinyl, piperidinyl, azepanyl, pyrrolidinyl and azetidinyl is optionally and independently substituted with one or more R^1, halo, OH, OR^1, $OC(O)R^1$, $OC(O)NH_2$, $OC(O)NHR^1$, $OC(O)NR^1R^1$, $OP(O)(OH)_2$, $OP(O)(OR^1)_2$, NO_2, NH_2, NHR^1, NR^1R^1, $N^+(-O^-)R^1R^1$, NHC(O)H, $NHC(O)R^1$, $NR^1C(O)R^1$, $NHC(O)NH_2$, $NHC(O)NR^1R^1$, $NR^1C(O)NHR^1$, SH, SR^1,

S(O)H, $S(O)R^1$, SO_2R^1, SO_2NH_2, SO_2NHR^1, $SO_2NR^1R^1$, CF_3, CN, CO_2H, CO_2R^1, CHO, $C(O)R^1$, $C(O)NH_2$, $C(O)NHR^1$, $C(O)NR^1R^1$, $CONHSO_2H$, $C(O)NHSO_2R^1$ or $C(O)NR^1SO_2R^1$;

and wherein each heteroaryl group contains one or more heteroatoms in its ring system, independently selected from O, N or S;

each R^1 is independently C_{1-6} alkyl or C_{2-6} alkenyl, optionally and independently substituted with halo, OH, OR^2, $OC(O)R^2$, $OC(O)NH_2$, $OC(O)NHR^2$, $OC(O)NR^2R^2$, $OP(O)(OH)_2$, $OP(O)(OR^2)_2$, NO_2, NH_2, NHR^2, NR^2R^2, $N^+(-O^-)R^2R^2$, $NHC(O)R^2$, $NR^2C(O)R^2$, $NHC(O)NH_2$, $NHC(O)NR^2R^2$, $NR^2C(O)NHR^2$, SH, SR^2, S(O)H, $S(O)R^2$, SO_2R^2, SO_2NH_2, SO_2NHR^2, $SO_2NR^2R^2$, CF_3, CN, CO_2H, CO_2R^2, CHO, $C(O)R^2$, $C(O)NH_2$, $C(O)NHR^2$, $C(O)NR^2R^2$, $C(O)NHSO_2R^2$, $C(O)NR^2SO_2R^2$, cyclic C_3-C_7 alkylamino, imidazolyl, piperazinyl, morpholinyl, piperidinyl, azepanyl, pyrrolidinyl or azetidinyl;

wherein each imidazolyl, piperazinyl, morpholinyl, piperidinyl, azepanyl, pyrrolidinyl and azetidinyl is optionally and independently substituted with one or more R^2, halo, OH, OR^2, $OC(O)R^2$, $OC(O)NH_2$, $OC(O)NHR^2$, $OC(O)NR^2R^2$, $OP(O)(OH)_2$, $OP(O)(OR^2)_2$, NO_2, NH_2, NHR^2, NR^2R^2, $N^+(-O^-)R^2R^2$, NHC(O)H, $NHC(O)R^2$, $NR^2C(O)R^2$, $NHC(O)NH_2$, $NHC(O)NR^2R^2$, $NR^2C(O)NHR^2$, SH, SR^2, S(O)H, $S(O)R^2$, SO_2R^2, SO_2NH_2, SO_2NHR^2, $SO_2NR^2R^2$, CF_3, CN, CO_2H, CO_2R^2, CHO, $C(O)R^2$, $C(O)NH_2$, $C(O)NHR^2$, $C(O)NR^2R^2$, $CONHSO_2H$, $C(O)NHSO_2R^2$ or $C(O)NR^2SO_2R^2$;

each R^2 is independently C_{1-6} alkyl, C_{2-6} alkenyl, OH, OMe, NO_2, NH_2, CF_3, CN, CO_2H or SH;

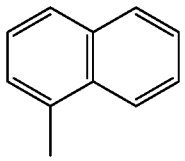
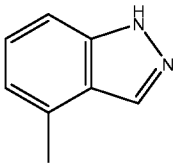
provided that V_1, V_1', V_2, V_2', V_3, V_3', V_4, V_4', and V_7 are not all hydrogen; and

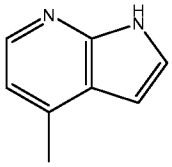
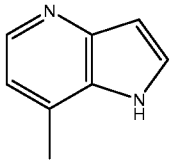
when E is S; V_1, V_1', and V_2' are all hydrogen; and V_2 is Cl; then V_3 is not CH_3 and V_4 is not Cl; and

when E is S and V_3' and V_4 are both hydrogen, then either V_3 or V_4' is also hydrogen; and

when E is S and V_1, V_1', V_2, V_2', V_3, V_3', and V_4' are all hydrogen, then V_4 is not COOH, $COOCH_3$, $C(O)CH_3$, CF_3, CH_3, OH, OCH_3, SCH_3, CN, O-phenyl, Cl, Br, or NO_2; and

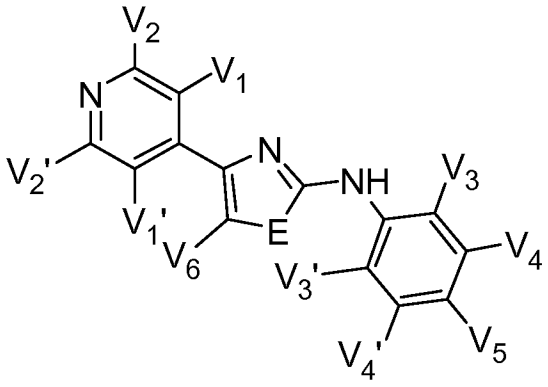
when E is S and V_1, V_1', V_2, V_2', V_3', V_4, and V_4' are all hydrogen, then V_3 is not CH_3, CH_2CH_3, F, Cl, NO_2, CF_3, OCH_3, OCH_2CH_3, or a substituted 1,4-dihydropyridyl ring; and

when E is S and V_1, V_1', V_2, V_2', V_3', and V_4' are all hydrogen; then when V_3 is Cl, V_4 is not Cl; when V_3 is CH_3, V_4 is not Cl; and V_3 and V_4, taken together with the ring to which they are attached, do not form  or  ; and

when E is S and V_1', V_2', V_3, V_3', V_4, and V_4' are all hydrogen, then V_1 and V_2, taken together with the ring to which they are attached, do not form  or  ; and

when V_3 and V_3' are both hydrogen, then V_4 and V_4' are not both CH_3.

[0023] In yet another aspect, the invention provides compounds represented by structural formula II:



Formula II

or a pharmaceutically acceptable salt, derivative, or prodrug thereof, wherein:

E is S, O, or N-V_7;

V_3' and V_4' are both hydrogen;

V_1, V_1', V_2, V_2', V_3, V_4, V_5, V_6, and V_7 are independently hydrogen, halo, R, OH, OR, OC(O)H, OC(O)R, $OC(O)NH_2$, OC(O)NHR, OC(O)NRR, $OP(O)(OH)_2$, $OP(O)(OR)_2$, NO_2, NH_2, NHR, NRR, $N^+(-O^-)RR$, NHC(O)H, NHC(O)R, NRC(O)R, $NHC(O)NH_2$, NHC(O)NRR, NRC(O)NHR, $N^2C(O)NHR$, SH, SR, S(O)H, S(O)R, SO_2R, SO_2NH_2, SO_2NHR, SO_2NRR, CF_3, CN, CO_2H, CO_2R, CHO, C(O)R, $C(O)NH_2$, C(O)NHR, C(O)NRR, $CONHSO_2H$, $C(O)NHSO_2R$, $C(O)NRSO_2R$, cyclic C_3-C_7 alkylamino, imidazolyl, piperazinyl, morpholinyl, piperidinyl, azepanyl, pyrrolidinyl or azetidinyl;

wherein each imidazolyl, piperazinyl, morpholinyl, piperidinyl, azepanyl, pyrrolidinyl and azetidinyl is optionally and independently substituted by one or more R^1, halo, OH, OR^1, $OC(O)R^1$, $OC(O)NH_2$, $OC(O)NHR^1$, $OC(O)NR^1R^1$, $OP(O)(OH)_2$, $OP(O)(OR^1)_2$, NO_2, NH_2, NHR^1, NR^1R^1, $N^+(-O^-)R^1R^1$, NHC(O)H, $NHC(O)R^1$, $NR^1C(O)R^1$, $NHC(O)NH_2$, $NHC(O)NR^1R^1$, $NR^1C(O)NHR^1$, SH, SR^1, S(O)H, $S(O)R^1$, SO_2R^1, SO_2NH_2, SO_2NHR^1, $SO_2NR^1R^1$, CF_3, CN, CO_2H, CO_2R^1, CHO, $C(O)R^1$, $C(O)NH_2$, $C(O)NHR^1$, $C(O)NR^1R^1$, $CONHSO_2H$, $C(O)NHSO_2R^1$ or $C(O)NR^1SO_2R^1$;

and wherein groups V_1 and V_2, groups V_3 and V_4, and groups V_4 and V_5, taken together with the atoms to which they are attached, optionally and independently form a cyclic structure having from 4 to 8 atoms in the ring;

each R is independently C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cyclic alkyl, aryl, aralkyl, heteroaryl, or heteroaralkyl, and is optionally and independently substituted with halo, OH, R^1, OR^1, $OC(O)R^1$, $OC(O)NH_2$, $OC(O)NHR^1$, $OC(O)NR^1R^1$, $OP(O)(OH)_2$, $OP(O)(OR^1)_2$, NO_2, NH_2, NHR^1, NR^1R^1, $N^+(-O^-)R^1R^1$, NHC(O)H, $NHC(O)R^1$, $NR^1C(O)R^1$, $NHC(O)NH_2$, $NHC(O)NR^1R^1$, $NR^1C(O)NHR^1$, SH, SR^1, S(O)H, $S(O)R^1$, SO_2R^1, SO_2NH_2, SO_2NHR^1, $SO_2NR^1R^1$, CF_3, CN, CO_2H, CO_2R^1, CHO, $C(O)R^1$, $C(O)NH_2$, $C(O)NHR^1$, $C(O)NR^1R^1$, $C(O)NHSO_2R^1$, $C(O)NR^1SO_2R^1$, cyclic C_3-C_7 alkylamino, imidazolyl, piperazinyl, morpholinyl, piperidinyl, azepanyl, pyrrolidinyl, or azetidinyl;

wherein each imidazolyl, piperazinyl, morpholinyl, piperidinyl, azepanyl, pyrrolidinyl and azetidinyl is optionally and independently substituted with one or more R^1, halo, OH, OR^1, $OC(O)R^1$, $OC(O)NH_2$, $OC(O)NHR^1$, $OC(O)NR^1R^1$,

$OP(O)(OH)_2$, $OP(O)(OR^1)_2$, NO_2, NH_2, NHR^1, NR^1R^1, $N^+(-O^-)R^1R^1$, NHC(O)H, $NHC(O)R^1$, $NR^1C(O)R^1$, $NHC(O)NH_2$, $NHC(O)NR^1R^1$, $NR^1C(O)NHR^1$, SH, SR^1, S(O)H, $S(O)R^1$, SO_2R^1, SO_2NH_2, SO_2NHR^1, $SO_2NR^1R^1$, CF_3, CN, CO_2H, CO_2R^1, CHO, $C(O)R^1$, $C(O)NH_2$, $C(O)NHR^1$, $C(O)NR^1R^1$, $CONHSO_2H$, $C(O)NHSO_2R^1$ or $C(O)NR^1SO_2R^1$;

and wherein each heteroaryl group contains one or more heteroatoms in its ring system, independently selected from O, N or S;

each R^1 is independently C_{1-6} alkyl or C_{2-6} alkenyl, optionally and independently substituted with halo, OH, OR^2, $OC(O)R^2$, $OC(O)NH_2$, $OC(O)NHR^2$, $OC(O)NR^2R^2$, $OP(O)(OH)_2$, $OP(O)(OR^2)_2$, NO_2, NH_2, NHR^2, NR^2R^2, $N^+(-O^-)R^2R^2$, $NHC(O)R^2$, $NR^2C(O)R^2$, $NHC(O)NH_2$, $NHC(O)NR^2R^2$, $NR^2C(O)NHR^2$, SH, SR^2, S(O)H, $S(O)R^2$, SO_2R^2, SO_2NH_2, SO_2NHR^2, $SO_2NR^2R^2$, CF_3, CN, CO_2H, CO_2R^2, CHO, $C(O)R^2$, $C(O)NH_2$, $C(O)NHR^2$, $C(O)NR^2R^2$, $C(O)NHSO_2R^2$, $C(O)NR^2SO_2R^2$, cyclic C_3-C_7 alkylamino, imidazolyl, piperazinyl, morpholinyl, piperidinyl, azepanyl, pyrrolidinyl or azetidinyl;

wherein each imidazolyl, piperazinyl, morpholinyl, piperidinyl, azepanyl, pyrrolidinyl and azetidinyl is optionally and independently substituted with one or more R^2, halo, OH, OR^2, $OC(O)R^2$, $OC(O)NH_2$, $OC(O)NHR^2$, $OC(O)NR^2R^2$, $OP(O)(OH)_2$, $OP(O)(OR^2)_2$, NO_2, NH_2, NHR^2, NR^2R^2, $N^+(-O^-)R^2R^2$, NHC(O)H, $NHC(O)R^2$, $NR^2C(O)R^2$, $NHC(O)NH_2$, $NHC(O)NR^2R^2$, $NR^2C(O)NHR^2$, SH, SR^2, S(O)H, $S(O)R^2$, SO_2R^2, SO_2NH_2, SO_2NHR^2, $SO_2NR^2R^2$, CF_3, CN, CO_2H, CO_2R^2, CHO, $C(O)R^2$, $C(O)NH_2$, $C(O)NHR^2$, $C(O)NR^2R^2$, $CONHSO_2H$, $C(O)NHSO_2R^2$ or $C(O)NR^2SO_2R^2$;

each R^2 is independently C_{1-6} alkyl, C_{2-6} alkenyl, OH, OMe, NO_2, NH_2, CF_3, CN, CO_2H or SH;

provided that V_1, V_1', V_2, V_2', V_3, V_4, V_5, V_6, and V_7 are not all hydrogen; and

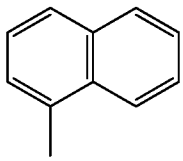
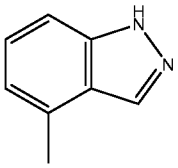
when E is S; V_1, V_1', and V_2' are all hydrogen; and V_2 is Cl; then V_3 is not CH_3 when V_4 is Cl; and V_5 is not CH_3, OCH_3, or Cl; and

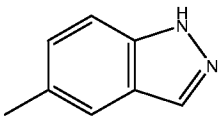
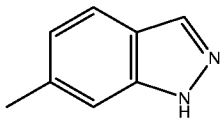
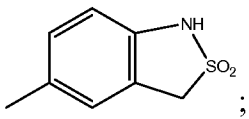
when E is S; V_1, V_1', and V_2' are all hydrogen; V_2 is H or NH_2; and V_4 is CF_3; then V_5 is not F; and

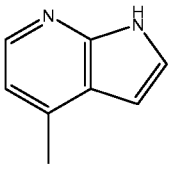
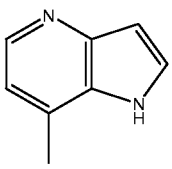
when E is S and V_1, V_1', V_2, V_2', V_3 and V_5 are all hydrogen, then V_4 is not COOH, $COOCH_3$, $C(O)CH_3$, CF_3, CH_3, OH, OCH_3, SCH_3, CN, O-phenyl, Cl, Br, or NO_2; and

when E is S and V_1, V_1', V_2, V_2', V_4 and V_5 are all hydrogen, then V_3 is not CH_3, CH_2CH_3, F, Cl, NO_2, CF_3, OCH_3, OCH_2CH_3, or a substituted 1,4-dihydropyridyl ring; and

when E is S and V_1, V_1', V_2, V_2', V_3 and V_4 are all hydrogen, then V_5 is not CH_3, CH_2CH_3, $C(O)CH_3$, CF_3, $S(O)_2$-NH_2, $S(O)_2$-NHR, $N(CH_3)_2$, $N(CH_2CH_3)_2$, N(*i*-Pr)phenyl, NO_2, OCH_2CH_3, NH-$C(O)CH_3$, NH_2, COOH, F, Cl, Br, I, OH, OCH_3, O-phenyl, O-C_{7-8}-alkyl, or $C(O)NHC(i\text{-Bu})C(O)NHCH_2CN$; and

when E is S and V_1, V_1', V_2, V_2', and V_5 are all hydrogen; then when V_3 is Cl, V_4 is not Cl; when V_3 is CH_3, then V_4 is not Cl; and V_3 and V_4, taken together with the ring to which they are attached, do not form  or  ; and

when E is S and V_1, V_1', V_2, V_2', and V_3 are all hydrogen; then when V_5 is O-C_{5-8}-alkyl, V_4 is not hydrogen, F, or CF_3; when V_5 is CH_3, V_4 is not CH_3; and V_4 and V_5, taken together with the ring to which they are attached, do not form  ,  , or  ;

when E is S and V_1', V_2', V_3, V_4, and V_5 are all hydrogen, then V_1 and V_2, taken together with the ring to which they are attached, do not form  or  .

[0024] In some embodiments of the invention, V_4 is hydrogen; halo; R; OH; OR; CF_3; NO_2; NH_2; NHR; NRR; $OP(O)(OH)_2$; or $OP(O)(OR)_2$.

[0025] In specific embodiments, V_4 is hydrogen; halo; C_{1-6} alkyl, optionally substituted with OH, NH_2, or $N(CH_3)_2$; OH; O-C_{1-6} alkyl, optionally substituted with OH, NH_2, or $N(CH_3)_2$; CF_3; NO_2; NH_2; or $OP(O)(OH)_2$.

[0026] In some embodiments, V_6 is hydrogen; R; CHO; CO_2R; $C(O)NH_2$; C(O)NHR; or C(O)NRR.

[0027] In specific embodiments, V_6 is hydrogen; C_{1-6} alkyl or C_{2-4} alkenyl, optionally substituted with OH, OR^1, CO_2R^1, NH_2, NHR^1, or NR^1R^1; CHO; or CO_2R.

[0028] In more specific embodiments, V_6 is hydrogen.

[0029] In some embodiments, V_1 and V_2 are independently hydrogen, halo, R, OH, OR, CF_3, NO_2, NH_2, NHR, NRR, or, taken together with the atoms to which they are attached, form a 5- or 6-membered ring structure.

[0030] In other embodiments, V_1, V_1', V_2, V_2' are all hydrogen.

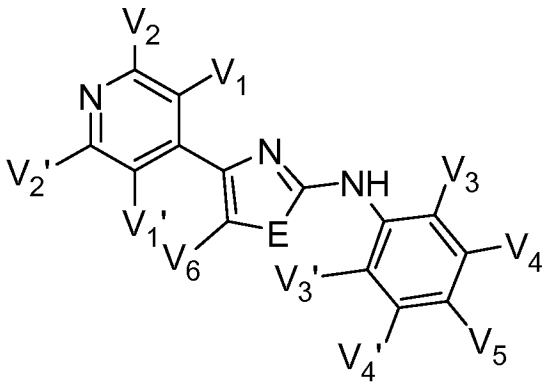
[0031] In certain embodiments, E is S or O.

[0032] In certain specific embodiments, E is S.

[0033] In another aspect, the invention provides a pharmaceutical composition comprising a compound as described above and a pharmacuetically acceptable carrier.

[0034] In certain embodiments, the pharmaceutical composition further comprises one or more chemotherapeutic agents.

[0035] In another aspect, the invention provides a method of treating or preventing a disease, comprising administering to a mammalian host a therapeutically-effective amount of a compound of Formula II or a pharmaceutically acceptable salt, derivative, or prodrug thereof:



Formula II

wherein:

E is S, O, or N-V_7;

V_1, V_1', V_2, V_2', V_3, V_3', V_4, V_4', V_5, V_6, and V_7 are independently hydrogen, halo, R, OH, OR, OC(O)H, OC(O)R, $OC(O)NH_2$, OC(O)NHR, OC(O)NRR, $OP(O)(OH)_2$, $OP(O)(OR)_2$, NO_2, NH_2, NHR, NRR, $N^+(-O^-)RR$, NHC(O)H, NHC(O)R, NRC(O)R, $NHC(O)NH_2$, NHC(O)NRR, NRC(O)NHR, $N^2C(O)NHR$, SH, SR, S(O)H, S(O)R, SO_2R, SO_2NH_2, SO_2NHR, SO_2NRR, CF_3, CN, CO_2H, CO_2R, CHO, C(O)R, $C(O)NH_2$, C(O)NHR, C(O)NRR, $CONHSO_2H$, $C(O)NHSO_2R$, $C(O)NRSO_2R$, cyclic C_3-C_7 alkylamino, imidazolyl, piperazinyl, morpholinyl, piperidinyl, azepanyl, pyrrolidinyl or azetidinyl;

wherein each imidazolyl, piperazinyl, morpholinyl, piperidinyl, azepanyl, pyrrolidinyl and azetidinyl is optionally and independently substituted by one or more R^1, halo, OH, OR^1, $OC(O)R^1$, $OC(O)NH_2$, $OC(O)NHR^1$, $OC(O)NR^1R^1$, $OP(O)(OH)_2$, $OP(O)(OR^1)_2$, NO_2, NH_2, NHR^1, NR^1R^1, $N^+(-O^-)R^1R^1$, NHC(O)H, $NHC(O)R^1$, $NR^1C(O)R^1$, $NHC(O)NH_2$, $NHC(O)NR^1R^1$, $NR^1C(O)NHR^1$, SH, SR^1, S(O)H, $S(O)R^1$, SO_2R^1, SO_2NH_2, SO_2NHR^1, $SO_2NR^1R^1$, CF_3, CN, CO_2H, CO_2R^1, CHO, $C(O)R^1$, $C(O)NH_2$, $C(O)NHR^1$, $C(O)NR^1R^1$, $CONHSO_2H$, $C(O)NHSO_2R^1$ or $C(O)NR^1SO_2R^1$;

and wherein groups V_1 and V_2, groups V_3 and V_4, and groups V_4 and V_5, taken together with the atoms to which they are attached, optionally and independently form a cyclic structure having from 4 to 8 atoms in the ring;

each R is independently C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cyclic alkyl, aryl, aralkyl, heteroaryl, or heteroaralkyl, and is optionally and independently substituted with halo, OH, R^1, OR^1, $OC(O)R^1$, $OC(O)NH_2$, $OC(O)NHR^1$, $OC(O)NR^1R^1$, $OP(O)(OH)_2$, $OP(O)(OR^1)_2$, NO_2, NH_2, NHR^1, NR^1R^1, $N^+(-O^-)R^1R^1$, NHC(O)H, $NHC(O)R^1$, $NR^1C(O)R^1$, $NHC(O)NH_2$, $NHC(O)NR^1R^1$, $NR^1C(O)NHR^1$, SH, SR^1, S(O)H, $S(O)R^1$, SO_2R^1, SO_2NH_2, SO_2NHR^1, $SO_2NR^1R^1$, CF_3, CN, CO_2H, CO_2R^1, CHO, $C(O)R^1$, $C(O)NH_2$, $C(O)NHR^1$, $C(O)NR^1R^1$, $C(O)NHSO_2R^1$, $C(O)NR^1SO_2R^1$, cyclic C_3-C_7 alkylamino, imidazolyl, piperazinyl, morpholinyl, piperidinyl, azepanyl, pyrrolidinyl, or azetidinyl;

wherein each imidazolyl, piperazinyl, morpholinyl, piperidinyl, azepanyl, pyrrolidinyl and azetidinyl is optionally and independently substituted with one or more R^1, halo, OH, OR^1, $OC(O)R^1$, $OC(O)NH_2$, $OC(O)NHR^1$, $OC(O)NR^1R^1$, $OP(O)(OH)_2$, $OP(O)(OR^1)_2$, NO_2, NH_2, NHR^1, NR^1R^1, $N^+(-O^-)R^1R^1$, NHC(O)H, $NHC(O)R^1$, $NR^1C(O)R^1$, $NHC(O)NH_2$, $NHC(O)NR^1R^1$, $NR^1C(O)NHR^1$, SH, SR^1, S(O)H, $S(O)R^1$, SO_2R^1, SO_2NH_2, SO_2NHR^1, $SO_2NR^1R^1$, CF_3, CN, CO_2H, CO_2R^1, CHO, $C(O)R^1$, $C(O)NH_2$, $C(O)NHR^1$, $C(O)NR^1R^1$, $CONHSO_2H$, $C(O)NHSO_2R^1$ or $C(O)NR^1SO_2R^1$;

and wherein each heteroaryl group contains one or more heteroatoms in its ring system, independently selected from O, N or S;

each R^1 is independently C_{1-6} alkyl or C_{2-6} alkenyl, optionally and independently substituted with halo, OH, OR^2, $OC(O)R^2$, $OC(O)NH_2$, $OC(O)NHR^2$, $OC(O)NR^2R^2$, $OP(O)(OH)_2$, $OP(O)(OR^2)_2$, NO_2, NH_2, NHR^2, NR^2R^2, $N^+(-O^-)R^2R^2$, $NHC(O)R^2$, $NR^2C(O)R^2$, $NHC(O)NH_2$, $NHC(O)NR^2R^2$, $NR^2C(O)NHR^2$, SH, SR^2, S(O)H, $S(O)R^2$, SO_2R^2, SO_2NH_2, SO_2NHR^2, $SO_2NR^2R^2$, CF_3, CN, CO_2H, CO_2R^2, CHO, $C(O)R^2$, $C(O)NH_2$, $C(O)NHR^2$, $C(O)NR^2R^2$, $C(O)NHSO_2R^2$, $C(O)NR^2SO_2R^2$, cyclic C_3-C_7 alkylamino, imidazolyl, piperazinyl, morpholinyl, piperidinyl, azepanyl, pyrrolidinyl or azetidinyl;

wherein each imidazolyl, piperazinyl, morpholinyl, piperidinyl, azepanyl, pyrrolidinyl and azetidinyl is optionally and independently substituted with one or more R^2, halo, OH, OR^2, $OC(O)R^2$, $OC(O)NH_2$, $OC(O)NHR^2$, $OC(O)NR^2R^2$, $OP(O)(OH)_2$, $OP(O)(OR^2)_2$, NO_2, NH_2, NHR^2, NR^2R^2, $N^+(-O^-)R^2R^2$, NHC(O)H, $NHC(O)R^2$, $NR^2C(O)R^2$, $NHC(O)NH_2$, $NHC(O)NR^2R^2$, $NR^2C(O)NHR^2$, SH, SR^2, S(O)H, $S(O)R^2$, SO_2R^2, SO_2NH_2, SO_2NHR^2, $SO_2NR^2R^2$, CF_3, CN, CO_2H, CO_2R^2, CHO, $C(O)R^2$, $C(O)NH_2$, $C(O)NHR^2$, $C(O)NR^2R^2$, $CONHSO_2H$, $C(O)NHSO_2R^2$ or $C(O)NR^2SO_2R^2$; and

each R^2 is independently C_{1-6} alkyl, C_{2-6} alkenyl, OH, OMe, NO_2, NH_2, CF_3, CN, CO_2H or SH.

[0036] In certain embodiments, the V_1, V_1', V_2, V_2', V_3, V_3', V_4, V_4', V_5, V_6, V_7, and E groups of the compound administered according to the methods of the invention have the specific definitions recited above.

[0037] In certain embodiments, the disease treated or prevented according to the methods of the invention is caused by a defect in the von Hippel-Lindau gene.

[0038] In certain embodiments, the compound administered according to the methods of the invention targets cells deficient in the von Hippel-Lindau gene.

[0039] In certain embodiments, the compound administered according to the methods of the invention induces autophagic cell death.

[0040] In certain embodiments, the disease is a cancer.

[0041] In specific embodiments, the cancer is a renal cell carcinoma, a pheochromocytoma, a hemangioblastoma of the central nervous system or retina, an endolymphatic sac tumor, a renal cyst, a pancreatic cyst, a neuroendocrine tumor, an endolymphatic sac tumor, or an epididymal or broad ligament cystadenoma.

[0042] In other specific embodiments, the cancer is a cancer of the retina, brain, spinal cord, ear, epidymis, broad ligament, adrenal gland, kidney, or pancreas.

[0043] In some embodiments, the methods further comprise the step of administering a therapeutically-effective amount of one or more chemotherapeutic agents to the mammalian host before, during, or after administration of the compound.

Listing of Drawings

[0044] Figure1. Effects of STF-62247 on VHL-deficient cells.

[0045] Figure 2. Detection of autophagic vacuoles in RCCs following treatment with STF-62247.

[0046] Figure 3. Role of ATG5 in autophagic cell death following treatment with STF-62247.

[0047] Figure 4. Golgi trafficking and role of PI3K following treatment with STF-62247.

[0048] Figure 5. Evaluation of autophagy in RCCs treated with STF-62247 analogs.

[0049] Figure 6. Effects of STF-62247 on Golgi trafficking proteins.

[0050] Figure 7. Screening assays.

[0051] Figure 8. Transmission electron microscopy of control and STF-62247-treated RCC4 cells.

[0052] Figure 9. Effects of STF-62247 and other treatments on VHL-deficient RCC4 and wild-type VHL cells.

[0053] Figure 10. Knockdown of genes using siRNA.

Detailed Description of the Invention

[0054] The instant invention provides novel heteroaryl compounds, compositions, and methods of use in targeting cells defective in the von Hippel-Lindau (VHL) gene and diseases associated with such defects. The provided compounds induce cytotoxicity and reduce tumor growth of VHL-deficient cells compared to genetically matched cells with wild-type VHL. The compounds thus selectively induce cell death in VHL-deficient cells and therefore represent a novel strategy for targeted therapy. See also Sutphin, P., et al., *Cancer Res.* **2007**, 67, 5896; Turcotte, S., et al., *Cancer Cell.* **2008**, 14, 90; Turcotte, S., et al., *Autophagy* **2008**, Oct 1;4(7):944-6. Epub 2008 Oct 13.

[0055] Before further description of the invention, certain terms employed in the specification, examples and appended claims are, for convenience, collected here.

[0056] The term "alkyl" refers to the radical of saturated aliphatic groups, including straight-chain alkyl groups, branched-chain alkyl groups, cycloalkyl (alicyclic) groups, alkyl-substituted cycloalkyl groups, and cycloalkyl-substituted alkyl groups. In some embodiments, a straight chain or branched chain alkyl has 30 or fewer carbon atoms in its backbone (*e.g.*, C_1-C_{30} for straight chains, C_3-C_{30} for branched chains), and more specifically 20 or fewer. Likewise, some cycloalkyls have from 3-10 carbon atoms in their ring structure, and more specifically have 5, 6 or 7 carbons in the ring structure.

[0057] Moreover, the term "alkyl" (or "lower alkyl") as used throughout the specification, examples, and claims is intended to include both "unsubstituted alkyls" and "substituted alkyls", the latter of which refers to alkyl moieties having substituents replacing a hydrogen on one or more carbons of the hydrocarbon backbone. Such substituents can include, for example, a halo, a hydroxyl, a carbonyl (such as a keto, a carboxy, an alkoxycarbonyl, a formyl, or an acyl), a

thiocarbonyl (such as a thioester, a thioacetate, or a thioformate), an alkoxyl, a phosphoryl, a phosphate, a phosphonate, a phosphinate, an amino, an amido, an amidine, an imine, a cyano, a nitro, an azido, a thio, an alkylthio, a sulfate, a sulfonate, a sulfamoyl, a sulfonamido, a sulfonyl, a heterocyclyl, an aralkyl, or an aromatic or heteroaromatic moiety. It will be understood by those skilled in the art that the moieties substituted on the hydrocarbon chain can themselves be substituted, if appropriate. For instance, the substituents of a substituted alkyl may include substituted and unsubstituted forms of amino, azido, imino, amido, phosphoryl (including phosphonate and phosphinate), sulfonyl (including sulfate, sulfonamido, sulfamoyl and sulfonate), and silyl groups, as well as ethers, alkylthios, carbonyls (including ketones, aldehydes, carboxylates, and esters), $-CF_3$, -CN and the like. Exemplary substituted alkyls are described below. Cycloalkyls can be further substituted with alkyls, alkenyls, alkoxys, alkylthios, aminoalkyls, carbonyl-substituted alkyls, $-CF_3$, -CN, and the like.

[0058] The term "C_{x-y}" when used in conjunction with a chemical moiety, such as, acyl, acyloxy, alkyl, alkenyl, alkynyl, or alkoxy is meant to include groups that contain from x to y carbons in the chain. For example, the term "C_{x-y}alkyl" refers to substituted or unsubstituted saturated hydrocarbon groups, including straight-chain alkyl and branched-chain alkyl groups that contain from x to y carbons in the chain, including haloalkyl groups such as trifluoromethyl and 2,2,2-trifluoroethyl, etc. "C_0-alkyl" indicates a hydrogen where the group is in a terminal position, or is a bond if internal. The terms "C_{2-y}-alkenyl" and "C_{2-y}-alkynyl" refer to substituted or unsubstituted unsaturated aliphatic groups analogous in length and possible substitution to the alkyls described above, but that contain at least one double or triple bond, respectively.

[0059] The term "alkylamino", as used herein, refers to an amino group substituted with at least one alkyl group.

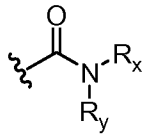
[0060] The term "alkylthio", as used herein, refers to a thiol group substituted with an alkyl group and may be represented by the general formula alkyl-S-.

[0061] The term "alkenyl", as used herein, refers to an aliphatic group containing at least one double bond and is intended to include both "unsubstituted alkenyls" and "substituted alkenyls", the latter of which refers to alkenyl moieties having

substituents replacing a hydrogen on one or more carbons of the alkenyl group. Such substituents may occur on one or more carbons that are included or not included in one or more double bonds. Moreover, such substituents include all those contemplated for alkyl groups, as discussed below, except where stability is prohibitive. For example, substitution of alkenyl groups by one or more alkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl groups is contemplated.

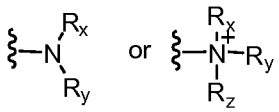
[0062] The term "alkynyl", as used herein, refers to an aliphatic group containing at least one triple bond and is intended to include both "unsubstituted alkynyls" and "substituted alkynyls", the latter of which refers to alkynyl moieties having substituents replacing a hydrogen on one or more carbons of the alkynyl group. Such substituents may occur on one or more carbons that are included or not included in one or more triple bonds. Moreover, such substituents include all those contemplated for alkyl groups, as discussed above, except where stability is prohibitive. For example, substitution of alkynyl groups by one or more alkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl groups is contemplated.

[0063] The term "amide", as used herein, refers to a group



wherein R_x and R_y each independently represent a hydrogen or hydrocarbyl group, or R_x and R_y taken together with the N atom to which they are attached complete a heterocycle having from 4 to 8 atoms in the ring structure.

[0064] The terms "amine" and "amino" are art-recognized and refer to both unsubstituted and substituted amines and salts thereof, *e.g.*, a moiety that can be represented by



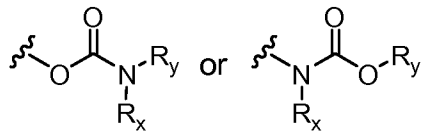
wherein R_x, R_y, and R_z each independently represent a hydrogen or a hydrocarbyl group, or R_x and R_y taken together with the N atom to which they are attached complete a heterocycle having from 4 to 8 atoms in the ring structure.

[0065] The term "aminoalkyl", as used herein, refers to an alkyl group substituted with an amino group.

[0066] The term "aralkyl", as used herein, refers to an alkyl group substituted with an aryl group.

[0067] The term "aryl" as used herein includes substituted or unsubstituted single-ring aromatic groups in which each atom of the ring is carbon. In certain embodiments, the ring is a 5- to 7-membered ring, and in more specific embodiments is a 6-membered ring. The term "aryl" also includes polycyclic ring systems having two or more cyclic rings in which two or more carbons are common to two adjoining rings wherein at least one of the rings is aromatic, *e.g.*, the other cyclic rings can be cycloalkyls, cycloalkenyls, cycloalkynyls, aryls, heteroaryls, and/or heterocyclyls. Aryl groups include benzene, naphthalene, phenanthrene, phenol, aniline, and the like.

[0068] The term "carbamate" is art-recognized and refers to a group



wherein R_x and R_y independently represent hydrogen or a hydrocarbyl group, or R_x and R_y taken together with the atoms to which they are attached complete a heterocycle having from 4 to 8 atoms in the ring structure.

[0069] The term "cycloalkyl" and "cyclic alkyl", as used herein, refers to a non-aromatic saturated or unsaturated ring in which each atom of the ring is carbon. In certain embodiments, a cycloalkyl ring contains from 3 to 10 atoms, and in more specific embodiments from 5 to 7 atoms.

[0070] The term "carbonate" is art-recognized and refers to a group $-OCO_2-R_4$, wherein R_4 represents a hydrocarbyl group.

[0071] The term "carboxy", as used herein, refers to a group represented by the formula $-CO_2H$.

[0072] The terms "halo" and "halogen" as used herein mean halogen and include chloro, fluoro, bromo, and iodo.

[0073] The terms "hetaralkyl" and "heteroaralkyl", as used herein, refer to an alkyl group substituted with a hetaryl group.

[0074] The terms "heteroaryl" and "hetaryl" include substituted or unsubstituted aromatic single ring structures, in certain specific embodiments 4- to 8-membered rings or 5- to 7-membered rings, more specifically 5- to 6-membered rings, whose

ring structures include at least one heteroatom, in some embodiments one to four heteroatoms, and in more specific embodiments one or two heteroatoms. The terms "heteroaryl" and "hetaryl" also include polycyclic ring systems having two or more cyclic rings in which two or more carbons are common to two adjoining rings wherein at least one of the rings is heteroaromatic, *e.g.*, the other cyclic rings can be cycloalkyls, cycloalkenyls, cycloalkynyls, aryls, heteroaryls, and/or heterocyclyls. Heteroaryl groups include, for example, pyrrole, furan, thiophene, imidazole, oxazole, thiazole, pyrazole, pyridine, pyrazine, pyridazine, and pyrimidine, and the like.

[0075] The term "heteroatom" as used herein means an atom of any element other than carbon or hydrogen. Typical heteroatoms are nitrogen, oxygen, and sulfur.

[0076] The terms "heterocyclyl", "heterocycle", and "heterocyclic" refer to substituted or unsubstituted non-aromatic ring structures, in certain specific embodiments 3- to 10-membered rings, more specifically 3- to 7-membered rings, whose ring structures include at least one heteroatom, in some embodiments one to four heteroatoms, and in more specific embodiments one or two heteroatoms. The terms "heterocyclyl" and "heterocyclic" also include polycyclic ring systems having two or more cyclic rings in which two or more carbons are common to two adjoining rings wherein at least one of the rings is heterocyclic, *e.g.*, the other cyclic rings can be cycloalkyls, cycloalkenyls, cycloalkynyls, aryls, heteroaryls, and/or heterocyclyls. Heterocyclyl groups include, for example, piperidine, piperazine, pyrrolidine, morpholine, lactones, lactams, and the like.

[0077] The term "heterocyclylalkyl", as used herein, refers to an alkyl group substituted with a heterocycle group.

[0078] The term "hydroxyalkyl", as used herein, refers to an alkyl group substituted with a hydroxy group.

[0079] The term "lower" when used in conjunction with a chemical moiety, such as, acyl, acyloxy, alkyl, alkenyl, alkynyl, or alkoxy is meant to include groups where there are ten or fewer non-hydrogen atoms in the substituent, and in certain embodiments, six or fewer. A "lower alkyl", for example, refers to an alkyl group that contains ten or fewer carbon atoms, and in specific embodiments six or fewer

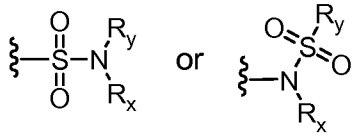
carbon atoms. In certain embodiments, the acyl, acyloxy, alkyl, alkenyl, alkynyl, and alkoxy substituents defined herein are respectively lower acyl, lower acyloxy, lower alkyl, lower alkenyl, lower alkynyl, and lower alkoxy, whether they appear alone or in combination with other substituents, such as in the recitations hydroxyalkyl and aralkyl (in which case, for example, the atoms within the aryl group are not counted when counting the carbon atoms in the alkyl substituent).

[0080] The term "substituted" refers to moieties having substituents replacing a hydrogen on one or more carbons of the backbone. It will be understood that "substitution" or "substituted with" includes the implicit proviso that such substitution is in accordance with permitted valence of the substituted atom and the substituent, and that the substitution results in a stable compound, *e.g.*, a compound that does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, etc., under conditions in which the compound is to be used. As used herein, the term "substituted" is contemplated to include all permissible substituents of organic compounds. In a broad aspect, the permissible substituents include acyclic and cyclic, branched and unbranched, carbocyclic and heterocyclic, aromatic and non-aromatic substituents of organic compounds. The permissible substituents can be one or more and the same or different for appropriate organic compounds. For purposes of this invention, the heteroatoms such as nitrogen may have hydrogen substituents and/or any permissible substituents of organic compounds described herein which satisfy the valences of the heteroatoms. Substituents may include any substituents described herein, for example, a halogen, a hydroxyl, a carbonyl (such as a keto, a carboxy, an alkoxycarbonyl, a formyl, or an acyl), a thiocarbonyl (such as a thioester, a thioacetate, or a thioformate), an alkoxyl, a phosphoryl, a phosphate, a phosphonate, a phosphinate, an amino, an amido, an amidine, an imine, a cyano, a nitro, an azido, a sulfhydryl, an alkylthio, a sulfate, a sulfonate, a sulfamoyl, a sulfonamido, a sulfonyl, a heterocyclyl, an aralkyl, or an aromatic or heteroaromatic moiety. It will be understood by those skilled in the art that the moieties substituted on the hydrocarbon chain may themselves be substituted, if appropriate.

[0081] Unless specifically described as "unsubstituted", references to chemical moieties herein are understood to include substituted variants. For example, reference to an "aryl" group or moiety implicitly includes both substituted and unsubstituted variants.

[0082] The term "sulfate" is art-recognized and refers to the group $-OSO_3H$, or a pharmaceutically acceptable salt thereof.

[0083] The term "sulfonamide" is art-recognized and refers to the group represented by the general formulae



wherein R_x and R_y independently represent hydrogen or hydrocarbyl.

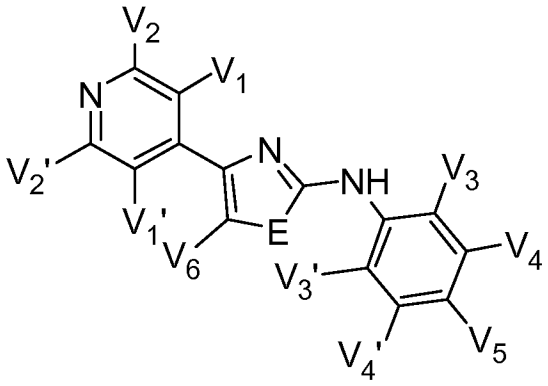
[0084] The term "sulfoxide" is art-recognized and refers to the group $-S(O)-R_x$, wherein R_x represents a hydrocarbyl.

[0085] The term "sulfonate" is art-recognized and refers to the group SO_3H, or a pharmaceutically acceptable salt thereof.

[0086] The term "sulfone" is art-recognized and refers to the group $-S(O)_2-R_x$, wherein R_x represents a hydrocarbyl.

Compounds

[0087] In one aspect, the present invention provides novel compounds that target cells deficient in the von Hippel-Lindau gene. In certain embodiments, the compounds are represented by Formula II:



Formula II

or a pharmaceutically acceptable salt, derivative, or prodrug thereof, wherein:

E is S, O, or N-V_7;

V_3, V_3', V_4', and V_5 are all hydrogen;

V_1, V_1', V_2, V_2', V_4, V_6, and V_7 are independently hydrogen, halo, R, OH, OR, OC(O)H, OC(O)R, $OC(O)NH_2$, OC(O)NHR, OC(O)NRR, $OP(O)(OH)_2$, $OP(O)(OR)_2$, NO_2, NH_2, NHR, NRR, $N^+(-O^-)RR$, NHC(O)H, NHC(O)R, NRC(O)R, $NHC(O)NH_2$, NHC(O)NRR, NRC(O)NHR, $N^2C(O)NHR$, SH, SR, S(O)H, S(O)R, SO_2R, SO_2NH_2, SO_2NHR, SO_2NRR, CF_3, CN, CO_2H, CO_2R, CHO, C(O)R, $C(O)NH_2$, C(O)NHR, C(O)NRR, $CONHSO_2H$, $C(O)NHSO_2R$, $C(O)NRSO_2R$, cyclic C_3-C_7 alkylamino, imidazolyl, piperazinyl, morpholinyl, piperidinyl, azepanyl, pyrrolidinyl or azetidinyl;

wherein each imidazolyl, piperazinyl, morpholinyl, piperidinyl, azepanyl, pyrrolidinyl and azetidinyl is optionally and independently substituted by one or more R^1, halo, OH, OR^1, $OC(O)R^1$, $OC(O)NH_2$, $OC(O)NHR^1$, $OC(O)NR^1R^1$, $OP(O)(OH)_2$, $OP(O)(OR^1)_2$, NO_2, NH_2, NHR^1, NR^1R^1, $N^+(-O^-)R^1R^1$, NHC(O)H, $NHC(O)R^1$, $NR^1C(O)R^1$, $NHC(O)NH_2$, $NHC(O)NR^1R^1$, $NR^1C(O)NHR^1$, SH, SR^1, S(O)H, $S(O)R^1$, SO_2R^1, SO_2NH_2, SO_2NHR^1, $SO_2NR^1R^1$, CF_3, CN, CO_2H, CO_2R^1, CHO, $C(O)R^1$, $C(O)NH_2$, $C(O)NHR^1$, $C(O)NR^1R^1$, $CONHSO_2H$, $C(O)NHSO_2R^1$ or $C(O)NR^1SO_2R^1$;

and wherein V_1 and V_2, taken together with the atoms to which they are attached, optionally form a cyclic structure having from 4 to 8 atoms in the ring;

each R is independently C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cyclic alkyl, aryl, aralkyl, heteroaryl, or heteroaralkyl, and is optionally and independently substituted with halo, OH, R^1, OR^1, $OC(O)R^1$, $OC(O)NH_2$, $OC(O)NHR^1$, $OC(O)NR^1R^1$, $OP(O)(OH)_2$, $OP(O)(OR^1)_2$, NO_2, NH_2, NHR^1, NR^1R^1, $N^+(-O^-)R^1R^1$, NHC(O)H, $NHC(O)R^1$, $NR^1C(O)R^1$, $NHC(O)NH_2$, $NHC(O)NR^1R^1$, $NR^1C(O)NHR^1$, SH, SR^1, S(O)H, $S(O)R^1$, SO_2R^1, SO_2NH_2, SO_2NHR^1, $SO_2NR^1R^1$, CF_3, CN, CO_2H, CO_2R^1, CHO, $C(O)R^1$, $C(O)NH_2$, $C(O)NHR^1$, $C(O)NR^1R^1$, $C(O)NHSO_2R^1$, $C(O)NR^1SO_2R^1$, cyclic C_3-C_7 alkylamino, imidazolyl, piperazinyl, morpholinyl, piperidinyl, azepanyl, pyrrolidinyl, or azetidinyl;

wherein each imidazolyl, piperazinyl, morpholinyl, piperidinyl, azepanyl, pyrrolidinyl and azetidinyl is optionally and independently substituted with one or

more R^1, halo, OH, OR^1, $OC(O)R^1$, $OC(O)NH_2$, $OC(O)NHR^1$, $OC(O)NR^1R^1$, $OP(O)(OH)_2$, $OP(O)(OR^1)_2$, NO_2, NH_2, NHR^1, NR^1R^1, $N^+(-O^-)R^1R^1$, $NHC(O)H$, $NHC(O)R^1$, $NR^1C(O)R^1$, $NHC(O)NH_2$, $NHC(O)NR^1R^1$, $NR^1C(O)NHR^1$, SH, SR^1, $S(O)H$, $S(O)R^1$, SO_2R^1, SO_2NH_2, SO_2NHR^1, $SO_2NR^1R^1$, CF_3, CN, CO_2H, CO_2R^1, CHO, $C(O)R^1$, $C(O)NH_2$, $C(O)NHR^1$, $C(O)NR^1R^1$, $CONHSO_2H$, $C(O)NHSO_2R^1$ or $C(O)NR^1SO_2R^1$;

and wherein each heteroaryl group contains one or more heteroatoms in its ring system, independently selected from O, N or S;

each R^1 is independently C_{1-6} alkyl or C_{2-6} alkenyl, optionally and independently substituted with halo, OH, OR^2, $OC(O)R^2$, $OC(O)NH_2$, $OC(O)NHR^2$, $OC(O)NR^2R^2$, $OP(O)(OH)_2$, $OP(O)(OR^2)_2$, NO_2, NH_2, NHR^2, NR^2R^2, $N^+(-O^-)R^2R^2$, $NHC(O)R^2$, $NR^2C(O)R^2$, $NHC(O)NH_2$, $NHC(O)NR^2R^2$, $NR^2C(O)NHR^2$, SH, SR^2, $S(O)H$, $S(O)R^2$, SO_2R^2, SO_2NH_2, SO_2NHR^2, $SO_2NR^2R^2$, CF_3, CN, CO_2H, CO_2R^2, CHO, $C(O)R^2$, $C(O)NH_2$, $C(O)NHR^2$, $C(O)NR^2R^2$, $C(O)NHSO_2R^2$, $C(O)NR^2SO_2R^2$, cyclic C_3-C_7 alkylamino, imidazolyl, piperazinyl, morpholinyl, piperidinyl, azepanyl, pyrrolidinyl or azetidinyl;

wherein each imidazolyl, piperazinyl, morpholinyl, piperidinyl, azepanyl, pyrrolidinyl and azetidinyl is optionally and independently substituted with one or more R^2, halo, OH, OR^2, $OC(O)R^2$, $OC(O)NH_2$, $OC(O)NHR^2$, $OC(O)NR^2R^2$, $OP(O)(OH)_2$, $OP(O)(OR^2)_2$, NO_2, NH_2, NHR^2, NR^2R^2, $N^+(-O^-)R^2R^2$, $NHC(O)H$, $NHC(O)R^2$, $NR^2C(O)R^2$, $NHC(O)NH_2$, $NHC(O)NR^2R^2$, $NR^2C(O)NHR^2$, SH, SR^2, $S(O)H$, $S(O)R^2$, SO_2R^2, SO_2NH_2, SO_2NHR^2, $SO_2NR^2R^2$, CF_3, CN, CO_2H, CO_2R^2, CHO, $C(O)R^2$, $C(O)NH_2$, $C(O)NHR^2$, $C(O)NR^2R^2$, $CONHSO_2H$, $C(O)NHSO_2R^2$ or $C(O)NR^2SO_2R^2$;

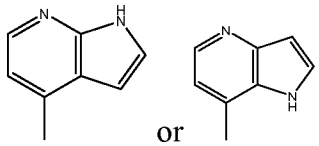
each R^2 is independently C_{1-6} alkyl, C_{2-6} alkenyl, OH, OMe, NO_2, NH_2, CF_3, CN, CO_2H or SH;

provided that V_1, V_1', V_2, V_2', V_4, V_6, and V_7 are not all hydrogen; and

when E is S; V_1, V_1', V_2', and V_6 are all hydrogen; and V_2 is Cl; then V_4 is not Cl; and

when E is S; and V_1, V_1', V_2, V_2', and V_6 are all hydrogen; then V_4 is not COOH, $COOCH_3$, $C(O)CH_3$, CF_3, CH_3, OH, OCH_3, SCH_3, CN, O-phenyl, Cl, Br, or NO_2; and

when E is S; V_1', V_2', V_4, and V_6 are all hydrogen; then V_1 and V_2, taken together with the ring to which they are attached, do not form



[0088] In some embodiments, R is independently C_{1-6} alkyl, C_{2-4} alkenyl, C_{3-7} cyclic alkyl, C_{4-8} aryl, or C_{4-8} heteroaryl, and is optionally and independently substituted with halo, OH, R^1, OR^1, $OC(O)R^1$, $OC(O)NH_2$, $OC(O)NHR^1$, $OC(O)NR^1R^1$, $OP(O)(OH)_2$, $OP(O)(OR^1)_2$, NO_2, NH_2, NHR^1, NR^1R^1, $N^+(-O^-)R^1R^1$, NHC(O)H, $NHC(O)R^1$, $NR^1C(O)R^1$, $NHC(O)NH_2$, $NHC(O)NR^1R^1$, $NR^1C(O)NHR^1$, SH, SR^1, S(O)H, $S(O)R^1$, SO_2R^1, SO_2NH_2, SO_2NHR^1, $SO_2NR^1R^1$, CF_3, CN, CO_2H, CO_2R^1, CHO, $C(O)R^1$, $C(O)NH_2$, $C(O)NHR^1$, $C(O)NR^1R^1$, $C(O)NHSO_2R^1$, $C(O)NR^1SO_2R^1$, cyclic C_3-C_7 alkylamino, imidazolyl, piperazinyl, morpholinyl, piperidinyl, azepanyl, pyrrolidinyl, or azetidinyl.

[0089] In some embodiments, V_4 is hydrogen; halo; R; OH; OR; CF_3; NO_2; NH_2; NHR; NRR; $OP(O)(OH)_2$; or $OP(O)(OR)_2$.

[0090] In more specific embodiments, V_4 is hydrogen; halo; C_{1-6} alkyl, optionally substituted with OH, NH_2, or $N(CH_3)_2$; OH; O-C_{1-6} alkyl, optionally substituted with OH, NH_2, or $N(CH_3)_2$; CF_3; NO_2; NH_2; or $OP(O)(OH)_2$.

[0091] In some embodiments, V_6 is hydrogen; R; CHO; CO_2R; $C(O)NH_2$; C(O)NHR; or C(O)NRR.

[0092] In more specific embodiments, V_6 is hydrogen; C_{1-6} alkyl or C_{2-4} alkenyl, optionally substituted with OH, OR^1, CO_2R^1, NH_2, NHR^1, or NR^1R^1; CHO; or CO_2R.

[0093] In even more specific embodiments, V_6 is hydrogen.

[0094] In some embodiments, V_1 and V_2 are independently hydrogen, halo, R, OH, OR, CF_3, NO_2, NH_2, NHR, NRR, or, taken together with the atoms to which they are attached, form a 5- or 6-membered ring structure.

[0095] In other embodiments, V_1, V_1', V_2, V_2' are all hydrogen.

[0096] In some embodiments, E is S or O.

[0097] In specific embodiments, E is S.

[0098] In certain embodiments, compounds of the invention are represented by Formula II, or a pharmaceutically acceptable salt, derivative, or prodrug thereof, wherein:

E is S, O, or N-V_7;

V_5 and V_6 are both hydrogen;

V_1, V_1', V_2, V_2', V_3, V_3', V_4, V_4', and V_7 are independently hydrogen, halo, R, OH, OR, OC(O)H, OC(O)R, $OC(O)NH_2$, OC(O)NHR, OC(O)NRR, $OP(O)(OH)_2$, $OP(O)(OR)_2$, NO_2, NH_2, NHR, NRR, $N^+(-O^-)RR$, NHC(O)H, NHC(O)R, NRC(O)R, $NHC(O)NH_2$, NHC(O)NRR, NRC(O)NHR, $N^2C(O)NHR$, SH, SR, S(O)H, S(O)R, SO_2R, SO_2NH_2, SO_2NHR, SO_2NRR, CF_3, CN, CO_2H, CO_2R, CHO, C(O)R, $C(O)NH_2$, C(O)NHR, C(O)NRR, $CONHSO_2H$, $C(O)NHSO_2R$, $C(O)NRSO_2R$, cyclic C_3-C_7 alkylamino, imidazolyl, piperazinyl, morpholinyl, piperidinyl, azepanyl, pyrrolidinyl or azetidinyl;

wherein each imidazolyl, piperazinyl, morpholinyl, piperidinyl, azepanyl, pyrrolidinyl and azetidinyl is optionally and independently substituted by one or more R^1, halo, OH, OR^1, $OC(O)R^1$, $OC(O)NH_2$, $OC(O)NHR^1$, $OC(O)NR^1R^1$, $OP(O)(OH)_2$, $OP(O)(OR^1)_2$, NO_2, NH_2, NHR^1, NR^1R^1, $N^+(-O^-)R^1R^1$, NHC(O)H, $NHC(O)R^1$, $NR^1C(O)R^1$, $NHC(O)NH_2$, $NHC(O)NR^1R^1$, $NR^1C(O)NHR^1$, SH, SR^1, S(O)H, $S(O)R^1$, SO_2R^1, SO_2NH_2, SO_2NHR^1, $SO_2NR^1R^1$, CF_3, CN, CO_2H, CO_2R^1, CHO, $C(O)R^1$, $C(O)NH_2$, $C(O)NHR^1$, $C(O)NR^1R^1$, $CONHSO_2H$, $C(O)NHSO_2R^1$ or $C(O)NR^1SO_2R^1$;

and wherein groups V_1 and V_2 and groups V_3 and V_4, taken together with the atoms to which they are attached, optionally and independently form a cyclic structure having from 4 to 8 atoms in the ring;

each R is independently C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cyclic alkyl, aryl, aralkyl, heteroaryl, or heteroaralkyl, and is optionally and independently substituted with halo, OH, R^1, OR^1, $OC(O)R^1$, $OC(O)NH_2$, $OC(O)NHR^1$, $OC(O)NR^1R^1$, $OP(O)(OH)_2$, $OP(O)(OR^1)_2$, NO_2, NH_2, NHR^1, NR^1R^1, $N^+(-O^-)R^1R^1$, NHC(O)H, $NHC(O)R^1$, $NR^1C(O)R^1$, $NHC(O)NH_2$, $NHC(O)NR^1R^1$, $NR^1C(O)NHR^1$, SH, SR^1, S(O)H, $S(O)R^1$, SO_2R^1, SO_2NH_2, SO_2NHR^1, $SO_2NR^1R^1$, CF_3, CN, CO_2H, CO_2R^1, CHO, $C(O)R^1$, $C(O)NH_2$, $C(O)NHR^1$, $C(O)NR^1R^1$, $C(O)NHSO_2R^1$, $C(O)NR^1SO_2R^1$, cyclic C_3-C_7

alkylamino, imidazolyl, piperazinyl, morpholinyl, piperidinyl, azepanyl, pyrrolidinyl, or azetidinyl;

wherein each imidazolyl, piperazinyl, morpholinyl, piperidinyl, azepanyl, pyrrolidinyl and azetidinyl is optionally and independently substituted with one or more R^1, halo, OH, OR^1, $OC(O)R^1$, $OC(O)NH_2$, $OC(O)NHR^1$, $OC(O)NR^1R^1$, $OP(O)(OH)_2$, $OP(O)(OR^1)_2$, NO_2, NH_2, NHR^1, NR^1R^1, $N^+(-O^-)R^1R^1$, $NHC(O)H$, $NHC(O)R^1$, $NR^1C(O)R^1$, $NHC(O)NH_2$, $NHC(O)NR^1R^1$, $NR^1C(O)NHR^1$, SH, SR^1, $S(O)H$, $S(O)R^1$, SO_2R^1, SO_2NH_2, SO_2NHR^1, $SO_2NR^1R^1$, CF_3, CN, CO_2H, CO_2R^1, CHO, $C(O)R^1$, $C(O)NH_2$, $C(O)NHR^1$, $C(O)NR^1R^1$, $CONHSO_2H$, $C(O)NHSO_2R^1$ or $C(O)NR^1SO_2R^1$;

and wherein each heteroaryl group contains one or more heteroatoms in its ring system, independently selected from O, N or S;

each R^1 is independently $C_{1\text{-}6}$ alkyl or $C_{2\text{-}6}$ alkenyl, optionally and independently substituted with halo, OH, OR^2, $OC(O)R^2$, $OC(O)NH_2$, $OC(O)NHR^2$, $OC(O)NR^2R^2$, $OP(O)(OH)_2$, $OP(O)(OR^2)_2$, NO_2, NH_2, NHR^2, NR^2R^2, $N^+(-O^-)R^2R^2$, $NHC(O)R^2$, $NR^2C(O)R^2$, $NHC(O)NH_2$, $NHC(O)NR^2R^2$, $NR^2C(O)NHR^2$, SH, SR^2, $S(O)H$, $S(O)R^2$, SO_2R^2, SO_2NH_2, SO_2NHR^2, $SO_2NR^2R^2$, CF_3, CN, CO_2H, CO_2R^2, CHO, $C(O)R^2$, $C(O)NH_2$, $C(O)NHR^2$, $C(O)NR^2R^2$, $C(O)NHSO_2R^2$, $C(O)NR^2SO_2R^2$, cyclic C_3-C_7 alkylamino, imidazolyl, piperazinyl, morpholinyl, piperidinyl, azepanyl, pyrrolidinyl or azetidinyl;

wherein each imidazolyl, piperazinyl, morpholinyl, piperidinyl, azepanyl, pyrrolidinyl and azetidinyl is optionally and independently substituted with one or more R^2, halo, OH, OR^2, $OC(O)R^2$, $OC(O)NH_2$, $OC(O)NHR^2$, $OC(O)NR^2R^2$, $OP(O)(OH)_2$, $OP(O)(OR^2)_2$, NO_2, NH_2, NHR^2, NR^2R^2, $N^+(-O^-)R^2R^2$, $NHC(O)H$, $NHC(O)R^2$, $NR^2C(O)R^2$, $NHC(O)NH_2$, $NHC(O)NR^2R^2$, $NR^2C(O)NHR^2$, SH, SR^2, $S(O)H$, $S(O)R^2$, SO_2R^2, SO_2NH_2, SO_2NHR^2, $SO_2NR^2R^2$, CF_3, CN, CO_2H, CO_2R^2, CHO, $C(O)R^2$, $C(O)NH_2$, $C(O)NHR^2$, $C(O)NR^2R^2$, $CONHSO_2H$, $C(O)NHSO_2R^2$ or $C(O)NR^2SO_2R^2$;

each R^2 is independently $C_{1\text{-}6}$ alkyl, $C_{2\text{-}6}$ alkenyl, OH, OMe, NO_2, NH_2, CF_3, CN, CO_2H or SH;

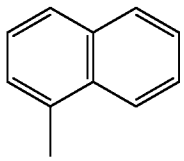
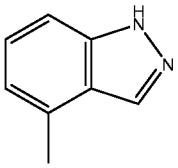
provided that V_1, V_1', V_2, V_2', V_3, V_3', V_4, V_4', and V_7 are not all hydrogen; and

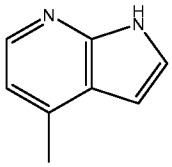
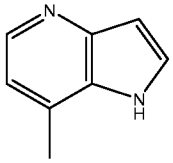
when E is S; V_1, V_1', and V_2' are all hydrogen; and V_2 is Cl; then V_3 is not CH_3 and V_4 is not Cl; and

when E is S and V_3' and V_4 are both hydrogen, then either V_3 or V_4' is also hydrogen; and

when E is S and V_1, V_1', V_2, V_2', V_3, V_3', and V_4' are all hydrogen, then V_4 is not COOH, $COOCH_3$, $C(O)CH_3$, CF_3, CH_3, OH, OCH_3, SCH_3, CN, O-phenyl, Cl, Br, or NO_2; and

when E is S and V_1, V_1', V_2, V_2', V_3', V_4, and V_4' are all hydrogen, then V_3 is not CH_3, CH_2CH_3, F, Cl, NO_2, CF_3, OCH_3, OCH_2CH_3, or a substituted 1,4-dihydropyridyl ring; and

when E is S and V_1, V_1', V_2, V_2', V_3', and V_4' are all hydrogen; then when V_3 is Cl, V_4 is not Cl; and when V_3 is CH_3, V_4 is not Cl; and V_3 and V_4, taken together with the ring to which they are attached, do not form  or  ; and

when E is S and V_1', V_2', V_3, V_3', V_4, and V_4' are all hydrogen, then V_1 and V_2, taken together with the ring to which they are attached, do not form  or  ; and

when V_3 and V_3' are both hydrogen, then V_4 and V_4' are not both CH_3.

[0099] In some embodiments, V_1 and V_2, taken together with the atoms to which they are attached, optionally and independently form a cyclic structure having from 4 to 8 atoms in the ring;

[0100] In some embodiments, R is independently C_{1-6} alkyl, C_{2-4} alkenyl, C_{3-7} cyclic alkyl, C_{4-8} aryl, or C_{4-8} heteroaryl, and is optionally and independently substituted with halo, OH, R^1, OR^1, $OC(O)R^1$, $OC(O)NH_2$, $OC(O)NHR^1$, $OC(O)NR^1R^1$, $OP(O)(OH)_2$, $OP(O)(OR^1)_2$, NO_2, NH_2, NHR^1, NR^1R^1, $N^+(-O^-)R^1R^1$,

$NHC(O)H$, $NHC(O)R^1$, $NR^1C(O)R^1$, $NHC(O)NH_2$, $NHC(O)NR^1R^1$, $NR^1C(O)NHR^1$, SH, SR^1, $S(O)H$, $S(O)R^1$, SO_2R^1, SO_2NH_2, SO_2NHR^1, $SO_2NR^1R^1$, CF_3, CN, CO_2H, CO_2R^1, CHO, $C(O)R^1$, $C(O)NH_2$, $C(O)NHR^1$, $C(O)NR^1R^1$, $C(O)NHSO_2R^1$, $C(O)NR^1SO_2R^1$, cyclic C_3-C_7 alkylamino, imidazolyl, piperazinyl, morpholinyl, piperidinyl, azepanyl, pyrrolidinyl, or azetidinyl.

[0101] In some embodiments, V_3 and V_4 are independently hydrogen; halo; R; OH; OR; CF_3; NO_2; NH_2; NHR; NRR; $OP(O)(OH)_2$; $OP(O)(OR)_2$; or, taken together with the atoms to which they are attached, form a 5- or 6-membered ring.

[0102] In specific embodiments, V_3 and V_4 are independently hydrogen; halo; C_{1-6} alkyl, optionally substituted with OH, NH_2, or $N(CH_3)_2$; OH; O-C_{1-6} alkyl, optionally substituted with OH, NH_2, or $N(CH_3)_2$; CF_3; NO_2; NH_2; or $OP(O)(OH)_2$.

[0103] In some embodiments, V_4 is hydrogen; halo; R; OH; OR; CF_3; NO_2; NH_2; NHR; NRR; $OP(O)(OH)_2$; or $OP(O)(OR)_2$.

[0104] In specific embodiments, V_4 is hydrogen; halo; C_{1-6} alkyl, optionally substituted with OH, NH_2, or $N(CH_3)_2$; OH; O-C_{1-6} alkyl, optionally substituted with OH, NH_2, or $N(CH_3)_2$; CF_3; NO_2; NH_2; or $OP(O)(OH)_2$.

[0105] In some embodiments, V_1 and V_2 are independently hydrogen, halo, R, OH, OR, CF_3, NO_2, NH_2, NHR, NRR, or, taken together with the atoms to which they are attached, form a 5- or 6-membered ring structure.

[0106] In some embodiments, V_1, V_1', V_2, V_2' are all hydrogen.

[0107] In some embodiments, E is S or O.

[0108] In specific embodiments, E is S.

[0109] In other embodiments, compounds of the invention are represented by Formula II, or a pharmaceutically acceptable salt, derivative, or prodrug thereof, wherein:

E is S, O, or N-V_7;

V_3' and V_4' are both hydrogen;

V_1, V_1', V_2, V_2', V_3, V_4, V_5, V_6, and V_7 are independently hydrogen, halo, R, OH, OR, OC(O)H, OC(O)R, $OC(O)NH_2$, OC(O)NHR, OC(O)NRR, $OP(O)(OH)_2$, $OP(O)(OR)_2$, NO_2, NH_2, NHR, NRR, $N^+(-O^-)RR$, NHC(O)H, NHC(O)R, NRC(O)R, $NHC(O)NH_2$, NHC(O)NRR, NRC(O)NHR, $N^2C(O)NHR$, SH, SR, S(O)H, S(O)R, SO_2R, SO_2NH_2, SO_2NHR, SO_2NRR, CF_3, CN, CO_2H,

CO_2R, CHO, C(O)R, $C(O)NH_2$, C(O)NHR, C(O)NRR, $CONHSO_2H$, $C(O)NHSO_2R$, $C(O)NRSO_2R$, cyclic C_3-C_7 alkylamino, imidazolyl, piperazinyl, morpholinyl, piperidinyl, azepanyl, pyrrolidinyl or azetidinyl;

wherein each imidazolyl, piperazinyl, morpholinyl, piperidinyl, azepanyl, pyrrolidinyl and azetidinyl is optionally and independently substituted by one or more R^1, halo, OH, OR^1, $OC(O)R^1$, $OC(O)NH_2$, $OC(O)NHR^1$, $OC(O)NR^1R^1$, $OP(O)(OH)_2$, $OP(O)(OR^1)_2$, NO_2, NH_2, NHR^1, NR^1R^1, $N^+(-O^-)R^1R^1$, NHC(O)H, $NHC(O)R^1$, $NR^1C(O)R^1$, $NHC(O)NH_2$, $NHC(O)NR^1R^1$, $NR^1C(O)NHR^1$, SH, SR^1, S(O)H, $S(O)R^1$, SO_2R^1, SO_2NH_2, SO_2NHR^1, $SO_2NR^1R^1$, CF_3, CN, CO_2H, CO_2R^1, CHO, $C(O)R^1$, $C(O)NH_2$, $C(O)NHR^1$, $C(O)NR^1R^1$, $CONHSO_2H$, $C(O)NHSO_2R^1$ or $C(O)NR^1SO_2R^1$;

and wherein groups V_1 and V_2, groups V_3 and V_4, and groups V_4 and V_5, taken together with the atoms to which they are attached, optionally and independently form a cyclic structure having from 4 to 8 atoms in the ring;

each R is independently C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cyclic alkyl, aryl, aralkyl, heteroaryl, or heteroaralkyl , and is optionally and independently substituted with halo, OH, R^1, OR^1, $OC(O)R^1$, $OC(O)NH_2$, $OC(O)NHR^1$, $OC(O)NR^1R^1$, $OP(O)(OH)_2$, $OP(O)(OR^1)_2$, NO_2, NH_2, NHR^1, NR^1R^1, $N^+(-O^-)R^1R^1$, NHC(O)H, $NHC(O)R^1$, $NR^1C(O)R^1$, $NHC(O)NH_2$, $NHC(O)NR^1R^1$, $NR^1C(O)NHR^1$, SH, SR^1, S(O)H, $S(O)R^1$, SO_2R^1, SO_2NH_2, SO_2NHR^1, $SO_2NR^1R^1$, CF_3, CN, CO_2H, CO_2R^1, CHO, $C(O)R^1$, $C(O)NH_2$, $C(O)NHR^1$, $C(O)NR^1R^1$, $C(O)NHSO_2R^1$, $C(O)NR^1SO_2R^1$, cyclic C_3-C_7 alkylamino, imidazolyl, piperazinyl, morpholinyl, piperidinyl, azepanyl, pyrrolidinyl, or azetidinyl;

wherein each imidazolyl, piperazinyl, morpholinyl, piperidinyl, azepanyl, pyrrolidinyl and azetidinyl is optionally and independently substituted with one or more R^1, halo, OH, OR^1, $OC(O)R^1$, $OC(O)NH_2$, $OC(O)NHR^1$, $OC(O)NR^1R^1$, $OP(O)(OH)_2$, $OP(O)(OR^1)_2$, NO_2, NH_2, NHR^1, NR^1R^1, $N^+(-O^-)R^1R^1$, NHC(O)H, $NHC(O)R^1$, $NR^1C(O)R^1$, $NHC(O)NH_2$, $NHC(O)NR^1R^1$, $NR^1C(O)NHR^1$, SH, SR^1, S(O)H, $S(O)R^1$, SO_2R^1, SO_2NH_2, SO_2NHR^1, $SO_2NR^1R^1$, CF_3, CN, CO_2H, CO_2R^1, CHO, $C(O)R^1$, $C(O)NH_2$, $C(O)NHR^1$, $C(O)NR^1R^1$, $CONHSO_2H$, $C(O)NHSO_2R^1$ or $C(O)NR^1SO_2R^1$;

and wherein each heteroaryl group contains one or more heteroatoms in its ring system, independently selected from O, N or S;

each R^1 is independently C_{1-6} alkyl or C_{2-6} alkenyl, optionally and independently substituted with halo, OH, OR^2, $OC(O)R^2$, $OC(O)NH_2$, $OC(O)NHR^2$, $OC(O)NR^2R^2$, $OP(O)(OH)_2$, $OP(O)(OR^2)_2$, NO_2, NH_2, NHR^2, NR^2R^2, $N^+(-O^-)R^2R^2$, $NHC(O)R^2$, $NR^2C(O)R^2$, $NHC(O)NH_2$, $NHC(O)NR^2R^2$, $NR^2C(O)NHR^2$, SH, SR^2, S(O)H, $S(O)R^2$, SO_2R^2, SO_2NH_2, SO_2NHR^2, $SO_2NR^2R^2$, CF_3, CN, CO_2H, CO_2R^2, CHO, $C(O)R^2$, $C(O)NH_2$, $C(O)NHR^2$, $C(O)NR^2R^2$, $C(O)NHSO_2R^2$, $C(O)NR^2SO_2R^2$, cyclic C_3-C_7 alkylamino, imidazolyl, piperazinyl, morpholinyl, piperidinyl, azepanyl, pyrrolidinyl or azetidinyl;

wherein each imidazolyl, piperazinyl, morpholinyl, piperidinyl, azepanyl, pyrrolidinyl and azetidinyl is optionally and independently substituted with one or more R^2, halo, OH, OR^2, $OC(O)R^2$, $OC(O)NH_2$, $OC(O)NHR^2$, $OC(O)NR^2R^2$, $OP(O)(OH)_2$, $OP(O)(OR^2)_2$, NO_2, NH_2, NHR^2, NR^2R^2, $N^+(-O^-)R^2R^2$, NHC(O)H, $NHC(O)R^2$, $NR^2C(O)R^2$, $NHC(O)NH_2$, $NHC(O)NR^2R^2$, $NR^2C(O)NHR^2$, SH, SR^2, S(O)H, $S(O)R^2$, SO_2R^2, SO_2NH_2, SO_2NHR^2, $SO_2NR^2R^2$, CF_3, CN, CO_2H, CO_2R^2, CHO, $C(O)R^2$, $C(O)NH_2$, $C(O)NHR^2$, $C(O)NR^2R^2$, $CONHSO_2H$, $C(O)NHSO_2R^2$ or $C(O)NR^2SO_2R^2$;

each R^2 is independently C_{1-6} alkyl, C_{2-6} alkenyl, OH, OMe, NO_2, NH_2, CF_3, CN, CO_2H or SH;

provided that V_1, V_1', V_2, V_2', V_3, V_4, V_5, V_6, and V_7 are not all hydrogen; and

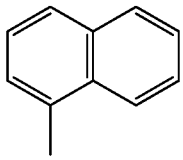
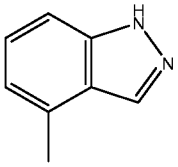
when E is S; V_1, V_1', and V_2' are all hydrogen; and V_2 is Cl; then V_3 is not CH_3 when V_4 is Cl; and V_5 is not CH_3, OCH_3, or Cl; and

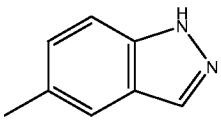
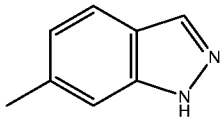
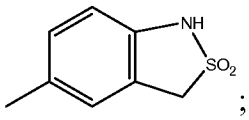
when E is S; V_1, V_1', and V_2' are all hydrogen; V_2 is H or NH_2; and V_4 is CF_3; then V_5 is not F; and

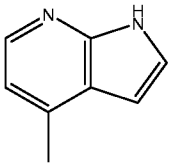
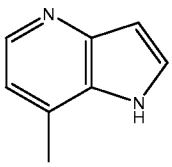
when E is S and V_1, V_1', V_2, V_2', V_3 and V_5 are all hydrogen, then V_4 is not COOH, $COOCH_3$, $C(O)CH_3$, CF_3, CH_3, OH, OCH_3, SCH_3, CN, O-phenyl, Cl, Br, or NO_2; and

when E is S and V_1, V_1', V_2, V_2', V_4 and V_5 are all hydrogen, then V_3 is not CH_3, CH_2CH_3, F, Cl, NO_2, CF_3, OCH_3, OCH_2CH_3, or a substituted 1,4-dihydropyridyl ring; and

when E is S and V_1, V_1', V_2, V_2', V_3 and V_4 are all hydrogen, then V_5 is not CH_3, CH_2CH_3, $C(O)CH_3$, CF_3, $S(O)_2$-NH_2, $S(O)_2$-NHR, $N(CH_3)_2$, $N(CH_2CH_3)_2$, N(*i*-Pr)phenyl, NO_2, OCH_2CH_3, NH-$C(O)CH_3$, NH_2, COOH, F, Cl, Br, I, OH, OCH_3, O-phenyl, O-C_{7-8}-alkyl, or $C(O)NHC(i\text{-}Bu)C(O)NHCH_2CN$; and

when E is S and V_1, V_1', V_2, V_2', and V_5 are all hydrogen; then when V_3 is Cl, V_4 is not Cl; when V_3 is CH_3, then V_4 is not Cl; and V_3 and V_4, taken together with the ring to which they are attached, do not form  or  ; and

when E is S and V_1, V_1', V_2, V_2', and V_3 are all hydrogen; then when V_5 is O-C_{5-8}-alkyl, V_4 is not hydrogen, F, or CF_3; when V_5 is CH_3, V_4 is not CH_3; and V_4 and V_5, taken together with the ring to which they are attached, do not form  ,  , or  ;

when E is S and V_1', V_2', V_3, V_4, and V_5 are all hydrogen, then V_1 and V_2, taken together with the ring to which they are attached, do not form  or  .

[0110] In some embodiments, R is independently C_{1-6} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-7} cyclic alkyl, C_{4-8} aryl, or C_{4-8} heteroaryl, and is optionally and independently substituted with halo, OH, R^1, OR^1, $OC(O)R^1$, $OC(O)NH_2$, $OC(O)NHR^1$, $OC(O)NR^1R^1$, $OP(O)(OH)_2$, $OP(O)(OR^1)_2$, NO_2, NH_2, NHR^1, NR^1R^1, $N^+(\text{-}O^-)R^1R^1$, NHC(O)H, $NHC(O)R^1$, $NR^1C(O)R^1$, $NHC(O)NH_2$, $NHC(O)NR^1R^1$, $NR^1C(O)NHR^1$, SH, SR^1, S(O)H, $S(O)R^1$, SO_2R^1, SO_2NH_2, SO_2NHR^1, $SO_2NR^1R^1$, CF_3, CN, CO_2H, CO_2R^1, CHO, $C(O)R^1$, $C(O)NH_2$, $C(O)NHR^1$, $C(O)NR^1R^1$, $C(O)NHSO_2R^1$, $C(O)NR^1SO_2R^1$, cyclic C_3-C_7

alkylamino, imidazolyl, piperazinyl, morpholinyl, piperidinyl, azepanyl, pyrrolidinyl, or azetidinyl.

[0111] In some embodiments, V_3, V_4, and V_5 are independently hydrogen; halo; R; OH; OR; CF_3; NO_2; NH_2; NHR; NRR; $OP(O)(OH)_2$; or $OP(O)(OR)_2$; and groups V_3 and V_4 and groups V_4 and V_5, taken together with the atoms to which they are attached, optionally and independently form a 5- or 6-membered ring structure.

[0112] In specific embodiments, V_3, V_4, and V_5 are independently hydrogen; halo; C_{1-6} alkyl, optionally substituted with OH, NH_2, or $N(CH_3)_2$; OH; O-C_{1-6} alkyl, optionally substituted with OH, NH_2, or $N(CH_3)_2$; CF_3; NO_2; NH_2; or $OP(O)(OH)_2$.

[0113] In some embodiments, V_4 is hydrogen; halo; R; OH; OR; CF_3; NO_2; NH_2; NHR; NRR; $OP(O)(OH)_2$; or $OP(O)(OR)_2$.

[0114] In specific embodiments, V_4 is hydrogen; halo; C_{1-6} alkyl, optionally substituted with OH, NH_2, or $N(CH_3)_2$; OH; O-C_{1-6} alkyl, optionally substituted with OH, NH_2, or $N(CH_3)_2$; CF_3; NO_2; NH_2; or $OP(O)(OH)_2$.

[0115] In some embodiments, V_1 and V_2 are independently hydrogen, halo, R, OH, OR, CF_3, NO_2, NH_2, NHR, NRR, or, taken together with the atoms to which they are attached, form a 5- or 6-membered ring structure.

[0116] In other embodiments, V_1, V_1', V_2, V_2' are all hydrogen.

[0117] In some embodiments, E is S or O.

[0118] In more specific embodiments, E is S.

[0119] In even more specific embodiments of the invention, the compound is selected from the following list of compounds:

N-Phenyl-4-(4-pyridinyl)-1,3-thiazol-2-amine,
N-(3-Methylphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine,
N-(3-Ethylphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine,
N-(3-Isopropylphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine,
N-(3-*tert*-Butylphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine,
3-{[4-(4-Pyridinyl)-1,3-thiazol-2-yl]amino}phenol,
N-(3-Methoxyphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine,
N-(3-Chlorophenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine,

4-(4-Pyridinyl)-*N*-[3-(trifluoromethyl)phenyl]-1,3-thiazol-2-amine,
N-(4-Methylphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine,
2-(4-{[4-(4-Pyridinyl)-1,3-thiazol-2-yl]amino}phenyl)ethanol,
4-{[4-(4-Pyridinyl)-1,3-thiazol-2-yl]amino}phenol,
N-(4-Methoxyphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine,
N-{4-[2-(Dimethylamino)ethoxy]phenyl}-4-(4-pyridinyl)-1,3-thiazol-2-amine,
N-(4-Chlorophenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine,
N-(4-Fluorophenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine,
N-(4-Nitrophenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine,
N-{4-[2-(Dimethylamino)ethyl]phenyl}-4-(4-pyridinyl)-1,3-thiazol-2-amine,
N^1-[4-(4-Pyridinyl)-1,3-thiazol-2-yl]-1,4-benzenediamine,
3-{[4-(4-Pyridinyl)-1,3-thiazol-2-yl]amino}phenyl Dihydrogen Phosphate,
4-{[4-(4-Pyridinyl)-1,3-thiazol-2-yl]amino}phenyl Dihydrogen Phosphate,
N-(3,4-Dimethylphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine,
N-(3,5-Dimethylphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine,
N-(2,3-Dihydro-1*H*-inden-5-yl)-4-(4-pyridinyl)-1,3-thiazol-2-amine,
2-Methyl-5-{[4-(4-pyridinyl)-1,3-thiazol-2-yl]amino}phenol,
2-Methoxy-5-{[4-(4-pyridinyl)-1,3-thiazol-2-yl]amino}phenol,
2-Methyl-4-{[4-(4-pyridinyl)-1,3-thiazol-2-yl]amino}phenol,
N-(3,4-Dimethoxyphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine,
N-(3,5-Dimethoxyphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine,
N-(1,3-Benzodioxol-5-yl)-4-(4-pyridinyl)-1,3-thiazol-2-amine,
N-(3,4-Dichlorophenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine,
4-(4-Pyridinyl)-*N*-(3,4,5-trimethoxyphenyl)-1,3-thiazol-2-amine,
N-(3-Methylphenyl)-4-(3-pyridinyl)-1,3-thiazol-2-amine,
4-{[4-(3-Pyridinyl)-1,3-thiazol-2-yl]amino}phenol,
N-(3-Methylphenyl)-4-(2-pyridinyl)-1,3-thiazol-2-amine,
4-{[4-(2-Pyridinyl)-1,3-thiazol-2-yl]amino}phenol,
5-Methyl-*N*-(3-methylphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine,
N-(2,3-Dihydro-1*H*-inden-5-yl)-5-methyl-4-(4-pyridinyl)-1,3-thiazol-2-amine,
[2-(Phenylamino)-4-(4-pyridinyl)-1,3-thiazol-5-yl]methanol,
[2-[(3-Methylphenyl)amino]-4-(4-pyridinyl)-1,3-thiazol-5-yl]methanol,

[2-[(4-Methylphenyl)amino]-4-(4-pyridinyl)-1,3-thiazol-5-yl]methanol,
[2-(2,3-Dihydro-1*H*-inden-5-ylamino)-4-(4-pyridinyl)-1,3-thiazol-5-yl]methanol,
2-[(3-Methylphenyl)amino]-4-(4-pyridinyl)-1,3-thiazole-5-carbaldehyde,
Methyl (2*E*)-3-[2-[(3-Methylphenyl)amino]-4-(4-pyridinyl)-1,3-thiazol-5-yl]-2-propenoate,
Methyl 3-[2-[(3-Methylphenyl)amino]-4-(4-pyridinyl)-1,3-thiazol-5-yl]propanoate,
3-[2-[(3-Methylphenyl)amino]-4-(4-pyridinyl)-1,3-thiazol-5-yl]-1-propanol,
N-(3-Methylphenyl)-5-[3-(4-morpholinyl)propyl]-4-(4-pyridinyl)-1,3-thiazol-2-amine,
5-[(Dimethylamino)methyl]-*N*-(3-methylphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine,
5-[(Diethylamino)methyl]-*N*-(3-methylphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine,
N-(3-Methylphenyl)-5-(1-piperidinylmethyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine,
N-(3-Methylphenyl)-5-(4-morpholinylmethyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine,
Ethyl 2-[(3-methylphenyl)amino]-4-(4-pyridinyl)-1,3-thiazole-5-carboxylate,
Ethyl 2-(2,3-dihydro-1*H*-inden-5-ylamino)-4-(4-pyridinyl)-1,3-thiazole-5-carboxylate,
2-[(3-Methylphenyl)amino]-4-(4-pyridinyl)-1,3-thiazole-5-carboxamide,
N,*N*-Dimethyl-2-[(3-methylphenyl)amino]-4-(4-pyridinyl)-1,3-thiazole-5-carboxamide,
N-[2-(Dimethylamino)ethyl]-2-[(3-methylphenyl)amino]-4-(4-pyridinyl)-1,3-thiazole-5-carboxamide,
2-[(3-Methylphenyl)amino]-*N*-[3-(4-morpholinyl)propyl]-4-(4-pyridinyl)-1,3-thiazole-5-carboxamide,
N-Methyl-*N*-(3-methylphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine,
N-Ethyl-*N*-(3-methylphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine,
2-{3-Methyl[4-(4-pyridinyl)-1,3-thiazol-2-yl]anilino}ethanol,
N-[4-(4-Pyridinyl)-1,3-thiazol-2-yl]benzamide,
3-Methyl-*N*-[4-(4-pyridinyl)-1,3-thiazol-2-yl]benzamide,
4-Methyl-*N*-[4-(4-pyridinyl)-1,3-thiazol-2-yl]benzamide,
4-Methoxy-*N*-[4-(4-pyridinyl)-1,3-thiazol-2-yl]benzamide,

N-(3-Methylbenzyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine,
N-(3-Methylphenyl)-4-(4-pyridinyl)-1,3-oxazol-2-amine,
2-{[4-(4-Pyridinyl)-1,3-thiazol-2-yl]amino}phenol,
N-(2-Methoxyphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine,
N-(2-Methylphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine,
N-(2-Fluorophenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine,
N-[2-Chlorophenyl]-4-(4-pyridinyl)-1,3-thiazol-2-amine,
4-(4-Pyridinyl)-*N*-[2-(trifluoromethyl)phenyl]-1,3-thiazol-2-amine,
N-[2-Nitrophenyl]-4-(4-pyridinyl)-1,3-thiazol-2-amine,
N-(3-Fluorophenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine,
N-(3-Bromophenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine,
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N-(3-Nitrophenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine,
1-(4-{[4-(4-Pyridinyl)-1,3-thiazol-2-yl]amino}phenyl)ethanone,
4-(4-Pyridinyl)-*N*-[4-(trifluoromethyl)phenyl]-1,3-thiazol-2-amine,
4-{[4-(4-Pyridinyl)-1,3-thiazol-2-yl]amino}benzonitrile,
N-(2,6-Dimethylphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine,
N-(2,6-Difluorophenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine,
N-{4-[2-(Methyloxy)-4-pyridinyl]-1,3-thiazol-2-yl}-*N*-(3-methylphenyl)amine,
N-(3-Methylphenyl)-4-(2-methyl-4-pyridinyl)-1,3-thiazol-2-amine,
4-(2-Fluoro-4-pyridinyl)-*N*-(3-methylphenyl)-1,3-thiazol-2-amine,
4-(2-Chloro-4-pyridinyl)-*N*-(3-methylphenyl)-1,3-thiazol-2-amine,
4-(2-Bromo-4-pyridinyl)-*N*-(3-methylphenyl)-1,3-thiazol-2-amine,
N-[4-(2,6-Dichloro-4-pyridinyl)-1,3-thiazol-2-yl]-*N*-(3-methylphenyl)amine,
4-(2-Ethynyl-4-pyridinyl)-*N*-(3-methylphenyl)-1,3-thiazol-2-amine,
4-(2-Ethyl-4-pyridinyl)-*N*-(3-methylphenyl)-1,3-thiazol-2-amine,
3-(4-{2-[(3-Methylphenyl)amino]-1,3-thiazol-4-yl}-2-pyridinyl)-2-propyn-1-ol,
3-(4-{2-[(3-Methylphenyl)amino]-1,3-thiazol-4-yl}-2-pyridinyl)-1-propanol,
N-(3-Methylphenyl)-4-(3-methyl-4-pyridinyl)-1,3-thiazol-2-amine,
4-(3-Fluoro-4-pyridinyl)-*N*-(3-methylphenyl)-1,3-thiazol-2-amine,
4-(3-Chloro-4-pyridinyl)-*N*-(3-methylphenyl)-1,3-thiazol-2-amine,

4-(3-Bromo-4-pyridinyl)-*N*-(3-methylphenyl)-1,3-thiazol-2-amine,
N-(3-Methylphenyl)-4-(2-nitro-4-pyridinyl)-1,3-thiazol-2-amine,
N-[4-(2-Amino-4-pyridinyl)-1,3-thiazol-2-yl]-*N*-(3-methylphenyl)amine,
N-(4-{2-[(3-Methylphenyl)amino]-1,3-thiazol-4-yl}-2-pyridinyl)acetamide,
4-(3-Ethynyl-4-pyridinyl)-*N*-(3-methylphenyl)-1,3-thiazol-2-amine,
4-(3-Ethyl-4-pyridinyl)-*N*-(3-methylphenyl)-1,3-thiazol-2-amine,
3-(4-{2-[(3-Methylphenyl)amino]-1,3-thiazol-4-yl}-3-pyridinyl)-2-propyn-1-ol,
3-(4-{2-[(3-Methylphenyl)amino]-1,3-thiazol-4-yl}-3-pyridinyl)-1-propanol,
N-(3-Methylphenyl)-4-(1-oxido-4-pyridinyl)-1,3-thiazol-2-amine,
N-(3-Methylphenyl)-4-(4-quinolinyl)-1,3-thiazol-2-amine,
N-(3-Methylphenyl)-4-(2-phenyl-4-quinolinyl)-1,3-thiazol-2-amine,
N-(3-Methylphenyl)-4-(4-pyridinyl)-1*H*-imidazol-2-amine,
N-(3-Methylphenyl)-4-[2-(4-morpholinyl)-4-pyridinyl]-1,3-thiazol-2-amine,
N-(3-Methylphenyl)-4-[2-(4-methyl-1-piperazinyl)-4-pyridinyl]-1,3-thiazol-2-amine, and
N,*N*-Dimethyl-4-{2-[(3-methylphenyl)amino]-1,3-thiazol-4-yl}-2-pyridinamine.

[0120] As used herein, the compounds of the invention are defined to include pharmaceutically acceptable salts, derivatives, or prodrugs thereof. A "pharmaceutically acceptable salt, derivative, or prodrug" means any pharmaceutically acceptable salt, ester, salt of an ester, or other derivative of a compound of this invention, which, upon administration to a recipient, is capable of providing or provides (directly or indirectly) a compound of the invention.

[0121] Accordingly, this invention also provides prodrugs of the compounds of the invention, which are derivatives that are designed to enhance biological properties such as oral absorption, clearance, metabolism, or compartmental distribution. Such derivations are well known in the art.

[0122] As the skilled practitioner realizes, the compounds of the invention may be modified by appending appropriate functionalities to enhance selective biological properties. Such modifications are known in the art and include those which increase biological penetration into a given biological compartment (*e.g.*, blood, lymphatic system, central nervous system), increase oral availability,

increase solubility to allow administration by injection, alter metabolism, or alter rate of excretion.

[0123] Certain derivatives and prodrugs are those that increase the bioavailability of the compounds of the invention when such compounds are administered to an individual (*e.g.*, by allowing an orally administered compound to be more readily absorbed into the blood), have more favorable clearance rates or metabolic profiles, or enhance delivery of the parent compound to a biological compartment (*e.g.*, the brain or lymphatic system) relative to the parent species. Examples of prodrugs include derivatives in which a group that enhances aqueous solubility or active transport through the gut membrane is appended to the structure.

[0124] In some embodiments, the compounds of the invention are provided in the form of pharmaceutically acceptable salts. Compounds containing an amine may be basic in nature and accordingly may react with any number of inorganic and organic acids to form pharmaceutically acceptable acid addition salts. Acids commonly employed to form such salts include inorganic acids such as hydrochloric, hydrobromic, hydriodic, sulfuric and phosphoric acid, as well as organic acids such as para-toluenesulfonic, methanesulfonic, oxalic, para-bromophenylsulfonic, carbonic, succinic, citric, benzoic and acetic acid, and related inorganic and organic acids. Such pharmaceutically acceptable salts thus include sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, propionate, decanoate, caprylate, acrylate, formate, isobutyrate, caprate, heptanoate, propiolate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, butyne-1,4-dioate, hexyne-1,6-dioate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, phthalate, terephathalate, sulfonate, xylenesulfonate, phenylacetate, phenylpropionate, phenylbutyrate, citrate, lactate, β-hydroxybutyrate, glycollate, maleate, tartrate, methanesulfonate, propanesulfonates, naphthalene-1-sulfonate, naphthalene-2-sulfonate, mandelate, hippurate, gluconate, lactobionate, and the like salts. In certain specific embodiments, pharmaceutically acceptable acid addition salts include those formed

with mineral acids such as hydrochloric acid and hydrobromic acid, and those formed with organic acids such as fumaric acid and maleic acid.

[0125] Compounds of the instant invention that are acidic in nature may accordingly react with any number of inorganic and organic bases to form pharmaceutically acceptable base salts. Specific bases include the mineral bases, such as NaOH and KOH, but one of skill in the art would appreciate that other bases may also be used. See Ando *et al.*, *Remington: The Science and Practice of Pharmacy, 20th ed.* 700-720 (Alfonso R. Gennaro ed.), 2000.

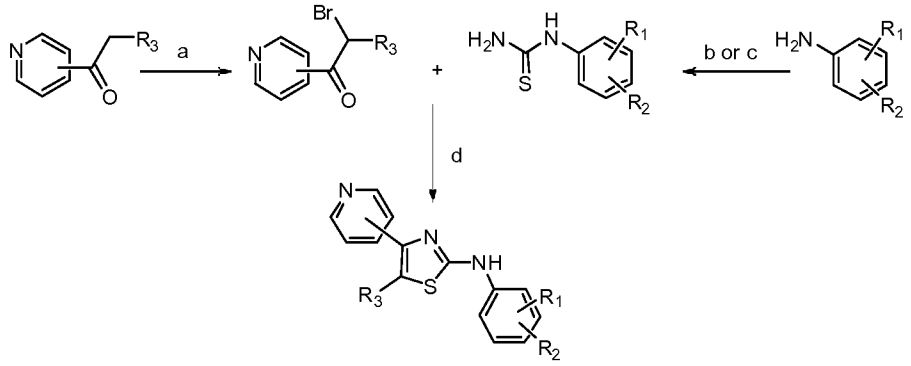
[0126] The pharmaceutically acceptable addition salts of the compounds of the invention may also exist as various solvates, such as with water, methanol, ethanol, dimethylformamide, and the like. Mixtures of such solvates may also be prepared. The source of such solvate may be from the solvent of crystallization, inherent in the solvent of preparation or crystallization, or adventitious to such solvent.

Methods For Preparing Compounds Of The Invention

[0127] Compounds of the invention may usefully be prepared according to the following general schemes. The detailed use of these schemes in the synthesis of specific compounds is provided below in the Examples.

[0128] A convenient synthesis of the compounds may be achieved using the Hantzsch thiazole synthesis, combining pyridylbromoketones with phenylthioureas (Scheme 1). The pyridylbromoketones may be readily synthesized from the corresponding ketopyridine. Thioureas are commercially available or may be conveniently prepared from the corresponding aniline, either directly by the condensation of the appropriate aniline and NH_4SCN, or by reaction of benzoyl isothiocyanate and the appropriate aniline to give the benzoyl thiourea, followed by hydrolysis under basic conditions, to give the corresponding thiourea (Rasmussen, C. R. et al., *Synthesis* **1988**, 456).

Scheme 1



Reagents:

a) Br_2, HOAc/HBr;

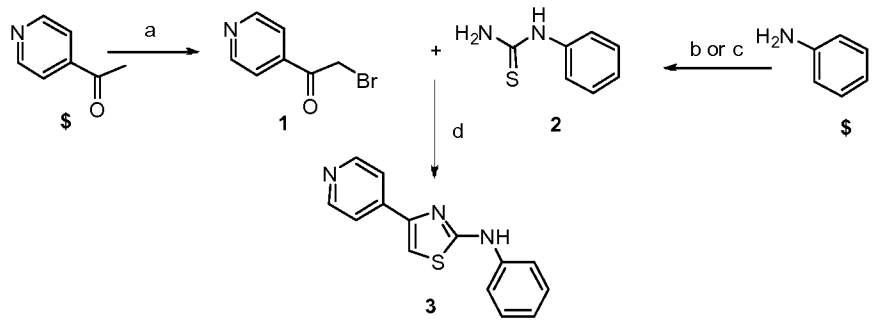
b) NH_4SCN, aqueous HCl;

c) PhCOCl, NH_4SCN, acetone; then aqueous NaOH

d) EtOH.

[0129] 1-(4-Pyridyl)-2-bromoethanone **1** is commercially available or may be readily synthesized by treatment of 4-acetylpyridine with bromine (Scheme 2). Thiourea **2** is commercially available or may be conveniently prepared from aniline by treatment with NH_4SCN in acidic solution. Alternatively, reaction of benzoyl isothiocyanate and aniline, followed by hydrolysis under basic conditions, gave the phenylthiourea. Reaction of 1-(4-pyridyl)-2-bromoethanone **1** with phenylthiourea **2** in EtOH gives aminothiazole **3**.

Scheme 2



Reagents:

a) Br_2, HOAc/HBr;

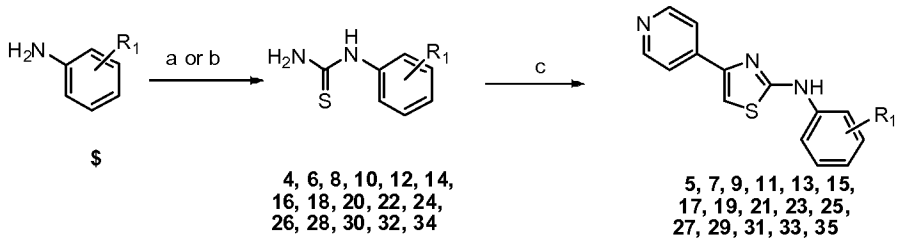
b) NH_4SCN, aqueous HCl;

c) PhCOCl, NH_4SCN, acetone; then aqueous NaOH;

d) EtOH.

[0130] Similarly, reaction of bromide **1** with thioureas **4**, **6**, **8**, **10**, **12**, **14**, **16**, **18**, **20**, **22**, **24**, **26**, **28**, **30**, **32** and **34** gives aminothiazoles **5**, **7**, **9**, **11**, **13**, **15**, **17**, **19**, **21**, **23**, **25**, **27**, **29**, **31**, **33** and **35**, respectively (Scheme 3). Alternatively, reaction of 4-(2-(dimethylamino)ethoxy)aniline with thiophosgene and iPr_2NEt in THF and subsequent reaction with NH_3 gives thiourea **28**.

Scheme 3



Reagents:

a) NH_4SCN, aqueous HCl;

b) PhCOCl, NH_4SCN, acetone; then aqueous NaOH;

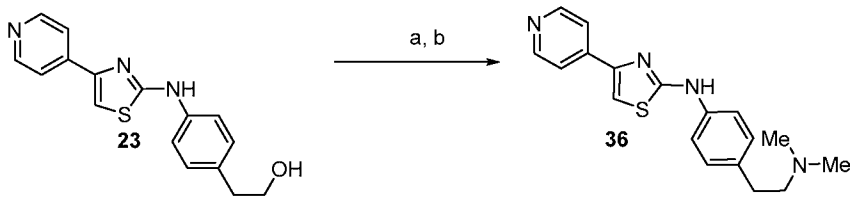
c) Bromide 1, EtOH.

R_1	**Thiourea**	**Aminothiazole**
3-Me	**4**	**5**
3-Et	**6**	**7**
3-*i*Pr	**8**	**9**
3-*t*Bu	**10**	**11**
3-OH	**12**	**13**
3-OMe	**14**	**15**
3-Cl	**16**	**17**
3-CF_3	**18**	**19**
4-Me	**20**	**21**
4-CH_2CH_2OH	**22**	**23**
4-OH	**24**	**25**
4-OMe	**26**	**27**
4-$OCH_2CH_2NMe_2$	**28**	**29**

4-Cl	**30**	**31**
4-F	**32**	**33**
4-NO_2	**34**	**35**

[0131] Mesylation of aminothiazole **23** with methanesulfonyl chloride and subsequent displacement with dimethylamine gives amine **36** (Scheme 4).

Scheme 4



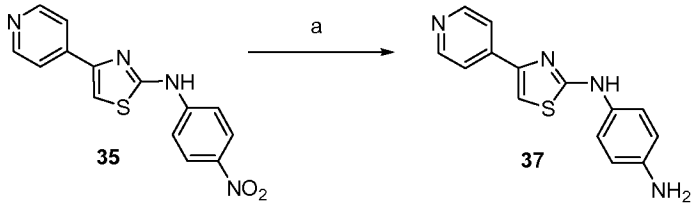
Reagents:

a) Mesyl chloride, *i*Pr_2NEt, DCM;

b) Me_2NH, DMF.

Catalytic hydrogenation of nitroaniline **35** with Pd/C gives diamine **37** (Scheme 5).

Scheme 5

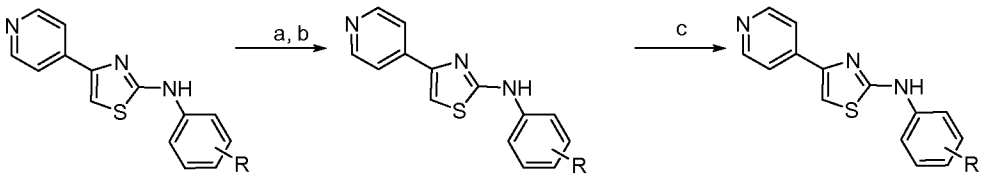


Reagents:

a) H_2, Pd/C, EtOH.

[0132] Reaction of phenols **13** and **25** with di-*tert*butyl di*iso*propylphosphoramidite and tetrazole followed by oxidation with MCPBA gives the diesters **38** and **40**, respectively. Hydrolysis of the diester gives the phosphates **39** and **41**, respectively (Scheme 6).

Scheme 6



13 3-OH
25 4-OH

38 R = 3-OP(O)(OtBu)$_2$
40 R = 4-OP(O)(OtBu)$_2$

39 R = 3-OP(O)(OH)$_2$
41 R = 4-OP(O)(OH)$_2$

Reagents:

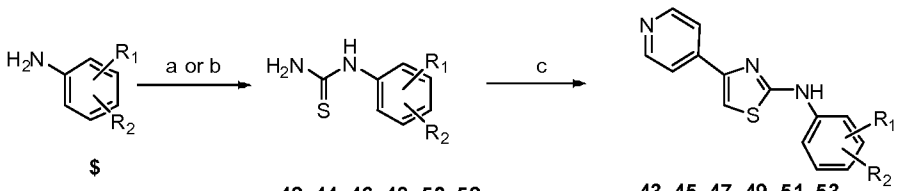
a) (tBuO)$_2$PNiPr$_2$, tetrazole, DCM;

b) MCPBA, DCM;

c) trifluoroacetic acid, DCM.

[0133] Reaction of bromide **1** with thioureas **42**, **44**, **46**, **48**, **50**, **52**, **54**, **56, 58, 60** and **62** gives aminothiazoles **43**, **45**, **47**, **49**, **50**, **51**, **53**, **55**, **57, 59, 61** and **63**, respectively (Scheme 7).

Scheme 7



$

42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62

43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63

Reagents:

a) NH$_4$SCN, aqueous HCl;

b) PhCOCl, NH$_4$SCN, acetone; then aqueous NaOH;

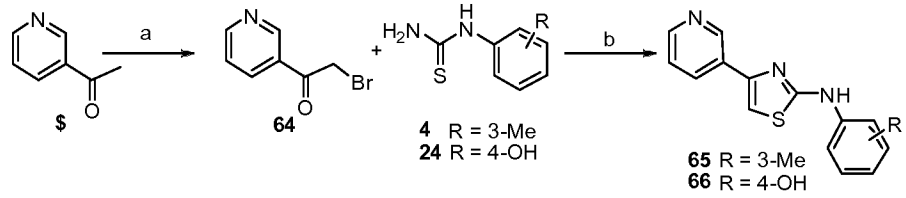
c) Bromide 1, EtOH.

R$_1$	**R$_2$**	**Thiourea**	**Aminothiazole**
3-Me	4-Me	**42**	**43**
3-Me	5-Me	**44**	**45**
3-CH$_2$CH$_2$CH$_2$-4		**46**	**47**
3-OH	4-Me	**48**	**49**
3-OH	4-OMe	**50**	**51**
3-Me	4-OH	**52**	**53**
3-OMe	4-OMe	**54**	**55**

3-OMe	5-OMe	**56**	**57**
3-OCH_2O-4		**58**	**59**
3-Cl	4-Cl	**60**	**61**
3,4,5-OMe_3		**62**	**63**

[0134] Treatment of 3-acetylpyridine with Br_2 gives 1-(3-pyridyl)-2-bromoethanone **64** which may be combined with phenylthioureas **4** and **24** to give aminothiazoles **65** and **66**, respectively (Scheme 8).

Scheme 8



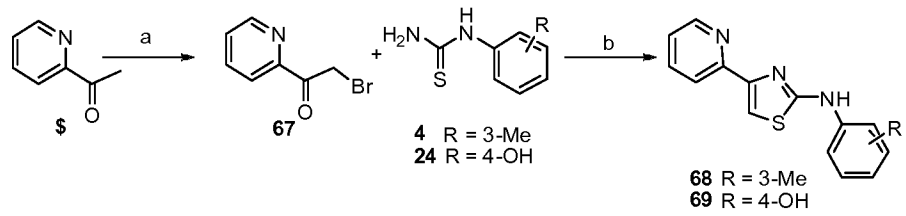
Reagents:

a) Br_2, HOAc/HBr;

b) EtOH.

[0135] Similarly, treatment of 2-acetylpyridine with Br_2 gives 1-(2-pyridyl)-2-bromoethanone **67** which may be combined with phenylthioureas **4** and **24** to give aminothiazoles **68** and **69**, respectively (Scheme 9).

Scheme 9



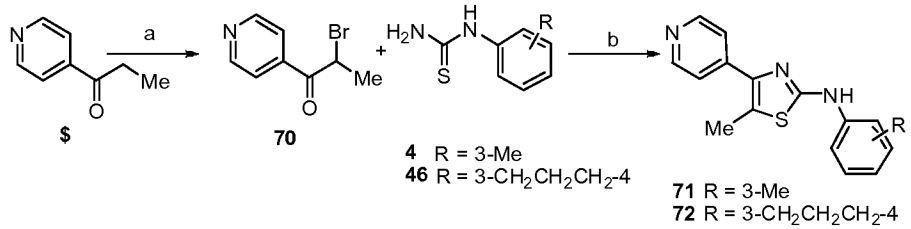
Reagents:

a) Br_2, HOAc/HBr;

b) EtOH.

[0136] Treatment of 4-propionylpyridine with Br_2 gives 1-(4-pyridyl)-2-bromopropanone **70** which may be combined with phenylthioureas **4** and **46** to give aminothiazoles **71** and **72**, respectively (Scheme 10).

Scheme 10



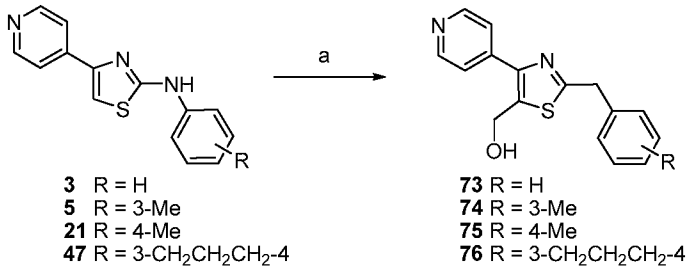
Reagents:

a) Br_2, HOAc/HBr;

b) EtOH.

[0137] Reaction of aminothiazoles **3**, **5**, **21** and **47** with formaldehyde gives the alcohols **73**–**76** (Scheme 11).

Scheme 11

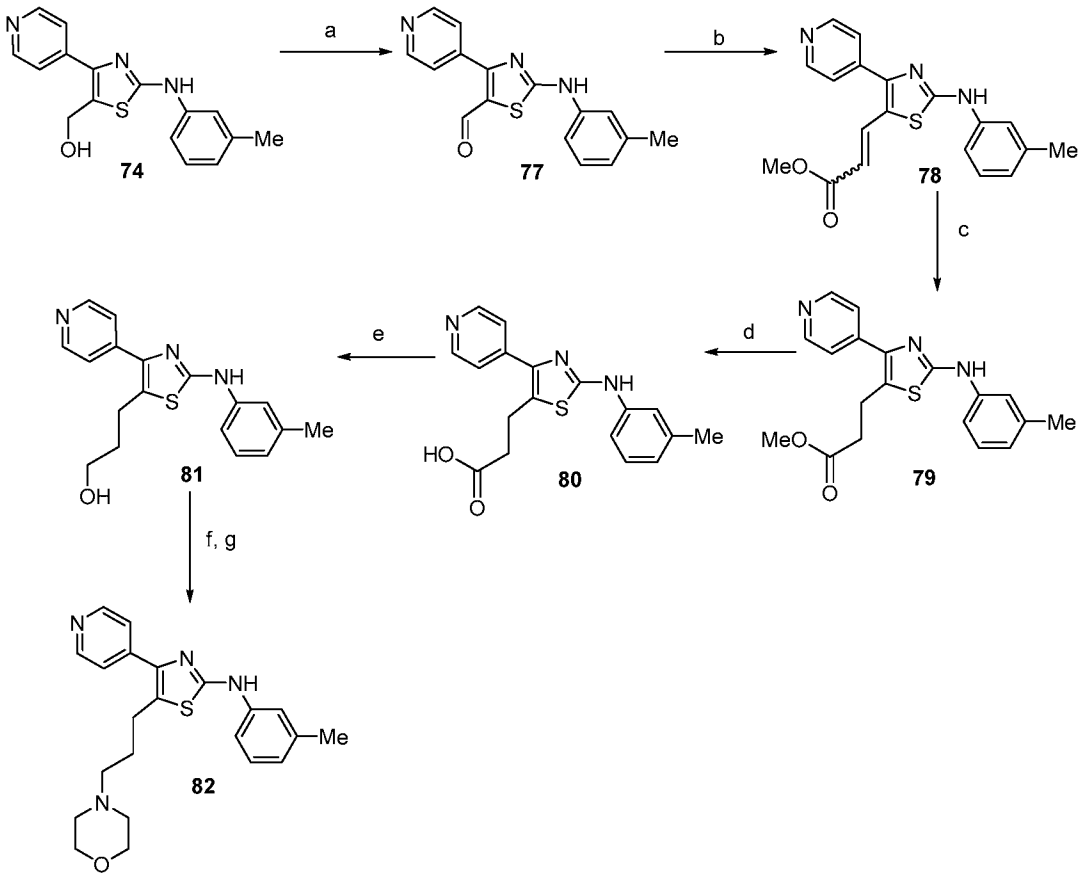


Reagents:

a) HCHO, Et_3N, THF.

[0138] Oxidation of alcohol **74**, with MnO_2 gives the aldehyde **77** which may undergo a Wittig reaction to give a mixture of *E/Z* isomers of the ester **78** (Scheme 12). Hydrogenation of the double bond over palladium catalyst gives the ester **79**, which may be hydrolysed to acid **80**. Reduction of acid **80** gives propanol **81** which may be activated with methane sulfonyl chloride and may undergo displacement with morpholine to give morpholide **82**.

Scheme 12



Reagents:

a) MnO_2, benzene;

b) $Ph_3P{=}CHCO_2Me$, DCM;

c) H_2, Pd/C, EtOH,EtOAc;

d) NaOH, EtOH;

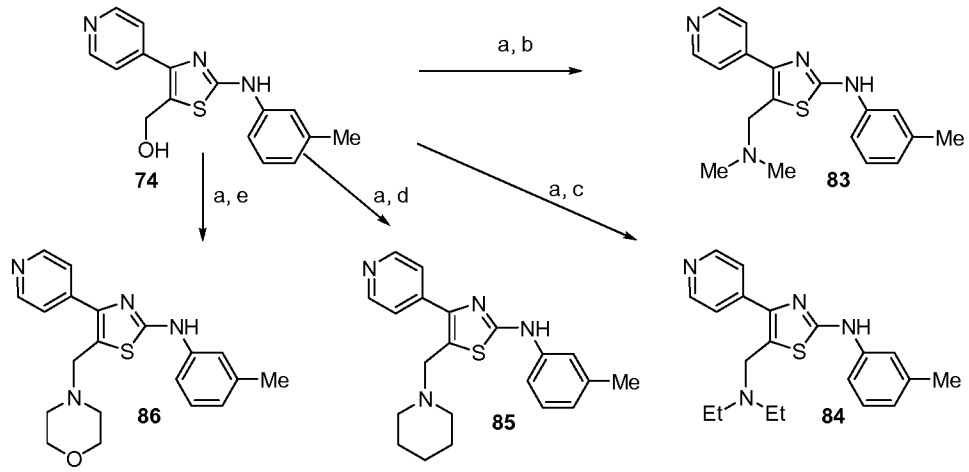
e) $LiAlH_4$, THF;

f) MsCl, $i Pr_2NEt$, DCM;

g) morpholine, DMF.

[0139] Reaction of alcohol **74** with methane sulfonyl chloride and subsequent reaction with a range of amines gave the amines **83**–**86** (Scheme 13).

Scheme 13



Reagents:

a) MsCl, iPr$_2$NEt, DCM;

b) HNMe$_2$, DMF;

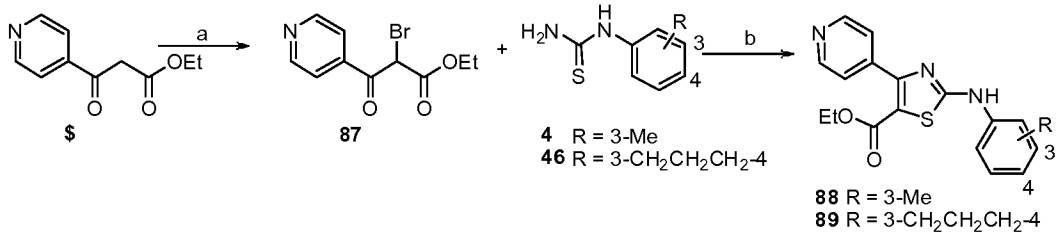
c) HNEt$_2$, DMF;

d) piperidine, DMF;

e) morpholine, DMF.

[0140] Treatment of ethyl isonicotinoylacetate with Br_2 in $CHCl_3$ gives bromoacetate **87**, which may be combined with phenylthioureas **4** and **46**, to give aminothiazoles **88** and **89**, respectively (Scheme 14).

Scheme 14



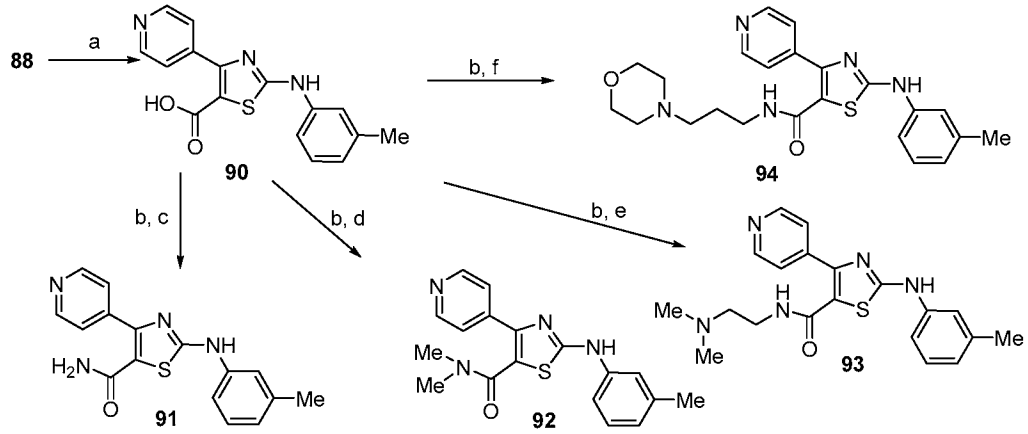
Reagents:

a) Br_2, $CHCl_3$;

b) EtOH.

[0141] Hydrolysis of ester **88** gives acid **90**, which may be converted into amides **91**–**94** (Scheme 15).

Scheme 15



Reagents:

a) NaOH, EtOH;

b) $(COCl)_2$, DMF, DCM

c) NH_3, DCM

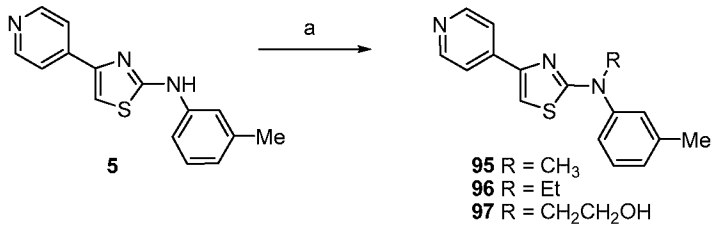
d) $HNMe_2$, DCM

e) *N*,*N*-Dimethylethylenediamine, DCM

f) 3-(4-Morpholinyl)propylamine, DCM.

[0142] Reaction of aminothiazole **5** with sodium hydride and various alkyl iodides gives aminothiazoles **95**–**97** (Scheme 16).

Scheme 16

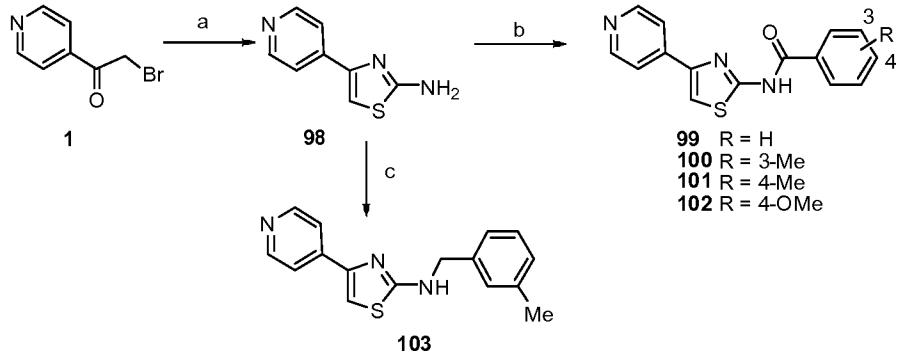


Reagents:

a) NaH, RI, DMF.

[0143] Treatment of bromoketone **1** with thiourea gives 2-aminothiazole **98** which may be condensed with various benzoyl chlorides to give amides **99**–**102** (Scheme 17). Reaction of amine **98** with 3-methylbenzaldehyde with subsequent reduction gives the benzylamine **103**.

Scheme 17



Reagents:

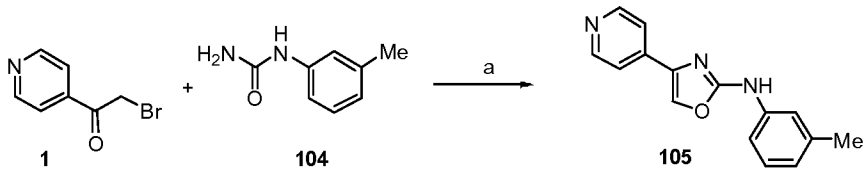
a) NH_2CSNH_2, EtOH;

b) Acid, $(COCl)_2$, DMF, DCM;

c) 3-Methylbenzaldehyde, THF; then $NaBH_4$, H_2O.

[0144] Condensation of bromide **1** with urea **104** gives oxazole **105** (Scheme 18).

Scheme 18

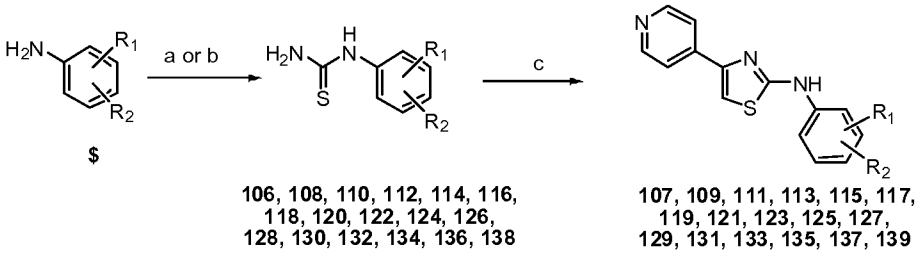


Reagents:

a) EtOH

[0145] Similarly, reaction of bromide **1** with thioureas **106**, **108**, **110**, **112**, **114**, **116**, **118**, **120**, **122**, **124**, **126**, **128**, **130**, **132**, **134**, **136** and **138** gives aminothiazoles **107**, **109**, **111**, **113**, **115**, **117**, **119**, **121**, **123**, **125**, **127**, **129**, **131**, **133**, **135**, **137**, and **139**, respectively (Scheme 19).

Scheme 19



Reagents:

a) NH_4SCN, aqueous HCl;

b) PhCOCl, NH_4SCN, acetone; then aqueous NaOH;

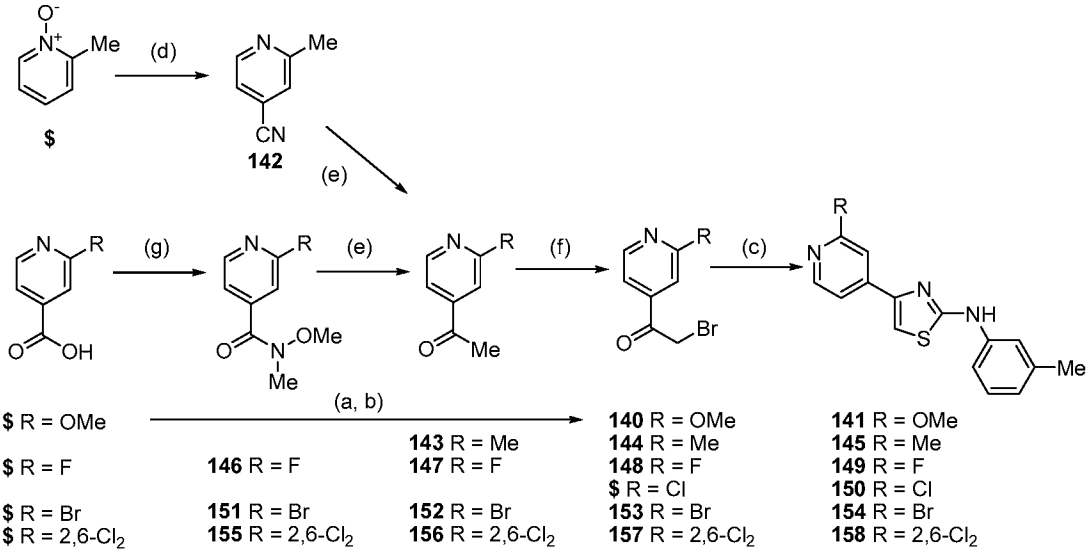
c) Bromide **1**, EtOH.

R_1	R_2	Thiourea	Aminothiazole
2-OH	H	**106**	**107**
2-OMe	H	**108**	**109**
2-Me	H	**110**	**111**
2-F	H	**112**	**113**
2-Cl	H	**114**	**115**
2-CF_3	H	**116**	**117**
2-NO_2	H	**118**	**119**
3-F	H	**120**	**121**
3-Br	H	**122**	**123**
3-$COCH_3$	H	**124**	**125**
3-CN	H	**126**	**127**
3-NO_2	H	**128**	**129**
4-$COCH_3$	H	**130**	**131**
4-CF_3	H	**132**	**133**
4-CN	H	**134**	**135**
2-Me	6-Me	**136**	**137**
2-F	6-F	**138**	**139**

[0146] 2-Methoxypyridine 4-carboxylic acid was converted to the acid chloride and treated with $TMSCH_2N_2$ and the intermediate diazoketone treated with HBr to give the bromoketone **140** (Scheme 20). Reaction of **140** with thiourea **4** gave amine **141**. Reaction of 2-picoline *N*-oxide with Me_2SO_4 and KCN gave the nitrile **142**, which was converted to the ketone **143** using MeMgBr. Bromination of **143** gave **144**, which reacted with thiourea **4** to give amine **145**. Formation of the Weinreb amide **146** and Grignard reaction gave ketone **147**. Bromination of **147** afforded **148** which reacted with thiourea **4** to amine **149**. Similarly, reaction of the

2-chloro bromoketone analogue gave amine **150**. A similar sequence was used to furnish amines **154** and **158** from their corresponding pyridylcarboxylic acids.

Scheme 20



Reagents:

a) $(COCl)_2$, DMF, DCM;

b) $TMSCH_2N_2$, THF; then HBr;

c) Arylthiourea **4**, EtOH;

d) Me_2SO_4, then KCN, aq. EtOH;

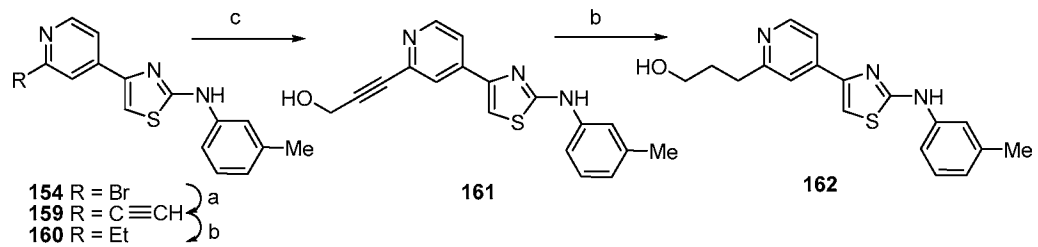
e) MeMgBr, THF;

f) Br_2, HOAc/HBr;

g) Me(OMe)NH·HCl, EDCI, HOBT, Et_3N, DCM.

[0147] Sonogashira reaction of bromide **154** with TMS-acetylene and subsequent deprotection gave the alkyne **159**, which was reduced to the alkane **160** (Scheme 21). Similarly, reaction of **154** with propargyl alcohol gave alkyne **161**, which was reduced to alkane **162**.

Scheme 21



Reagents:

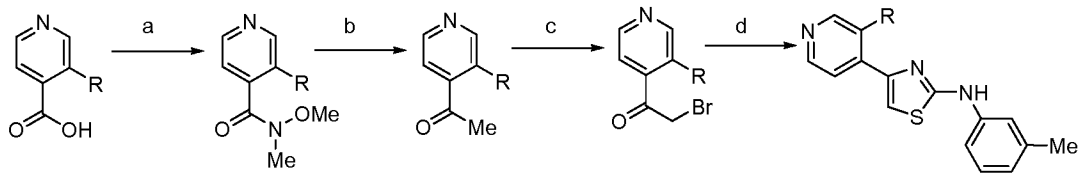
a) $PdCl_2(PPh_3)_2$, CuI, TMSC≡CH, Et_3N, DMF, then TBAF;

b) H_2, Pd/C, EtOH;

c) $PdCl_2(PPh_3)_2$, CuI, HC≡CCH_2OH, Et_3N, DMF.

[0148] A series of 3-substituted pyridine carboxylic acids were elaborated to Weinreb amides **163**, **167**, **171** and **175**, and then converted to the corresponding ketones **164**, **168**, **172**, and **176** (Scheme 22). Bromination and condensation with thiourea **4** gave the amines **166**, **170**, **174**, and **178**. Nitration of 4-acetyl pyridine gave the 3-nitroketone **179**, which was brominated to give **180** and then condensed with thiourea **4** to give amine **181**. Reduction of **181** gave the 3-amino analogue **182**, which was acetylated to give **183**.

Scheme 22



Reagents:

a) Me(OMe)NH·HCl, EDCI, HOBT, Et_3N, DCM;

b) MeMgBr, THF;

c) Br_2, HOAc/HBr;

d) 3-methylphenylthiourea **4**, EtOH;

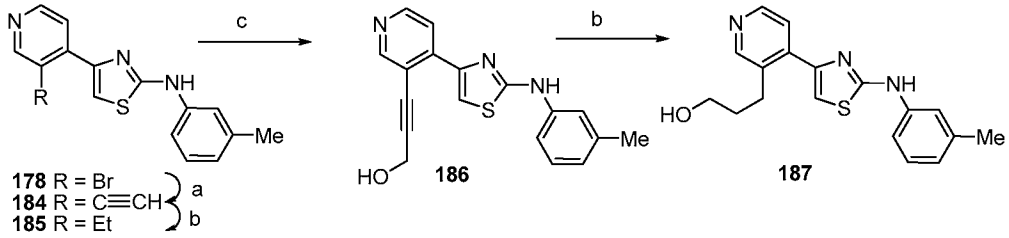
e) H_2, Pd/C, EtOH;

f) Ac_2O, dioxane.

[0149] Sonogashira reaction of bromide **178** with TMS-acetylene and subsequent deprotection gave the alkyne **184**, which was reduced to the alkane **185** (Scheme

23). Similarly, reaction of **178** with propargyl alcohol gave alkyne **186**, which was reduced to alkane **187**.

Scheme 23



Reagents:

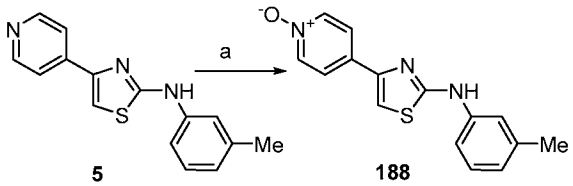
a) $PdCl_2(PPh_3)_2$, CuI, $TMSC{\equiv}CH$, Et_3N, DMF, then TBAF;

b) H_2, Pd/C, EtOH;

c) $PdCl_2(PPh_3)_2$, CuI, $HC{\equiv}CCH_2OH$, Et_3N, DMF.

[0150] Oxidation of amine **5** with MCPBA gave the *N*-oxide **188** (Scheme 24).

Scheme 24

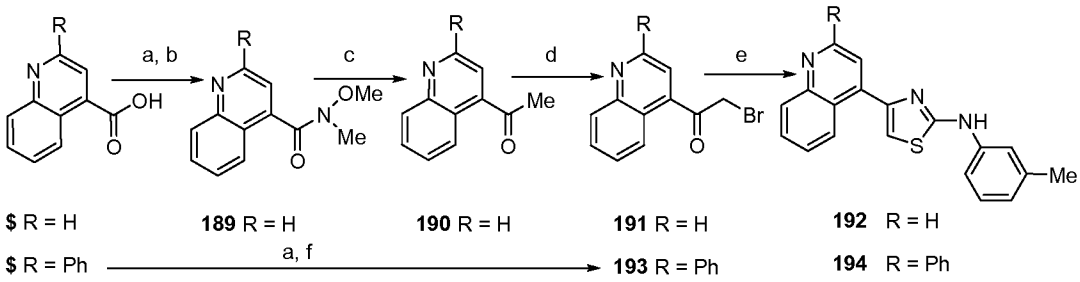


Reagents:

a) MCPBA, DCM.

[0151] Reaction of 4-quinoline carboxylic acid gave the Weinreb amide **189** which underwent alkylation to give the ketone **190** (Scheme 25). Bromination of **190** gave the bromoketone **191** which was condensed with thiourea **4** to give amine **192**. Alternatively, formation of the acid chloride and reaction with $TMSCH_2N_2$ and subsequent reaction with Br_2 gave the bromoketone **191**. Similarly, reaction of 2-phenyl-4-quinoline carboxylic acid gave the bromoketone **193**. Reaction with thiourea **4** gave amine **194**.

Scheme 25



Reagents:

a) $(COCl)_2$, DMF, DCM;

b) Me(OMe)NH·HCl, Et_3N, DCM;

c) MeMgBr, THF;

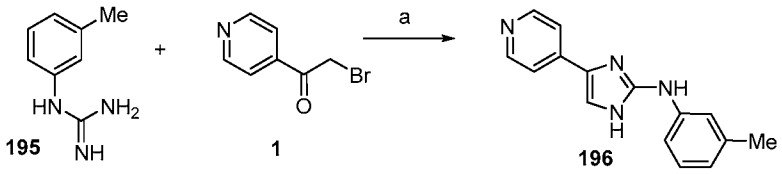
d) Br_2, HOAc/HBr;

e) Arylthiourea **4**, EtOH;

f) $TMSCH_2N_2$, THF; then HBr.

[0152] Condensation of 3-methylphenyl guanidine **204** with bromoketone **1** gave the imidazole **205** (Scheme 26).

Scheme 26

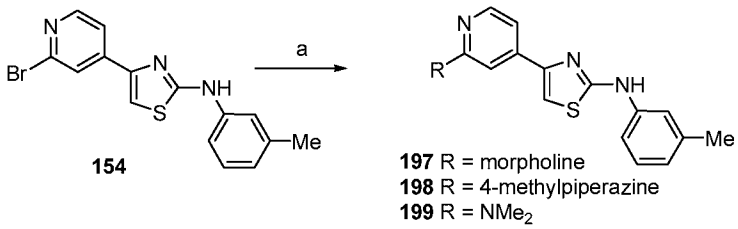


Reagents:

a) EtOH.

[0153] Reaction of bromide **154** with morpholine gave the amine **197** (Scheme 27). Similarly reaction of **154** with 1-methylpiperazine or aqueous dimethylamine gave the corresponding amines **198** and **199**.

Scheme 27



Reagents:

a) Amine.

Pharmaceutical Compositions

[0154] In another aspect, the compounds of the invention may be administered as a pharmaceutical composition containing, for example, any of the above-described compounds and a pharmaceutically acceptable carrier.

[0155] Pharmaceutically acceptable carriers are well known in the art and include, for example, aqueous solutions such as water or physiologically buffered saline or other solvents or vehicles such as glycols, glycerol, oils such as olive oil or injectable organic esters. In a specific embodiment, when such pharmaceutical compositions are for human administration, the aqueous solution is pyrogen free, or substantially pyrogen free. The excipients may be chosen, for example, to effect delayed release of an agent or to selectively target one or more cells, tissues or organs. The pharmaceutical composition may be in dosage unit form such as tablet, capsule, sprinkle capsule, granule, powder, syrup, suppository, injection or the like. The composition may also be present in a transdermal delivery system, *e.g.*, a skin patch.

[0156] A pharmaceutically acceptable carrier may contain physiologically acceptable agents that act, for example, to stabilize or to increase the absorption of a compound of the instant invention. Such physiologically acceptable agents include, for example, carbohydrates, such as glucose, sucrose or dextrans, antioxidants, such as ascorbic acid or glutathione, chelating agents, low molecular weight proteins or other stabilizers or excipients. The choice of a pharmaceutically acceptable carrier, including a physiologically acceptable agent, depends, for example, on the route of administration of the composition. The pharmaceutical composition also may comprise a liposome or other polymer matrix, which may have incorporated therein, for example, a compound of the invention. Liposomes, for example, which consist of phospholipids or other lipids, are nontoxic,

physiologically acceptable and metabolizable carriers that are relatively simple to make and administer.

[0157] The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms that are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

[0158] The phrase "pharmaceutically acceptable carrier" as used herein means a pharmaceutically acceptable material, composition, or vehicle, such as a liquid or solid filler, diluent, excipient, solvent, or encapsulating material, involved in carrying or transporting the subject compounds from one organ, or portion of the body, to another organ, or portion of the body. Each carrier must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not injurious to the patient. Some examples of materials that can serve as pharmaceutically acceptable carriers include: (1) sugars, such as lactose, glucose and sucrose; (2) starches, such as corn starch and potato starch; (3) cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; (4) powdered tragacanth; (5) malt; (6) gelatin; (7) talc; (8) excipients, such as cocoa butter and suppository waxes; (9) oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; (10) glycols, such as propylene glycol; (11) polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol; (12) esters, such as ethyl oleate and ethyl laurate; (13) agar; (14) buffering agents, such as magnesium hydroxide and aluminum hydroxide; (15) alginic acid; (16) pyrogen-free water; (17) isotonic saline; (18) Ringer's solution; (19) ethyl alcohol; (20) phosphate buffer solutions; and (21) other non-toxic compatible substances employed in pharmaceutical formulations. See *Remington: The Science and Practice of Pharmacy, 20th ed.* (Alfonso R. Gennaro ed.), 2000.

[0159] A pharmaceutical composition containing a compound of the instant invention may be administered to a host by any of a number of routes of administration including, for example, orally (for example, drenches as in aqueous

or non-aqueous solutions or suspensions, tablets, boluses, powders, granules, pastes for application to the tongue); sublingually; anally, rectally, or vaginally (for example, as a pessary, cream, or foam); parenterally (including intramusclularly, intravenously, subcutaneously, or intrathecally as, for example, a sterile solution or suspension); nasally; intraperitoneally; subcutaneously; transdermally (for example as a patch applied to the skin); or topically (for example, as a cream, ointment or spray applied to the skin). The compound may also be formulated for inhalation. In certain embodiments, a compound of the instant invention may be simply dissolved or suspended in sterile water. Details of appropriate routes of administration and compositions suitable for same can be found in, for example, U.S. Patent Nos. 6,110,973; 5,763,493; 5,731,000; 5,541,231; 5,427,798; 5,358,970; and 4,172,896, as well as in patents cited therein.

[0160] The formulations of the present invention may conveniently be presented in unit dosage form and may be prepared by any methods well known in the art of pharmacy. The amount of active ingredient that can be combined with a carrier material to produce a single dosage form will vary depending upon the host being treated and the particular mode of administration. The amount of active ingredient that can be combined with a carrier material to produce a single dosage form will generally be that amount of the compound that produces a therapeutic effect. Generally, out of one hundred percent, this amount will range from about 1 percent to about 99 percent of active ingredient, in some embodiments from about 5 percent to about 70 percent, and in more specific embodiments from about 10 percent to about 30 percent.

[0161] Methods of preparing these formulations or compositions include the step of bringing into association a compound of the present invention with the carrier and, optionally, one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association a compound of the present invention with liquid carriers, or finely divided solid carriers, or both, and then, if necessary, shaping the product.

[0162] Formulations of the invention suitable for oral administration may be in the form of capsules, cachets, pills, tablets, lozenges (using a flavored basis, usually sucrose and acacia or tragacanth), powders, granules, or as a solution or a

suspension in an aqueous or non-aqueous liquid, or as an oil-in-water or water-in-oil liquid emulsion, or as an elixir or syrup, or as pastilles (using an inert base, such as gelatin and glycerin, or sucrose and acacia) and/or as mouth washes and the like, each containing a predetermined amount of a compound of the present invention as an active ingredient. A compound of the present invention may also be administered as a bolus, electuary, or paste.

[0163] In solid dosage forms of the invention for oral administration (capsules, tablets, pills, dragees, powders, granules and the like), the active ingredient is mixed with one or more pharmaceutically acceptable carriers, such as sodium citrate or dicalcium phosphate, and/or any of the following: (1) fillers or extenders, such as starches, lactose, sucrose, glucose, mannitol, and/or silicic acid; (2) binders, such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinyl pyrrolidone, sucrose and/or acacia; (3) humectants, such as glycerol; (4) disintegrating agents, such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate; (5) solution retarding agents, such as paraffin; (6) absorption accelerators, such as quaternary ammonium compounds; (7) wetting agents, such as, for example, cetyl alcohol and glycerol monostearate; (8) absorbents, such as kaolin and bentonite clay; (9) lubricants, such a talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof; and (10) coloring agents. In the case of capsules, tablets and pills, the pharmaceutical compositions may also comprise buffering agents. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugars, as well as high molecular weight polyethylene glycols and the like.

[0164] The tablets, and other solid dosage forms of the pharmaceutical compositions of the present invention, such as dragees, capsules, pills and granules, may optionally be scored or prepared with coatings and shells, such as enteric coatings and other coatings well known in the pharmaceutical-formulating art. They may also be formulated so as to provide slow or controlled release of the active ingredient therein using, for example, hydroxypropylmethyl cellulose in varying proportions to provide the desired release profile, other polymer matrices, liposomes and/or microspheres. They may be sterilized by, for example, filtration

through a bacteria-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions that can be dissolved in sterile water, or some other sterile injectable medium immediately before use. These compositions may also optionally contain opacifying agents and may be of a composition that they release the active ingredient(s) only, or preferentially, in a certain portion of the gastrointestinal tract, optionally, in a delayed manner. Examples of embedding compositions that may be used include polymeric substances and waxes. The active ingredient may also be in micro-encapsulated form, if appropriate, with one or more of the above-described excipients.

[0165] Liquid dosage forms for oral administration of the compounds of the invention include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active ingredient, the liquid dosage forms may contain inert diluents commonly used in the art, such as, for example, water or other solvents, solubilizing agents and emulsifiers, such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor and sesame oils), glycerol, tetrahydrofuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof.

[0166] Besides inert diluents, the oral compositions may also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, coloring, perfuming, and preservative agents.

[0167] Suspensions, in addition to the active compounds, may contain suspending agents as, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar, and tragacanth, and mixtures thereof.

[0168] Formulations of the pharmaceutical compositions of the invention for rectal, vaginal, or urethral administration may be presented as a suppository, which may be prepared by mixing one or more compounds of the invention with one or more suitable nonirritating excipients or carriers comprising, for example, cocoa butter, polyethylene glycol, a suppository wax or a salicylate, and which is solid at

room temperature, but liquid at body temperature and, therefore, will melt in the rectum or vaginal cavity and release the active compound.

[0169] Alternatively or additionally, compositions may be formulated for delivery via a catheter, stent, wire, or other intraluminal device. Delivery via such devices may be especially useful for delivery to the bladder, urethra, ureter, rectum, or intestine.

[0170] Formulations of the present invention which are suitable for vaginal administration also include pessaries, tampons, creams, gels, pastes, foams, or spray formulations containing such carriers as are known in the art to be appropriate.

[0171] Dosage forms for the topical or transdermal administration of a compound of this invention include powders, sprays, ointments, pastes, creams, lotions, gels, solutions, patches, and inhalants. The active compound may be mixed under sterile conditions with a pharmaceutically acceptable carrier, and with any preservatives, buffers, or propellants that may be required.

[0172] The ointments, pastes, creams, and gels may contain, in addition to an active compound of this invention, excipients, such as animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures thereof.

[0173] Powders and sprays may contain, in addition to a compound of this invention, excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates, and polyamide powder, or mixtures of these substances. Sprays may additionally contain customary propellants, such as chlorofluorohydrocarbons and volatile unsubstituted hydrocarbons, such as butane and propane.

[0174] Transdermal patches have the added advantage of providing controlled delivery of a compound of the present invention to the body. Such dosage forms may be made by dissolving or dispersing the compound in the proper medium. Absorption enhancers may also be used to increase the flux of the compound across the skin. The rate of such flux may be controlled by either providing a rate controlling membrane or dispersing the compound in a polymer matrix or gel.

[0175] Ophthalmic formulations, eye ointments, powders, solutions, and the like, are also contemplated as being within the scope of this invention.

[0176] The phrases "parenteral administration" and "administered parenterally" as used herein means modes of administration other than enteral and topical administration, usually by injection, and includes, without limitation, intravenous, intramuscular, intraarterial, intrathecal, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intraarticular, subcapsular, subarachnoid, intraspinal, and intrasternal injection and infusion.

[0177] Pharmaceutical compositions of this invention suitable for parenteral administration comprise one or more compounds of the invention in combination with one or more pharmaceutically acceptable sterile isotonic aqueous or nonaqueous solutions, dispersions, suspensions, or emulsions, or sterile powders which may be reconstituted into sterile injectable solutions or dispersions just prior to use, which may contain antioxidants, buffers, bacteriostats, solutes which render the formulation isotonic with the blood of the intended recipient or suspending or thickening agents.

[0178] Examples of suitable aqueous and nonaqueous carriers that may be employed in the pharmaceutical compositions of the invention include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable oils, such as olive oil, and injectable organic esters, such as ethyl oleate. Proper fluidity may be maintained, for example, by the use of coating materials, such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

[0179] These compositions may also contain adjuvants such as preservatives, wetting agents, emulsifying agents, and dispersing agents. Prevention of the action of microorganisms may be ensured by the inclusion of various antibacterial and antifungal agents, for example, paraben, chlorobutanol, phenol sorbic acid, chelators and the like. It may also be desirable to include isotonic agents, such as sugars, sodium chloride, and the like into the compositions. In addition, prolonged absorption of the injectable pharmaceutical form may be brought about by the inclusion of agents that delay absorption such as aluminum monostearate and gelatin.

[0180] In some cases, in order to prolong the effect of a drug, it is desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material having poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution, which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle.

[0181] Injectable depot forms are made by forming microencapsuled matrices of the subject compounds in biodegradable polymers such as polylactide-polyglycolide. Depending on the ratio of drug to polymer, and the nature of the particular polymer employed, the rate of drug release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the drug in liposomes or microemulsions that are compatible with body tissue.

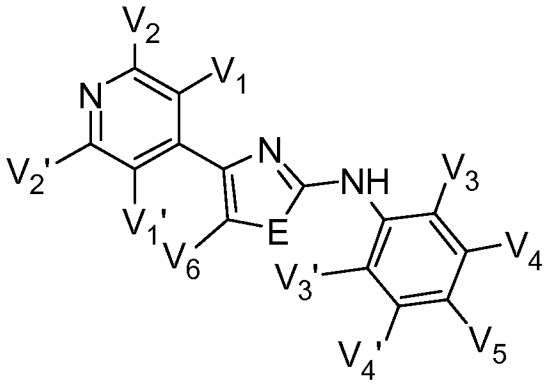
[0182] Methods of introduction may also be provided by rechargeable or biodegradable devices. Various slow release polymeric devices have been developed and tested *in vivo* in recent years for the controlled delivery of drugs. A variety of biocompatible polymers (including hydrogels), including both biodegradable and non-degradable polymers, may be used to form an implant for the sustained release of a compound at a particular target site.

[0183] In certain embodiments, the present invention provides compositions comprising at least one compound, as described above, or an analog, derivative, or functional equivalent thereof. As further detailed below, the inventive compositions may also comprise, or may be used in combination with, one or more known cytotoxic, vascular targeting agents or chemotherapeutic agents including, but not limited to, Xeloda™ (capecitabine), Paclitaxel™, FUDR (fluorouridine) Fludara™ (fludarabine phosphate), Gemzar™ (gemcitabine), methotrexate, cisplatin, carboplatin, adriamycin, avastin, tarceva, taxol, tamoxifen, Femora, temezolamide, cyclophosphamide, Erbitux, and Sutent.

Methods of Use

[0184] As noted above, von Hippel-Lindau (VHL) disease is a hereditary condition that predisposes subjected individuals to the development of various malignant and benign tumors. Among the tumors resulting from this condition are renal cell carcinoma (RCC), in particular clear cell-RCC, pheochromocytomas, hemangioblastomas of the central nervous system and retina, endolymphatic sac tumors, renal cysts, pancreatic cysts, neuroendocrine tumors, endolymphatic sac tumors, and epididymal and broad ligament cystadenomas. Park, D.M., et al., *PLoS Med.* **2007**, *4*, E60. Accordingly, individuals affected by VHL disease may develop tumors of the retina, brain, spinal cord, ear, epidymis, broad ligament, adrenal gland, kidney, and pancreas. Accordingly, the invention further provides methods of using the compounds and compositions described herein in the treatment and prevention of such conditions.

[0185] In one aspect, the pharmaceutical compositions of the invention are used in methods for treating or preventing a disease. Accordingly, the methods comprise administering to the mammalian host in need thereof a therapeutically-effective amount of a compound of Formula II, or a pharmaceutically acceptable salt, derivative, or prodrug thereof:



Formula II

wherein:

E is S, O, or N-V_7;

V_1, V_1', V_2, V_2', V_3, V_3', V_4, V_4', V_5, V_6, and V_7 are independently hydrogen, halo, R, OH, OR, OC(O)H, OC(O)R, $OC(O)NH_2$, OC(O)NHR, OC(O)NRR, $OP(O)(OH)_2$, $OP(O)(OR)_2$, NO_2, NH_2, NHR, NRR, $N^+(-O^-)RR$, NHC(O)H, NHC(O)R, NRC(O)R, $NHC(O)NH_2$, NHC(O)NRR, NRC(O)NHR,

$N^2C(O)NHR$, SH, SR, S(O)H, S(O)R, SO_2R, SO_2NH_2, SO_2NHR, SO_2NRR, CF_3, CN, CO_2H, CO_2R, CHO, C(O)R, $C(O)NH_2$, C(O)NHR, C(O)NRR, $CONHSO_2H$, $C(O)NHSO_2R$, $C(O)NRSO_2R$, cyclic C_3-C_7 alkylamino, imidazolyl, piperazinyl, morpholinyl, piperidinyl, azepanyl, pyrrolidinyl or azetidinyl;

wherein each imidazolyl, piperazinyl, morpholinyl, piperidinyl, azepanyl, pyrrolidinyl and azetidinyl is optionally and independently substituted by one or more R^1, halo, OH, OR^1, $OC(O)R^1$, $OC(O)NH_2$, $OC(O)NHR^1$, $OC(O)NR^1R^1$, $OP(O)(OH)_2$, $OP(O)(OR^1)_2$, NO_2, NH_2, NHR^1, NR^1R^1, $N^+(-O^-)R^1R^1$, NHC(O)H, $NHC(O)R^1$, $NR^1C(O)R^1$, $NHC(O)NH_2$, $NHC(O)NR^1R^1$, $NR^1C(O)NHR^1$, SH, SR^1, S(O)H, $S(O)R^1$, SO_2R^1, SO_2NH_2, SO_2NHR^1, $SO_2NR^1R^1$, CF_3, CN, CO_2H, CO_2R^1, CHO, $C(O)R^1$, $C(O)NH_2$, $C(O)NHR^1$, $C(O)NR^1R^1$, $CONHSO_2H$, $C(O)NHSO_2R^1$ or $C(O)NR^1SO_2R^1$;

and wherein groups V_1 and V_2, groups V_3 and V_4, and groups V_4 and V_5, taken together with the atoms to which they are attached, optionally and independently form a cyclic structure having from 4 to 8 atoms in the ring;

each R is independently C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cyclic alkyl, aryl, aralkyl, heteroaryl, or heteroaralkyl , and is optionally and independently substituted with halo, OH, R^1, OR^1, $OC(O)R^1$, $OC(O)NH_2$, $OC(O)NHR^1$, $OC(O)NR^1R^1$, $OP(O)(OH)_2$, $OP(O)(OR^1)_2$, NO_2, NH_2, NHR^1, NR^1R^1, $N^+(-O^-)R^1R^1$, NHC(O)H, $NHC(O)R^1$, $NR^1C(O)R^1$, $NHC(O)NH_2$, $NHC(O)NR^1R^1$, $NR^1C(O)NHR^1$, SH, SR^1, S(O)H, $S(O)R^1$, SO_2R^1, SO_2NH_2, SO_2NHR^1, $SO_2NR^1R^1$, CF_3, CN, CO_2H, CO_2R^1, CHO, $C(O)R^1$, $C(O)NH_2$, $C(O)NHR^1$, $C(O)NR^1R^1$, $C(O)NHSO_2R^1$, $C(O)NR^1SO_2R^1$, cyclic C_3-C_7 alkylamino, imidazolyl, piperazinyl, morpholinyl, piperidinyl, azepanyl, pyrrolidinyl, or azetidinyl;

wherein each imidazolyl, piperazinyl, morpholinyl, piperidinyl, azepanyl, pyrrolidinyl and azetidinyl is optionally and independently substituted with one or more R^1, halo, OH, OR^1, $OC(O)R^1$, $OC(O)NH_2$, $OC(O)NHR^1$, $OC(O)NR^1R^1$, $OP(O)(OH)_2$, $OP(O)(OR^1)_2$, NO_2, NH_2, NHR^1, NR^1R^1, $N^+(-O^-)R^1R^1$, NHC(O)H, $NHC(O)R^1$, $NR^1C(O)R^1$, $NHC(O)NH_2$, $NHC(O)NR^1R^1$, $NR^1C(O)NHR^1$, SH, SR^1, S(O)H, $S(O)R^1$, SO_2R^1, SO_2NH_2, SO_2NHR^1, $SO_2NR^1R^1$, CF_3, CN, CO_2H, CO_2R^1,

CHO, $C(O)R^1$, $C(O)NH_2$, $C(O)NHR^1$, $C(O)NR^1R^1$, $CONHSO_2H$, $C(O)NHSO_2R^1$ or $C(O)NR^1SO_2R^1$;

and wherein each heteroaryl group contains one or more heteroatoms in its ring system, independently selected from O, N or S;

each R^1 is independently C_{1-6} alkyl or C_{2-6} alkenyl, optionally and independently substituted with halo, OH, OR^2, $OC(O)R^2$, $OC(O)NH_2$, $OC(O)NHR^2$, $OC(O)NR^2R^2$, $OP(O)(OH)_2$, $OP(O)(OR^2)_2$, NO_2, NH_2, NHR^2, NR^2R^2, $N^+(-O^-)R^2R^2$, $NHC(O)R^2$, $NR^2C(O)R^2$, $NHC(O)NH_2$, $NHC(O)NR^2R^2$, $NR^2C(O)NHR^2$, SH, SR^2, S(O)H, $S(O)R^2$, SO_2R^2, SO_2NH_2, SO_2NHR^2, $SO_2NR^2R^2$, CF_3, CN, CO_2H, CO_2R^2, CHO, $C(O)R^2$, $C(O)NH_2$, $C(O)NHR^2$, $C(O)NR^2R^2$, $C(O)NHSO_2R^2$, $C(O)NR^2SO_2R^2$, cyclic C_3-C_7 alkylamino, imidazolyl, piperazinyl, morpholinyl, piperidinyl, azepanyl, pyrrolidinyl or azetidinyl;

wherein each imidazolyl, piperazinyl, morpholinyl, piperidinyl, azepanyl, pyrrolidinyl and azetidinyl is optionally and independently substituted with one or more R^2, halo, OH, OR^2, $OC(O)R^2$, $OC(O)NH_2$, $OC(O)NHR^2$, $OC(O)NR^2R^2$, $OP(O)(OH)_2$, $OP(O)(OR^2)_2$, NO_2, NH_2, NHR^2, NR^2R^2, $N^+(-O^-)R^2R^2$, NHC(O)H, $NHC(O)R^2$, $NR^2C(O)R^2$, $NHC(O)NH_2$, $NHC(O)NR^2R^2$, $NR^2C(O)NHR^2$, SH, SR^2, S(O)H, $S(O)R^2$, SO_2R^2, SO_2NH_2, SO_2NHR^2, $SO_2NR^2R^2$, CF_3, CN, CO_2H, CO_2R^2, CHO, $C(O)R^2$, $C(O)NH_2$, $C(O)NHR^2$, $C(O)NR^2R^2$, $CONHSO_2H$, $C(O)NHSO_2R^2$ or $C(O)NR^2SO_2R^2$; and

each R^2 is independently C_{1-6} alkyl, C_{2-6} alkenyl, OH, OMe, NO_2, NH_2, CF_3, CN, CO_2H or SH.

[0186] In some embodiments, R is independently C_{1-6} alkyl, C_{2-4} alkenyl, C_{3-7} cyclic alkyl, C_{4-8} aryl, or C_{4-8} heteroaryl, and is optionally and independently substituted with halo, OH, R^1, OR^1, $OC(O)R^1$, $OC(O)NH_2$, $OC(O)NHR^1$, $OC(O)NR^1R^1$, $OP(O)(OH)_2$, $OP(O)(OR^1)_2$, NO_2, NH_2, NHR^1, NR^1R^1, $N^+(-O^-)R^1R^1$, NHC(O)H, $NHC(O)R^1$, $NR^1C(O)R^1$, $NHC(O)NH_2$, $NHC(O)NR^1R^1$, $NR^1C(O)NHR^1$, SH, SR^1, S(O)H, $S(O)R^1$, SO_2R^1, SO_2NH_2, SO_2NHR^1, $SO_2NR^1R^1$, CF_3, CN, CO_2H, CO_2R^1, CHO, $C(O)R^1$, $C(O)NH_2$, $C(O)NHR^1$, $C(O)NR^1R^1$, $C(O)NHSO_2R^1$, $C(O)NR^1SO_2R^1$, cyclic C_3-C_7 alkylamino, imidazolyl, piperazinyl, morpholinyl, piperidinyl, azepanyl, pyrrolidinyl, or azetidinyl.

[0187] In some embodiments, V_3, V_4, and V_5 are independently hydrogen; halo; R; OH; OR; CF_3; NO_2; NH_2; NHR; NRR; $OP(O)(OH)_2$; or $OP(O)(OR)_2$; and groups V_3 and V_4 and groups V_4 and V_5, taken together with the atoms to which they are attached, optionally and independently form a 5- or 6-membered ring structure.

[0188] In specific embodiments, V_3, V_4, and V_5 are independently hydrogen; halo; C_{1-6} alkyl, optionally substituted with OH, NH_2, or $N(CH_3)_2$; OH; O-C_{1-6} alkyl, optionally substituted with OH, NH_2, or $N(CH_3)_2$; CF_3; NO_2; NH_2; or $OP(O)(OH)_2$.

[0189] In some embodiments, V_4 is hydrogen; halo; R; OH; OR; CF_3; NO_2; NH_2; NHR; NRR; $OP(O)(OH)_2$; or $OP(O)(OR)_2$.

[0190] In more specific embodiments, V_4 is hydrogen; halo; C_{1-6} alkyl, optionally substituted with OH, NH_2, or $N(CH_3)_2$; OH; O-C_{1-6} alkyl, optionally substituted with OH, NH_2, or $N(CH_3)_2$; CF_3; NO_2; NH_2; or $OP(O)(OH)_2$.

[0191] In some embodiments, V_6 is hydrogen; R; CHO; CO_2R; $C(O)NH_2$; C(O)NHR; or C(O)NRR.

[0192] In more specific embodiments, V_6 is hydrogen; C_{1-6} alkyl or C_{2-4} alkenyl, optionally substituted with OH, OR^1, CO_2R^1, NH_2, NHR^1, or NR^1R^1; CHO; or CO_2R.

[0193] In even more specific embodiments, V_6 is hydrogen.

[0194] In some embodiments, V_1 and V_2 are independently hydrogen, halo, R, OH, OR, CF_3, NO_2, NH_2, NHR, NRR, or, taken together with the atoms to which they are attached, form a 5- or 6-membered ring structure.

[0195] In certain embodiments, the compound is a compound of Formula II, wherein V_1, V_1', V_2, V_2' are all hydrogen.

[0196] In some embodiments, the compound is a compound of of Formula II, wherein E is S or O.

[0197] In more specific embodiments, E is S.

[0198] In even more specific embodiments, the compound is:

N-Phenyl-4-(4-pyridinyl)-1,3-thiazol-2-amine,

N-(3-Methylphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine,

N-(3-Ethylphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine,

N-(3-Isopropylphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine,
N-(3-*tert*-Butylphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine,
3-{[4-(4-Pyridinyl)-1,3-thiazol-2-yl]amino}phenol,
N-(3-Methoxyphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine,
N-(3-Chlorophenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine,
4-(4-Pyridinyl)-*N*-[3-(trifluoromethyl)phenyl]-1,3-thiazol-2-amine,
N-(4-Methylphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine,
2-(4-{[4-(4-Pyridinyl)-1,3-thiazol-2-yl]amino}phenyl)ethanol,
4-{[4-(4-Pyridinyl)-1,3-thiazol-2-yl]amino}phenol,
N-(4-Methoxyphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine,
N-{4-[2-(Dimethylamino)ethoxy]phenyl}-4-(4-pyridinyl)-1,3-thiazol-2-amine,
N-(4-Chlorophenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine,
N-(4-Fluorophenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine,
N-(4-Nitrophenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine,
N-{4-[2-(Dimethylamino)ethyl]phenyl}-4-(4-pyridinyl)-1,3-thiazol-2-amine,
N^1-[4-(4-Pyridinyl)-1,3-thiazol-2-yl]-1,4-benzenediamine,
3-{[4-(4-Pyridinyl)-1,3-thiazol-2-yl]amino}phenyl Dihydrogen Phosphate,
4-{[4-(4-Pyridinyl)-1,3-thiazol-2-yl]amino}phenyl Dihydrogen Phosphate,
N-(3,4-Dimethylphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine,
N-(3,5-Dimethylphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine,
N-(2,3-Dihydro-1*H*-inden-5-yl)-4-(4-pyridinyl)-1,3-thiazol-2-amine,
2-Methyl-5-{[4-(4-pyridinyl)-1,3-thiazol-2-yl]amino}phenol,
2-Methoxy-5-{[4-(4-pyridinyl)-1,3-thiazol-2-yl]amino}phenol,
2-Methyl-4-{[4-(4-pyridinyl)-1,3-thiazol-2-yl]amino}phenol,
N-(3,4-Dimethoxyphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine,
N-(3,5-Dimethoxyphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine,
N-(1,3-Benzodioxol-5-yl)-4-(4-pyridinyl)-1,3-thiazol-2-amine,
N-(3,4-Dichlorophenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine,
4-(4-Pyridinyl)-*N*-(3,4,5-trimethoxyphenyl)-1,3-thiazol-2-amine,
N-(3-Methylphenyl)-4-(3-pyridinyl)-1,3-thiazol-2-amine,
4-{[4-(3-Pyridinyl)-1,3-thiazol-2-yl]amino}phenol,
N-(3-Methylphenyl)-4-(2-pyridinyl)-1,3-thiazol-2-amine,

4-{[4-(2-Pyridinyl)-1,3-thiazol-2-yl]amino}phenol,
5-Methyl-*N*-(3-methylphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine,
N-(2,3-Dihydro-1*H*-inden-5-yl)-5-methyl-4-(4-pyridinyl)-1,3-thiazol-2-amine,
[2-(Phenylamino)-4-(4-pyridinyl)-1,3-thiazol-5-yl]methanol,
[2-[(3-Methylphenyl)amino]-4-(4-pyridinyl)-1,3-thiazol-5-yl]methanol,
[2-[(4-Methylphenyl)amino]-4-(4-pyridinyl)-1,3-thiazol-5-yl]methanol,
[2-(2,3-Dihydro-1*H*-inden-5-ylamino)-4-(4-pyridinyl)-1,3-thiazol-5-yl]methanol,
2-[(3-Methylphenyl)amino]-4-(4-pyridinyl)-1,3-thiazole-5-carbaldehyde,
Methyl (2*E*)-3-[2-[(3-Methylphenyl)amino]-4-(4-pyridinyl)-1,3-thiazol-5-yl]-2-propenoate,
Methyl 3-[2-[(3-Methylphenyl)amino]-4-(4-pyridinyl)-1,3-thiazol-5-yl]propanoate,
3-[2-[(3-Methylphenyl)amino]-4-(4-pyridinyl)-1,3-thiazol-5-yl]-1-propanol,
N-(3-Methylphenyl)-5-[3-(4-morpholinyl)propyl]-4-(4-pyridinyl)-1,3-thiazol-2-amine,
5-[(Dimethylamino)methyl]-*N*-(3-methylphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine,
5-[(Diethylamino)methyl]-*N*-(3-methylphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine,
N-(3-Methylphenyl)-5-(1-piperidinylmethyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine,
N-(3-Methylphenyl)-5-(4-morpholinylmethyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine,
Ethyl 2-[(3-methylphenyl)amino]-4-(4-pyridinyl)-1,3-thiazole-5-carboxylate,
Ethyl 2-(2,3-dihydro-1*H*-inden-5-ylamino)-4-(4-pyridinyl)-1,3-thiazole-5-carboxylate,
2-[(3-Methylphenyl)amino]-4-(4-pyridinyl)-1,3-thiazole-5-carboxamide,
N,*N*-Dimethyl-2-[(3-methylphenyl)amino]-4-(4-pyridinyl)-1,3-thiazole-5-carboxamide,
N-[2-(Dimethylamino)ethyl]-2-[(3-methylphenyl)amino]-4-(4-pyridinyl)-1,3-thiazole-5-carboxamide,
2-[(3-Methylphenyl)amino]-*N*-[3-(4-morpholinyl)propyl]-4-(4-pyridinyl)-1,3-thiazole-5-carboxamide,
N-Methyl-*N*-(3-methylphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine,
N-Ethyl-*N*-(3-methylphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine,

2-{3-Methyl[4-(4-pyridinyl)-1,3-thiazol-2-yl]anilino}ethanol,
N-[4-(4-Pyridinyl)-1,3-thiazol-2-yl]benzamide,
3-Methyl-*N*-[4-(4-pyridinyl)-1,3-thiazol-2-yl]benzamide,
4-Methyl-*N*-[4-(4-pyridinyl)-1,3-thiazol-2-yl]benzamide,
4-Methoxy-*N*-[4-(4-pyridinyl)-1,3-thiazol-2-yl]benzamide,
N-(3-Methylbenzyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine,
N-(3-Methylphenyl)-4-(4-pyridinyl)-1,3-oxazol-2-amine,
2-{[4-(4-Pyridinyl)-1,3-thiazol-2-yl]amino}phenol,
N-(2-Methoxyphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine,
N-(2-Methylphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine,
N-(2-Fluorophenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine,
N-[2-Chlorophenyl]-4-(4-pyridinyl)-1,3-thiazol-2-amine,
4-(4-Pyridinyl)-*N*-[2-(trifluoromethyl)phenyl]-1,3-thiazol-2-amine,
N-[2-Nitrophenyl]-4-(4-pyridinyl)-1,3-thiazol-2-amine,
N-(3-Fluorophenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine,
N-(3-Bromophenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine,
1-(3-{[4-(4-Pyridinyl)-1,3-thiazol-2-yl]amino}phenyl)ethanone,
3-{[4-(4-Pyridinyl)-1,3-thiazol-2-yl]amino}benzonitrile,
N-(3-Nitrophenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine,
1-(4-{[4-(4-Pyridinyl)-1,3-thiazol-2-yl]amino}phenyl)ethanone,
4-(4-Pyridinyl)-*N*-[4-(trifluoromethyl)phenyl]-1,3-thiazol-2-amine,
4-{[4-(4-Pyridinyl)-1,3-thiazol-2-yl]amino}benzonitrile,
N-(2,6-Dimethylphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine,
N-(2,6-Difluorophenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine,
N-{4-[2-(Methyloxy)-4-pyridinyl]-1,3-thiazol-2-yl}-*N*-(3-methylphenyl)amine,
N-(3-Methylphenyl)-4-(2-methyl-4-pyridinyl)-1,3-thiazol-2-amine,
4-(2-Fluoro-4-pyridinyl)-*N*-(3-methylphenyl)-1,3-thiazol-2-amine,
4-(2-Chloro-4-pyridinyl)-*N*-(3-methylphenyl)-1,3-thiazol-2-amine,
4-(2-Bromo-4-pyridinyl)-*N*-(3-methylphenyl)-1,3-thiazol-2-amine,
N-[4-(2,6-Dichloro-4-pyridinyl)-1,3-thiazol-2-yl]-*N*-(3-methylphenyl)amine,
4-(2-Ethynyl-4-pyridinyl)-*N*-(3-methylphenyl)-1,3-thiazol-2-amine,
4-(2-Ethyl-4-pyridinyl)-*N*-(3-methylphenyl)-1,3-thiazol-2-amine,

3-(4-{2-[(3-Methylphenyl)amino]-1,3-thiazol-4-yl}-2-pyridinyl)-2-propyn-1-ol,
3-(4-{2-[(3-Methylphenyl)amino]-1,3-thiazol-4-yl}-2-pyridinyl)-1-propanol,
N-(3-Methylphenyl)-4-(3-methyl-4-pyridinyl)-1,3-thiazol-2-amine,
4-(3-Fluoro-4-pyridinyl)-*N*-(3-methylphenyl)-1,3-thiazol-2-amine,
4-(3-Chloro-4-pyridinyl)-*N*-(3-methylphenyl)-1,3-thiazol-2-amine,
4-(3-Bromo-4-pyridinyl)-*N*-(3-methylphenyl)-1,3-thiazol-2-amine,
N-(3-Methylphenyl)-4-(2-nitro-4-pyridinyl)-1,3-thiazol-2-amine,
N-[4-(2-Amino-4-pyridinyl)-1,3-thiazol-2-yl]-*N*-(3-methylphenyl)amine,
N-(4-{2-[(3-Methylphenyl)amino]-1,3-thiazol-4-yl}-2-pyridinyl)acetamide,
4-(3-Ethynyl-4-pyridinyl)-*N*-(3-methylphenyl)-1,3-thiazol-2-amine,
4-(3-Ethyl-4-pyridinyl)-*N*-(3-methylphenyl)-1,3-thiazol-2-amine,
3-(4-{2-[(3-Methylphenyl)amino]-1,3-thiazol-4-yl}-3-pyridinyl)-2-propyn-1-ol,
3-(4-{2-[(3-Methylphenyl)amino]-1,3-thiazol-4-yl}-3-pyridinyl)-1-propanol,
N-(3-Methylphenyl)-4-(1-oxido-4-pyridinyl)-1,3-thiazol-2-amine,
N-(3-Methylphenyl)-4-(4-quinolinyl)-1,3-thiazol-2-amine,
N-(3-Methylphenyl)-4-(2-phenyl-4-quinolinyl)-1,3-thiazol-2-amine,
N-(3-Methylphenyl)-4-(4-pyridinyl)-1*H*-imidazol-2-amine,
N-(3-Methylphenyl)-4-[2-(4-morpholinyl)-4-pyridinyl]-1,3-thiazol-2-amine,
N-(3-Methylphenyl)-4-[2-(4-methyl-1-piperazinyl)-4-pyridinyl]-1,3-thiazol-2-amine, or
N,*N*-Dimethyl-4-{2-[(3-methylphenyl)amino]-1,3-thiazol-4-yl}-2-pyridinamine.

[0199] In certain embodiments, the disease treated or prevented according to the methods of the invention is a disease caused by a defect in the von Hippel-Lindau gene.

[0200] In some embodiments, the compounds of the invention target cells deficient in the von Hippel-Lindau gene.

[0201] In some embodiments, the compounds of the invention induce autophagic cell death.

[0202] In certain embodiments, the disease treated or prevented according to the methods of the invention is cancer.

[0203] In more specific embodiments, the cancer is a renal cell carcinoma, such as a clear cell-RCC, a pheochromocytoma, a hemangioblastoma of the central nervous system or retina, an endolymphatic sac tumor, a renal cyst, a pancreatic cyst, a neuroendocrine tumor, an endolymphatic sac tumor, or an epididymal or broad ligament cystadenoma.

[0204] In some embodiments, the tumors treated or prevented according to the methods of the invention are tumors of the retina, brain, spinal cord, ear, epidymis, broad ligament, adrenal gland, kidney, or pancreas.

[0205] The host receiving treatment according to the disclosed methods is any mammal in need of such treatment. Such mammals include, *e.g.*, humans, ovines, bovines, equines, porcines, canines, felines, non-human primate, mice, and rats. In certain specific embodiments, the host is a human. In certain other specific embodiments, the host is a non-human mammal. In some embodiments, the host is a farm animal. In other embodiments, the host is a pet.

[0206] By "therapeutically-effective amount" is meant the concentration of a compound that is sufficient to elicit the desired therapeutic effect (*e.g.*, treatment or prevention of a disease). It is generally understood that the effective amount of the compound will vary according to the weight, gender, age, and medical history of the host. Other factors that influence the effective amount may include, but are not limited to, the severity of the patient's condition, the disorder being treated, the stability of the compound, and, if desired, another type of therapeutic agent being administered with the compound of the invention. A larger total dose may be delivered by multiple administrations of the agent. Methods to determine efficacy and dosage are known to those skilled in the art. See, *e.g.*, Roden, *Harrison's Principles of Internal Medicine*, Ch. 3, McGraw-Hill, 2004.

[0207] Actual dosage levels of the active ingredients in the pharmaceutical compositions of the invention may be varied so as to obtain an amount of the active ingredient that is effective to achieve the desired therapeutic response for a particular patient, composition, and mode of administration, without being toxic to the patient.

[0208] A physician or veterinarian having ordinary skill in the art can readily determine and prescribe the effective amount of the pharmaceutical composition

required. For example, the physician or veterinarian could start doses of the compounds of the invention employed in the pharmaceutical composition at levels lower than that required in order to achieve the desired therapeutic effect and gradually increase the dosage until the desired effect is achieved.

[0209] In general, a suitable daily dose of a compound of the invention will be that amount of the compound that is the lowest dose effective to produce a therapeutic effect. Such an effective dose will generally depend upon the factors described above.

[0210] If desired, the effective daily dose of the active compound may be administered as one, two, three, four, five, six, or more sub-doses administered separately at appropriate intervals throughout the day, optionally, in unit dosage forms. In certain embodiments of the present invention, the active compound may be administered two or three times daily. In specific embodiments, the active compound is administered once daily.

[0211] The preferred frequency of administration and effective dosage will vary from one individual to another and will depend upon the particular disease being treated and may be determined by one skilled in the art. However, it is contemplated that effective dosages of the inventive inhibitors may range from as low as about 1 mg per day to as high as about 1000 mg per day, including all intermediate dosages therebetween. More preferably, effective dosages may range from about 10 mg per day to about 100 mg per day, including all intermediate dosages therebetween. The inventive compositions may be administered in a single dosage, or in multiple, divided dosages.

[0212] As described above, the methods methods of the invention may in some embodiments be used for treating or preventing cancer. Such methods may, in certain embodiments, further comprise administration of a chemotherapeutic agent. Chemotherapeutic agents that may be coadministered with compounds and pharmaceutical compositions of the instant invention include: alemtuzumab, aminoglutethimide, amsacrine, anastrozole, asparaginase, bcg, bevacizumab, bicalutamide, bleomycin, bortezomib, buserelin, busulfan, campothecin, capecitabine, carboplatin, carmustine, CeaVac, cetuximab, chlorambucil, cisplatin, cladribine, clodronate, colchicine, cyclophosphamide, cyproterone, cytarabine,

dacarbazine, daclizumab, dactinomycin, daunorubicin, dienestrol, diethylstilbestrol, docetaxel, doxorubicin, edrecolomab, epirubicin, epratuzumab, erlotinib, estradiol, estramustine, etoposide, everolimus, exemestane, filgrastim, fludarabine, fludrocortisone, fluorouracil, fluoxymesterone, flutamide, gemcitabine, gemtuzumab, genistein, goserelin, huJ591, hydroxyurea, ibritumomab, idarubicin, ifosfamide, IGN-101, imatinib, interferon, interleukin-2, irinotecan, ironotecan, letrozole, leucovorin, leuprolide, levamisole, lintuzumab, lomustine, MDX-210, mechlorethamine, medroxyprogesterone, megestrol, melphalan, mercaptopurine, mesna, methotrexate, mitomycin, mitotane, mitoxantrone, mitumomab, nilutamide, nocodazole, octreotide, oxaliplatin, paclitaxel, pamidronate, pentostatin, pertuzumab, plicamycin, porfimer, procarbazine, raltitrexed, rituximab, sorafinib, streptozocin, sunitinib, suramin, tamoxifen, temozolomide, temsirolimus, teniposide, testosterone, thalidomide, thioguanine, thiotepa, titanocene dichloride, topotecan, tositumomab, trastuzumab, tretinoin, vatalanib, vinblastine, vincristine, vindesine, and vinorelbine.

[0213] Other useful chemotherapeutic agents for combination with the compounds of the present invention include MDX-010; MAb, AME; ABX-EGF; EMD 72 000; apolizumab; labetuzumab; ior-t1; MDX-220; MRA; H-11 scFv; Oregovomab; huJ591 MAb, BZL; visilizumab; TriGem; TriAb; R3; MT-201; G-250, unconjugated; ACA-125; Onyvax-105; CDP-860; BrevaRex MAb; AR54; IMC-1C11 ;GlioMAb-H; ING-1; Anti-LCG MAbs; MT-103; KSB-303; Therex; KW-2871; Anti-HMI.24; Anti-PTHrP; 2C4 antibody; SGN-30; TRAIL-RI MAb, CAT; Prostate cancer antibody; H22xKi-4; ABX-MA1; Imuteran; and Monopharm-C.

[0214] These chemotherapeutic agents may be categorized by their mechanism of action into, for example, the following groups: anti-metabolites/anti-cancer agents, such as pyrimidine analogs (*e.g.*, 5-fluorouracil, floxuridine, capecitabine, gemcitabine and cytarabine) and purine analogs, folate antagonists and related inhibitors (*e.g.*, mercaptopurine, thioguanine, pentostatin and 2-chlorodeoxyadenosine (cladribine)); antiproliferative/antimitotic agents including natural products such as vinca alkaloids (*e.g.*, vinblastine, vincristine, and vinorelbine), microtubule disruptors such as taxane (paclitaxel, docetaxel),

vincristin, vinblastin, nocodazole, epothilones and navelbine, epidipodophyllotoxins (teniposide), DNA damaging agents (*e.g.*, actinomycin, amsacrine, anthracyclines, bleomycin, busulfan, camptothecin, carboplatin, chlorambucil, cisplatin, cyclophosphamide, cytoxan, dactinomycin, daunorubicin, docetaxel, doxorubicin, epirubicin, hexamethylmelamineoxaliplatin, iphosphamide, melphalan, merchlorethamine, mitomycin, mitoxantrone, nitrosourea, paclitaxel, plicamycin, procarbazine, teniposide, triethylenethiophosphoramide and etoposide (VP16)); antibiotics such as dactinomycin (actinomycin D), daunorubicin, doxorubicin (adriamycin), idarubicin, anthracyclines, mitoxantrone, bleomycins, plicamycin (mithramycin) and mitomycin; enzymes (*e.g.*, L-asparaginase, which systemically metabolizes L-asparagine and deprives cells which do not have the capacity to synthesize their own asparagine); antiplatelet agents; antiproliferative/antimitotic alkylating agents such as nitrogen mustards (*e.g.*, mechlorethamine, cyclophosphamide and analogs, melphalan, chlorambucil), ethylenimines and methylmelamines (*e.g.*, hexamethylmelamine and thiotepa), alkyl sulfonates-busulfan, nitrosoureas (*e.g.*, carmustine (BCNU) and analogs, streptozocin), trazenes - dacarbazinine (DTIC); antiproliferative/antimitotic antimetabolites such as folic acid analogs (*e.g.*, methotrexate); platinum coordination complexes (*e.g.*, cisplatin, carboplatin), procarbazine, hydroxyurea, mitotane, aminoglutethimide; hormones, hormone analogs (*e.g.*, estrogen, tamoxifen, goserelin, bicalutamide, nilutamide) and aromatase inhibitors (*e.g.*, letrozole, anastrozole); anticoagulants (*e.g.*, heparin, synthetic heparin salts and other inhibitors of thrombin); fibrinolytic agents (such as tissue plasminogen activator, streptokinase and urokinase), aspirin, COX-2 inhibitors, dipyridamole, ticlopidine, clopidogrel, abciximab; antimigratory agents; antisecretory agents (*e.g.*, breveldin); immunosuppressives (*e.g.*, cyclosporine, tacrolimus (FK-506), sirolimus (rapamycin), azathioprine, mycophenolate mofetil); anti-angiogenic compounds (*e.g.*, TNP-470, genistein) and growth factor inhibitors (*e.g.*, vascular endothelial growth factor (VEGF) inhibitors, fibroblast growth factor (FGF) inhibitors, epidermal growth factor (EGF) inhibitors); angiotensin receptor blocker; nitric oxide donors; anti-sense oligonucleotides; antibodies (*e.g.*, trastuzumab and others listed above); cell cycle inhibitors and differentiation

inducers (*e.g.*, tretinoin); mTOR inhibitors, topoisomerase inhibitors (*e.g.*, doxorubicin (adriamycin), amsacrine, camptothecin, daunorubicin, dactinomycin, eniposide, epirubicin, etoposide, idarubicin, irinotecan (CPT-11) and mitoxantrone, topotecan, irinotecan), corticosteroids (*e.g.*, cortisone, dexamethasone, hydrocortisone, methylpednisolone, prednisone, and prenisolone); growth factor signal transduction kinase inhibitors; mitochondrial dysfunction inducers and caspase activators; chromatin disruptors.

[0215] The pharmaceutical compositions of the instant invention may be coadministered with chemotherapeutic agents either singly or in combination.

[0216] Combination therapies comprising the inhibitors of the instant invention and a conventional chemotherapeutic agent may be advantageous over combination therapies known in the art because the combination allows the conventional chemotherapeutic agent to exert greater effect at lower dosage. In a specific embodiment, the effective dose (ED_{50}) for a chemotherapeutic agent, or combination of conventional chemotherapeutic agents, when used in combination with an epoxide inhibitor of the instant invention is at least 2 fold less than the ED_{50} for the chemotherapeutic agent alone, and even more preferably at 5-fold, 10-fold, or even 25-fold less. Conversely, the therapeutic index (TI) for such chemotherapeutic agent or combination of such chemotherapeutic agent when used in combination with an epoxide inhibitor of the instant invention can be at least 2-fold greater than the TI for conventional chemotherapeutic regimen alone, and even more preferably at 5-fold, 10-fold, or even 25-fold greater.

[0217] In another aspect, the compounds and pharmaceutical compositions may be administered in combination with radiation therapy.

[0218] It will be readily apparent to one of ordinary skill in the relevant arts that other suitable modifications and adaptations to the methods and applications described herein may be made without departing from the scope of the invention or any embodiment thereof. Having now described the present invention in detail, the same will be more clearly understood by reference to the following Examples, which are included herewith for purposes of illustration only and are not intended to be limiting of the invention.

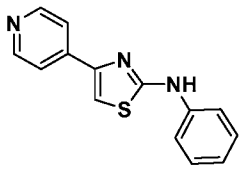
EXAMPLES

Synthetic Reactions

[0219] Analyses were carried out in the Campbell Microanalytical Laboratory, University of Otago, Dunedin, NZ. Melting points were determined on an Electrothermal 2300 Melting Point Apparatus. NMR spectra were obtained on a Bruker Avance 400 spectrometer at 400 MHz for ^{1}H and 100 MHz for ^{13}C spectra. Spectra were obtained in [$(CD_3)_2SO$] unless otherwise specified, and were referenced to Me_4Si. Chemical shifts and coupling constants were recorded in units of ppm and Hz, respectively. Assignments were determined using COSY, HSQC, and HMBC two-dimensional experiments. Low resolution mass spectra were gathered by direct injection of methanolic solutions into a Surveyor MSQ mass spectrometer using an atmospheric pressure chemical ionization (APCI) mode with a corona voltage of 50 V and a source temperature of 400 °C. Solutions in organic solvents were dried with anhydrous $MgSO_4$. Solvents were evaporated under reduced pressure on a rotary evaporator. Thin-layer chromatography was carried out on aluminium-backed silica gel plates (Merck 60 F_{254}) with visualization of components by UV light (254 nm) or exposure to I_2. Column chromatography was carried out on silica gel (Merck 230-400 mesh). DCM refers to dichloromethane; DME refers to dimethoxyethane, DMF refers to dry *N,N*-dimethylformamide; Et_2O refers to diethyl ether; EtOAc refers to ethyl acetate; EtOH refers to ethanol; MeOH refers to methanol; pet. ether refers to petroleum ether, boiling range 40-60 °C; THF refers to tetrahydrofuran dried over sodium benzophenone ketyl.

Example 1-1

***N*-Phenyl-4-(4-pyridinyl)-1,3-thiazol-2-amine (3).**



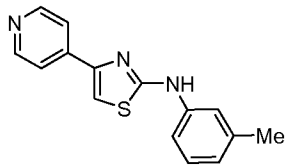
[0220] **2-Bromo-1-(pyridin-4-yl)ethanone Hydrobromide (1).** Br_2 (4.45 mL, 86.7 mmol) was added dropwise to a stirred a solution of 4-acetylpyridine (10.0 g, 82.5 mmol) in 30% HBr/HOAc (100 mL) at 0–5 °C. The mixture was stirred at 40 °C for 1 h and then 75 °C for 1 h. The mixture was cooled to 20 °C, diluted with

Et_2O (400 mL) and stirred for 30 min. The precipitate was filtered, washed with Et_2O (25 mL) and dried under vacuum to give the hydrobromide salt **1** (22.39 g, 97%) as a cream powder: mp (HOAc/ether) 190–195 °C [lit. (Ogawa, K. *J. Chem. Soc Perkin 1.* 1985, 2417) mp 197–200 °C]; ^{1}H NMR δ 9.02 (br d, J = 5.5 Hz, 2 H, H-2′, H-6′), 8.71 (br s, 1 H, N·HBr), 8.15 (br d, J = 5.5 Hz, 2 H, H-3′, H-5′), 5.06 (s, 2 H, CH_2Br).

[0221] ***N*-Phenyl-4-(4-pyridinyl)-1,3-thiazol-2-amine (3).** A mixture of bromoketone hydrobromide **1** (0.91 g, 3.24 mmol) and phenylthiourea **2** (0.49 g, 3.24 mmol) in EtOH (20 mL) was stirred at reflux temperature for 2 h. The mixture was cooled to 20 °C, diluted with water (50 mL), the pH adjusted to ca. 8 with aqueous NH_3 and the mixture stirred at 20 °C for 2 h. The precipitate was filtered, washed with water (5 mL) and dried to give amine **3** (0.77 g, 94%) as a white powder: mp (H_2O) 222–225 °C [lit. (Westphal, G. *J. Prakt. Chem.* 1976, *318*, 875) mp (EtOH) 222 °C]; ^{1}H NMR δ 10.45 (br s, 1 H, NH), 8.75 (dd, J = 5.1, 1.4 Hz, 2 H, H-2′, H-6′), 8.15 (dd, J = 5.1, 1.4 Hz, 2 H, H-3′, H-5′), 8.01 (s, 1 H, H-5), 7.74 (dd, J = 8.5, 0.9 Hz, 2 H, H-2″, H-6″) 7.37 (br dd, J = 8.5, 7.4 Hz, 2 H, H-3″, H-5″), 6.99 (br t, J = 7.4 Hz, 1 H, H-4″); ^{13}C NMR δ 163.6, 146.4, 146.0, 144.8, 140.7 (2), 128.9 (2), 121.6, 121.0 (2), 117.0 (2), 111.5; MS *m/z* 254.4 (MH^+, 100%).

Example 1-2

***N*-(3-Methylphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (5).**



[0222] **3-Methylphenylthiourea (4).** NH_4SCN (3.55 g, 46.7 mmol) was added to a stirred solution of *m*-toluidine (5.00 g, 46.7 mmol) in 1 M HCl (47 mL) at 100 °C and the solution stirred at 100 °C for 16 h. The solution was diluted with water (60 mL) and stood at 5 °C for 2 h. The precipitate was filtered, washed with water (5 mL), washed with ether (5 mL), and dried to give thiourea **4** (3.21 g, 41%) as a white powder: mp (H_2O) 95–97 °C [lit. (Rasmussen, C. R. et al., *Synthesis* 1988,

456) mp (MeOH) 110–113 °C]; ^{1}H NMR δ 9.58 (s, 1 H, NH), 7.38 (br s, 2 H, NH_2), 7.15–7.23 (m, 3 H, H-2, H-4, H-5), 6.93 (br d, J = 6.9 Hz, 1 H, H-6), 2.30 (s, 3 H, CH_3).

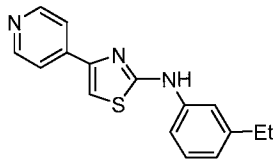
[0223] Alternative Preparation of 3-Methylphenylthiourea (4). Benzoyl chloride (7.5 mL, 64.7 mmol) was added dropwise to a solution of NH_4SCN (5.28 g, 69.3 mmol) in dry acetone (30 mL). The mixture was stirred at reflux temperature for 15 min. The heating was removed and *m*-toluidine (5.0 mL, 46.2 mmol) was added dropwise keeping the solution at reflux. The mixture was stirred at reflux temperature for a further 30 min, cooled to 20 °C and poured onto ice. The mixture was stirred for 30 min and then the precipitate was filtered and washed with water (15 mL) and dried. The solid was added to a solution of NaOH (10% w/v, 100 mL) at 80 °C and stirred at 80 °C for 30 min, then cooled to 20 °C and poured onto ice/HCl (6 M, 50 mL). The pH of the mixture was adjusted to 10 with cNH_3 solution and stirred for 30 min. The precipitate was filtered and washed with water (20 mL) and dried. The precipitate was purified by column chromatography, eluting with a gradient (30–100%) of EtOAc/pet. ether, to give thiourea **4** (6.62 g, 86%) as a white powder: mp (EtOAc) 109–111 °C [lit. (Rasmussen, C. R. et al., *Synthesis* 1988, 456) mp (MeOH) 110–113 °C]; ^{1}H NMR δ 9.58 (s, 1 H, NH), 7.38 (br s, 2 H, NH_2), 7.15–7.23 (m, 3 H, H-2, H-4, H-5), 6.93 (br d, J = 6.9 Hz, 1 H, H-6), 2.30 (s, 3 H, CH_3).

[0224] *N*-(3-Methylphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (5) ("STF-62247"). A mixture of bromoketone hydrobromide **1** (1.13 g, 4.03 mmol) and 3-methylphenylthiourea **4** (0.67 g, 4.03 mmol) in EtOH (20 mL) was stirred at reflux temperature for 3 h. The mixture was cooled to 20 °C, diluted with water (50 mL), the pH adjusted to ca. 8 with aqueous NH_3 and the mixture stirred at 20 °C for 2 h. The precipitate was filtered, washed with water (5 mL) and dried. The crude solid was purified by column chromatography, eluting with a gradient (50–100%) of EtOAc/pet. ether, to give amine **5** (0.94 g, 87%) as a cream powder: mp (EtOAc/pet. ether) 158–160 °C; ^{1}H NMR δ 10.27 (br s, 1 H, NH), 8.62 (dd, J = 4.6, 1.6 Hz, 2 H, H-2′, H-6′), 7.84 (dd, J = 4.6, 1.6 Hz, 2 H, H-3′, H-5′), 7.69 (s, 1

H, H-5), 7.57 (br d, J = 7.9 Hz, 1 H, H-6″), 7.47 (br s, 1 H, H-2″), 7.24 (dd, J = 7.8, 7.5 Hz, 1 H, H-5″), 6.81 (br d, J = 7.5 Hz, 1 H, H-4″), 2.33 (s, 3 H, CH_3); ^{13}C NMR δ 163.5, 150.1 (2), 147.6, 140.9, 140.8, 138.1, 128.8, 122.2, 119.8 (2), 117.5, 114.1, 107.2, 21.2; MS *m/z* 268.4 (MH^+, 100%). Anal. calcd for $C_{15}H_{13}N_3S \cdot ¼H_2O$: C, 66.27; H, 5.01; N, 15.46. Found: C, 64.48; H, 5.08; N, 15.08%.

Example 1-3

***N*-(3-Ethylphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (7).**



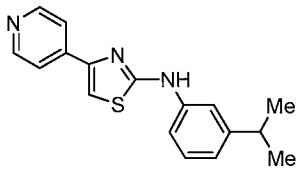
[0225] 3-Ethylphenylthiourea (6). Benzoyl chloride (3.9 mL, 33.8 mmol) was added dropwise to a stirred solution of NH_4SCN (2.76 g, 36.2 mmol) in acetone (50 mL). The mixture was stirred at reflux temperature for 15 mins, the heating was removed and 3-ethylaniline (3.0 mL, 24.1 mmol) was added dropwise, keeping the solution at reflux temperature. The mixture was stirred at reflux temperature for 30 min, then poured onto ice (50 mL) and stirred for 15 min. The resulting mixture was filtered and washed with water (5 mL), and dried. The solid was added to a stirred solution of NaOH (10% w/v, 80 mL) at 80 °C. The solution was stirred at 80 °C for 30 mins and then poured onto ice/HCl (6 M, 30 mL) and stirred for 10 mins. The pH was adjusted to 10 with cNH_3 solution, the resulting precipitate filtered and washed with water (10 mL) and dried. The crude solid was purified by column chromatography, eluting with a gradient (20–50%) of EtOAc/pet. ether, to give thiourea **6** (2.73 g, 63%) as an white powder: mp (EtOAc) 82–83 °C; ^1H NMR δ 9.60 (s, 1 H, NH), 7.42 (br s, 2 H, NH_2), 7.19–7.24 (m, 3 H, H-2, H-5, H-6), 6.95–6.99 (m, 1 H, H-4), 2.58 (q, J = 7.4 Hz, 2 H, CH_2), 1.17 (t, J = 7.4 Hz, 3 H, CH_3); MS *m/z* 181.5 (MH^+, 100%). Anal. calcd for $C_9H_{12}N_2S$: C, 59.96; H, 6.71; N, 15.54. Found: C, 60.09; H, 6.97; N, 15.59%.

[0226] *N*-(3-Ethylphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (7). A mixture of bromoketone hydrobromide **1** (0.47 g, 1.7 mmol) and 3-ethylphenylthiourea (**6**) (0.30 g, 1.7 mmol) in EtOH (30 mL) was stirred at reflux temperature for 2 h. The

mixture was cooled to 20 °C, diluted with water (50 mL), the pH adjusted to ca. 8 with aqueous NH_3 and the mixture stirred at 0 °C for 2 h. The precipitate was filtered, washed with water (5 mL) and dried. The crude solid was purified by column chromatography, eluting with a gradient (50–80%) of EtOAc/pet. ether, to give amine **7** (0.45 g, 95%) as a cream powder: mp (EtOAc/pet. ether) 172–174 °C; ^{1}H NMR δ 10.28 (s, 1 H, NH), 8.62 (dd, *J* = 4.5, 1.6 Hz, 2 H, H-2′, H-6′), 7.84 (dd, *J* = 4.5, 1.6 Hz, 2 H, H-3′, H-5′), 7.68 (s, 1 H, H-5), 7.53–7.57 (m, 2 H, H-2″, H-6″), 7.26 (dd, *J* = 8.0, 7.6 Hz, 1 H, H-5″), 6.85 (br d, *J* = 7.6 Hz, 1 H, H-4″), 2.62 (q, *J* = 7.6 Hz, 2 H, CH_2), 1.22 (t, *J* = 7.6 Hz, 3 H, CH_3); ^{13}C NMR δ 163.5, 150.0 (2), 147.6, 144.4, 141.0, 140.9, 128.8, 121.0, 119.7 (2), 116.3, 114.4, 107.2, 28.2, 15.2; MS *m/z* 282.5 (MH^+, 100%). Anal. calcd for $C_{16}H_{15}N_3S$: C, 68.30; H, 5.37; N, 14.93. Found: C, 68.53; H, 5.52; N, 14.92%.

Example 1-4

***N*-(3-Isopropylphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (9).**



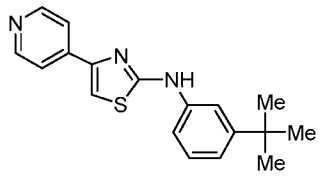
[0227] 3-Isopropylphenylthiourea (8). NH_4SCN (2.40 g, 31.7 mmol) was added to a stirred solution of 3-isopropylaniline (4.28 g, 31.7 mmol) in 1 M HCl (32 mL) at 100 °C and the solution stirred at 100 °C for 16 h. The solution was diluted with water (60 mL) and stood at 5 °C for 2 h. The precipitate was filtered, washed with water (5 mL), washed with ether (5 mL), and dried. The crude solid was purified by column chromatography, eluting with EtOAc, to give thiourea **8** (1.38 g, 22%) as an oil: ^{1}H NMR δ 9.60 (s, 1 H, NH), 7.35 (br s, 2 H, NH_2), 7.19–7.26 (m, 3 H, H-2, H-4, H-5), 7.00 (dt, *J* = 4.5, 1.6 Hz, 1 H, H-6), 2.86 (sept, *J* = 6.9 Hz, 1 H, CH), 1.19 (d, *J* = 6.9 Hz, 6 H, 2 × CH_3); MS *m/z* 195.5 (MH^+, 100%). Anal. calcd for $C_{10}H_{14}N_2S \cdot ¼H_2O$: C, 60.42; H, 7.35; N, 14.09. Found: C, 60.41; H, 7.22; N, 13.85%.

[0228] *N*-(3-Isopropylphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (9). A mixture of bromoketone hydrobromide **1** (0.92 g, 3.3 mmol) and 3-

isopropylphenylthiourea (**8**) (0.64 g, 3.3 mmol) in EtOH (30 mL) was stirred at reflux temperature for 3 h. The mixture was cooled to 20 °C, diluted with water (50 mL), the pH adjusted to ca. 8 with aqueous NH_3 and the mixture stirred at 0 °C for 2 h. The precipitate was filtered, washed with water (5 mL) and dried. The crude solid was purified by column chromatography, eluting with a gradient (50–100%) of EtOAc/pet. ether, to give amine **9** (0.81 g, 84%) as a cream powder: mp (EtOAc/pet. ether) 200–202 °C; ^{1}H NMR δ 10.29 (s, 1 H, NH), 8.61 (dd, *J* = 4.5, 1.6 Hz, 2 H, H-2′, H-6′), 7.84 (dd, *J* = 4.5, 1.6 Hz, 2 H, H-3′, H-5′), 7.69 (s, 1 H, H-5), 7.64 (t, *J* = 1.8 Hz, 1 H, H-2″), 7.52 (ddd, *J* = 7.7, 2.0, 1.4 Hz, 1 H, H-6″), 7.26 (t, *J* = 7.8 Hz, 1 H, H-5″), 6.89 (br d, *J* = 7.8 Hz, 1 H, H-4″), 2.90 (sept, *J* = 6.9 Hz, 1 H, CH), 1.24 (d, *J* = 6.9 Hz, 6 H, 2 × CH_3); ^{13}C NMR δ 163.5, 150.0 (2), 149.1, 147.5, 141.0, 140.9, 128.8, 119.7, 119.6 (2), 114.8, 114.5, 107.2, 33.4, 23.7 (2); MS *m/z* 296.5 (MH^+, 100%). Anal. calcd for $C_{17}H_{17}N_3S$: C, 69.12; H, 5.80; N, 14.22. Found: C, 69.18; H, 5.92; N, 14.34%.

Example 1-5

***N*-(3-tert-Butylphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (11).**



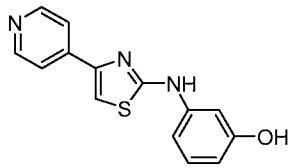
[0229] 3-tert-Butylphenylthiourea (10). Benzoyl chloride (5.4 mL, 46.9 mmol) was added dropwise to a stirred solution of NH_4SCN (3.83 g, 50.3 mmol) in acetone (50 mL). The mixture was stirred at reflux temperature for 15 mins, the heating was removed and 3-*t*-butylaniline (5.0 g, 33.5 mmol) was added dropwise, keeping the solution at reflux temperature. The mixture was stirred at reflux temperature for 30 min, then poured onto ice (50 mL) and stirred for 15 min. The resulting mixture was filtered and washed with water (5 mL), and dried. The solid was added to a stirred solution of NaOH (10% w/v, 100 mL) at 80 °C. The solution was stirred at 80 °C for 30 mins and then poured onto ice/HCl (6 M, 30 mL) and stirred for 10 mins. The pH was adjusted to 10 with cNH_3 solution, the resulting precipitate filtered and washed with water (10 mL) and dried. The crude solid was purified by column chromatography, eluting with 50% EtOAc/pet. ether, to give

thiourea **10** (6.53 g, 94%) as a gum: ^{1}H NMR ($CDCl_3$) δ 7.95 (s, 1 H, NH), 7.35–7.38 (m, 2 H, H-4, H-5), 7.23–7.25 (m, 1 H, H-2), 7.04–7.07 (m, 1 H, H-6), 6.07 (br s, 2 H, NH_2), 1.31 [s, 9 H, $C(CH_3)_3$]. Anal. calcd for $C_{11}H_{16}N_2S$: C, 63.42; H, 7.74; N, 13.45. Found: C, 63.83; H, 7.64; N, 12.81%.

[0230] ***N*-(3-*tert*-Butylphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (11).** A mixture of bromoketone hydrobromide **1** (0.56 g, 2.0 mmol) and 3-*tert*-butylphenylthiourea (**10**) (0.41 g, 2.0 mmol) in EtOH (30 mL) was stirred at reflux temperature for 2 h. The mixture was cooled to 20 °C, diluted with water (50 mL), the pH adjusted to ca. 8 with aqueous NH_3 and the mixture stirred at 0 °C for 2 h. The precipitate was filtered, washed with water (5 mL) and dried. The crude solid was purified by column chromatography, eluting with 50% EtOAc/pet. ether, to give amine **11** (0.50 g, 81%) as a cream powder: mp (EtOAc/pet. ether) 208–210 °C; ^{1}H NMR δ 10.30 (br s, 1 H, NH), 8.61 (dd, J = 4.5, 1.6 Hz, 2 H, H-2′, H-6′), 7.83–7.87 (m, 3 H, H-3′, H-5′, H-2″), 7.69 (s, 1 H, H-5), 7.48 (ddd, J = 8.0, 1.7, 0.8 Hz, 1 H, H-6″), 7.28 (dd, J = 8.0, 7.8 Hz, 1 H, H-5″), 7.02 (ddd, J = 7.8, 1.7, 0.8 Hz, 1 H, H-4″), 1.32 [s, 9 H, $C(CH_3)_3$]; ^{13}C NMR δ 163.5, 151.4, 150.0 (2), 147.5, 141.0, 140.6, 128.5, 119.7 (2), 118.4, 114.2, 114.0, 107.2, 34.4, 31.0 (3); MS *m/z* 310.5 (MH^+, 100%). Anal. calcd for $C_{18}H_{19}N_3S$: C, 69.87; H, 6.19; N, 13.58. Found: C, 69.93; H, 6.07; N, 13.57%.

Example 1-6

3-{[4-(4-Pyridinyl)-1,3-thiazol-2-yl]amino}phenol (13).



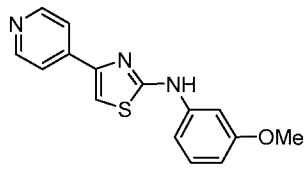
[0231] **3-Hydroxyphenylthiourea (12).** NH_4SCN (3.54 g, 46.6 mmol) was added to a stirred solution of 3-aminophenol (5.08 g, 46.6 mmol) in 1 M HCl (47 mL) at 100 °C and the solution stirred at 100 °C for 16 h. The solution was diluted with water (60 mL) and stood at 5 °C for 2 h. The precipitate was filtered, washed with water (5 mL), washed with ether (5 mL), and dried to give thiourea **12** (0.64 g, 8%) as a white powder: mp (H_2O) 172–175 °C; ^{1}H NMR δ 9.94 (s, 1 H, NH),

9.41 (br s, 1 H, OH), 7.34 (br s, 2 H, NH_2), 7.09 (t, J = 8.0 Hz, 1 H, H-5), 6.88 (t, J = 2.1 Hz, 1 H, H-2), 6.76 (ddd, J = 8.0, 1.2 Hz, 1 H, H-4), 6.52 (ddd, J = 8.1, 2.3, 0.8 Hz, 1 H, H-6).

[0232] 3-{[4-(4-Pyridinyl)-1,3-thiazol-2-yl]amino}phenol (13). A mixture of bromoketone hydrobromide **1** (1.02 g, 3.63 mmol) and 3-hydroxyphenylthiourea (**12**) (0.61 g, 3.63 mmol) in EtOH (25 mL) was stirred at reflux temperature for 3 h. The mixture was cooled to 20 °C, diluted with water (50 mL), the pH adjusted to ca. 8 with aqueous NH_3 and the mixture stirred at 5 °C for 1 h. The mixture was filtered, washed with water (5 mL) and Et_2O (5 mL) and dried to give phenol **13** (0.98 g, 99%) as a cream powder: mp (H_2O) 228–231 °C; ^{1}H NMR δ 10.26 (br s, 1 H, NH), 9.41 (br s, 1 H, OH), 8.67 (dd, J = 4.7, 1.5 Hz, 2 H, H-2″, H-6″), 7.99 (dd, J = 4.7, 1.5 Hz, 2 H, H-3″, H-5″), 7.80 (s, 1 H, H-5′), 7.35 (t, J = 2.1 Hz, 1 H, H-2), 7.12 (t, J = 8.0 Hz, 1 H, H-5), 7.13 (ddd, J = 7.9, 2.2, 0.8 Hz, 1 H, H-6), 6.41 (ddd, J = 7.9, 2.2, 0.8 Hz, 1 H, H-4); ^{13}C NMR δ 163.4, 157.8, 148.4 (2), 147.1, 142.5, 141.8, 129.5, 120.3 (2), 108.8, 108.7, 107.9, 104.1; MS *m/z* 270.3 (MH^+, 100%). Anal. calcd for $C_{14}H_{11}N_3OS \cdot 1¼H_2O$: C, 57.62; H, 4.66; N, 14.39. Found: C, 57.47; H, 4.14, N, 14.21%.

Example 1-7

***N*-(3-Methoxyphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (15).**



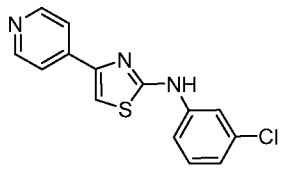
[0233] 3-Methoxyphenylthiourea (14). NH_4SCN (3.09 g, 40.6 mmol) was added to a stirred solution of *m*-anisidine (5.00 g, 40.6 mmol) in 1 M HCl (41 mL) at 100 °C and the solution stirred at 100 °C for 16 h. The solution was diluted with water (60 mL) and stood at 5 °C for 2 h. The precipitate was filtered, washed with water (5 mL), washed with ether (5 mL), and dried to give thiourea **14** (1.34 g, 18%) as a white powder: mp (H_2O) 154–157 °C [lit. (Rasmussen et al., *Synthesis* 1988, 456) mp (MeOH) 157–159 °C]; ^{1}H NMR δ 9.65 (s, 1 H, NH), 7.42 (br s, 2 H, NH_2), 7.21 (dd, J = 8.3, 7.9 Hz, 1 H, H-5), 7.12 (t, J = 2.0 Hz, 1 H, H-2), 6.91

(dd, J = 7.9, 1.3 Hz, 1 H, H-4), 6.69 (ddd, J = 8.3, 2.4, 0.6 Hz, 1 H, H-6), 3.73 (s, 3 H, OCH_3).

[0234] ***N*-(3-Methoxyphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (15).** A mixture of bromoketone hydrobromide **1** (1.02 g, 3.62 mmol) and 3-methoxyphenylthiourea (**14**) (0.66 g, 3.62 mmol) in EtOH (20 mL) was stirred at reflux temperature for 3 h. The mixture was cooled to 20 °C, diluted with water (50 mL), the pH adjusted to ca. 8 with aqueous NH_3 and the mixture stirred at 5 °C for 2 h. The precipitate was filtered, washed with water (5 mL) and dried. The crude solid was purified by column chromatography, eluting with a gradient (50-100%) of EtOAc/pet. ether, to give amine **15** (0.69 g, 68%) as a cream powder: mp (EtOAc/pet. ether) 176–178 °C; ^{1}H NMR δ 10.36 (br s, 1 H, NH), 8.62 (dd, J = 4.5, 1.6 Hz, 2 H, H-2′, H-6′), 7.84 (dd, J = 4.5, 1.6 Hz, 2 H, H-3′, H-5′), 7.71 (s, 1 H, H-5), 7.51 (t, J = 2.2 Hz, 1 H, H-2″), 7.25 (t, J = 8.1 Hz, 1 H, H-5″), 7.18 (br d, J = 8.0 Hz, 1 H, H-4″), 6.56 (br d, J = 8.0 Hz, 1 H, H-6″), 3.79 (s, 3 H, OCH_3); ^{13}C NMR δ 163.3, 159.8, 150.1 (2), 147.6, 142.0, 140.9, 129.7, 119.7 (2), 109.4, 107.5, 106.8, 102.7, 54.8; MS *m/z* 284.5 (MH^+, 100%). Anal. calcd for $C_{15}H_{13}N_3OS$: C, 63.58; H, 4.62; N, 14.83. Found: C, 63.79; H, 4.68; N, 14.87%.

Example 1-8

***N*-(3-Chlorophenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (17).**



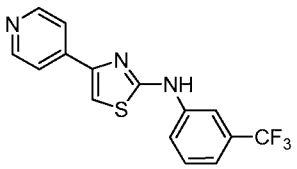
[0235] **3-Chlorophenylthiourea (16).** NH_4SCN (2.98 g, 39.2 mmol) was added to a stirred solution of 3-chloroaniline (5.00 g, 39.2 mmol) in 1 M HCl (40 mL) at 100 °C and the solution stirred at 100 °C for 16 h. The solution was diluted with water (60 mL) and stood at 5 °C for 2 h. The precipitate was filtered, washed with water (5 mL), washed with ether (5 mL), and dried to give thiourea **16** (3.63 g, 50%) as a white powder: mp (H_2O) 139–142 °C [lit. (Rasmussen, C. R. et al., *Synthesis* 1988, 456) mp (acetone/H_2O) 140–140.5 °C]; ^{1}H NMR δ 9.78 (s, 1 H,

NH), 7.78 (br s, 2 H, NH_2), 7.70 (br s, 1 H, H-2), 7.30–7.35 (m, 2 H, H-4, H-5), 7.17–7.16 (m, 1 H, H-6).

[0236] ***N*-(3-Chlorophenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (17).** A mixture of bromoketone hydrobromide **1** (1.13 g, 4.02 mmol) and 3-chlorophenylthiourea (**16**) (0.75 g, 4.02 mmol) in EtOH (20 mL) was stirred at reflux temperature for 3 h. The mixture was cooled to 20 °C, diluted with water (50 mL), the pH adjusted to ca. 8 with aqueous NH_3 and the mixture stirred at 5 °C for 2 h. The precipitate was filtered, washed with water (5 mL) and dried. The crude solid was purified by column chromatography, eluting with a gradient (50-100%) of EtOAc/pet. ether, to give amine **17** (0.95 g, 82%) as a lemon powder: mp (EtOAc/pet. ether) 208–210 °C; ^{1}H NMR δ 10.57 (br s, 1 H, NH), 8.63 (dd, J = 4.5, 1.6 Hz, 2 H, H-2′, H-6′), 7.93(t, J = 2.1 Hz, 1 H, H-2″), 7.83 (dd, J = 4.5, 1.6 Hz, 2 H, H-3′, H-5′), 7.77 (s, 1 H, H-5), 7.61 (ddd, J = 8.3, 2.0, 0.8 Hz, 1 H, H-6″), 7.38 (dd, J = 8.3, 8.0 Hz, 1 H, H-4″), 7.03 (ddd, J = 8.0, 2.0, 0.8 Hz, 1 H, H-4″); ^{13}C NMR δ 162.9, 150.1 (2), 147.6, 142.1, 140.8, 133.2, 130.6, 120.8, 119.7 (2), 116.8, 115.3, 108.3. Anal. calcd for $C_{14}H_{10}ClN_3S \cdot ¼EtOAc$: C, 58.16; H, 3.90; N, 13.56. Found: C, 58.21; H, 3.88; N, 13.78%

Example 1-9

4-(4-Pyridinyl)-*N*-[3-(trifluoromethyl)phenyl]-1,3-thiazol-2-amine (19).

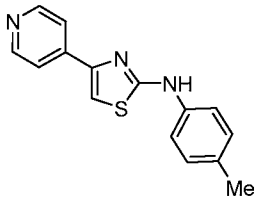


[0237] A mixture of bromoketone hydrobromide **1** (0.64 g, 2.27 mmol) and 3-trifluoromethylphenylthiourea (**18**) (0.50 g, 2.27 mmol) in EtOH (20 mL) was stirred at reflux temperature for 2 h. The mixture was cooled to 20 °C, diluted with water (50 mL), the pH adjusted to ca. 8 with aqueous NH_3 and the mixture stirred at 20 °C for 1 h. The mixture was extracted with EtOAc (2 × 50 mL) and the combined organic fraction dried and the solvent evaporated. The residue was purified by column chromatography, eluting with a gradient (50–100%) of EtOAc/pet. ether, to give amine **19** (0.66 g, 90%) as a cream powder: mp

(EtOAc/pet. ether) 239–241 °C; ^{1}H NMR δ 10.73 (br s, 1 H, NH), 8.63 (dd, *J* = 4.5, 1.6 Hz, 2 H, H-2′, H-6′), 8.30 (br s, 1 H, H-2″), 7.90 (br dd, *J* = 8.2, 1.8 Hz, 1 H, H-4″), 7.84 (dd, *J* = 4.5, 1.6 Hz, 2 H, H-3′, H-5′), 7.80 (s, 1 H, H-5), 7.59 (dd, *J* = 8.1, 7.9 Hz, 1 H, H-5″), 7.31 (d, *J* = 7.9 Hz, 1 H, H-6″); ^{13}C NMR δ 162.9, 150.1 (2), 147.5, 141.4, 140.8, 130.1, 129.6 (q, *J* = 31 Hz), 124.4 (q, *J* = 272 Hz), 120.3, 119.7 (2), 117.3 (q, *J* = 4 Hz), 112.7 (d, *J* = 4 Hz), 108.3; MS *m/z* 321.4 (MH^+, 100%). Anal. calcd for $C_{15}H_{10}F_3N_3S$: C, 56.07; H, 3.14; N, 13.08. Found: C, 55.67; H, 3.07, N, 12.85%.

Example 1-10

***N*-(4-Methylphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (21).**



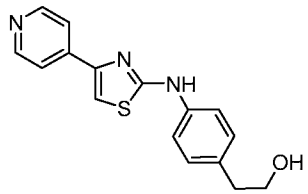
[0238] 4-Methylphenylthiourea (20). NH_4SCN (3.55 g, 46.7 mmol) was added to a stirred solution of *p*-toluidine (5.00 g, 46.7 mmol) in 1 M HCl (50 mL) at 100 °C and the solution stirred at 100 °C for 16 h. The solution was diluted with water (60 mL) and stood at 5 °C for 2 h. The precipitate was filtered, washed with water (5 mL), washed with ether (5 mL), and dried to give thiourea **20** (1.88 g, 24%) as a white powder: mp (H_2O) 181–183 °C [lit. (Rasmussen et al., *Synthesis* 1988, 456) mp (MeOH) 194 °C]; ^{1}H NMR δ 9.45 (br s, 1 H, NH), 7.35 (br s, 2 H, NH_2), 7.24 (d, *J* = 8.3 Hz, 2 H, H-3, H-5), 7.24 (d, *J* = 8.36 Hz, 2 H, H-2, H-6), 2.27 (s, 3 H, CH_3).

[0239] *N*-(4-Methylphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (21). A mixture of bromoketone hydrobromide **1** (0.72 g, 2.56 mmol) and 4-methylphenylthiourea (**20**) (0.43 g, 2.56 mmol) in EtOH (20 mL) was stirred at reflux temperature for 3 h. The mixture was cooled to 20 °C, diluted with water (50 mL), the pH adjusted to ca. 8 with aqueous NH_3 and the mixture stirred at 5 °C for 2 h. The precipitate was filtered, washed with water (5 mL) and dried. The crude solid was purified by column chromatography, eluting with a gradient (50–100%)

of EtOAc/pet. ether, to give amine **21** (0.51 g, 74%) as a cream powder: mp (EtOAc) 230–233 °C; ^{1}H NMR δ 10.23 (br s, 1 H, NH), 8.61 (dd, *J* = 4.5, 1.6 Hz, 2 H, H-2′, H-6′), 7.82 (dd, *J* = 4.5, 1.6 Hz, 2 H, H-3′, H-5′), 7.66 (s, 1 H, H-5), 7.60 (br d, *J* = 8.4 Hz, 2 H, H-2″, H-6″), 7.16 (br d, *J* = 8.4 Hz, 2 H, H-3″, H-5″), 2.27 (s, 3 H, CH_3); ^{13}C NMR δ 163.7, 150.0 (2), 147.6, 141.0, 138.5, 130.3, 129.3 (2), 119.8 (2), 117.1 (2), 107.0, 20.2; MS *m/z* 268.4 (MH^+, 100%). Anal. calcd for $C_{15}H_{13}N_3S$: C, 67.39; H, 4.90; N, 15.72. Found: C, 67.53; H, 4.92; N, 15.50%.

Example 1-11

2-(4-{[4-(4-Pyridinyl)-1,3-thiazol-2-yl]amino}phenyl)ethanol (23).



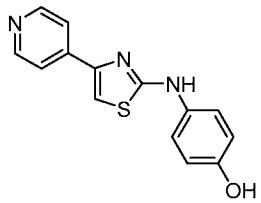
[0240] 1-(4-(2-Hydroxyethyl)phenyl)thiourea (22). NH_4SCN (2.91 g, 38.2 mmol) was added to a stirred solution of 2-(4-aminophenyl)ethanol (5.24 g, 38.2 mmol) in 1 M HCl (38 mL) at 100 °C and the mixture stirred at 100 °C for 48 h. The mixture was cooled to 20 °C, diluted with water (60 mL) and cooled at 0 °C for 1 h. The mixture was extracted with EtOAc (3 × 50 mL) and the combined organic fraction dried and the solvent evaporated. The residue was purified by column chromatography, eluting with EtOAc, to give thiourea **22** (0.41 g, 5%) as a tan gum: ^{1}H NMR δ 9.56 (br s, 1 H, NH), 7.30 (br s, 2 H, NH_2), 7.26 (br d, *J* = 8.4 Hz, 2 H, H-3, H-5), 7.16 (br d, *J* = 8.4 Hz, 2 H, H-2, H-6), 4.58 (t, *J* = 5.2 Hz, 1 H, OH), 3.55–3.61 (m, 2 H, H-1), 2.68 (t, *J* = 7.0 Hz, 2 H, H-2); MS *m/z* 197.3 (MH^+, 100%).

[0241] 2-(4-{[4-(4-Pyridinyl)-1,3-thiazol-2-yl]amino}phenyl)ethanol (23). A mixture of bromoketone hydrobromide **1** (0.58 g, 2.06 mmol) and thiourea **22** (0.41 g, 2.06 mmol) in EtOH (30 mL) was stirred at reflux temperature for 4 h. The mixture was cooled to 20 °C, diluted with water (50 mL), the pH adjusted to ca. 8 with aqueous NH_3 and the mixture stirred at 0 °C for 1 h. The precipitate was filtered, washed with water (5 mL), and dried. The crude solid was purified by

column chromatography, eluting with EtOAc, to give alcohol **23** (0.33 g, 54%) as a white powder: mp (EtOAc) 179–181 °C; ^{1}H NMR δ 10.24 (br s, 1 H, NH), 8.61 (dd, *J* = 4.5, 1.6 Hz, 2 H, H-2‴, H-6‴), 7.84 (dd, *J* = 4.5, 1.6 Hz, 2 H, H-3‴, H-5‴), 7.66 (s, 1 H, H-5″), 7.60 (br d, *J* = 8.5 Hz, 2 H, H-3′, H-5′), 7.20 (br d, *J* = 8.5 Hz, 2 H, H-2′, H-6′), 4.58 (t, *J* = 5.2 Hz, 1 H, OH), 3.55–3.61 (m, 2 H, H-1), 2.69 (t, *J* = 7.1 Hz, 2 H, H-2); ^{13}C NMR δ 163.6, 150.0 (2), 147.6, 141.0, 138.9, 132.5 (2), 119.8 (2), 117.0 (2), 107.0, 62.2, 38.3; MS *m/z* 298.4 (MH^+, 100%). Anal. calcd for $C_{16}H_{15}N_3OS \cdot ¼CH_3OH$: C, 63.91; H, 5.28; N, 13.76. Found: C, 63.94; H, 5.26; N, 14.03%.

Example 1-12

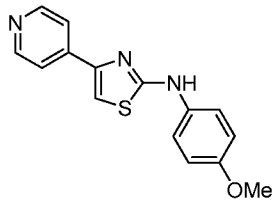
4-{[4-(4-Pyridinyl)-1,3-thiazol-2-yl]amino}phenol (25).



[0242] A mixture of bromoketone hydrobromide **1** (1.05 g, 3.74 mmol) and 4-hydroxyphenylthiourea (**24**) (0.63 g, 3.74 mmol) in EtOH (30 mL) was stirred at reflux temperature for 3 h. The mixture was cooled to 20 °C, diluted with water (50 mL), the pH adjusted to ca. 8 with aqueous NH_3 and the mixture stirred at 0 °C for 1 h. The precipitate was filtered, washed with water (5 mL), washed with Et_2O (5 mL), and dried to give phenol **25** (0.82 g, 81%) as a cream powder: mp (H_2O) 269–272 °C; ^{1}H NMR δ 9.97 (br s, 1 H, NH), 9.11 (s, 1 H, OH), 8.59 (dd, *J* = 4.5, 1.6 Hz, 2 H, H-2″, H-6″), 7.81 (dd, *J* = 4.5, 1.6 Hz, 2 H, H-3″, H-5″), 7.57 (s, 1 H, H-5′), 7.48 (ddd, *J* = 8.9, 3.4, 2.2 Hz, 2 H, H-3, H-5), 6.78 (ddd, *J* = 8.9, 3.4, 2.2 Hz, 2 H, H-2, H-6); ^{13}C NMR δ 164.6, 152.4, 150.0 (2), 147.6, 141.1, 132.9, 119.8 (2), 119.4 (2), 115.4 (2), 106.3; MS *m/z* 270.3 (MH^+, 100%). Anal. calcd for $C_{14}H_{11}N_3OS$: C, 62.43; H, 4.12; N, 15.60. Found: C, 62.19; H, 4.24; N, 15.48%.

Example 1-13

***N*-(4-Methoxyphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (27).**

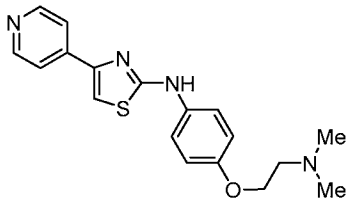


[0243] 4-Methoxyphenylthiourea (26). NH_4SCN (3.09 g, 40.6 mmol) was added to a stirred solution of *p*-anisidine (5.00 g, 40.6 mmol) in 1 M HCl (41 mL) at 100 °C and the solution stirred at 100 °C for 16 h. The solution was diluted with water (60 mL) and stood at 5 °C for 2 h. The precipitate was filtered, washed with water (5 mL), washed with ether (5 mL), and dried to give thiourea **26** (0.85 g, 11%) as a white powder: mp (H_2O) 206–209 °C [lit. (Rasmussen et al., *Synthesis* 1988, 456) mp (MeOH) 212–214 °C]; ^{1}H NMR δ 9.44 (s, 1 H, NH), 7.15–7.30 (m, 4 H, NH_2, H-3, H-5), 6.89 (ddd, J = 9.0, 3.4, 2.2 Hz, 2 H, H-2, H-6), 3.74 (s, 3 H, OCH_3).

[0244] *N*-(4-Methoxyphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (27). A mixture of bromoketone hydrobromide **1** (1.26 g, 4.50 mmol) and 4-methoxyphenylthiourea (**26**) (0.82 g, 4.50 mmol) in EtOH (20 mL) was stirred at reflux temperature for 1 h. The mixture was cooled to 20 °C, diluted with water (50 mL), the pH adjusted to ca. 8 with aqueous NH_3 and the mixture stirred at 5 °C for 2 h. The precipitate was filtered, washed with water (5 mL) and dried. The crude solid was purified by column chromatography, eluting with EtOAc, to give amine 27 (0.76 g, 60%) as a cream powder: mp (EtOAc) 178–180 °C; ^{1}H NMR δ 10.13 (br s, 1 H, NH), 8.61 (dd, J = 4.5, 1.6 Hz, 2 H, H-2′, H-6′), 7.83 (dd, J = 4.5, 1.6 Hz, 2 H, H-3′, H-5′), 7.60 (m, 3 H, H-5, H-3″, H-5″), 6.95 (ddd, J = 6.8, 3.5, 2.2 Hz, 2 H, H-2″, H-6″), 3.74 (s, 3 H, OCH_3); ^{13}C NMR δ 164.1, 154.2, 150.0 (2), 147.6, 141.0, 134.4, 119.8 (2), 118.7 (2), 114.2 (2), 106.6, 55.1; MS *m/z* 284.5 (MH^+, 100%). Anal. calcd for $C_{15}H_{13}N_3OS$: C, 63.58; H, 4.62; N, 14.83. Found: C, 63.45; H, 4.65; N, 14.82%.

Example 1-14

***N*-{4-[2-(Dimethylamino)ethoxy]phenyl}-4-(4-pyridinyl)-1,3-thiazol-2-amine (29).**



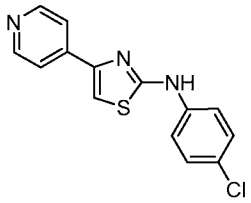
[0245] 1-(4-(2-(Dimethylamino)ethoxy)phenyl)thiourea (28). Thiophosgene (0.95 mL, 12.45 mmol) was added dropwise to a stirred solution of 4-(2-(dimethylamino)ethoxy)aniline (2.04 g, 11.32 mmol) and *i*Pr_2NEt (2.37 mL, 13.58 mmol) in dry THF (50 mL) at 0 °C and the solution stirred at 20 °C for 2 h. The solution was partitioned between DCM (50 mL) and water (50 mL), the organic fraction dried and the solvent evaporated. The residue was dissolved in DME (80 mL) and dry NH_3 gas bubbled through the solution for 10 min. The solution was stirred at 20 °C for 16 h and the solvent evaporated to give thiourea **28** (1.78 g, 66%) as a gum: ^{1}H NMR δ 9.63 (br s, 1 H, NH), 7.34 (br s, 2 H, NH_2), 7.26 (br d, *J* = 8.9 Hz, 2 H, H-3, H-5), 6.90 (br d, *J* = 8.9 Hz, 2 H, H-2, H-6), 4.08 (t, *J* = 5.7 Hz, 2 H, CH_2O), 2.76 (t, *J* = 5.7 Hz, 2 H, CH_2N), 2.32 [s, 6 H, $N(CH_3)_2$]; MS *m/z* 240.4 (MH^+, 100%).

[0246] *N*-{4-[2-(Dimethylamino)ethoxy]phenyl}-4-(4-pyridinyl)-1,3-thiazol-2-amine (29). A mixture of bromoketone hydrobromide **1** (0.63 g, 2.25 mmol) and 1-(4-(2-(dimethylamino)ethoxy)phenyl)thiourea (**28**) (0.54 g, 2.25 mmol) in EtOH (20 mL) was stirred at reflux temperature for 2 h. The mixture was cooled to 20 °C, diluted with water (50 mL), the pH adjusted to ca. 8 with aqueous NH_3 and the mixture stirred at 0 °C for 1 h. The precipitate was filtered, washed with water (5 mL), and dried. The crude solid was purified by column chromatography, eluting with a gradient (0–20%) of MeOH/EtOAc, followed by 1% aqueous NH_3/MeOH/EtOAc, to give amine **29** (447 mg, 58%) as a an oil: ^{1}H NMR δ 10.13 (s, 1 H, NH), 8.60 (dd, *J* = 4.5, 1.6 Hz, 2 H, H-2′, H-6′), 7.83 (dd, *J* = 4.5, 1.6 Hz, 2 H, H-3′, H-5′), 7.59–7.64 (m, 3 H, H-5, H-2″, H-6″), 6.95 (ddd, *J* = 9.0, 3.5, 2.2 Hz, 2 H, H-3″, H-5″), 4.02 (br t, *J* = 5.9 Hz, 2 H, CH_2O), 2.61 (br t, *J* = 5.9 Hz, 2 H, CH_2N), 2.22 [s, 6 H, $N(CH_3)_3$]; ^{13}C NMR δ 164.0, 153.4, 150.0 (2), 147.6, 141.0, 134.4, 119.8 (2), 118.7 (2), 114.8 (2), 106.6, 66.0, 57.6, 45.4 (2); MS *m/z* 341.5 (MH^+, 100%). The dihydrochloride salt was crystallized from

MeOH/EtOAc: mp (MeOH/EtOAc) 160–164 °C. Anal. calcd for $C_{18}H_{22}Cl_2N_4OS \cdot 1¼H_2O$: C, 49.60; H, 5.66; N, 12.85. Found: C, 49.49; H, 5.75; N, 12.67%.

Example 1-15

***N*-(4-Chlorophenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (31).**



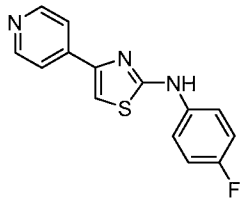
[0247] 4-Chlorophenylthiourea (30). NH_4SCN (3.04 g, 40.0 mmol) was added to a stirred solution of 4-chloroaniline (5.10 g, 40.0 mmol) in 1 M HCl (40 mL) at 100 °C and the solution stirred at 100 °C for 16 h. The solution was diluted with water (60 mL) and stood at 5 °C for 2 h. The precipitate was filtered, washed with water (5 mL), washed with ether (5 mL), and dried. The crude solid was purified by column chromatography, eluting with a gradient (50–100%) of EtOAc/pet. ether, to give thiourea **30** (3.28 g, 44%) as a white powder: mp (EtOAc/pet. ether) 172–172 °C [lit. (Rasmussen et al., *Synthesis* 1988, 456) mp (iPrOH) 176–178 °C]; ^{1}H NMR δ 9.92 (s, 1 H, NH), 7.55 (br s, 2 H, NH_2), 6.47 (ddd, J = 8.9, 3.0, 2.2 Hz, 2 H, H-2, H-6), 6.35 (ddd, J = 8.9, 3.0, 2.2 Hz, 2 H, H-3, H-5).

[0248] *N*-(4-Chlorophenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (31). A mixture of bromoketone hydrobromide **1** (1.24 g, 4.41 mmol) and 4-chlorophenylthiourea (**30**) (0.82 g, 4.41 mmol) in EtOH (20 mL) was stirred at reflux temperature for 3 h. The mixture was cooled to 20 °C, diluted with water (50 mL), the pH adjusted to ca. 8 with aqueous NH_3 and the mixture stirred at 5 °C for 2 h. The precipitate was filtered, washed with water (5 mL) and dried. The crude solid was purified by column chromatography, eluting with a gradient (50–100%) of EtOAc/pet. ether, to give amine **31** (0.49 g, 39%) as a cream powder: mp (EtOAc/pet. ether) 259–261 °C; ^{1}H NMR δ 10.49 (br s, 1 H, NH), 8.61 (dd, J = 4.5, 1.6 Hz, 2 H, H-2′, H-6′), 7.86 (dd, J = 4.5, 1.6 Hz, 2 H, H-3′, H-5′), 7.76 (ddd, J = 9.0, 3.2, 2.1 Hz, 2 H, H-2″, H-6″), 7.74 (s, 1 H, H-5), 7.40 (ddd, J = 8.9, 3.2,

2.1 Hz, 2 H, H-3″, H-5″); ^{13}C NMR δ 163.1, 150.0 (2), 147.6, 140.8, 139.8, 128.7 (2), 124.6, 119.8 (2), 118.3 (2), 107.8. Anal. calcd for $C_{14}H_{10}ClN_3S$: C, 58.43; H, 3.50; N, 14.60. Found: C, 58.46; H, 3.60; N, 14.57%.

Example 1-16

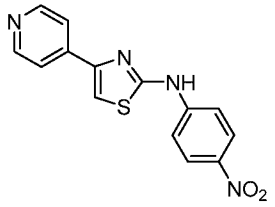
***N*-(4-Fluorophenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (33).**



[0249] A mixture of bromoketone hydrobromide **1** (0.83 g, 2.94 mmol) and 4-fluorophenylthiourea (**32**) (0.50 g, 2.94 mmol) in EtOH (20 mL) was stirred at reflux temperature for 2 h. The mixture was cooled to 20 °C, diluted with water (50 mL), the pH adjusted to ca. 8 with aqueous NH_3 and the mixture stirred at 5 °C for 2 h. The precipitate was filtered, washed with water (5 mL) and dried. The crude solid was purified by column chromatography, eluting with a gradient (50–100%) of EtOAc/pet. ether, to give amine **33** (0.76 g, 96%) as a cream powder: mp (EtOAc/pet. ether) 211–213 °C; ^{1}H NMR δ 10.37 (br s, 1 H, NH), 8.61 (dd, *J* = 4.5, 1.6 Hz, 2 H, H-2′, H-6′), 7.84 (dd, *J* = 4.5, 1.6 Hz, 2 H, H-3′, H-5′), 7.73–7.78 (m, 2 H, H-3′, H-5′), 7.70 (s, 1 H, H-5), 7.17–7.23 (m, 2 H, H-2″, H-6″); ^{13}C NMR δ 163.5, 156.9 (d, *J* = 241 Hz), 150.0 (2), 147.6, 140.9, 137.4, 119.8 (2), 118.4 (2, d, *J* = 7 Hz), 115.4 (2, d, *J* = 22 Hz), 107.3. Anal. calcd for $C_{14}H_{10}FN_3S$: C, 61.98; H, 3.72; N, 15.49. Found: C, 62.14; H, 3.79; N, 15.49%.

Example 1-17

***N*-(4-Nitrophenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (35).**



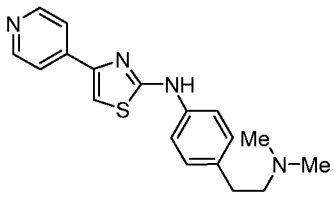
[0250] **4-Nitrophenylthiourea (34).** NH_4SCN (2.75 g, 36.2 mmol) was added to a stirred solution of 4-nitroaniline (5.00 g, 36.2 mmol) in 1 M HCl (40 mL) at 100

°C and the solution stirred at 100 °C for 16 h. The solution was diluted with water (60 mL) and stood at 5 °C for 2 h. The precipitate was filtered, washed with water (5 mL), washed with ether (5 mL), and dried. The crude solid was purified by column chromatography, eluting with a gradient (50–100%) of EtOAc/pet. ether, to give thiourea **34** (2.16 g, 30%) as a tan powder: mp (EtOAc/pet. ether) 213–215 °C [lit. (Rasmussen et al., *Synthesis* 1988, 456) mp (acetone) 220–242 °C]; ^{1}H NMR δ 10.24 (s, 1 H, NH), 8.18 (ddd, J = 9.2, 3.1, 2.2 Hz, 2 H, H-3, H-5), 8.00 (br s, 2 H, NH_2), 7.85 (ddd, J = 9.2, 3.1, 2.2 Hz, 2 H, H-2, H-6).

[0251] ***N*-(4-Nitrophenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (35).** A mixture of bromoketone hydrobromide **1** (1.91 g, 6.80 mmol) and 4-nitrophenylthiourea (**34**) (1.34 g, 6.80 mmol) in EtOH (50 mL) was stirred at reflux temperature for 2 h. The mixture was cooled to 20 °C, diluted with water (50 mL), the pH adjusted to ca. 8 with aqueous NH_3 and the mixture extracted with EtOAc (3 × 50 mL). The organic fraction was dried and the solvent evaporated. The crude solid was purified by column chromatography, eluting with a gradient (0–10%) of MeOH/EtOAc, to give amine **35** (1.93 g, 95%) as a cream powder: mp (MeOH/EtOAc) >290 °C; ^{1}H NMR δ 11.16 (br s, 1 H, NH), 8.63 (dd, J = 4.5, 1.6 Hz, 2 H, H-2′, H-6′), 8.27 (ddd, J = 9.3, 3.1, 2.0 Hz, 2 H, H-3″, H-5″), 7.96 (ddd, J = 9.3, 3.1, 2.0 Hz, 2 H, H-2″, H-6″), 7.90–7.93 (m, 3 H, H-5, H-3′, H-5′); ^{13}C NMR δ 162.2, 150.0 (2), 147.9, 146.6, 140.6, 140.3, 125.5 (2), 120.0 (2), 116.4 (2), 109.7. Anal. calcd for $C_{14}H_{10}N_4O_2S \cdot ¼EtOAc$: C, 56.24; H, 3.78; N, 17.49. Found: C, 56.49; H, 4.08; N, 17.07%.

Example 1-18

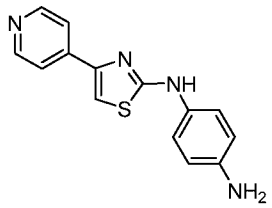
***N*-{4-[2-(Dimethylamino)ethyl]phenyl}-4-(4-pyridinyl)-1,3-thiazol-2-amine (36).**



[0252] Methanesulfonyl chloride (77 μL, 1.00 mmol) was added dropwise to a stirred solution of alcohol **23** (270 mg, 0.91 mmol) and *i*Pr_2NEt (190 μL, 1.09 mmol) in dry DCM (30 mL) and the solution was stirred at 20 °C for 4 h. The solution was diluted with DCM (50 mL) and washed with 1 M HCl (10 mL), saturated aqueous $KHCO_3$ solution (20 mL), brine (10 mL), dried, and the solvent evaporated. The residue was dissolved in DMF (5 mL) and anhydrous Me_2NH gas was bubbled through the solution for 5 min and the solution stirred at 20 °C for 16 h. The solvent was evaporated and the residue was purified by column chromatography, eluting with a gradient (0–20%) of MeOH/EtOAc, followed by 1% aqueous NH_3/20% MeOH/EtOAc, to give amine **36** (165 mg, 56%) as a oil: ^{1}H NMR δ 10.25 (br s, 1 H, NH), 8.61 (dd, *J* = 4.5, 1.6 Hz, 2 H, H-2′, H-6′), 7.84 (dd, *J* = 4.5, 1.6 Hz, 2 H, H-3′, H-5′), 7.66 (s, 1 H, H-5), 7.61 (br d, *J* = 8.5 Hz, 2 H, H-3″, H-5″), 7.20 (br d, *J* = 8.5 Hz, 2 H, H-2″, H-6″), 2.66 (br dd, *J* = 8.2, 7.1 Hz, 2 H, CH_2), 2.44 (br dd, *J* = 8.2, 7.1 Hz, 2 H, CH_2N), 2.19 [s, 6 H, $N(CH_3)_3$]; ^{13}C NMR δ 163.6, 150.0 (2), 147.6, 141.0, 138.8, 133.5, 129.0 (2), 119.8 (2), 117.0 (2), 107.0, 60.8, 44.9 (2), 33.5; MS *m/z* 325.5 (MH^+, 100%). The hydrochloride salt was crystallized from MeOH/EtOAc: mp (MeOH/EtOAc) 234–237 °C. Anal. calcd for $C_{18}H_{21}ClN_4S·½CH_3OH$: C, 58.95; H, 6.15; N, 14.86. Found: C, 58.96; H, 6.04; N, 15.06%.

Example 1-19

***N*^{1}-[4-(4-Pyridinyl)-1,3-thiazol-2-yl]-1,4-benzenediamine (37).**

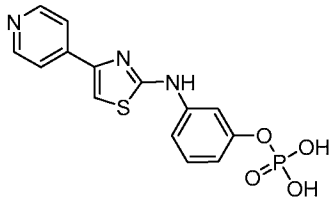


[0253] A mixture of amine **35** (0.20 g, 0.67 mmol) and Pd/C (100 mg) in EtOH (150 mL) was stirred under H_2 (60 psi) for 16 h. The mixture was cooled, filtered through Celite, washed with EtOH (3 × 20 mL) and the solvent evaporated to give diamine **37** (0.16 g, 90%) as a tan powder: mp (MeOH/EtOAc) 209–211 °C; ^{1}H NMR δ 9.79 (br s, 1 H, NH), 8.58 (dd, *J* = 4.5, 1.6 Hz, 2 H, H-2″, H-6″), 7.80 (dd, *J* = 4.5, 1.6 Hz, 2 H, H-3″, H-5″), 7.54 (s, 1 H, H-5′), 7.28 (ddd, *J* = 8.7, 3.1, 2.0

Hz, 2 H, H-2, H-6), 6.57 (ddd, J = 8.7, 3.1, 2.0 Hz, 2 H, H-3, H-5), 4.88 (br s, 2 H, NH_2); ^{13}C NMR δ 165.6, 150.0 (2), 147.7, 144.4, 141.2, 120.2 (2), 119.8 (2), 115.3, 114.3 (2), 105.9. Anal. calcd for $C_{14}H_{12}N_4S$: C, 62.66; H, 4.51. Found: C, 62.64; H, 5.00%.

Example 1-20

3-{[4-(4-Pyridinyl)-1,3-thiazol-2-yl]amino}phenyl Dihydrogen Phosphate (39)



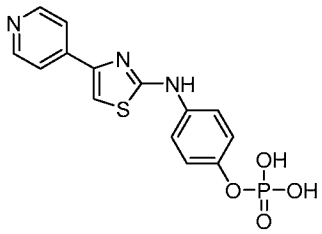
[0254] Di(*tert*-butyl) 3-{[4-(4-Pyridinyl)-1,3-thiazol-2-yl]amino}phenyl Phosphate (38). A solution of tetrazole (3% w/w, 14.4 mL, 4.9 mmol) in MeCN was added to a stirred solution of phenol **13** (450 mg, 1.7 mmol) and di-tert-butyl diisopropylphosphoramidite (0.68 mL, 2.2 mmol) in dry THF (15 mL) and the solution stirred at 20 °C under N_2 for 16 h. The solution was cooled to –40 °C and a dried solution of MCPBA (50%, 0.82 g, 2.4 mmol) in DCM (10 mL) was added and the solution stirred at –40 °C for 15 minutes. A solution of $NaHSO_3$ (10%, 2 mL) was added and the mixture partitioned between water and DCM. The organic fraction was washed with dilute aqueous ammonia, dried, and the solvent evaporated. The residue was purified by chromatography, eluting with a gradient (50–100%) of EtOAc/pet. ether, to give diester **38** (0.36 g, 46%) as a soft solid: ^1H NMR δ 8.63 (dd, J = 4.7, 1.4 Hz, 2 H, H-2″, H-6″), 7.72 (dd, J = 4.7, 1.4 Hz, 2 H, H-3″, H-5″), 7.53 (br s, 1 H, H-2), 7.24 (dd, J = 8.1, 7.8 Hz, 1 H, H-5), 7.18 (br d, J = 7.8 Hz, 1 H, H-6), 7.03 (s, 1 H, H-5′), 6.92 (dd, J = 8.1, 1.0 Hz, 1 H, H-4), 1.54 (s, 18 H, 2 × O*t*Bu), NH not observed.

[0255] 3-{[4-(4-Pyridinyl)-1,3-thiazol-2-yl]amino}phenyl Dihydrogen Phosphate (39). Trifluoroacetic acid (0.59 mL, 7.7 mmol) was added to a stirred solution of phosphate diester **38** (355 mg, 0.77 mmol) in DCM (20 mL) and the solution stirred at 20 °C for 16 h. The solvent was evaporated and the residue triturated with MeOH to give the phosphate as the trifluoroacetate salt **39** (127 mg,

36%) as a white solid, mp (MeOH) 258–261 °C; ^{1}H NMR δ 10.45 (br s, 1 H, NH), 8.61 (br d, *J* = 5.0 Hz, 2 H, H-2″, H-6″), 7.94 (br d, *J* = 5.0 Hz, 2 H, H-3″, H-5″), 7.84 (br s, 1 H, H-2), 7.77 (s, 1 H, H-5′), 7.38 (br d, *J* = 8.0 Hz, 1 H, H-6), 7.29 (br t, *J* = 8.0 Hz, 1 H, H-5), 6.56 (br d, *J* = 8.0 Hz, 1 H, H-4), 2 × OH not observed.

Example 1-21

4-{[4-(4-Pyridinyl)-1,3-thiazol-2-yl]amino}phenyl Dihydrogen Phosphate (41)



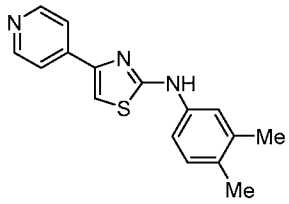
[0256] Di(*tert*-butyl) 4-{[4-(4-Pyridinyl)-1,3-thiazol-2-yl]amino}phenyl Phosphate (40). A solution of tetrazole (3% w/w, 34.5 mL, 14.8 mmol) in MeCN was added to a stirred solution of alcohol **25** (1.08 g, 4.0 mmol) and di-tert-butyl diisopropylphosphoramidite (1.64 mL, 5.2 mmol) in dry THF (50 mL) and the solution stirred at 20 °C under N_2 for 16 h. The solution was cooled to –40 °C and a dried solution of MCPBA (50%, 1.66 g, 4.8 mmol) in DCM (10 mL) was added and the solution stirred at –40 °C for 15 minutes. A solution of $NaHSO_3$ (10%, 2 mL) was added and the mixture partitioned between water and DCM. The organic fraction was washed with dilute aqueous ammonia, dried, and the solvent evaporated. The residue was purified by chromatography, eluting with a gradient (50–100%) of EtOAc/pet. ether, to give diester **40** (550 mg, 30%) as a gum: ^{1}H NMR (CD_3OD) δ 8.50 (dd, *J* = 4.7, 1.6 Hz, 2 H, H-2″, H-6″), 7.86 (dd, *J* = 4.7, 1.6 Hz, 2 H, H-3″, H-5″), 7.69 (ddd, *J* = 8.9, 3.0, 1.9 Hz, 2 H, H-3, H-5), 7.38 (s, 1 H, H-5′), 7.16 (ddd, *J* = 8.9, 3.0, 1.9 Hz, 2 H, H-2, H-6), 1.50 (s, 18 H, 2 × O*t*Bu); MS *m/z* 462.9 (MH^+, 100%).

[0257] 4-{[4-(4-Pyridinyl)-1,3-thiazol-2-yl]amino}phenyl Dihydrogen Phosphate (41). Trifluoroacetic acid (1.2 mL, 15.6 mmol) was added to a stirred solution of phosphate diester **40** (476 mg, 1.05 mmol) in DCM (20 mL) and the solution stirred at 20 °C for 3 h. The solvent was evaporated and the residue triturated with ether to give phosphate **41** (430 mg, 88%) as a tan gum: ^{1}H NMR δ

11.50 (br s, 2 H, 2 × OH), 10.30 (br s, 1 H, NH), 8.62 (d, J = 6.0 Hz, 2 H, H-2″, H-6″), 7.88 (d, J = 6.0 Hz, 2 H, H-3″, H-5″), 7.88 (d, J = 8.9 Hz, 2 H, H-3, H-5), 7.71 (s, 1 H, H-5′), 7.17 (d, J = 8.9, 3.0, 1.9 Hz, 2 H, H-2, H-6).

Example 1-22

***N*-(3,4-Dimethylphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (43).**



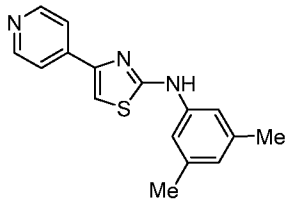
[0258] 3,4-Dimethylphenylthiourea (42). NH_4SCN (6.3 g, 83.3 mmol) was added to a stirred solution of 3,4-dimethylaniline (10.1 g, 83.3 mmol) in 1 M HCl (84 mL) at 100 °C and the solution stirred at 100 °C for 16 h. The solution was diluted with water (60 mL) and stood at 5 °C for 2 h. The precipitate was filtered, washed with water (5 mL), washed with ether (5 mL), and dried to give thiourea **42** (2.04 g, 14%) as a white powder: mp (H_2O) 181–182 °C [lit. (Rasmussen, C. R. et al., *Synthesis* 1988, 456) mp (DME/Et_2O) 184–186 °C]; ^{1}H NMR δ 9.48 (s, 1 H, NH), 7.05–7.25 (m, 5 H, H-2, H-5, H-6, NH_2), 2.18 (s, 6 H, 2 × CH_3).

[0259] *N*-(3,4-Dimethylphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (43). A mixture of bromoketone hydrobromide **1** (0.70 g, 2.5 mmol) and 3,4-dimethylphenylthiourea **42** (0.45 g, 2.5 mmol) in EtOH (20 mL) was stirred at reflux temperature for 3 h. The mixture was cooled to 20 °C, diluted with water (50 mL), the pH adjusted to ca. 8 with aqueous NH_3 and the mixture stirred at 0 °C for 1 h. The precipitate was filtered, washed with water (5 mL) and dried. The crude solid was purified by column chromatography, eluting with 50% EtOAc/pet. ether, to give amine **43** (0.59 g, 85%) as a cream powder: mp (MeOH/EtOAc) 177–179 °C; ^{1}H NMR δ 10.15 (br s, 1 H, NH), 8.61 (dd, J = 4.5, 1.6 Hz, 2 H, H-2′, H-6′), 7.83 (dd, J = 4.5, 1.6 Hz, 2 H, H-3′, H-5′), 7.64 (s, 1 H, H-5), 7.47 (dd, J = 8.1, 2.2 Hz, 1 H, H-6″), 7.42 (d, J = 2.2 Hz, 1 H, H-2″), 7.10 (d, J = 8.1 Hz, 1 H, H-5″), 2.34 (s, 3 H, CH_3), 2.18 (s, 3 H, CH_3); ^{13}C NMR δ 163.8, 150.0 (2), 147.6, 141.0, 138.7, 136.5, 129.8, 129.2, 119.7 (2), 118.4, 114.6, 106.8, 19.7, 18.5; MS *m/z*

282.5 (MH^+, 100%). Anal. calcd for $C_{16}H_{15}N_3S \cdot \frac{1}{4}CH_3OH$: C, 67.45; H, 5.57; N, 14.52. Found: C, 67.54; H, 5.61; N, 14.58%.

Example 1-23

***N*-(3,5-Dimethylphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (45).**



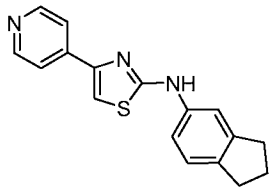
[0260] 3,5-Dimethylphenylthiourea (44). NH_4SCN (2.51 g, 33.0 mmol) was added to a stirred solution of *m*-toluidine (4.00 g, 33.0 mmol) in 1 M HCl (35 mL) at 100 °C and the solution stirred at 100 °C for 16 h. The solution was diluted with water (60 mL) and stood at 5 °C for 2 h. The precipitate was filtered, washed with water (5 mL), washed with ether (5 mL), and dried to give thiourea **44** (1.61 g, 17%) as a white powder: mp (H_2O) 174–176 °C [lit. (Rasmussen, C. R. et al., *Synthesis* 1988, 456) mp (iPrOH) 172–173 °C]; ^{1}H NMR δ 9.52 (s, 1 H, NH), 7.36 (br s, 2 H, NH_2), 6.96 (s, 2 H, H-2, H-6), 6.76 (s, 1 H, H-4), 2.24 (s, 6 H, 2 × CH_3); 13C NMR δ 180.7, 138.6, 137.7 (2), 126.0, 120.7 (2), 20.8 (2); MS *m/z* 181.4 (MH^+, 100%).

[0261] *N*-(3,5-Dimethylphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (45). A mixture of bromoketone hydrobromide **1** (842 mg, 3.0 mmol) and thiourea **44** (540 mg, 3.0 mmol) in EtOH (30 mL) was stirred at reflux temperature for 3 h. The mixture was cooled to 20 °C, diluted with water (50 mL), the pH adjusted to ca. 8 with aqueous NH_3 and the mixture stirred at 20 °C for 2 h. The precipitate was filtered, washed with water (5 mL) and dried. The crude solid was purified by column chromatography, eluting with a gradient (50–100%) of EtOAc/pet. ether, to give amine **45** (767 mg, 91%) as a cream powder: mp (EtOAc/pet. ether) 218–220 °C; ^{1}H NMR δ 10.21 (br s, 1 H, NH), 8.63 (dd, J = 4.6, 1.6 Hz, 2 H, H-2′, H-6′), 7.86 (dd, J = 4.6, 1.6 Hz, 2 H, H-3′, H-5′), 7.71 (s, 1 H, H-5), 7.33 (s, 2 H, H-2″, H-6″), 6.64 (s, 1 H, H-4″), 2.28 (s, 6 H, 2 × CH_3); ^{13}C NMR δ 163.6, 149.6 (2), 147.4, 140.7, 137.9 (2), 123.1, 119.9 (2), 114.8 (2), 107.6, 21.2 (2); MS *m/z* 282.4

(MH^+, 100%). Anal. calcd for $C_{16}H_{15}N_3S$: C, 68.30; H, 5.37; N, 14.93. Found: C,67.91; H, 5.20; N, 14.92%.

Example 1-24

***N*-(2,3-Dihydro-1*H*-inden-5-yl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (47).**



[0262] *N*-(2,3-Dihydro-1*H*-inden-5-yl)thiourea (46). NH_4SCN (2.87 g, 37.8 mmol) was added to a stirred solution of 5-indanamine (5.03 g, 37.8 mmol) in 1 M HCl (40 mL) at 100 °C and the solution stirred at 100 °C for 16 h. The solution was diluted with water (60 mL) and stood at 5 °C for 2 h. The precipitate was filtered, washed with water (5 mL), washed with ether (5 mL), and dried to give thiourea **46** (2.21 g, 30%) as a tan powder: mp (H_2O) 163–166 °C [lit. (Rasmussen et al., *Synthesis* 1988, 456) mp (acetone) 176–179 °C]; ^{1}H NMR δ 9.52 (s, 1 H, NH), 7.27 (br s, 2 H, NH_2), 7.21 (br s, 1 H, H-4), 7.16 (d, J = 8.0 Hz, 1 H, H-7), 7.04 (br dd, J = 8.0, 1.6 Hz, 1 H, H-6), 2.79–2.87 (m, 4 H, H-1, H-3), 1.96–2.05 (m, 2 H, H-2).

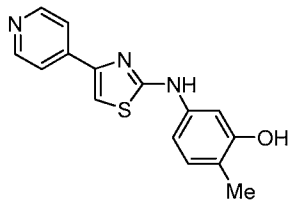
[0263] Alternative Preparation of *N*-(2,3-Dihydro-1*H*-inden-5-yl)thiourea (46). Benzoyl chloride (6.3 mL, 54.5 mmol) was added dropwise to a solution of NH_4SCN (4.44 g, 58.4 mmol) in dry acetone (50 mL). The mixture was stirred at reflux temperature for 15 min. The heating was removed and a solution of 5-indanamine (5.18 g, 38.9 mmol) in acetone (20 mL) was added dropwise keeping the solution at reflux. The mixture was stirred at reflux temperature for a further 30 min, cooled to 20 °C and poured onto ice. The mixture was stirred for 30 min and the precipitate was filtered and washed with water (15 mL) and dried. The solid was added to a solution of NaOH (10% w/v, 100 mL) at 80 °C and stirred at 80 °C for 30 min, then cooled to 20 °C and poured onto ice/HCl (6 M, 50 mL). The pH of the mixture was adjusted to 10 with cNH_3 solution and stirred for 30 min. The precipitate was filtered and washed with water (20 mL) and dried. The precipitate was purified by column chromatography, eluting with a gradient (30–100%) of

EtOAc/pet. ether, to give thiourea **46** (5.91 g, 79%) as cream needles: mp (EtOAc/pet ether) 175–177 °C [lit. (Rasmussen et al., *Synthesis* 1988, 456) mp (acetone) 176–179 °C]; ^{1}H NMR δ 9.52 (s, 1 H, NH), 7.27 (br s, 2 H, NH_2), 7.21 (br s, 1 H, H-4), 7.16 (d, J = 8.0 Hz, 1 H, H-7), 7.04 (br dd, J = 8.0, 1.6 Hz, 1 H, H-6), 2.79–2.87 (m, 4 H, H-1, H-3), 1.96–2.05 (m, 2 H, H-2).

[0264] ***N*-(2,3-Dihydro-1*H*-inden-5-yl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (47).** A mixture of bromoketone hydrobromide **1** (0.73 g, 2.60 mmol) and 1-(2,3-dihydro-1*H*-inden-5-yl)thiourea (**46**) (0.50 g, 2.60 mmol) in EtOH (25 mL) was stirred at reflux temperature for 3 h. The mixture was cooled to 20 °C, diluted with water (50 mL), the pH adjusted to ca. 8 with aqueous NH_3 and the mixture stirred at 5 °C for 1 h. The mixture was filtered, washed with water (5 mL) and Et_2O (5 mL) and dried. The residue was purified by column chromatography, eluting with a gradient (0–10%) of MeOH/EtOAc, to give amine **47** (0.66 g, 87%) as a tan powder: mp (MeOH/EtOAc) 190–192 °C; ^{1}H NMR δ 10.18 (s, 1 H, NH), 8.61 (dd, J = 4.5, 1.6 Hz, 2 H, H-2′, H-6′), 7.83 (dd, J = 4.5, 1.6 Hz, 2 H, H-3′, H-5′), 7.65 (s, 1 H, H-5), 7.56 (br s, 1 H, H-4″), 7.45 (dd, J = 8.1, 2.0 Hz, 1 H, H-6″), 7.19 (d, J = 8.1 Hz, 1 H, H-7″), 2.89 (br t, J = 7.4 Hz, 2 H, H-1″), 2.82 (br t, J = 7.3 Hz, 2 H, H-3″), 2.03 (pent, J = 7.4 Hz, 2 H, H-2″); ^{13}C NMR δ 163.9, 150.0 (2), 147.6, 144.4, 141.0, 139.3, 136.8, 124.3, 119.8 (2), 115.4, 113.3, 106.8, 32.5, 31.6, 25.1; MS m/z 294.4 (MH^+, 100%). Anal. calcd for $C_{17}H_{15}N_3S \cdot ½CH_3OH$: C, 67.93; H, 5.53; N, 13.58. Found: C, 67.58; H, 5.21, N, 13.53%.

Example 1-25

2-Methyl-5-{[4-(4-pyridinyl)-1,3-thiazol-2-yl]amino}phenol (49).



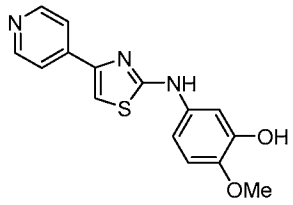
[0265] **3-Hydroxy-4-methylphenylthiourea (48).** NH_4SCN (3.78 g, 49.6 mmol) was added to a stirred solution of 3-hydroxy-4-methoxyaniline (6.11 g, 49.6 mmol) in 1 M HCl (50 mL) at 100 °C and the solution stirred at 100 °C for 16 h. The

solution was diluted with water (60 mL) and stood at 5 °C for 2 h. The precipitate was filtered, washed with water (5 mL), washed with ether (5 mL), and dried to give thiourea **48** (3.34 g, 37%) as a tan powder: ^{1}H NMR δ 9.46 (s, 1 H, NH), 9.34 (s, 1 H, OH), 7.25 (br s, 2 H, NH_2), 6.98 (d, J = 8.0 Hz, 1 H, H-5), 6.74 (d, J = 2.0 Hz, 1 H, H-2), 6.63 (dd, J = 8.0, 2.0 Hz, 1 H, H-6), 2.07 (s, 3 H, CH_3).

[0266] 2-Methyl-5-{[4-(4-pyridinyl)-1,3-thiazol-2-yl]amino}phenol (49). A mixture of bromoketone hydrobromide **1** (1.23 g, 4.39 mmol) and 3-hydroxy-4-methylphenylthiourea (**48**) (0.80 g, 4.39 mmol) in EtOH (25 mL) was stirred at reflux temperature for 3 h. The mixture was cooled to 20 °C, diluted with water (50 mL), the pH adjusted to ca. 8 with aqueous NH_3 and the mixture stirred at 5 °C for 1 h. The mixture was filtered, washed with water (5 mL) and Et_2O (5 mL) and dried. The residue was purified by column chromatography, eluting with a gradient (50–80%) of EtOAc/pet. ether, to give phenol **49** (0.94 g, 74%) as a white powder: mp (EtOAc/pet. ether) 213–215 °C; ^{1}H NMR δ 10.10 (s, 1 H, NH), 9.35 (br s, 1 H, OH), 8.60 (dd, J = 4.5, 1.6 Hz, 2 H, H-2″, H-6″), 7.89 (dd, J = 4.5, 1.6 Hz, 2 H, H-3″, H-5″), 7.64 (s, 1 H, H-5′), 7.36 (d, J = 2.1 Hz, 1 H, H-2), 6.99 (d, J = 8.4 Hz, 1 H, H-6), 6.91 (dd, J = 8.4, 2.1 Hz, 1 H, H-5), 2.08 (s, 3 H, CH_3); ^{13}C NMR δ 163.6, 155.5, 149.9 (2), 147.6, 141.0, 139.5, 130.4, 119.9 (2), 117.0, 107.9, 106.8, 104.1, 15.3; MS *m/z* 284.9 (MH^+, 100%). Anal. calcd for $C_{15}H_{13}N_3OS$: C, 63.58; H, 4.62; N, 14.83. Found: C, 63.48; H, 4.71, N, 14.89%.

Example 1-26

2-Methoxy-5-{[4-(4-pyridinyl)-1,3-thiazol-2-yl]amino}phenol (51).



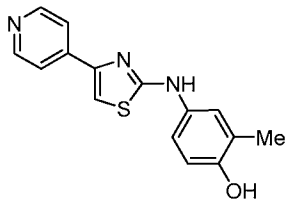
[0267] 3-Hydroxy-4-methoxyphenylthiourea (50). NH_4SCN (2.65 g, 34.8 mmol) was added to a stirred solution of 3-hydroxy-4-methoxyaniline (4.84 g, 34.8 mmol) in 1 M HCl (40 mL) at 100 °C and the solution stirred at 100 °C for 16 h. The solution was diluted with water (60 mL) and stood at 5 °C for 2 h. The

precipitate was filtered, washed with water (5 mL), washed with ether (5 mL), and dried to give thiourea **50** (3.10 g, 45%) as a tan powder: ^{1}H NMR δ 9.37 (s, 1 H, NH), 9.07 (s, 1 H, OH), 7.20 (br s, 2 H, NH_2), 6.85 (d, J = 8.6 Hz, 1 H, H-5), 6.78 (d, J = 2.5 Hz, 1 H, H-2), 6.66 (dd, J = 8.6, 2.5 Hz, 1 H, H-6), 3.74 (s, 3 H, OCH_3).

[0268] 2-Methoxy-5-{[4-(4-pyridinyl)-1,3-thiazol-2-yl]amino}phenol (51). A mixture of bromoketone hydrobromide **1** (1.40 g, 4.99 mmol) and 3-hydroxy-4-methoxyphenylthiourea (**50**) (0.96 g, 4.99 mmol) in EtOH (30 mL) was stirred at reflux temperature for 3 h. The mixture was cooled to 20 °C, diluted with water (50 mL), the pH adjusted to ca. 8 with aqueous NH_3 and the mixture stirred at 5 °C for 1 h. The mixture was filtered, washed with water (5 mL) and Et_2O (5 mL) and dried. The residue was purified by column chromatography, eluting with a gradient (50–100%) of EtOAc/pet. ether, to give phenol **51** (1.06 g, 71%) as a white powder: mp (EtOAc) 230–232 °C; ^{1}H NMR δ 10.02 (s, 1 H, NH), 9.10 (br s, 1 H, OH), 8.60 (dd, J = 4.6, 1.6 Hz, 2 H, H-2″, H-6″), 7.85 (dd, J = 4.6, 1.6 Hz, 2 H, H-3″, H-5″), 7.61 (s, 1 H, H-5′), 7.29 (d, J = 2.6 Hz, 1 H, H-2), 7.03 (dd, J = 8.7, 2.6 Hz, 1 H, H-6), 6.89 (d, J = 8.7 Hz, 1 H, H-5), 3.74 (s, 3 H, OCH_3); ^{13}C NMR δ 163.9, 149.9 (2), 147.6, 146.8, 142.8, 141.0, 134.9, 119.8 (2), 113.2, 107.9, 106.5, 106.0, 56.0; MS m/z 300.4 (MH^+, 100%). Anal. calcd for $C_{15}H_{13}N_3O_2S \cdot ¼CH_3OH$: C, 59.60; H, 4.59; N, 13.67. Found: C, 59.67; H, 4.51, N, 13.83%.

Example 1-27

2-Methyl-4-{[4-(4-pyridinyl)-1,3-thiazol-2-yl]amino}phenol (53).



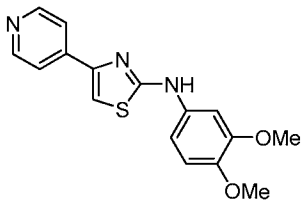
[0269] 4-Hydroxy-3-methylphenylthiourea (52). NH_4SCN (2.56 g, 33.6 mmol) was added to a stirred solution of 4-hydroxy-3-methylaniline (4.14 g, 33.6 mmol) in 1 M HCl (35 mL) at 100 °C and the solution stirred at 100 °C for 16 h. The solution was diluted with water (60 mL) and stood at 5 °C for 2 h. The mixture was extracted with EtOAc (3 × 50 mL), the combined organic fraction dried and the

solvent evaporated. The residue was purified by column chromatography, eluting with a gradient (50–60%) of EtOAc/pet. ether, to give thiourea **52** (0.77 g, 13%) as a tan powder: mp (EtOAc/pet. ether) 166–170 °C; ^{1}H NMR δ 9.27 (s, 1 H, NH), 9.23 (s, 1 H, OH), 7.11 (br s, 2 H, NH_2), 6.94 (br s, 1 H, H-2), 6.87 (br d, J = 8.4 Hz, 1 H, H-5), 6.72 (d, J = 8.4 Hz, 1 H, H-6), 2.09 (s, 3 H, CH_3). Anal. calcd for $C_8H_{10}N_2OS$: C, 52.72; H, 5.53; N, 15.37. Found: C, 52.71; H, 5.62, N, 15.19%.

[0270] 2-Methyl-4-{[4-(4-pyridinyl)-1,3-thiazol-2-yl]amino}phenol (53). A mixture of bromoketone hydrobromide **1** (0.79 g, 2.81 mmol) and 1-(4-hydroxy-3-methylphenyl)thiourea (**52**) (0.51 g, 2.81 mmol) in EtOH (30 mL) was stirred at reflux temperature for 3 h. The mixture was cooled to 20 °C, diluted with water (50 mL), the pH adjusted to ca. 8 with aqueous NH_3 and the mixture stirred at 5 °C for 1 h. The mixture was filtered, washed with water (5 mL) and Et_2O (5 mL) and dried. The residue was purified by column chromatography, eluting with a gradient (50–100%) of EtOAc/pet. ether, to give phenol **53** (0.64 g, 80%) as a white powder: mp (EtOAc/pet. ether) 212–215 °C; ^{1}H NMR δ 9.89 (s, 1 H, NH), 9.00 (br s, 1 H, OH), 8.59 (dd, J = 4.5, 1.6 Hz, 2 H, H-2″, H-6″), 7.81 (dd, J = 4.5, 1.6 Hz, 2 H, H-3″, H-5″), 7.56 (s, 1 H, H-5′), 6.35 (dd, J = 8.5, 2.7 Hz, 1 H, H-5), 7.29 (d, J = 2.7 Hz, 1 H, H-3), 6.77 (d, J = 8.5 Hz, 1 H, H-6), 2.15 (s, 3 H, CH_3); ^{13}C NMR δ 164.8, 150.6, 150.0 (2), 147.6, 141.0, 132.7, 124.1, 120.9, 119.7 (2), 116.7, 114.8, 106.1, 16.2; MS m/z 284.3 (MH^+, 100%). Anal. calcd for $C_{15}H_{13}N_3OS$: C, 63.58; H, 4.62; N, 14.83. Found: C, 63.88; H, 4.69, N, 14.85%.

Example 1-28

***N*-(3,4-Dimethoxyphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (55).**



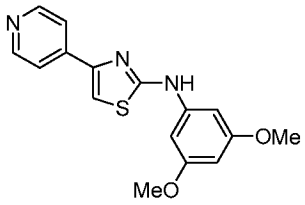
[0271] 3,4-Dimethoxyphenylthiourea (54). NH_4SCN (2.48 g, 32.6 mmol) was added to a stirred solution of 3,4-dimethoxymethylaniline (5.00 g, 32.6 mmol) in 1 M HCl (35 mL) at 100 °C and the solution stirred at 100 °C for 16 h. The solution

was diluted with water (60 mL) and stood at 5 °C for 2 h. The precipitate was filtered, washed with water (5 mL), washed with ether (5 mL), and dried to give thiourea **54** (2.33 g, 34%) as a tan powder: ^{1}H NMR δ 9.48 (s, 1 H, NH), 7.25 (br s, 2 H, NH_2), 7.00 (br s, 1 H, H-2), 6.90 (d, J = 8.6 Hz, 1 H, H-5), 6.79 (dd, J = 8.6, 2.3 Hz, 1 H, H-6), 3.73 (s, 6 H, 2 × OCH_3).

[0272] ***N*-(3,4-Dimethoxyphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (55).** A mixture of bromoketone hydrobromide **1** (1.08 g, 3.84 mmol) and 3,4-methoxyphenylthiourea (**54**) (0.82 g, 3.84 mmol) in EtOH (25 mL) was stirred at reflux temperature for 3 h. The mixture was cooled to 20 °C, diluted with water (50 mL), the pH adjusted to ca. 8 with aqueous NH_3 and the mixture stirred at 5 °C for 1 h. The mixture was filtered, washed with water (5 mL) and Et_2O (5 mL) and dried. The residue was purified by column chromatography, eluting with a gradient (50–100%) of EtOAc/pet. ether, to give amine **55** (1.04 g, 87%) as a cream powder: mp (EtOAc/pet. ether) 192–194 °C; ^{1}H NMR δ 10.16 (s, 1 H, NH), 8.60 (dd, J = 4.5, 1.6 Hz, 2 H, H-2′, H-6′), 7.82 (dd, J = 4.5, 1.6 Hz, 2 H, H-3′, H-5′), 7.63 (s, 1 H, H-5), 7.49 (d, J = 2.5 Hz, 1 H, H-2″), 7.17 (dd, J = 8.7, 2.5 Hz, 1 H, H-6″), 6.95 (d, J = 8.7 Hz, 1 H, H-5″), 3.81 (s, 3 H, OCH_3), 3.74 (s, 3 H, OCH_3); ^{13}C NMR δ 163.9, 150.2 (2), 148.9, 147.5, 143.7, 141.0, 134.9, 119.7 (2), 112.8, 108.9, 106.7, 102.8, 55.8, 55.2; MS *m/z* 314.4 (MH^+, 100%). Anal. calcd for $C_{16}H_{15}N_3O_2S$: C, 61.32; H, 4.82; N, 13.41. Found: C, 61.24; H, 4.79, N, 13.45%.

Example 1-29

***N*-(3,5-Dimethoxyphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (57).**



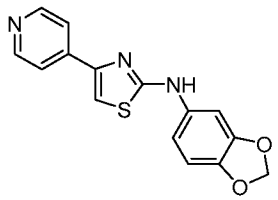
[0273] **3,5-Dimethoxyphenylthiourea (56).** NH_4SCN (2.51 g, 33.0 mmol) was added to a stirred solution of 3,5-dimethoxyaniline (5.06 g, 33.0 mmol) in 1 M HCl (35 mL) at 100 °C and the solution stirred at 100 °C for 16 h. The solution was diluted with water (60 mL) and stood at 5 °C for 2 h. The precipitate was filtered,

washed with water (5 mL), washed with ether (5 mL), and dried to give thiourea **56** (2.92 g, 42%) as a white powder: mp (EtOAc/pet. ether) 173–175 °C ^{1}H NMR δ 9.61 (s, 1 H, NH), 7.44 (br s, 2 H, NH_2), 6.63 (d, J = 2.2 Hz, 2 H, H-2, H-6), 6.26 (t, J = 2.2 Hz, 1 H, H-4), 3.72 (s, 6 H, 2 × OCH_3); ^{13}C NMR δ 180.7, 160.3 (2), 140.5, 100.7 (2), 96.3, 55.0 (2); MS *m/z* 213.4 (MH^+, 100%). Anal. calcd for $C_9H_{12}N_2O_2S$: C, 50.92; H, 5.70; N, 13.20. Found: C, 51.02; H, 5.76; N, 13.24%.

[0274] ***N*-(3,5-Dimethoxyphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (57).** A mixture of bromoketone hydrobromide **1** (842 mg, 3.0 mmol) and thiourea **56** (636 mg, 3.0 mmol) in EtOH (30 mL) was stirred at reflux temperature for 3 h. The mixture was cooled to 20 °C, diluted with water (50 mL), the pH adjusted to ca. 8 with aqueous NH_3 and the mixture stirred at 5 °C for 2 h. The precipitate was filtered, washed with water (5 mL) and dried. The crude solid was purified by column chromatography, eluting with a gradient (50–100%) of EtOAc/pet. ether, to give amine **57** (860 mg, 91%) as a cream powder: mp (EtOAc/pet. ether) 229–231 °C; ^{1}H NMR δ 10.34 (br s, 1 H, NH), 8.62 (dd, J = 4.5, 1.6 Hz, 2 H, H-2′, H-6′), 7.82 (dd, J = 4.5, 1.6 Hz, 2 H, H-3′, H-5′), 7.72 (s, 1 H, H-5), 6.96 (d, J = 2.2 Hz, 2 H, H-2″, H-6″), 6.17 (t, J = 2.2 Hz,1 H, H-4″), 3.77 (s, 6 H, 2 × OCH_3); ^{13}C NMR δ 163.6, 160.7 (2), 150.2 (2), 147.6, 142.4, 140.9, 119.7 (2), 107.6, 95.5 (2), 93.6, 59.4 (2); MS *m/z* 314.5 (MH^+, 100%). Anal. calcd for $C_{16}H_{15}N_3O_2S \cdot ¼H_2O$: C, 60.46; H, 4.92; N, 13.22. Found: C, 60.65; H, 4.75; N, 13.51%.

Example 1-30

***N*-(1,3-Benzodioxol-5-yl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (59).**



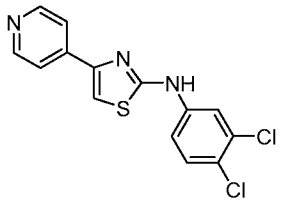
[0275] ***N*-(1,3-Benzodioxol-5-yl)thiourea (58).** NH_4SCN (2.78 g, 36.5 mmol) was added to a stirred solution of benzo[*d*][1,3]dioxol-5-amine (5.00 g, 36.5 mmol) in 1 M HCl (40 mL) at 100 °C and the solution stirred at 100 °C for 16 h. The solution was diluted with water (60 mL) and stood at 5 °C for 2 h. The precipitate

was filtered, washed with water (5 mL), washed with ether (5 mL), and dried to give thiourea **58** (2.50 g, 35%) as a tan powder: mp (H_2O) 190–193 °C [lit. (Rasmussen et al., *Synthesis* 1988, 456) mp (MeOH) 209–211 °C]; ^{1}H NMR δ 9.46 (s, 1 H, NH), 7.47 (br s, 2 H, NH_2), 7.00 (br d, J = 2.1 Hz, 1 H, H-4), 6.85 (d, J = 8.3 Hz, 1 H, H-7), 6.69 (dd, J = 8.3, 2.1 Hz, 1 H, H-6), 6.00 (s, 2 H, H-2).

[0276] ***N*-(1,3-Benzodioxol-5-yl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (59).** A mixture of bromoketone hydrobromide **1** (0.73 g, 2.61 mmol) and 1-(benzo[*d*][1,3]dioxol-5-yl)thiourea (**58**) (0.51 g, 2.61 mmol) in EtOH (25 mL) was stirred at reflux temperature for 3 h. The mixture was cooled to 20 °C, diluted with water (50 mL), the pH adjusted to ca. 8 with aqueous NH_3 and the mixture stirred at 5 °C for 1 h. The mixture was filtered, washed with water (5 mL) and Et_2O (5 mL) and dried. The residue was purified by column chromatography, eluting with 5% MeOH/DCM, to give amine **59** (0.71 g, 92%) as a tan powder: mp (MeOH/EtOAc) 201–203 °C; ^{1}H NMR δ 10.21 (s, 1 H, NH), 8.60 (dd, J = 4.5, 1.6 Hz, 2 H, H-2′, H-6′), 7.81 (dd, J = 4.5, 1.6 Hz, 2 H, H-3′, H-5′), 7.64 (s, 1 H, H-5), 7.44 (d, J = 2.2 Hz, 1 H, H-4″), 7.08 (dd, J = 8.4, 2.2 Hz, 1 H, H-6″), 6.90 (d, J = 8.4 Hz, 1 H, H-5″), 6.00 (s, 2 H, H-2″); ^{13}C NMR δ 163.8, 150.0 (2), 147.5, 147.3, 141.7, 140.9, 135.6, 119.7 (2), 109.7, 108.2, 106.9, 100.8, 99.6; MS *m/z* 298.3 (MH^+, 100%). Anal. calcd for $C_{15}H_{11}N_3O_2S \cdot ¾H_2O$: C, 57.96; H, 4.05; N, 13.51. Found: C, 58.03; H, 3.76, N, 13.16%.

Example 1-31

***N*-(3,4-Dichlorophenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (61).**

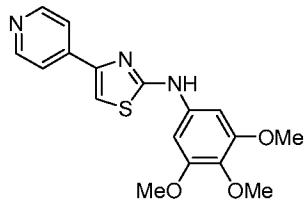


[0277] A mixture of bromoketone hydrobromide **1** (0.69 g, 2.44 mmol) and 3,4-dichlorophenylthiourea (**60**) (0.54 g, 2.44 mmol) in EtOH (25 mL) was stirred at reflux temperature for 2 h. The mixture was cooled to 20 °C, diluted with water (50 mL), the pH adjusted to ca. 8 with aqueous NH_3 and the mixture stirred at 5 °C for

1 h. The mixture was extracted with EtOAc (3 × 50 mL) and the combined organic fraction dried and the solvent evaporated. The residue was purified by column chromatography, eluting with a gradient (50–100%) of EtOAc/pet. ether, to give amine **61** (0.77 g, 97%) as a cream powder: mp (EtOAc) 242–244 °C; ^{1}H NMR δ 10.68 (br s, 1 H, NH), 8.63 (dd, *J* = 4.5, 1.6 Hz, 2 H, H-2′, H-6′), 8.13 (d, *J* = 2.5 Hz, 1 H, H-2″), 7.83 (dd, *J* = 4.5, 1.6 Hz, 2 H, H-3′, H-5′), 7.80 (s, 1 H, H-5), 7.64 (dd, *J* = 8.8, 2.5 Hz, 1 H, H-6″), 7.57 (d, *J* = 8.8 Hz, 1 H, H-5″); ^{13}C NMR δ 162.7, 150.1 (2), 147.6, 140.7, 140.6, 131.0, 130.7, 122.3, 119.7 (2), 117.8, 117.0, 108.4. Anal. calcd for $C_{14}H_9Cl_2N_3S·¼EtOAc$: C, 52.38; H, 3.27; N, 12.21. Found: C, 52.51; H, 3.51, N, 11.96%.

Example 1-32

4-(4-Pyridinyl)-*N*-(3,4,5-trimethoxyphenyl)-1,3-thiazol-2-amine (63).



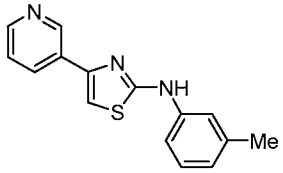
[0278] 3,4,5-Trimethoxyphenylthiourea (62). NH_4SCN (2.51 g, 33.0 mmol) was added to a stirred solution of 3,4,5-trimethoxyaniline (6.04 g, 33.0 mmol) in 1 M HCl (35 mL) at 100 °C and the solution stirred at 100 °C for 16 h. The solution was diluted with water (60 mL) and stood at 5 °C for 2 h. The precipitate was filtered, washed with water (5 mL), washed with ether (5 mL), and dried to give thiourea **62** (1.18 g, 15%) as a white powder: mp (EtOAc/pet. ether) 201–203 °C [lit. (Protiva, M., et. al., *Coll. Czech. Chem. Commun.* 1975, *40*, 3904.) mp 203–205 °C]; ^{1}H NMR δ 9.55 (s, 1 H, NH), 7.39 (br s, 2 H, NH_2), 6.70 (s, 2 H, H-2, H-6), 3.73 (s, 6 H, 2 × OCH_3), 3.64 (s, 3 H, OCH_3); ^{13}C NMR δ 180.6, 156.2 (2), 134.5, 134.4, 101.0 (2), 59.9, 55.7 (2); MS *m/z* 242 (MH^+, 100%). Anal. calcd for $C_{10}H_{14}N_2O_3S$: C, 49.57; H, 5.82; N, 11.56. Found: C, 49.84; H, 5.80; N, 11.57%.

[0279] 4-(4-Pyridinyl)-*N*-(3,4,5-trimethoxyphenyl)-1,3-thiazol-2-amine (63). A mixture of bromoketone hydrobromide **1** (842 mg, 3.0 mmol) and 3,4,5-trimethoxyphenylthiourea (**62**) (726 mg, 3.0 mmol) in EtOH (30 mL) was stirred at

reflux temperature for 3 h. The mixture was cooled to 20 °C, diluted with water (50 mL), the pH adjusted to ca. 8 with aqueous NH_3 and the mixture stirred at 5 °C for 2 h. The precipitate was filtered, washed with water (5 mL) and dried. The crude solid was purified by column chromatography, eluting with a gradient (50–100%) of EtOAc/pet. ether, to give amine **63** (215 mg, 21%) as a cream powder: mp (MeOH/EtOAc) 207–209 °C; ^{1}H NMR δ 10.34 (br s, 1 H, NH), 8.62 (dd, J = 4.5, 1.6 Hz, 2 H, H-2″, H-6″), 7.82 (dd, J = 4.5, 1.6 Hz, 2 H, H-3″, H-5″), 7.72 (s, 1 H, H-5), 6.96 (d, J = 2.2 Hz, 2 H, H-2′, H-6′), 3.77 (s, 6 H, 2 × OCH_3), 3.64 (s, 3 H, OCH_3); ^{13}C NMR δ 163.5, 152.9, 150.0 (2), 147.4, 141.0, 137.0 (2), 132.1, 119.7 (2), 107.3, 94.9 (2), 60.0, 55.7 (2); MS *m/z* 314.5 (MH^+, 100%). Anal. calcd for $C_{17}H_{17}N_3O_3S·¼CH_3OH$: C, 58.96; H, 5.16; N, 11.96. Found: C, 58.79; H, 5.08; N, 11.95%.

Example 1-33

***N*-(3-Methylphenyl)-4-(3-pyridinyl)-1,3-thiazol-2-amine (65).**



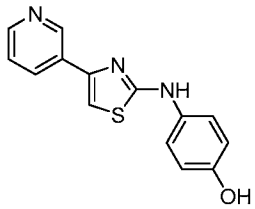
[0280] 2-Bromo-1-(pyridin-3-yl)ethanone hydrobromide (64). Br_2 (2.0 mL, 38.6 mmol) was added dropwise to a stirred a solution of 3-acetylpyridine (4.45 g, 36.7 mmol) in 30% HBr/HOAc (75 mL) at 10–15 °C. The mixture was stirred at 40 °C for 1 h and then 75 °C for 1 h. The mixture was cooled to 20 °C, diluted with Et_2O (200 mL) and stirred for 30 min. The precipitate was filtered, washed with Et_2O (20 mL) and dried under vacuum to give bromoketone **64** as the hydrobromide salt (9.79 g, 95%) as a cream powder: mp 195–198 °C [lit. (McKennis, H. et al., *J. Org. Chem.* 1963, *28*, 383.) mp (MeOH/ether) 185–188 °C]; ^{1}H NMR δ 9.23 (dd, J = 2.2, 0.7 Hz, 1 H, H-2′), 8.91 (dd, J = 5.1, 1.6 Hz, 1 H, H-6′), 8.53 (dd, J = 8.1, 2.0 Hz, 1 H, H-4′), 7.78 (dd, J = 8.1, 5.1 Hz, 1 H, H-5′), 7.70 (br s, 1 H, N·HBr), 5.02 (s, 2 H, H-2).

[0281] *N*-(3-Methylphenyl)-4-(3-pyridinyl)-1,3-thiazol-2-amine (65). A mixture of bromoketone hydrobromide **64** (1.17 g, 4.2 mmol) and 3-

methylphenylthiourea (**4**) (0.64 g, 4.2 mmol) in EtOH (25 mL) was stirred at reflux temperature for 3 h. The mixture was cooled to 20 °C, diluted with water (50 mL), the pH adjusted to ca. 8 with aqueous NH_3 and the mixture stirred at 0 °C for 1 h. The precipitate was filtered, washed with water (5 mL) and dried. The crude solid was purified by column chromatography, eluting with EtOAc, to give amine **65** (0.86 g, 77%) as a cream powder: mp (EtOAc) 171–173 °C; ^{1}H NMR δ 10.24 (br s, 1 H, NH), 9.13 (dd, *J* = 2.2, 0.7 Hz, 1 H, H-2′), 8.51 (dd, *J* = 4.7, 1.6 Hz, 1 H, H-6′), 8.24 (ddd, *J* = 8.0, 2.1, 1.7 Hz, 1 H, H-4′), 7.57 (dd, *J* = 8.1, 1.9 Hz, 1 H, H-6″), 7.50 (s, 1 H, H-5), 7.48 (d, *J* = 1.9 Hz, 1 H, H-2″), 7.45 (ddd, *J* = 8.0, 4.7, 0.7 Hz, 1 H, H-5′), 7.24 (dd, *J* = 7.9, 7.5 Hz, 1 H, H-5″), 6.80 (br d, *J* = 7.5 Hz, 1 H, H-4″), 2.32 (s, 3 H, CH_3); ^{13}C NMR δ 163.6, 148.3, 147.1, 146.8, 140.9, 138.0, 132.6, 130.0, 128.8, 123.6, 122.1, 117.4, 114.9, 104.3, 21.2; MS *m/z* 268.4 (MH^+, 100%). Anal. calcd for $C_{15}H_{13}N_3$: C, 67.39; H, 4.90; N, 15.72. Found: C, 67.20; H, 5.07; N, 15.77%.

Example 1-34

4-{[4-(3-Pyridinyl)-1,3-thiazol-2-yl]amino}phenol (66).

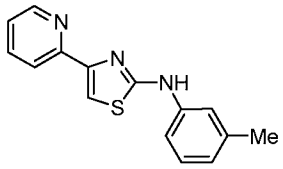


[0282] 4-{[4-(3-Pyridinyl)-1,3-thiazol-2-yl]amino}phenol (66). A mixture of bromoketone hydrobromide **64** (0.84 g, 3.0 mmol) and 1-(4-hydroxyphenyl)thiourea (**24**) (0.50 g, 3.0 mmol) in EtOH (20 mL) was stirred at reflux temperature for 3 h. The mixture was cooled to 20 °C, diluted with water (50 mL), the pH adjusted to ca. 8 with aqueous NH_3 and the mixture stirred at 0 °C for 1 h. The precipitate was filtered, washed with water (5 mL) and dried to give phenol **66** (0.77 g, 95%) as a cream powder: mp (H_2O) 275–278 °C; ^{1}H NMR δ 9.95 (br s, 1 H, NH), 9.10 (m, 2 H, H-2″, OH), 8.49 (dd, *J* = 4.7, 1.6 Hz, 1 H, H-6″), 8.21 (ddd, *J* = 8.3, 2.1, 1.6 Hz, 1 H, H-4″), 7.47 (ddd, *J* = 8.9, 3.4, 2.2 Hz, 2 H, H-3, H-5), 7.44 (ddd, *J* = 8.3, 4.7, 0.7 Hz, 1 H, H-5″), 7.38 (s, 1 H, H-5′), 6.77 (ddd, *J* = 8.9, 3.4, 2.2 Hz, 2 H, H-2, H-6); ^{13}C NMR δ 164.7, 152.4, 148.2, 147.1,

146.8, 133.0, 132.6, 130.2, 123.5, 119.3 (2), 115.4 (2), 103.3; MS *m/z* 270.4 (MH^+, 100%). Anal. calcd for $C_{14}H_{11}N_3OS \cdot \frac{1}{4}H_2O$: C, 61.41; H, 4.23; N, 15.34. Found: C, 61.66; H, 4.45; N, 15.46%.

Example 1-35

***N*-(3-Methylphenyl)-4-(2-pyridinyl)-1,3-thiazol-2-amine (68).**



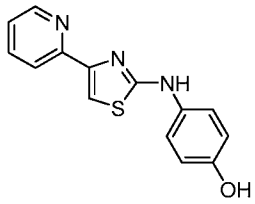
[0283] 2-Bromo-1-(pyridin-2-yl)ethanone hydrobromide (67). Br_2 (4.1 mL, 80.6 mmol) was added dropwise to a stirred a solution of 2-acetylpyridine (9.30 g, 76.8 mmol) in 30% HBr/HOAc (150 mL) at 10–15 °C. The mixture was stirred at 40 °C for 1 h and then 75 °C for 1 h. The mixture was cooled to 20 °C, diluted with Et_2O (200 mL) and stirred for 30 min. The precipitate was filtered, washed with Et_2O (30 mL) and dried under vacuum to give the bromoketone hydrobromide salt **67** (19.46 g, 90%) as a cream powder: mp 200–205 °C (dec) [lit. (Ogawa, K. *J. Chem. Soc. Perkin 1* 1985, 2417.) mp 203–205 °C]; ^{1}H NMR δ 8.74 (ddd, *J* = 4.5, 1.5, 1.0 Hz, 1 H, H-6′), 8.00–8.08 (m, 2 H, H-3′, H-5′), 7.71 (ddd, *J* = 6.9, 4.5, 2.0 Hz, 1 H, H-4′), 7.70 (br s, 1 H, N·HBr), 5.01 (s, 2 H, H-2).

[0284] *N*-(3-Methylphenyl)-4-(2-pyridinyl)-1,3-thiazol-2-amine (68). A mixture of bromoketone hydrobromide **67** (0.96 g, 3.4 mmol) and 3-methylphenylthiourea (**4**) (0.57 g, 3.4 mmol) in EtOH (25 mL) was stirred at reflux temperature for 3 h. The mixture was cooled to 20 °C, diluted with water (40 mL), the pH adjusted to ca. 8 with aqueous NH_3 and the mixture stirred at 0 °C for 1 h. The precipitate was filtered, washed with water (5 mL) and dried. The crude solid was purified by column chromatography, eluting with EtOAc, to give amine **68** (0.74 g, 81%) as a cream powder: mp (EtOAc) 164–166 °C; ^{1}H NMR δ 10.20 (br s, 1 H, NH), 8.58 (ddd, *J* = 4.7, 1.7, 0.8 Hz, 1 H, H-6′), 7.99 (dt, *J* = 7.9, 0.9 Hz, 1 H, H-3′), 7.99 (ddd, *J* = 7.9, 7.5, 1.8 Hz, 1 H, H-4′), 7.58 (br d, *J* = 8.1 Hz, 1 H, H-6′), 7.52 (s, 1 H, H-5), 7.47 (br s, 1 H, H-2″), 7.31 (ddd, *J* = 7.5, 4.7, 1.2 Hz, 1 H, H-5′), 7.24 (t, *J* = 7.8 Hz, 1 H, H-5″), 6.80 (br d, *J* = 7.5 Hz, 1 H, H-4″), 2.33 (s, 3

H, CH_3); ^{13}C NMR δ 163.3, 152.0, 150.2, 149.3, 141.0, 138.0, 137.1, 128.8, 122.4, 122.0, 120.2, 117.4, 114.0, 106.5, 21.2; MS *m/z* 268.4 (MH^+, 100%). Anal. calcd for $C_{15}H_{13}N_3$: C, 67.39; H, 4.90; N, 15.72. Found: C, 67.13; H, 5.10; N, 15.67%.

Example 1-36

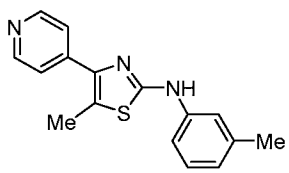
4-{[4-(2-Pyridinyl)-1,3-thiazol-2-yl]amino}phenol (69).



[0285] 4-{[4-(2-Pyridinyl)-1,3-thiazol-2-yl]amino}phenol (69). A mixture of bromoketone hydrobromide **67** (0.78 g, 2.8 mmol) and 1-(4-hydroxyphenyl)thiourea (**24**) (0.46 g, 2.8 mmol) in EtOH (20 mL) was stirred at reflux temperature for 3 h. The mixture was cooled to 20 °C, diluted with water (50 mL), the pH adjusted to ca. 8 with aqueous NH_3 and the mixture stirred at 0 °C for 1 h. The precipitate was filtered, washed with water (5 mL) and dried. The crude solid was purified by column chromatography, eluting with EtOAc, to give phenol **69** (0.67 g, 90%) as a cream powder: mp (EtOAc) 185–186 °C; ^1H NMR δ 9.91 (br s, 1 H, NH), 9.09 (s, 1 H, OH), 8.56 (ddd, *J* = 4.7, 1.7, 0.8 Hz, 1 H, H-6″), 7.95 (br d, *J* = 7.9 Hz, 1 H, H-3″), 7.87 (ddd, *J* = 7.9, 7.5 Hz, 1 H, H-4″), 7.49 (ddd, *J* = 8.9, 3.4, 2.2 Hz, 2 H, H-3, H-5), 7.43 (s, 1 H, H-5′), 7.30 (ddd, *J* = 7.5, 4.7, 1.2 Hz, 1 H, H-5″), 6.77 (ddd, *J* = 8.9, 3.4, 2.2 Hz, 2 H, H-2, H-6); ^{13}C NMR δ 164.4, 152.3, 152.2, 150.2, 149.2, 137.0, 133.1, 122.3, 120.2, 119.2 (2), 115.4 (2), 105.5; MS *m/z* 270.4 (MH^+, 100%). Anal. calcd for $C_{14}H_{11}N_3OS$: C, 62.43; H, 4.12; N, 15.60. Found: C, 62.30; H, 4.37; N, 15.69%.

Example 1-37

5-Methyl-*N*-(3-methylphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (71).

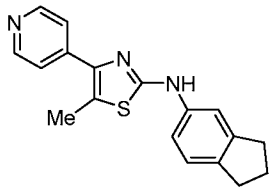


[0286] 2-Bromo-1-(4-pyridinyl)-1-propanone Hydrobromide (70). Br_2 (4.0 mL, 78.6 mmol) was added dropwise to a stirred a solution of 4-propionylpyridine (10.1 g, 74.9 mmol) in 30% HBr/HOAc (80 mL) at 15 °C. The mixture was stirred at 40 °C for 1 h and then at 80 °C for 1 h. The mixture was cooled to 20 °C, diluted with Et_2O (400 mL) and stirred at 0 °C for 30 min. The precipitate was filtered, washed with Et_2O (25 mL) and dried under vacuum to give the bromoketone hydrobromide salt **70** (21.21 g, 96%) as a white powder: mp (Et_2O/H_2O) 195–197 °C; ^{1}H NMR δ 8.98 (dd, *J* = 4.8, 1.6 Hz, 2 H, H-2′, H-6′), 8.15 (dd, *J* = 4.8, 1.6 Hz, 2 H, H-3′, H-5′), 6.48 (br s, 1 H, N·HBr), 5.87 (q, *J* = 6.5 Hz, 1 H, H-2), 1.81 (d, *J* = 6.5 Hz, 3 H, H-3).

[0287] 5-Methyl-*N*-(3-methylphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (71). A mixture of bromide **70** (0.92 g, 3.1 mmol) and 3-methylphenylthiourea (**4**) (0.52 g, 3.1 mmol) in EtOH (30 mL) was stirred at reflux temperature for 3 h. The mixture was cooled to 20 °C, diluted with water (50 mL), the pH adjusted to ca. 9 with aqueous NH_3 and the mixture stirred at 5 °C for 2 h. The precipitate was filtered, washed with water (5 mL) and dried. The crude solid was purified by column chromatography, eluting with EtOAc, to give amine **71** (0.82 g, 94%) as a cream powder: mp (EtOAc) 193–195 °C; ^{1}H NMR δ 10.03 (s, 1 H, NH), 8.62 (dd, *J* = 4.5, 1.6 Hz, 2 H, H-2′, H-6′), 7.67 (dd, *J* = 4.5, 1.6 Hz, 2 H, H-3′, H-5′), 7.50 (br dd, *J* = 8.0, 1.9 Hz, 1 H, H-6″), 7.38 (br s, 1 H, H-2″), 7.19 (dd, *J* = 8.0, 7.5 Hz, 1 H, H-5″), 6.77 (br d, *J* = 7.5 Hz, 1 H, H-4″), 2.30 (s, 6 H, 2 × CH_3); ^{13}C NMR δ 159.5, 149.7 (2), 142.3, 141.8, 140.9, 138.0, 128.7, 121.9 (2), 121.8, 120.5, 117.3, 113.9, 21.2, 11.9; MS *m/z* 282.5 (MH^+, 100%). Anal. calcd for $C_{16}H_{15}N_3S$: C, 68.30; H, 5.37; N, 14.93. Found: C, 68.33; H, 5.51; N, 14.90%.

Example 1-38

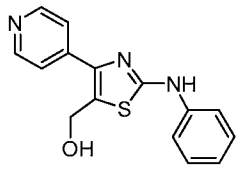
***N*-(2,3-Dihydro-1*H*-inden-5-yl)-5-methyl-4-(4-pyridinyl)-1,3-thiazol-2-amine (72).**



[0288] ***N*-(2,3-Dihydro-1*H*-inden-5-yl)-5-methyl-4-(4-pyridinyl)-1,3-thiazol-2-amine (72).** A mixture of bromide **70** (0.50 g, 1.7 mmol) and thiourea **46** (0.32 g, 1.7 mmol) in EtOH (30 mL) was stirred at reflux temperature for 2 h. The mixture was cooled to 20 °C, diluted with water (60 mL), the pH adjusted to ca. 9 with aqueous NH_3 and the mixture stirred at 0 °C for 1 h. The precipitate was filtered, washed with water (5 mL) and dried. The crude solid was purified by column chromatography, eluting with 50% EtOAc/pet ether, to give amine **72** (0.47 g, 90%) as a tan powder: mp (EtOAc/Et_2O) 180–181 °C; ^{1}H NMR δ 9.95 (s, 1 H, NH), 8.63 (dd, *J* = 4.5, 1.6 Hz, 2 H, H-2′, H-6′), 7.65 (dd, *J* = 4.5, 1.6 Hz, 2 H, H-3′, H-5′), 7.48 (br s, 1 H, H-4‴), 7.38 (dd, *J* = 8.1, 2.0 H, 1 H, H-6‴), 7.15 (d, *J* = 8.1 Hz, 1 H, H-7‴), 2.84 (br t, *J* = 7.4 Hz, 2 H, H-3‴), 2.79 (br t, *J* = 7.4 Hz, 2 H, H-1‴), 2.49 (s, 3 H, H-1′), 2.01 (br sept, *J* = 7.4 Hz, 2 H, H-2‴); ^{13}C NMR δ 159.9, 149.7 (2), 144.3, 142.4, 141.9, 139.4, 136.4, 124.6, 121.9 (2), 120.0, 115.2, 113.1, 32.5, 31.6, 25.1, 11.9; MS *m/z* 308.5 (MH^+, 100%). Anal. calcd for $C_{18}H_{17}N_3S·Et_2O$: C, 70.02; H, 6.03; N, 12.89. Found: C, 70.47; H, 6.02; N, 12.88%.

Example 1-39

[2-(Phenylamino)-4-(4-pyridinyl)-1,3-thiazol-5-yl]methanol (73).

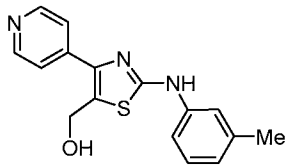


[0289] **[2-(Phenylamino)-4-(4-pyridinyl)-1,3-thiazol-5-yl]methanol (73).** A mixture of amine **3** (0.37 g, 1.46 mmol), 40% aqueous formaldehyde solution (5 mL) and Et_3N (1 mL) in THF (5 mL) was stirred in a glass pressure vessel at 130 °C for 1 h. The mixture was cooled to 20 °C, the reaction quenched with cNH_3 solution (2 mL) and the mixture diluted with water (50 mL). The mixture was extracted with EtOAc (3 × 20 mL), the combined organic fraction was dried and

the solvent evaporated. The crude solid was purified by column chromatography, eluting with a gradient (0–5%) of MeOH/DCM, to give (i) starting material **3** (71 mg, 19%) and (ii) alcohol **73** (258 mg, 62%) as a white powder: mp (MeOH/DCM) 170–172 °C; ^{1}H NMR δ 10.19 (br s, 1 H, NH), 8.64 (dd, *J* = 4.5, 1.6 Hz, 2 H, H-2″, H-6″), 7.65–7.69 (m, 4 H, H-3″, H-5″, H-2‴, H-6‴), 7.33 (tt, *J* = 7.4, 1.9 Hz, 2 H, H-3‴, H-5‴), 6.96 (br t, *J* = 7.4 Hz, 1 H, H-4‴), 5.72 (t, *J* = 5.4 Hz, 1 H, OH), 4.70 (d, *J* = 5.4 Hz, 2 H, H-1); ^{13}C NMR δ 161.1, 149.8 (2), 142.7, 141.5, 140.9, 128.9 (2), 127.7, 122.1 (2), 121.2, 116.8 (2), 55.4; MS *m/z* 284.4 (MH^+, 100%). Anal. calcd for $C_{15}H_{13}N_3OS·H_2O$: C, 59.78; H, 5.01; N, 13.94. Found: C, 60.12; H, 4.57; N, 13.92%.

Example 1-40

[2-[(3-Methylphenyl)amino]-4-(4-pyridinyl)-1,3-thiazol-5-yl]methanol (74).

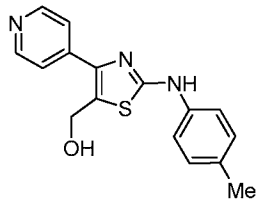


[0290] [2-[(3-Methylphenyl)amino]-4-(4-pyridinyl)-1,3-thiazol-5-yl]methanol (74). A mixture of amine **5** (1.02 g, 1.87 mmol), 40% aqueous formaldehyde solution (10 mL) and Et_3N (3 mL) in THF (10 mL) was stirred in a glass pressure vessel at 130 °C for 1 h. The mixture was cooled to 20 °C, the reaction quenched with cNH_3 solution (6 mL) and the mixture diluted with water (100 mL). The mixture was extracted with EtOAc (3 × 50 mL), the combined organic fraction was dried and the solvent evaporated. The crude solid was purified by column chromatography, eluting with a gradient (0–5%) of MeOH/DCM, to give (i) starting material **5** (93 mg, 9%) and (ii) alcohol **74** (874 mg, 77%) as a white powder: mp (MeOH/DCM) 161–163 °C; ^{1}H NMR δ 10.12 (br s, 1 H, NH), 8.64 (dd, *J* = 4.5, 1.6 Hz, 2 H, H-2″, H-6″), 7.65 (dd, *J* = 4.5, 1.6 Hz, 2 H, H-3″, H-5″), 7.52 (dd, *J* = 8.0, 1.8 Hz, 1 H, H-6‴), 7.40 (br s, 1 H, H-2‴), 7.21 (dd, *J* = 8.0, 7.5 Hz, 1 H, H-5‴), 6.79 (br d, *J* = 7.5 Hz, 1 H, H-4‴), 5.71 (t, *J* = 5.5 Hz, 1 H, OH), 4.70 (d, *J* = 5.5 Hz, 2 H, H-1), 2.30 (s, 3 H, CH_3); ^{13}C NMR δ 161.2, 149.8 (2), 142.7, 141.5, 140.9, 138.0, 128.7, 127.6, 122.1 (2), 122.0, 117.4, 114.1, 55.4, 21.2;

MS *m/z* 298.5 (MH^+, 100%). Anal. calcd for $C_{16}H_{15}N_3OS$: C, 64.62; H, 5.08; N, 14.13. Found: C, 64.70; H, 5.18; N, 14.08%.

Example 1-41

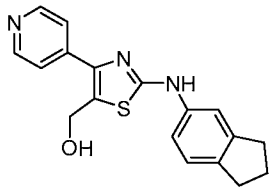
[2-[(4-Methylphenyl)amino]-4-(4-pyridinyl)-1,3-thiazol-5-yl]methanol (75).



[0291] [2-[(4-Methylphenyl)amino]-4-(4-pyridinyl)-1,3-thiazol-5-yl]methanol (75). A mixture of amine **21** (0.25 g, 0.94 mmol), 40% aqueous formaldehyde solution (5 mL) and Et_3N (1 mL) in THF (5 mL) was stirred in a glass pressure vessel at 130 °C for 2 h. The mixture was cooled to 20 °C, the reaction quenched with cNH_3 solution (2 mL) and the mixture diluted with water (50 mL). The mixture was extracted with EtOAc (3 × 20 mL), the combined organic fraction was dried and the solvent evaporated. The crude solid was purified by column chromatography, eluting with a gradient (0–5%) of MeOH/DCM, to give (i) starting material **21** (95 mg, 38%) and (ii) alcohol **75** (162 mg, 58%) as a white powder: mp (MeOH/DCM) 208–212 °C (dec.); ^{1}H NMR δ 10.08 (br s, 1 H, NH), 8.64 (dd, *J* = 4.5, 1.6 Hz, 2 H, H-2″, H-6″), 7.64 (dd, *J* = 4.5, 1.6 Hz, 2 H, H-3″, H-5″), 7.53 (br d, *J* = 8.5 Hz, 2 H, H-2‴, H-6‴), 7.13 (br d, *J* = 8.5 Hz, 2 H, H-3‴, H-5‴), 5.70 (t, *J* = 5.4 Hz, 1 H, OH), 4.68 (d, *J* = 5.4 Hz, 2 H, H-1), 2.25 (s, 3 H, CH_3); ^{13}C NMRδ 161.4, 149.8 (2), 142.8, 141.5, 138.5, 130.1, 129.3 (2), 127.3, 122.1 (2), 117.1 (2), 55.4, 20.2; MS *m/z* 298.5 (MH^+, 100%). Anal. calcd for $C_{16}H_{15}N_3OS \cdot \frac{1}{3}CH_2Cl_2$: C, 60.24; H, 4.85; N, 12.90. Found: C, 60.05; H, 4.94; N, 12.82%.

Example 1-42

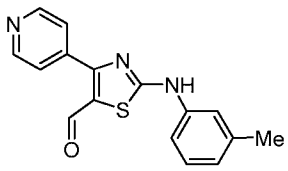
[2-(2,3-Dihydro-1*H*-inden-5-ylamino)-4-(4-pyridinyl)-1,3-thiazol-5-yl]methanol (76).



[0292] [2-(2,3-Dihydro-1*H*-inden-5-ylamino)-4-(4-pyridinyl)-1,3-thiazol-5-yl]methanol (76). A mixture of amine **47** (0.25 g, 0.77 mmol), 40% aqueous formaldehyde solution (5 mL) and Et_3N (1 mL) in THF (5 mL) was stirred in a glass pressure vessel at 130 °C for 2 h. The mixture was cooled to 20 °C, the reaction quenched with cNH_3 solution (2 mL) and the mixture diluted with water (50 mL). The mixture was extracted with EtOAc (3 × 20 mL), the combined organic fraction was dried and the solvent evaporated. The crude solid was purified by column chromatography, eluting with a gradient (0–5%) of MeOH/DCM, to give alcohol **76** (172 mg, 69%) as a white powder: mp (MeOH/EtOAc) 185–187 °C; ^{1}H NMR δ 10.05 (br s, 1 H, NH), 8.64 (dd, *J* = 4.5, 1.6 Hz, 2 H, H-2″, H-6″), 7.64 (dd, *J* = 4.5, 1.6 Hz, 2 H, H-3″, H-5″), 7.49 (d, *J* = 2.0 Hz, 1 H, H-4‴), 7.39 (dd, *J* = 8.1, 2.0 Hz, 1 H, H-6‴), 7.16 (d, *J* = 8.1 Hz, 1 H, H-5‴), 5.68 (t, *J* = 5.4 Hz, 1 H, OH), 4.68 (d, *J* = 5.4 Hz, 2 H, H-1), 2.85 (t, *J* = 7.4 Hz, 2 H, H-3‴), 2.80 (t, *J* = 7.4 Hz, 2 H, H-1‴), 2.00 (sept, *J* = 7.4 Hz, 2 H, H-2‴); ^{13}C NMR δ 161.6, 149.7 (2), 144.3, 142.8, 141.5, 139.3, 136.6, 127.1, 124.3, 122.1 (2), 115.3, 113.2, 55.4, 32.5, 31.6, 25.1; MS *m/z* 324.6 (MH^+, 100%). Anal. calcd for $C_{18}H_{17}N_3OS$: C, 66.85; H, 5.30; N, 12.99. Found: C, 66.80; H, 5.30; N, 12.98%.

Example 1-43

2-[(3-Methylphenyl)amino]-4-(4-pyridinyl)-1,3-thiazole-5-carbaldehyde (77).

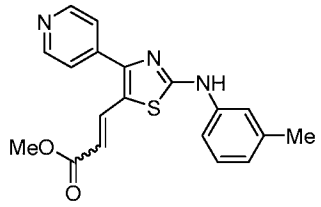


[0293] 2-[(3-Methylphenyl)amino]-4-(4-pyridinyl)-1,3-thiazole-5-carbaldehyde (77). MnO_2 (1.23 g, 14.1 mmol) was added to a stirred solution of alcohol **74** (0.84 g, 2.8 mmol) in benzene (40 mL) at 80 °C and the mixture stirred at 80 °C for 2 h. The mixture was cooled to 20 °C, filtered through Celite, which was washed with benzene (2 × 40 mL). The solvent of combined organic fraction

was evaporated. The crude solid was purified by column chromatography, eluting with a gradient (0–5%) of MeOH/DCM, to give aldehyde **77** (346 mg, 42%) as a white powder: mp (MeOH/EtOAc) 220–223 °C; ^{1}H NMR δ 11.12 (s, 1 H, CHO), 9.81 (br s, 1 H, NH), 8.74 (dd, *J* = 4.4, 1.6 Hz, 2 H, H-2′, H-6′), 7.80 (dd, *J* = 4.4, 1.6 Hz, 2 H, H-3′, H-5′), 7.50 (br dd, *J* = 8.0, 1.7 Hz, 1 H, H-6″), 7.40 (br s, 1 H, H-2″), 7.28 (dd, *J* = 8.0, 7.6 Hz, 1 H, H-5″), 6.94 (br d, *J* = 7.6 Hz, 1 H, H-4″), 2.32 (s, 3 H, CH_3); ^{13}C NMR δ 181.9, 167.6, 151.4, 150.1 (2), 140.0, 139.3, 138.5, 129.0, 124.8, 124.3, 123.6 (2), 119.2, 115.9, 21.0; MS *m/z* 296.4 (MH^+, 100%). Anal. calcd for $C_{16}H_{13}N_3OS$: C, 65.06; H, 4.44; N, 14.23. Found: C, 64.75; H, 4.56; N, 14.08%.

Example 1-44

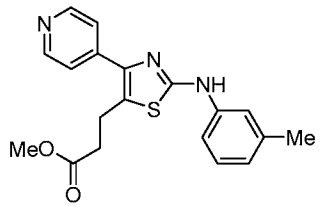
Methyl (2*E*)-3-[2-[(3-Methylphenyl)amino]-4-(4-pyridinyl)-1,3-thiazol-5-yl]-2-propenoate (78).



[0294] Methyl (2*E*)-3-[2-[(3-Methylphenyl)amino]-4-(4-pyridinyl)-1,3-thiazol-5-yl]-2-propenoate (78). A solution of aldehyde **77** (123 mg, 0.42 mmol) and methyl (triphenylphosphoranylidene)acetate (139 mg, 0.42 mmol) in DCM (10 mL) was stirred at 20 °C for 48 h. The solvent was evaporated and the crude solid was purified by column chromatography, eluting with 50% EtOAc/pet ether, to give ester **78** (80 mg, 54%) as a white powder: mp (EtOAc/pet. ether) 205–207 °C; ^{1}H NMR δ 10.78 (br s, 1 H, NH), 8.74 (dd, *J* = 4.4, 1.6 Hz, 2 H, H-2″, H-6″), 7.67 (d, *J* = 15.3 Hz, 1 H, H-3), 7.60 (dd, *J* = 4.4, 1.6 Hz, 2 H, H-3″, H-5″), 7.51 (br dd, *J* = 8.0, 2.0 Hz, 1 H, H-6‴), 7.40 (br s, 1 H, H-2‴), 7.25 (dd, *J* = 8.0, 7.5 Hz, 1 H, H-5‴), 6.88 (br d, *J* = 7.5 Hz, 1 H, H-4‴), 6.02 (d, *J* = 15.3 Hz, 1 H, H-2), 3.68 (s, 3 H, OCH_3), 2.31 (s, 3 H, CH_3); ^{13}C NMR δ 166.2, 163.4, 152.4, 150.1 (2), 140.8, 139.8, 138.3, 133.9, 128.9, 123.4, 123.2 (2), 119.7, 118.6, 116.2, 115.2, 51.3, 21.1; MS *m/z* 352.7 (MH^+, 100%). Anal. calcd for $C_{19}H_{17}N_3O_2S$: C, 64.94; H, 4.88; N, 11.96. Found: C, 64.67; H, 5.12; N, 11.74%.

Example 1-45

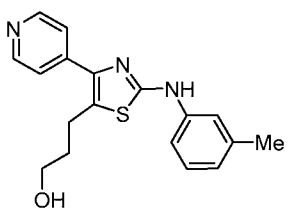
Methyl 3-[2-[(3-Methylphenyl)amino]-4-(4-pyridinyl)-1,3-thiazol-5-yl]propanoate (79).



[0295] Methyl 3-[2-[(3-Methylphenyl)amino]-4-(4-pyridinyl)-1,3-thiazol-5-yl]propanoate (79). A suspension of alkene **78** (1.06 g, 3.0 mmol) and Pd/C (100 mg) in EtOH/EtOAc (1:1, 100 mL) under H_2 (60 psi) was stirred at 20 °C for 16 h. The mixture was filtered through Celite, washed with EtOH (30 mL) and the solvent was evaporated. The crude solid was purified by column chromatography, eluting with a gradient (50–100%) of EtOAc/pet ether, to give ester **79** (791 mg, 74%) as a yellow powder: mp (EtOAc/pet. ether) 121–123 °C; ^{1}H NMR δ 10.08 (br s, 1 H, NH), 8.65 (dd, *J* = 4.6, 1.5 Hz, 2 H, H-2″, H-6″), 7.62 (dd, *J* = 4.6, 1.5 Hz, 2 H, H-3″, H-5″), 7.49 (br d, *J* = 8.0 Hz, 1 H, H-6‴), 7.37 (br s, 1 H, H-2‴), 7.19 (br t, *J* = 7.8 Hz, 1 H, H-5‴), 6.77 (br d, *J* = 7.4 Hz, 1 H, H-4‴), 3.59 (s, 3 H, OCH_3), 3.25 (br t, *J* = 7.3 Hz, 2 H, H-3), 2.70 (br t, *J* = 7.3 Hz, 2 H, H-2), 2.29 (s, 3 H, CH_3); ^{13}C NMR δ 171.9, 160.4, 149.8 (2), 143.2, 141.9, 140.9, 138.0, 128.7, 124.1, 122.4 (2), 122.0, 117.4, 114.0, 51.3, 34.9, 21.7, 21.2; MS *m/z* 354.6 (MH^+, 100%). Anal. calcd for $C_{19}H_{19}N_3O_2S$: C, 64.57; H, 5.42; N, 11.89. Found: C, 64.55; H, 5.35; N, 11.97%.

Example 1-46

3-[2-[(3-Methylphenyl)amino]-4-(4-pyridinyl)-1,3-thiazol-5-yl]-1-propanol (81).

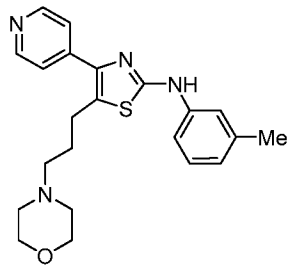


[0296] 3-[2-[(3-Methylphenyl)amino]-4-(4-pyridinyl)-1,3-thiazol-5-yl]propanoic Acid (80). A solution of NaOH (2 M, 20 mL, 40 mM) was added to a stirred solution of ester **79** (703 mg) in MeOH (50 mL) at 20 °C and the solution was stirred at 20 °C for 6 h. The MeOH was evaporated and the pH of the residual solution adjusted to 6 with 6 M HCl. The suspension was chilled at 5 °C for 16 h, the precipitate filtered and washed with water (2 mL) and dried. The crude solid was triturated with DCM and dried to give acid **80** (674 mg, 99%) as a white powder: mp (H_2O) 235–239 °C; ^{1}H NMR δ 10.10 (br s, 1 H, NH), 8.62 (dd, J = 4.5, 1.6 Hz, 2 H, H-2″, H-6″), 7.64 (dd, J = 4.5, 1.6 Hz, 2 H, H-3″, H-5″), 7.50 (br d, J = 8.1 Hz, 1 H, H-6‴), 7.37 (br s, 1 H, H-2‴), 7.18 (br t, J = 7.7 Hz, 1 H, H-5‴), 6.76 (br d, J = 7.5 Hz, 1 H, H-4‴), 3.08 (br t, J = 7.4 Hz, 2 H, H-3), 2.45 (br t, J = 7.4 Hz, 2 H, H-2), 2.28 (s, 3 H, CH_3), OH not observed; MS *m/z* 340.6 (MH^+, 100%). Anal. calcd for $C_{18}H_{17}N_3O_2S·1⅓H_2O$: C, 59.50; H, 5.45; N, 11.56. Found: C, 59.18; H, 4.94; N, 11.35%.

[0297] 3-[2-[(3-Methylphenyl)amino]-4-(4-pyridinyl)-1,3-thiazol-5-yl]-1-propanol (81). $LiAlH_4$ (60 mg, 1.7 mmol) was added to a stirred solution of acid **80** (270 mg, 0.8 mmol) in THF (40 mL) at 0 °C and the mixture stirred at 20 °C for 4 h. Water (5 mL) was added dropwise to the stirred solution and the mixture stirred for 5 min, then 6 M HCl (5 mL) was added and the mixture stirred at 20 °C for 1 h. The organic solvent was evaporated and the residue was partitioned between EtOAc (50 mL) and dilute aqueous NH_3 solution (50 mL). The organic fraction was dried and the solvent evaporated. The crude solid was purified by column chromatography, eluting with EtOAc, to give propanol **81** (131 mg, 50%) as a white powder: mp (EtOAc) 150–152 °C; ^{1}H NMR δ 10.05 (br s, 1 H, NH), 8.63 (dd, J = 4.5, 1.6 Hz, 2 H, H-2″, H-6″), 7.65 (dd, J = 4.5, 1.6 Hz, 2 H, H-3″, H-5″), 7.50 (br d, J = 8.0 Hz, 1 H, H-6‴), 7.38 (br s, 1 H, H-2‴), 7.20 (br t, J = 7.8 Hz, 1 H, H-5‴), 6.78 (br d, J = 7.5 Hz, 1 H, H-4‴), 4.56 (t, J = 5.0 Hz, 1 H, OH), 3.48 (dt, J = 5.9, 5.0 Hz, 2 H, H-1), 2.95 (br t, J = 7.9 Hz, 2 H, H-3), 2.29 (s, 3 H, CH_3), 1.75–1.82 (m, 2 H, H-2); ^{13}C NMR δ 160.0, 149.8 (2), 142.3, 142.1, 141.0, 138.0, 128.7, 126.5, 122.2 (2), 121.9, 117.3, 114.0, 59.6, 34.4, 22.9, 21.2; MS *m/z* 326.6 (MH^+, 100%).

Example 1-47

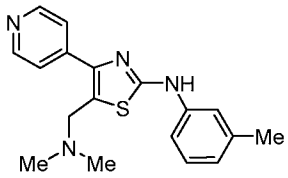
***N*-(3-Methylphenyl)-5-[3-(4-morpholinyl)propyl]-4-(4-pyridinyl)-1,3-thiazol-2-amine (82).**



[0298] ***N*-(3-Methylphenyl)-5-[3-(4-morpholinyl)propyl]-4-(4-pyridinyl)-1,3-thiazol-2-amine (82).** MsCl (23 μL, 0.30 mmol) was added to a stirred solution of alcohol **81** (74 mg, 0.23 mmol) and *i*Pr_2NEt (60 μL, 0.34 mmol) in DCM (10 mL) at 0 °C and the mixture stirred at 20 °C for 4 h. The solvent was evaporated and the residue dissolved in morpholine (4 mL) and the mixture was stirred at 60 °C for 6 h. The solvent was evaporated and the residue was partitioned between aqueous NH_3 solution (20 mL) and EtOAc (50 mL). The organic fraction was washed with water (2 × 5 mL), washed with brine (5 mL) and the solution was dried and the solvent was evaporated. The crude solid was purified by column chromatography, eluting with a gradient (0–5%) of MeOH/DCM, to give morpholide **82** (64 mg, 70%) as a white powder: mp (MeOH/EtOAc) 128–131 °C; ^{1}H NMR δ 10.06 (br s, 1 H, NH), 8.63 (dd, *J* = 4.6, 1.5 Hz, 2 H, H-2′, H-6′), 7.65 (dd, *J* = 4.6, 1.5 Hz, 2 H, H-3′, H-5′), 7.50 (br d, *J* = 7.8 Hz, 1 H, H-6‴), 7.37 (br s, 1 H, H-2‴), 7.20 (br t, *J* = 7.8 Hz, 1 H, H-5‴), 6.77 (br d, *J* = 7.5 Hz, 1 H, H-4‴), 3.55 (bt t, *J* = 4.5 Hz, 4 H, 2 × CH_2O), 2.93 (br t, *J* = 7.3 Hz, 2 H, H-1″), 2.27–2.33 (m, 9 H, 3 × CH_2N, CH_3), 1.75–1.81 (m, 2 H, H-2″); ^{13}C NMR δ 160.1, 149.7 (2), 142.6, 142.1, 140.9, 138.0, 128.7, 126.1, 122.3 (2), 121.9, 117.3, 114.0, 66.1 (2), 56.5, 53.1 (2), 27.7, 23.5, 21.2; MS *m/z* 367.7 (MH^+, 100%).

Example 1-48

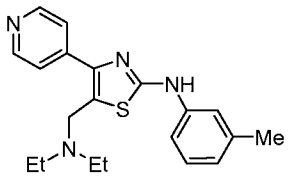
5-[(Dimethylamino)methyl]-*N*-(3-methylphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (83).



[0299] 5-[(Dimethylamino)methyl]-*N*-(3-methylphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (83). MsCl (120 μL, 1.5 mmol) was added to a stirred solution of alcohol **74** (340 mg, 1.1 mmol) and *i*Pr_2NEt (300 μL, 1.7 mmol) in DCM (30 mL) at 0 °C and the mixture stirred at 20 °C for 3 h. The solvent was evaporated and the residue dissolved in DMF (3 mL) and 40% aqueous $MeNH_2$ was added (2.9 mL, 23 mmol) and the mixture was stirred at 80 °C for 4 h. The solvent was evaporated and the residue partitioned between aqueous Na_2CO_3 solution (5% w/v, 20 mL) and EtOAc (50 mL). The organic fraction was washed with water (2 × 5 mL), washed with brine (5 mL) and the solution dried, and the solvent was evaporated. The crude solid was purified by column chromatography, eluting with a gradient (0–5%) of MeOH/DCM, to give amine **83** (124 mg, 33%) as a white powder: mp (MeOH/DCM) 157–159 °C; ^{1}H NMR δ 10.12 (br s, 1 H, NH), 8.64 (dd, *J* = 4.5, 1.6 Hz, 2 H, H-2′, H-6′), 7.66 (dd, *J* = 4.5, 1.6 Hz, 2 H, H-3′, H-5′), 7.51 (br dd, *J* = 7.9, 1.9 Hz, 1 H, H-6″), 7.39 (br s, 1 H, H-2″), 7.20 (dd, *J* = 7.9, 7.5 Hz, 1 H, H-5‴), 6.79 (d, *J* = 7.5 Hz, 1 H, H-4‴), 3.63 (s, 2 H, H-1‴), 2.33 (s, 3 H, CH_3), 2.23 [s, 6 H, $N(CH_3)_2$]; ^{13}C NMR δ 161.5, 149.7 (2), 143.6, 141.8, 140.9, 138.0, 128.7, 125.1, 122.5 (2), 122.0, 117.4, 114.1, 54.8, 44.9 (2), 21.2; MS *m/z* 325.6 (MH^+, 100%). Anal. calcd for $C_{18}H_{20}N_4S$: C, 66.63; H, 6.21; N, 17.27. Found: C, 66.51; H, 6.29; N, 17.04%.

Example 1-49

5-[(Diethylamino)methyl]-*N*-(3-methylphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (84).

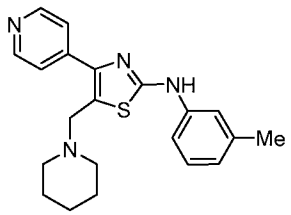


[0300] 5-[(Diethylamino)methyl]-*N*-(3-methylphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (84). MsCl (105 μL, 1.3 mmol) was added to a stirred solution of

alcohol **74** (306 mg, 1.0 mmol) and *i*Pr_2NEt (270 μL, 1.6 mmol) in DCM (20 mL) at 0 °C and the mixture stirred at 20 °C for 3 h. The solvent was evaporated and the residue dissolved in DMF (3 mL) and Et_2NH (2.1 mL, 21 mmol) was added and the mixture was stirred at 50 °C for 4 h. The solvent was evaporated and the residue partitioned between aqueous Na_2CO_3 solution (5% w/v, 20 mL) and EtOAc (50 mL). The organic fraction was washed with water (2 × 5 mL), washed with brine (5 mL) and the solution dried, and the solvent was evaporated. The crude solid was purified by column chromatography, eluting with a gradient (0–5%) of MeOH/DCM, to give amine **84** (168 mg, 46%) as a white powder: mp (MeOH/EtOAc) 123–125 °C; ^{1}H NMR δ 10.02 (br s, 1 H, NH), 8.62 (dd, *J* = 4.5, 1.6 Hz, 2 H, H-2′, H-6′), 7.64 (dd, *J* = 4.5, 1.6 Hz, 2 H, H-3′, H-5′), 7.50 (br dd, *J* = 8.5, 2.3 Hz, 1 H, H-6″), 7.39 (br s, 1 H, H-2″), 7.20 (dd, *J* = 8.5, 7.5 Hz, 1 H, H-5″), 6.77 (d, *J* = 7.5 Hz, 1 H, H-4″), 3.80 (s, 2 H, H-1‴), 2.52 (q, *J* = 7.1 Hz, 4 H, 2 × CH_2N), 2.29 (s, 3 H, CH_3), 0.98 (t, *J* = 7.1 Hz, 6 H, 2 × CH_3); ^{13}C NMR δ 161.4, 149.7 (2), 142.7, 142.0, 141.0, 138.0, 128.7, 128.0, 122.4 (2), 121.9, 117.4, 114.0, 49.4, 46.4 (2), 21.2, 11.6 (2); MS *m/z* 353.6 (MH^+, 100%). Anal. calcd for $C_{20}H_{24}N_4S·½CH_3OH$: C, 66.82; H, 7.11; N, 15.20. Found: C, 66.41; H, 7.09; N, 14.94%.

Example 1-50

***N*-(3-Methylphenyl)-5-(1-piperidinylmethyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (85).**

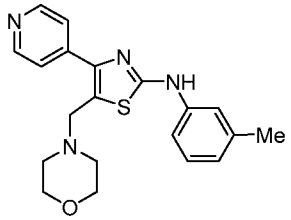


[0301] ***N*-(3-Methylphenyl)-5-(1-piperidinylmethyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (85).** MsCl (107 μL, 1.4 mmol) was added to a stirred solution of alcohol **74** (311 mg, 1.0 mmol) and *i*Pr_2NEt (273 μL, 1.6 mmol) in DCM (20 mL) at 0 °C and the mixture stirred at 20 °C for 3 h. The solvent was evaporated and the residue dissolved in DMF (3 mL) and piperidine (2.1 mL, 21 mmol) was added and the mixture was stirred at 50 °C for 4 h. The solvent was evaporated and the

residue partitioned between aqueous Na_2CO_3 solution (5% w/v, 20 mL) and EtOAc (50 mL). The organic fraction was washed with water (2 × 5 mL), washed with brine (5 mL) and the solution dried, and the solvent was evaporated. The crude solid was purified by column chromatography, eluting with a gradient (0–5%) of MeOH/DCM, to give amine **85** (208 mg, 54%) as a white powder: mp (MeOH/DCM) 150–151 °C; ^{1}H NMR δ 10.05 (br s, 1 H, NH), 8.63 (dd, J = 4.5, 1.6 Hz, 2 H, H-2′, H-6′), 7.64 (dd, J = 4.5, 1.6 Hz, 2 H, H-3′, H-5′), 7.51 (br d, J = 7.7 Hz, 1 H, H-6″), 7.38 (br s, 1 H, H-2″), 7.20 (br t, J = 7.7 Hz, 1 H, H-5″), 6.78 (d, J = 7.5 Hz, 1 H, H-4″), 3.67 (s, 2 H, H-1‴), 2.39–2.44 (m, 4 H, 2 × CH_2N), 2.29 (s, 3 H, CH_3), 1.47–1.53 (m, 4 H, 2 × CH_2), 1.36–1.42 (m, 2 H, CH_2); ^{13}C NMR δ 161.6, 149.7 (2), 143.4, 141.9, 140.9, 138.0, 128.8, 125.6, 122.5 (2), 122.0, 117.5, 114.1, 54.3, 53.9 (2), 25.4 (2), 23.7, 21.2; MS *m/z* 365.8 (MH^+, 100%). Anal. calcd for $C_{21}H_{24}N_4S·½CH_3OH$: C, 67.86; H, 6.89; N, 14.72. Found: C, 67.74; H, 6.72; N, 14.90%.

Example 1-51

***N*-(3-Methylphenyl)-5-(4-morpholinylmethyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (86).**

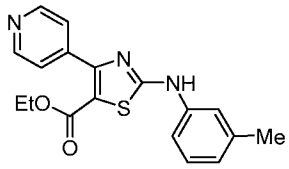


[0302] ***N*-(3-Methylphenyl)-5-(4-morpholinylmethyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (86).** MsCl (58 μL, 0.74 mmol) was added to a stirred solution of alcohol **74** (200 mg, 0.67 mmol) and *i*Pr_2NEt (234 μL, 1.4 mmol) in DCM (20 mL) at 0 °C and the mixture stirred at 20 °C for 1 h. The solvent was evaporated and the residue dissolved in DMF (3 mL) and morpholine (1.2 mL, 13.5 mmol) was added and the mixture was stirred at 80 °C for 4 h. The solvent was evaporated and the residue partitioned between aqueous Na_2CO_3 solution (5% w/v, 20 mL) and EtOAc (50 mL). The organic fraction was washed with water (2 × 5 mL), washed with brine (5 mL) and the solution dried, and the solvent was evaporated. The crude solid was purified by column chromatography, eluting with a gradient (0–5%) of

MeOH/DCM, to give morpholide **86** (153 mg, 62%) as a white powder: mp (MeOH/DCM) 160–161 °C; ^{1}H NMR δ 10.09 (br s, 1 H, NH), 8.64 (dd, J = 4.5, 1.6 Hz, 2 H, H-2′, H-6′), 7.66 (dd, J = 4.5, 1.6 Hz, 2 H, H-3′, H-5′), 7.50 (br dd, J = 8.1, 1.9 Hz, 1 H, H-6‴), 7.38 (br s, 1 H, H-2‴), 7.20 (dd, J = 8.1, 7.5 Hz, 1 H, H-5‴), 6.78 (d, J = 7.5 Hz, 1 H, H-4‴), 3.72 (s, 2 H, H-1″), 3.58 (br t, J = 4.5 Hz, 4 H, 2 × CH_2N), 2.47 (br t, J = 4.5 Hz, 4 H, 2 × CH_2O), 2.30 (s, 3 H, CH_3); ^{13}C NMR δ 161.7, 149.7 (2), 143.9, 141.8, 140.9, 138.0, 128.8, 124.0, 122.5 (2), 122.0, 117.5, 114.1, 66.1 (2), 53.8, 53.0 (2), 21.2; MS *m/z* 367.7 (MH^+, 100%). Anal. calcd for $C_{20}H_{22}N_4OS$: C, 65.55; H, 6.05; N, 15.29. Found: C, 65.42; H, 6.02; N, 15.25%.

Example 1-52

Ethyl 2-[(3-Methylphenyl)amino]-4-(4-pyridinyl)-1,3-thiazole-5-carboxylate (88).



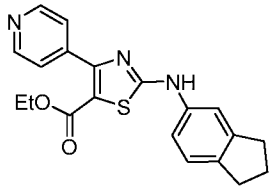
[0303] Ethyl 2-Bromo-3-oxo-3-(4-pyridinyl)propanoate Hydrobromide (87). Br_2 (1.4 mL, 27.7 mmol) was added dropwise to a stirred a solution of ethyl isonicotinoyl acetate (5.09 g, 26.3 mmol) in $CHCl_3$ (100 mL) at 5 °C. The mixture was stirred at 40 °C for 1 h and then at 70 °C for 1 h. The mixture was cooled to 20 °C, diluted with Et_2O (200 mL) and stirred at 5 °C for 30 min. The precipitate was filtered, washed with Et_2O (25 mL) and dried under vacuum to give the bromoketone hydrobromide salt **87** (8.19 g, 88%) as a white powder: mp (Et_2O/$CHCl_3$) 141–143 °C; ^{1}H NMR δ 8.93 (dd, J = 4.6, 1.7 Hz, 2 H, H-2′, H-6′), 7.97 (dd, J = 4.6, 1.7 Hz, 2 H, H-3′, H-5′), 6.48 (br s, 1 H, N·HBr), 6.70 (s, 1 H, CHBr), 4.21 (q, J = 7.1 Hz, 2 H, CH_2O), 1.15 (t, J = 7.1 Hz, 3 H, CH_3).

[0304] Ethyl 2-[(3-Methylphenyl)amino]-4-(4-pyridinyl)-1,3-thiazole-5-carboxylate (88). A mixture of bromide **87** (0.51 g, 1.4 mmol) and 3-methylphenylthiourea **4** (0.24 g, 1.4 mmol) in EtOH (20 mL) was stirred at reflux temperature for 2 h. The mixture was cooled to 0 °C for 2 h and the precipitate was

filtered, washed with EtOH (2 mL) and dried to give ester **88** (0.25 g, 51%) as a yellow powder: mp (EtOH) 233–235 °C; ^{1}H NMR δ 10.89 (s, 1 H, NH), 8.91 (dd, *J* = 5.2, 1.4 Hz, 2 H, H-2′, H-6′), 7.67 (dd, *J* = 5.2, 1.4 Hz, 2 H, H-3′, H-5′), 7.48 (br dd, *J* = 8.0, 1.9 Hz, 1 H, H-6″), 7.37 (br s, 1 H, H-2″), 7.26 (br dd, *J* = 8.0, 7.5 Hz, 1 H, H-5″), 6.92 (br d, *J* = 7.5 Hz, 1 H, H-4″), 4.20 (q, *J* = 7.1 H, 2 H, CH_2O), 2.31 (s, 3 H, CH_3), 1.21 (t, *J* = 7.1 Hz, 3 H, CH_3); ^{13}C NMR δ 165.3, 160.3, 151.5, 148.9, 142.6 (2), 139.5, 138.4, 129.0, 126.8 (2), 123.9, 118.8, 115.4, 114.5, 61.2, 21.1, 13.8; MS *m/z* 340.6 (MH^+, 100%).

Example 1-53

Ethyl 2-(2,3-Dihydro-1*H*-inden-5-ylamino)-4-(4-pyridinyl)-1,3-thiazole-5-carboxylate (89).

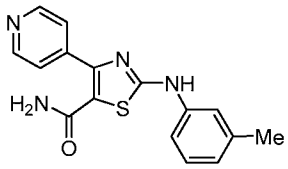


[0305] Ethyl 2-(2,3-Dihydro-1*H*-inden-5-ylamino)-4-(4-pyridinyl)-1,3-thiazole-5-carboxylate (89). A mixture of bromide **87** (1.80 g, 5.1 mmol) and *N*-(2,3-dihydro-1*H*-inden-5-yl)thiourea (**46**) (0.98 g, 5.1 mmol) in EtOH (40 mL) was stirred at reflux temperature for 2 h. The mixture was cooled to 20 °C, diluted with water (100 mL), the pH adjusted to ca. 9 with aqueous NH_3 and the mixture stirred at 0 °C for 1 h. The precipitate was filtered, washed with water (15 mL) and dried. The crude solid was purified by column chromatography, eluting with a gradient (0–5%) of MeOH/DCM, to give ester **89** (0.50 g, 76%) as a yellow powder: mp (MeOH/DCM) 203–205 °C; ^{1}H NMR δ 10.72 (s, 1 H, NH), 8.65 (dd, *J* = 4.4, 1.6 Hz, 2 H, H-2′, H-6′), 7.68 (dd, *J* = 4.4, 1.6 Hz, 2 H, H-3′, H-5′), 7.42 (br s, 1 H, H-4″), 7.32 (dd, *J* = 8.1, 2.0 Hz, 1 H, H-6″), 7.21 (d, *J* = 8.1 Hz, 1 H, H-7″), 4.15 (q, *J* = 7.1 H, 2 H, CH_2O), 2.86 (br t, *J* = 7.4 Hz, 2 H, H-3″), 2.81 (br t, *J* = 7.4 Hz, 2 H, H-1″), 2.01 (sept, J = 7.4 Hz, 2 H, H-2″), 1.17 (t, *J* = 7.1 Hz, 3 H, CH_3); ^{13}C NMR δ 165.7, 160.6, 154.9, 149.2 (2), 144.7, 141.6, 138.6, 138.1, 124.6, 123.9 (2), 116.7, 114.7, 111.1, 60.6, 32.4, 31.6, 25.0, 13.8; MS *m/z* 366.7 (MH^+, 100%).

Anal. calcd for $C_{20}H_{19}N_3O_2S$: C, 65.73; H, 5.24; N, 11.50. Found: C, 65.44; H, 5.27; N, 11.75%.

Example 1-54

2-[(3-Methylphenyl)amino]-4-(4-pyridinyl)-1,3-thiazole-5-carboxamide (91).



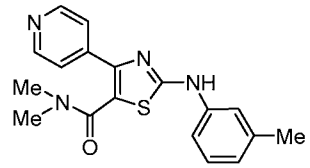
[0306] 2-[(3-Methylphenyl)amino]-4-(4-pyridinyl)-1,3-thiazole-5-carboxylic acid (90). A mixture of ester **88** (480 mg, 1.4 mmol) and aqueous NaOH (1 M, 20 mL, 20 mmol) in MeOH (20 mL) was stirred at 60 °C for 2 h. The organic solvent was evaporated and the pH adjusted to 6 with 6 M HCl and the mixture was stood at 5 °C for 16 h. The precipitate was filtered and dried and the solid was triturated with DCM to give carboxylic acid **90** (245 mg, 56%) as a yellow powder: mp (H_2O) 160–162 °C; ^{1}H NMR δ 13.0 (br s, 1 H, CO_2H), 10.67 (s, 1 H, NH), 8.64 (dd, J = 4.5, 1.6 Hz, 2 H, H-2′, H-6′), 7.74 (dd, J = 4.5, 1.6 Hz, 2 H, H-3′, H-5′), 7.46 (br d, J = 8.0 Hz, 1 H, H-6″), 7.36 (br s, 1 H, H-2″), 7.25 (br t, J = 7.8 Hz, 1 H, H-5″), 6.87 (br d, J = 7.5 Hz, 1 H, H-4″), 2.30 (s, 3 H, CH_3); ^{13}C NMR δ 164.5, 162.1, 153.5, 149.0 (2), 141.7, 139.9, 138.3, 128.9, 124.0 (2), 123.4, 118.4, 115.1, 114.0, 21.1; MS *m/z* 312.5 (MH^+, 100%). Anal. calcd for $C_{16}H_{13}N_3O_2S{\cdot}H_2O$: C, 58.35; H, 4.59; N, 12.76. Found: C, 58.67; H, 4.32; N, 12.79%.

[0307] 2-[(3-Methylphenyl)amino]-4-(4-pyridinyl)-1,3-thiazole-5-carboxamide (91). Oxalyl chloride (34 μL, 0.40 mmol) was added dropwise to a stirred solution of acid **90** (83 mg, 0.27 mmol) and DMF (1 drop) in DCM (5 mL) and the mixture was stirred at 20 °C for 2 h. The solvent as evaporated and the residue suspended in DCM (5 mL) and NH_3 gas was bubbled through the mixture for 5 min the mixture stirred at 20 °C for 16 h. The solvent was evaporated and the crude solid was purified by column chromatography, eluting with a gradient (0–10%) of MeOH/DCM, to give carboxamide **91** (6 mg, 7%) as a tan gum: ^{1}H NMR δ 10.45 (s, 1 H, NH), 8.63 (dd, J = 4.5, 1.6 Hz, 2 H, H-2′, H-6′), 7.70 (dd, J = 4.5, 1.6 Hz, 2 H, H-3′, H-5′), 7.48–7.54 (m, 3 H, H-6″, $CONH_2$), 7.38 (br s, 1 H, H-2″),

7.23 (br t, J = 7.8 Hz, 1 H, H-5″), 6.85 (br d, J = 7.5 Hz, 1 H, H-4″), 2.30 (s, 3 H, CH_3); MS m/z 311.5 (MH^+, 100%).

Example 1-55

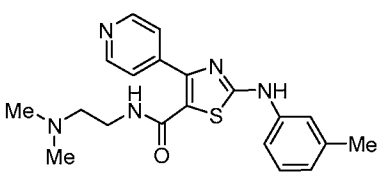
***N*,*N*-Dimethyl-2-[(3-methylphenyl)amino]-4-(4-pyridinyl)-1,3-thiazole-5-carboxamide (92).**



[0308] *N*,*N*-Dimethyl-2-[(3-methylphenyl)amino]-4-(4-pyridinyl)-1,3-thiazole-5-carboxamide (92). Oxalyl chloride (34 μL, 0.40 mmol) was added dropwise to a stirred solution of acid **90** (83 mg, 0.27 mmol) and DMF (1 drop) in DCM (5 mL) and the mixture was stirred at 20 °C for 2 h. The solvent as evaporated and the residue suspended in DCM (5 mL) and dimethylamine (40% aqueous solution, 5 mL) was added and the mixture stirred at 20 °C for 16 h. The solvent was evaporated and the mixture was partitioned between EtOAc (50 mL) and dilute aqueous NH_3 (20 mL). The organic fraction was dried and the solvent evaporated. The crude solid was purified by column chromatography, eluting with a gradient (0–10%) of MeOH/DCM, to give carboxamide **92** (27 mg, 30%) as a tan solid: mp (MeOH/EtOAc) 193–196 °C; ^{1}H NMR δ 10.42 (s, 1 H, NH), 8.65 (dd, J = 4.5, 1.6 Hz, 2 H, H-2′, H-6′), 7.57 (dd, J = 4.5, 1.6 Hz, 2 H, H-3′, H-5′), 7.53 (br d, J = 8.1 Hz, 1 H, H-6″), 7.43 (br s, 1 H, H-2″), 7.25 (br t, J = 7.8 Hz, 1 H, H-5″), 6.85 (br d, J = 7.5 Hz, 1 H, H-4″), 2.89 [br s, 6 H, $CON(CH_3)_2$], 2.32 (s, 3 H, CH_3); MS m/z 339.6 (MH^+, 100%).

Example 1-56

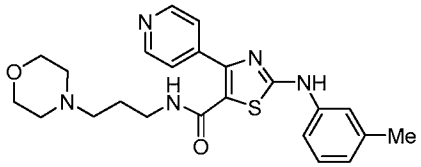
***N*-[2-(Dimethylamino)ethyl]-2-[(3-methylphenyl)amino]-4-(4-pyridinyl)-1,3-thiazole-5-carboxamide (93).**



[0309] ***N*-[2-(Dimethylamino)ethyl]-2-[(3-methylphenyl)amino]-4-(4-pyridinyl)-1,3-thiazole-5-carboxamide (93).** Oxalyl chloride (53 μL, 0.63 mmol) was added dropwise to a stirred solution of acid **90** (130 mg, 0.42 mmol) and DMF (1 drop) in DCM (5 mL) and the mixture was stirred at 20 °C for 2 h. The solvent as evaporated and the residue suspended in DCM (5 mL) and *N*,*N*-dimethylethylenediamine (140 μL, 1.25 mmol) was added and the mixture stirred at 20 °C for 16 h. The mixture was partitioned between EtOAc (50 mL) and dilute aqueous NH_3 (20 mL). The organic fraction was dried and the solvent evaporated. The crude solid was purified by column chromatography, eluting with a gradient (0–10%) of MeOH/DCM, to give carboxamide **93** (39 mg, 24%) as a tan powder: mp (MeOH/DCM) 189–191 °C; ^{1}H NMR δ 10.46 (s, 1 H, NH), 8.63 (dd, *J* = 4.5, 1.6 Hz, 2 H, H-2′, H-6′), 8.02 (t, *J* = 5.5 Hz, 1 H, CONH), 7.70 (dd, *J* = 4.5, 1.6 Hz, 2 H, H-3′, H-5′), 7.49 (br d, *J* = 8.1 Hz, 1 H, H-6″), 7.39 (br s, 1 H, H-2″), 7.25 (br t, *J* = 7.8 Hz, 1 H, H-5″), 6.85 (br d, *J* = 7.5 Hz, 1 H, H-4″), 3.22–3.24 (m, 2 H, CH_2N), 2.40 (br t, *J* = 6.4 Hz, 2 H, CH_2N), 2.32 (s, 3 H, CH_3), 2.20 [s, 6 H, $N(CH_3)_2$]; ^{13}C NMR δ 162.2, 160.7, 149.5 (2), 146.8, 141.2, 140.3, 138.2, 128.9, 122.8, 122.7 (2), 118.4, 118.0, 114.6, 57.3, 44.7 (2), 37.0, 21.1; MS *m/z* 382.8 (MH^+, 100%). Anal. calcd for $C_{20}H_{23}N_5OS \cdot ¼CH_2Cl_2$: C, 60.39; H, 5.88; N, 17.39. Found: C, 60.04; H, 5.95; N, 17.06%.

Example 1-57

2-[(3-Methylphenyl)amino]-*N*-[3-(4-morpholinyl)propyl]-4-(4-pyridinyl)-1,3-thiazole-5-carboxamide (94).

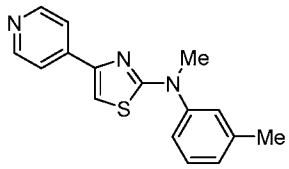


[0310] **2-[(3-Methylphenyl)amino]-*N*-[3-(4-morpholinyl)propyl]-4-(4-pyridinyl)-1,3-thiazole-5-carboxamide (94).** Oxalyl chloride (41 μL, 0.48 mmol) was added dropwise to a stirred solution of acid **90** (100 mg, 0.32 mmol) and DMF (1 drop) in DCM (5 mL) and the mixture was stirred at 20 °C for 2 h. The solvent as evaporated and the residue suspended in DCM (5 mL) and 3-(4-morpholinyl)propylamine (140 μL, 0.96 mmol) was added and the mixture stirred

at 20 °C for 16 h. The mixture was partitioned between EtOAc (50 mL) and dilute aqueous NH_3 (20 mL). The organic fraction was dried and the solvent evaporated. The crude solid was purified by column chromatography, eluting with a gradient (0–10%) of MeOH/DCM, to give carboxamide **94** (30 mg, 21%) as a tan powder: mp (MeOH/EtOAc) 190–192 °C; ^{1}H NMR δ 10.46 (s, 1 H, NH), 8.62 (dd, J = 4.5, 1.6 Hz, 2 H, H-2′, H-6′), 8.24 (t, J = 5.5 Hz, 1 H, CONH), 7.66 (dd, J = 4.5, 1.6 Hz, 2 H, H-3′, H-5′), 7.50 (br d, J = 8.1 Hz, 1 H, H-6″), 7.39 (br s, 1 H, H-2″), 7.23 (br t, J = 7.8 Hz, 1 H, H-5″), 6.85 (br d, J = 7.5 Hz, 1 H, H-4″), 3.52–3.58 (m, 4 H, 2 × CH_2O), 3.20 (dt, J = 6.7, 5.9 Hz, 2 H, CH_2N), 2.25 (m, 9 H, 3 × CH_2N, CH_3), 1.58–1.65 (m, 2 H, CH_2); ^{13}C NMR δ 162.0, 160.8, 149.5 (2), 146.7, 141.3, 140.3, 138.2, 128.9, 122.8, 122.7 (2), 118.3, 117.9, 114.6, 66.0 (2), 55.8, 53.1 (2), 37.8, 25.2, 21.1; MS *m/z* 439.0 (MH^+, 100%). Anal. calcd for $C_{23}H_{27}N_5O_2S·H_2O$: C, 60.64; H, 6.42; N, 15.37. Found: C, 60.70; H, 6.27; N, 15.18%.

Example 1-58

***N*-Methyl-*N*-(3-methylphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (95).**

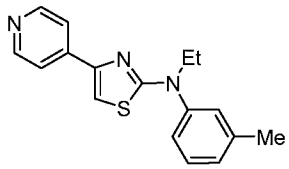


[0311] ***N*-Methyl-*N*-(3-methylphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (95).** NaH (216 mg, 5.4 mmol) was added to a stirred solution of amine **5** (760 mg, 2.8 mmol) in DMF (5 mL) and the mixture stirred at 20 °C for 2 min. MeI (0.18 mL, 2.8 mmol) was added dropwise and the mixture stirred at 20 °C for 1 h. The reaction was quenched with saturated aqueous NH_4Cl solution (15 mL) and the mixture extracted with EtOAc (3 × 15 mL). The combined organic fraction was dried and the solvent evaporated. The crude solid was purified by column chromatography, eluting with a gradient (50–100%) of EtOAc/pet. ether, to give amine **95** (0.69 g, 86%) as a colourless oil: ^{1}H NMR ($CDCl_3$) δ 8.60 (dd, J = 4.6, 1.5 Hz, 2 H, H-2′, H-6′), 7.71 (dd, J = 4.6, 1.6 Hz, 2 H, H-3′, H-5′), 7.33 (dd, J = 7.8, 7.6 Hz, 1 H, H-5″), 7.20–7.24 (m, 2 H, H-2″, H-6″), 7.11 (br d, J = 7.6 Hz, 1 H, H-4″), 6.90 (s, 1 H, H-5), 3.60 (s, 3 H, NCH_3), 2.39 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 170.1, 150.1 (2), 149.0, 146.1, 141.9, 139.9, 129.6, 127.5, 125.7, 122.1,

120.2 (2), 105.4, 40.4, 21.4; MS *m/z* 282.5 (MH^+, 100%). Anal. calcd for $C_{16}H_{15}N_3S$: C, 68.30; H, 5.37; N, 14.93. Found: C, 67.97; H, 5.45; N, 14.86%.

Example 1-59

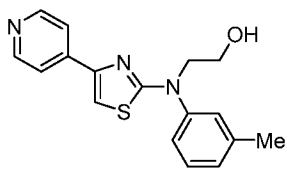
***N*-Ethyl-*N*-(3-methylphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (96).**



[0312] ***N*-Ethyl-*N*-(3-methylphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (96).** NaH (151 mg, 3.8 mmol) was added to a stirred solution of amine **5** (533 mg, 2.0 mmol) in DMF (8 mL) and the mixture stirred at 20 °C for 2 min. EtI (0.16 mL, 2.0 mmol) was added dropwise and the mixture stirred at 20 °C for 1 h. The reaction was quenched with saturated aqueous NH_4Cl solution (10 mL) and the mixture extracted with EtOAc (3 × 15 mL). The combined organic fraction was dried and the solvent evaporated. The crude solid was purified by column chromatography, eluting with 50% EtOAc/pet. ether, to give amine **96** (0.55 g, 93%) as a colourless oil: ^{1}H NMR ($CDCl_3$) δ 8.60 (dd, *J* = 4.6, 1.5 Hz, 2 H, H-2′, H-6′), 7.71 (dd, *J* = 4.6, 1.6 Hz, 2 H, H-3′, H-5′), 7.34 (br dd, *J* = 8.6, 7.4 Hz, 1 H, H-5″), 7.14–7.20 (m, 3 H, H-2″, H-4″, H-6″), 6.87 (s, 1 H, H-5), 4.08 (q, *J* = 7.1 Hz, 2 H, CH_2N), 2.39 (s, 3 H, CH_3), 1.32 (t, *J* = 7.1 Hz, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 170.0, 150.1 (2), 149.0, 144.6, 142.0, 140.1, 129.8, 128.2, 127.6, 124.1, 120.2 (2), 105.0, 47.7, 21.4, 13.1; MS *m/z* 296.5 (MH^+, 100%). Anal. calcd for $C_{17}H_{17}N_3S$: C, 69.12; H, 5.80; N, 14.22. Found: C, 68.90; H, 5.89; N, 14.28%.

Example 1-60

2-{3-Methyl[4-(4-pyridinyl)-1,3-thiazol-2-yl]anilino}ethanol (97).

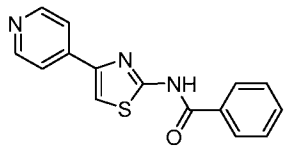


[0313] **2-{3-Methyl[4-(4-pyridinyl)-1,3-thiazol-2-yl]anilino}ethanol (97).** NaH (107 mg, 2.7 mmol) was added to a stirred solution of amine **5** (649 mg, 2.4 mmol) in DMF (10 mL) and the mixture stirred at 20 °C for 2 min. Iodoethanol (0.19 mL,

2.4 mmol) was added dropwise and the mixture stirred at 20 °C for 48 h. The reaction was quenched with saturated aqueous NH_4Cl solution (10 mL) and the mixture extracted with EtOAc (3 × 15 mL). The combined organic fraction was dried and the solvent evaporated. The crude solid was purified by column chromatography, eluting with a gradient (50–100%) of EtOAc/pet. ether, to give (i) starting material **5** (0.22 g, 34%) and (ii) amine **97** (0.15 g, 19%) as a white powder: mp (EtOAc/pet. ether) 149–151 °C; ^{1}H NMR δ 8.58 (dd, *J* = 4.5, 1.6 Hz, 2 H, H-2‴, H-6‴), 7.78 (dd, *J* = 4.5, 1.6 Hz, 2 H, H-3‴, H-5‴), 7.47 (s, 1 H, H-5″), 7.30–7.40 (m, 3 H, H-2′, H-4′, H-5′), 7.34 (br dd, *J* = 7.4 Hz, 1 H, H-6′), 4.80 (t, *J* = 5.5 Hz, 1 H, OH), 4.03 (t, *J* = 6.2 Hz, 2 H, H-2), 3.71 (dt, *J* = 6.2, 5.5 Hz, 2 H, H-1), 2.35 (s, 3 H, CH_3); ^{13}C NMR δ 169.4, 149.9 (2), 147.7, 144.8, 141.1, 139.4, 129.6, 127.9, 127.0, 123.6, 119.8 (2), 106.6, 57.7, 54.9, 20.8; MS *m/z* 312.6 (MH^+, 100%). Anal. calcd for $C_{17}H_{17}N_3OS$: C, 65.57; H, 5.50; N, 13.49. Found: C, 65.87; H, 5.43; N, 13.65%.

Example 1-61

***N*-[4-(4-Pyridinyl)-1,3-thiazol-2-yl]benzamide (99).**

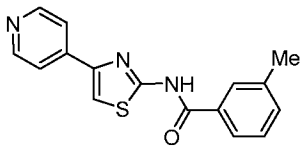


[0314] 4-(4-Pyridinyl)-1,3-thiazol-2-amine (98). A mixture of bromoketone hydrobromide **1** (5.0 g, 17.8 mmol) and thiourea (1.36 g, 17.8 mmol) in EtOH (100 mL) was stirred at reflux temperature for 2 h. The mixture was cooled to 20 °C, diluted with water (50 mL), the pH adjusted to ca. 8 with aqueous NH_3 and the mixture stirred at 0 °C for 1 h. The precipitate was filtered, washed with water (5 mL) and ether (5 mL) and dried to give amine **98** (2.70 g, 86%) as a pink powder: mp (EtOH/H_2O) 278–282 °C [lit. (Westphal, G. et al., *J. Prakt. Chemie (Leipzig)* 1976, *318*, 875) mp (EtOH) 276–277 °C]; ^{1}H NMR δ 8.53 (dd, *J* = 4.6, 1.6 Hz, 2 H, H-2′, H-6′), 7.91 (dd, *J* = 4.6, 1.6 Hz, 2 H, H-3′, H-5′), 7.38 (s, 1 H, H-5), 7.16 (br s, 2 H, NH_2); MS *m/z* 178.3 (MH^+, 100%).

[0315] ***N*-[4-(4-Pyridinyl)-1,3-thiazol-2-yl]benzamide (99).** Benzoyl chloride (0.44 mL, 3.8 mmol) was added to a stirred solution of amine **98** (0.44 g, 2.5 mmol) and DMAP (30 mg, 0.25 mmol) in pyridine (30 mL) and the solution stirred at 20 °C for 16 h. The solvent was evaporated and the residue partitioned between water (70 mL) and EtOAc (70 mL). The organic fraction was washed with water (30 mL), dried and the solvent evaporated. The crude solid was purified by column chromatography, eluting with a gradient (0–10%) of MeOH/DCM, to give benzamide **99** (448 mg, 61%) as a white powder: mp (MeOH/DCM) 241–243 °C; ^{1}H NMR δ 12.84 (s, 1 H, NHCO), 8.64 (dd, *J* = 4.5, 1.6 Hz, 2 H, H-2″, H-6″), 8.14 (br d, *J* = 7.1 Hz, 2 H, H-2, H-6), 8.04 (s, 1 H, H-5′), 7.90 (dd, *J* = 4.5, 1.6 Hz, 2 H, H-3″, H-5″), 7.56 (tt, *J* = 7.4, 1.3 Hz, 1 H, H-4), 7.35–7.39 (m, 2 H, H-3, H-5); ^{13}C NMR δ 165.3, 159.0, 150.1 (2), 146.6, 140.9, 132.6, 131.7, 128.5 (2), 128.1 (2), 119.9 (2), 112.6; MS *m/z* 282.4 (MH^+, 100%). Anal. calcd for $C_{15}H_{11}N_3OS$: C, 64.04; H, 3.94; N, 14.94. Found: C, 63.75; H, 4.12, N, 14.93%.

Example 1-62

3-Methyl-*N*-[4-(4-pyridinyl)-1,3-thiazol-2-yl]benzamide (100).

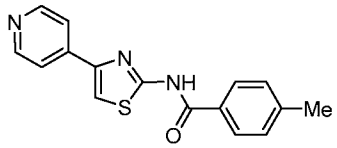


[0316] **3-Methyl-*N*-[4-(4-pyridinyl)-1,3-thiazol-2-yl]benzamide (100).** Oxalyl chloride (0.26 mL, 3.0 mmol) was added to a stirred solution of *m*-toluic acid (0.41 g, 3.0 mmol) and DMF (3 drops) in DCM (30 mL) and the solution stirred at 20 °C for 1 h. A solution of amine **98** (354 mg, 2.0 mmol) was added and the mixture stirred at 20 °C for 16 h. The solvent was evaporated and the residue partitioned between water (70 mL) and EtOAc (70 mL). The organic fraction was washed with water (30 mL), dried and the solvent evapporated. The crude solid was purified by column chromatography, eluting with a gradient (0–10%) of MeOH/EtOAc, to give benzamide **100** (110 mg, 19%) as a cream powder: mp (MeOH/EtOAc) 201–202 °C; ^{1}H NMR δ 12.77 (br s, 1 H, CONH), 8.64 (dd, *J* = 4.6, 1.6 Hz, 2 H, H-2″, H-6″), 8.05 (s, 1 H, H-5), 7.98 (br s, 1 H, H-2), 7.92 (br d, *J* = 6.9 Hz, 1 H, H-6), 7.88 (dd, *J* = 4.6, 1.6 Hz, 2 H, H-3″, H-5″), 7.42–7.48 (m, 2 H, H-4, H-5), 2.41 (s,

3 H, CH_3); ^{13}C NMR δ 165.4, 159.0, 150.1 (2), 146.5, 140.9, 137.8, 133.1, 131.7, 128.6, 128.3, 125.2, 119.2 (2), 112.5, 20.7; MS *m/z* 296.4 (MH^+, 100%). Anal. calcd for $C_{16}H_{13}N_3OS$: C, 65.06; H, 4.44; N, 14.23. Found: C, 65.19 H, 4.56; N, 14.31%.

Example 1-63

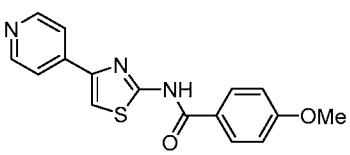
4-Methyl-*N*-[4-(4-pyridinyl)-1,3-thiazol-2-yl]benzamide (101).



[0317] 4-Methyl-*N*-[4-(4-pyridinyl)-1,3-thiazol-2-yl]benzamide (101). Oxalyl chloride (0.26 mL, 3.0 mmol) was added to a stirred solution of *p*-toluic acid (0.41 g, 3.0 mmol) and DMF (3 drops) in DCM (30 mL) and the solution stirred at 20 °C for 1 h. A solution of amine **98** (354 mg, 2.0 mmol) was added and the mixture stirred at 20 °C for 16 h. The solvent was evaporated and the residue partitioned between water (70 mL) and EtOAc (70 mL). The organic fraction was washed with water (30 mL), dried and the solvent evaporated. The crude solid was purified by column chromatography, eluting with a gradient (0–10%) of MeOH/EtOAc, to give benzamide **101** (328 mg, 56%) as a cream powder: mp (MeOH/EtOAc) 238–241 °C; ^1H NMR δ 12.74 (s, 1 H, CONH), 8.63 (dd, *J* = 4.5, 1.6 Hz, 2 H, H-2″, H-6″), 8.04 (br d, *J* = 8.0 Hz, 2 H, H-2, H-6), 8.02 (s, 1 H, H-5), 7.89 (dd, *J* = 4.6, 1.6 Hz, 2 H, H-3″, H-5″), 7.35 (br d, *J* = 8.0 Hz, 2 H, H-3, H-5), 2.39 (s, 3 H, CH_3); ^{13}C NMR δ 165.2, 159.0, 150.1 (2), 146.5, 142.9, 140.9, 129.2 (2), 128.9, 128.1 (2), 119.2 (2), 112.5, 20.9; MS *m/z* 296.4 (MH^+, 100%). Anal. calcd for $C_{16}H_{13}N_3OS$: C, 65.06; H, 4.44; N, 14.23. Found: C, 64.96 H, 4.62; N, 14.24%.

Example 1-64

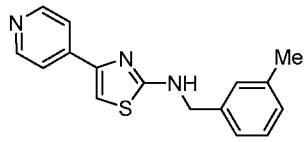
4-Methoxy-*N*-[4-(4-pyridinyl)-1,3-thiazol-2-yl]benzamide (102).



[0318] 4-Methoxy-*N*-[4-(4-pyridinyl)-1,3-thiazol-2-yl]benzamide (102). 4-Methoxybenzoyl chloride (0.77 mL, 5.5 mmol) was added to a stirred solution of amine **98** (0.89 g, 5.0 mmol) and DMAP (60 mg, 0.5 mmol) in pyridine (30 mL) and the solution stirred at 20 °C for 16 h. The solvent was evaporated and the residue partitioned between water (70 mL) and EtOAc (70 mL). The organic fraction was washed with water (30 mL), dried and the solvent evaporated. The crude solid was purified by column chromatography, eluting with a gradient (0–10%) of MeOH/DCM, to give benzamide **102** (448 mg, 61%) as a white powder: mp (MeOH/DCM) 271–274 °C; ^{1}H NMR δ 12.66 (s, 1 H, NHCO), 8.63 (dd, *J* = 4.5, 1.6 Hz, 2 H, H-2″, H-6″), 8.15 (ddd, *J* = 8.9, 2.9, 2.0 Hz, 2 H, H-2, H-6), 8.01 (s, 1 H, H-5′), 7.88 (dd, *J* = 4.5, 1.6 Hz, 2 H, H-3″, H-5″), 7.09 (ddd, *J* = 8.9, 2.9, 2.0 Hz, 2 H, H-3, H-5), 3.86 (s, 3 H, OCH_3); ^{13}C NMR δ 164.6, 162.7, 159.2, 150.1 (2), 146.5, 141.0, 130.2 (2), 123.8, 119.9 (2), 113.8 (2), 112.4, 55.4; MS *m/z* 312.5 (MH^+, 100%). Anal. calcd for $C_{16}H_{13}N_3O_2S$: C, 61.72; H, 4.21; N, 13.50. Found: C, 61.38; H, 4.48, N, 13.41%.

Example 1-65

***N*-(3-Methylbenzyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (103).**

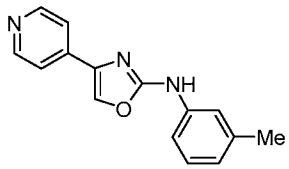


[0319] *N*-(3-Methylbenzyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (103). A mixture of 2-aminothiazole **98** (0.31 g, 1.8 mmol) and 3-methylbenzaldehyde (0.25 mL, 2.1 mmol) in THF (20 mL) was stirred at reflux temperature for 4 h. The mixture was cooled to 20 °C and a solution of $NaBH_4$ (265 mg, 7.0 mmol) in water (4 mL) was added dropwise and the mixture was stirred at 20 °C for 30 min. The mixture was diluted with water (30 mL) and extracted with EtOAc (3 × 25 mL). The combined organic fraction was dried and the solvent evaporated. The crude solid was purified by column chromatography, eluting with a gradient (50–100%) of EtOAc/pet. ether, to give amine **103** (0.11 g, 22%) as a cream powder: mp (MeOH/EtOAc) 192–194 °C; ^{1}H NMR δ 8.54 (dd, *J* = 4.5, 1.6 Hz, 2 H, H-2′, H-6′), 8.30 (t, *J* = 5.8 Hz, 1 H, NH), 7.75 (dd, *J* = 4.5, 1.6 Hz, 2 H, H-3′, H-5′), 7.42

(s, 1 H, H-5), 7.17–7.24 (m, 3 H, H-2″, H-4″, H-5″), 7.07 (br d, J = 6.9 Hz, 1 H, H-6″), 4.48 (d, J = 5.8 Hz, 2 H, CH_2N), 2.30 (s, 3 H, CH_3); MS *m/z* 282.5 (MH^+, 100%). Anal. calcd for $C_{16}H_{15}N_3S \cdot ¼CH_3OH$: C, 67.87; H, 5.48; N, 14.72. Found: C, 67.78; H, 5.42; N, 14.92%.

Example 1-66

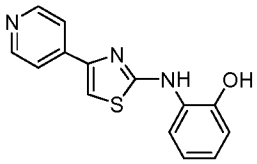
***N*-(3-Methylphenyl)-4-(4-pyridinyl)-1,3-oxazol-2-amine (105).**



[0320] ***N*-(3-Methylphenyl)-4-(4-pyridinyl)-1,3-oxazol-2-amine (105).** A mixture of bromoketone hydrobromide **1** (0.32 g, 1.15 mmol) and 3-methylphenylurea **104** (0.17 g, 1.15 mmol) in EtOH (20 mL) was stirred at reflux temperature for 16 h. The mixture was cooled to 20 °C, diluted with water (50 mL), the pH adjusted to ca. 8 with aqueous NH_3 and the mixture stirred at 20 °C for 2 h. The precipitate was filtered, washed with water (5 mL) and dried. The crude solid was purified by column chromatography, eluting with a gradient (0–5%) of MeOH/DCM, to give amine **105** (49 mg, 17%) as a cream powder: mp (EtOAc/DCM) 201–204 °C; ^{1}H NMR δ 10.18 (br s, 1 H, NH), 8.60 (dd, J = 4.5, 1.6 Hz, 2 H, H-2′, H-6′), 8.40 (s, 1 H, H-5), 7.71 (dd, J = 4.5, 1.6 Hz, 2 H, H-3′, H-5′), 7.54 (dd, J = 8.1, 1.9 Hz, 1 H, H-6″), 7.46 (br s, 1 H, H-2″), 7.23 (dd, J = 8.1, 7.5 Hz, 1 H, H-5″), 6.80 (br d, J = 7.5 Hz, 1 H, H-4″), 2.32 (s, 3 H, CH_3); ^{13}C NMR δ 157.1, 150.0 (2), 139.1, 138.5, 138.0, 136.9, 130.8, 128.7, 122.1, 119.1 (2), 117.1, 113.7, 21.2; MS *m/z* 252.4 (MH^+, 100%). Anal. calcd for $C_{15}H_{13}N_3O \cdot ¼CH_3OH$: C, 70.64; H, 5.44; N, 16.21. Found: C, 70.64; H, 5.44; N, 16.51%.

Example 1-67

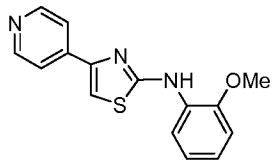
2-{[4-(4-Pyridinyl)-1,3-thiazol-2-yl]amino}phenol (107).



[0321] 2-{[4-(4-Pyridinyl)-1,3-thiazol-2-yl]amino}phenol (107). A mixture of bromoketone hydrobromide **1** (0.34 g, 1.2 mmol) and *N*-(2-hydroxyphenyl)thiourea (**106**) (0.20 g, 1.2 mmol) in EtOH (15 mL) was stirred at reflux temperature for 1 h. The mixture was cooled to 20 °C, diluted with water (50 mL), the pH adjusted to ca. 8 with aqueous NH_3 and the mixture stirred at 0 °C for 1 h. The precipitate was filtered, washed with water (5 mL) and dried. The crude solid was purified by column chromatography, eluting with a gradient (50–100%) of EtOAc/pet. ether, to give amine **107** (0.28 g, 86%) as a cream powder: mp (EtOAc/pet. ether) 221–223 °C; ^{1}H NMR δ 9.86 (br s, 1 H, OH), 9.56 (br s, 1 H, NH), 8.60 (dd, *J* = 4.5, 1.6 Hz, 2 H, H-2″, H-6″), 8.26–8.31 (m, 1 H, H-4), 7.82 (dd, *J* = 4.5, 1.6 Hz, 2 H, H-3″, H-5″), 7.63 (s, 1 H, H-5′), 6.83–6.91 (m, 3 H, H-3, H-5, H-6); ^{13}C NMR δ 164.5, 150.0 (2), 147.1, 146.4, 141.1, 128.9, 122.4, 119.7 (2), 119.1, 119.0, 114.9, 107.6; MS *m/z* 270.5 (MH^+, 100%). Anal. calcd for $C_{14}H_{11}N_3OS$: C, 62.43; H, 4.12; N, 15.60. Found: C, 62.59; H, 4.25; N, 15.42%.

Example 1-68

***N*-(2-Methoxyphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (109).**

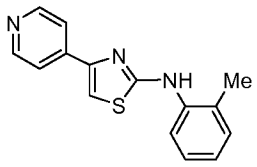


[0322] 2-Methoxyphenylthiourea (108). NH_4SCN (3.37 g, 44.3 mmol) was added to a stirred solution of *o*-anisidine (5.00 g, 44.3 mmol) in 1 M HCl (45 mL) at 100 °C and the solution stirred at 100 °C for 16 h. The solution was diluted with water (60 mL) and the pH adjusted to 8 with aqueous NH_3 and the mixture at 5 °C for 2 h. The precipitate was filtered, washed with water (5 mL), washed with ether (5 mL), and dried. The crude solid was purified by column chromatography, eluting with 40% EtOAc/pet. ether, to give thiourea **108** (1.93 g, 24%) as a white powder: mp (EtOAc/pet. ether) 151–153 °C [lit. (Rasmussen, C. R. et al., *Synthesis* **1988**, 456) mp (MeOH) 153–155 °C]; ^{1}H NMR δ 8.99 (s, 1 H, NH), 7.81 (br d, *J* = 7.7 Hz, 1 H, H-3), 7.40 br s, 2 H, NH_2), 7.13 (ddd, *J* = 8.2, 7.6, 1.6 Hz, 1 H, H-5), 7.04 (dd, *J* = 8.2, 1.3 Hz, 1 H, H-6), 6.90 (ddd, *J* = 7.7, 7.6, 1.3 Hz, 1 H, H-4), 3.81 (s, 3 H, OCH_3); MS *m/z* 183.3 (MH^+, 100%).

[0323] ***N*-(2-Methoxyphenyl]-4-(4-pyridinyl)-1,3-thiazol-2-amine (109).** A mixture of bromoketone hydrobromide **1** (0.29 g, 1.1 mmol) and 2-methoxyphenylthiourea (**108**) (0.19 g, 1.1 mmol) in EtOH (15 mL) was stirred at reflux temperature for 1 h. The mixture was cooled to 20 °C, diluted with water (50 mL), the pH adjusted to ca. 8 with aqueous NH_3 and the mixture stirred at 0 °C for 1 h. The precipitate was filtered, washed with water (5 mL) and dried. The crude solid was purified by column chromatography, eluting with a gradient (50–100%) of EtOAc/pet. ether, to give amine **109** (0.28 g, 93%) as a cream powder: mp (EtOAc/pet. ether) 190–191 °C; ^{1}H NMR δ 9.67 (br s, 1 H, NH), 8.60 (dd, J = 4.5, 1.6 Hz, 2 H, H-2′, H-6′), 8.48 (br d, J = 7.7 Hz, 1 H, H-3″), 7.83 (dd, J = 4.5, 1.6 Hz, 2 H, H-3′, H-5′), 7.66 (s, 1 H, H-5), 6.97–7.00 (m, 3 H, H-4″, H-5″, H-6″), 3.87 (s, 3 H, OCH_3); ^{13}C NMR δ 164.0, 150.0 (2), 148.0, 147.2, 141.0, 129.0, 122.1, 120.6, 119.7 (2), 118.2, 110.9, 108.0, 55.6; MS *m/z* 284.5 (MH^+, 100%). Anal. calcd for $C_{15}H_{13}N_3OS$: C, 63.58; H, 4.62; N, 14.83. Found: C, 63.63; H, 4.64; N, 14.77%.

Example 1-69

***N*-(2-Methylphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (111).**

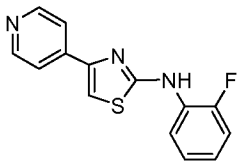


[0324] **2-Methylphenylthiourea (110).** NH_4SCN (3.55 g, 46.7 mmol) was added to a stirred solution of *o*-toluidine (5.00 g, 46.7 mmol) in 1 M HCl (47 mL) at 100 °C and the solution stirred at 100 °C for 16 h. The solution was diluted with water (60 mL) and the pH adjusted to 8 with aqueous NH_3 and the mixture at 5 °C for 2 h. The precipitate was filtered, washed with water (5 mL), washed with ether (5 mL), and dried. The crude solid was purified by column chromatography, eluting with 40% EtOAc/pet. ether, to give thiourea **110** (0.74 g, 10%) as a white powder: mp (EtOAc/pet. ether) 149–151 °C [lit. (Rasmussen, C. R. et al., *Synthesis* **1988**, 456) mp (MeOH) 160.5–162.5 °C]; ^{1}H NMR δ 9.18 (s, 1 H, NH), 7.11 (m, 6 H, H-2, H-4, H-5, H-6, NH_2), 2.18 (s, 3 H, CH_3); MS *m/z* 167.3 (MH^+, 100%).

[0325] ***N*-(2-Methylphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (111).** A mixture of bromoketone hydrobromide **1** (291 mg, 1.0 mmol) and 2-methylphenylthiourea (**110**) (172 mg, 1.0 mmol) in EtOH (10 mL) was stirred at reflux temperature for 3 h. The mixture was cooled to 20 °C, diluted with water (50 mL), the pH adjusted to ca. 8 with aqueous NH_3 and the mixture stirred at 20 °C for 2 h. The precipitate was filtered, washed with water (5 mL) and dried. The crude solid was purified by column chromatography, eluting with a gradient (50–100%) of EtOAc/pet. ether, to give amine **111** (0.24 g, 87%) as a cream powder: mp (EtOAc/pet. ether) 158–160 °C; ^{1}H NMR δ 9.44 (br s, 1 H, NH), 8.58 (dd, *J* = 4.6, 1.5 Hz, 2 H, H-2′, H-6′), 7.96 (br d, *J* = 8.0 Hz, 1 H, H-3″), 7.78 (dd, *J* = 4.6, 1.5 Hz, 2 H, H-3′, H-5′), 7.61 (s, 1 H, H-5), 7.21–7.26 (m, 2 H, H-5″, H-6″), 7.04 (dt, *J* = 7.4, 0.9 Hz, 1 H, H-4″), 2.29 (s, 3 H, CH_3); ^{13}C NMR δ 165.8, 150.0 (2), 147.4, 141.1, 139.1, 130.6, 129.1, 126.5, 123.6, 121.2, 119.7 (2), 107.2, 17.9; MS *m/z* 268.5 (MH^+, 100%). Anal. calcd for $C_{15}H_{13}N_3S$: C, 67.39; H, 4.90; N, 15.72. Found: C, 67.67; H, 4.97; N, 15.61%.

Example 1-70

***N*-(2-Fluorophenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (113).**

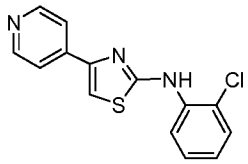


[0326] ***N*-(2-Fluorophenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (113).** A mixture of bromoketone hydrobromide **1** (0.37 g, 1.3 mmol) and *N*-(2-fluorophenyl)thiourea (**112**) (0.22 g, 1.3 mmol) in EtOH (15 mL) was stirred at reflux temperature for 1 h. The mixture was cooled to 20 °C, diluted with water (50 mL), the pH adjusted to ca. 8 with aqueous NH_3 and the mixture stirred at 0 °C for 1 h. The precipitate was filtered, washed with water (5 mL) and dried. The crude solid was purified by column chromatography, eluting with a gradient (50–100%) of EtOAc/pet. ether, to give amine **113** (0.31 g, 87%) as a cream powder: mp (EtOAc/pet. ether) 190–192 °C; ^{1}H NMR δ 10.16 (br s, 1 H, NH), 8.63 (dd, *J* = 4.5, 1.6 Hz, 2 H, H-2′, H-6′), 8.56 (dt, *J* = 8.4, 1.5 Hz, 1 H, H-3″), 7.84 (dd, *J* =

4.5, 1.6 Hz, 2 H, H-3′, H-5′), 7.73 (s, 1 H, H-5), 7.22–7.30 (m, 2 H, H-4″, H-6″), 7.01–7.06 (m, 1 H, H-5″); ^{13}C NMR δ 163.5, 151.6 (d, J = 243 Hz), 150.4 (2), 147.3, 140.9, 128.7 (d, J = 11 Hz), 124.6 (d, J = 3 Hz), 122.3 (d, J = 7 Hz), 119.8, 119.8 (2), 115.0 (d, J = 19 Hz), 108.5; MS *m/z* 272.5 (MH^+, 100%). Anal. calcd for $C_{14}H_{10}FN_3S$: C, 61.98; H, 3.72; N, 15.49. Found: C, 61.89; H, 3.37; N, 15.68%.

Example 1-71

***N*-[2-Chlorophenyl]-4-(4-pyridinyl)-1,3-thiazol-2-amine (115).**



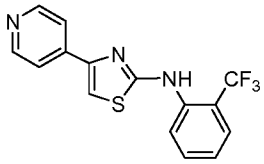
[0327] 2-Chlorophenylthiourea (114). NH_4SCN (3.12 g, 47.5 mmol) was added to a stirred solution of 2-chloroaniline (6.07 g, 47.5 mmol) in 1 M HCl (48 mL) at 100 °C and the solution stirred at 100 °C for 16 h. The solution was diluted with water (60 mL) and the pH adjusted to 8 with aqueous NH_3 and the mixture was stirred at 5 °C for 2 h. The precipitate was filtered, washed with water (5 mL), washed with ether (5 mL), and dried. The crude solid was purified by column chromatography, eluting with 40% EtOAc/pet. ether, to give thiourea **114** (1.23 g, 14%) as a white powder: mp (EtOAc/pet. ether) 141–143 °C [lit. (Rasmussen, C. R. et al., *Synthesis* **1988**, 456) mp (acetone) 145–146.5 °C]; ^{1}H NMR δ 9.28 (s, 1 H, NH), 7.65 (dd, J = 8.0, 1.4 Hz, 1 H, H-3), 7.48 (dd, J = 8.0, 1.4 Hz, 1 H, H-6), 7.38 (br s, 2 H, NH_2), 7.32 (ddd, J = 8.0, 7.6, 1.4 Hz, 1 H, H-5), 7.23 (ddd, J = 8.0, 7.6, 1.4 Hz, 1 H, H-4); MS *m/z* 187.5/189.4 (MH^+, 100%).

[0328] *N*-[2-Chlorophenyl]-4-(4-pyridinyl)-1,3-thiazol-2-amine (115). A mixture of bromoketone hydrobromide **1** (0.30 g, 1.1 mmol) and 2-chlorophenylthiourea (**114**) (0.20 g, 1.1 mmol) in EtOH (15 mL) was stirred at reflux temperature for 1 h. The mixture was cooled to 20 °C, diluted with water (50 mL), the pH adjusted to ca. 8 with aqueous NH_3 and the mixture stirred at 0 °C for 1 h. The precipitate was filtered, washed with water (5 mL) and dried. The crude solid was purified by column chromatography, eluting with a gradient (50–100%) of EtOAc/pet. ether, to give amine **115** (0.27 g, 90%) as a cream powder: mp

(EtOAc/pet. ether) 152–154 °C; ^{1}H NMR δ 9.79 (br s, 1 H, NH), 8.58 (dd, *J* = 4.5, 1.6 Hz, 2 H, H-2′, H-6′), 8.44 (dd, *J* = 8.3, 1.4 Hz, 1 H, H-3″), 7.82 (dd, *J* = 4.5, 1.6 Hz, 2 H, H-3′, H-5′), 7.73 (s, 1 H, H-5), 7.50 (dd, *J* = 8.0, 1.4 Hz, 1 H, H-6″), 7.40 (ddd, *J* = 8.0, 7.5, 1.5 Hz, 1 H, H-5″), 7.09 (ddd, *J* = 8.3, 7.5, 1.5 Hz, 1 H, H-4″); MS *m/z* 288.5/290.5 (MH^+, 100%). Anal. calcd for $C_{14}H_{10}ClN_3S$: C, 58.43; H, 3.50; N, 14.60. Found: C, 58.34; H, 3.62; N, 14.63%.

Example 1-72

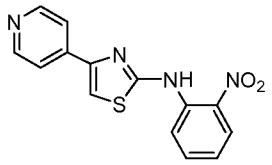
4-(4-Pyridinyl)-*N*-[2-(trifluoromethyl)phenyl]-1,3-thiazol-2-amine (117).



[0329] 4-(4-Pyridinyl)-*N*-[2-(trifluoromethyl)phenyl]-1,3-thiazol-2-amine (117). A mixture of bromoketone hydrobromide **1** (0.30 g, 1.1 mmol) and 2-trifluorophenylthiourea (**116**) (0.23 g, 1.1 mmol) in EtOH (15 mL) was stirred at reflux temperature for 1 h. The mixture was cooled to 20 °C, diluted with water (50 mL), the pH adjusted to ca. 8 with aqueous NH_3 and the mixture stirred at 0 °C for 1 h. The precipitate was filtered, washed with water (5 mL) and dried. The crude solid was purified by column chromatography, eluting with a gradient (50–100%) of EtOAc/pet. ether, to give amine **117** (0.31 g, 93%) as a cream powder: mp (EtOAc/pet. ether) 170–172 °C; ^{1}H NMR δ 9.61 (br s, 1 H, NH), 8.57 (dd, *J* = 4.5, 1.6 Hz, 2 H, H-2″, H-6″), 8.11 (br d, *J* = 8.1 Hz, 1 H, H-3′), 7.67–7.76 (m, 5 H, H-5′, H-6′, H-3″, H-5″), 7.37 (br t, *J* = 7.6 Hz, 1 H, H-4′); ^{13}C NMR δ 165.7, 150.0 (2), 147.3, 140.9, 138.3, 133.3, 126.4 (q, *J* = 5 Hz), 125.8, 124.5, 123.7 (q, *J* = 273 Hz), 121.2 (q, *J* = 29 Hz), 119.7 (2), 108.6; MS *m/z* 322.6 (MH^+, 100%). Anal. calcd for $C_{15}H_{10}F_3N_3S$: C, 56.07; H, 3.14; N, 17.74. Found: C, 56.07; H, 3.27; N, 13.08%.

Example 1-73

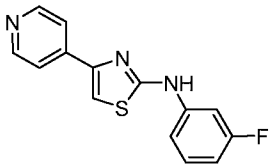
***N*-[2-Nitrophenyl]-4-(4-pyridinyl)-1,3-thiazol-2-amine (119).**



[0330] ***N*-[2-Nitrophenyl]-4-(4-pyridinyl)-1,3-thiazol-2-amine (119).** A mixture of bromoketone hydrobromide **1** (0.32 g, 1.1 mmol) and 2-nitrophenylthiourea (**118**) (0.22 g, 1.1 mmol) in EtOH (15 mL) was stirred at reflux temperature for 1 h. The mixture was cooled to 20 °C, diluted with water (50 mL), the pH adjusted to ca. 8 with aqueous NH_3 and the mixture stirred at 0 °C for 1 h. The precipitate was filtered, washed with water (5 mL) and dried. The crude solid was purified by column chromatography, eluting with a gradient (50–100%) of EtOAc/pet. ether, to give amine **119** (0.32 g, 93%) as a cream powder: mp (EtOAc/pet. ether) 127–130 °C; ^{1}H NMR δ 10.55 (br s, 1 H, NH), 8.60 (dd, *J* = 4.5, 1.6 Hz, 2 H, H-2′, H-6′), 8.27 (dd, *J* = 8.4, 1.0 Hz, 1 H, H-3″), 8.07 (dd, *J* = 8.3, 1.0 Hz, 1 H, H-6″), 7.85 (s, 1 H, H-5), 7.72–7.76 (m, 3 H, H-3′, H-5′, H-5″), 7.24 (ddd, *J* = 8.4, 7.4, 1.2 Hz, 1 H, H-4″); ^{13}C NMR δ 162.7, 150.0 (2), 147.3, 140.6, 138.3, 134.9, 134.8, 125.4, 122.3, 121.6, 119.8 (2), 110.3; MS *m/z* 299.5 (MH^+, 100%). Anal. calcd for $C_{14}H_{10}N_4O_2S$: C, 56.37; H, 3.38; N, 18.78. Found: C, 56.29; H, 3.39; N, 18.84%.

Example 1-74

***N*-(3-Fluorophenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (121).**

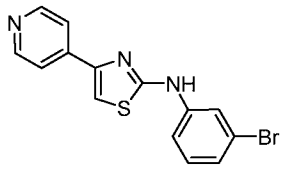


[0331] **3-Fluorophenylthiourea (120).** Reaction of NH_4SCN (0.53 g, 7.0 mmol) and benzoylchloride (0.82 mL, 7.2 mmol) with 3-chloroaniline (0.45 mL, 4.6 mmol) gave thiourea **120** (0.49 g, 62%) as a white powder: mp (H_2O) 100–102 °C [lit. (Schnur, R. C.; et.al. *J. Med. Chem.* **1991**, *34*, 914–918.) mp 113–114 °C]; ^{1}H NMR δ 9.81 (s, 1 H, NH), 7.60 (br s, 2 H, NH_2), 7.55 (dt, J = 11.5, 2.4 Hz, 1 H, H-2), 7.33 (dt, *J* = 9.2, 6.8 Hz, 1 H, H-5), 7.16 (ddd, *J* = 6.8, 1.9, 1.0 Hz, 1 H, H-6), 6.85–6.93 (m 1 H, H-4).

[0332] ***N*-(3-Fluorophenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (121).** Reaction of bromoketone hydrobromide **1** (0.65 g, 2.3 mmol) and 3-fluorophenylthiourea (**120**) (0.39 g, 2.3 mmol) gave amine **121** (0.45 g, 71%) as a white powder: mp (EtOAc/pet. ether) 229–230 °C; ^{1}H NMR δ 10.59 (br s, 1 H, NH), 8.63 (dd, *J* = 4.5, 1.6 Hz, 2 H, H-2′, H-6′), 7.35 (dd, *J* = 4.5, 1.6 Hz, 2 H, H-3′, H-5′), 7.28–7.31 (m, 1 H, H-2″), 7.76 (s, 1 H, H-5), 7.34–7.41 (m, 2 H, H-5″, H-6″), 6.77–6.84 (m, 1 H, H-4″); ^{13}C NMR δ 163.0, 162.4 (d, *J* = 240 Hz), 150.1 (2), 147.6, 142.4 (d, *J* = 11 Hz), 140.8, 130.5 (d, *J* = 10 Hz), 119.8 (2), 112.7 (d, *J* = 2 Hz), 108.0, 107.5 (d, *J* = 21 Hz), 103.5 (d, *J* = 26 Hz). Anal. calcd for $C_{14}H_{10}FN_3S$: C, 61.98; H, 3.72; N, 15.49. Found: C, 61.91; H, 3.79; N, 15.20%.

Example 1-75

***N*-(3-Bromophenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (123).**

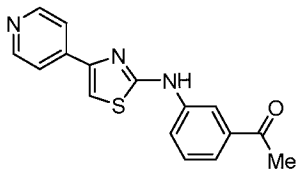


[0333] 3-Bromophenylthiourea (122). Benzoyl chloride (4.5 mL, 38.6 mmol) was added dropwise to a stirred solution of NH_4SCN (3.14 g, 41.3 mmol) in acetone (50 mL). The mixture was stirred at reflux temperature for 15 min, the heating was removed and 3-bromoaniline (3.0 mL, 27.5 mmol) was added dropwise, keeping the solution at reflux temperature. The mixture was stirred at reflux temperature for 30 min, then poured onto ice (100 mL) and stirred for 15 min. The resulting mixture was filtered and washed with water (5 mL), and dried. The solid was added to a stirred solution of NaOH (10% w/v, 100 mL) at 80 °C. The solution was stirred at 80 °C for 30 min and then poured onto ice/HCl (6 M, 30 mL) and stirred for 10 mins. The pH was adjusted to 10 with cNH_3 solution, the resulting precipitate filtered and washed with water (10 mL) and dried. The crude solid was purified by column chromatography, eluting with a gradient (20–50%) of EtOAc/pet. ether, to give thiourea **122** (5.18 g, 82%) as a tan powder: mp (EtOAc/pet. ether) 151–152 °C [lit (Mahapatra, G. N. *J. Indian Chem. Soc.* **1956**, *33*, 923–924) mp (EtOH) 138 °C]; ^{1}H NMR δ 9.78 (s, 1 H, NH), 7.83 (br s, 1 H, H-2,), 7.58 (br s, 2 H, NH_2), 7.35–7.38 (m, 1 H, H-5), 7.25–7.29 (m, 2 H, H-4, H-6).

[0334] ***N*-(3-Bromophenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (123).** A mixture of bromoketone hydrobromide **1** (0.72 g, 2.6 mmol) and 3-bromophenylthiourea (**122**) (0.59 g, 2.6 mmol) in EtOH (40 mL) was stirred at reflux temperature for 2 h. The mixture was cooled to 20 °C, diluted with water (50 mL), the pH adjusted to ca. 8 with aqueous NH_3 and the mixture stirred at 0 °C for 2 h. The precipitate was filtered, washed with water (5 mL) and dried. The crude solid was purified by column chromatography, eluting with EtOAc, to give amine **123** (0.62 g, 72%) as a cream powder: mp (EtOAc/pet. ether) 219–221 °C; ^{1}H NMR δ 10.55 (br s, 1 H, NH), 8.63 (dd, *J* = 4.5, 1.6 Hz, 2 H, H-2′, H-6′), 8.07 (t, *J* = 2.0 Hz, 1 H, H-2″), 7.85 (dd, *J* = 4.5, 1.6 Hz, 2 H, H-3′, H-5′), 7.78 (s, 1 H, H-5), 7.67 (ddd, *J* = 8.2, 2.0, 0.8 Hz, 1 H, H-6″), 7.31 (br t, *J* = 8.1 Hz, 1 H, H-5″), 7.16 (ddd, *J* = 7.9, 2.0, 0.8 Hz, 1 H, H-4″); ^{13}C NMR δ 162.9, 150.1 (2), 147.6, 142.3, 140.8, 130.8, 127.3, 121.7, 119.7 (2), 119.1, 115.6, 108.1; MS *m/z* 332.5/334.5 (MH^+, 100%). Anal. calcd for $C_{14}H_{10}BrN_3S \cdot ¼CH_3CO_2CH_2CH_3$: C, 50.86; H, 3.41; N, 11.86. Found: C, 51.02; H, 3.41; N, 11.86%.

Example 1-76

1-(3-{[4-(4-Pyridinyl)-1,3-thiazol-2-yl]amino}phenyl)ethanone (125).

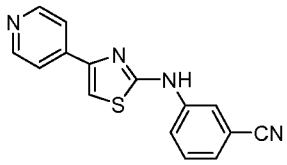


[0335] ***N*-(3-Acetylphenyl)thiourea (124).** NH_4SCN (2.88 g, 37.8 mmol) was added to a stirred solution of 3-aminoacetophenone (5.11 g, 37.8 mmol) in 1 M HCl (38 mL) at 100 °C and the solution stirred at 100 °C for 16 h. The solution was diluted with water (60 mL) and stood at 5 °C for 1 h. The precipitate was filtered, washed with water (5 mL), washed with ether (5 mL), and dried. The crude solid was purified by column chromatography, eluting with a gradient (50–100%) of EtOAc/pet. ether, to give to give thiourea **124** (0.81 g, 11%) as a white powder: mp (EtOAc/pet. ether) 153–156 °C; ^{1}H NMR δ 9.83 (s, 1 H, NH), 7.50 (br s, 2 H, NH_2), 8.02 (t, *J* = 1.8 Hz, 1 H, H-2′), 7.67–7.73 (m, 2 H, H-4′, H-6′), 7.46 (t, *J* = 7.9 Hz, 1 H, H-5′), 2.56 (s, 3 H, $COCH_3$).

[0336] 1-(3-{[4-(4-Pyridinyl)-1,3-thiazol-2-yl]amino}phenyl)ethanone (125). A mixture of bromoketone hydrobromide **1** (0.87 g, 3.1 mmol) and *N*-(3-acetylphenyl)thiourea (**124**) (0.60 g, 3.1 mmol) in EtOH (20 mL) was stirred at reflux temperature for 3 h. The mixture was cooled to 20 °C, diluted with water (50 mL), the pH adjusted to ca. 8 with aqueous NH_3 and the mixture stirred at 20 °C for 2 h. The precipitate was filtered, washed with water (5 mL) and dried. The crude solid was purified by column chromatography, eluting with a gradient (50–100%) of EtOAc/pet. ether, to give amine **125** (0.85 g, 93%) as a white powder: mp (EtOAc/pet. ether) 203–206 °C; ^{1}H NMR δ 10.58 (br s, 1 H, NH), 8.62 (dd, *J* = 4.5, 1.6 Hz, 2 H, H-2‴, H-6″), 8.45 (t, *J* = 1.9 Hz, 1 H, H-2′), 7.95 (ddd, *J* = 8.0, 2.3, 1.0 Hz, 1 H, H-4′), 7.88 (dd, *J* = 4.5, 1.6 Hz, 2 H, H-3‴, H-5‴), 7.76 (s, 1 H, H-5″), 7.59 (dt, *J* = 8.0, 1.5 Hz, 1 H, H-5′), 7.51 (br t, *J* = 7.9 Hz, 1 H, H-5′), 2.61 (s, 3 H, H-2); ^{13}C NMR δ 197.5, 163.1, 150.0 (2), 147.6, 141.1, 140.8, 137.5, 129.3, 121.2 (2), 119.8 (2), 116.0, 107.9, 26.6; MS *m/z* 296.6 (MH^+, 100%). Anal. calcd for $C_{16}H_{13}N_3OS$: C, 65.06; H, 4.44; N, 14.23. Found: C, 64.76; H, 4.29; N, 14.36%.

Example 1-77

3-{[4-(4-Pyridinyl)-1,3-thiazol-2-yl]amino}benzonitrile (127).

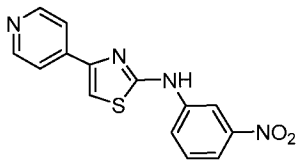


[0337] 3-Cyanophenylthiourea (126). A mixture of 3-aminobenzonitrile (1.0 g, 8.5 mmol) and NH_4SCN (0.64 g, 8.5 mmol) in dilute HCl (1 M, 9 mL) was stirred at reflux temperature for 16 h. The mixture was cooled and water (50 ml) added and the pH was adjusted to 10 with cNH_3 solution, the resulting precipitate was filtered and washed with water (10 mL) and dried. The crude solid was purified by column chromatography, eluting with 40% EtOAc/DCM, to give thiourea **126** (0.22 g, 15%) as a tan powder: mp (EtOAc/DCM) 158–160 °C; ^{1}H NMR δ 9.89 (s, 1 H, NH), 8.03 (br s, 1 H, H-2), 7.70 (dt, *J* = 7.6, 2.0 Hz, 1 H, H-4), 7.60 (br s, 2 H, NH_2), 7.48–7.55 (m, 2 H, H-5, H-6).

[0338] 3-{[4-(4-Pyridinyl)-1,3-thiazol-2-yl]amino}benzonitrile (127). A mixture of bromoketone **1** (0.17 g, 0.62 mmol) and 3-cyanophenythiourea (**126**) (0.11 g, 0.62 mmol) in EtOH (10 mL) was stirred at reflux temperature for 2 h. The mixture was cooled to 20 °C, diluted with water (50 mL), the pH adjusted to ca. 8 with aqueous NH_3 and the mixture stirred at 20 °C for 1 h. The precipitate was filtered, washed with water (5 mL) and dried. The crude solid was purified by column chromatography, eluting with 5% MeOH/DCM, to give amine **127** (0.15 g, 90%) as a white powder: mp (MeOH/DCM) 252–253 °C; ^{1}H NMR δ 10.73 (s, 1 H, NH), 8.64 (dd, *J* = 4.5, 1.6 Hz, 2 H, H-2″, H-6″), 8.18 (t, *J* = 1.8 Hz, 1 H, H-2), 8.01 (ddd, *J* = 8.4, 2.3, 0.9 Hz, 1 H, H-6), 7.86 (dd, *J* = 4.5, 1.6 Hz, 2 H, H-3″, H-5″), 7.81 (s, 1 H, H-5′), 7.58 (br t, *J* = 8.0 Hz, 1 H, H-5), 7.43 (dt, *J* = 7.7, 1.1 Hz, 1 H, H-4); MS *m/z* 279.5 (MH^+, 100%). Anal. calcd for $C_{15}H_{10}N_4S·½H_2O$: C, 63.70; H, 3.74; N, 19.81. Found: C, 63.63; H, 3.92; N, 19.72%.

Example 1-78

***N*-(3-Nitrophenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (129).**

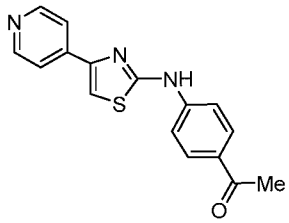


[0339] 3-Nitrophenylthiourea (128). NH_4SCN (2.89 g, 38.0 mmol) was added to a stirred solution of *m*-nitroaniline (5.00 g, 36.2 mmol) in 1 M HCl (37 mL) at 100 °C and the solution stirred at 100 °C for 16 h. The solution was diluted with water (60 mL) and stood at 5 °C for 2 h. The precipitate was filtered, washed with water (5 mL), washed with ether (5 mL). The precipitate was purified by column chromatography, eluting with a gradient (50–80%) of EtOAc/pet. ether, to give thiourea **128** (0.45 g, 6%) as an orange powder: mp (EtOAc) 152–154 °C; ^{1}H NMR δ 10.07 (s, 1 H, NH), 8.61 (t, *J* = 2.2 Hz, 1 H, H-2), 7.93 (ddd, *J* = 8.2, 2.2, 0.9 Hz, 1 H, H-6), 7.83 (ddd, *J* = 8.2, 2.2, 0.9 Hz, 1 H, H-4), 7.60 (br s, 2 H, NH_2), 7.58 (t, *J* = 8.2 Hz, 1 H, H-5).

[0340] ***N*-(3-Nitrophenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (129).** A mixture of bromoketone hydrobromide **1** (0.58 g, 2.1 mmol) and 3-nitrophenylthiourea (**128**) (0.41 g, 2.1 mmol) in EtOH (40 mL) was stirred at reflux temperature for 2 h. The mixture was cooled to 20 °C, diluted with water (50 mL), the pH adjusted to ca. 8 with aqueous NH_3 and the mixture stirred at 0 °C for 2 h. The precipitate was filtered, washed with water (5 mL) and dried. The crude solid was purified by column chromatography, eluting with EtOAc, to give amine **129** (0.43 g, 69%) as a orange powder: mp (EtOAc/pet. ether) 244–247 °C; ^{1}H NMR δ 10.89 (br s, 1 H, NH), 8.95 (t, *J* = 2.2 Hz, 1 H, H-2″), 8.64 (dd, *J* = 4.5, 1.6 Hz, 2 H, H-2′, H-6′), 7.97 (ddd, *J* = 8.2, 2.1, 0.7 Hz, 1 H, H-4″), 7.88 (dd, *J* = 4.5, 1.6 Hz, 2 H, H-3′, H-5′), 7.80–7.84 (m, 2 H, H-5, H-6″), 7.63 (t, *J* = 8.2 Hz, 1 H, H-5″); ^{13}C NMR δ 162.6, 150.1 (2), 148.2, 147.6, 141.8, 140.7, 130.2, 122.8, 119.7 (2), 115.5, 110.7, 108.6; MS *m/z* 299.5 (MH^+, 100%). Anal. calcd for $C_{14}H_{10}N_4O_2S{\cdot}¼CH_3OH$: C, 55.87; H, 3.62; N, 18.29. Found: C, 55.85; H, 3.56; N, 18.21%.

Example 1-79

1-(4-{[4-(4-Pyridinyl)-1,3-thiazol-2-yl]amino}phenyl)ethanone (131).

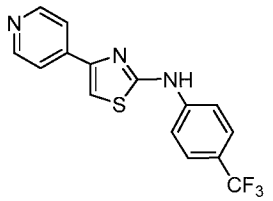


[0341] **4-Acetylphenylthiourea (130).** NH_4SCN (2.85 g, 37.4 mmol) was added to a stirred solution of 4-acetylaniline (5.05 g, 37.4 mmol) in 1 M HCl (40 mL) at 100 °C and the solution stirred at 100 °C for 16 h. The solution was diluted with water (60 mL) and stood at 5 °C for 2 h. The precipitate was filtered, washed with water (5 mL), washed with ether (5 mL), and dried. The crude solid was suspended in hot acetone/MeOH, filtered, and the solvent evaporated to give thiourea **130** (1.70 g, 23%) as a white powder: mp (acetone/MeOH) 202–205 °C; ^{1}H NMR δ 9.90 (s, 1 H, NH), 7.90 (ddd, *J* = 8.8, 2.3, 2.0 Hz, 2 H, H-3′, H-5′), 7.68 (ddd, *J* = 8.8, 2.3, 2.0 Hz, 2 H, H-2′, H-6′), 7.60 (br s, 2 H, NH_2), 2.53 (s, 3 H, $COCH_3$).

[0342] 1-(4-{[4-(4-Pyridinyl)-1,3-thiazol-2-yl]amino}phenyl)ethanone (131). A mixture of bromoketone hydrobromide **1** (0.60 g, 2.14 mmol) and 4-acetylphenylthiourea (**130**) (0.41 g, 2.14 mmol) in EtOH (20 mL) was stirred at reflux temperature for 3 h. The mixture was cooled to 20 °C, diluted with water (50 mL), the pH adjusted to ca. 8 with aqueous NH_3 and the mixture stirred at 20 °C for 2 h. The precipitate was filtered, washed with water (5 mL) and dried. The crude solid was purified by column chromatography, eluting with 50% EtOAc/pet. ether, to give amine **131** (0.40 g, 64%) as a cream powder: mp (EtOAc/pet. ether) 229–231 °C; ^{1}H NMR δ 10.80 (br s, 1 H, NH), 8.63 (dd, *J* = 4.5, 1.6 Hz, 2 H, H-2‴, H-6‴), 8.01 (br d, *J* = 8.8 Hz, 2 H, H-2′, H-6′), 7.89 (dd, *J* = 4.5, 1.6 Hz, 2 H, H-3‴, H-5‴), 7.85 (br d, *J* = 8.8 Hz, 2 H, H-3′, H-5′), 7.82 (s, 1 H, H-5″), 2.53 (s, 3 H, H-2); ^{13}C NMR δ 195.9, 162.5, 150.1 (2), 147.7, 144.8, 140.7, 129.8 (2), 119.8 (2), 116.0 (2), 108.7, 26.1, one carbon not observed. Anal. calcd for $C_{16}H_{13}N_3OS$: C, 65.06; H, 4.44; N, 14.23. Found: C, 65.11; H, 4.40; N, 14.13%.

Example 1-80

4-(4-Pyridinyl)-*N*-[4-(trifluoromethyl)phenyl]-1,3-thiazol-2-amine (133).

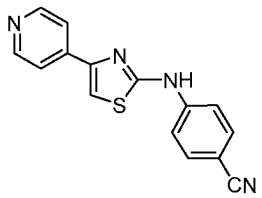


[0343] *N*-[4-(Trifluoromethyl)phenyl]thiourea (132). NH_4SCN (2.74 g, 36.0 mmol) was added to a stirred solution of 4-trifluoromethylaniline (5.80 g, 36.0 mmol) in 1 M HCl (40 mL) at 100 °C and the solution stirred at 100 °C for 16 h. The solution was diluted with water (60 mL) and stood at 5 °C for 2 h. The precipitate was filtered, washed with water (5 mL), washed with ether (5 mL), and dried. The crude solid was purified by column chromatography, eluting with a gradient (50–100%) of EtOAc/pet. ether, to give thiourea **132** (0.98 g, 12%) as a white powder: mp (EtOAc/pet. ether) 122–125 °C [lit. (Rasmussen et al., *Synthesis* **1988**, 456) mp (toluene) 143.5–146 °C]; ^{1}H NMR δ 9.97 (s, 1 H, NH), 9.80 (br s, 2 H, NH_2), 7.73 (d, *J* = 8.6 Hz, 2 H, H-3′, H-5′), 7.65 (br d, *J* = 8.6 Hz, 2 H, H-2′, H-6′), MS *m/z* 221.4 (MH^+, 100%).

[0344] 4-(4-Pyridinyl)-*N*-[4-(trifluoromethyl)phenyl]-1,3-thiazol-2-amine (133). A mixture of bromoketone hydrobromide **1** (0.27 g, 1.0 mmol) and 4-trifluoromethylphenylthiourea (**132**) (0.22 g, 1.0 mmol) in EtOH (15 mL) was stirred at reflux temperature for 3 h. The mixture was cooled to 20 °C, diluted with water (50 mL), the pH adjusted to ca. 8 with aqueous NH_3 and the mixture stirred at 20 °C for 2 h. The precipitate was filtered, washed with water (5 mL) and dried. The crude solid was purified by column chromatography, eluting with EtOAc/pet. ether, to give amine **133** (0.17 g, 54%) as a cream powder: mp (EtOAc/pet. ether) 238–241 °C; ^{1}H NMR δ 10.77 (br s, 1 H, NH), 8.63 (dd, *J* = 4.5, 1.6 Hz, 2 H, H-2″, H-6″), 7.94 (br d, *J* = 8.6 Hz, 2 H, H-3′, H-5′), 7.89 (dd, *J* = 4.5, 1.6 Hz, 2 H, H-3″, H-5″), 7.81 (s, 1 H, H-5″), 7.71 (br d, *J* = 8.6 Hz, 2 H, H-2′, H-6′); ^{13}C NMR δ 162.7, 150.1 (2), 147.7, 144.1, 140.7, 126.2 (q, *J* = 4 Hz, 2), 124.5 (q, *J* = 271 Hz), 121.0 (q, *J* = 32 Hz), 119.8 (2), 116.6 (2), 108.6; MS *m/z* 322.5 (MH^+, 100%). Anal. calcd for $C_{15}H_{10}F_3N_3S$: C, 56.07; H, 3.14; N, 13.08. Found: C, 56.47; H, 3.20; N, 13.15%.

Example 1-81

4-{[4-(4-Pyridinyl)-1,3-thiazol-2-yl]amino}benzonitrile (135).



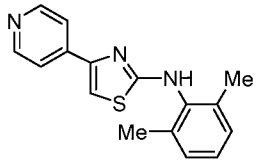
[0345] *N*-(4-Cyanophenyl)thiourea (134). NH_4SCN (3.83 g, 50.4 mmol) was added to a stirred solution of 4-aminobenzonitrile (5.95 g, 50.4 mmol) in 1 M HCl (50 mL) at 100 °C and the solution stirred at 100 °C for 16 h. The solution was diluted with water (60 mL) and stood at 5 °C for 2 h. The precipitate was filtered, washed with water (5 mL), washed with ether (5 mL), and dried. The crude solid was purified by column chromatography, eluting with 40% EtOAc/DCM, to give thiourea **134** (3.58 g, 40%) as a white powder: mp (EtOAc/DCM) >310 °C [lit. (Cohen, V. I. et. al. Bull. Soc. Chim. France **1965**, 8, 2314–2317) mp 239 °C]; ^{1}H

NMR δ 10.06 (s, 1 H, NH), 7.70–7.80 (m, 6 H, NH_2, H-2′, H-3′, H-5′, H-6′); MS *m/z* 178.4 (MH^+, 100%).

[0346] 4-{[4-(4-Pyridinyl)-1,3-thiazol-2-yl]amino}benzonitrile (135). A mixture of bromoketone hydrobromide **1** (0.31 g, 1.1 mmol) and *N*-(4-cyanophenyl)thiourea (**134**) (0.19 g, 1.1 mmol) in EtOH (15 mL) was stirred at reflux temperature for 1 h. The mixture was cooled to 20 °C, diluted with water (50 mL), the pH adjusted to ca. 8 with aqueous NH_3 and the mixture stirred at 20 °C for 2 h. The precipitate was filtered, washed with water (5 mL) and dried. The crude solid was purified by column chromatography, eluting with a gradient (50–100%) of EtOAc/pet. ether, to give amine **135** (0.27 g, 90%) as a cream powder: mp (EtOAc/pet. ether) >300 °C; ^{1}H NMR δ 10.89 (br s, 1 H, NH), 8.64 (dd, *J* = 4.6, 1.5 Hz, 2 H, H-2″, H-6″), 7.86 (m, 4 H, H-2, H-6, H-3″, H-5″), 7.84 (s, 1 H, H-5′), 7.78 (br d, *J* = 8.8 Hz, 2 H, H-3, H-5); ^{13}C NMR δ 162.4, 150.1 (2), 147.8, 144.5, 140.7, 133.4 (2), 119.9 (2), 119.3, 116.8 (2), 109.1, 102.4; MS *m/z* 279.5 (MH^+, 100%). Anal. calcd for $C_{15}H_{10}N4S$: C, 64.73; H, 3.62; N, 20.13. Found: C, 64.50; H, 3.80; N, 20.17%.

Example 1-82

***N*-(2,6-Dimethylphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (137).**

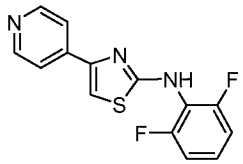


[0347] *N*-(2,6-dimethylphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (137). A mixture of bromoketone hydrobromide **1** (0.30 g, 1.1 mmol) and *N*-(2,6-difluorophenyl)thiourea (**136**) (0.20 g, 1.1 mmol) in EtOH (15 mL) was stirred at reflux temperature for 1 h. The mixture was cooled to 20 °C, diluted with water (50 mL), the pH adjusted to ca. 8 with aqueous NH_3 and the mixture stirred at 0 °C for 1 h. The precipitate was filtered, washed with water (5 mL) and dried. The crude solid was purified by column chromatography, eluting with EtOAc, to give amine **137** (0.28 g, 91%) as a white powder: mp (EtOAc/pet. ether) 208–210 °C; ^{1}H NMR δ 9.34 (s, 1 H, NH), 8.55 (dd, *J* = 4.6, 1.6 Hz, 2 H, H-2′, H-6′), 7.72 (dd, *J* =

4.6, 1.6 Hz, 2 H, H-3′, H-5′), 7.46 (s, 1 H, H-5), 7.12–7.19 (m, 3 H, H-3″, H-4″, H-5″), 2.23 (s, 6 H, 2 × CH_3); ^{13}C NMR δ 168.5, 149.9 (2), 147.9, 141.4, 137.7, 135.7 (2), 128.4 (2), 127.0, 119.8 (2), 106.1, 17.8 (2); MS *m/z* 282.6 (MH^+, 100%). Anal. calcd for $C_{16}H_{15}N_3S$: C, 68.30; H, 5.37; N, 14.93. Found: C, 68.52; H, 5.47; N, 15.14%.

Example 1-83

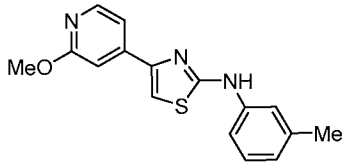
***N*-(2,6-Difluorophenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (139).**



[0348] ***N*-(2,6-Difluorophenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (139).** A mixture of bromoketone hydrobromide **1** (0.30 g, 1.1 mmol) and *N*-(2-fluorophenyl)thiourea (**138**) (0.20 g, 1.1 mmol) in EtOH (15 mL) was stirred at reflux temperature for 1 h. The mixture was cooled to 20 °C, diluted with water (50 mL), the pH adjusted to ca. 8 with aqueous NH_3 and the mixture stirred at 0 °C for 1 h. The precipitate was filtered, washed with water (5 mL) and dried. The crude solid was purified by column chromatography, eluting with EtOAc, to give amine **139** (0.29 g, 91%) as a white powder: mp (EtOAc/pet. ether) 209–211 °C; ^{1}H NMR δ 9.75 (s, 1 H, NH), 8.55 (dd, *J* = 4.5, 1.6 Hz, 2 H, H-2′, H-6′), 7.69 (dd, *J* = 4.5, 1.6 Hz, 2 H, H-3′, H-5′), 7.65 (s, 1 H, H-5), 7.32–7.40 (m, 1 H, H-4″), 7.20–7.26 (m, 2 H, H-3″, H-5″); ^{13}C NMR δ 165.9, 157.4 (dd, *J* = 49, 5 Hz, 2), 150.0 (2), 147.5, 140.8, 127.1 (t, *J* = 10 Hz), 119.7 (2), 117.2 (t, *J* = 16 Hz), 112.6 (dd, *J* = 18, 5 Hz, 2), 108.2; MS *m/z* 290.5 (MH^+, 100%). Anal. calcd for $C_{14}H_9F_2N_3S$: C, 58.12; H, 3.14; N, 14.52. Found: C, 58.26; H, 3.42; N, 14.40%.

Example 1-84

***N*-{4-[2-(Methyloxy)-4-pyridinyl]-1,3-thiazol-2-yl}-*N*-(3-methylphenyl)amine (141).**



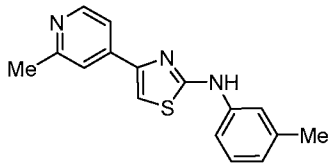
[0349] 2-Bromo-1-[2-(methyloxy)-4-pyridinyl]ethanone (140). Oxalyl chloride (3.6 mL, 42.4 mmol) was added to a stirred suspension of 2-methoxy-4-pyridinecarboxylic acid (1.30 g, 8.5 mmol) and DMF (3 drops) in DCM (30 mL) and the mixture was stirred at 20 °C for 3 days. The solvent was evaporated and the residue dissolved in THF (20 mL) and added to a stirred solution of $TMSCH_2N_2$ (2 M in pet. ether) (10.6 mL, 21.2 mmol) at 0 °C. The mixture was stirred at 0 °C for 5 h and then 48% HBr (9 mL) was added dropwise and the mixture stirred at 20 °C for 16 h. The mixture was neutralised with saturated aqueous $KHCO_3$ and extracted with EtOAc (3 × 50 mL). The organic fraction was washed with water (30 mL), washed with brine (30 mL), dried and the solvent evaporated. The residue was purified by column chromatography, eluting with a gradient (10–20%) of EtOAc/pet. ether, to give bromide **140** (1.08 g, 55%) as a cream powder: ^{1}H NMR δ 8.35 (dd, *J* = 5.3, 0.7 Hz, 1 H, H-6′), 7.40 (dd, *J* = 5.3, 0.7 Hz, 1 H, H-5′), 7.31 (dd, *J* = 1.4, 0.7 Hz, 1 H, H-3′), 6.60 (br s, 1 H, NH·HBr), 4.97 (s, 2 H, H-2), 3.91 (s, 3 H, OCH_3); MS *m/z* 230.4/232.4 (MH^+, 100%). The HBr salt was a cream solid: mp 116 °C (dec.). Anal. calcd for $C_8H_9BrNO_2$: C, 30.90; H, 2.92; N, 4.50. Found: C, 31.16; H, 3.05; N, 4.43%.

[0350] *N*-{4-[2-(Methyloxy)-4-pyridinyl]-1,3-thiazol-2-yl}-*N*-(3-methylphenyl)amine (141). A mixture of bromoketone hydrobromide **140** (0.21 g, 0.9 mmol) and 3-methylphenylthiourea (**4**) (0.15 g, 0.9 mmol) in EtOH (20 mL) was stirred at reflux temperature for 3 h. The mixture was cooled to 20 °C, diluted with water (30 mL), the pH adjusted to ca. 8 with aqueous NH_3 and the mixture stirred at 5 °C for 2 h. The precipitate was filtered, washed with water (5 mL) and dried. The crude solid was purified by column chromatography, eluting with 20% EtOAc/pet. ether, to give amine **141** (0.20 g, 87%) as a cream powder: mp (EtOAc/pet. ether) 131–133 °C; ^{1}H NMR δ 10.25 (br s, 1 H, NH), 8.18 (dd, *J* = 5.5, 0.4 Hz, 1 H, H-6″), 7.67 (s, 1 H, H-5), 7.56 (br d, *J* = 8.1 Hz, 1 H, H-6′), 7.45–7.48 (m, 2 H, H-2′, H-5″), 7.27 (br s, 1 H, H-3″), 7.23 (br t, *J* = 7.8 Hz, 1 H, H-5′), 6.81 (d, *J* = 7.5 Hz, 1 H, H-4′), 3.89 (s, 3 H, OCH_3), 2.32 (s, 3 H, CH_3); ^{13}C NMR δ 164.3, 163.3, 147.5, 147.2, 144.1, 140.8, 138.0, 128.8, 122.1, 117.5, 114.1,

113.8, 107.3, 106.0, 53.0, 21.2; MS *m/z* 298.5 (MH^+, 100%). Anal. calcd for $C_{16}H_{15}N_3OS$: C, 64.62; H, 5.08; N, 14.13. Found: C, 64.71; H, 5.13; N, 14.22%.

Example 1-85

***N*-(3-Methylphenyl)-4-(2-methyl-4-pyridinyl)-1,3-thiazol-2-amine (145).**



[0351] 2-Methyl-4-pyridinecarbonitrile (142). Me_2SO_4 (6.2 mL, 65.6 mmol) was added to 2-methylpyridine 1-oxide at 20 °C and the mixture stirred at 20 °C for 16 h. A solution of KCN (47 g, 72 mmol) in water/EtOH (1:1, 150 mL) was added and the mixture stirred at 20 °C for 16 h. The solvent was reduced to half volume and the mixture extracted with $CHCl_3$ (3 × 50 mL), the combined organic fraction washed with brine (50 mL) and dried. The solvent as evaporated and the residue purified by column chromatography, eluting with 20% EtOAc/pet. ether, to give nitrile **142** as an oil: ^{1}H NMR ($CDCl_3$) δ 8.67 (d, *J* = 5.1 Hz, 1 H, H-6), 7.39 (br s, 1 H, H-3), 7.33 (dd, *J* = 5.1, 0.7 Hz, 1 H, H-5), 2.63 (s, 3 H, CH_3); MS *m/z* 119.3 (MH^+, 100%).

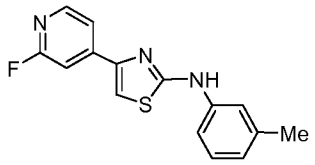
[0352] 1-(2-Methyl-4-pyridinyl)ethanone (143). A solution of MeMgBr (3 M in hexanes, 6.0 mL, 17.9 mmol) was added slowly to a stirred solution of nitrile **142** (1.76 g, 14.9 mmol) in dry THF (100 mL) at 0 °C and the mixture was stirred at reflux temperature for 16 h. The mixture was cooled to 20 °C and the reaction quenched with 6 M HCl (30 mL). The aqueous fraction was separated and the organic fraction extracted with 1 M HCl (30 mL). The combined acidic fraction was stirred at 80 °C for 1 h, cooled to 0 °C and made basic with cNH_3 solution. The mixture was extracted with $CHCl_3$ (3 × 50 mL), the combined organic fraction was washed with brine (50 mL), dried and the solvent evaporated. The residue was purified by column chromatography, eluting with 50% EtOAc/pet. ether, to give ketone **143** (0.50 g, 25%) as an oil: ^{1}H NMR ($CDCl_3$) δ 8.68 (d, *J* = 5.1 Hz, 1 H, H-6′), 7.59 (br s, 1 H, H-3′), 7.52 (d, *J* = 5.1 Hz, 1 H, H-5′), 2.65 (s, 3 H, H-2), 2.61 (s, 3 H, CH_3); MS *m/z* 136.5 (MH^+, 100%).

[0353] 2-Bromo-1-(2-methyl-4-pyridinyl)ethanone (144). Br_2 (0.2 mL, 3.9 mmol) was added dropwise to a stirred a solution of ketone **143** (0.50 g, 3.3 mmol) in 30% HBr/HOAc (10 mL) at 15 °C. The mixture was stirred at 40 °C for 1 h and then at 80 °C for 1 h. The mixture was cooled to 20 °C, diluted with Et_2O (40 mL) and stirred at 0 °C for 30 min. The precipitate was filtered, washed with Et_2O (5 mL) and dried under vacuum to give the hydrobromide salt **144** (0.98 g, 90%) as a white powder: mp (Et_2O/H_2O) 183–186 °C; ^{1}H NMR δ 8.90 (d, J = 5.4 Hz, 1 H, H-6′), 8.14 (s, 1 H, H-3′), 8.03 (d, J = 5.4 Hz, 1 H, H-5′), 5.80 (br s, 1 H, N·HBr), 5.03 (s, 2 H, H-2), 2.72 (s, 3 H, CH_3). Anal. calcd for $C_8H_9BrNO·1¼HBr$: C, 30.49; H, 2.96; N, 4.44. Found: C, 30.65; H, 3.39; N, 4.34%.

[0354] *N*-(3-Methylphenyl)-4-(2-methyl-4-pyridinyl)-1,3-thiazol-2-amine (145). A mixture of bromide **144** (0.45 g, 1.5 mmol) and 3-methylphenylthiourea (**4**) (0.25 g, 1.5 mmol) in EtOH (20 mL) was stirred at reflux temperature for 2 h. The mixture was cooled to 20 °C, diluted with water (40 mL), the pH adjusted to ca. 9 with aqueous NH_3 and the mixture stirred at 0 °C for 1 h. The precipitate was filtered, washed with water (5 mL) and dried. The crude solid was purified by column chromatography, eluting with a gradient (50–100%) of EtOAc/pet. ether, to give amine **145** (0.37 g, 87%) as a cream powder: mp (EtOAc/pet. ether) 198–200 °C; ^{1}H NMR δ 10.25 (s, 1 H, NH), 8.48 (d, J = 5.1 Hz, 1 H, H-6′), 7.71 (br s, 1 H, H-3′), 7.62–7.66 (m, 2 H, H-5, H-5′), 7.56 (br d, J = 8.1 Hz, 1 H, H-6″), 7.48 (br s, 1 H, H-2″), 7.24 (dd, J = 8.1, 7.5 Hz, 1 H, H-5″), 6.80 (br d, J = 7.5 Hz, 1 H, H-4″), 2.54 (s, 3 H, CH_3), 2.33 (s, 3 H, CH_3); ^{13}C NMR δ 163.4, 158.2, 149.3, 147.8, 141.2, 140.8, 138.0, 128.8, 122.1, 118.9, 117.5, 117.1, 114.1, 106.8, 24.1, 21.2; MS *m/z* 282.5 (MH^+, 100%). Anal. calcd for $C_{16}H_{15}N_3S$: C, 68.30; H, 5.37; N, 14.93. Found: C, 67.99; H, 5.25; N, 14.95%.

Example 1-86

4-(2-Fluoro-4-pyridinyl)-*N*-(3-methylphenyl)-1,3-thiazol-2-amine (149).



[0355] 2-Fluoro-*N*-methyl-*N*-(methyloxy)-4-pyridinecarboxamide (146). Et_3N (7.9 mL, 57 mmol) was added to a stirred suspension of 2-fluoro-4-pyridinecarboxylic acid (2.0 g, 14.2 mmol), EDCI (3.0 g, 15.6 mmol), HOBT (2.1 g, 15.6 mmol) and MeNHOMe·HCl (2.1 g, 21.3 mmol) in dry DCM (55 mL), and the mixture was stirred at 20 °C for 20 h. The resulting solution was diluted with DCM (110 mL) and washed with water (2 × 50 mL), washed with brine (50 mL), dried and the solvent evaporated. The residue was purified by column chromatography, eluting with 50% EtOAc/pet. ether, to give amide **146** (1.68 g, 64%) a colourless oil: ^{1}H NMR ($CDCl_3$) δ 8.30 (d, *J* = 5.1 Hz, 1 H, H-6), 7.41 (dt, *J* = 5.1, 1.7 Hz, 1 H, H-5), 7.2 (br s, 1 H, H-3), .56 (s, 3 H, OCH_3), 3.38 (s, 3 H, NCH_3); MS *m/z* 185.5 (MH^+, 100%).

[0356] 1-(2-Fluoro-4-pyridinyl)ethanone (147). A solution of MeMgBr (3 M in Et_2O, 3.8 mL, 11.4 mmol) was added slowly to a stirred solution of amide **146** (1.4 g, 7.6 mmol) in dry THF (40 mL) at 0 °C and the mixture was stirred at 0 °C for 1 h. The reaction mixture was quenched with saturated aqueous NH_4Cl solution (15 mL) and the mixture extracted with EtOAc (3 × 50 mL). The combined organic fraction was washed with water (50 mL) washed with brine (50 mL), dried and the solvent evaporated. The residue was purified by column chromatography, eluting with 30% EtOAc/pet. ether, to give ketone **147** (1.01 g, 96%) as a colourless liquid that crystallized upon standing: mp (EtOAc/pet. ether) 38–39 °C; ^{1}H NMR ($CDCl_3$) δ 8.41 (d, *J* = 5.1 Hz, 1 H, H-6′), 7.63 (ddd, *J* = 5.2, 3.2, 1.2 Hz, 1 H, H-5′), 7.37 (br s, 1 H, H-3′), 2.63 (s, 3 H, H-2); MS *m/z* 140.5 (MH^+), 172.5 (MH^+ + MeOH, 100%).

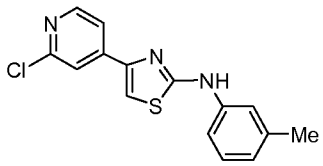
[0357] 2-Fluoro-1-(2-bromo-4-pyridinyl)ethanone Hydrobromide (148). 1-(2-Fluoro-4-pyridinyl)ethanone (**147**) (938 mg, 6.74 mmol) was dissolved in glacial acetic acid and treated with bromine (0.39 mL, 7.5 mmol) followed by HBr/AcOH (30% w/v, 1.5 mL, 7.5 mmol) at 5–10 °C. The reaction mixture was stirred at 20

°C for 3 h, and then diluted with Et_2O (100 mL) and the formed precipitate was filtered off. The solid was washed with Et_2O and dried under high vacuum to afford the crude bromoketone **148** (941 mg) as white solid, which was used in the next step without further purification.

[0358] 4-(2-Fluoro-4-pyridinyl)-*N*-(3-methylphenyl)-1,3-thiazol-2-amine (149). A mixture of bromoketone hydrobromide **148** (941 mg, 3.15 mmol) and 3-methylphenylthiourea (**4**) (524 mg, 3.15 mmol) in EtOH (25 mL) was stirred at reflux temperature for 3 h. The mixture was cooled to 20 °C, diluted with water (80 mL), the pH adjusted to ca. 8 with aqueous NH_3 and the mixture stirred at 20 °C for 2 h. The precipitate was filtered, washed with water (20 mL) and dried. The crude solid was purified by column chromatography, eluting with a gradient (10–20%) of EtOAc/pet. ether, to give a crude solid, which was further purified by preparative HPLC to give amine **149** (25 mg, 3 %) as a white solid: mp (CH_3CN/H_2O) 162–164 °C; ^{1}H NMR (CD_3OD) δ 8.19 (d, J = 5.4 Hz, 1 H, H-6″), 7.78 (dt, J = 5.4, 1.8 Hz, 1 H, H-5″), 7.52–7.50 (m, 3 H, H-3″, H-5, H-6′), 7.44 (br s, 1 H, H-2′), 7.23 (t, J = 7.8 Hz, 1 H, H-5′), 6.85 (br d, J = 7.5, 1 H, H-4′), 2.34 (s, 3 H, CH_3), NH not observed; ^{13}C NMR (CD_3OD) δ 164.3, 164.1 (d, J = 235.7 Hz), 147.6 (d, J = 9 Hz), 146.7, 146.6 (d, J = 14.5 Hz), 140.4, 138.1, 128.1, 122.1, 117.6 (d, J = 3.7 Hz), 117.4, 114.0, 107.2, 104.7 (d, J = 38.3 Hz), 19.8; MS *m/z* 286.5 (MH^+, 100%). Anal. calcd for $C_{15}H_{12}FN_3S \cdot ½H_2O$: C, 61.21; H, 4.45; N, 14.28. Found: C, 60.89; H, 4.25; N, 14.07%.

Example 1-87

4-(2-Chloro-4-pyridinyl)-*N*-(3-methylphenyl)-1,3-thiazol-2-amine (150).

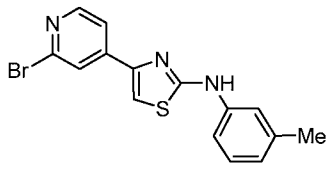


[0359] 4-(2-Chloro-4-pyridinyl)-*N*-(3-methylphenyl)-1,3-thiazol-2-amine (150). A mixture of 2-bromo-1-(2-chloro-4-pyridinyl)ethanone (0.51 g, 2.2 mmol) and 3-methylphenylthiourea (**4**) (0.36 g, 2.2 mmol) in EtOH (35 mL) was stirred at reflux temperature for 1 h. The mixture was cooled to 20 °C, diluted with water (80

mL), the pH adjusted to ca. 8 with aqueous NH_3 and the mixture stirred at 0 °C for 1 h. The precipitate was filtered, washed with water (5 mL) and dried. The crude solid was purified by column chromatography, eluting with EtOAc, to give amine **150** (0.62 g, 94%) as a white powder: mp (EtOAc/pet. ether) 195–197 °C; ^{1}H NMR δ 10.30 (s, 1 H, NH), 8.45 (br d, J = 5.1 Hz, 1 H, H-6′), 7.93 (br d, J = 1.2 Hz, 1 H, H-3′), 7.87 (dd, J = 5.2, 1.4 Hz, 1 H, H-5′), 7.84 (s, 1 H, H-5), 7.55 (br d, J = 8.0 Hz, 1 H, H-6″), 7.47 (br s, 1 H, H-2″), 7.25 (br t, J = 7.8 Hz, 1 H, H-5″), 6.82 (br d, J = 7.4 Hz, 1 H, H-4″), 2.33 (s, 3 H, CH_3); ^{13}C NMR δ 163.6, 151.0 (2), 150.3, 146.2, 144.4, 140.6, 138.1, 128.8, 122.3, 119.7, 117.6, 114.2, 109.1, 21.9; MS *m/z* 302.5 (MH^+, 100%). Anal. calcd for $C_{15}H_{12}ClN_3S$: C, 59.70; H, 4.01; N, 13.92. Found: C, 59.75; H, 4.07; N, 13.82%.

Example 1-88

4-(2-Bromo-4-pyridinyl)-*N*-(3-methylphenyl)-1,3-thiazol-2-amine (154).



[0360] 2-Bromo-*N*-methyl-*N*-(methyloxy)-4-pyridinecarboxamide (151). Et_3N (14.9 mL, 107 mmol) was added to a stirred suspension of 2-bromo-4-pyridinecarboxylic acid (5.40 g, 26.7 mmol), EDCI (5.64 g, 29.4 mmol), HOBT (3.97 g, 29.4 mmol) and MeNHOMe·HCl (3.91 g, 40.0 mmol) in dry DCM (100 mL), and the mixture was stirred at 20 °C for 16 h. The resulting solution was diluted with DCM (200 mL) and washed with water (2 × 50 mL), washed with brine (50 mL), dried and the solvent evaporated. The residue was purified by column chromatography, eluting with 50% EtOAc/pet. ether, to give amide **151** (4.56 g, 70%) as an oil: ^{1}H NMR ($CDCl_3$) δ 8.45 (d, J = 5.0 Hz, 1 H, H-6), 7.72 (br s, 1 H, H-3), 7.48 (dd, J = 5.0, 1.3 Hz, 1 H, H-5), 3.56 (s, 3 H, OCH_3), 3.67 (s, 3 H, NCH_3); MS *m/z* 245.3/247.3 (MH^+, 100%).

[0361] 1-(2-Bromo-4-pyridinyl)ethanone (152). A solution of MeMgBr (3 M in hexanes, 9.3 mL, 27.9 mmol) was added slowly to a stirred solution of amide **151** (4.56 g, 18.6 mmol) in dry THF (100 mL) at 0 °C and the mixture was stirred at 0

°C for 3 h. The reaction mixture was quenched with saturated aqueous NH_4Cl solution (30 mL) and the mixture extracted with EtOAc (3 × 50 mL). The combined organic fraction was washed with water (50 mL) washed with brine (50 mL), dried and the solvent evaporated. The residue was purified by column chromatography, eluting with 30% EtOAc/pet. ether, to give ketone **152** (3.51 g, 94%) as an oil: ^{1}H NMR ($CDCl_3$) δ 8.57 (dd, J = 5.1, 0.4 Hz, 1 H, H-6′), 7.91 (dd, J = 1.4, 0.4 Hz, 1 H, H-3′), 7.68 (dd, J = 5.1, 1.4 Hz, 1 H, H-5′), 2.61 (s, 3 H, H-2); MS *m/z* 200.3/204.3 (MH^+, 100%). Anal. calcd for $C_7H_6BrNO·¼CH_3CO_2CH_2CH_3$: C, 42.68; H, 3.34; N, 6.63. Found: C, 42.62; H, 3.06; N, 6.97%.

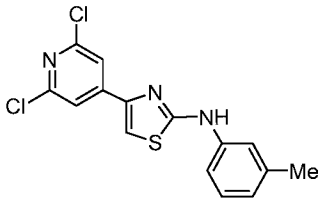
[0362] 2-Bromo-1-(2-bromo-4-pyridinyl)ethanone Hydrobromide (153). Br_2 (0.81 mL, 15.9 mmol) was added dropwise to a stirred a solution of ketone **152** (3.02 g, 15.1 mmol) in 30% HBr/HOAc (20 mL) at 15 °C. The mixture was stirred at 20 °C for 1 h, then at 40 °C for 1 h and then at 75 °C for 1 h. The mixture was cooled to 20 °C, diluted with Et_2O (50 mL) and stirred for 30 min at 0 °C. The precipitate was filtered, washed with Et_2O (5 mL) and dried under vacuum to give the hydrobromide salt **153** (5.28 g, 97%) as a white powder: mp (HOAc/ether) >290 °C; ^{1}H NMR δ 8.71 (br s, 1 H, N·HBr), 8.63 (dd, J = 5.1, 0.5 Hz, 1 H, H-6′), 8.10 (br s, 1 H, H-3′), 7.88 (dd, J = 5.1, 1.5 Hz, 1 H, H-5′), 5.00 (s, 2 H, H-2); MS *m/z* 310.4/312.4/314.4 (MH + $MeOH^+$, 60, 100, 60%).

[0363] 4-(2-Bromo-4-pyridinyl)-*N*-(3-methylphenyl)-1,3-thiazol-2-amine (154). A mixture of bromoketone hydrobromide **153** (0.62 g, 1.7 mmol) and 3-methylphenylthiourea (**4**) (0.25 g, 1.7 mmol) in EtOH (20 mL) was stirred at reflux temperature for 2 h. The mixture was cooled to 20 °C, diluted with water (50 mL), the pH adjusted to ca. 8 with aqueous NH_3 and the mixture stirred at 20 °C for 2 h. The precipitate was filtered, washed with water (5 mL) and dried. The crude solid was purified by column chromatography, eluting with 40% EtOAc/pet. ether, to give amine **154** (0.50 g, 84%) as a cream powder: mp (EtOAc/pet. ether) 202–204 °C; ^{1}H NMR δ 10.31 (br s, 1 H, NH), 8.42 (d, J = 5.2 Hz, 1 H, H-6″), 8.06 (br s, 1 H, H-3″), 7.90 (dd, J = 5.2, 1.4 Hz, 1 H, H-5″), 7.85 (s, 1 H, H-5), 7.52 (br d, J = 8.0 Hz, 1 H, H-6′), 7.47 (br s, 1 H, H-2′), 7.25 (br t, J = 7.8 Hz, 1 H, H-5′), 6.83 (br

d, J = 7.5 Hz, 1 H, H-4′), 2.32 (s, 3 H, CH_3); ^{13}C NMR δ 163.6, 150.8, 146.0, 144.1, 142.1, 140.7, 138.1, 128.8, 123.4, 122.3, 119.5, 117.6, 114.2, 109.1, 21.2; MS *m/z* 346.5/348.5 (MH^+, 100%). Anal. calcd for $C_{15}H_{12}BrN_3S$: C, 52.03; H, 3.49; N, 12.14. Found: C, 52.21; H, 3.51; N, 12.13%.

Example 1-89

***N*-[4-(2,6-Dichloro-4-pyridinyl)-1,3-thiazol-2-yl]-*N*-(3-methylphenyl)amine (158).**



[0364] 2,6-Dichloro-*N*-methyl-*N*-(methyloxy)-4-pyridinecarboxamide (155). Et_3N (5.8 mL, 41.6 mmol) was added to a stirred suspension of 2,6-dichloro-4-pyridinecarboxylic acid (2.0 g, 10.4 mmol), EDCI (2.2 g, 11.4 mmol), HOBT (1.54 g, 11.4 mmol) and MeNHOMe·HCl (1.52 g, 15.6 mmol) in dry DCM (50 mL), and the mixture was stirred at 20 °C for 20 h. The resulting solution was diluted with DCM (100 mL) and washed with water (2 × 50 mL), washed with brine (50 mL), dried and the solvent evaporated. The residue was purified by column chromatography, eluting with 20% EtOAc/pet. ether, to give amide **155** (2.01 g, 83%) as a colourless oil: ^1H NMR ($CDCl_3$) δ 7.51 (s, 2 H, H-2′, H-6′), 3.59 (s, 3 H, OCH_3), 3.38 (s, 3 H, NCH_3); MS *m/z* 235.4, 237.4 (MH^+, 100, 70%).

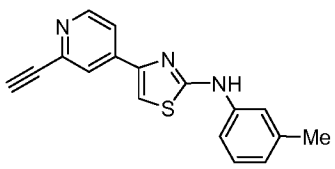
[0365] 1-(2,6-Dichloro-4-pyridinyl)ethanone (156). A solution of MeMgBr (3 M in Et_2O, 4.3 mL, 12.8 mmol) was added slowly to a stirred solution of amide **155** (2.0 g, 8.5 mmol) in dry THF (40 mL) at 0 °C and the mixture was stirred at 0 °C for 3 h. The reaction mixture was quenched with aq. NH_4Cl solution (15 mL) and the mixture extracted with EtOAc (3 × 50 mL). The combined organic fraction was washed with water (50 mL), washed with brine (50 mL), dried and the solvent evaporated. The crude product was recrystallized to give the ketone **156** as white crystals (1.61 g, 99%): mp (EtOAc) 50–51° C; ^1H NMR ($CDCl_3$) δ 7.68 (s, 2 H, H-3′, H-5′), 2.61 (s, 3 H, H-2); MS *m/z* 190.4, 192.4 (MH^+, 100, 70%).

[0366] 2,6-Dichloro-1-(2-bromo-4-pyridinyl)ethanone Hydrobromide (157). 1-(3-Chloro-4-pyridinyl)ethanone **156** (653 mg, 4.2 mmol) was dissolved in HOAc and treated with Br_2 (0.24 mL, 4.66 mmol) followed by HBr/AcOH (30% w/v, 0.93 mL, 4.66 mmol) at 5–10 °C. The reaction mixture was stirred at 20 °C for 3 h and then diluted with Et_2O (100 mL), washed with sat. aq. $Na_2S_2O_3$ solution (30 mL), washed with water (30 mL), washed with brine (30 mL) and dried. The solvent was evaporated and the crude product was dried under high vacuum to afford the bromoketone **157** (1.32 g) as a pale yellow solid which was used without further purification.

[0367] 4-(2,6-Dichloro-4-pyridinyl)-*N*-(3-methylphenyl)-1,3-thiazol-2-amine (158). A mixture of bromoketone hydrobromide **157** (1.32 g, 3.8 mmol) and 3-methylphenylthiourea (**4**) (632 mg, 3.8 mmol) in EtOH (25 mL) was stirred at reflux temperature for 3 h. The mixture was cooled to 20 °C, diluted with water (80 mL), the pH adjusted to ca. 8 with aq. NH_3 and the mixture stirred at 20 °C for 2 h. The precipitate was filtered, washed with water (20 mL) and dried. The crude solid was purified by column chromatography, eluting with 20% EtOAc/pet. ether, to give amine **158** (904 mg, 71 %) as a beige solid: mp (EtOAc/pet. ether) 204–206 °C; ^{1}H NMR δ 10.34 (s, 1 H, NH), 7.99 (s, 1 H, H-5), 7.97 (s, 2 H, H-3″, H-5″), 7.52 (br d, J = 8.0 Hz, 1 H, H-6′), 7.45 (br s, 1 H, H-2′), 7.26 (t, J = 7.8 Hz, 1 H, H-5′), 6.83 (d, J = 7.5 Hz, 1 H, H-4′), 2.32 (s, 3 H, CH_3); ^{13}C NMR δ 163.8, 149.9 (2), 147.2, 145.2, 140.6, 138.2, 129.0, 122.6, 119.2 (2), 117.8, 114.4, 111.0, 21.3; MS *m/z* 336.6, 338.6 (MH^+, 100, 70%). Anal. calcd for $C_{15}H_{11}Cl_2N_3S$: C, 53.58; H, 3.30; N, 12.50. Found: C, 53.55; H, 3.25; N, 12.28%.

Example 1-90

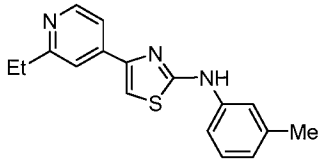
4-(2-Ethynyl-4-pyridinyl)-*N*-(3-methylphenyl)-1,3-thiazol-2-amine (159).



[0368] 4-(2-Ethynyl-4-pyridinyl)-*N*-(3-methylphenyl)-1,3-thiazol-2-amine (159). $PdCl_2(PPh_3)_2$ (35 mg, 0.05 mmol) was added to a purged mixture of bromide (**154**) (346 mg, 1.0 mmol), trimethylsilylacetylene (0.15 mL, 1.1 mmol), CuI (10 mg, 0.05 mmol) in Et_3N (3 mL) and DMF (3 mL) and the mixture was stirred at 50 °C for 16 h in a sealed tube. The mixture was cooled to 20 °C, diluted with water (100 mL), and extracted with EtOAc (3 × 50 mL). The combined organic fraction was washed with water (2 × 40 mL), washed with brine (50 mL) and dried. The solvent was evaporated and the crude solid was dissolved in THF (20 mL) and a solution of TBAF (1.0 M, 1.5 mL, 1.5 mmol) was added. The mixture was stirred at 20 °C for 16 h and the solvent was evaporated. The residue was suspended in water (50 mL), and extracted with EtOAc (3 × 30 mL). The combined organic fraction was washed with water (40 mL), washed with brine (40 mL) and dried. The solvent was evaporated and the crude solid was purified by column chromatography, eluting with 50% EtOAc/pet. ether, to give amine **159** (0.18 g, 62%) as a tan powder: mp (EtOAc/pet. ether) 192–194 °C; ^{1}H NMR δ 10.29 (s, 1 H, NH), 8.60 (dd, *J* = 5.2, 1.7 Hz, 1 H, H-6″), 8.02 (d, *J* = 1.6, 0.7 Hz, 1 H, H-3″), 7.87 (dd, *J* = 5.2, 1.7 Hz, 1 H, H-5″), 7.81 (s, 1 H, H-5), 7.56 (br d, *J* = 8.0 Hz, 1 H, H-6′), 7.47 (br s, 1 H, H-2′), 7.25 (br t, *J* = 7.8 Hz, 1 H, H-5′), 6.82 (br d, *J* = 7.5 Hz, 1 H, H-4′), 4.34 (s, 1 H, CH), 2.33 (s, 3 H, CH_3); ^{13}C NMR δ 163.6, 150.7, 146.7, 142.2, 141.6, 140.8, 138.2, 128.9, 123.2, 122.3, 119.8, 117.5, 114.1, 108.5, 83.2, 80.1, 21.3; MS *m/z* 292.6 (MH^+, 100%). Anal. calcd for $C_{17}H_{13}N_3S \cdot ¼CH_3OH$: C, 69.21; H, 4.71; N, 14.04. Found: C, 69.44; H, 4.57; N, 13.86%.

Example 1-91

4-(2-Ethyl-4-pyridinyl)-*N*-(3-methylphenyl)-1,3-thiazol-2-amine (160).

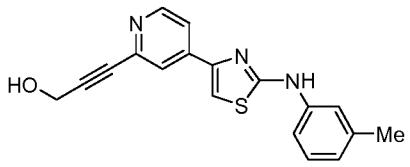


[0369] 4-(2-Ethyl-4-pyridinyl)-*N*-(3-methylphenyl)-1,3-thiazol-2-amine (160). A mixture of amine **159** (120 mg, 0.41 mmol) and Pd/C (25 mg) in EtOH (20 mL) was stirred under H_2 (60 psi) for16 h. The mixture was filtered through Celite,

washed with EtOH. The solvent was evaporated and the crude solid was purified by column chromatography, eluting with 50% EtOAc/pet. ether, to give amine **160** (45 mg, 37%) as a white powder: mp (EtOAc/pet. ether) 206–209 °C; ^{1}H NMR δ 10.30 (s, 1 H, NH), 8.50 (d, *J* = 5.2 Hz, 1 H, H-6″), 7.13 (br s, 1 H, H-3″), 7.65–7.68 (m, 2 H, H-5, H-5″), 7.50–7.54 (m, 2 H, H-2′, H-6′), 7.24 (br t, *J* = 7.7 Hz, 1 H, H-5′), 6.81 (br d, *J* = 7.5 Hz, 1 H, H-4′), 2.80 (q, *J* = 7.6 Hz, 2 H, CH_2), 2.32 (s, 3 H, CH_3), 1.27 (t, *J* = 7.6 Hz, 3 H, CH_3); ^{13}C NMR δ 163.4, 163.2, 149.4, 147.9, 141.4, 140.8, 138.1, 128.8, 122.1, 117.8, 117.5, 117.3, 114.1, 106.8, 30.6, 21.2, 13.5; MS *m/z* 296.6 (MH^+, 100%). Anal. calcd for $C_{17}H_{17}N_3S$: C, 69.12; H, 5.80; N, 14.22. Found: C, 69.14; H, 5.87; N, 14.22%.

Example 1-92

3-(4-{2-[(3-Methylphenyl)amino]-1,3-thiazol-4-yl}-2-pyridinyl)-2-propyn-1-ol (161).

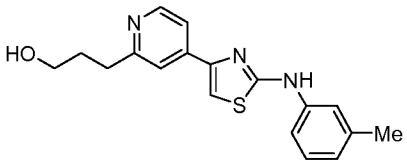


[0370] 3-(4-{2-[(3-Methylphenyl)amino]-1,3-thiazol-4-yl}-2-pyridinyl)-2-propyn-1-ol (161). $PdCl_2(PPh_3)_2$ (108 mg, 0.15 mmol) was added to a purged mixture of bromide **154** (1.07 g, 3.1 mmol), propargyl alcohol (0.20 mL, 3.4 mmol), CuI (29 mg, 0.15 mmol) in Et_3N (4 mL) and DMF (5 mL) and the mixture was stirred at 50 °C for 16 h in a sealed tube. The mixture was cooled to 20 °C, diluted with water (100 mL), and extracted with EtOAc (3 × 50 mL). The combined organic fraction was washed with water (2 × 40 mL), washed with brine (50 mL) and dried. The solvent was evaporated and the crude solid was purified by column chromatography, eluting with EtOAc, to give amine **161** (0.81 g, 81%) as a tan powder: mp (EtOAc/pet. ether) 143–145 °C; ^{1}H NMR δ 10.28 (s, 1 H, NH), 8.59 (d, *J* = 5.2 Hz, 1 H, H-6′), 7.95 (d, *J* = 1.6 Hz, 1 H, H-3′), 7.82 (dd, *J* = 5.2, 1.7 Hz, 1 H, H-5′), 7.79 (s, 1 H, H-5″), 7.57 (br d, *J* = 8.1 Hz, 1 H, H-6‴), 7.43 (br s, 1 H, H-2‴), 7.24 (br t, *J* = 7.8 Hz, 1 H, H-5‴), 6.81 (br d, *J* = 7.4 Hz, 1 H, H-4‴), 5.42 (t, *J* = 6.0 Hz, 1 H, OH), 4.36 (d, *J* = 6.0 Hz, 2 H, H-1), 2.32 (s, 3 H, CH_3); ^{13}C NMR δ 163.5, 150.6, 146.8, 142.7, 141.5, 140.7, 138.1, 128.8, 122.6,

122.3, 119.2, 117.5, 114.1, 108.1, 89.2, 83.6, 49.2, 21.2; MS *m/z* 322.6 (MH^+, 100%). Anal. calcd for $C_{18}H_{15}N_3OS$: C, 67.27; H, 4.70; N, 13.07. Found: C, 67.05; H, 4.81; N, 12.62%.

Example 1-93

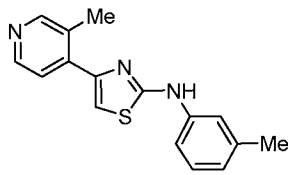
3-(4-{2-[(3-Methylphenyl)amino]-1,3-thiazol-4-yl}-2-pyridinyl)-1-propanol (162).



[0371] 3-(4-{2-[(3-Methylphenyl)amino]-1,3-thiazol-4-yl}-2-pyridinyl)-1-propanol (162). A mixture of amine **161** (700 mg, 2.17 mmol) and Pd/C (100 mg) in EtOH (50 mL) was stirred under H_2 (60 psi) for16 h. The mixture was filtered through Celite, washed with EtOH. The solvent was evaporated and the crude solid was purified by column chromatography, eluting with 50% EtOAc/pet. ether, to give amine **162** (470 mg, 67%) as a yellow foam: ^{1}H NMR δ 10.25 (s, 1 H, NH), 8.50 (d, *J* = 5.2 Hz, 1 H, H-6′), 7.72 (br s, 1 H, H-3′), 7.63–7.67 (m, 2 H, H-5′, H-5″), 7.49–7.54 (m, 2 H, H-2‴, H-6‴), 7.25 (br t, *J* = 7.7 Hz, 1 H, H-5‴), 6.81 (br d, *J* = 7.5 Hz, 1 H, H-4‴), 4.49 (t, *J* = 5.1 Hz, 1 H, OH), 3.45–3.50 (m, 2 H, H-1), 2.81 (dd, *J* = 7.9, 7.5 Hz, 2 H, H-3), 2.33 (s, 3 H, CH_3), 1.92 (m, 2 H, H-2); ^{13}C NMR δ 163.4, 162.0, 149.4, 147.9, 141.3, 140.8, 138.1, 128.8, 122.1, 118.5, 117.5, 117.3, 114.1, 106.8, 60.2, 34.1, 32.3, 21.2; MS *m/z* 326.6 (MH^+, 100%). Anal. calcd for $C_{18}H_{19}N_3OS \cdot ¼CH_3OH$: C, 65.74; H, 6.05; N, 12.60. Found: C, 65.72; H, 6.20; N, 12.58%.

Example 1-94

***N*-(3-Methylphenyl)-4-(3-methyl-4-pyridinyl)-1,3-thiazol-2-amine (166).**



[0372] *N*,3-Dimethyl-*N*-(methyloxy)-4-pyridinecarboxamide (163). Et_3N (4.1 mL, 29.4 mmol) was added to a stirred suspension of 3-methyl-4-

pyridinecarboxylic acid (1.00 g, 7.4 mmol), EDCI (1.55 g, 8.1 mmol), HOBT (1.09 g, 8.1 mmol) and MeNHOMe·HCl (1.08 g, 11.0 mmol) in dry DCM (80 mL), and the mixture was stirred at 20 °C for 16 h. The resulting solution was diluted with DCM (100 mL) and washed with water (2 × 30 mL), washed with brine (30 mL), dried and the solvent evaporated. The residue was purified by column chromatography, eluting with a gradient of (50–100%) of EtOAc/pet. ether, to give amide **163** (0.84 g, 63%) as an oil: ^{1}H NMR ($CDCl_3$) δ 8.50 (s, 1 H, H-2), 8.48 (d, J = 4.9 Hz, 1 H, H-6), 7.17 (d, J = 4.9 Hz, 1 H, H-5), 3.45 (s, 3 H, OCH_3), 3.35 (s, 3 H, NCH_3), 2.32 (s, 3 H, CH_3); MS *m/z* 181.4 (MH^+, 100%).

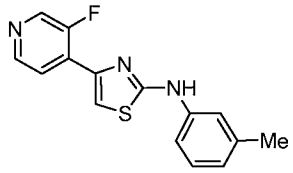
[0373] 1-(3-Methyl-4-pyridinyl)ethanone (164). A solution of MeMgBr (3 M in hexanes, 1.7 mL, 5.1 mmol) was added slowly to a stirred solution of amide **163** (0.84 g, 4.6 mmol) in dry THF (30 mL) at 0 °C and the mixture was stirred at 0 °C for 3 h. The reaction mixture was quenched with saturated aqueous NH_4Cl solution (20 mL) and the mixture extracted with EtOAc (3 × 50 mL). The combined organic fraction was washed with water (40 mL) washed with brine (40 mL), dried and the solvent evaporated. The residue was purified by column chromatography, eluting with 50% EtOAc/pet. ether, to give ketone **164** (0.49 g, 78%) as an oil: ^{1}H NMR ($CDCl_3$) δ 8.58 (d, J = 5.0 Hz, 1 H, H-6′), 8.56 (s, 1 H, H-2′), 7.42 (d, J = 5.0 Hz, 1 H, H-5′), 2.58 (s, 3 H, H-2), 2.47 (s, 3 H, CH_3); MS *m/z* 136.5 (MH^+, 100%).

[0374] 2-Bromo-1-(3-methyl-4-pyridinyl)ethanone Hydrobromide (165). Br_2 (0.21 mL, 4.0 mmol) was added dropwise to a stirred a solution of ketone **164** (0.49 g, 3.7 mmol) in 30% HBr/HOAc (10 mL) at 20 °C. The mixture was stirred at 20 °C for 1 h, then at 40 °C for 1 h and then at 75 °C for 1 h. The mixture was cooled to 20 °C, diluted with Et_2O (40 mL) and stirred for 30 min at 0 °C. The precipitate was filtered, washed with Et_2O (5 mL) and dried under vacuum to give the crude hydrobromide salt **165** (0.75 g, 69%) as an tan powder: ^{1}H NMR δ 8.80–8.84 (m, 2 H, H-2′, H-6′), 8.04 (d, J = 5.5 Hz, 1 H, H-5′), 5.15 (br s, 1 H, N·HBr), 4.63 (s, 2 H, H-2); MS *m/z* 216.3/218.3 (MH^+, 100%).

[0375] ***N*-(3-Methylphenyl)-4-(3-methyl-4-pyridinyl)-1,3-thiazol-2-amine (166).** A mixture of bromoketone **165** (0.53 g, 1.8 mmol) and 3-methylphenylthiourea (**4**) (0.30 g, 1.8 mmol) in EtOH (20 mL) was stirred at reflux temperature for 2 h. The mixture was cooled to 20 °C, diluted with water (50 mL), the pH adjusted to ca. 8 with aqueous NH_3 and the mixture stirred at 20 °C for 2 h. The precipitate was filtered, washed with water (5 mL) and dried. The crude solid was purified by column chromatography, eluting with 50% EtOAc/pet. ether, to give amine **166** (0.42 g, 83%) as a tan powder: mp (EtOAc/pet. ether) 170–172 °C; ^{1}H NMR δ 10.22 (br s, 1 H, NH), 8.48 (s, 1 H, H-2′), 8.45 (d, *J* = 5.1 Hz, 1 H, H-6′), 7.68 (d, *J* = 5.1 Hz, 1 H, H-5′), 7.52 (br s, 1 H, H-2″), 7.49 (br d, *J* = 8.1 Hz, 1 H, H-6″), 7.30 (s, 1 H, H-5), 7.20 (br t, *J* = 7.8 Hz, 1 H, H-5″), 6.79 (br d, *J* = 7.5 Hz, 1 H, H-4″), 2.53 (s, 3 H, CH_3), 2.30 (s, 3 H, CH_3); ^{13}C NMR δ 162.6, 151.7, 147.7, 147.3, 140.9, 140.7, 138.0, 129.7, 128.7, 122.3, 122.0, 117.4, 114.0, 108.9, 21.2, 18.3; MS *m/z* 282.5 (MH^+, 100%). Anal. calcd for $C_{16}H_{15}N_3S$: C, 68.30; H, 5.37; N, 14.93. Found: C, 68.09; H, 5.43; N, 14.67%.

Example 1-95

4-(3-Fluoro-4-pyridinyl)-*N*-(3-methylphenyl)-1,3-thiazol-2-amine (170).



[0376] **3-Fluoro-*N*-methyl-*N*-(methyloxy)-4-pyridinecarboxamide (167).** Et_3N (7.9 mL, 57 mmol) was added to a stirred suspension of 3-fluoro-4-pyridinecarboxylic acid (2.0 g, 14.2 mmol), EDCI (3.0 g, 15.6 mmol), HOBt (2.1 g, 15.6 mmol) and MeNHOMe·HCl (2.1 g, 21.3 mmol) in dry DCM (55 mL), and the mixture was stirred at 20 °C for 20 h. The resulting solution was diluted with DCM (110 mL) and washed with water (2 × 50 mL), washed with brine (50 mL), dried and the solvent evaporated. The residue was purified by column chromatography, eluting with 50% EtOAc/pet. ether, to give amide **167** (1.60 g, 62%) as a colourless oil: ^{1}H NMR ($CDCl_3$) δ 8.55 (s, 1 H, H-2), 8.50 (dd, *J* = 4.8, 1.1 Hz, 1 H, H-6), 7.35 (t, *J* = 5.1 Hz, 1 H, H-5); 3.54 (br s, 3 H, OCH_3), 3.38 (br s, 3 H, NCH_3); MS *m/z* 185.5 (MH^+, 100%).

[0377] 1-(3-Fluoro-4-pyridinyl)ethanone (168). A solution of MeMgBr (3 M in Et_2O, 4.1 mL, 12.2 mmol) was added slowly to a stirred solution of amide **167** (1.5 g, 8.14 mmol) in dry THF (40 mL) at 0 °C and the mixture was stirred at 0 °C for 3 h. The reaction mixture was quenched with saturated aqueous NH_4Cl solution (15 mL) and the mixture extracted with EtOAc (3 × 50 mL). The combined organic fraction was washed with water (50 mL) washed with brine (50 mL), dried and the solvent evaporated. The residue was purified by column chromatography, eluting with 30% EtOAc/pet. ether, to give ketone **168** (1.00 g, 88%) as a colourless liquid: ^{1}H NMR ($CDCl_3$) δ (2 rotamers) δ 8.64 (s, 0.5 H, H-2′), 8.63 (s, 0.5 H, H-2′), 8.57 (d, J = 4.9 Hz, 0.5 H, H-6′), 8.56 (d, J = 4.9 Hz, 0.5 H, H-6′), 7.68 (dd, J = 4.9, 0.4 Hz, 0.5 H, H-5′), 7.66 (dd, J = 4.9, 0.4 Hz, 0.5 H, H-5′), 2.69 (s, 1.5 H, H-2), 2.68 (s, 1.5 H, H-2); MS *m/z* 140.5 (MH^+, 100%), 172.5 (MH^+ + MeOH).

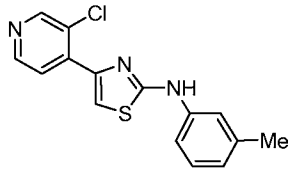
[0378] 3-Fluoro-1-(2-bromo-4-pyridinyl)ethanone Hydrobromide (169). 1-(3-Fluoro-4-pyridinyl)ethanone (**168**) (880 mg, 6.33 mmol) was dissolved in glacial acetic acid (20 mL) and treated with bromine (0.36 mL, 7.0 mmol) followed by HBr/AcOH (30% w/v, 1.4 mL, 7.0 mmol) at 5–10 °C. The reaction mixture was stirred at 20 °C for 3 h, it was then diluted with Et_2O (100 mL) and the precipitate was filtered off, washed with Et_2O and dried under high vacuum to afford the crude bromoketone **169** (1.65 g) as a pale yellow solid that was used without further purification.

[0379] 4-(3-Fluoro-4-pyridinyl)-*N*-(3-methylphenyl)-1,3-thiazol-2-amine (170). A mixture of bromoketone hydrobromide **169** (1.5 g, 5.0 mmol) and 3-methylphenylthiourea (**4**) (831 mg, 5.0 mmol) in EtOH (20 mL) was stirred at reflux temperature for 3 h. The mixture was cooled to 20 °C, diluted with water (80 mL), the pH adjusted to ca. 8 with aqueous NH_3 and the mixture stirred at 20 °C for 2 h. The precipitate was filtered, washed with water (20 mL) and dried. The crude solid was purified by column chromatography, eluting with 20% EtOAc/pet. ether, to give amine **170** (1.02 g, 72%) as a beige solid: mp (EtOAc/pet. ether) 159–161 °C ^{1}H NMR δ (2 rotamers) δ 10.31 (s, 1 H, NH), 8.64 (s, 0.5 H, H-2′),

8.63 (s, 0.5 H, H-2′), 8.54 (d, J = 5.0 Hz, 0.5 H, H-6′), 8.53 (d, J = 5.0 Hz, 0.5 H, H-6′), 8.03 (d, J = 5 Hz, 0.5 H, H-5′), 8.01 (d, J = 5 Hz, 0.5 H, H-5′), 7.60–7.54 (m, 2 H, H-5, H-6″), 7.47 (br s, 1 H, H-2″), 7.25 (t, J = 7.8 Hz, 1 H, H-5″), 6.82 (d, J = 7.5 Hz, 1 H, H-4″), 2.33 (s, 3 H, CH_3); ^{13}C NMR δ 163.0, 156.0 (d, J = 256.4 Hz), 146.5 (d, J = 4.8 Hz), 141.5 (d, J = 2.4 Hz), 140.8, 138.4 (d, J = 24.6 Hz), 138.2, 128.9, 128.4 (d, J = 8.7 Hz), 122.5 (d, J = 11.0 Hz), 117.7, 114.3, 112.2 (d, J = 14.2 Hz), 21.3, 1 resonance not observed; MS m/z 286.6 (MH^+, 100%); HRMS calcd for $C_{15}H_{13}FN_3S$ (MH^+) m/z 286.0814, found 286.0813.

Example 1-96

4-(3-Chloro-4-pyridinyl)-*N*-(3-methylphenyl)-1,3-thiazol-2-amine (174).



[0380] 3-Chloro-*N*-methyl-*N*-(methyloxy)-4-pyridinecarboxamide (171). Et_3N (7.1 mL, 50.8 mmol) was added to a stirred suspension of 3-chloro-4-pyridinecarboxylic acid (2.0 g, 12.7 mmol), EDCI (2.68 g, 14 mmol), HOBT (1.9 g, 14.0 mmol) and MeNHOMe·HCl (1.86 g, 19.0 mmol) in dry DCM (50 mL), and the mixture was stirred at 20 °C for 20 h. The resulting solution was diluted with DCM (110 mL) and washed with water (2 × 50 mL), washed with brine (50 mL), dried and the solvent evaporated. The residue was purified by column chromatography, eluting with 50% EtOAc/pet. ether, to give amide **171** (1.46 g, 58%) as a white solid: mp (EtOAc/pet. ether) 54-56 °C; ^1H NMR ($CDCl_3$) δ 8.65 (*s*, 1 H, H-2), 8.55 (d, J = 4.8 Hz, 1 H, H-6), 7.25 (d, J = 4.8 Hz, 1 H, H-5), 3.49 (s, 3 H, OCH_3), 3.39 (s, 3 H, NCH_3); MS m/z 201.4/203.4 (MH^+, 100%).

[0381] 1-(3-Chloro-4-pyridinyl)ethanone (172). A solution of MeMgBr (3 M in Et_2O, 3.2 mL, 9.6 mmol) was added slowly to a stirred solution of amide **171** (1.28 g, 6.4 mmol) in dry THF (40 mL) at 0 °C and the mixture was stirred at 0 °C for 3 h then 1 h at 20 °C. The reaction mixture was quenched with saturated aqueous NH_4Cl solution (15 mL) and the mixture extracted with EtOAc (3 × 50 mL). The combined organic fraction was washed with water (50 mL), washed with brine (50

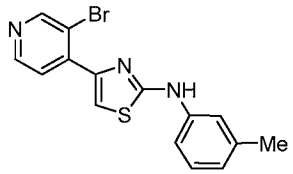
mL), dried and the solvent evaporated. The residue was purified by column chromatography, eluting with 30% EtOAc/pet. ether, to give ketone **172** (883 mg, 89%) as a colourless liquid: ^{1}H NMR ($CDCl_3$) δ 8.69 (s, 1 H, H-2′), 8.59 (d, J = 4.9 Hz, 1 H, H-6′), 7.37 (dd, J = 4.9, 0.6 Hz, H-5′), 2.65 (s, 3 H, CH_3); MS *m/z* 156.4 (MH^+, 100%), 188.4 (MH^+ + MeOH).

[0382] 3-Chloro-1-(2-bromo-4-pyridinyl)ethanone Hydrobromide (173). 1-(3-Chloro-4-pyridinyl)ethanone (**172**) (653 mg, 4.2 mmol) was dissolved in glacial acetic acid and treated with Br_2 (0.24 mL, 4.66 mmol) followed by HBr/AcOH (30% w/v, 0.93 mL, 4.66 mmol) at 5–10 °C. The reaction mixture was stirred at 20 °C for 3 h, it was then diluted with Et_2O (80 mL) and the formed precipitate was filtered off and washed with Et_2O and dried under high vacuum to afford the crude bromoketone hydrobromide **173** (1.27 g) as a pale yellow solid which was used in the next step without further purification.

[0383] 4-(3-Chloro-4-pyridinyl)-*N*-(3-methylphenyl)-1,3-thiazol-2-amine (174). A mixture of bromoketone hydrobromide **173** (1.23 g, 4 mmol) and 3-methylphenylthiourea (**4**) (651 mg, 4 mmol) in EtOH (25 mL) was stirred at reflux temperature for 3 h. The mixture was cooled to 20 °C, diluted with water (80 mL), the pH adjusted to ca. 8 with aqueous NH_3 and the mixture stirred at 20 °C for 2 h. The precipitate was filtered, washed with water (20 mL) and dried. The crude solid was purified by column chromatography, eluting with 20% EtOAc/pet. ether, to give amine **174** (340 mg, 28%) as beige crystals: mp (EtOAc) 161–163 °C; ^{1}H NMR ($CDCl_3$) δ 8.64 (s, 1 H, H-2″), 8.52 (d, J = 5.1 Hz, 1 H, H-6″), 7.96 (d, J = 5.1 Hz, 1 H, H-5″), 7.55 (s, 1 H, H-5), 7.29–7.24 (m, 2 H, H-5′, H-6′), 7.18 (br s, 1 H, H-2′), 6.94 (br d, J = 7.2 Hz, 1 H, H-4′), 2.38 (s, 3 H, CH_3); NH not observed; ^{13}C NMR ($CDCl_3$) δ 163.8, 150.7, 148.0, 145.2, 139.9, 139.6, 139.4, 129.4, 128.6, 124.5, 124.4, 119.3, 115.6, 110.7, 21.5; MS *m/z* 302.6/304.6 (MH^+, 100, 35%); HRMS calcd for $C_{15}H_{13}{}^{35}ClN_3S$ (MH^+) *m/z* 302.05187, found 302.05141.

Example 1-97

4-(3-Bromo-4-pyridinyl)-*N*-(3-methylphenyl)-1,3-thiazol-2-amine (178).



[0384] 3-Bromo-*N*-methyl-*N*-(methyloxy)-4-pyridinecarboxamide (175). Et_3N (5.9 mL, 42.4 mmol) was added to a stirred suspension of 3-bromo-4-pyridinecarboxylic acid (2.14 g, 10.6 mmol), EDCI (2.23 g, 11.7 mmol), HOBT (1.57 g, 11.7 mmol) and MeNHOMe·HCl (1.55 g, 15.9 mmol) in dry DCM (100 mL), and the mixture was stirred at 20 °C for 16 h. The resulting solution was diluted with DCM (100 mL) and washed with water (2 × 30 mL), washed with brine (30 mL), dried and the solvent evaporated. The residue was purified by column chromatography, eluting with 50% EtOAc/pet. ether, to give amide **175** (1.74 g, 67%) as an oil: ^{1}H NMR ($CDCl_3$) δ 8.81 (br s, 1 H, H-2), 8.64 (d, J = 4.8 Hz, 1 H, H-6), 7.53 (d, J = 4.8 Hz, 1 H, H-5), 3.47 (s, 3 H, OCH_3), 3.28 (s, 3 H, NCH_3); MS *m/z* 245.3/247.3 (MH^+, 100%).

[0385] 1-(3-Bromo-4-pyridinyl)ethanone (176). A solution of MeMgBr (3 M in hexanes, 3.5 mL, 10.5 mmol) was added slowly to a stirred solution of amide **175** (1.72 g, 7.0 mmol) in dry THF (50 mL) at 0 °C and the mixture was stirred at 0 °C for 3 h. The reaction mixture was quenched with saturated aqueous NH_4Cl solution (20 mL) and the mixture extracted with EtOAc (3 × 50 mL). The combined organic fraction was washed with water (40 mL) washed with brine (40 mL), dried and the solvent evaporated. The residue was purified by column chromatography, eluting with 30% EtOAc/pet. ether, to give ketone **176** (0.91 g, 65%) as an oil: ^{1}H NMR ($CDCl_3$) δ 8.81 (s, 1 H, H-2′), 8.64 (d, J = 4.9 Hz, 1 H, H-6′), 7.30 (d, J = 4.8 Hz, 1 H, H-5′), 2.63 (s, 3 H, H-2); MS *m/z* 200.3/204.3 (MH^+, 100%). Also recovered: starting material (0.33 g, 19%).

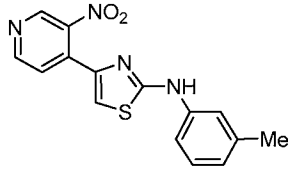
[0386] 2-Bromo-1-(3-bromo-4-pyridinyl)ethanone Hydrobromide (177). Br_2 (0.26 mL, 5.0 mmol) was added dropwise to a stirred a solution of ketone **176** (0.90 g, 4.5 mmol) in 30% HBr/HOAc (10 mL) at 15 °C. The mixture was stirred at 20 °C for 1 h, then at 40 °C for 1 h and then at 75 °C for 1 h. The mixture was cooled to 20 °C, diluted with Et_2O (40 mL) and stirred for 30 min at 0 °C. The

precipitate was filtered, washed with Et_2O (5 mL) and dried under vacuum to give the hydrobromide salt. The salt was dissolved in water, the solution neutralised with cNH_3 and extracted with EtOAc. The combined organic extract was dried and the solvent evaporated. The residue was purified by column chromatography, eluting with 50% EtOAc/pet. ether, to give the crude bromoketone **177** (0.31 g, 25%) as an oil: ^{1}H NMR ($CDCl_3$) δ 8.81 (s, 1 H, H-2′), 8.62 (d, J = 4.9 Hz, 1 H, H-6′), 7.30 (d, J = 4.9 Hz, 1 H, H-5′), 2.63 (s, 3 H, H-2); which was used directly.

[0387] 4-(3-Bromo-4-pyridinyl)-*N*-(3-methylphenyl)-1,3-thiazol-2-amine (178). A mixture of bromoketone **177** (0.30 g, 1.1 mmol) and 3-methylphenylthiourea (**4**) (0.18 g, 1.1 mmol) in EtOH (20 mL) was stirred at reflux temperature for 2 h. The mixture was cooled to 20 °C, diluted with water (50 mL), the pH adjusted to ca. 8 with aqueous NH_3 and the mixture stirred at 20 °C for 2 h. The precipitate was filtered, washed with water (5 mL) and dried. The crude solid was purified by column chromatography, eluting with 60% EtOAc/pet. ether, to give amine **178** (0.29 g, 77%) as a tan powder: mp (EtOAc/pet. ether) 180–182 °C; ^{1}H NMR δ 10.27 (br s, 1 H, NH), 8.82 (s, 1 H, H-2″), 8.61 (d, J = 5.0 Hz, 1 H, H-6″), 7.87 (d, J = 5.0 Hz, 1 H, H-5″), 7.68 (s, 1 H, H-5), 7.58–7.64 (m, 2 H, H-2′, H-6′), 7.22 (br dd, J = 8.1, 7.7 Hz, 1 H, H-5′), 6.80 (br d, J = 7.7 Hz, 1 H, H-4′), 2.30 (s, 3 H, CH_3); ^{13}C NMR δ 162.7, 152.6, 148.5, 145.5, 141.3, 140.7, 138.0, 128.7, 124.9, 122.2, 118.1, 117.5, 114.1, 110.6, 21.7; MS *m/z* 346.5/348.5 (MH^+, 100%). Anal. calcd for $C_{15}H_{12}BrN_3S$: C, 52.03; H, 3.49; N, 12.14. Found: C, 51.85; H, 3.50; N, 12.04%.

Example 1-98

***N*-(3-Methylphenyl)-4-(2-nitro-4-pyridinyl)-1,3-thiazol-2-amine (181).**



[0388] 1-(2-Nitro-4-pyridinyl)ethanone (179). 4-Acetylpyridine (2.0 mL, 18.2 mmol) was added slowly to TFAA (10.6 mL, 76.4 mmol) at 0 °C and the mixture was stirred at 0 °C for 1 h. $cHNO_3$ (2.4 mL, 38.2 mmol) was added to the mixture

dropwise and the mixture stirred at 0 °C for 8 h. The reaction mixture was added dropwise to a stirred solution of $Na_2S_2O_5$ (2.54 g, 18.2 mmol) in water (20 mL) at 0 °C and the mixture stirred at 0 °C for 16 h. The pH of the solution was adjusted to 6–7 with 1 M NaOH solution and the mixture was extracted with DCM (3 × 50 mL). The combined organic fraction was washed with water (50 mL), washed with brine (50 mL), dried and the solvent evaporated. The residue was purified by column chromatography, eluting with 50% EtOAc/pet. ether, to give ketone **179** (Katritzky, A. R. et. al. *Org. Biomolec. Chem.* 2005, *3*, 538–541) (1.66 g, 55%) as an oil: ^{1}H NMR ($CDCl_3$) δ 9.37 (s, 1 H, H-2′), 8.96 (d, *J* = 4.9 Hz, 1 H, H-6′), 7.33 (dd, *J* = 4.9, 0.4 Hz, 1 H, H-5′), 2.59 (s, 3 H, H-2); MS *m/z* 167.4 (MH^+, 100%).

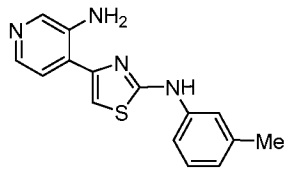
[0389] 2-Bromo-1-(2-nitro-4-pyridinyl)ethanone Hydrobromide (180). Br_2 (0.53 mL, 10.4 mmol) was added dropwise to a stirred a solution of ketone **179** (1.64 g, 9.9 mmol) in 30% HBr/HOAc (20 mL) at 15 °C. The mixture was stirred at 20 °C for 16 h. The mixture diluted with Et_2O (80 mL) and stirred for 30 min at 0 °C. The precipitate was filtered, washed with Et_2O (5 mL) and dried under vacuum to give the crude hydrobromide salt **180** (2.76 g, 86%) as a white powder: ^{1}H NMR δ 9.48 (s, 1 H, H-2′), 9.10 (d, *J* = 4.9 Hz, 1 H, H-6′), 7.81 (dd, *J* = 4.9, 0.4 Hz, 1 H, H-5′), 4.86 (s, 2 H, H-2) N·HBr not observed; MS *m/z* 277.4/279.4 (MH^+, 100%).

[0390] *N*-(3-Methylphenyl)-4-(2-nitro-4-pyridinyl)-1,3-thiazol-2-amine (181). A mixture of bromoketone hydrobromide **180** (2.00, 6.1 mmol) and 3-methylphenylthiourea (**4**) (1.02 g, 6.1 mmol) in EtOH (50 mL) was stirred at reflux temperature for 2 h. The mixture was cooled to 20 °C, diluted with water (100 mL), the pH adjusted to ca. 8 with aqueous NH_3 and the mixture stirred at 20 °C for 2 h. The precipitate was filtered, washed with water (5 mL) and dried. The crude solid was purified by column chromatography, eluting with 60% EtOAc/pet. ether, to give amine **181** (1.74 g, 91%) as an orange powder: mp (EtOAc/pet. ether) 198–200 °C; ^{1}H NMR δ 10.29 (br s, 1 H, NH), 9.01 (br s, 1 H, H-2′) 8.09, (d, *J* = 5.2 Hz, 1 H, H-6′), 7.96 (d, *J* = 5.2 Hz, 1 H, H-5′), 7.79 (s, 1 H, H-5), 7.54 (br s, 1 H, H-2″), 7.15–7.19 (m, 2 H, H-5″, H-6″), 6.76–7.81 (m, 1 H, H-4″), 2.342

(s, 3 H, CH_3); ^{13}C NMR δ 163.4, 152.1, 144.7, 144.3, 143.1, 140.5, 138.3, 133.8, 128.6, 122.8, 122.3, 117.3, 114.1, 111.5, 21.1; MS *m/z* 313.6 (MH^+, 100%). Anal. calcd for $C_{15}H_{12}N_4O_2S$: C, 57.68; H, 3.87; N, 17.94. Found: C, 57.81; H, 3.92; N, 18.00%.

Example 1-99

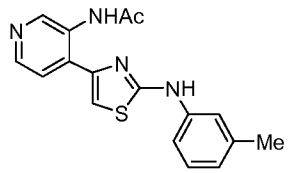
***N*-[4-(2-Amino-4-pyridinyl)-1,3-thiazol-2-yl]-*N*-(3-methylphenyl)amine (182).**



[0391] *N*-[4-(2-Amino-4-pyridinyl)-1,3-thiazol-2-yl]-*N*-(3-methylphenyl)amine (182). A mixture of nitropyridine **181** (511 mg, 1.64 mmol) and Pd/C (50 mg) in EtOH (100 mL) was stirred under H_2 (60 psi) for 16 h. The mixture was filtered through Celite, washed with EtOH. The solvent was evaporated and the crude solid was purified by column chromatography, eluting with a gradient (50–100%) of EtOAc/pet. ether, to give amine **182** (338 mg, 73%) as a white powder: mp (EtOAc/pet. ether) 159–161 °C; ^1H NMR δ 10.26 (s, 1 H, NH), 8.10 (br s, 1 H, H-2″), 7.77 (d, *J* = 5.1 Hz, 1 H, H-6″), 7.44 (d, *J* = 5.1 Hz, 1 H, H-5″), 7.41 (br s, 1 H, H-2), 7.38 (s, 1 H, H-5′), 7.30 (br d, *J* = 8.1 Hz, 1 H, H-6), 7.22 (br t, *J* = 7.8 Hz, 1 H, H-5), 6.82 (br d, *J* = 7.4 Hz, 1 H, H-4′), 6.21 (br s, 2 H, NH_2), 2.33 (s, 3 H, CH_3); ^{13}C NMR δ 163.3, 147.8, 141.3, 140.8, 139.4, 138.4, 136.8, 129.0, 122.4, 122.2, 120.9, 117.8, 114.4, 105.7, 21.3; MS *m/z* 283.6 (MH^+, 100%). Anal. calcd for $C_{15}H_{14}N4S$: C, 63.80; H, 5.00; N, 19.84. Found: C, 64.09; H, 5.21; N, 19.54%.

Example 1-100

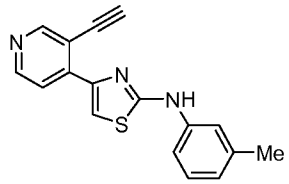
***N*-(4-{2-[(3-Methylphenyl)amino]-1,3-thiazol-4-yl}-2-pyridinyl)acetamide (183).**



[0392] ***N*-(4-{2-[(3-Methylphenyl)amino]-1,3-thiazol-4-yl}-2-pyridinyl)acetamide (183).** Ac_2O (0.23 mL, 2.4 mmol) was added to a stirred solution of amine **182** (230 mg, 0.8 mmol) in dioxane (10 mL) and the mixture was stirred at 20 °C for 3 days. The mixture was diluted with water (30 mL), and extracted with EtOAc (3 × 50 mL). The combined organic fraction was dried and the solvent evaporated. The crude solid was purified by column chromatography, eluting with a gradient (50–100%) of EtOAc/pet. ether, to give amine **183** (148 mg, 56%) as a tan powder: mp (EtOAc/pet. ether) 189–191 °C; ^{1}H NMR δ 10.79 (s, 1 H, NH), 10.38 (s, 1 H, NH), 9.29 (br s, 1 H, H-2′), 8.33 (d, *J* = 5.1 Hz, 1 H, H-6′), 7.76 (d, *J* = 5.1 Hz, 1 H, H-5′), 7.44 (br d, *J* = 8.1 Hz, 1 H, H-6‴), 7.34 (br s, 1 H, H-2‴), 7.60 (s, 1 H, H-5″), 7.27 (br t, *J* = 7.8 Hz, 1 H, H-5‴), 6.86 (br d, *J* = 7.5 Hz, 1 H, H-4‴), 2.32 (s, 3 H, CH_3), 1.99 (s, 3 H, CH_3); ^{13}C NMR δ 168.2, 164.1, 145.7, 144.7 (2), 140.5, 138.5, 131.4, 130.2, 129.1, 123.0, 121.5, 118.3, 114.9, 109.1, 24.0, 21.2; MS *m/z* 325.7 (MH^+, 100%). Anal. calcd for $C_{17}H_{16}N_4OS$: C, 62.94; H, 4.97; N, 17.27. Found: C, 62.98; H, 4.90; N, 17.03%.

Example 1-101

4-(3-Ethynyl-4-pyridinyl)-*N*-(3-methylphenyl)-1,3-thiazol-2-amine (184).

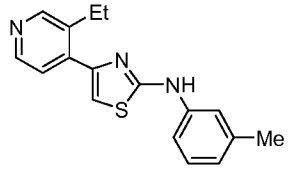


[0393] **4-(3-Ethynyl-4-pyridinyl)-*N*-(3-methylphenyl)-1,3-thiazol-2-amine (184).** $PdCl_2(PPh_3)_2$ (52 mg, 0.07 mmol) was added to a purged mixture of bromide (**178**) (517 mg, 1.5 mmol), trimethylsilylacetylene (0.23 mL, 1.6 mmol), CuI (14 mg, 0.07 mmol) in Et_3N (3 mL) and DMF (3 mL) and the mixture was stirred at 50 °C for 16 h in a sealed tube. The mixture was cooled to 20 °C, diluted with water (100 mL), and extracted with EtOAc (3 × 50 mL). The combined organic fraction was washed with water (2 × 40 mL), washed with brine (50 mL) and dried. The solvent was evaporated and the crude solid was dissolved in THF (20 mL) and a solution of TBAF (1.0 M, 2.2 mL, 2.2 mmol) was added. The mixture was stirred at 20 °C for 16 h and the solvent was evaporated. The residue was suspended in water (50 mL), and extracted with EtOAc (3 × 30 mL). The

combined organic fraction was washed with water (40 mL), washed with brine (40 mL) and dried. The solvent was evaporated and the crude solid was purified by column chromatography, eluting with 50% EtOAc/pet. ether, to give amine **184** (0.39 g, 89%) as a tan powder: mp (EtOAc/pet. ether) 158–160 °C; ^{1}H NMR δ 10.27 (s, 1 H, NH), 8.73 (s, 1 H, H-2′), 8.64 (d, *J* = 5.5 Hz, 1 H, H-6′), 8.00 (s, 1 H, H-5), 7.98 (dd, *J* = 5.5, 0.4 Hz, 1 H, H-5′), 7.58 (br d, *J* = 8.1 Hz, 1 H, H-6″), 7.48 (br s, 1 H, H-2″), 7.24 (br t, *J* = 7.8 Hz, 1 H, H-5″), 6.81 (br d, *J* = 7.5 Hz, 1 H, H-4″), 4.72 (s, 1 H, CH), 2.32 (s, 3 H, CH_3); ^{13}C NMR δ 162.6, 154.4, 149.4, 145.7, 141.5, 140.7, 138.0, 128.8, 122.2, 121.6, 117.5, 114.3, 114.1, 110.7, 88.1, 80.9, 21.2; MS *m/z* 296.6 (MH^+, 100%). Anal. calcd for $C_{17}H_{13}N_3S$: C, 69.12; H, 5.80; N, 14.22. Found: C, 68.70; H, 5.83; N, 14.13%.

Example 1-102

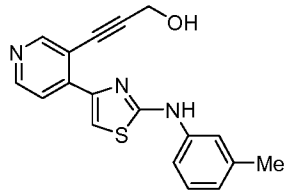
4-(3-Ethyl-4-pyridinyl)-*N*-(3-methylphenyl)-1,3-thiazol-2-amine (185).



[0394] 4-(3-Ethyl-4-pyridinyl)-*N*-(3-methylphenyl)-1,3-thiazol-2-amine (185). A mixture of amine **184** (233 mg, 0.80 mmol) and Pd/C (25 mg) in EtOH (20 mL) was stirred under H_2 (60 psi) for 16 h. The mixture was filtered through Celite, washed with EtOH. The solvent was evaporated and the crude solid was purified by column chromatography, eluting with 50% EtOAc/pet. ether, to give amine **185** (47 mg, 20%) as a cream powder: mp (EtOAc/pet. ether) 151–153 °C; ^{1}H NMR δ 10.20 (s, 1 H, NH), 8.51 (br s, 1 H, H-2″), 8.43 (d, *J* = 5.0 Hz, 1 H, H-6″), 7.54 (d, *J* = 5.0 Hz, 1 H, H-5″), 7.50 (br s, 1 H, H-2′), 7.44 (br d, *J* = 8.1 Hz, 1 H, H-6′), 7.24 (s, 1 H, H-5), 7.19 (br t, *J* = 7.8 Hz, 1 H, H-5′), 6.78 (br d, *J* = 7.5 Hz, 1 H, H-4′), 2.98 (q, *J* = 7.5 Hz, 2 H, CH_2), 2.29 (s, 3 H, CH_3), 1.18 (t, *J* = 7.5 Hz, 3 H, CH_3); ^{13}C NMR δ 162.9, 150.9, 148.1, 147.1, 140.8, 140.5, 137.8, 135.9, 128.6, 122.9, 122.0, 117.2, 114.0, 108.1, 23.7, 21.1, 15.3; MS *m/z* 296.6 (MH^+, 100%). Anal. calcd for $C_{17}H_{17}N_3S$: C, 69.12; H, 5.80; N, 14.22. Found: C, 68.70; H, 5.83; N, 14.13%.

Example 1-103

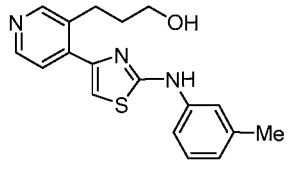
3-(4-{2-[(3-Methylphenyl)amino]-1,3-thiazol-4-yl}-3-pyridinyl)-2-propyn-1-ol (186).



[0395] 3-(4-{2-[(3-Methylphenyl)amino]-1,3-thiazol-4-yl}-3-pyridinyl)-2-propyn-1-ol (186). $PdCl_2(PPh_3)_2$ (101 mg, 0.15 mmol) was added to a purged mixture of bromide **178** (1.00 g, 2.9 mmol), propargyl alcohol (0.19 mL, 3.2 mmol), CuI (28 mg, 0.15 mmol) in Et_3N (4 mL) and DMF (5 mL) and the mixture was stirred at 50 °C for 16 h in a sealed tube. The mixture was cooled to 20 °C, diluted with water (100 mL), and extracted with EtOAc (3 × 50 mL). The combined organic fraction was washed with water (2 × 40 mL), washed with brine (50 mL) and dried. The solvent was evaporated and the crude solid was purified by column chromatography, eluting with EtOAc, to give amine **186** (0.34 g, 34%) as a tan powder: mp (EtOAc/pet. ether) 155–158 °C; ^{1}H NMR δ 10.27 (s, 1 H, NH), 8.66 (s, 1 H, H-2′), 8.60 (d, *J* = 5.1 Hz, 1 H, H-6′), 8.12 (s, 1 H, H-5″), 8.02 (d, *J* = 5.1 Hz, 1 H, H-5′), 7.60 (br d, *J* = 8.0 Hz, 1 H, H-6‴), 7.45 (br s, 1 H, H-2‴), 7.25 (br t, *J* = 7.8 Hz, 1 H, H-5‴), 6.81 (br d, *J* = 7.5 Hz, 1 H, H-4‴), 5.45 (br s, 1 H, OH), 4.45 (d, *J* = 3.7 Hz, 2 H, H-1), 2.32 (s, 3 H, CH_3); ^{13}C NMR δ 162.3, 153.6, 149.0, 145.7, 140.9, 140.8, 138.0, 128.8, 122.2, 121.6, 117.5, 114.7, 114.1, 110.8, 97.3, 81.2, 49.6, 21.2; MS *m/z* 322.6 (MH^+, 100%). Anal. calcd for $C_{18}H_{15}N_3OS \cdot ¼CH_3OH$: C, 66.54; H, 4.90; N, 12.76. Found: C, 66.87; H, 5.02; N, 12.42%.

Example 1-104

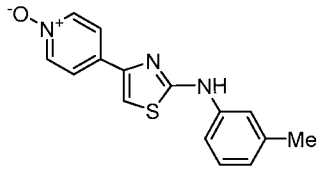
3-(4-{2-[(3-Methylphenyl)amino]-1,3-thiazol-4-yl}-3-pyridinyl)-1-propanol (187).



[0396] 3-(4-{2-[(3-Methylphenyl)amino]-1,3-thiazol-4-yl}-3-pyridinyl)-1-propanol (187). A mixture of amine **186** (205 mg, 0.64 mmol) and Pd/C (40 mg) in EtOH (50 mL) was stirred under H_2 (60 psi) for 16 h. The mixture was filtered through Celite, washed with EtOH. The solvent was evaporated and the crude solid was purified by column chromatography, eluting with EtOAc, to give amine **187** (78 mg, 37%) as a tan gum: ^{1}H NMR δ 10.20 (s, 1 H, NH), 8.48 (s, 1 H, H-2′), 8.43 (d, J = 5.1 Hz, 1 H, H-6′), 7.57 (d, J = 5.1 Hz, 1 H, H-5′), 7.44–7.48 (m, 2 H, H-2‴, H-6‴), 7.26 (s, 1 H, H-5″), 7.20 (br t, J = 7.8 Hz, 1 H, H-5‴), 6.78 (br d, J = 7.5 Hz, 1 H, H-4‴), 4.45 (t, J = 5.1 Hz, 1 H, OH), 3.35–3.42 (m, 2 H, H-1), 3.00 (br t, J = 7.8 Hz, 2 H, H-3), 2.30 (s, 3 H, CH_3), 1.67–1.72 (m, 2 H, H-2); ^{13}C NMR δ 162.9, 151.3, 148.0, 147.2, 140.8, 140.7, 138.0, 134.3, 128.7, 123.0, 122.0, 117.3, 114.0, 108.2, 60.1, 33.3, 27.0, 21.1; MS *m/z* 326.6 (MH^+, 100%). Anal. calcd for $C_{18}H_{19}N_3OS$: C, 66.43; H, 5.88; N, 12.91. Found: C, 66.03; H, 6.04; N, 12.58%.

Example 1-105

***N*-(3-Methylphenyl)-4-(1-oxido-4-pyridinyl)-1,3-thiazol-2-amine (188).**

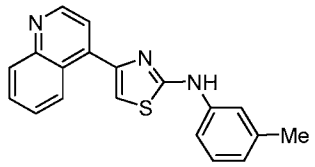


[0397] *N*-(3-Methylphenyl)-4-(1-oxido-4-pyridinyl)-1,3-thiazol-2-amine (188). MCPBA (50–55%, 710 mg, 2.1 mmol) was added to a solution of amine **5** (500 mg, 1.9 mmol) in DCM (30 mL) and the reaction mixture was stirred at 20 °C for 24 h. The mixture was diluted with DCM (50 mL), washed with sat. aq. $NaHCO_3$ solution (50 mL), washed with sat. aq. $Na_2S_2O_5$ solution (50 mL), and washed with brine (50 mL). The solution was dried, the solvent was evaporated and the residue was purified by chromatography, eluting with 5% DCM/MeOH, to give the *N*-oxide **188** (240 mg, 45%) as a yellow powder: mp (EtOAc/pet.ether) 162–164 °C; ^{1}H NMR δ 10.26 (s, 1 H, NH), 8.24 (dt, J = 7.2, 2.5 Hz, 2 H, H-2′, H-6′) 7.86 (dt, J = 7.2, 2.5 Hz, 2 H, H-3′, H-5′), 7.58-7.56 (m, 2 H, H-5, H-6″), 7.44 (br s, 1 H, H-2″), 7.23 (t, J = 7.7 Hz, 1 H, H-5″), 6.81 (d, J = 7.5 Hz, 1 H, H-4″), 2.32 (s, 3 H, CH_3); ^{13}C NMR δ 163.6, 146.6, 140.9, 138.8 (2), 138.2, 130.8, 128.9, 122.6 (2),

122.3, 117.6, 114.2, 106.1, 21.3; MS *m/z* 284.6 (MH^+, 100%). Anal. calcd for $C_{15}H_{13}N_3OS$: C, 63.58; H, 4.62; N, 14.83. Found: C, 63.08; H, 4.59; N, 14.86%.

Example 1-106

***N*-(3-Methylphenyl)-4-(4-quinolinyl)-1,3-thiazol-2-amine (192).**



[0398] ***N*-Methyl-*N*-(methyloxy)-4-quinolinecarboxamide (189).** A suspension of quinoline 4-carboxylic acid (1.13 g, 6.53 mmol) and DMF (3 drops) in thionyl chloride (15 mL) was stirred at 40 °C for 3 h. Thionyl chloride was evaporated and the residue was dissolved in dry DCM (50 mL) and MeNHOMe·HCl (0.96 g, 9.8 mmol) and Et_3N (2.7 mL, 19.6 mmol) was added. The mixture was stirred at 20 °C for 16 h. The resulting solution was diluted with DCM (100 mL) and washed with water (2 × 30 mL), washed with brine (30 mL), dried and the solvent evaporated. The residue was purified by column chromatography, eluting with EtOAc, to give amide **189** (1.36 g, 96%) as soft solid: ^{1}H NMR ($CDCl_3$) δ 8.97 (d, *J* = 4.3 Hz, 1 H, H-2), 8.16 (d, *J* = 8.5 Hz, 1 H, H-5), 7.87 (d, *J* = 8.3 Hz, 1 H, H-8), 7.73–7.78 (m, 1 H, H-7), 7.56–7.62 (m, 1 H, H-6), 7.39 (d, *J* = 4.3 Hz, 1 H, H-3), 3.47 (s, 3 H, OCH_3), 3.41 (s, 3 H, NCH_3); MS *m/z* 216.4 (MH^+, 100%).

[0399] **1-(4-Quinolinyl)ethanone (190).** A solution of MeMgBr (3 M in hexanes, 3.1 mL, 9.4 mmol) was added slowly to a stirred solution of amide **189** (1.36 g, 6.3 mmol) in dry THF (50 mL) at 0 °C and the mixture was stirred at 0 °C for 3 h. The reaction mixture was quenched with saturated aqueous NH_4Cl solution (20 mL) and the mixture extracted with EtOAc (3 × 50 mL). The combined organic fraction was washed with water (40 mL) washed with brine (40 mL), dried and the solvent evaporated. The residue was purified by column chromatography, eluting with a gradient (50–100%) of EtOAc/pet. ether, to give ketone **190** (0.76 g, 70%) as an oil: ^{1}H NMR ($CDCl_3$) δ 9.03 (d, *J* = 4.4 Hz, 1 H, H-2′), 8.45 (dd, *J* = 8.5, 0.8 Hz, 1 H, H-5′), 8.17 (dd, *J* = 8.5, 0.7 Hz, 1 H, H-8′), 7.78 (ddd, *J* = 8.5, 6.9, 1.4 Hz,

1 H, H-7′), 7.65 (ddd, J = 8.5, 6.9, 1.4 Hz, 1 H, H-6′), 7.62 (d, J = 4.4 Hz, 1 H, H-3′), 2.75 (s, 3 H, H-2); MS *m/z* 172.4 (MH^+, 100%).

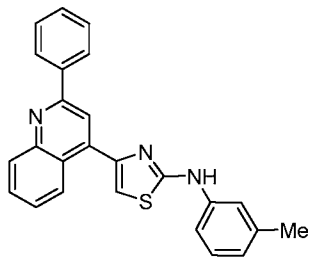
[0400] 2-Bromo-1-(4-quinolinyl)ethanone Hydrobromide (191). Br_2 (0.24 mL, 4.6 mmol) was added dropwise to a stirred a solution of ketone **190** (0.75 g, 4.4 mmol) in 30% HBr/HOAc (10 mL) at 15 °C. The mixture was stirred at 20 °C for 1 h, then at 40 °C for 1 h and then at 75 °C for 1 h. The mixture was cooled to 20 °C, diluted with Et_2O (40 mL) and stirred for 30 min at 0 °C. The precipitate was filtered, washed with Et_2O (5 mL) and dried under vacuum to give the crude hydrobromide salt **191** (1.37 g, 95%) as an tan powder: ^{1}H NMR δ 9.05 (d, J = 4.5 Hz, 1 H, H-2′), 8.23 (br d, J = 8.5 Hz, 1 H, H-8′), 8.16 (br d, J = 8.4 Hz, 1 H, H-5′), 8.08 (d, J = 4.5 Hz, 1 H, H-3′), 7.87–7.92 (m, 1 H, H-7′), 7.75–7.80 (m, 1 H, H-6′), 5.80 (br s, 1 H, N·HBr), 5.10 (s, 2 H, H-2).

[0401] *N*-(3-Methylphenyl)-4-(4-quinolinyl)-1,3-thiazol-2-amine (192). A mixture of bromoketone **191** (0.40 g, 1.2 mmol) and 3-methylphenylthiourea (**4**) (0.20 g, 1.2 mmol) in EtOH (20 mL) was stirred at reflux temperature for 2 h. The mixture was cooled to 20 °C, diluted with water (50 mL), the pH adjusted to ca. 8 with aqueous NH_3 and the mixture stirred at 5 °C for 2 h. The precipitate was filtered, washed with water (5 mL) and dried. The crude solid was purified by column chromatography, eluting with 50% EtOAc/pet. ether, to give amine **192** (0.26 g, 68%) as a tan powder: mp (EtOAc/Et_2O) 169–171 °C; ^{1}H NMR δ 10.33 (br s, 1 H, NH), 8.95 (d, J = 4.5 Hz, 1 H, H-2′), 8.75 (dd, J = 8.5, 0.9 Hz, 1 H, H-5′), 8.09 (dd, J = 8.5, 0.8 Hz, 1 H, H-8′), 7.80 (ddd, J = 8.5, 6.8, 1.4 Hz, 1 H, H-7′), 7.75 (d, J = 4.5 Hz, 1 H, H-3′), 7.65 (ddd, J = 8.5, 6.8, 1.4 Hz, 1 H, H-6′), 7.58 (br s, 1 H, H-2″), 7.44–7.48 (m, 2 H, H-5, H-6″), 7.20 (br t, J = 7.7 Hz, 1 H, H-5″), 6.80 (br d, J = 7.5 Hz, 1 H, H-4″), 2.29 (s, 3 H, CH_3); ^{13}C NMR δ 163.4, 150.1, 148.4, 147.6, 140.9, 140.0, 138.1, 129.4, 129.2, 128.7, 126.4, 126.1, 125.2, 122.1, 120.4, 117.4, 114.1, 109.4, 21.2; MS *m/z* 318.5 (MH^+, 100%). Anal. calcd for $C_{19}H_{15}N_3S \cdot ¼(CH_3CH_2)_2O$: C, 71.51; H, 5.25; N, 12.51. Found: C, 71.62; H, 5.25; N, 12.51%.

[0402] Alternative Preparation of 2-Bromo-1-(4-quinolinyl)ethanone Hydrobromide (191). A suspension of quinoline 4-carboxylic acid (0.74 g, 4.3 mmol) and DMF (2 drops) in thionyl chloride (15 mL) was stirred at 40 °C for 3 h. Thionyl chloride was evaporated and the residue was dissolved in dry THF (50 mL) and cooled to 0 °C. A solution of $TMSCH_2N_2$ in hexanes (2.5 M, 5.3 mL, 10.7 mmol) was added and the mixture was stirred at 0 °C for 5 h. cHBr (9 mL) was added carefully and the mixture stirred at 20 °C for 16 h. The mixture was neutralized with saturated aqueous $KHCO_3$ and then extracted with EtOAc (3 × 50 mL). The combined organic fraction was washed with water (40 mL), washed with brine (40 mL), dried and the solvent evaporated. The residue was purified by column chromatography, eluting with a gradient (20–50%) of EtOAc/pet. ether, to give crude bromide **191** (0.76 g, 71%) as oil: ^{1}H NMR ($CDCl_3$) δ 9.05 (d, J = 4.4 Hz, 1 H, H-2′), 8.34 (dd, J = 8.6, 0.8 Hz, 1 H, H-8′), 8.20 (dd, J = 8.4, 0.6 Hz, 1 H, H-5′), 7.81 (ddd, J = 8.6, 6.9, 1.4 Hz, 1 H, H-7′), 7.68 (ddd, J = 8.4, 6.9, 1.3 Hz, 1 H, H-6′), 7.62 (d, J = 4.4 Hz, 1 H, H-3′), 4.52 (s, 2 H, H-2); MS *m/z* 251.4 (MH^+, 100%). The bromide was converted to the hydrobromide salt and used directly.

Example 1-107

***N*-(3-Methylphenyl)-4-(2-phenyl-4-quinolinyl)-1,3-thiazol-2-amine (194).**



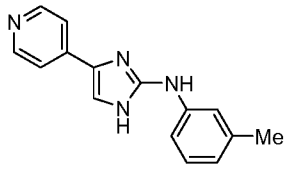
[0403] 2-Bromo-1-(2-phenyl-4-quinolinyl)ethanone Hydrobromide (193). A suspension of 2-phenyl-4-quinolinecarboxylic acid (0.80 g, 3.2 mmol) and DMF (2 drops) in thionyl chloride (15 mL) was stirred at 40 °C for 3 h. Thionyl chloride was evaporated and the residue was dissolved in dry THF (50 mL) and cooled to 0 °C. A solution of $TMSCH_2N_2$ in hexanes (2.5 M, 3.2 mL, 8.0 mmol) was added and the mixture was stirred at 0 °C for 5 h. cHBr (5 mL) was added carefully and the mixture stirred at 20 °C for 16 h. The mixture was neutralized with saturated aqueous $KHCO_3$ and then extracted with EtOAc (3 × 50 mL). The combined

organic fraction was washed with water (40 mL), washed with brine (40 mL), dried and the solvent evaporated. The residue was purified by column chromatography, eluting with 5% EtOAc/pet. ether, to give bromide **193** (0.50 g, 48%) as an oil: ^{1}H NMR ($CDCl_3$) δ 8.30 (dd, *J* = 8.6, 0.8 Hz, 1 H, H-8′), 8.25 (d, *J* = 8.5 Hz, 1 H, H-5′), 8.15–8.19 (m, 2 H, H-2″, H-6″), 8.07 (s, 1 H, H-3′), 7.80 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1 H, H-7′), 7.64 (ddd, *J* = 8.4, 6.9, 1.3 Hz, 1 H, H-6′), 7.50–7.59 (m, 3 H, H-3″, H-4″, H-5″), 4.58 (s, 2 H, H-2); MS *m/z* 326.5/328.5 (MH^+, 100%). The bromide was converted to the hydrobromide salt and used directly.

[0404] ***N*-(3-Methylphenyl)-4-(2-phenyl-4-quinolinyl)-1,3-thiazol-2-amine (194).** A mixture of bromoketone hydrobromide **193** (0.23 g, 0.56 mmol) and 3-methylphenylthiourea (**4**) (94 mg, 0.56 mmol) in EtOH (10 mL) was stirred at reflux temperature for 2 h. The mixture was cooled to 20 °C, diluted with water (50 mL), the pH adjusted to ca. 8 with aqueous NH_3 and the mixture stirred at 5 °C for 2 h. The precipitate was filtered, washed with water (5 mL) and dried. The crude solid was purified by column chromatography, eluting with 50% EtOAc/pet. ether, to give amine **194** (0.18 g, 85%) as a tan powder: mp (EtOAc/Et_2O) 192–194 °C; ^{1}H NMR δ 10.36 (br s, 1 H, NH), 8.76 (dd, *J* = 8.5, 0.8 Hz, 1 H, H-8′), 8.32–8.36 (m, 3 H, H-3′, H-2″, H-6″), 8.15 (dd, *J* = 8.4, 0.6 Hz, 1 H, H-5′), 7.82 (ddd, *J* = 8.5, 6.8, 1.4 Hz, 1 H, H-7′), 7.50–7.67 (m, 6 H, H-5, H-6′, H-3″, H-4″, H-5″, H-2‴), 7.42 (br d, *J* = 8.1 Hz, 1 H, H-8‴), 7.21 (br t, *J* = 7.8 Hz, 1 H, H-5‴), 6.80 (d, *J* = 7.5 Hz, 1 H, H-4‴), 2.31 (s, 3 H, CH_3); ^{13}C NMR δ 163.3, 155.7, 148.4, 147.9, 141.1, 140.9, 138.5, 138.1, 129.6, 129.5, 129.4, 128.8, 128.7 (2), 127.1 (2), 126.2, 126.0, 124.4, 122.1, 117.7, 117.5, 114.1, 109.6, 21.2; MS *m/z* 394.6 (MH^+, 100%). Anal. calcd for $C_{25}H_{19}N_3S$: C, 76.31; H, 4.87; N, 10.68. Found: C, 76.01; H, 4.79; N, 10.59%.

Example 1-108

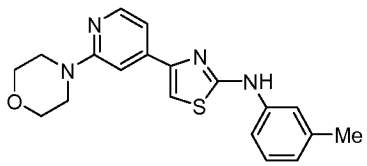
***N*-(3-Methylphenyl)-4-(4-pyridinyl)-1*H*-imidazol-2-amine (196).**



[0405] ***N*-(3-Methylphenyl)-4-(4-pyridinyl)-1*H*-imidazol-2-amine (196).** KOH (80 mg, 1.4 mmol) was added to a stirred suspension of *N*-(3-methylphenyl)guanidine nitrate **195** (Tavares, X. T. et. al. *J. Med. Chem.* **2004**, *47*, 4716.) (300 mg, 1.4 mmol) in absolute ethanol (30 mL), and the mixture was heated at 80 °C for 10 min. A solution of bromoketone hydrobromide **1** (393 mg, 1.4 mmol) and NEt_3 (0.4 mL, 2.8 mmol) in absolute ethanol (10 mL) was added within 5 min and the reaction mixture was stirred at 80 °C for 4 h. The mixture was then cooled to 20 °C and the solvent was evaporated. Dilute aqueous ammonia solution was added (15 mL), and the residue was extracted with EtOAc (3 × 50 mL). The combined organic phases were dried, filtered and the solvent was removed under reduced pressure. The residue was purified by column chromatography, eluting with a gradient (5–10%) of MeOH/DCM, to give imidazole **196** (40 mg, 12%) as a beige solid: mp (DCM/MeOH) 170–171 °C; ^{1}H NMR δ 8.45 (dd, *J* = 4.6, 1.6 Hz, 2 H, H-2′, H-6′), 7.67 (s, 1 H, H-5), 7.61 (dd, *J* = 4.5, 1.6 Hz, 2 H, H-3′, H-5′), 7.42 (t, *J* = 7.7 Hz, 1 H, H-5″), 7.34 (br s, 1 H, H-2″), 7.30 (br d, *J* = 7.7 Hz, 1 H, H-6″), 7.23 (d, *J* = 7.5 Hz, 1 H, H-4″), 5.66 (br s, 1 H, NH), 2.38 (s, 3 H, CH_3), imidazole NH not observed; ^{13}C NMR (CD_3OD) δ 151.5, 150.2 (2), 144.1, 141.6, 137.8, 135.3, 130.9, 130.3, 126.6, 123.1, 120.3 (2), 116.9, 21.4; MS *m/z* 251.5 (MH^+, 100%).

Example 1-109

[0406] ***N*-(3-Methylphenyl)-4-[2-(4-morpholinyl)-4-pyridinyl]-1,3-thiazol-2-amine (197).**

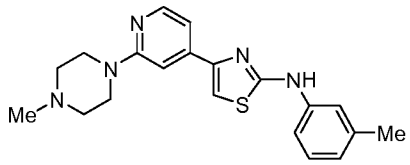


***N*-(3-Methylphenyl)-4-[2-(4-morpholinyl)-4-pyridinyl]-1,3-thiazol-2-amine (197).** A mixture of 4-(2-bromo-4-pyridinyl)-*N*-(3-methylphenyl)-1,3-thiazol-2-amine (**154**) (0.16 g, 0.45 mmol) in morpholine (5 mL) was stirred at 100 °C for 48 h. The mixture was cooled to 20 °C, diluted with water (80 mL), extracted with EtOAc (3 × 20 mL). The organic fraction was washed with water (10 mL), washed with brine (10 mL) and dried. The solvent was evaporated and the crude solid was

purified by column chromatography, eluting with a gradient (20–50%) of EtOAc, to give amine **197** (0.10 g, 64%) as a white powder: mp (EtOAc/pet. ether) 190–191 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 10.23 (s, 1 H, NH), 8.17 (d, J = 5.1 Hz, 1 H, H-6′), 7.61 (s, 1 H, H-5), 7.58 (br s, 1 H, H-2″), 7.45 (br d, J = 8.0 Hz, 1 H, H-6″), 7.49 (br s, 1 H, H-3′), 7.23 (br t, J = 7.8 Hz, 1 H, H-5″), 7.18 (dd, J = 5.1, 1.2 Hz, 1 H, H-5′), 6.80 (br d, J = 7.5 Hz, 1 H, H-4″), 3.74 (br dd, J = 5.1, 4.6 Hz, 4 H, 2 × CH_2O), 3.51 (br dd, J = 5.1, 4.6 Hz, 4 H, 2 × CH_2N), 2.33 (s, 3 H, CH_3); ^{13}C NMR [$(CD_3)_2SO$] δ 163.2, 159.9, 148.5, 148.1, 142.7, 141.0, 138.2, 128.9, 122.1, 117.6, 114.2, 110.5, 106.4, 102.9, 66.0 (2), 45.2 (2), 21.3; MS *m/z* 352.6 (MH^+, 100%). Anal. calcd for $C_{19}H_{20}N_4OS$: C, 64.75; H, 5.72; N, 15.90. Found: C, 64.74; H, 5.85; N, 15.91%.

Example 1-110

[0407] *N*-(3-Methylphenyl)-4-[2-(4-methyl-1-piperazinyl)-4-pyridinyl]-1,3-thiazol-2-amine (198).

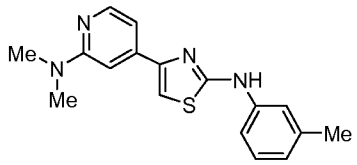


***N*-(3-Methylphenyl)-4-[2-(4-methyl-1-piperazinyl)-4-pyridinyl]-1,3-thiazol-2-amine (198).** A mixture of 4-(2-bromo-4-pyridinyl)-*N*-(3-methylphenyl)-1,3-thiazol-2-amine (**154**) (0.16 g, 0.45 mmol) in 1-methylpiperazine (5 mL) was stirred at 100 °C for 16 h. The mixture was cooled to 20 °C, diluted with water (80 mL), extracted with EtOAc (3 × 20 mL). The organic fraction was washed with water (10 mL), washed with brine (10 mL) and dried. The solvent was evaporated and the crude solid was purified by column chromatography, eluting with 5% MeOH/DCM, to give amine **198** (0.09 g, 57%) as a white powder: mp (EtOAc/pet. ether) 141–143 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 10.23 (s, 1 H, NH), 8.15 (d, J = 5.1 Hz, 1 H, H-6′), 7.62 (br s, 1 H, H-2″), 7.60 (s, 1 H, H-5), 7.42 (br d, J = 8.0 Hz, 1 H, H-6″), 7.29 (br s, 1 H, H-3′), 7.22 (br t, J = 7.8 Hz, 1 H, H-5″), 7.14 (dd, J = 5.1, 1.0 Hz, 1 H, H-5′), 6.80 (br d, J = 7.5 Hz, 1 H, H-4″), 3.55 (br dd, J = 5.0, 4.7 Hz, 4 H, 2 × CH_2N), 2.44 (br dd, J = 5.0, 4.7 Hz, 4 H, 2 × CH_2N), 2.32 (s, 3 H, CH_3), 2.24 (s, 3 H, CH_3); ^{13}C NMR [$(CD_3)_2SO$] δ 163.2, 159.8, 148.6, 148.1, 142.6, 141.0,

138.1, 128.8, 122.1, 117.6, 114.2, 110.0, 106.3, 103.0, 54.4 (2), 45.8, 44.7 (2), 21.3; MS *m/z* 366.9 (MH^+, 100%). Anal. calcd for $C_{20}H_{23}N_5S$: C, 65.72; H, 6.34; N, 19.16. Found: C, 65.51; H, 6.48; N, 18.86%.

Example 1-111

[0408] *N*,*N*-Dimethyl-4-{2-[(3-methylphenyl)amino]-1,3-thiazol-4-yl}-2-pyridinamine (199).



***N*,*N*-Dimethyl-4-{2-[(3-methylphenyl)amino]-1,3-thiazol-4-yl}-2-pyridinamine (199).** A mixture of 4-(2-bromo-4-pyridinyl)-*N*-(3-methylphenyl)-1,3-thiazol-2-amine (**154**) (0.17 g, 0.45 mmol) in 40% aqueous dimethylamine (5 mL) was stirred at 80 °C for 16 h. The mixture was cooled to 20 °C, diluted with water (80 mL), extracted with EtOAc (3 × 20 mL). The organic fraction was washed with water (10 mL), washed with brine (10 mL) and dried. The solvent was evaporated and the crude solid was purified by column chromatography, eluting with 40% EtOAc/pet. ether, to give amine **199** (0.08 g, 55%) as a tan powder: mp (EtOAc/pet. ether) 148–150 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 10.22 (s, 1 H, NH), 8.11 (d, *J* = 5.1 Hz, 1 H, H-6), 7.65 (br s, 1 H, H-2″), 7.55 (s, 1 H, H-5′), 7.40 (br d, *J* = 8.0 Hz, 1 H, H-6″), 7.22 (br t, *J* = 7.8 Hz, 1 H, H-5″), 7.14 (br s, 1 H, H-3), 7.05 (dd, *J* = 5.1, 1.0 Hz, 1 H, H-5), 6.80 (br d, *J* = 7.5 Hz, 1 H, H-4″), 3.09 [s, 6 H, $N(CH_3)_2$], 2.32 (s, 3 H, CH_3); ^{13}C NMR [$(CD_3)_2SO$] δ 163.1, 159.8, 148.8, 148.0, 142.3, 141.0, 138.1, 128.8, 122.1, 117.6, 114.2, 108.4, 106.1, 101.9, 37.7 (2), 21.3; MS *m/z* 311.7 (MH^+, 100%). Anal. calcd for $C_{17}H_{18}N_4S$: C, 65.78; H, 5.84; N, 18.05. Found: C, 65.99; H, 6.08; N, 17.74%.

Example 2

Identification of novel molecules targeting VHL-deficient renal cell carcinoma

Materials and Methods

[0409] Cell Culture and Cell Treatments: RCC4 parental and RCC4 with VHL-reintroduced (RCC4/VHL), SN12C and SN12C-CSCG-VHL shRNA, MEF ATG5+/+ and ATG5-/- were maintained in DMEM supplemented with 10% FCS. Cells were plated at 70% confluency, and treated with 1.25 μM (RCC4) or 3.75 μM (SN12C) of STF-62247 ("compound **5**") overnight in presence or absence of 2 mM 3-methyladenine ("3-MA"), 1 μg/ml Brefeldin A, 15 μM LY294002, 2 μg/ml Tunicamycin, or 10 μM U0126 (Sigma Chemical Co).

[0410] Cell Viability and XTT assays. For cell viability, 100,000 cells were plated in a 12-well plate. The following day, 1.25 μM STF-62247 was added in the presence or absence of 1 mM 3-MA for 24 hours at 37°C. Cells were trypsinized and counted by trypan blue exclusion. For XTT assays, 5000 RCC4 with and without VHL cells or 2,500 SN12C with and without VHL shRNA cells were plated in 96-well plates. The following day, vehicle (DMSO), STF-62247 or each of 19 analogs were added to media by serial dilution. Four days later, the media was aspirated and XTT solution containing 0.3 mg/ml of XTT (Sigma Chemical Co) in Phenol Red-free media, 20% FCS and 2.65 mg/ml N-methyl dibenzopyrazine methyl sulfate (PMS) was added to the cells and incubated at 37°C for 1-2 hours. Metabolism of XTT was quantified by measuring the absorbance at 450 nm on a plate reader.

[0411] Clonogenic Cell Survival Assay. RCC4, RCC4/VHL, SN12C and SN12C-VHL shRNA were plated at 300 cells per 60 mm tissue culture dish. The following day, vehicle or STF-62247 was added and cells were incubated in the presence of drug for 10 days in RCC4 and RCC4/VHL and 7-10 days for SN12C and SN12C-VHL shRNA. The colonies were stained with crystal violet, and quantified. Each experiment was performed at least three times in triplicate.

[0412] Western blot analysis. After treatments, cells were lysed in urea buffer (9M urea, 75mM Tris (pH 7.5), 150mM b-mercaptoethanol), placed on ice for 10 minutes and sonicated briefly (15 seconds). Extracts were centrifugated at 8,000 x g for 10 minutes to eliminate insoluble material. Lysates were quantitated using

Bio-Rad protein Assay (Bio-Rad Laboratories) and 20-30 μg of proteins were separated on a 7.5% or 15% bis-acrylamide gels and then transferred onto PVDF membranes. Proteins were visualized using HIF-2α (Novus Biological), HIF-1α, pVHL and BiP (BD Biosciences), LC3 (MBL), Atg5, or α-tubulin antibodies.

[0413] Quantification of Acidic Vesicle Organelles with Acridine Orange. In acridine orange-stained cells, the cytoplasm and nucleus are bright green and dim red, whereas acidic compartments are bright red. The intensity of the red fluorescence is proportional to the degree of acidity. Following 20 hours of treatment with STF-62247 or analogs, cells were stained with 1 μg/ml of acridine orange for 15 min. Cells were trypsinized and then analyzed by flow cytometry using FACScan cytometer and CellQuest software.

[0414] Immunofluorescence staining. Cells were seeded on glass coverslips and at subconfluence, STF-62247 was added at 1.25 μM for RCC4 and 3.75 μM for SN12C. After 20 hours, cells were fixed in 3.7% formaldehyde for 10 min at room temperature and washed in PBS. Then cells were permeabilized in 0.2% Triton X-100 for 5 min at room temperature and washed in PBS. The coverslips were incubated with primary antibody LC3 diluted 1:500 in PBS containing 0.2% BSA for 1 hour at room temperature. Cells were washed three times in PBS-BSA and the bound primary antibody was detected using a fluorescein-conjugated secondary antibody (ALEXA) diluted 1:500 in PBS-BSA and incubated for 1 hour. Coverslips were washed and mounted in mounting medium from Vector Laboratories according to the manufacturer's instructions. Cells were examined with a confocal microscope

[0415] Visualization of Monodansylcadaverine (MDC) vacuoles. Cells were incubated in the presence of drug for 20 hours and labeled with 50 μM of the autofluorescent marker MDC (Sigma Chemical Co) in PBS at 37°C for 10 minutes. Then, cells are fixed with 3.7% formaldehyde for 10 min at room temperature and washed in PBS. MDC was observed by fluorescence microscopy (Nikon Eclipse E800).

[0416] In vivo studies. 2-3 x 10^6 SN12C and SN12C-VHL shRNA cells were injected in male scid mice 4-6 weeks old. When tumor volume reached 150 mm^3, mice were randomized into vehicle control group or STF-62247 treatment group.

Mice were treated every day with 10-30 μM of STF-62247 intraperitoneally. Tumor growth was measured every 2-3 days after the drug treatment was started.

[0417] shRNA constructs, plasmids and retroviral infection. The CMV-EYFP fluorescent protein and the HIF-2α P531A/P847A double mutant were cloned into pBabe-puro vector. The sequence used for HIF-1α and HIF-2α shRNA were gaggaactaccattatat and ggagacggaggtggtctat respectively. Retrovirus were produced by transfecting plasmids into ΦNX-amphotropic cell lines according to manufacturer's instructions with Lipofectamine Plus (Invitrogen). The next day after transfection, cells were placed at 32°C. Retrovirus was harvested 48 and 72 hours after transfection. Puromycin was used to select for stable retroviral integrants.

[0418] Transient transfection of RCC. Cells were transfected with siRNA against Atg5, CHMP6, PAK2, Rab11a, OSBP3, ALG5, Atg7, Atg9 (SMART pool) and siControl2 non-targeting pool from Dharmacon using Dharmafect Reagent 1 for 48 hours. Cells were split for clonogenic assay, harvested for RNA or protein.

[0419] Screen in yeast and killing curves. Genotypes of the parental yeast strain BY4743, construction of the homozygous diploid deletion strains, and construction of the homozygous diploid deletion pool have been described previously (Thomas, G.V., et al., *Nat. Med.* **2006**, *12*, 122). A mutant pool of 4728 nonessential homozygous diploid deletion strains was used. The parental diploid strain BY4743 was used as control in survival and complementation assays. For clonogenic survival, equivalent numbers of early log-phase cells parental and deletion strains for ALG5, APS1, OSH3, CLA4, DRS2, DAP1, VPS20, VPS25, FIG4, SPT4 were suspended in yeast extract peptone dextrose (YPD) and treated with STF-62247 (0-100 μM) for 1 h while being shaken at 300 rpm at 30°C. Cells were then pelleted, washed once with buffer (10 mM Tris and 5 mM EDTA), pelleted, and resuspended in the same buffer. Cells were then plated at appropriate dilutions onto YPD solid medium to allow for accurate counting of surviving colonies (range, 50–250). Plates were incubated for 2 days at 30°C before counting colonies. Full survival curves were performed in triplicates for each selected deletion strain.

[0420] Quantitative RT-PCR (qRT-PCR). RNA from cells transfected with siControl or siAtg was prepared using TRIzol (Invitrogen, Carlsbad,CA) according to the manufacturer's protocol. The reverse transcription was performed with Moloney Murine Leukemia Virus MMLV reverse transcriptase (Invitrogen) using two μgrams of RNA and 5 μ*M*-random primers (Invitrogen) according to the manufacturer's instructions. Approximately 0.5% of each RT reaction was used for the quantitative RT (qRT)-PCR reactions containing 5 μl 2× SYBR Green master mix (ABI, Foster City, CA) and 200 n*M* forward and reverse primers specific of the different genes of interest in a volume of 10 μl. Detection and data analysis was carried out with the ABI PRISM 7900 sequence detection system using TBP primers as an internal control. PCR primer sequences are obtained from the Primer Bank database (see Primerbank web site, Harvard University) and synthesized in the Stanford Protein and Nucleic Acid Biotechnology Facility.

[0421] Figure 1 shows that STF-62247 induces cytotoxicity and reduces tumor growth in VHL-deficient cells in HIF-independent manner. A. RCC4 and RCC4/VHL cells were labeled with EYFP and the effect of STF-62247 was monitored by fluorescence in each cell type separately. Cells are pseudocolored. B. Clonogenic assay in RCC4, RCC4/VHL, SN12C, SN12C-VHL shRNA cells in the presence of STF-62247 (0-30 μM). Each point of the cell survival is calculated by the average of three different experiments in triplicate as the percent of treated on untreated plate. The error bars represented the standard error of the mean (SEM). C. Upper Panel, clonogenic assay in RCC4 infected with HIF-1α or HIF-2α shRNA by retroviral infection in presence of drug in same conditions described above. Bottom panel, HIF-1α or HIF-2α protein expression evaluated by western blot in RCC4 cells with HIF-1α or HIF-2α shRNA. Tubulin is used as loading control. D. Upper Panel, clonogenic assay with STF-62247 in RCC4 where HIF-2α was stably introduced into VHL-positive cells by retroviral infection. Bottom panel, western blot for HIF-1α or HIF-2α in RCC4 VHL-positive cells. E. SN12C and SN12C-VHL shRNA (2-3 x 10^6 cells) are injected in SCID mice. When the tumors reach 120 mm^3, a daily treatment with vehicle or 10-30 μM of STF-62247 was administrated intraperitoneally. Tumor volume was measured every 2-3 days

and data are represented in fold. Five tumors in each condition were analyzed where * $p<0.05$, ** $p<0.01$ and *** $p<0.005$.

[0422] Figure 2 shows the presence of autophagic vacuoles upon treatment with STF-62247 in RCCs. A. Phase contrast pictures of VHL-deficient RCC4 and SN12C-VHL shRNA cells and VHL-positive cells RCC4 and SN12C after 20 hrs of 1.25 μM STF-62247. B. Immunostaining for LC3 following STF-62247 treatment at 1.25 μM for 20 hrs with or without 2 mM of 3-MA in RCC4 with and without VHL cells. After treatment, cells were fixed, permeabilized and processed for the detection of punctuate staining by indirect immunofluorescence. C. Autophagic vacuoles stained with monodansylcadaverine (MDC). After STF-62247 treatment in the same conditions, MDC was added for the last 10 minutes. Cells were fixed, washed with PBS and observed directly under microscope. D. Western blot for LC3 in RCC4, RCC4/VHL, SN12C, and SN12C-VHL shRNA cells after STF-62247 treatment with or without 3-MA. Nutrient starvation (EBSS) is used as positive control. E. Western blot for LC3 in RCC4 and RCC4/VHL with different concentrations of STF-62247. Tubulin was used as loading control. F. Cell viability assay in VHL-deficient RCC4 and wild-type VHL cells treated with 1 mM of 3-MA, 1.25 μM of STF-62247 alone or in combination for 24 hrs. Viability is measured by trypan blue exclusion assay and is represented by the average of three different experiments in duplicate as the percent of treated on untreated cells. The error bars are represented as SEM.

[0423] Figure 3 shows the effects of STF-62247 on ATG5 in autophagic cell death. A. MEFs ATG5+/+ and ATG5-/- were treated in presence of 3 μM of STF-62247 and examined under light microscopy 20 hrs later. B. LC3 processing evaluated by Western blot following 24 hours of drug treatment in MEFs. C. Cell Survival measured by clonogenic assay with STF-62247 in RCC4 and RCC4/VHL cells transiently transfected with siRNA to Atg5. Colony formation was evaluated as described before. The error bars are represented as SEM. *** $p<0.005$ represents the difference between RCC4 and RCC4 with siAtg5 cells in presence of STF-62247. D. Western blot for LC3 and Atg5 in RCC4 and RCC4/VHL cells transiently transfected with siRNA against AtgG5. Tubulin was used as loading control. E. mRNA level of Atg5 quantified by qRT-PCR in RCC4 and RCC4/VHL

cells transfected with siRNA to Atg5 for 48 hours. F, G. Left and middle panels, Clonogenic assay with STF-62247 in cells transfected with Atg7 and Atg9 siRNA in VHL-deficient RCC4, RCC10 and wild-type VHL cells. Colony formation was evaluated as described before. The error bars are represented as SEM. **p<0.01 represents the difference between siControl cells and siAtg cells in response to STF-62247. Right panels, mRNA levels of Atg7 and Atg9 (and Atg5 in RCC10 cells) quantified by qRT-PCR after 48 hours of transfection using siRNA to Atg7 and Atg9 (and Atg5 in RCC10 cells) in RCC4 and RCC10 cells with or without VHL.

[0424] Figure 4 shows the effects of STF-62247 on Golgi trafficking, PI3K, and vesicle acidification. A. VHL-deficient RCC4 and wild-type VHL were incubated in presence of 10 μM LY294002, or 1 μg/ml Brefeldin A with 1.25 μM of STF-62247 for 20 hrs and the presence of vacuoles was examined under light microscopy. B,C. LC3 processing was evaluated by Western blot after the treatment with Brefeldin A or LY294002 in presence or absence of STF-62247 as described above. Tubulin was used as loading control. D. Cells were treated with 1.25 μM of STF-62247 with or without 2 mM of 3-MA, 1 μg/ml of Brefeldin A for 20 hrs. For the last 15 min, acidic components were stained with 1 μg/ml of acridine orange and visualized under fluorescence microscope. E. FACS analysis to measure the acidic vesicle organelles (AVO) in cells treated in D. y axis represents the concentrated dye in the acidic vesicles, whereas the cytoplasm and the nucleus showed green fluorescence in x axis. F. Quantification of the FACS analysis. The data are calculated as the average of three different experiments as relative units of treated over untreated cells. The error bars are represented as the standard error of the mean (SEM).

[0425] Figure 5 shows an evaluation of autophagy in RCC treated with analogs of STF-62247. A. RCC4 and RCC4/VHL were treated with 1.25 μM of each 19 analogs for 20 hours and the presence of vacuoles was examined under light microscopy. B. Western blot for LC3 after treatment with each compound. Tubulin was used as loading control. Ratio is the relative from the IC50 in RCC4/VHL cells/IC50 in RCC4 cells. C. Acidic vesicle organelles (AVO) measured by FACS

analysis in cells treated with 1.25 μM of STF-62247 or with compounds **21**, **15**, **25**, **47**, and **53** and stained with acridine orange.

[0426] Figure 6 shows the effects of STF-62247 on Golgi trafficking proteins. A. Killing curves for 8 deletion yeast strains. Wild-type, ALG5, APS1, CLA4, DRS2, OSH3, VPS20, VPS25, YPT31 were incubated with STF-62247 (0-100 μM) for 1 hour and colony formation was evaluated after two days. Each point of the survival is calculated by the average of two different experiments in triplicate and as the percent of treated on untreated plate. B. Quantitative real time PCR for CHMP6, PAK2, RAB11a, OSBP3 and ALG5 in RCC4 and RCC4/VHL. Histogram is calculated by the average of three different experiments in triplicate as the percent of RCC4/VHL on RCC4 cells. The error bars are represented as SEM and *$p<0.05$, **$p<0.01$. C. VHL cells were transiently transfected with siRNA for CHMP6, OSBP3 and ALG5 for 72 hours. The last 24 hours, 1.25 μM of STF-62247 was added and the vacuole formation was examined under light microscopy. D. Clonogenic assay with STF-62247 (0-30 μM) in RCC4/VHL cells transiently transfected in the same condition than in C. Colony formation was evaluated as described before. *$p<0.05$ represents the difference between VHL cells and VHL with siRNA in presence of 5 μM of STF-62247.

[0427] Figure 7 shows A. Structure of STF-62247 (also termed "30661" and "compound **5**"). B. XTT assay in RCC4 and RCC4/VHL in presence of STF-62247 (0-40 μM). Each point of the cell survival is calculated by the average of three different experiments in duplicate as the percent of treated on untreated plate. The error bars are represented as the standard error of the mean (SEM) C. qRT-PCR for Glut1, VEGF, PDF and PGK in RCC4 cells with or without HIF-1α, HIF-2α shRNA and in RCC4/VHL. D. Hoescht staining in RCC4 and RCC4/VHL cells with 1.25 μM of STF-62247 for 2 days. Camptothecin was used as positive control E. FACS analysis for apoptosis after an annexin V-FITC staining in presence or absence of propidium iodine (PI) in cells after a treatment in same conditions than in C. F. Immunoblot for active caspase-3 in RCC4 and RCC4/VHL following treatment with 1.25 μM of STF-62247 for 24 hours. Staurosporine was used as positive control (0.2 μM for 24 hours). G,H. Immunostaining of caspase-3 and Ki67 respectively in SN12C and SN12C+shVHL tumor samples untreated or

treated with 30 μM of STF-62247. I. Immunoblot for p53 and Ser15 phospho-p53 in RCC4 and RCC4/VHL cells after a treatment with 1.25 μM of STF-62247 or doxorubicin for 24 hours.

[0428] Figure 8 shows A. Transmission electron microscopy in RCC4 cells treated with vehicle control (DMSO) or with 1.25 μM STF-62247 for 20 hrs. Arrows represent autophagic vacuoles during drug treatment. N. Nucleus. B. RCC4 cells treated with STF-62247 observed at higher magnification. M. Mitochondria L. Lysosome AV. Autophagic Vacuole

[0429] Figure 9 shows A. VHL-deficient RCC4 and wild-type VHL incubated in the presence of 10 μM U0126, or 2 μg/ml tunicamycin with 1.25 μM of STF-62247 for 20 hrs and the presence of vacuoles was examined under light microscopy. B,C. LC3 processing was evaluated by Western blot after the treatment with U0126 or tunicamycin in presence or absence of STF-62247 as described above. Tubulin was used as loading control. D. FACS analysis to measure the acidic vesicle organelles after staining with acridine orange in SN12C and SN12C-VHL shRNA following treatment with STF-62247 for 24 hours. E. AVO quantification from the FACS analysis in A. F. Autophagic vacuoles stained with MDC. After STF-62247 treatment with or without 3-MA, NH_4Cl, MDC was added the last 10 minutes. Then, cells were fixed, washed with PBS and observed directly under microscope.

[0430] Figure 10 shows knockdown of various genes using siRNA.

Results

STF-62247 induces cytotoxicity and reduces tumor growth in VHL-deficient cells in a HIF-independent manner

[0431] In this study, the possibility of selectively targeting VHL-deficient cells using small molecule cytotoxins was evaluated. A library of 64,000 compounds was screened against wild-type VHL and VHL-deficient RCCs that were stably transfected with EYFP. The effect of small molecules on each cell type was monitored separately by fluorescence (Figure 1A). The drug STF-62247 was identified in this screen (Figure 7A) and decreases the viability of VHL-deficient cells in a short term assay (Figure 7B). Moreover, STF-62247 specifically results

in cytotoxicity in renal cells that have lost VHL as demonstrated by two genetic models: RCC4 cells deficient in VHL and their matched counterparts where wild-type VHL has been reintroduced, and SN12C cells stably expressing shRNA to VHL and SN12C cells with wild-type VHL (Thomas, G.V., et al., *Nat. Med.* **2006**, 12, 122). Clonogenic assays demonstrated that STF-62247 is selectively toxic to VHL-deficient cells compared to their VHL wild-type counterparts (Figure 1B).

[0432] Since VHL is an important negative regulator of HIF-α through its E3-ligase activity, VHL-null RCC4 cells expressing shRNA to HIF-1α or HIF2α were used to determine whether STF-62247 cytotoxicity was dependent on HIF (Figure 1C bottom panel). The level of HIF target genes was quantified by qRT-PCR verifying functional knockdown of HIF (Figure 7C). Clonogenic assays demonstrated that the reduction of either HIF-1α or HIF-2α in VHL-null cells did not affect cell death induced by STF-62247 (Figure 1C upper panel). Also, a decrease level in ARNT (HIF-1β) using shRNA did not change the cell survival by STF-62247 (data not shown). Previous studies have indicated that HIF-2 is critical for tumor growth of RCCs (Kondo, K., et al., *PLoS Biol.* **2003**, *1*, E83; Zimmer, M., et al., *Mol. Cancer Res.* **2004**, *2*, 89). To investigate the effect of HIF-2 in the sensitivity of RCC4 cells to STF-62247, a VHL cell line that stably expressed a normoxically stable, constitutively active HIF-2αmutant P531A N547A was generated. Two individual HIF-2α RCC4/VHL clones were randomly chosen that had elevated HIF-2α expression under normoxic conditions (Figure 1D bottom panel). Results showed that cytotoxicity of STF-62247 was unaffected by the presence of HIF-2α expression under normoxic conditions when compared to RCC4/VHL cells. Thus, by using complementary approaches, the results indicate that STF-62247 induces cytotoxicity in VHL-null cells in a HIF-independent manner.

[0433] To evaluate the effect of STF-62247 on tumor growth *in vivo*, SN12C or SN12C-VHL shRNA were implanted subcutaneously in immune deficient mice. Daily treatment with STF-62247 significantly reduced tumor growth in VHL-deficient cells (Figure 1E). This decrease in tumor growth was concentration-dependent. Importantly, drug treatment did not have any effect on the growth of SN12C tumor cells that have wild-type VHL. Together, these results show that

STF-62247 selectively kills RCC cells with a loss of VHL *in vitro* and also significantly reduces tumor growth in cells deficient in VHL.

Autophagy is induced by STF-62247 treatment

[0434] It was found that STF-62247 did not induce apoptosis *in vitro* in VHL-deficient cells as assayed by Hoechst (Figure 7D), Annexin V staining (Figure 7E) or caspase-3 (Figure 7F). These results were further confirmed by immunostaining for caspase-3 in tumor sections (Figure 7G). There was no difference in proliferation as assayed by Ki67 staining in response to STF-62247 in RCC deficient in VHL or with wild-type VHL (Figure 7H). STF-62247 did not induce DNA damage as measured by the comet assay (data not shown). In addition, the phosphorylation of p53 on serine 15 and total p53 levels were unaffected by STF-62247 treatment, further supporting the lack of a DNA damage signal in cell killing induced by STF-62247 (Figure 7I). It was observed that STF-62247-treated cells accumulated intracytoplasmic vacuoles characteristic of cells undergoing autophagy. Moreover, these vacuoles were larger in VHL-deficient RCC4 and SN12C-VHL shRNA cells than in wild-type VHL cells (Figure 2A). Vacuole formation in RCC cells with and without VHL was monitored by time-lapse for 48 hours, showing that vacuoles appeared as soon as 3 hours after addition of STF-62247. Time-lapse microscopy also indicated that wild-type VHL prevents the formation of larger vacuoles present in VHL-deficient cells.

[0435] Induction of autophagy was confirmed by immunostaining and Western blotting for LC3. STF-62247 increased punctate staining of LC3, which is associated with processing of LC3 to its lipidated form (Figure 2B). LC3-II, corresponding to the lipidated form found with the formation of double-membranes, was induced by STF-62247 treatment, indicating that STF-62247 stimulates autophagy (Figure 2D). Transmission electron microscopy (TEM) was also used to monitor autophagy in response to STF-62247. There were large numbers of autophagic vacuoles present in STF-62247-treated cells, but not in untreated cells (Figure 8A). The presence of double-membrane containing cellular organelles was observed in RCC4 treated cells at higher magnification (Figure 8B).

[0436] The increase of the LC3-II form was abrogated by 3-methyladenine (3-MA), an autophagy inhibitor that inhibits PI3 kinase. It is noteworthy that although the stimulation of LC3 is higher in VHL-deficient cells treated with STF-62247, the increase was also observed in wild-type VHL cells, and therefore the presence of autophagosomes cannot by themselves explain the difference in toxicity observed between RCC cells with and without VHL. Cells were also stained with the autofluorescent compound monodansylcadaverine (MDC), which acts as a lysosomotropic agent and labels some of the acidic compartments that are observed after fusion with lysosomes (autolysosomes) (Figure 2C). Staining with MDC in RCC4 cells was primarily observed around the larger vacuoles compared to the punctate staining of LC3, suggesting that these large vacuoles are associated with the acidic components of autolysosomes.

[0437] Since autophagy might be an early response to drug treatment, LC3 processing was monitored in cells exposed to increasing concentrations of drug. Results show that the LC3-lipidated form increases in a concentration-dependent manner, indicating that the autophagic process is tightly linked with drug cytotoxicity (Figure 2E). To determine whether autophagy induced by STF-62247 was responsible for the reduced viability observed in VHL-deficient cells, the viability after 24 hours of cells treated with 3-MA to inhibit autophagy was measured. The viability of VHL-deficient cells was partially restored by 3-MA, indicating that STF-62247 induced autophagy leads to cell death in VHL-deficient cells (Figure 2F).

ATG5, ATG7 and ATG9 are involved in autophagosome formation in STF-62247 treated cells

[0438] The autophagy-related gene 5 (Atg5) is involved in the formation of the autophagosome and the Atg12-Atg5 ubiquitin-like conjugate has been previously reported to be necessary for LC3 modification (Kabeya, Y., et al., *Embo J.* **2000**, *19*, 5720; Mizushima, N., et al., *J. Cell Biol.* **2001**, *152*, 657). Thus, hypothically, if autophagy was important in STF-62247 cytotoxicity of VHL-deficient cells, ATG5-/- cells would be resistant to STF-62247-induced cell death. Significantly more autophagic vacuoles were found during STF-62247 treatment in ATG5+/+

cells compared to ATG5-/- cells (Figure 3A). This effect correlates with the LC3 processing that was observed only in ATG5+/+ cells in response to STF-62247 and was concentration dependent (Figure 3B). Importantly, it was confirmed that ATG5 is involved in STF-62247-induced toxicity in VHL-deficient RCC cells. Silencing ATG5 by siRNA protected RCC4 cells deficient in VHL to killing induced by STF-62247 as assessed by clonogenic assay (Figure 3C). VHL-positive RCC4 cells were unaffected by ATG5 siRNA, suggesting that the cell death observed at higher concentrations in VHL-positive cells is independent of Atg5 and autophagy. A reduction in Atg12-Atg5 levels by siRNA decreases LC3 formation by STF-62247, indicating a critical role for Atg5 in STF-62247 autophagic response in RCC VHL-deficient cells (Figure 3D). The siRNA to Atg7 and Atg9 also prevents the STF-62247 cytotoxicity in RCC4 VHL-deficient cells, consistent with the essential role of the autophagy pathway in STF-62247 cytotoxicity (Figure 3F). Atg7 acts as an E1 enzyme in the autophagy conjugation system where in combination with an E2 enzyme, conjugates the phosphatidyl ethanolamine to LC3I to form, LC3II. No lipidation of LC3 occurs in the brain of Atg7 deficient mice (Tanida, I., et al., *J. Biol. Chem.* **2002**, *277*, 13739). On the other hand, Atg9 has been reported to cycle between the trans-Golgi network and endosomes and its disruption impairs formation of autophagosomes (Young, A. R., et al., *J. Cell Sci.* **2006**, *119*, 3888). Protection against autophagic cell death induced by STF-62247 by disruption of Atg5, Atg7 and Atg9 is also demonstrated using VHL-deficient RCC10 and wild-type VHL RCC10 cells (Figure 3G).

PI3K and Golgi trafficking are required as initial signals in STF-62247-induced autophagy

[0439] Previous studies have implicated PI3K and ERK signaling as well as Golgi trafficking and endoplasmic reticulum (ER) stress in autophagy (Ogata, M., et al., *Mol. Cell. Biol.* **2006**, *26*, 9220; Yorimitsu, T., et al., *J. Biol. Chem.* **2006**, *281*, 30299). To evaluate a role for PI3K in response to STF-62247, the effects of the autophagy inhibitor 3-MA were compared to LY294002, another PI3K inhibitor. LY294002 significantly decreased large vacuole formation and the LC3-lipidation form in VHL-deficient cells during STF-62247 treatment to a level

similar as 3-MA (Figure 4 A-B and 2D), indicating a role for PI3K in STF-62247 signaling. In contrast, the MEK inhibitor U0126, which inhibits ERK activation, had little effect on autophagy induced by STF-62247 (Figure 9A, 9B), indicating that MEK signaling is not involved in STF-62247 induced autophagy.

Furthermore, it was found that Brefeldin A (BFA), a blocker of protein transport from the ER to the Golgi apparatus, abolished the formation of autophagic vacuoles and LC3-II stimulated by STF-62247 in VHL-deficient RCC cells. Without intending to be bound by theory, this suggests that Golgi trafficking is involved in the cytotoxicity of STF-62247 in cells that have loss VHL (Figure 4 A-C). In contrast, no vacuole or LC3 processing was observed during STF-62247 treatment with tunicamycin, although it induced BiP (Grp78), a marker of ER stress (Figure 9A, 9C). Taken together, but without intending to be bound by theory, the results suggest that Golgi trafficking and PI3K are part of the initial signal for the induction of autophagy in RCC cells treated with STF-62247.

STF-62247 increases acidification in VHL-deficient cells

[0440] Although autophagosome formation in response to STF-62247 is independent of VHL status, how STF-62247 specifically kills cells that have lost VHL was investigated. A late step in the autophagic cell death process is the fusion of lysosomes with autophagosomes into autolysosomes, which can be detected by measuring their acidification with acridine orange staining. Interestingly, we found acridine orange staining significantly increased in VHL-deficient RCC4 cells compared to their wild-type VHL counterparts (Figure 4D). This observation was quantified and confirmed by FACS analyses and illustrates a significant difference in the acidification of the acidic vesicular organelles (AVOs) in RCC4 and SN12C-VHL shRNA cells (Figure 4E-F and 9D-E) compared to wild-type VHL cells. Blocking autophagy with 3-MA or BFA resulted in a decrease in autolysosomal acidification, demonstrating that acidification induced by STF-62247 is linked to the autophagic pathway. In addition, MDC staining performed using NH_4Cl to block vesicle acidification attenuated the functional staining following drug treatment (Figure 9F). However, even if the acidification level in VHL cells increases following STF-62247 treatment, this level of acidification remained

significantly lower than in VHL-deficient cells. Without intending to be bound by theory, these results suggest that the fusion of autophagosomes with lysosomes is a key step leading to autophagic cell death in VHL-deficient cells.

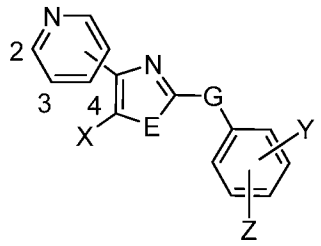
Structure-activity studies

[0441] Based on the STF-62247 structure, other compounds were designed and synthesized to evaluate their ability to induce selective cell death in VHL-deficient cells. Analysis of the high throughput screening (HTS) data indicated the importance of a 4-pyridyl unit linked to the 4-position of the thiazole, while the tested 3-pyridyl analogs were inactive. Without intending to be bound by theory, the importance of a thiazole NH suggests an H-bond contact in this region. Substituents at the 2-position on the aryl ring were not tolerated in the tested compounds. With these constraints in mind, we prepared a focused set of analogs of STF-62247 to probe structure-activity relationships (SAR) (Tables 1 and 2). The IC50 for these analogs shows that the STF-62247 has a low IC50 in VHL-deficient RCC4 cells and a high IC50 ratio (wild-type VHL/VHL-deficient cells). The compound 30603 with a methyl group in 4-position also has a high ratio but also a higher IC50 for both RCC4 and RCC4/VHL cells. In some cases, the IC50 could not be determined because of poor compound solubility.

[0442] To associate the cytotoxicity of these compounds with autophagy, the vacuole formation and LC3 processing were evaluated (Figure 5A-B). For the tested compounds, those with an IC50 ratio VHL/VHLdeficient cells >5 correlated positively with the presence of large vacuoles in VHL-deficient cells and the processing of LC3. As observed with STF-62247 treatment, the LC3-lipidated form was present in both VHL wild type and deficient cell lines. To confirm that the cell death observed in VHL-deficient cells is associated with the acidification of autophagic vesicules, the level of AVOs was measured in response to 5 different analogs (Figure 5C). The amount of AVOs was consistently higher in VHL-deficient cells treated with compounds 30603, 31184, and 30651, three analogs where the IC50 was relatively low, but which induced significant vacuole formation and the LC3-lipidated form. In contrast, AVO staining was not influenced in response to compound 31185 and 31270, two analogs where no

toxicity or autophagy were observed. These results with STF-62247 analogs confirm that the autophagic cell death observed in VHL-deficient cells is related to the acidification of the vacuoles. Without intending to be bound by theory, the strong relationship between autophagic cell death and vacuole acidification might explain why autophagy leads to cell death in VHL-deficient cells and not in wild-type cells.

Table 1. IC_{50} values and selectivity ratios for compounds of the invention

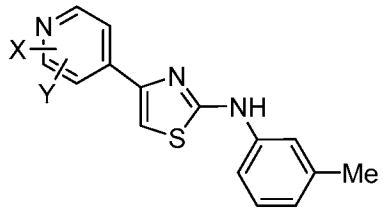


SN #	Cpd. No	pyridyl	E	X	Y	Z	G	RCC4 µM	Ratio
30602	**3**	4	S		H		NH	7	>10
30661 STF-62247	**5**	4	S		3-Me		NH	2.1	19
32032	**7**	4	S		3-Et		NH	2.5	9.6
31910	**9**	4	S		3-iPr		NH	17	1.4
31938	**11**	4	S		3-tBu		NH	>40	nd
31185	**13**	4	S		3-OH		NH	28.5	>3
30651	**15**	4	S		3-OMe		NH	3	17
30654	**17**	4	S		3-Cl		NH	3	5
30670	**19**	4	S		3-CF_3		NH	>40	nd
30603	**21**	4	S		4-Me		NH	2.5	20
31274	**23**	4	S		4-CH_2CH_2OH		NH	5	16
31184	**25**	4	S		4-OH		NH	5.3	8
30644	**27**	4	S		4-OMe		NH	14	3.6
31289	**29**	4	S		4-$OCH_2CH_2NMe_2$		NH	60	1.3
30671	**31**	4	S		4-Cl		NH	38	>2
30709	**33**	4	S		4-F		NH	6	>7
30715	**35**	4	S		4-NO_2		NH	>40	nd

31283	**36**	4	S		4-$CH_2CH_2NMe_2$		NH	50	1.2
30723	**37**	4	S		4-NH_2		NH	nd	nd
31892	**39**	4	S		3-$OP(O)(OH)_2$		NH	29	1.1
31857	**41**	4	S		4-$OP(O)(OH)_2$		NH	3	6.3
31886	**43**	4	S		3-Me	4-Me	NH	6.5	6.4
31849	**45**	4	S		3-Me	5-Me	NH	4.5	>9
31187	**47**	4	S		3-$CH_2CH_2CH_2$-4		NH	2.0	10
31258	**49**	4	S		3-OH	4-Me	NH	12	4.6
31259	**51**	4	S		3-OH	4-OMe	NH	nd	nd
31270	**53**	4	S		3-Me	4-OH	NH	70	2.3
31181	**55**	4	S		3-OMe	4-OMe	NH	24	1.9
31850	**57**	4	S		3-OMe	5-OMe	NH	>40	nd
31186	**59**	4	S		3-OCH_2O-4		NH	>40	nd
30713	**61**	4	S		3-Cl	4-Cl	NH	13.5	>3
31851	**63**	4	S		3,4,5-OMe_3		NH	>40	nd
31884	**65**	3	S		3-Me		NH	>40	nd
31888	**66**	3	S		4-OH		NH	>40	nd
31885	**68**	2	S		3-Me		NH	37	0.9
31889	**69**	2	S		4-OH		NH	36	0.7
32010	**71**	4	S	Me	3-Me		NH	10	>4
32015	**72**	4	S	Me	3-$CH_2CH_2CH_2$-4		NH	12	1.5
31961	**73**	4	S	CH_2OH			NH	30	>1.3
31982	**74**	4	S	CH_2OH	3-Me		NH	7	2.4
31981	**75**	4	S	CH_2OH	4-Me		NH	14	1.2
31978	**76**	4	S	CH_2OH	3-$CH_2CH_2CH_2$-4		NH	6.8	1.4
32009	**77**	4	S	CHO	3-Me		NH	15	n.d.
32014	**78**	4	S	$CH=CHCO_2Me$	3-Me		NH	2.5	2.8
32087	**79**	4	S	$CH_2CH_2CO_2Me$	3-Me		NH	>40	nd
32098	**81**	4	S	$CH_2CH_2CH_2OH$	3-Me		NH	3.6	3.7
32109	**82**	4	S	$CH_2HC_2CH_2$ Nmorph	3-Me		NH	5.8	1.6
32008	**83**	4	S	CH_2NMe_2	3-Me		NH	16	2.3
32048	**84**	4	S	CH_2NEt_2	3-Me		NH	13	1.4

32049	**85**	4	S	CH_2Npiperidine	3-Me		NH	13	1.9
32007	**86**	4	S	CH_2Nmorpholine	3-Me		NH	2.5	4.8
32013	**88**	4	S	CO_2Et	3-Me		NH	>40	n.d.
32016	**89**	4	S	CO_2Et	3-$CH_2CH_2CH_2$-4		NH	>40	n.d.
32097	**91**	4	S	$CONH_2$	3-Me		NH	19.2	>2.0
32096	**92**	4	S	$CONMe_2$	3-Me		NH	16	>2.5
32091	**93**	4	S	$CONHCH_2CH_2NMe_2$	3-Me		NH	>40	nd
32093	**94**	4	S	$CONHCH_2CH_2CH_2$Nmorph	3-Me		NH	>40	nd
31922	**95**	4	S		3-Me		NMe	28	0.6
31923	**96**	4	S		3-Me		NEt	40	0.6
31940	**97**	4	S		3-Me		NCH_2CH_2OH	>40	nd
31875	**99**	4	S				NHCO	>40	nd
31852	**100**	4	S		3-Me		NHCO	>40	nd
31872	**101**	4	S		4-Me		NHCO	>40	nd
31876	**102**	4	S		4-OMe		NHCO	>40	nd
31903	**103**	4	S		3-Me		$NHCH_2$	>40	nd
32084	**105**	4	O		3-Me		NH	>40	nd
32680	**107**	4	S		2-OH		NH	12.8	>3.1
32523	**109**	4	S		2-OMe		NH	33.4	>1.2
32522	**111**	4	S		2-Me		NH	>40	nd
32685	**113**	4	S		2-F		NH	14.3	>2.8
32540	**115**	4	S		2-Cl		NH	27.6	>1.4
32591	**117**	4	S		2-CF_3		NH	>40	nd
32594	**119**	4	S		2-NO_2		NH	>40	nd
32185	**121**	4	S		3-F		NH	>40	nd
32291	**123**	4	S		3-Br		NH	12.4	>3.2
32623	**125**	4	S		3-$COCH_3$		NH	13	>3.1
32518	**127**	4	S		3-CN		NH	>40	nd
32292	**129**	4	S		3-NO_2		NH	>40	nd
32558	**131**	4	S		4-$COCH_3$		NH	3.8	3.1
32552	**133**	4	S		4-CF_3		NH	>40	nd
32542	**135**	4	S		4-CN		NH	>40	nd
32682	**137**	4	S		2-CH_3	6-CH_3	NH	>40	nd
32678	**139**	4	S		2-F	6-F	NH	>40	nd
32842	**196**	4	NH		3-CH_3		NH		

Table 2. IC_{50} values and selectivity ratios for compounds of the invention



SN #	Cpd. No	X	Y	RCC4 µM	Ratio
32201	**141**	2-OMe		28.7	1.2
32181	**145**	2-Me		>40	nd
32769	**149**	2-F		4.5	>8.9
32684	**150**	2-Cl		2.2	3.8
32312	**154**	2-Br		3.9	>10
32780	**158**	2-Cl	6-Cl	15	2.3
32715	**159**	2-C≡CH		17.8	>2.2
32718	**160**	2-Et		6.4	>6.3
32712	**161**	2-C≡CCH_2OH		9.3	1.6
32717	**162**	2-$CH_2CH_2CH_2OH$		5.2	>7.7
32398	**166**	3-CH_3		5.2	>7.7
32770	**170**	3-F		2.0	>20
32740	**174**	3-Cl		2.9	>13.8
32346	**178**	3-Br		3.9	>10
32758	**181**	3-NO_2		8.2	4.1
32761	**182**	3-NH_2		>40	nd
32767	**183**	3-NHAc		33.3	1.0
32732	**184**	3-C≡CH		1.35	4.4
32734	**185**	3-Et		6.2	2.8
32733	**186**	3-C≡CCH_2OH		0.24	11.9
32735	**187**	3-$CH_2CH_2CH_2OH$		6.8	>5.9
32764	**188**	N^+-O^-		>40	nd
32208	**192**	4-quinolinyl		12.3	1.6
32311	**194**	2-phenyl-4-quinolinyl		25.4	>1.6
32884	**197**	2-morpholine			
32887	**198**	2-(4-Me-piperazine)			
32892	**199**	2-NMe_2			

Golgi trafficking proteins are sensitive and a target for the STF-62247.

[0443] To identify a target for STF-62247, a screen of the yeast deletion pool was performed to determine which genes affect STF-62247 sensitivity. It was

found that proteins involved in Golgi trafficking and in morphogenesis were the most sensitive to STF-62247 (Table 3). To validate the data obtained from this screen, the sensitivity of several deleted yeast strains following STF-62247 treatment were evaluated (Figure 6A). The killing curves for CLA4, VPS20, ALG5, OSH3, and YPT31 deletion strains show a significant toxicity in response to STF-62247. The ATG8 deletion strain was also evaluated and did not exhibit sensitivity to STF-62247 as expected based on human Atg studies (data not shown). The human orthologs for CLA4, VPS20, ALG5, OSH3 and YPT31 strains are PAK2, CHMP6, ALG5, OSBP3 and Rab11a respectively. In mammalian cells, it was found that the glucosyltransferase ALG5, the oxysterol binding protein 3 (OSBP3), and CHMP6, a key component of the endosomal sorting complex (ESCRT III) are VHL-regulated (Figure 6B). These three proteins play a role in coordinating vesicular transport between the ER, the trans-Golgi network (TGN) and lysosomes. Moreover, the knockdown of these genes using siRNA (Figure 10) increases the vacuole formation in response to STF-62247 (Figure 6C) and cytotoxicity in VHL cells suggesting their loss partially phenocopies the loss of VHL (Figure 6D). Taken together, the results demonstrate that the Trans-Golgi Network is a target of the STF-62247 and a drug-selective pathway synthetically lethal in VHL-deficient cells.

Table 3: Yeast screen in response to STF-62247

ORF	Gene	Human homolog	Description
YPL170W	DAP1	PGRMC1	Heme-binding protein involved in regulation of cytochrome P450 protein Erg11p; damage response protein, related to mammalian membrane progesterone receptors; mutations lead to defects in telomeres, mitochondria, and sterol synthesis
YHR073W	OSH3	OSBPL3	Member of an oxysterol-binding protein family with seven members in S. cerevisiae; family members have overlapping, redundant functions in sterol metabolism and collectively perform a function essential for viability
YLR170C	APS1	LOC653653	Small subunit of the clathrin-associated adaptor complex AP-1, which is involved in protein sorting at the trans-Golgi network; homolog of the sigma subunit of the mammalian clathrin AP-1 complex

YAL026C	DRS2	ATP8A2	Aminophospholipid translocase (flippase) that maintains membrane lipid asymmetry in post-Golgi secretory vessicles; localizes to the trans-Golgi network; contributes to clathrin-coated vesicle formation and endocytosis; type 4 P-type ATPase
YER031C	YPT31	RAB11A	GTPase of the Ypt/Rab family, involved in the exocytic pathway; mediates intra-Golgi traffic or the budding of post-Golgi vesicles from the trans-Golgi
YPL227C	ALG5	ALG5p/ALG5	UDP-glucose:dolichyl-phosphate glucosyltransferase, involved in asparagine-linked glycosylation in the endoplasmic reticulum
YGR063C	SPT4	SUPT4H1	Protein that forms a complex with Spt5p and mediates both activation and inhibition of transcription elongation, and plays a role in pre-mRNA processing; in addition, Spt4p is involved in kinetochore function and gene silencing
YMR077C	VPS20	CHMP6	Myristoylated subunit of ESCRTIII, the endosomal sorting complex required for transport of transmembrane proteins into the multivesicular body pathway to the lysosomal/vacuolar lumen; cytoplasmic protein recruited to endosomal membranes
YJR102C	VPS25	VPS25	Component of the ESCRT-II complex, which is involved in ubiquitin-dependent sorting of proteins into the endosome
YNL298W	CLA4	PAK2	Cdc42p activated signal transducing kinase of the PAK (p21-activated kinase) family, involved in septin ring assembly and cytokinesis; directly phosphorylates septins Cdc3p and Cdc10p; other yeast PAK family members are Ste20p and Skm1p
YNL325C	Fig4	KIAA0274	Protein required for efficient mating, member of a family of eukaryotic proteins that contain a domain homologous to Sac1p
YBL078C	ATG8	LC3	Biological marker for autophagy

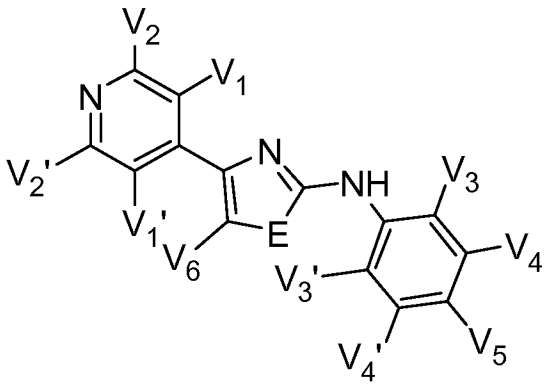
[0444] All of the above-cited references and publications are incorporated by reference herein in their entireties.

[0445] Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, numerous equivalents to the specific method

and reagents described herein. Such equivalents are considered to be within the scope of this invention and are covered by the following claims.

What is Claimed is:

1. A compound of Formula II:



Formula II

or a pharmaceutically acceptable salt, derivative, or prodrug thereof, wherein:

E is S, O, or N-V_7;

V_3, V_3', V_4', and V_5 are all hydrogen;

V_1, V_1', V_2, V_2', V_4, V_6, and V_7 are independently hydrogen, halo, R, OH, OR, OC(O)H, OC(O)R, $OC(O)NH_2$, OC(O)NHR, OC(O)NRR, $OP(O)(OH)_2$, $OP(O)(OR)_2$, NO_2, NH_2, NHR, NRR, $N^+(-O^-)RR$, NHC(O)H, NHC(O)R, NRC(O)R, $NHC(O)NH_2$, NHC(O)NRR, NRC(O)NHR, $N^2C(O)NHR$, SH, SR, S(O)H, S(O)R, SO_2R, SO_2NH_2, SO_2NHR, SO_2NRR, CF_3, CN, CO_2H, CO_2R, CHO, C(O)R, $C(O)NH_2$, C(O)NHR, C(O)NRR, $CONHSO_2H$, $C(O)NHSO_2R$, $C(O)NRSO_2R$, cyclic C_3-C_7 alkylamino, imidazolyl, piperazinyl, morpholinyl, piperidinyl, azepanyl, pyrrolidinyl or azetidinyl;

wherein each imidazolyl, piperazinyl, morpholinyl, piperidinyl, azepanyl, pyrrolidinyl and azetidinyl is optionally and independently substituted by one or more R^1, halo, OH, OR^1, $OC(O)R^1$, $OC(O)NH_2$, $OC(O)NHR^1$, $OC(O)NR^1R^1$, $OP(O)(OH)_2$, $OP(O)(OR^1)_2$, NO_2, NH_2, NHR^1, NR^1R^1, $N^+(-O^-)R^1R^1$, NHC(O)H, $NHC(O)R^1$, $NR^1C(O)R^1$, $NHC(O)NH_2$, $NHC(O)NR^1R^1$, $NR^1C(O)NHR^1$, SH, SR^1, S(O)H, $S(O)R^1$, SO_2R^1, SO_2NH_2, SO_2NHR^1, $SO_2NR^1R^1$, CF_3, CN, CO_2H, CO_2R^1, CHO, $C(O)R^1$, $C(O)NH_2$, $C(O)NHR^1$, $C(O)NR^1R^1$, $CONHSO_2H$, $C(O)NHSO_2R^1$ or $C(O)NR^1SO_2R^1$;

and wherein V_1 and V_2, taken together with the atoms to which they are attached, optionally form a cyclic structure having from 4 to 8 atoms in the ring;

each R is independently C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cyclic alkyl, aryl, aralkyl, heteroaryl, or heteroaralkyl, and is optionally and independently substituted with halo, OH, R^1, OR^1, $OC(O)R^1$, $OC(O)NH_2$, $OC(O)NHR^1$, $OC(O)NR^1R^1$, $OP(O)(OH)_2$, $OP(O)(OR^1)_2$, NO_2, NH_2, NHR^1, NR^1R^1, $N^+(-O^-)R^1R^1$, NHC(O)H, $NHC(O)R^1$, $NR^1C(O)R^1$, $NHC(O)NH_2$, $NHC(O)NR^1R^1$, $NR^1C(O)NHR^1$, SH, SR^1, S(O)H, $S(O)R^1$, SO_2R^1, SO_2NH_2, SO_2NHR^1, $SO_2NR^1R^1$, CF_3, CN, CO_2H, CO_2R^1, CHO, $C(O)R^1$, $C(O)NH_2$, $C(O)NHR^1$, $C(O)NR^1R^1$, $C(O)NHSO_2R^1$, $C(O)NR^1SO_2R^1$, cyclic C_3-C_7 alkylamino, imidazolyl, piperazinyl, morpholinyl, piperidinyl, azepanyl, pyrrolidinyl, or azetidinyl;

wherein each imidazolyl, piperazinyl, morpholinyl, piperidinyl, azepanyl, pyrrolidinyl and azetidinyl is optionally and independently substituted with one or more R^1, halo, OH, OR^1, $OC(O)R^1$, $OC(O)NH_2$, $OC(O)NHR^1$, $OC(O)NR^1R^1$, $OP(O)(OH)_2$, $OP(O)(OR^1)_2$, NO_2, NH_2, NHR^1, NR^1R^1, $N^+(-O^-)R^1R^1$, NHC(O)H, $NHC(O)R^1$, $NR^1C(O)R^1$, $NHC(O)NH_2$, $NHC(O)NR^1R^1$, $NR^1C(O)NHR^1$, SH, SR^1, S(O)H, $S(O)R^1$, SO_2R^1, SO_2NH_2, SO_2NHR^1, $SO_2NR^1R^1$, CF_3, CN, CO_2H, CO_2R^1, CHO, $C(O)R^1$, $C(O)NH_2$, $C(O)NHR^1$, $C(O)NR^1R^1$, $CONHSO_2H$, $C(O)NHSO_2R^1$ or $C(O)NR^1SO_2R^1$;

and wherein each heteroaryl group contains one or more heteroatoms in its ring system, independently selected from O, N or S;

each R^1 is independently C_{1-6} alkyl or C_{2-6} alkenyl, optionally and independently substituted with halo, OH, OR^2, $OC(O)R^2$, $OC(O)NH_2$, $OC(O)NHR^2$, $OC(O)NR^2R^2$, $OP(O)(OH)_2$, $OP(O)(OR^2)_2$, NO_2, NH_2, NHR^2, NR^2R^2, $N^+(-O^-)R^2R^2$, $NHC(O)R^2$, $NR^2C(O)R^2$, $NHC(O)NH_2$, $NHC(O)NR^2R^2$, $NR^2C(O)NHR^2$, SH, SR^2, S(O)H, $S(O)R^2$, SO_2R^2, SO_2NH_2, SO_2NHR^2, $SO_2NR^2R^2$, CF_3, CN, CO_2H, CO_2R^2, CHO, $C(O)R^2$, $C(O)NH_2$, $C(O)NHR^2$, $C(O)NR^2R^2$, $C(O)NHSO_2R^2$, $C(O)NR^2SO_2R^2$, cyclic C_3-C_7 alkylamino, imidazolyl, piperazinyl, morpholinyl, piperidinyl, azepanyl, pyrrolidinyl or azetidinyl;

wherein each imidazolyl, piperazinyl, morpholinyl, piperidinyl, azepanyl, pyrrolidinyl and azetidinyl is optionally and independently substituted with one or more R^2, halo, OH, OR^2, $OC(O)R^2$, $OC(O)NH_2$, $OC(O)NHR^2$, $OC(O)NR^2R^2$, $OP(O)(OH)_2$, $OP(O)(OR^2)_2$, NO_2, NH_2, NHR^2, NR^2R^2, $N^+(-O^-)R^2R^2$, NHC(O)H,

$NHC(O)R^2$, $NR^2C(O)R^2$, $NHC(O)NH_2$, $NHC(O)NR^2R^2$, $NR^2C(O)NHR^2$, SH, SR^2, S(O)H, $S(O)R^2$, SO_2R^2, SO_2NH_2, SO_2NHR^2, $SO_2NR^2R^2$, CF_3, CN, CO_2H, CO_2R^2, CHO, $C(O)R^2$, $C(O)NH_2$, $C(O)NHR^2$, $C(O)NR^2R^2$, $CONHSO_2H$, $C(O)NHSO_2R^2$ or $C(O)NR^2SO_2R^2$;

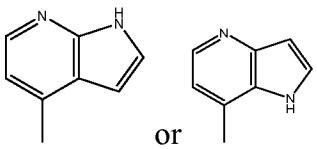
each R^2 is independently C_{1-6} alkyl, C_{2-6} alkenyl, OH, OMe, NO_2, NH_2, CF_3, CN, CO_2H or SH;

provided that V_1, V_1', V_2, V_2', V_4, V_6, and V_7 are not all hydrogen; and

when E is S; V_1, V_1', V_2', and V_6 are all hydrogen; and V_2 is Cl; then V_4 is not Cl; and

when E is S and V_1, V_1', V_2, V_2', and V_6 are all hydrogen; then V_4 is not COOH, $COOCH_3$, $C(O)CH_3$, CF_3, CH_3, OH, OCH_3, SCH_3, CN, O-phenyl, Cl, Br, or NO_2; and

when E is S and V_1', V_2', V_4, and V_6 are all hydrogen; then V_1 and V_2, taken together with the ring to which they are attached, do not form



.

2. The compound of claim 1, wherein V_4 is hydrogen; halo; R; OH; OR; CF_3; NO_2; NH_2; NHR; NRR; $OP(O)(OH)_2$; or $OP(O)(OR)_2$.

3. The compound of claim 1, wherein V_4 is hydrogen; halo; C_{1-6} alkyl, optionally substituted with OH, NH_2, or $N(CH_3)_2$; OH; O-C_{1-6} alkyl, optionally substituted with OH, NH_2, or $N(CH_3)_2$; CF_3; NO_2; NH_2; or $OP(O)(OH)_2$.

4. The compound of claim 1, wherein V_6 is hydrogen; R; CHO; CO_2R; $C(O)NH_2$; C(O)NHR; or C(O)NRR.

5. The compound of claim 1, wherein V_6 is hydrogen; C_{1-6} alkyl or C_{2-4} alkenyl, optionally substituted with OH, OR^1, CO_2R^1, NH_2, NHR^1, or NR^1R^1; CHO; or CO_2R.

6. The compound of claim 1, wherein V_6 is hydrogen.

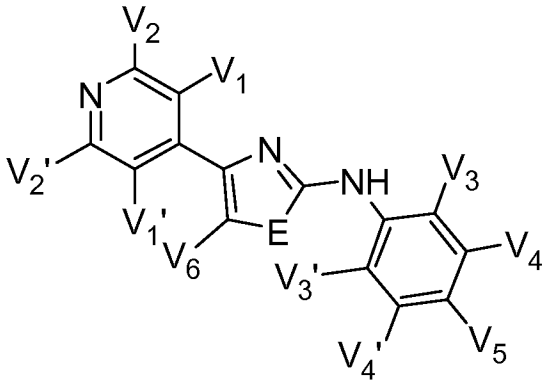
7. The compound of claim 1, wherein V_1 and V_2 are independently hydrogen, halo, R, OH, OR, CF_3, NO_2, NH_2, NHR, NRR, or, taken together with the atoms to which they are attached, form a 5- or 6-membered ring structure.

8. The compound of any one of claims 1-6, wherein
V_1, V_1', V_2, V_2' are all hydrogen.

9. The compound of any one of claims 1-8, wherein
E is S or O.

10. The compound of claim 9, wherein
E is S.

11. A compound of Formula II:



Formula II

or a pharmaceutically acceptable salt, derivative, or prodrug thereof, wherein:

E is S, O, or N-V_7;

V_5 and V_6 are both hydrogen;

V_1, V_1', V_2, V_2', V_3, V_3', V_4, V_4', and V_7 are independently hydrogen, halo, R, OH, OR, OC(O)H, OC(O)R, $OC(O)NH_2$, OC(O)NHR, OC(O)NRR, $OP(O)(OH)_2$, $OP(O)(OR)_2$, NO_2, NH_2, NHR, NRR, $N^+(-O^-)RR$, NHC(O)H, NHC(O)R, NRC(O)R, $NHC(O)NH_2$, NHC(O)NRR, NRC(O)NHR, $N^2C(O)NHR$, SH, SR, S(O)H, S(O)R, SO_2R, SO_2NH_2, SO_2NHR, SO_2NRR, CF_3, CN, CO_2H,

CO_2R, CHO, C(O)R, $C(O)NH_2$, C(O)NHR, C(O)NRR, $CONHSO_2H$, $C(O)NHSO_2R$, $C(O)NRSO_2R$, cyclic C_3-C_7 alkylamino, imidazolyl, piperazinyl, morpholinyl, piperidinyl, azepanyl, pyrrolidinyl or azetidinyl;

wherein each imidazolyl, piperazinyl, morpholinyl, piperidinyl, azepanyl, pyrrolidinyl and azetidinyl is optionally and independently substituted by one or more R^1, halo, OH, OR^1, $OC(O)R^1$, $OC(O)NH_2$, $OC(O)NHR^1$, $OC(O)NR^1R^1$, $OP(O)(OH)_2$, $OP(O)(OR^1)_2$, NO_2, NH_2, NHR^1, NR^1R^1, $N^+(-O^-)R^1R^1$, NHC(O)H, $NHC(O)R^1$, $NR^1C(O)R^1$, $NHC(O)NH_2$, $NHC(O)NR^1R^1$, $NR^1C(O)NHR^1$, SH, SR^1, S(O)H, $S(O)R^1$, SO_2R^1, SO_2NH_2, SO_2NHR^1, $SO_2NR^1R^1$, CF_3, CN, CO_2H, CO_2R^1, CHO, $C(O)R^1$, $C(O)NH_2$, $C(O)NHR^1$, $C(O)NR^1R^1$, $CONHSO_2H$, $C(O)NHSO_2R^1$ or $C(O)NR^1SO_2R^1$;

and wherein groups V_1 and V_2 and groups V_3 and V_4, taken together with the atoms to which they are attached, optionally and independently form a cyclic structure having from 4 to 8 atoms in the ring;

each R is independently C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cyclic alkyl, aryl, aralkyl, heteroaryl, or heteroaralkyl, and is optionally and independently substituted with halo, OH, R^1, OR^1, $OC(O)R^1$, $OC(O)NH_2$, $OC(O)NHR^1$, $OC(O)NR^1R^1$, $OP(O)(OH)_2$, $OP(O)(OR^1)_2$, NO_2, NH_2, NHR^1, NR^1R^1, $N^+(-O^-)R^1R^1$, NHC(O)H, $NHC(O)R^1$, $NR^1C(O)R^1$, $NHC(O)NH_2$, $NHC(O)NR^1R^1$, $NR^1C(O)NHR^1$, SH, SR^1, S(O)H, $S(O)R^1$, SO_2R^1, SO_2NH_2, SO_2NHR^1, $SO_2NR^1R^1$, CF_3, CN, CO_2H, CO_2R^1, CHO, $C(O)R^1$, $C(O)NH_2$, $C(O)NHR^1$, $C(O)NR^1R^1$, $C(O)NHSO_2R^1$, $C(O)NR^1SO_2R^1$, cyclic C_3-C_7 alkylamino, imidazolyl, piperazinyl, morpholinyl, piperidinyl, azepanyl, pyrrolidinyl, or azetidinyl;

wherein each imidazolyl, piperazinyl, morpholinyl, piperidinyl, azepanyl, pyrrolidinyl and azetidinyl is optionally and independently substituted with one or more R^1, halo, OH, OR^1, $OC(O)R^1$, $OC(O)NH_2$, $OC(O)NHR^1$, $OC(O)NR^1R^1$, $OP(O)(OH)_2$, $OP(O)(OR^1)_2$, NO_2, NH_2, NHR^1, NR^1R^1, $N^+(-O^-)R^1R^1$, NHC(O)H, $NHC(O)R^1$, $NR^1C(O)R^1$, $NHC(O)NH_2$, $NHC(O)NR^1R^1$, $NR^1C(O)NHR^1$, SH, SR^1, S(O)H, $S(O)R^1$, SO_2R^1, SO_2NH_2, SO_2NHR^1, $SO_2NR^1R^1$, CF_3, CN, CO_2H, CO_2R^1, CHO, $C(O)R^1$, $C(O)NH_2$, $C(O)NHR^1$, $C(O)NR^1R^1$, $CONHSO_2H$, $C(O)NHSO_2R^1$ or $C(O)NR^1SO_2R^1$;

and wherein each heteroaryl group contains one or more heteroatoms in its ring system, independently selected from O, N or S;

each R^1 is independently C_{1-6} alkyl or C_{2-6} alkenyl, optionally and independently substituted with halo, OH, OR^2, $OC(O)R^2$, $OC(O)NH_2$, $OC(O)NHR^2$, $OC(O)NR^2R^2$, $OP(O)(OH)_2$, $OP(O)(OR^2)_2$, NO_2, NH_2, NHR^2, NR^2R^2, $N^+(-O^-)R^2R^2$, $NHC(O)R^2$, $NR^2C(O)R^2$, $NHC(O)NH_2$, $NHC(O)NR^2R^2$, $NR^2C(O)NHR^2$, SH, SR^2, S(O)H, $S(O)R^2$, SO_2R^2, SO_2NH_2, SO_2NHR^2, $SO_2NR^2R^2$, CF_3, CN, CO_2H, CO_2R^2, CHO, $C(O)R^2$, $C(O)NH_2$, $C(O)NHR^2$, $C(O)NR^2R^2$, $C(O)NHSO_2R^2$, $C(O)NR^2SO_2R^2$, cyclic C_3-C_7 alkylamino, imidazolyl, piperazinyl, morpholinyl, piperidinyl, azepanyl, pyrrolidinyl or azetidinyl;

wherein each imidazolyl, piperazinyl, morpholinyl, piperidinyl, azepanyl, pyrrolidinyl and azetidinyl is optionally and independently substituted with one or more R^2, halo, OH, OR^2, $OC(O)R^2$, $OC(O)NH_2$, $OC(O)NHR^2$, $OC(O)NR^2R^2$, $OP(O)(OH)_2$, $OP(O)(OR^2)_2$, NO_2, NH_2, NHR^2, NR^2R^2, $N^+(-O^-)R^2R^2$, NHC(O)H, $NHC(O)R^2$, $NR^2C(O)R^2$, $NHC(O)NH_2$, $NHC(O)NR^2R^2$, $NR^2C(O)NHR^2$, SH, SR^2, S(O)H, $S(O)R^2$, SO_2R^2, SO_2NH_2, SO_2NHR^2, $SO_2NR^2R^2$, CF_3, CN, CO_2H, CO_2R^2, CHO, $C(O)R^2$, $C(O)NH_2$, $C(O)NHR^2$, $C(O)NR^2R^2$, $CONHSO_2H$, $C(O)NHSO_2R^2$ or $C(O)NR^2SO_2R^2$;

each R^2 is independently C_{1-6} alkyl, C_{2-6} alkenyl, OH, OMe, NO_2, NH_2, CF_3, CN, CO_2H or SH;

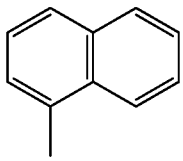
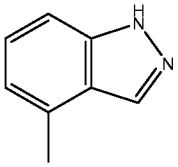
provided that V_1, V_1', V_2, V_2', V_3, V_3', V_4, V_4', and V_7 are not all hydrogen; and

when E is S; V_1, V_1', and V_2' are all hydrogen; and V_2 is Cl; then V_3 is not CH_3 and V_4 is not Cl; and

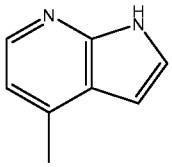
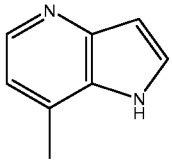
when E is S and V_3' and V_4 are both hydrogen, then either V_3 or V_4' is also hydrogen; and

when E is S and V_1, V_1', V_2, V_2', V_3, V_3', and V_4' are all hydrogen, then V_4 is not COOH, $COOCH_3$, $C(O)CH_3$, CF_3, CH_3, OH, OCH_3, SCH_3, CN, O-phenyl, Cl, Br, or NO_2; and

when E is S and V_1, V_1', V_2, V_2', V_3', V_4, and V_4' are all hydrogen, then V_3 is not CH_3, CH_2CH_3, F, Cl, NO_2, CF_3, OCH_3, OCH_2CH_3, or a substituted 1,4-dihydropyridyl ring; and

when E is S and V_1, V_1', V_2, V_2', V_3', and V_4' are all hydrogen; then when V_3 is Cl, V_4 is not Cl; when V_3 is CH_3, V_4 is not Cl; and V_3 and V_4, taken together with the ring to which they are attached, do not form  or  ; and

when E is S and V_1', V_2', V_3, V_3', V_4, and V_4' are all hydrogen, then V_1 and V_2, taken together with the ring to which they are attached, do not form

 or  ; and

when V_3 and V_3' are both hydrogen, then V_4 and V_4' are not both CH_3.

12. The compound of claim 11, wherein V_3 and V_4 are independently hydrogen; halo; R; OH; OR; CF_3; NO_2; NH_2; NHR; NRR; $OP(O)(OH)_2$; $OP(O)(OR)_2$; or, taken together with the atoms to which they are attached, form a 5- or 6-membered ring.

13. The compound of claim 11, wherein V_3 and V_4 are independently hydrogen; halo; C_{1-6} alkyl, optionally substituted with OH, NH_2, or $N(CH_3)_2$; OH; O-C_{1-6} alkyl, optionally substituted with OH, NH_2, or $N(CH_3)_2$; CF_3; NO_2; NH_2; or $OP(O)(OH)_2$.

14. The compound of claim 11, wherein V_1 and V_2 are independently hydrogen, halo, R, OH, OR, CF_3, NO_2, NH_2, NHR, NRR, or, taken together with the atoms to which they are attached, form a 5- or 6-membered ring structure.

15. The compound of any one of claims 11-13, wherein

V_1, V_1', V_2, V_2' are all hydrogen.

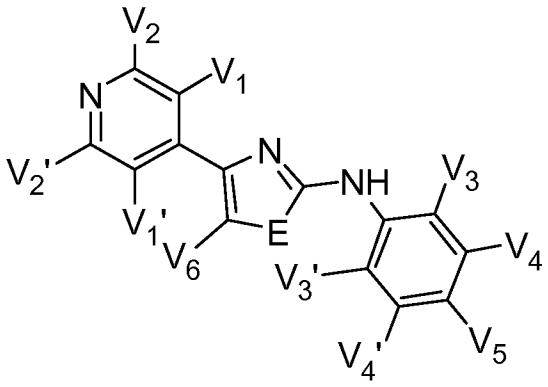
16. The compound of any one of claims 11-15, wherein

E is S or O.

17. The compound of claim 16, wherein

E is S.

18. A compound of Formula II:



Formula II

or a pharmaceutically acceptable salt, derivative, or prodrug thereof, wherein:

E is S, O, or N-V_7;

V_3' and V_4' are both hydrogen;

V_1, V_1', V_2, V_2', V_3, V_4, V_5, V_6, and V_7 are independently hydrogen, halo, R, OH, OR, OC(O)H, OC(O)R, $OC(O)NH_2$, OC(O)NHR, OC(O)NRR, $OP(O)(OH)_2$, $OP(O)(OR)_2$, NO_2, NH_2, NHR, NRR, $N^+(-O^-)RR$, NHC(O)H, NHC(O)R, NRC(O)R, $NHC(O)NH_2$, NHC(O)NRR, NRC(O)NHR, $N^2C(O)NHR$, SH, SR, S(O)H, S(O)R, SO_2R, SO_2NH_2, SO_2NHR, SO_2NRR, CF_3, CN, CO_2H, CO_2R, CHO, C(O)R, $C(O)NH_2$, C(O)NHR, C(O)NRR, $CONHSO_2H$, $C(O)NHSO_2R$, $C(O)NRSO_2R$, cyclic C_3-C_7 alkylamino, imidazolyl, piperazinyl, morpholinyl, piperidinyl, azepanyl, pyrrolidinyl or azetidinyl;

wherein each imidazolyl, piperazinyl, morpholinyl, piperidinyl, azepanyl, pyrrolidinyl and azetidinyl is optionally and independently substituted by one or more R^1, halo, OH, OR^1, $OC(O)R^1$, $OC(O)NH_2$, $OC(O)NHR^1$, $OC(O)NR^1R^1$, $OP(O)(OH)_2$, $OP(O)(OR^1)_2$, NO_2, NH_2, NHR^1, NR^1R^1, $N^+(-O^-)R^1R^1$, NHC(O)H, $NHC(O)R^1$, $NR^1C(O)R^1$, $NHC(O)NH_2$, $NHC(O)NR^1R^1$, $NR^1C(O)NHR^1$, SH, SR^1,

S(O)H, S(O)R^1, SO_2R^1, SO_2NH_2, SO_2NHR^1, $SO_2NR^1R^1$, CF_3, CN, CO_2H, CO_2R^1, CHO, C(O)R^1, $C(O)NH_2$, $C(O)NHR^1$, $C(O)NR^1R^1$, $CONHSO_2H$, $C(O)NHSO_2R^1$ or $C(O)NR^1SO_2R^1$;

and wherein groups V_1 and V_2, groups V_3 and V_4, and groups V_4 and V_5, taken together with the atoms to which they are attached, optionally and independently form a cyclic structure having from 4 to 8 atoms in the ring;

each R is independently C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cyclic alkyl, aryl, aralkyl, heteroaryl, or heteroaralkyl, and is optionally and independently substituted with halo, OH, R^1, OR^1, $OC(O)R^1$, $OC(O)NH_2$, $OC(O)NHR^1$, $OC(O)NR^1R^1$, $OP(O)(OH)_2$, $OP(O)(OR^1)_2$, NO_2, NH_2, NHR^1, NR^1R^1, $N^+(-O^-)R^1R^1$, NHC(O)H, $NHC(O)R^1$, $NR^1C(O)R^1$, $NHC(O)NH_2$, $NHC(O)NR^1R^1$, $NR^1C(O)NHR^1$, SH, SR^1, S(O)H, $S(O)R^1$, SO_2R^1, SO_2NH_2, SO_2NHR^1, $SO_2NR^1R^1$, CF_3, CN, CO_2H, CO_2R^1, CHO, $C(O)R^1$, $C(O)NH_2$, $C(O)NHR^1$, $C(O)NR^1R^1$, $C(O)NHSO_2R^1$, $C(O)NR^1SO_2R^1$, cyclic C_3-C_7 alkylamino, imidazolyl, piperazinyl, morpholinyl, piperidinyl, azepanyl, pyrrolidinyl, or azetidinyl;

wherein each imidazolyl, piperazinyl, morpholinyl, piperidinyl, azepanyl, pyrrolidinyl and azetidinyl is optionally and independently substituted with one or more R^1, halo, OH, OR^1, $OC(O)R^1$, $OC(O)NH_2$, $OC(O)NHR^1$, $OC(O)NR^1R^1$, $OP(O)(OH)_2$, $OP(O)(OR^1)_2$, NO_2, NH_2, NHR^1, NR^1R^1, $N^+(-O^-)R^1R^1$, NHC(O)H, $NHC(O)R^1$, $NR^1C(O)R^1$, $NHC(O)NH_2$, $NHC(O)NR^1R^1$, $NR^1C(O)NHR^1$, SH, SR^1, S(O)H, $S(O)R^1$, SO_2R^1, SO_2NH_2, SO_2NHR^1, $SO_2NR^1R^1$, CF_3, CN, CO_2H, CO_2R^1, CHO, $C(O)R^1$, $C(O)NH_2$, $C(O)NHR^1$, $C(O)NR^1R^1$, $CONHSO_2H$, $C(O)NHSO_2R^1$ or $C(O)NR^1SO_2R^1$;

and wherein each heteroaryl group contains one or more heteroatoms in its ring system, independently selected from O, N or S;

each R^1 is independently C_{1-6} alkyl or C_{2-6} alkenyl, optionally and independently substituted with halo, OH, OR^2, $OC(O)R^2$, $OC(O)NH_2$, $OC(O)NHR^2$, $OC(O)NR^2R^2$, $OP(O)(OH)_2$, $OP(O)(OR^2)_2$, NO_2, NH_2, NHR^2, NR^2R^2, $N^+(-O^-)R^2R^2$, $NHC(O)R^2$, $NR^2C(O)R^2$, $NHC(O)NH_2$, $NHC(O)NR^2R^2$, $NR^2C(O)NHR^2$, SH, SR^2, S(O)H, $S(O)R^2$, SO_2R^2, SO_2NH_2, SO_2NHR^2, $SO_2NR^2R^2$, CF_3, CN, CO_2H, CO_2R^2, CHO, $C(O)R^2$, $C(O)NH_2$, $C(O)NHR^2$, $C(O)NR^2R^2$,

$C(O)NHSO_2R^2$, $C(O)NR^2SO_2R^2$, cyclic C_3-C_7 alkylamino, imidazolyl, piperazinyl, morpholinyl, piperidinyl, azepanyl, pyrrolidinyl or azetidinyl;

wherein each imidazolyl, piperazinyl, morpholinyl, piperidinyl, azepanyl, pyrrolidinyl and azetidinyl is optionally and independently substituted with one or more R^2, halo, OH, OR^2, $OC(O)R^2$, $OC(O)NH_2$, $OC(O)NHR^2$, $OC(O)NR^2R^2$, $OP(O)(OH)_2$, $OP(O)(OR^2)_2$, NO_2, NH_2, NHR^2, NR^2R^2, $N^+(-O^-)R^2R^2$, NHC(O)H, $NHC(O)R^2$, $NR^2C(O)R^2$, $NHC(O)NH_2$, $NHC(O)NR^2R^2$, $NR^2C(O)NHR^2$, SH, SR^2, S(O)H, $S(O)R^2$, SO_2R^2, SO_2NH_2, SO_2NHR^2, $SO_2NR^2R^2$, CF_3, CN, CO_2H, CO_2R^2, CHO, $C(O)R^2$, $C(O)NH_2$, $C(O)NHR^2$, $C(O)NR^2R^2$, $CONHSO_2H$, $C(O)NHSO_2R^2$ or $C(O)NR^2SO_2R^2$;

each R^2 is independently C_{1-6} alkyl, C_{2-6} alkenyl, OH, OMe, NO_2, NH_2, CF_3, CN, CO_2H or SH;

provided that V_1, V_1', V_2, V_2', V_3, V_4, V_5, V_6, and V_7 are not all hydrogen; and

when E is S; V_1, V_1', and V_2' are all hydrogen; and V_2 is Cl; then V_3 is not CH_3 when V_4 is Cl; and V_5 is not CH_3, OCH_3, or Cl; and

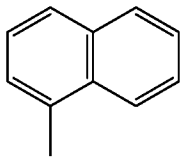
when E is S; V_1, V_1', and V_2' are all hydrogen; V_2 is H or NH_2; and V_4 is CF_3; then V_5 is not F; and

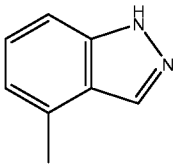
when E is S and V_1, V_1', V_2, V_2', V_3 and V_5 are all hydrogen, then V_4 is not COOH, $COOCH_3$, $C(O)CH_3$, CF_3, CH_3, OH, OCH_3, SCH_3, CN, O-phenyl, Cl, Br, or NO_2; and

when E is S and V_1, V_1', V_2, V_2', V_4 and V_5 are all hydrogen, then V_3 is not CH_3, CH_2CH_3, F, Cl, NO_2, CF_3, OCH_3, OCH_2CH_3, or a substituted 1,4-dihydropyridyl ring; and

when E is S and V_1, V_1', V_2, V_2', V_3 and V_4 are all hydrogen, then V_5 is not CH_3, CH_2CH_3, $C(O)CH_3$, CF_3, $S(O)_2$-NH_2, $S(O)_2$-NHR, $N(CH_3)_2$, $N(CH_2CH_3)_2$, N(*i*-Pr)phenyl, NO_2, OCH_2CH_3, NH-$C(O)CH_3$, NH_2, COOH, F, Cl, Br, I, OH, OCH_3, O-phenyl, O-C_{7-8}-alkyl, or $C(O)NHC(i\text{-Bu})C(O)NHCH_2CN$; and

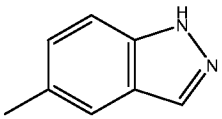
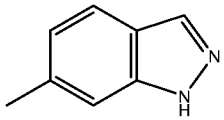
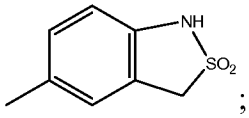
when E is S and V_1, V_1', V_2, V_2', and V_5 are all hydrogen; then when V_3 is Cl, V_4 is not Cl; when V_3 is CH_3, then V_4 is not Cl; and V_3 and V_4, taken together

with the ring to which they are attached, do not form  or

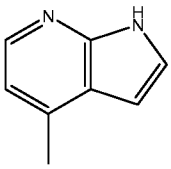
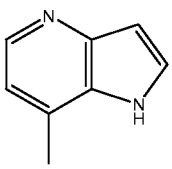


; and

when E is S and V_1, V_1', V_2, V_2', and V_3 are all hydrogen; then when V_5 is O-C_{5-8}-alkyl, V_4 is not hydrogen, F, or CF_3; when V_5 is CH_3, V_4 is not CH_3; and V_4 and V_5, taken together with the ring to which they are attached, do not form

, , or ;

when E is S and V_1', V_2', V_3, V_4, and V_5 are all hydrogen, then V_1 and V_2, taken together with the ring to which they are attached, do not form

 or .

19. The compound of claim 18, wherein V_3, V_4, and V_5 are independently hydrogen; halo; R; OH; OR; CF_3; NO_2; NH_2; NHR; NRR; $OP(O)(OH)_2$; or $OP(O)(OR)_2$; and groups V_3 and V_4 and groups V_4 and V_5, taken together with the atoms to which they are attached, optionally and independently form a 5- or 6-membered ring structure.

20. The compound of claim 18, wherein V_3, V_4, and V_5 are independently hydrogen; halo; C_{1-6} alkyl, optionally substituted with OH, NH_2, or $N(CH_3)_2$; OH; O-C_{1-6} alkyl, optionally substituted with OH, NH_2, or $N(CH_3)_2$; CF_3; NO_2; NH_2; or $OP(O)(OH)_2$.

21. The compound of claim 18, wherein V_1 and V_2 are independently hydrogen, halo, R, OH, OR, CF_3, NO_2, NH_2, NHR, NRR, or, taken together with the atoms to which they are attached, form a 5- or 6-membered ring structure.

22. The compound of any one of claims 18-20, wherein

V_1, V_1', V_2, V_2' are all hydrogen.

23. The compound of any one of claims 18-22, wherein

E is S or O.

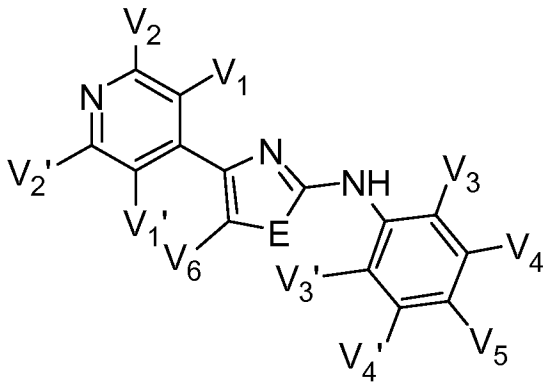
24. The compound of claim 23, wherein

E is S.

25. A pharmaceutical composition comprising a compound of any one of claims 1-24 and a pharmacuetically acceptable carrier.

26. The pharmaceutical composition of claim 25, further comprising one or more chemotherapeutic agents.

27. A method of treating or preventing a disease, comprising administering to a mammalian host a therapeutically-effective amount of a compound of Formula II or a pharmaceutically acceptable salt, derivative, or prodrug thereof:



Formula II

wherein:

E is S, O, or N-V_7;

V_3, V_3', V_4', and V_5 are all hydrogen;

V_1, V_1', V_2, V_2', V_4, V_6, and V_7 are independently hydrogen, halo, R, OH, OR, OC(O)H, OC(O)R, $OC(O)NH_2$, OC(O)NHR, OC(O)NRR, $OP(O)(OH)_2$,

$OP(O)(OR)_2$, NO_2, NH_2, NHR, NRR, $N^+(-O^-)RR$, NHC(O)H, NHC(O)R, NRC(O)R, $NHC(O)NH_2$, NHC(O)NRR, NRC(O)NHR, $N^2C(O)NHR$, SH, SR, S(O)H, S(O)R, SO_2R, SO_2NH_2, SO_2NHR, SO_2NRR, CF_3, CN, CO_2H, CO_2R, CHO, C(O)R, $C(O)NH_2$, C(O)NHR, C(O)NRR, $CONHSO_2H$, $C(O)NHSO_2R$, $C(O)NRSO_2R$, cyclic C_3-C_7 alkylamino, imidazolyl, piperazinyl, morpholinyl, piperidinyl, azepanyl, pyrrolidinyl or azetidinyl;

wherein each imidazolyl, piperazinyl, morpholinyl, piperidinyl, azepanyl, pyrrolidinyl and azetidinyl is optionally and independently substituted by one or more R^1, halo, OH, OR^1, $OC(O)R^1$, $OC(O)NH_2$, $OC(O)NHR^1$, $OC(O)NR^1R^1$, $OP(O)(OH)_2$, $OP(O)(OR^1)_2$, NO_2, NH_2, NHR^1, NR^1R^1, $N^+(-O^-)R^1R^1$, NHC(O)H, $NHC(O)R^1$, $NR^1C(O)R^1$, $NHC(O)NH_2$, $NHC(O)NR^1R^1$, $NR^1C(O)NHR^1$, SH, SR^1, S(O)H, $S(O)R^1$, SO_2R^1, SO_2NH_2, SO_2NHR^1, $SO_2NR^1R^1$, CF_3, CN, CO_2H, CO_2R^1, CHO, $C(O)R^1$, $C(O)NH_2$, $C(O)NHR^1$, $C(O)NR^1R^1$, $CONHSO_2H$, $C(O)NHSO_2R^1$ or $C(O)NR^1SO_2R^1$;

and wherein V_1 and V_2, taken together with the atoms to which they are attached, optionally form a cyclic structure having from 4 to 8 atoms in the ring;

each R is independently C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cyclic alkyl, aryl, aralkyl, heteroaryl, or heteroaralkyl, and is optionally and independently substituted with halo, OH, R^1, OR^1, $OC(O)R^1$, $OC(O)NH_2$, $OC(O)NHR^1$, $OC(O)NR^1R^1$, $OP(O)(OH)_2$, $OP(O)(OR^1)_2$, NO_2, NH_2, NHR^1, NR^1R^1, $N^+(-O^-)R^1R^1$, NHC(O)H, $NHC(O)R^1$, $NR^1C(O)R^1$, $NHC(O)NH_2$, $NHC(O)NR^1R^1$, $NR^1C(O)NHR^1$, SH, SR^1, S(O)H, $S(O)R^1$, SO_2R^1, SO_2NH_2, SO_2NHR^1, $SO_2NR^1R^1$, CF_3, CN, CO_2H, CO_2R^1, CHO, $C(O)R^1$, $C(O)NH_2$, $C(O)NHR^1$, $C(O)NR^1R^1$, $C(O)NHSO_2R^1$, $C(O)NR^1SO_2R^1$, cyclic C_3-C_7 alkylamino, imidazolyl, piperazinyl, morpholinyl, piperidinyl, azepanyl, pyrrolidinyl, or azetidinyl;

wherein each imidazolyl, piperazinyl, morpholinyl, piperidinyl, azepanyl, pyrrolidinyl and azetidinyl is optionally and independently substituted with one or more R^1, halo, OH, OR^1, $OC(O)R^1$, $OC(O)NH_2$, $OC(O)NHR^1$, $OC(O)NR^1R^1$, $OP(O)(OH)_2$, $OP(O)(OR^1)_2$, NO_2, NH_2, NHR^1, NR^1R^1, $N^+(-O^-)R^1R^1$, NHC(O)H, $NHC(O)R^1$, $NR^1C(O)R^1$, $NHC(O)NH_2$, $NHC(O)NR^1R^1$, $NR^1C(O)NHR^1$, SH, SR^1, S(O)H, $S(O)R^1$, SO_2R^1, SO_2NH_2, SO_2NHR^1, $SO_2NR^1R^1$, CF_3, CN, CO_2H, CO_2R^1,

CHO, $C(O)R^1$, $C(O)NH_2$, $C(O)NHR^1$, $C(O)NR^1R^1$, $CONHSO_2H$, $C(O)NHSO_2R^1$ or $C(O)NR^1SO_2R^1$;

and wherein each heteroaryl group contains one or more heteroatoms in its ring system, independently selected from O, N or S;

each R^1 is independently C_{1-6} alkyl or C_{2-6} alkenyl, optionally and independently substituted with halo, OH, OR^2, $OC(O)R^2$, $OC(O)NH_2$, $OC(O)NHR^2$, $OC(O)NR^2R^2$, $OP(O)(OH)_2$, $OP(O)(OR^2)_2$, NO_2, NH_2, NHR^2, NR^2R^2, $N^+(-O^-)R^2R^2$, $NHC(O)R^2$, $NR^2C(O)R^2$, $NHC(O)NH_2$, $NHC(O)NR^2R^2$, $NR^2C(O)NHR^2$, SH, SR^2, S(O)H, $S(O)R^2$, SO_2R^2, SO_2NH_2, SO_2NHR^2, $SO_2NR^2R^2$, CF_3, CN, CO_2H, CO_2R^2, CHO, $C(O)R^2$, $C(O)NH_2$, $C(O)NHR^2$, $C(O)NR^2R^2$, $C(O)NHSO_2R^2$, $C(O)NR^2SO_2R^2$, cyclic C_3-C_7 alkylamino, imidazolyl, piperazinyl, morpholinyl, piperidinyl, azepanyl, pyrrolidinyl or azetidinyl;

wherein each imidazolyl, piperazinyl, morpholinyl, piperidinyl, azepanyl, pyrrolidinyl and azetidinyl is optionally and independently substituted with one or more R^2, halo, OH, OR^2, $OC(O)R^2$, $OC(O)NH_2$, $OC(O)NHR^2$, $OC(O)NR^2R^2$, $OP(O)(OH)_2$, $OP(O)(OR^2)_2$, NO_2, NH_2, NHR^2, NR^2R^2, $N^+(-O^-)R^2R^2$, NHC(O)H, $NHC(O)R^2$, $NR^2C(O)R^2$, $NHC(O)NH_2$, $NHC(O)NR^2R^2$, $NR^2C(O)NHR^2$, SH, SR^2, S(O)H, $S(O)R^2$, SO_2R^2, SO_2NH_2, SO_2NHR^2, $SO_2NR^2R^2$, CF_3, CN, CO_2H, CO_2R^2, CHO, $C(O)R^2$, $C(O)NH_2$, $C(O)NHR^2$, $C(O)NR^2R^2$, $CONHSO_2H$, $C(O)NHSO_2R^2$ or $C(O)NR^2SO_2R^2$; and

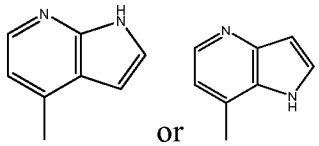
each R^2 is independently C_{1-6} alkyl, C_{2-6} alkenyl, OH, OMe, NO_2, NH_2, CF_3, CN, CO_2H or SH;

provided that V_1, V_1', V_2, V_2', V_4, V_6, and V_7 are not all hydrogen; and

when E is S; V_1, V_1', V_2', and V_6 are all hydrogen; and V_2 is Cl; then V_4 is not Cl; and

when E is S and V_1, V_1', V_2, V_2', and V_6 are all hydrogen; then V_4 is not COOH, $COOCH_3$, $C(O)CH_3$, CF_3, CH_3, OH, OCH_3, SCH_3, CN, O-phenyl, Cl, Br, or NO_2; and

when E is S and V_1', V_2', V_4, and V_6 are all hydrogen; then V_1 and V_2, taken together with the ring to which they are attached, do not form

 or .

28. The method of claim 27, wherein in the compound of Formula II:

V_4 is hydrogen; halo; R; OH; OR; CF_3; NO_2; NH_2; NHR; NRR; $OP(O)(OH)_2$; or $OP(O)(OR)_2$.

29. The method of claim 27, wherein in the compound of Formula II:

V_4 is hydrogen; halo; C_{1-6} alkyl, optionally substituted with OH, NH_2, or $N(CH_3)_2$; OH; O-C_{1-6} alkyl, optionally substituted with OH, NH_2, or $N(CH_3)_2$; CF_3; NO_2; NH_2; or $OP(O)(OH)_2$.

30. The method of claim 27, wherein in the compound of Formula II:

V_6 is hydrogen; R; CHO; CO_2R; $C(O)NH_2$; C(O)NHR; or C(O)NRR.

31. The method of claim 27, wherein in the compound of Formula II:

V_6 is hydrogen; C_{1-6} alkyl or C_{2-4} alkenyl, optionally substituted with OH, OR^1, CO_2R^1, NH_2, NHR^1, or NR^1R^1; CHO; or CO_2R.

32. The method of claim 27, wherein in the compound of Formula II:

V_6 is hydrogen.

33. The method of claim 27, wherein V_1 and V_2 are independently hydrogen, halo, R, OH, OR, CF_3, NO_2, NH_2, NHR, NRR, or, taken together with the atoms to which they are attached, form a 5- or 6-membered ring structure.

34. The method of any one of claims 27-32, wherein in the compound of Formula II:

V_1, V_1', V_2, V_2' are all hydrogen.

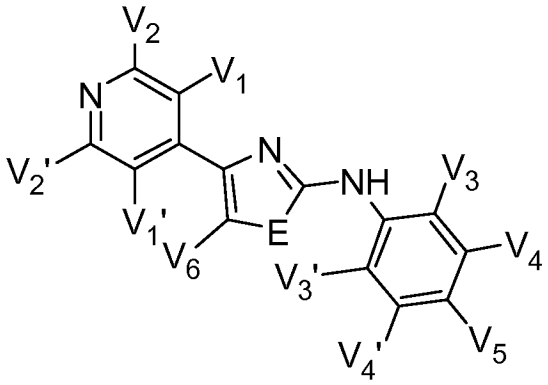
35. The method of any one of claims 27-34, wherein in the compound of Formula II:

E is S or O.

36. The method of claim 35, wherein in the compound of Formula II:

E is S.

37. A method of treating or preventing a disease, comprising administering to a mammalian host a therapeutically-effective amount of a compound of Formula II or a pharmaceutically acceptable salt, derivative, or prodrug thereof:



Formula II

wherein:

E is S, O, or N-V_7;

V_5 and V_6 are both hydrogen;

V_1, V_1', V_2, V_2', V_3, V_3', V_4, V_4', and V_7 are independently hydrogen, halo, R, OH, OR, OC(O)H, OC(O)R, $OC(O)NH_2$, OC(O)NHR, OC(O)NRR, $OP(O)(OH)_2$, $OP(O)(OR)_2$, NO_2, NH_2, NHR, NRR, $N^+(-O^-)RR$, NHC(O)H, NHC(O)R, NRC(O)R, $NHC(O)NH_2$, NHC(O)NRR, NRC(O)NHR, $N^2C(O)NHR$, SH, SR, S(O)H, S(O)R, SO_2R, SO_2NH_2, SO_2NHR, SO_2NRR, CF_3, CN, CO_2H, CO_2R, CHO, C(O)R, $C(O)NH_2$, C(O)NHR, C(O)NRR, $CONHSO_2H$, $C(O)NHSO_2R$, $C(O)NRSO_2R$, cyclic C_3-C_7 alkylamino, imidazolyl, piperazinyl, morpholinyl, piperidinyl, azepanyl, pyrrolidinyl or azetidinyl;

wherein each imidazolyl, piperazinyl, morpholinyl, piperidinyl, azepanyl, pyrrolidinyl and azetidinyl is optionally and independently substituted by one or

more R^1, halo, OH, OR^1, $OC(O)R^1$, $OC(O)NH_2$, $OC(O)NHR^1$, $OC(O)NR^1R^1$, $OP(O)(OH)_2$, $OP(O)(OR^1)_2$, NO_2, NH_2, NHR^1, NR^1R^1, $N^+(-O^-)R^1R^1$, NHC(O)H, $NHC(O)R^1$, $NR^1C(O)R^1$, $NHC(O)NH_2$, $NHC(O)NR^1R^1$, $NR^1C(O)NHR^1$, SH, SR^1, S(O)H, $S(O)R^1$, SO_2R^1, SO_2NH_2, SO_2NHR^1, $SO_2NR^1R^1$, CF_3, CN, CO_2H, CO_2R^1, CHO, $C(O)R^1$, $C(O)NH_2$, $C(O)NHR^1$, $C(O)NR^1R^1$, $CONHSO_2H$, $C(O)NHSO_2R^1$ or $C(O)NR^1SO_2R^1$;

and wherein groups V_1 and V_2 and groups V_3 and V_4, taken together with the atoms to which they are attached, optionally and independently form a cyclic structure having from 4 to 8 atoms in the ring;

each R is independently C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cyclic alkyl, aryl, aralkyl, heteroaryl, or heteroaralkyl, and is optionally and independently substituted with halo, OH, R^1, OR^1, $OC(O)R^1$, $OC(O)NH_2$, $OC(O)NHR^1$, $OC(O)NR^1R^1$, $OP(O)(OH)_2$, $OP(O)(OR^1)_2$, NO_2, NH_2, NHR^1, NR^1R^1, $N^+(-O^-)R^1R^1$, NHC(O)H, $NHC(O)R^1$, $NR^1C(O)R^1$, $NHC(O)NH_2$, $NHC(O)NR^1R^1$, $NR^1C(O)NHR^1$, SH, SR^1, S(O)H, $S(O)R^1$, SO_2R^1, SO_2NH_2, SO_2NHR^1, $SO_2NR^1R^1$, CF_3, CN, CO_2H, CO_2R^1, CHO, $C(O)R^1$, $C(O)NH_2$, $C(O)NHR^1$, $C(O)NR^1R^1$, $C(O)NHSO_2R^1$, $C(O)NR^1SO_2R^1$, cyclic C_3-C_7 alkylamino, imidazolyl, piperazinyl, morpholinyl, piperidinyl, azepanyl, pyrrolidinyl, or azetidinyl;

wherein each imidazolyl, piperazinyl, morpholinyl, piperidinyl, azepanyl, pyrrolidinyl and azetidinyl is optionally and independently substituted with one or more R^1, halo, OH, OR^1, $OC(O)R^1$, $OC(O)NH_2$, $OC(O)NHR^1$, $OC(O)NR^1R^1$, $OP(O)(OH)_2$, $OP(O)(OR^1)_2$, NO_2, NH_2, NHR^1, NR^1R^1, $N^+(-O^-)R^1R^1$, NHC(O)H, $NHC(O)R^1$, $NR^1C(O)R^1$, $NHC(O)NH_2$, $NHC(O)NR^1R^1$, $NR^1C(O)NHR^1$, SH, SR^1, S(O)H, $S(O)R^1$, SO_2R^1, SO_2NH_2, SO_2NHR^1, $SO_2NR^1R^1$, CF_3, CN, CO_2H, CO_2R^1, CHO, $C(O)R^1$, $C(O)NH_2$, $C(O)NHR^1$, $C(O)NR^1R^1$, $CONHSO_2H$, $C(O)NHSO_2R^1$ or $C(O)NR^1SO_2R^1$;

and wherein each heteroaryl group contains one or more heteroatoms in its ring system, independently selected from O, N or S;

each R^1 is independently C_{1-6} alkyl or C_{2-6} alkenyl, optionally and independently substituted with halo, OH, OR^2, $OC(O)R^2$, $OC(O)NH_2$, $OC(O)NHR^2$, $OC(O)NR^2R^2$, $OP(O)(OH)_2$, $OP(O)(OR^2)_2$, NO_2, NH_2, NHR^2,

NR^2R^2, $N^+(-O^-)R^2R^2$, $NHC(O)R^2$, $NR^2C(O)R^2$, $NHC(O)NH_2$, $NHC(O)NR^2R^2$, $NR^2C(O)NHR^2$, SH, SR^2, S(O)H, $S(O)R^2$, SO_2R^2, SO_2NH_2, SO_2NHR^2, $SO_2NR^2R^2$, CF_3, CN, CO_2H, CO_2R^2, CHO, $C(O)R^2$, $C(O)NH_2$, $C(O)NHR^2$, $C(O)NR^2R^2$, $C(O)NHSO_2R^2$, $C(O)NR^2SO_2R^2$, cyclic C_3-C_7 alkylamino, imidazolyl, piperazinyl, morpholinyl, piperidinyl, azepanyl, pyrrolidinyl or azetidinyl;

wherein each imidazolyl, piperazinyl, morpholinyl, piperidinyl, azepanyl, pyrrolidinyl and azetidinyl is optionally and independently substituted with one or more R^2, halo, OH, OR^2, $OC(O)R^2$, $OC(O)NH_2$, $OC(O)NHR^2$, $OC(O)NR^2R^2$, $OP(O)(OH)_2$, $OP(O)(OR^2)_2$, NO_2, NH_2, NHR^2, NR^2R^2, $N^+(-O^-)R^2R^2$, NHC(O)H, $NHC(O)R^2$, $NR^2C(O)R^2$, $NHC(O)NH_2$, $NHC(O)NR^2R^2$, $NR^2C(O)NHR^2$, SH, SR^2, S(O)H, $S(O)R^2$, SO_2R^2, SO_2NH_2, SO_2NHR^2, $SO_2NR^2R^2$, CF_3, CN, CO_2H, CO_2R^2, CHO, $C(O)R^2$, $C(O)NH_2$, $C(O)NHR^2$, $C(O)NR^2R^2$, $CONHSO_2H$, $C(O)NHSO_2R^2$ or $C(O)NR^2SO_2R^2$;

each R^2 is independently C_{1-6} alkyl, C_{2-6} alkenyl, OH, OMe, NO_2, NH_2, CF_3, CN, CO_2H or SH;

provided that V_1, V_1', V_2, V_2', V_3, V_3', V_4, V_4', and V_7 are not all hydrogen; and

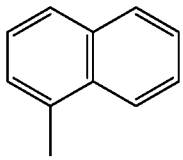
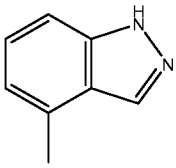
when E is S; V_1, V_1', and V_2' are all hydrogen; and V_2 is Cl; then V_3 is not CH_3 and V_4 is not Cl; and

when E is S and V_3' and V_4 are both hydrogen, then either V_3 or V_4' is also hydrogen; and

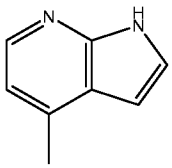
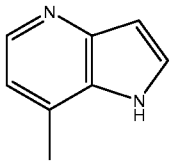
when E is S and V_1, V_1', V_2, V_2', V_3, V_3', and V_4' are all hydrogen, then V_4 is not COOH, $COOCH_3$, $C(O)CH_3$, CF_3, CH_3, OH, OCH_3, SCH_3, CN, O-phenyl, Cl, Br, or NO_2; and

when E is S and V_1, V_1', V_2, V_2', V_3', V_4, and V_4' are all hydrogen, then V_3 is not CH_3, CH_2CH_3, F, Cl, NO_2, CF_3, OCH_3, OCH_2CH_3, or a substituted 1,4-dihydropyridyl ring; and

when E is S and V_1, V_1', V_2, V_2', V_3', and V_4' are all hydrogen; then when V_3 is Cl, V_4 is not Cl; when V_3 is CH_3, V_4 is not Cl; and V_3 and V_4, taken together

with the ring to which they are attached, do not form  or  ; and

when E is S and V_1', V_2', V_3, V_3', V_4, and V_4' are all hydrogen, then V_1 and V_2, taken together with the ring to which they are attached, do not form

 or  ; and

when V_3 and V_3' are both hydrogen, then V_4 and V_4' are not both CH_3.

38. The method of claim 37, wherein V_3 and V_4 are independently hydrogen; halo; R; OH; OR; CF_3; NO_2; NH_2; NHR; NRR; $OP(O)(OH)_2$; $OP(O)(OR)_2$; or, V_3 and V_4, taken together with the atoms to which they are attached, form a 5- or 6-membered ring structure..

39. The method of claim 37, wherein V_3 and V_4 are independently hydrogen; halo; C_{1-6} alkyl, optionally substituted with OH, NH_2, or $N(CH_3)_2$; OH; O-C_{1-6} alkyl, optionally substituted with OH, NH_2, or $N(CH_3)_2$; CF_3; NO_2; NH_2; or $OP(O)(OH)_2$.

40. The method of claim 37, wherein V_1 and V_2 are independently hydrogen, halo, R, OH, OR, CF_3, NO_2, NH_2, NHR, NRR, or, taken together with the atoms to which they are attached, form a 5- or 6-membered ring structure.

41. The method of any one of claims 37-39, wherein

V_1, V_1', V_2, V_2' are all hydrogen.

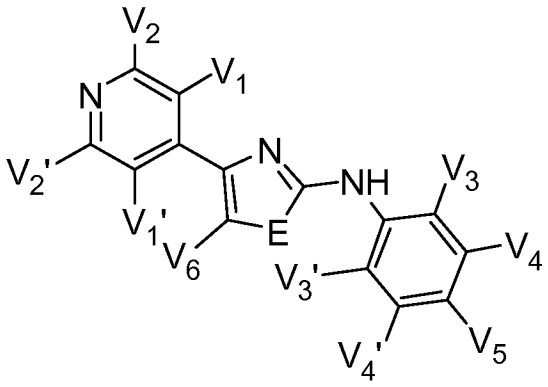
42. The method of any one of claims 37-41, wherein

E is S or O.

43. The method of claim 42, wherein

E is S.

44. A method of treating or preventing a disease, comprising administering to a mammalian host a therapeutically-effective amount of a compound of Formula II or a pharmaceutically acceptable salt, derivative, or prodrug thereof:



Formula II

wherein:

E is S, O, or N-V_7;

V_3' and V_4' are both hydrogen;

V_1, V_1', V_2, V_2', V_3, V_4, V_5, V_6, and V_7 are independently hydrogen, halo, R, OH, OR, OC(O)H, OC(O)R, $OC(O)NH_2$, OC(O)NHR, OC(O)NRR, $OP(O)(OH)_2$, $OP(O)(OR)_2$, NO_2, NH_2, NHR, NRR, $N^+(-O^-)RR$, NHC(O)H, NHC(O)R, NRC(O)R, $NHC(O)NH_2$, NHC(O)NRR, NRC(O)NHR, $N^2C(O)NHR$, SH, SR, S(O)H, S(O)R, SO_2R, SO_2NH_2, SO_2NHR, SO_2NRR, CF_3, CN, CO_2H, CO_2R, CHO, C(O)R, $C(O)NH_2$, C(O)NHR, C(O)NRR, $CONHSO_2H$, $C(O)NHSO_2R$, $C(O)NRSO_2R$, cyclic C_3-C_7 alkylamino, imidazolyl, piperazinyl, morpholinyl, piperidinyl, azepanyl, pyrrolidinyl or azetidinyl;

wherein each imidazolyl, piperazinyl, morpholinyl, piperidinyl, azepanyl, pyrrolidinyl and azetidinyl is optionally and independently substituted by one or more R^1, halo, OH, OR^1, $OC(O)R^1$, $OC(O)NH_2$, $OC(O)NHR^1$, $OC(O)NR^1R^1$, $OP(O)(OH)_2$, $OP(O)(OR^1)_2$, NO_2, NH_2, NHR^1, NR^1R^1, $N^+(-O^-)R^1R^1$, NHC(O)H, $NHC(O)R^1$, $NR^1C(O)R^1$, $NHC(O)NH_2$, $NHC(O)NR^1R^1$, $NR^1C(O)NHR^1$, SH, SR^1,

S(O)H, S(O)R^1, SO_2R^1, SO_2NH_2, SO_2NHR^1, $SO_2NR^1R^1$, CF_3, CN, CO_2H, CO_2R^1, CHO, C(O)R^1, C(O)NH_2, C(O)NHR^1, C(O)NR^1R^1, $CONHSO_2H$, C(O)$NHSO_2R^1$ or C(O)$NR^1SO_2R^1$;

and wherein groups V_1 and V_2, groups V_3 and V_4, and groups V_4 and V_5, taken together with the atoms to which they are attached, optionally and independently form a cyclic structure having from 4 to 8 atoms in the ring;

each R is independently C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cyclic alkyl, aryl, aralkyl, heteroaryl, or heteroaralkyl, and is optionally and independently substituted with halo, OH, R^1, OR^1, OC(O)R^1, OC(O)NH_2, OC(O)NHR^1, OC(O)NR^1R^1, OP(O)$(OH)_2$, OP(O)$(OR^1)_2$, NO_2, NH_2, NHR^1, NR^1R^1, $N^+(-O^-)R^1R^1$, NHC(O)H, NHC(O)R^1, $NR^1C(O)R^1$, NHC(O)NH_2, NHC(O)NR^1R^1, $NR^1C(O)NHR^1$, SH, SR^1, S(O)H, S(O)R^1, SO_2R^1, SO_2NH_2, SO_2NHR^1, $SO_2NR^1R^1$, CF_3, CN, CO_2H, CO_2R^1, CHO, C(O)R^1, C(O)NH_2, C(O)NHR^1, C(O)NR^1R^1, C(O)$NHSO_2R^1$, C(O)$NR^1SO_2R^1$, cyclic C_3-C_7 alkylamino, imidazolyl, piperazinyl, morpholinyl, piperidinyl, azepanyl, pyrrolidinyl, or azetidinyl;

wherein each imidazolyl, piperazinyl, morpholinyl, piperidinyl, azepanyl, pyrrolidinyl and azetidinyl is optionally and independently substituted with one or more R^1, halo, OH, OR^1, OC(O)R^1, OC(O)NH_2, OC(O)NHR^1, OC(O)NR^1R^1, OP(O)$(OH)_2$, OP(O)$(OR^1)_2$, NO_2, NH_2, NHR^1, NR^1R^1, $N^+(-O^-)R^1R^1$, NHC(O)H, NHC(O)R^1, $NR^1C(O)R^1$, NHC(O)NH_2, NHC(O)NR^1R^1, $NR^1C(O)NHR^1$, SH, SR^1, S(O)H, S(O)R^1, SO_2R^1, SO_2NH_2, SO_2NHR^1, $SO_2NR^1R^1$, CF_3, CN, CO_2H, CO_2R^1, CHO, C(O)R^1, C(O)NH_2, C(O)NHR^1, C(O)NR^1R^1, $CONHSO_2H$, C(O)$NHSO_2R^1$ or C(O)$NR^1SO_2R^1$;

and wherein each heteroaryl group contains one or more heteroatoms in its ring system, independently selected from O, N or S;

each R^1 is independently C_{1-6} alkyl or C_{2-6} alkenyl, optionally and independently substituted with halo, OH, OR^2, OC(O)R^2, OC(O)NH_2, OC(O)NHR^2, OC(O)NR^2R^2, OP(O)$(OH)_2$, OP(O)$(OR^2)_2$, NO_2, NH_2, NHR^2, NR^2R^2, $N^+(-O^-)R^2R^2$, NHC(O)R^2, $NR^2C(O)R^2$, NHC(O)NH_2, NHC(O)NR^2R^2, $NR^2C(O)NHR^2$, SH, SR^2, S(O)H, S(O)R^2, SO_2R^2, SO_2NH_2, SO_2NHR^2, $SO_2NR^2R^2$, CF_3, CN, CO_2H, CO_2R^2, CHO, C(O)R^2, C(O)NH_2, C(O)NHR^2, C(O)NR^2R^2,

$C(O)NHSO_2R^2$, $C(O)NR^2SO_2R^2$, cyclic C_3-C_7 alkylamino, imidazolyl, piperazinyl, morpholinyl, piperidinyl, azepanyl, pyrrolidinyl or azetidinyl;

wherein each imidazolyl, piperazinyl, morpholinyl, piperidinyl, azepanyl, pyrrolidinyl and azetidinyl is optionally and independently substituted with one or more R^2, halo, OH, OR^2, $OC(O)R^2$, $OC(O)NH_2$, $OC(O)NHR^2$, $OC(O)NR^2R^2$, $OP(O)(OH)_2$, $OP(O)(OR^2)_2$, NO_2, NH_2, NHR^2, NR^2R^2, $N^+(-O^-)R^2R^2$, NHC(O)H, $NHC(O)R^2$, $NR^2C(O)R^2$, $NHC(O)NH_2$, $NHC(O)NR^2R^2$, $NR^2C(O)NHR^2$, SH, SR^2, S(O)H, $S(O)R^2$, SO_2R^2, SO_2NH_2, SO_2NHR^2, $SO_2NR^2R^2$, CF_3, CN, CO_2H, CO_2R^2, CHO, $C(O)R^2$, $C(O)NH_2$, $C(O)NHR^2$, $C(O)NR^2R^2$, $CONHSO_2H$, $C(O)NHSO_2R^2$ or $C(O)NR^2SO_2R^2$;

each R^2 is independently C_{1-6} alkyl, C_{2-6} alkenyl, OH, OMe, NO_2, NH_2, CF_3, CN, CO_2H or SH;

provided that V_1, V_1', V_2, V_2', V_3, V_4, V_5, V_6, and V_7 are not all hydrogen; and

when E is S; V_1, V_1', and V_2' are all hydrogen; and V_2 is Cl; then V_3 is not CH_3 when V_4 is Cl; and V_5 is not CH_3, OCH_3, or Cl; and

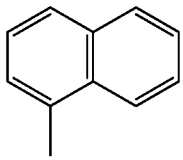
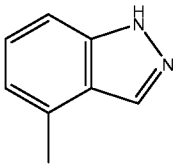
when E is S; V_1, V_1', and V_2' are all hydrogen; V_2 is H or NH_2; and V_4 is CF_3; then V_5 is not F; and

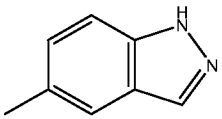
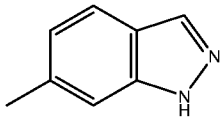
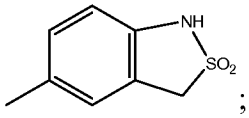
when E is S and V_1, V_1', V_2, V_2', V_3 and V_5 are all hydrogen, then V_4 is not COOH, $COOCH_3$, $C(O)CH_3$, CF_3, CH_3, OH, OCH_3, SCH_3, CN, O-phenyl, Cl, Br, or NO_2; and

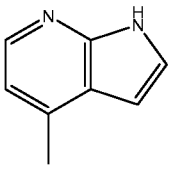
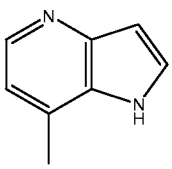
when E is S and V_1, V_1', V_2, V_2', V_4 and V_5 are all hydrogen, then V_3 is not CH_3, CH_2CH_3, F, Cl, NO_2, CF_3, OCH_3, OCH_2CH_3, or a substituted 1,4-dihydropyridyl ring; and

when E is S and V_1, V_1', V_2, V_2', V_3 and V_4 are all hydrogen, then V_5 is not CH_3, CH_2CH_3, $C(O)CH_3$, CF_3, $S(O)_2$-NH_2, $S(O)_2$-NHR, $N(CH_3)_2$, $N(CH_2CH_3)_2$, N(*i*-Pr)phenyl, NO_2, OCH_2CH_3, NH-$C(O)CH_3$, NH_2, COOH, F, Cl, Br, I, OH, OCH_3, O-phenyl, O-C_{7-8}-alkyl, or $C(O)NHC(i\text{-Bu})C(O)NHCH_2CN$; and

when E is S and V_1, V_1', V_2, V_2', and V_5 are all hydrogen; then when V_3 is Cl, V_4 is not Cl; when V_3 is CH_3, then V_4 is not Cl; and V_3 and V_4, taken together

with the ring to which they are attached, do not form  or  ; and

when E is S and V_1, V_1', V_2, V_2', and V_3 are all hydrogen; then when V_5 is O-C_{5-8}-alkyl, V_4 is not hydrogen, F, or CF_3; when V_5 is CH_3, V_4 is not CH_3; and V_4 and V_5, taken together with the ring to which they are attached, do not form , , or ;

when E is S and V_1', V_2', V_3, V_4, and V_5 are all hydrogen, then V_1 and V_2, taken together with the ring to which they are attached, do not form  or .

45. The method of claim 44, wherein V_3, V_4, and V_5 are independently hydrogen; halo; R; OH; OR; CF_3; NO_2; NH_2; NHR; NRR; $OP(O)(OH)_2$; or $OP(O)(OR)_2$; and groups V_3 and V_4 and groups V_4 and V_5, taken together with the atoms to which they are attached, optionally and independently form a 5- or 6-membered ring structure.

46. The method of claim 44, wherein V_3, V_4, and V_5 are independently hydrogen; halo; C_{1-6} alkyl, optionally substituted with OH, NH_2, or $N(CH_3)_2$; OH; O-C_{1-6} alkyl, optionally substituted with OH, NH_2, or $N(CH_3)_2$; CF_3; NO_2; NH_2; or $OP(O)(OH)_2$.

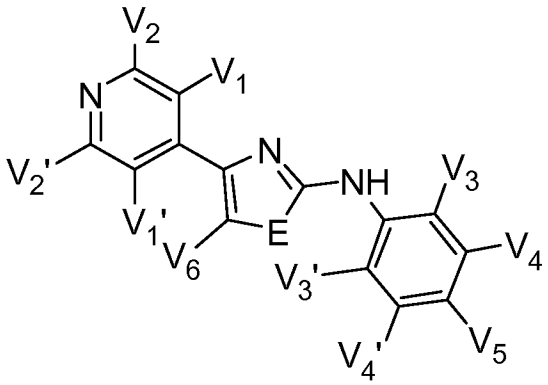
47. The method of claim 44, wherein V_1 and V_2 are independently hydrogen, halo, R, OH, OR, CF_3, NO_2, NH_2, NHR, NRR, or, taken together with the atoms to which they are attached, form a 5- or 6-membered ring structure.

48. The method of any one of claims 44-46, wherein
V_1, V_1', V_2, V_2' are all hydrogen.

49. The method of any one of claims 44-48, wherein
E is S or O.

50. The method of claim 49, wherein
E is S.

51. A method of treating or preventing a disease, comprising administering to a mammalian host a therapeutically-effective amount of a compound of Formula II or a pharmaceutically acceptable salt, derivative, or prodrug thereof:



Formula II

wherein:

E is S, O, or N-V_7;

V_1, V_1', V_2, V_2', V_3, V_3', V_4, V_4', V_5, V_6, and V_7 are independently hydrogen, halo, R, OH, OR, OC(O)H, OC(O)R, $OC(O)NH_2$, OC(O)NHR, OC(O)NRR, $OP(O)(OH)_2$, $OP(O)(OR)_2$, NO_2, NH_2, NHR, NRR, $N^+(-O^-)RR$, NHC(O)H, NHC(O)R, NRC(O)R, $NHC(O)NH_2$, NHC(O)NRR, NRC(O)NHR, $N^2C(O)NHR$, SH, SR, S(O)H, S(O)R, SO_2R, SO_2NH_2, SO_2NHR, SO_2NRR, CF_3, CN, CO_2H, CO_2R, CHO, C(O)R, $C(O)NH_2$, C(O)NHR, C(O)NRR, $CONHSO_2H$, $C(O)NHSO_2R$, $C(O)NRSO_2R$, cyclic C_3-C_7 alkylamino, imidazolyl, piperazinyl, morpholinyl, piperidinyl, azepanyl, pyrrolidinyl or azetidinyl;

wherein each imidazolyl, piperazinyl, morpholinyl, piperidinyl, azepanyl, pyrrolidinyl and azetidinyl is optionally and independently substituted by one or more R^1, halo, OH, OR^1, $OC(O)R^1$, $OC(O)NH_2$, $OC(O)NHR^1$, $OC(O)NR^1R^1$, $OP(O)(OH)_2$, $OP(O)(OR^1)_2$, NO_2, NH_2, NHR^1, NR^1R^1, $N^+(-O^-)R^1R^1$, NHC(O)H, $NHC(O)R^1$, $NR^1C(O)R^1$, $NHC(O)NH_2$, $NHC(O)NR^1R^1$, $NR^1C(O)NHR^1$, SH, SR^1, S(O)H, $S(O)R^1$, SO_2R^1, SO_2NH_2, SO_2NHR^1, $SO_2NR^1R^1$, CF_3, CN, CO_2H, CO_2R^1, CHO, $C(O)R^1$, $C(O)NH_2$, $C(O)NHR^1$, $C(O)NR^1R^1$, $CONHSO_2H$, $C(O)NHSO_2R^1$ or $C(O)NR^1SO_2R^1$;

and wherein groups V_1 and V_2, groups V_3 and V_4, and groups V_4 and V_5, taken together with the atoms to which they are attached, optionally and independently form a cyclic structure having from 4 to 8 atoms in the ring;

each R is independently C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cyclic alkyl, aryl, aralkyl, heteroaryl, or heteroaralkyl, and is optionally and independently substituted with halo, OH, R^1, OR^1, $OC(O)R^1$, $OC(O)NH_2$, $OC(O)NHR^1$, $OC(O)NR^1R^1$, $OP(O)(OH)_2$, $OP(O)(OR^1)_2$, NO_2, NH_2, NHR^1, NR^1R^1, $N^+(-O^-)R^1R^1$, NHC(O)H, $NHC(O)R^1$, $NR^1C(O)R^1$, $NHC(O)NH_2$, $NHC(O)NR^1R^1$, $NR^1C(O)NHR^1$, SH, SR^1, S(O)H, $S(O)R^1$, SO_2R^1, SO_2NH_2, SO_2NHR^1, $SO_2NR^1R^1$, CF_3, CN, CO_2H, CO_2R^1, CHO, $C(O)R^1$, $C(O)NH_2$, $C(O)NHR^1$, $C(O)NR^1R^1$, $C(O)NHSO_2R^1$, $C(O)NR^1SO_2R^1$, cyclic C_3-C_7 alkylamino, imidazolyl, piperazinyl, morpholinyl, piperidinyl, azepanyl, pyrrolidinyl, or azetidinyl;

wherein each imidazolyl, piperazinyl, morpholinyl, piperidinyl, azepanyl, pyrrolidinyl and azetidinyl is optionally and independently substituted with one or more R^1, halo, OH, OR^1, $OC(O)R^1$, $OC(O)NH_2$, $OC(O)NHR^1$, $OC(O)NR^1R^1$, $OP(O)(OH)_2$, $OP(O)(OR^1)_2$, NO_2, NH_2, NHR^1, NR^1R^1, $N^+(-O^-)R^1R^1$, NHC(O)H, $NHC(O)R^1$, $NR^1C(O)R^1$, $NHC(O)NH_2$, $NHC(O)NR^1R^1$, $NR^1C(O)NHR^1$, SH, SR^1, S(O)H, $S(O)R^1$, SO_2R^1, SO_2NH_2, SO_2NHR^1, $SO_2NR^1R^1$, CF_3, CN, CO_2H, CO_2R^1, CHO, $C(O)R^1$, $C(O)NH_2$, $C(O)NHR^1$, $C(O)NR^1R^1$, $CONHSO_2H$, $C(O)NHSO_2R^1$ or $C(O)NR^1SO_2R^1$;

and wherein each heteroaryl group contains one or more heteroatoms in its ring system, independently selected from O, N or S;

each R^1 is independently C_{1-6} alkyl or C_{2-6} alkenyl, optionally and independently substituted with halo, OH, OR^2, $OC(O)R^2$, $OC(O)NH_2$, $OC(O)NHR^2$, $OC(O)NR^2R^2$, $OP(O)(OH)_2$, $OP(O)(OR^2)_2$, NO_2, NH_2, NHR^2, NR^2R^2, $N^+(-O^-)R^2R^2$, $NHC(O)R^2$, $NR^2C(O)R^2$, $NHC(O)NH_2$, $NHC(O)NR^2R^2$, $NR^2C(O)NHR^2$, SH, SR^2, S(O)H, $S(O)R^2$, SO_2R^2, SO_2NH_2, SO_2NHR^2, $SO_2NR^2R^2$, CF_3, CN, CO_2H, CO_2R^2, CHO, $C(O)R^2$, $C(O)NH_2$, $C(O)NHR^2$, $C(O)NR^2R^2$, $C(O)NHSO_2R^2$, $C(O)NR^2SO_2R^2$, cyclic C_3-C_7 alkylamino, imidazolyl, piperazinyl, morpholinyl, piperidinyl, azepanyl, pyrrolidinyl or azetidinyl;

wherein each imidazolyl, piperazinyl, morpholinyl, piperidinyl, azepanyl, pyrrolidinyl and azetidinyl is optionally and independently substituted with one or more R^2, halo, OH, OR^2, $OC(O)R^2$, $OC(O)NH_2$, $OC(O)NHR^2$, $OC(O)NR^2R^2$, $OP(O)(OH)_2$, $OP(O)(OR^2)_2$, NO_2, NH_2, NHR^2, NR^2R^2, $N^+(-O^-)R^2R^2$, NHC(O)H, $NHC(O)R^2$, $NR^2C(O)R^2$, $NHC(O)NH_2$, $NHC(O)NR^2R^2$, $NR^2C(O)NHR^2$, SH, SR^2, S(O)H, $S(O)R^2$, SO_2R^2, SO_2NH_2, SO_2NHR^2, $SO_2NR^2R^2$, CF_3, CN, CO_2H, CO_2R^2, CHO, $C(O)R^2$, $C(O)NH_2$, $C(O)NHR^2$, $C(O)NR^2R^2$, $CONHSO_2H$, $C(O)NHSO_2R^2$ or $C(O)NR^2SO_2R^2$;

each R^2 is independently C_{1-6} alkyl, C_{2-6} alkenyl, OH, OMe, NO_2, NH_2, CF_3, CN, CO_2H or SH;

and wherein the disease is caused by a defect in the von Hippel-Lindau gene.

52. The method of claim 51, wherein in the compound of Formula II:

V_3, V_4, and V_5 are independently hydrogen; halo; R; OH; OR; CF_3; NO_2; NH_2; NHR; NRR; $OP(O)(OH)_2$; or $OP(O)(OR)_2$; and groups V_3 and V_4 and groups V_4 and V_5, taken together with the atoms to which they are attached, optionally and independently form a 5- or 6-membered ring structure.

53. The method of claim 51, wherein in the compound of Formula II:

V_3, V_4, and V_5 are independently hydrogen; halo; C_{1-6} alkyl, optionally substituted with OH, NH_2, or $N(CH_3)_2$; OH; O-C_{1-6} alkyl, optionally substituted with OH, NH_2, or $N(CH_3)_2$; CF_3; NO_2; NH_2; or $OP(O)(OH)_2$.

54. The method of claim 51, wherein in the compound of Formula II:

V_6 is hydrogen; R; CHO; CO_2R; $C(O)NH_2$; C(O)NHR; or C(O)NRR.

55. The method of claim 51, wherein in the compound of Formula II:

V_6 is hydrogen; C_{1-6} alkyl or C_{2-4} alkenyl, optionally substituted with OH, OR^1, CO_2R^1, NH_2, NHR^1, or NR^1R^1; CHO; or CO_2R.

56. The method of claim 51, wherein in the compound of Formula II:

V_6 is hydrogen.

57. The method of claim 51, wherein V_1 and V_2 are independently hydrogen, halo, R, OH, OR, CF_3, NO_2, NH_2, NHR, NRR, or, taken together with the atoms to which they are attached, form a 5- or 6-membered ring structure.

58. The method of any one of claims 51-56, wherein in the compound of Formula II:

V_1, V_1', V_2, V_2' are all hydrogen.

59. The method of any one of claims 51-58, wherein in the compound of Formula II:

E is S or O.

60. The method of claim 59, wherein in the compound of Formula II:

E is S.

61. The method of claim 51, wherein the compound is selected from any one of the following compounds:

N-Phenyl-4-(4-pyridinyl)-1,3-thiazol-2-amine,

N-(3-Methylphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine,

N-(3-Ethylphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine,

N-(3-Isopropylphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine,

N-(3-*tert*-Butylphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine,

3-{[4-(4-Pyridinyl)-1,3-thiazol-2-yl]amino}phenol,

N-(3-Methoxyphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine,

N-(3-Chlorophenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine,

4-(4-Pyridinyl)-*N*-[3-(trifluoromethyl)phenyl]-1,3-thiazol-2-amine,

N-(4-Methylphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine,

2-(4-{[4-(4-Pyridinyl)-1,3-thiazol-2-yl]amino}phenyl)ethanol,

4-{[4-(4-Pyridinyl)-1,3-thiazol-2-yl]amino}phenol,

N-(4-Methoxyphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine,

N-{4-[2-(Dimethylamino)ethoxy]phenyl}-4-(4-pyridinyl)-1,3-thiazol-2-amine,

N-(4-Chlorophenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine,

N-(4-Fluorophenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine,

N-(4-Nitrophenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine,

N-{4-[2-(Dimethylamino)ethyl]phenyl}-4-(4-pyridinyl)-1,3-thiazol-2-amine,

N^1-[4-(4-Pyridinyl)-1,3-thiazol-2-yl]-1,4-benzenediamine,

3-{[4-(4-Pyridinyl)-1,3-thiazol-2-yl]amino}phenyl Dihydrogen Phosphate,

4-{[4-(4-Pyridinyl)-1,3-thiazol-2-yl]amino}phenyl Dihydrogen Phosphate,

N-(3,4-Dimethylphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine,

N-(3,5-Dimethylphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine,

N-(2,3-Dihydro-1*H*-inden-5-yl)-4-(4-pyridinyl)-1,3-thiazol-2-amine,

2-Methyl-5-{[4-(4-pyridinyl)-1,3-thiazol-2-yl]amino}phenol,

2-Methoxy-5-{[4-(4-pyridinyl)-1,3-thiazol-2-yl]amino}phenol,

2-Methyl-4-{[4-(4-pyridinyl)-1,3-thiazol-2-yl]amino}phenol,

N-(3,4-Dimethoxyphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine,

N-(3,5-Dimethoxyphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine,

N-(1,3-Benzodioxol-5-yl)-4-(4-pyridinyl)-1,3-thiazol-2-amine,

N-(3,4-Dichlorophenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine,

4-(4-Pyridinyl)-*N*-(3,4,5-trimethoxyphenyl)-1,3-thiazol-2-amine,

N-(3-Methylphenyl)-4-(3-pyridinyl)-1,3-thiazol-2-amine,

4-{[4-(3-Pyridinyl)-1,3-thiazol-2-yl]amino}phenol,

N-(3-Methylphenyl)-4-(2-pyridinyl)-1,3-thiazol-2-amine,

4-{[4-(2-Pyridinyl)-1,3-thiazol-2-yl]amino}phenol,

5-Methyl-*N*-(3-methylphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine,

N-(2,3-Dihydro-1*H*-inden-5-yl)-5-methyl-4-(4-pyridinyl)-1,3-thiazol-2-amine,

[2-(Phenylamino)-4-(4-pyridinyl)-1,3-thiazol-5-yl]methanol,
[2-[(3-Methylphenyl)amino]-4-(4-pyridinyl)-1,3-thiazol-5-yl]methanol,
[2-[(4-Methylphenyl)amino]-4-(4-pyridinyl)-1,3-thiazol-5-yl]methanol,
[2-(2,3-Dihydro-1*H*-inden-5-ylamino)-4-(4-pyridinyl)-1,3-thiazol-5-yl]methanol,
2-[(3-Methylphenyl)amino]-4-(4-pyridinyl)-1,3-thiazole-5-carbaldehyde,
Methyl (2*E*)-3-[2-[(3-Methylphenyl)amino]-4-(4-pyridinyl)-1,3-thiazol-5-yl]-2-propenoate,
Methyl 3-[2-[(3-Methylphenyl)amino]-4-(4-pyridinyl)-1,3-thiazol-5-yl]propanoate,
3-[2-[(3-Methylphenyl)amino]-4-(4-pyridinyl)-1,3-thiazol-5-yl]-1-propanol,
N-(3-Methylphenyl)-5-[3-(4-morpholinyl)propyl]-4-(4-pyridinyl)-1,3-thiazol-2-amine,
5-[(Dimethylamino)methyl]-*N*-(3-methylphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine,
5-[(Diethylamino)methyl]-*N*-(3-methylphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine,
N-(3-Methylphenyl)-5-(1-piperidinylmethyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine,
N-(3-Methylphenyl)-5-(4-morpholinylmethyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine,
Ethyl 2-[(3-methylphenyl)amino]-4-(4-pyridinyl)-1,3-thiazole-5-carboxylate,
Ethyl 2-(2,3-dihydro-1*H*-inden-5-ylamino)-4-(4-pyridinyl)-1,3-thiazole-5-carboxylate,
2-[(3-Methylphenyl)amino]-4-(4-pyridinyl)-1,3-thiazole-5-carboxamide,
N,*N*-Dimethyl-2-[(3-methylphenyl)amino]-4-(4-pyridinyl)-1,3-thiazole-5-carboxamide,
N-[2-(Dimethylamino)ethyl]-2-[(3-methylphenyl)amino]-4-(4-pyridinyl)-1,3-thiazole-5-carboxamide,
2-[(3-Methylphenyl)amino]-*N*-[3-(4-morpholinyl)propyl]-4-(4-pyridinyl)-1,3-thiazole-5-carboxamide,
N-Methyl-*N*-(3-methylphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine,
N-Ethyl-*N*-(3-methylphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine,
2-{3-Methyl[4-(4-pyridinyl)-1,3-thiazol-2-yl]anilino}ethanol,
N-(3-Methylphenyl)-4-(4-pyridinyl)-1,3-oxazol-2-amine,
2-{[4-(4-Pyridinyl)-1,3-thiazol-2-yl]amino}phenol,

N-(2-Methoxyphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine,
N-(2-Methylphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine,
N-(2-Fluorophenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine,
N-[2-Chlorophenyl]-4-(4-pyridinyl)-1,3-thiazol-2-amine,
4-(4-Pyridinyl)-*N*-[2-(trifluoromethyl)phenyl]-1,3-thiazol-2-amine,
N-[2-Nitrophenyl]-4-(4-pyridinyl)-1,3-thiazol-2-amine,
N-(3-Fluorophenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine,
N-(3-Bromophenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine,
1-(3-{[4-(4-Pyridinyl)-1,3-thiazol-2-yl]amino}phenyl)ethanone,
3-{[4-(4-Pyridinyl)-1,3-thiazol-2-yl]amino}benzonitrile,
N-(3-Nitrophenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine,
1-(4-{[4-(4-Pyridinyl)-1,3-thiazol-2-yl]amino}phenyl)ethanone,
4-(4-Pyridinyl)-*N*-[4-(trifluoromethyl)phenyl]-1,3-thiazol-2-amine,
4-{[4-(4-Pyridinyl)-1,3-thiazol-2-yl]amino}benzonitrile,
N-(2,6-Dimethylphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine,
N-(2,6-Difluorophenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine,
N-{4-[2-(Methyloxy)-4-pyridinyl]-1,3-thiazol-2-yl}-*N*-(3-methylphenyl)amine,
N-(3-Methylphenyl)-4-(2-methyl-4-pyridinyl)-1,3-thiazol-2-amine,
4-(2-Fluoro-4-pyridinyl)-*N*-(3-methylphenyl)-1,3-thiazol-2-amine,
4-(2-Chloro-4-pyridinyl)-*N*-(3-methylphenyl)-1,3-thiazol-2-amine,
4-(2-Bromo-4-pyridinyl)-*N*-(3-methylphenyl)-1,3-thiazol-2-amine,
N-[4-(2,6-Dichloro-4-pyridinyl)-1,3-thiazol-2-yl]-*N*-(3-methylphenyl)amine,
4-(2-Ethynyl-4-pyridinyl)-*N*-(3-methylphenyl)-1,3-thiazol-2-amine,
4-(2-Ethyl-4-pyridinyl)-*N*-(3-methylphenyl)-1,3-thiazol-2-amine,
3-(4-{2-[(3-Methylphenyl)amino]-1,3-thiazol-4-yl}-2-pyridinyl)-2-propyn-1-ol,
3-(4-{2-[(3-Methylphenyl)amino]-1,3-thiazol-4-yl}-2-pyridinyl)-1-propanol,
N-(3-Methylphenyl)-4-(3-methyl-4-pyridinyl)-1,3-thiazol-2-amine,
4-(3-Fluoro-4-pyridinyl)-*N*-(3-methylphenyl)-1,3-thiazol-2-amine,
4-(3-Chloro-4-pyridinyl)-*N*-(3-methylphenyl)-1,3-thiazol-2-amine,
4-(3-Bromo-4-pyridinyl)-*N*-(3-methylphenyl)-1,3-thiazol-2-amine,
N-(3-Methylphenyl)-4-(2-nitro-4-pyridinyl)-1,3-thiazol-2-amine,
N-[4-(2-Amino-4-pyridinyl)-1,3-thiazol-2-yl]-*N*-(3-methylphenyl)amine,

N-(4-{2-[(3-Methylphenyl)amino]-1,3-thiazol-4-yl}-2-pyridinyl)acetamide,
4-(3-Ethynyl-4-pyridinyl)-*N*-(3-methylphenyl)-1,3-thiazol-2-amine,
4-(3-Ethyl-4-pyridinyl)-*N*-(3-methylphenyl)-1,3-thiazol-2-amine,
3-(4-{2-[(3-Methylphenyl)amino]-1,3-thiazol-4-yl}-3-pyridinyl)-2-propyn-1-ol,
3-(4-{2-[(3-Methylphenyl)amino]-1,3-thiazol-4-yl}-3-pyridinyl)-1-propanol,
N-(3-Methylphenyl)-4-(1-oxido-4-pyridinyl)-1,3-thiazol-2-amine,
N-(3-Methylphenyl)-4-(4-quinolinyl)-1,3-thiazol-2-amine,
N-(3-Methylphenyl)-4-(2-phenyl-4-quinolinyl)-1,3-thiazol-2-amine,
N-(3-Methylphenyl)-4-(4-pyridinyl)-1*H*-imidazol-2-amine,
N-(3-Methylphenyl)-4-[2-(4-morpholinyl)-4-pyridinyl]-1,3-thiazol-2-amine,
N-(3-Methylphenyl)-4-[2-(4-methyl-1-piperazinyl)-4-pyridinyl]-1,3-thiazol-2-amine, and
N,*N*-Dimethyl-4-{2-[(3-methylphenyl)amino]-1,3-thiazol-4-yl}-2-pyridinamine.

62. The method of any one of claims 51-61, wherein the disease is caused by a defect in the von Hippel-Lindau gene.

63. The method of any one of claims 51-61, wherein the compound targets cells deficient in the von Hippel-Lindau gene.

64. The method of any one of claims 51-61, wherein the compound induces autophagic cell death.

65. The method of any one of claims 51-61, wherein the disease is a cancer.

66. The method of claim 65, wherein the cancer is a renal cell carcinoma, a pheochromocytoma, a hemangioblastoma of the central nervous system or retina, an endolymphatic sac tumor, a renal cyst, a pancreatic cyst, a neuroendocrine tumor, an endolymphatic sac tumor, or an epididymal or broad ligament cystadenoma.

67. The method of claim 66, wherein the cancer is a clear cell renal carcinoma.

68. The method of claim 66, wherein the cancer is a cancer of the retina, brain, spinal cord, ear, epidymis, broad ligament, adrenal gland, kidney, or pancreas.

69. The method of any one of claims 51-68, further comprising the step of administering a therapeutically-effective amount of one or more chemotherapeutic agents to the mammalian host before, during, or after administration of the compound.

70. The method of claim 69, wherein the chemotherapeutic agent is alemtuzumab, aminoglutethimide, amsacrine, anastrozole, asparaginase, bcg, bevacizumab, bicalutamide, bleomycin, bortezomib, buserelin, busulfan, campothecin, capecitabine, carboplatin, carmustine, CeaVac, cetuximab, chlorambucil, cisplatin, cladribine, clodronate, colchicine, cyclophosphamide, cyproterone, cytarabine, dacarbazine, daclizumab, dactinomycin, daunorubicin, dienestrol, diethylstilbestrol, docetaxel, doxorubicin, edrecolomab, epirubicin, epratuzumab, erlotinib, estradiol, estramustine, etoposide, everolimus, exemestane, filgrastim, fludarabine, fludrocortisone, fluorouracil, fluoxymesterone, flutamide, gemcitabine, gemtuzumab, genistein, goserelin, huJ591, hydroxyurea, ibritumomab, idarubicin, ifosfamide, IGN-101, imatinib, interferon, interleukin-2, irinotecan, ironotecan, letrozole, leucovorin, leuprolide, levamisole, lintuzumab, lomustine, MDX-210, mechlorethamine, medroxyprogesterone, megestrol, melphalan, mercaptopurine, mesna, methotrexate, mitomycin, mitotane, mitoxantrone, mitumomab, nilutamide, nocodazole, octreotide, oxaliplatin, paclitaxel, pamidronate, pentostatin, pertuzumab, plicamycin, porfimer, procarbazine, raltitrexed, rituximab, sorafinib, streptozocin, sunitinib, suramin, tamoxifen, temozolomide, temsirolimus, teniposide, testosterone, thalidomide, thioguanine, thiotepa, titanocene dichloride, topotecan, tositumomab, trastuzumab, tretinoin, vatalanib, vinblastine, vincristine, vindesine, or and vinorelbine.

71. The method of claim 69, wherein the chemotherapeutic agent is ionizing radiation.

72. The method as claimed in any one of claims 51-71 wherein the mammalian host is a human.

Figure 1

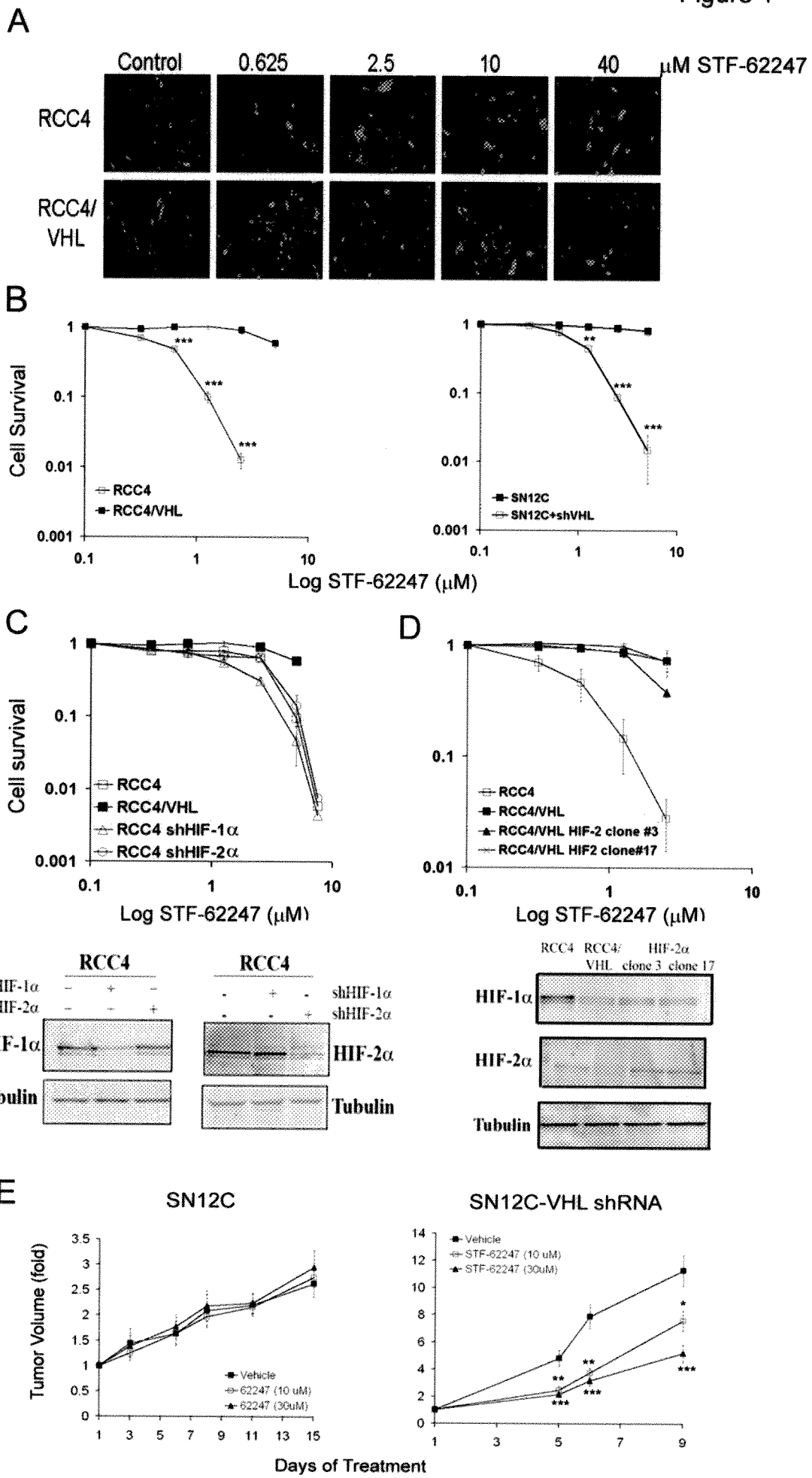

A
Control
0.625
2.5
10
40
μM STF-62247
RCC4
RCC4/ VHL
B
Cell Survival
RCC4
RCC4/VHL
SN12C
SN12C+shVHL
Log STF-62247 (μM)
C
Cell survival
RCC4
RCC4/VHL
RCC4 shHIF-1α
RCC4 shHIF-2α
Log STF-62247 (μM)
D
RCC4
RCC4/VHL
RCC4/VHL HIF-2 clone #3
RCC4/VHL HIF2 clone#17
Log STF-62247 (μM)
RCC4
RCC4
shHIF-1α
shHIF-2α
HIF-1α
HIF-2α
Tubulin
RCC4 RCC4/ VHL
HIF-2α clone 3 clone 17
HIF-1α
HIF-2α
Tubulin
E
SN12C
SN12C-VHL shRNA
Tumor Volume (fold)
Vehicle
62247 (10 uM)
62247 (30uM)
STF-62247 (10 uM)
STF-62247 (30uM)
Days of Treatment

Figure 2

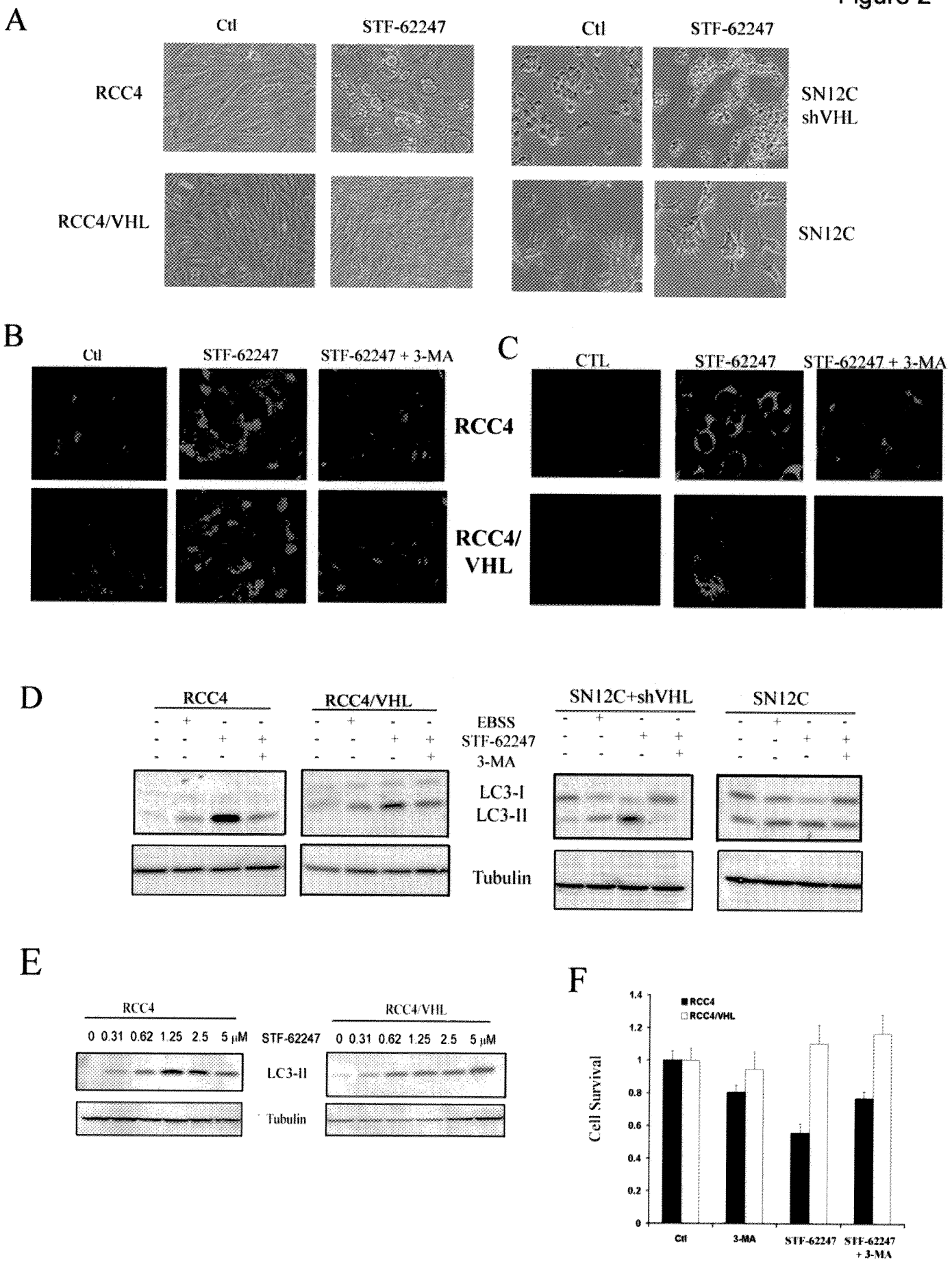

A
Ctl
STF-62247
Ctl
STF-62247
RCC4
SN12C shVHL
RCC4/VHL
SN12C
B
Ctl
STF-62247
STF-62247 + 3-MA
RCC4
RCC4/ VHL
C
CTL
STF-62247
STF-62247 + 3-MA
D
RCC4
RCC4/VHL
SN12C+shVHL
SN12C
EBSS
STF-62247
3-MA
LC3-I
LC3-II
Tubulin
E
RCC4
RCC4/VHL
0 0.31 0.62 1.25 2.5 5 μM
STF-62247
0 0.31 0.62 1.25 2.5 5 μM
LC3-II
Tubulin
F
RCC4
RCC4/VHL
Cell Survival
1.4
1.2
1
0.8
0.6
0.4
0.2
0
Ctl
3-MA
STF-62247
STF-62247 + 3-MA

Figure 3

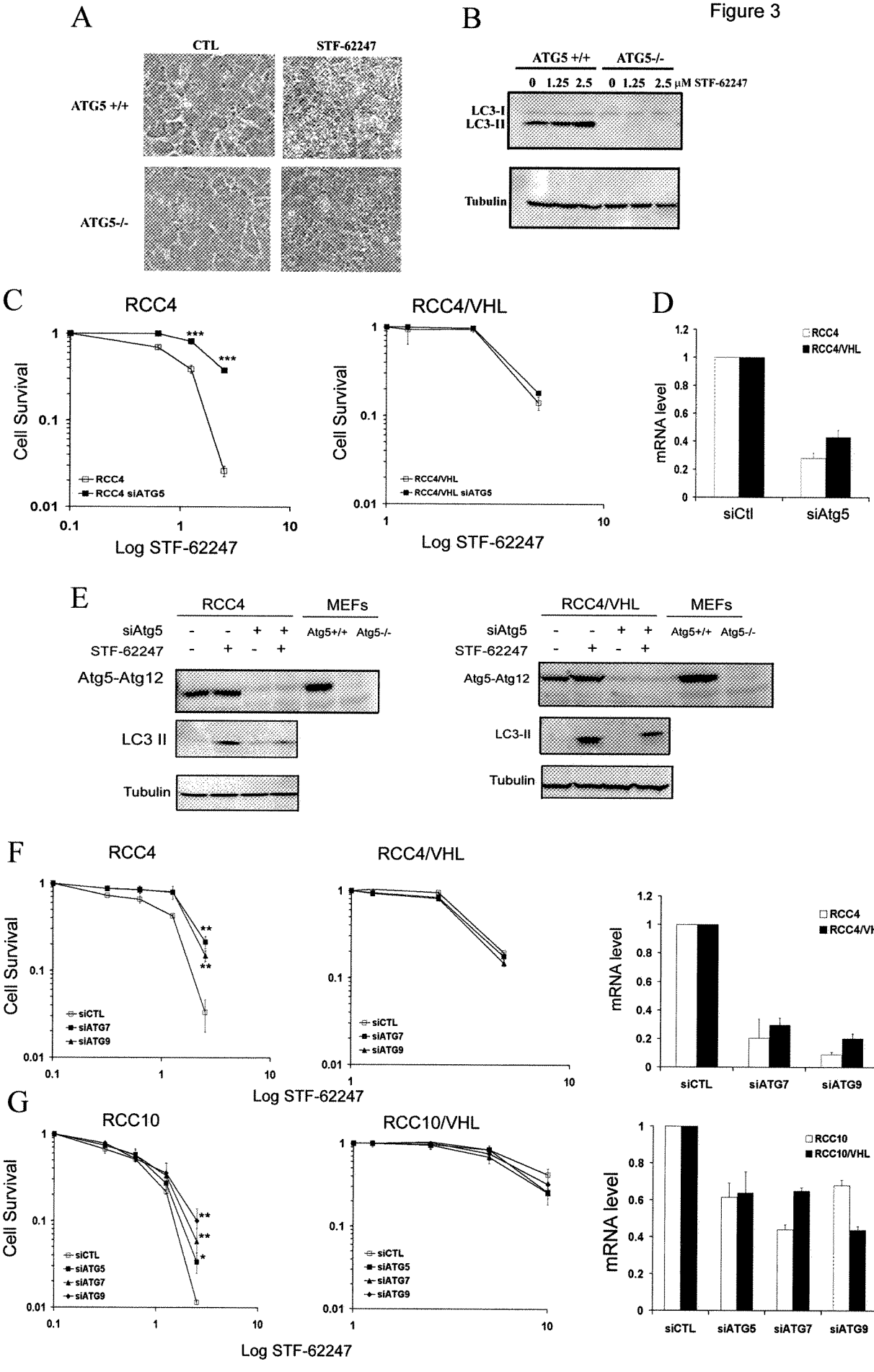

A
CTL
STF-62247
ATG5 +/+
ATG5-/-
B
ATG5 +/+
ATG5-/-
0 1.25 2.5 0 1.25 2.5 μM STF-62247
LC3-I
LC3-II
Tubulin
C
RCC4
RCC4/VHL
Cell Survival
RCC4
RCC4 siATG5
RCC4/VHL
RCC4/VHL siATG5
Log STF-62247
D
RCC4
RCC4/VHL
mRNA level
siCtl
siAtg5
E
RCC4
MEFs
siAtg5
STF-62247
Atg5+/+
Atg5-/-
Atg5-Atg12
LC3 II
LC3-II
Tubulin
RCC4/VHL
F
RCC4
RCC4/VHL
Cell Survival
siCTL
siATG7
siATG9
Log STF-62247
mRNA level
siCTL
siATG7
siATG9
G
RCC10
RCC10/VHL
Cell Survival
siCTL
siATG5
siATG7
siATG9
Log STF-62247
mRNA level

Figure 4

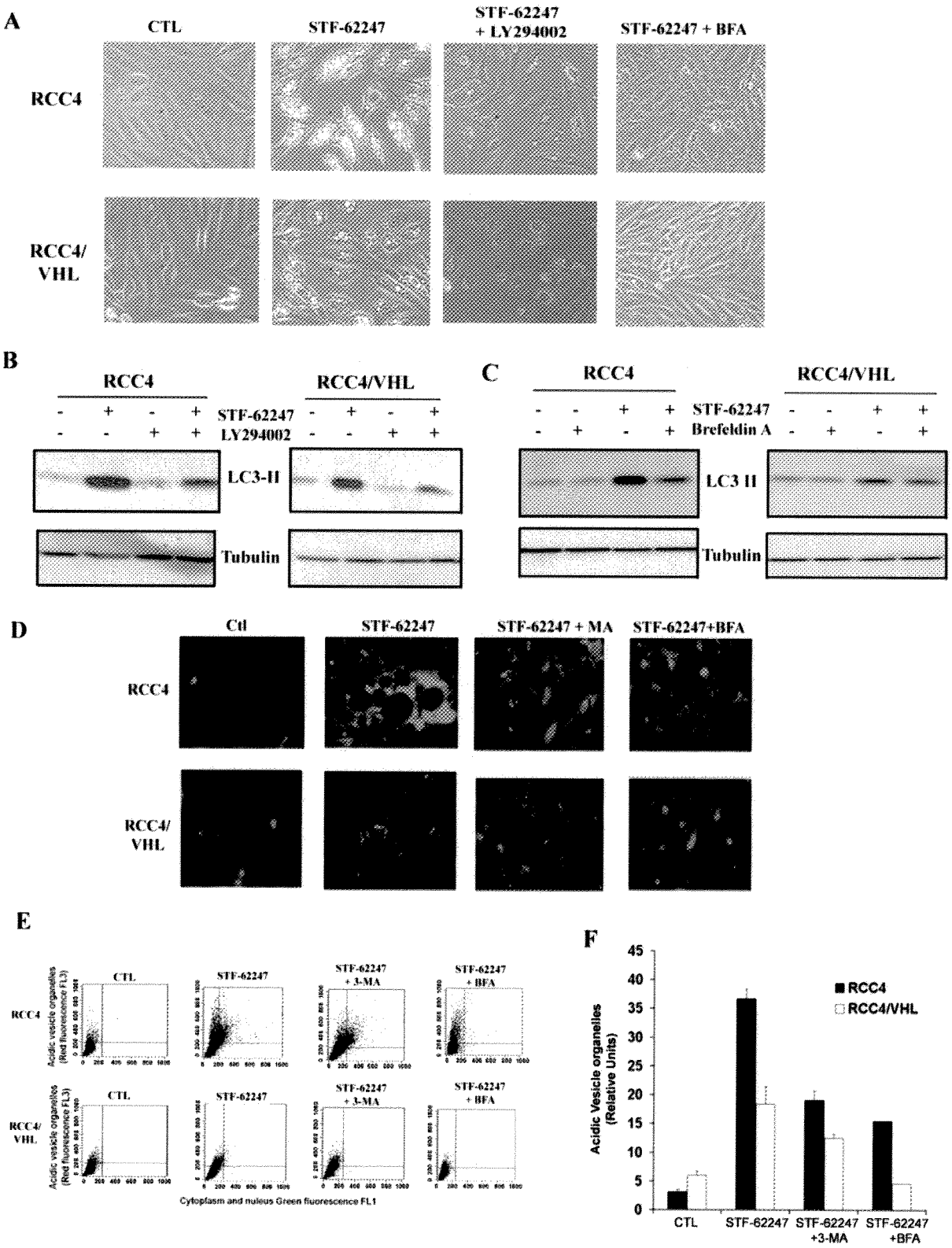

A
CTL
STF-62247
STF-62247 + LY294002
STF-62247 + BFA
RCC4
RCC4/ VHL
B
RCC4
RCC4/VHL
STF-62247
LY294002
LC3-II
Tubulin
C
RCC4
RCC4/VHL
STF-62247
Brefeldin A
LC3 II
Tubulin
D
Ctl
STF-62247
STF-62247 + MA
STF-62247+BFA
RCC4
RCC4/ VHL
E
CTL
STF-62247
STF-62247 + 3-MA
STF-62247 + BFA
RCC4
RCC4/ VHL
Acidic vesicle organelles (Red fluorescence FL3)
Cytoplasm and nuleus Green fluorescence FL1
F
Acidic Vesicle organelles (Relative Units)
RCC4
RCC4/VHL
CTL
STF-62247
STF-62247 +3-MA
STF-62247 +BFA

Figure 5

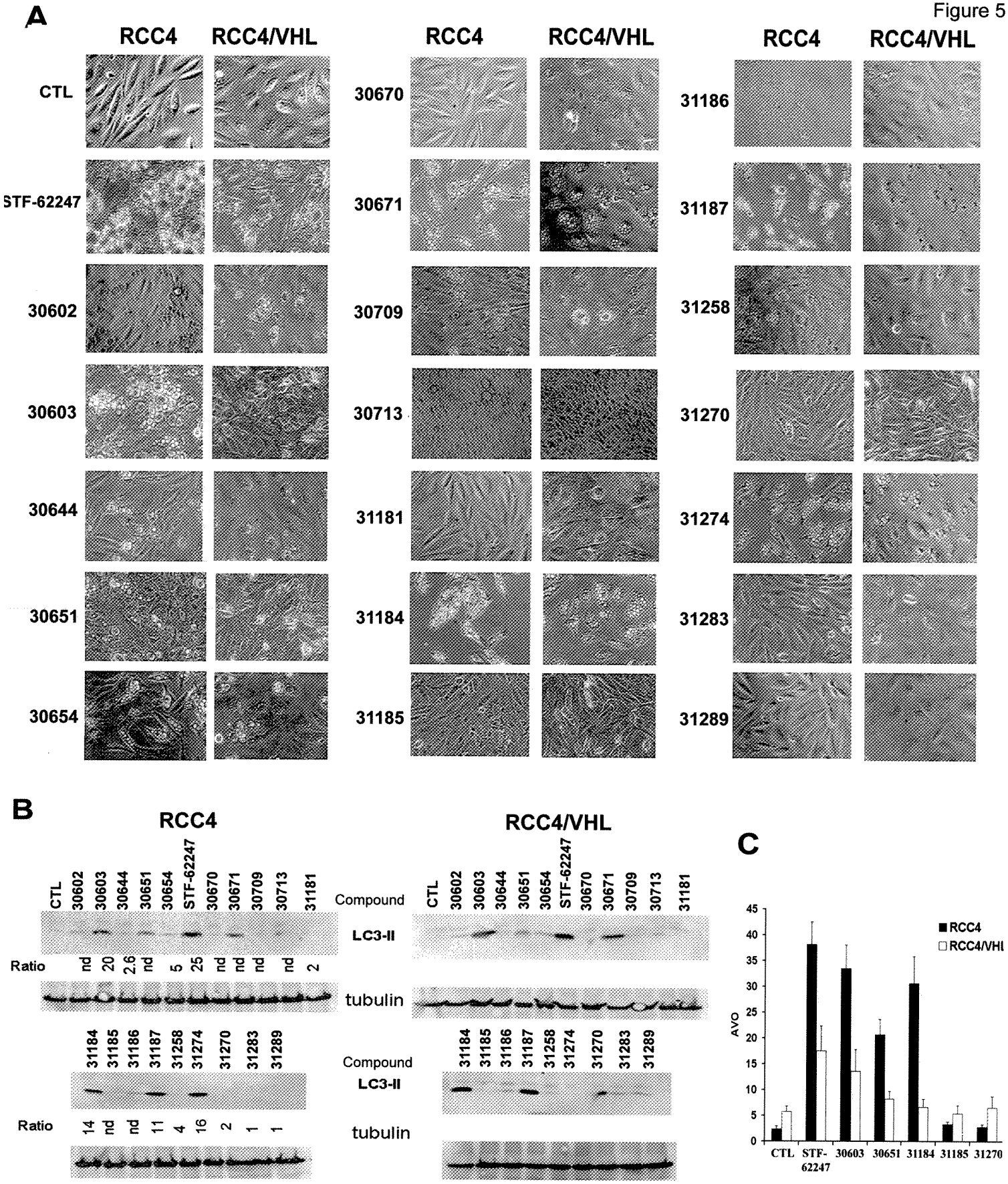

A
RCC4
RCC4/VHL
CTL
STF-62247
30602
30603
30644
30651
30654
30670
30671
30709
30713
31181
31184
31185
31186
31187
31258
31270
31274
31283
31289
B
RCC4
RCC4/VHL
Compound
LC3-II
tubulin
Ratio
C
RCC4
RCC4/VHL
AVO
CTL
STF-62247
30603
30651
31184
31185
31270

Figure 6

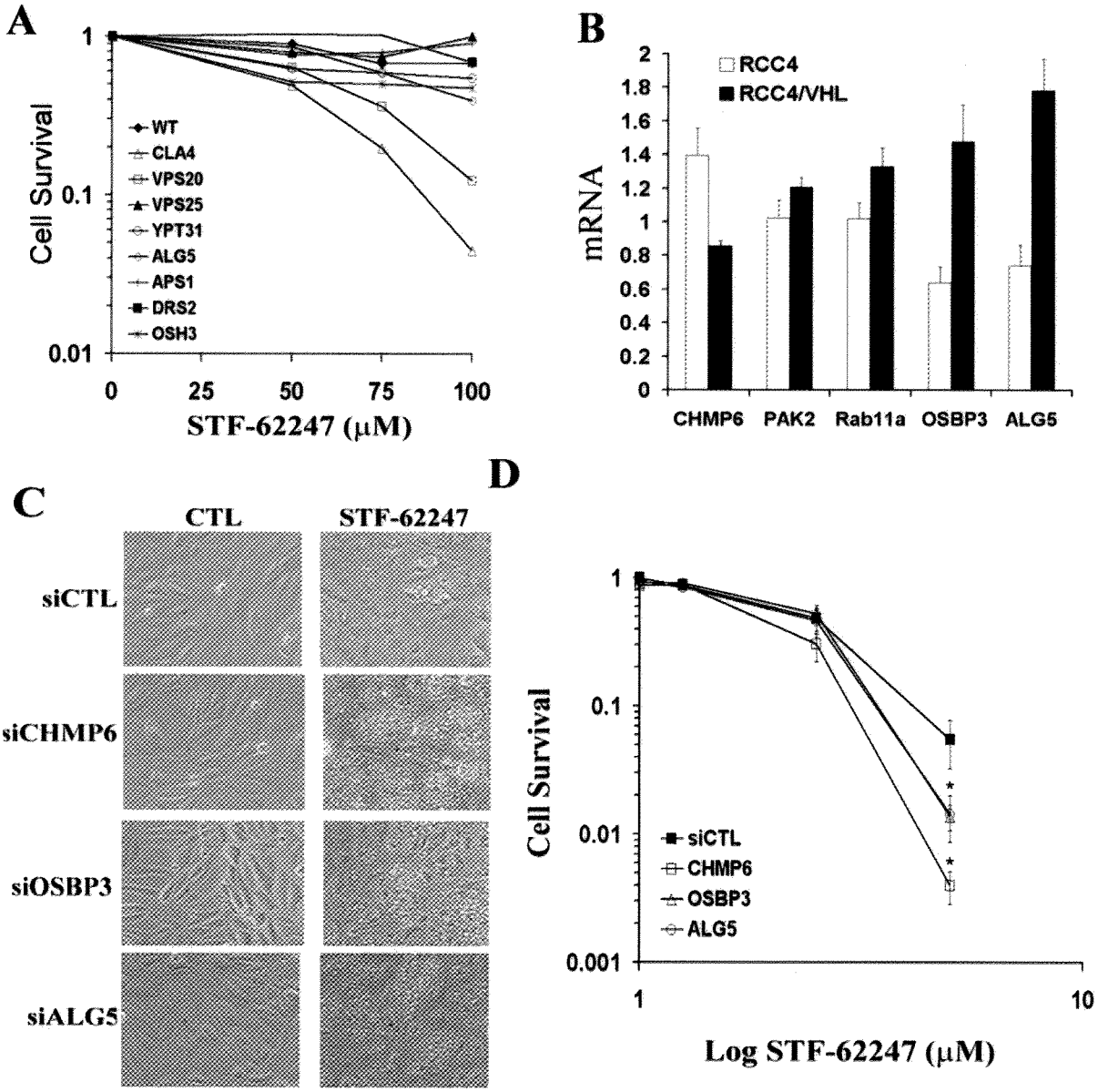

A
Cell Survival
1
0.1
0.01
0
25
50
75
100
STF-62247 (μM)
WT
CLA4
VPS20
VPS25
YPT31
ALG5
APS1
DRS2
OSH3
B
mRNA
RCC4
RCC4/VHL
CHMP6
PAK2
Rab11a
OSBP3
ALG5
C
CTL
STF-62247
siCTL
siCHMP6
siOSBP3
siALG5
D
Cell Survival
Log STF-62247 (μM)
siCTL
CHMP6
OSBP3
ALG5

Figure 7

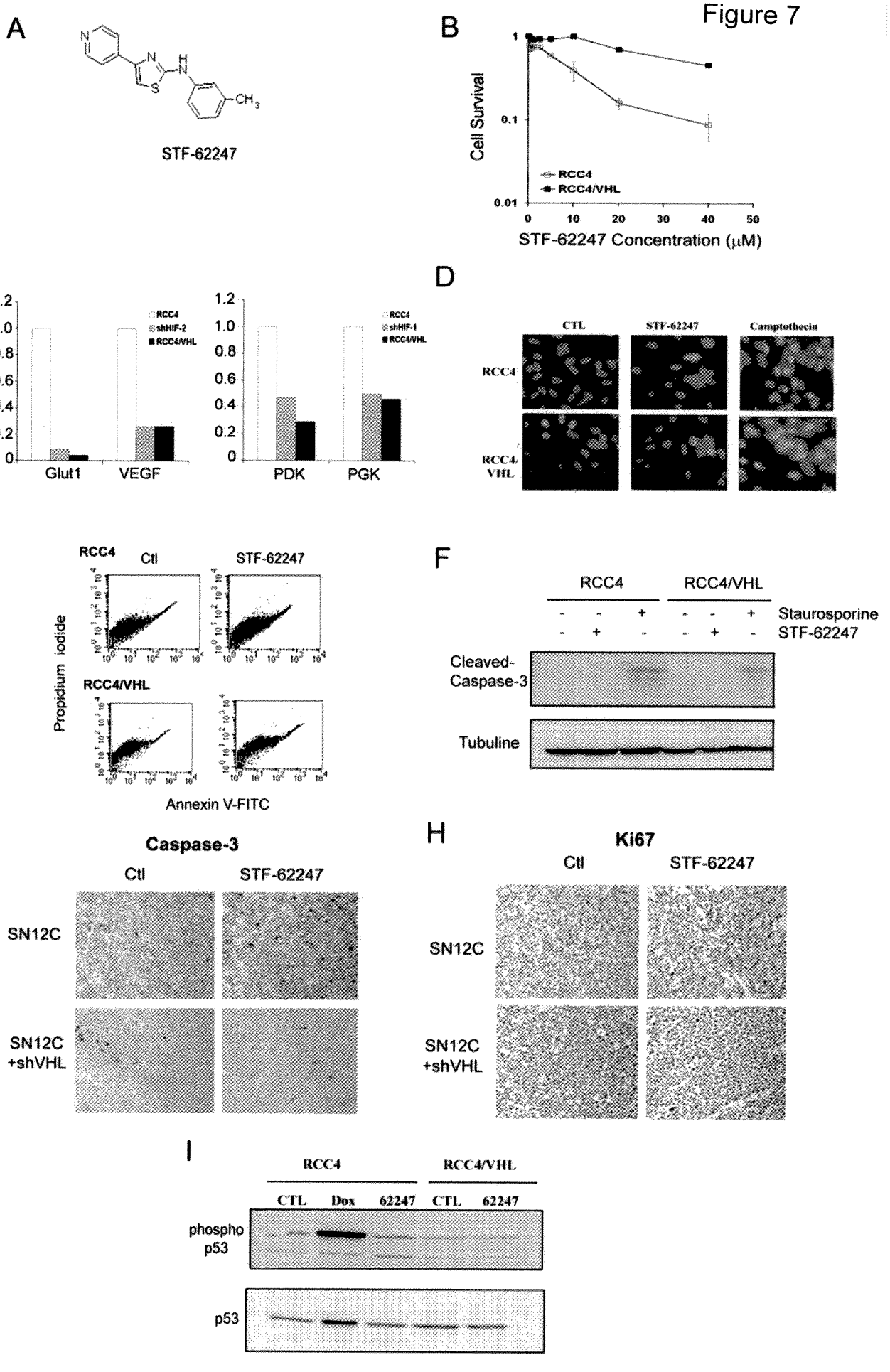

A
STF-62247
B
Cell Survival
RCC4
RCC4/VHL
STF-62247 Concentration (μM)
C
mRNA level
RCC4
shHIF-2
RCC4/VHL
Glut1
VEGF
shHIF-1
PDK
PGK
D
CTL
STF-62247
Camptothecin
RCC4
RCC4/VHL
E
RCC4
Ctl
STF-62247
RCC4/VHL
Propidium iodide
Annexin V-FITC
F
RCC4
RCC4/VHL
Staurosporine
STF-62247
Cleaved-Caspase-3
Tubuline
G
Caspase-3
Ctl
STF-62247
SN12C
SN12C +shVHL
H
Ki67
Ctl
STF-62247
SN12C
SN12C +shVHL
I
RCC4
RCC4/VHL
CTL
Dox
62247
CTL
62247
phospho p53
p53

Figure 8

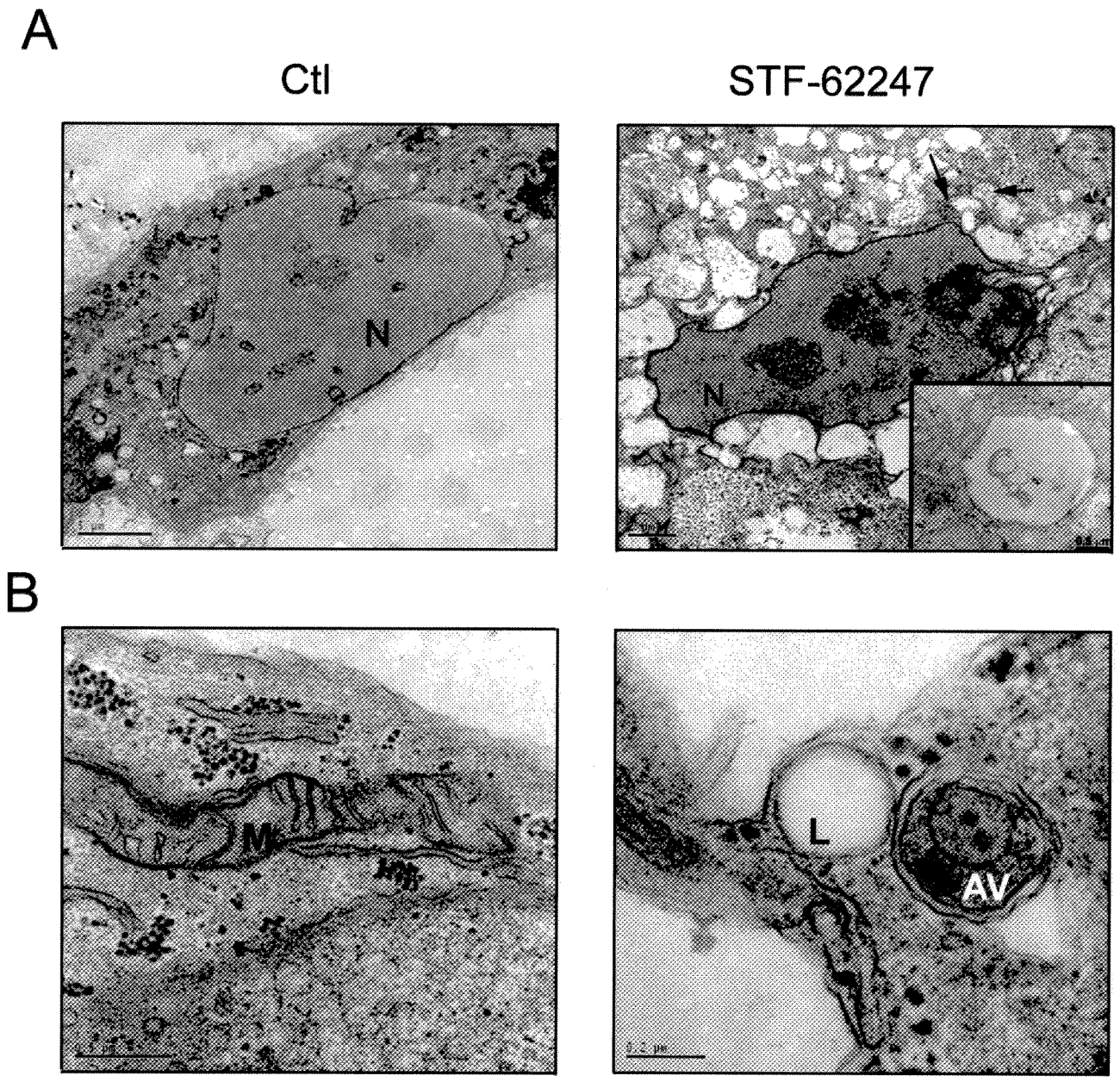


Figure 9

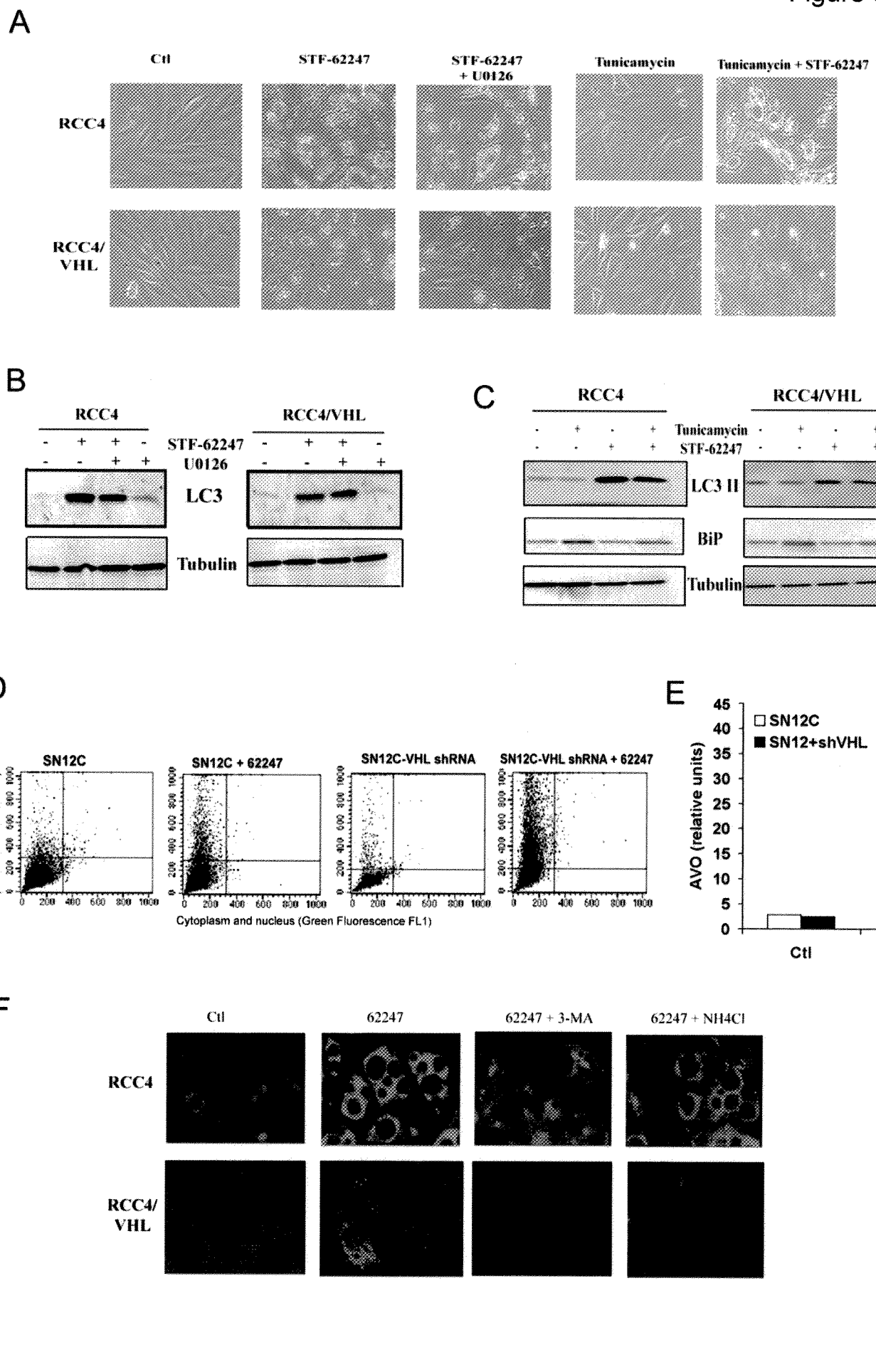
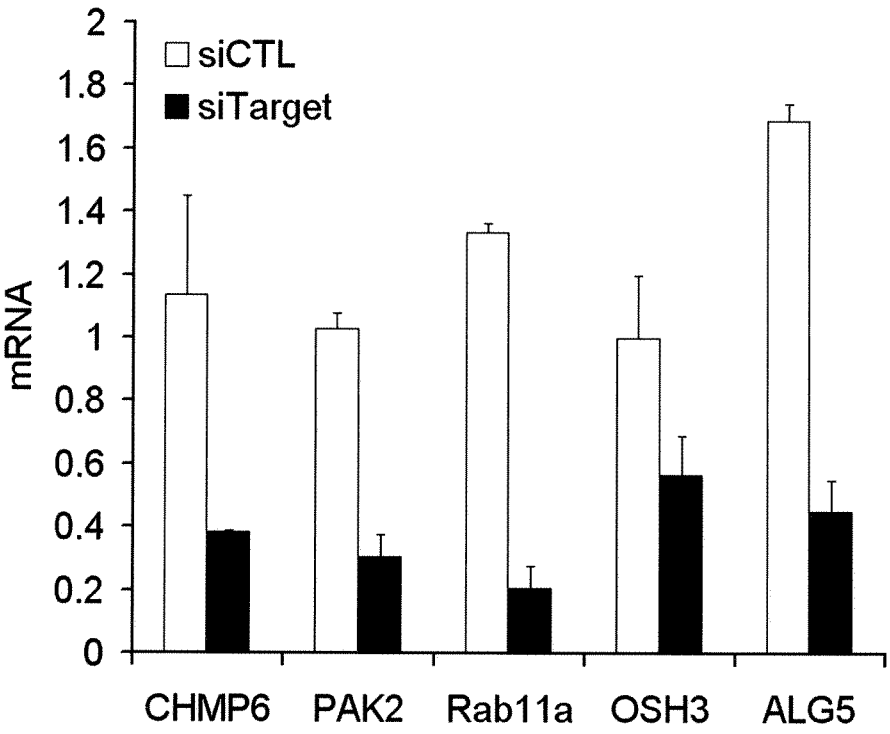

A
Ctl
STF-62247
STF-62247 + U0126
Tunicamycin
Tunicamycin + STF-62247
RCC4
RCC4/VHL
B
RCC4
RCC4/VHL
STF-62247
U0126
LC3
Tubulin
C
RCC4
RCC4/VHL
Tunicamycin
STF-62247
LC3 II
BiP
Tubulin
D
SN12C
SN12C + 62247
SN12C-VHL shRNA
SN12C-VHL shRNA + 62247
Acidic vesicle organelles (Red Fluorescence FL3)
Cytoplasm and nucleus (Green Fluorescence FL1)
E
SN12C
SN12+shVHL
AVO (relative units)
Ctl
62247
F
Ctl
62247
62247 + 3-MA
62247 + NH4Cl
RCC4
RCC4/VHL

Figure 10


2
1.8
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
mRNA
siCTL
siTarget
CHMP6
PAK2
Rab11a
OSH3
ALG5

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2009/036696

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D401/04 C07D417/04 A61K31/4436 A61K31/4439

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2007/065939 A (AB SCIENCE [FR]; CIUFOLINI MARCO A [CA]; LERMET ANNE [FR]; PEZ DIDIER) 14 June 2007 (2007-06-14) compound 3	1-50
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-/--

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
31 July 2009	13/08/2009

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Bakboord, Joan

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2009/036696

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X	DE 36 01 196 A1 (MERCK PATENT GMBH [DE]) 23 July 1987 (1987-07-23) column 31, line 56 - line 57 column 28, line 67 - line 68	1-50
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-/--

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2009/036696

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	TURCOTTE S. ET AL: "A molecule targeting VHL-deficient renal cell carcinoma that induces autophagy" CANCER CELL, vol. 14, 2008, pages 90-102, XP002538117 the whole document	1-72

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2009/036696

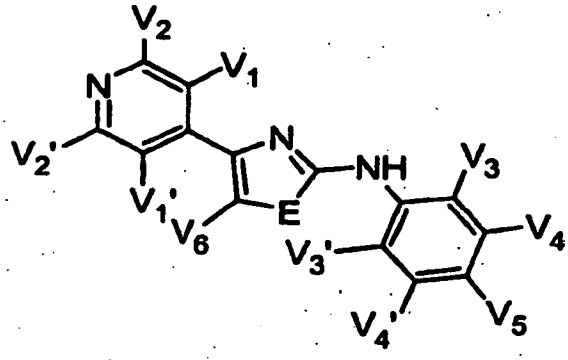
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		EP 1702917 A1	20-09-2006

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2009/036696

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Formula II