

Supporting Information

4-Pyridylanilinothiazoles that selectively target von Hippel-Lindau deficient Renal Cell Carcinoma by inducing autophagic cell death

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General procedures

Analyses were carried out in the Campbell Microanalytical Laboratory, University of Otago, Dunedin, NZ. All final products were analysed by reverse-phase HPLC, (Altima C18 5 μ m column, 150 \times 3.2 mm; Alltech Associated, Inc., Deerfield, IL) using an Agilent HP1100 equipped with a diode-array detector. Mobile phases were gradients of 80% acetonitrile/20% H₂O (v/v) in 45 mM ammonium formate at pH 3.5 and 0.5 mL/min. Purity was determined by monitoring at 330 \pm 50 nM and was >95% in all cases. 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 ¹H and 100 MHz for ¹³C spectra. Spectra were obtained in [(CD₃)₂SO] unless otherwise specified, and were referenced to Me₄Si. 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 MgSO₄. Solvents were evaporated under reduced pressure on a rotary evaporator. Thin-layer chromatography was carried out on aluminium-backed silica gel plates (Merck 60 F₂₅₄) with visualization of components by UV light (254 nm) or exposure to I₂. 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; ether 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.

General Method A. Preparation of Pyridyl 2-Bromoethanones. Br₂ (80 mmol) was added dropwise to a stirred a solution of acetylpyridine (80 mmol) in 30% HBr/HOAc (100 mL) at 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 Et₂O (400 mL) and stirred for 30 min. The precipitate was filtered, washed with Et₂O (25 mL) and dried under vacuum to give the bromoethanone as the hydrobromide salt.

General Method B. Preparation of Thioureas. NH_4SCN (50 mmol) was added to a stirred solution of m-toluidine (50 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 precipitate was purified by column chromatography, eluting with an appropriate blend (30–100%) of EtOAc/pet. ether, to give the thiourea.

General Method C. Alternative Preparation of Thioureas.¹ Benzoyl chloride (65 mmol) was added dropwise to a solution of NH_4SCN (69 mmol) in dry acetone (50 mL). The mixture was stirred at reflux temperature for 15 min. The heating was removed and m-toluidine (46 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 an appropriate blend (30–100%) of EtOAc/pet. ether, to give the thiourea.

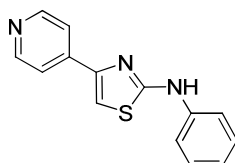
General Method D. Preparation of Thiazoles. A mixture of bromoketone hydrobromide (3 mmol) and phenylthiourea (3 mmol) in EtOH (20 mL) was stirred at reflux temperature for 1 h. The mixture was cooled to 20 °C, diluted with water (50 mL), the pH adjusted to ca. 8 with aqueous NH_3 and the mixture stirred at 20 °C for 2 h. The precipitate was filtered, washed with water (5 mL) and dried. The solid was purified by column chromatography, eluting with an appropriate blend (30–100%) of EtOAc/pet. ether, to give the thiazole.

General Method E. Preparation of pyridyl amides. Et_3N (6.0 mmol) was added to a stirred suspension of 4-pyridinylacetic acid (1.5 mmol), EDCI (1.7 mmol), HOBT· H_2O (1.7 mmol) and MeNHOMe·HCl (2.3 mmol) in dry DCM (50 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 an appropriate blend (0–10%) of MeOH/EtOAc, to give the amide.

General Method F. Preparation of pyridyl ketones. A solution of MeMgBr (3 M in hexanes, 7.5 mmol) was added slowly to a stirred solution of amide * (5 mmol) in dry THF (50 mL) at 0 °C and the mixture was stirred at 0 °C for 8 h. The reaction mixture was quenched with saturated aqueous NH₄Cl 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.

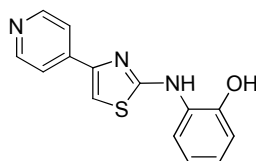
***N*-Phenyl-4-(4-pyridinyl)-1,3-thiazol-2-amine (1).**



2-Bromo-1-(pyridin-4-yl)ethanone Hydrobromide (109). Method A. Reaction of Br₂ (4.45 mL, 86.7 mmol) with 4-acetylpyridine (10.0 g, 82.5 mmol) gave the hydrobromide salt (22.39 g, 97%) as a cream powder: mp (HOAc/ether) 190–195 °C [lit.² mp 197–200 °C]; ¹H 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, CH₂Br).

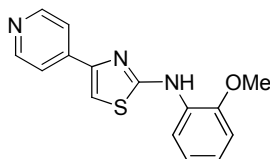
***N*-Phenyl-4-(4-pyridinyl)-1,3-thiazol-2-amine (1). Method D.** Reaction of bromoketone **109** (0.91 g, 3.24 mmol) and phenylthiourea **110** (0.49 g, 3.24 mmol) in EtOH (20 mL) gave amine **1** (0.77 g, 94%) as a white powder: mp (H₂O) 222–225 °C [lit.³ mp (EtOH) 222 °C]; ¹H NMR δ 10.45 (br s, 1 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''); ¹³C 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%).

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



2-[[4-(4-Pyridinyl)-1,3-thiazol-2-yl]amino}phenol (2**). Method D.** Reaction of bromoketone hydrobromide **109** (0.34 g, 1.2 mmol) and *N*-(2-hydroxyphenyl)thiourea **111** (0.20 g, 1.2 mmol) gave amine **2** (0.28 g, 86%) as a cream powder: mp (EtOAc/pet. ether) 221–223 °C; ¹H 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); ¹³C 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 C₁₄H₁₁N₃OS: C, 62.43; H, 4.12; N, 15.60. Found: C, 62.59; H, 4.25; N, 15.42%.

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



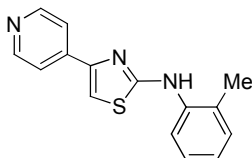
2-Methoxyphenylthiourea (112**). Method B.** Reaction of NH₄SCN (3.37 g, 44.3 mmol) and *o*-anisidine (5.00 g, 44.3 mmol) gave thiourea **112** (1.93 g, 24%) as a white powder: mp (EtOAc/pet. ether) 151–153 °C [lit.¹ mp (acetone/water) 153–155 °C]; ¹H NMR δ 8.99 (s, 1 H, NH), 7.81 (br d, *J* = 7.7 Hz, 1 H, H-3), 7.40 br s, 2 H, NH₂), 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, OCH₃); MS *m/z* 183.3 (MH⁺, 100%).

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

Reaction of bromoketone hydrobromide **109** (0.29 g, 1.1 mmol) and 2-methoxyphenylthiourea **112** (0.19 g, 1.1 mmol) gave amine **3** (0.28 g, 93%) as a cream powder: mp (EtOAc/pet. ether) 190–191 °C; ¹H 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, OCH₃); ¹³C 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%.

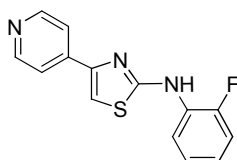
***N*-(2-Methylphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (4).**



2-Methylphenylthiourea (113). Method B. Reaction of NH_4SCN (3.55 g, 46.7 mmol) and *o*-toluidine (5.00 g, 46.7 mmol) gave thiourea **113** (0.74 g, 10%) as a white powder: mp (EtOAc/pet. ether) 149–151 °C [lit. 1mp (acetone/MeOH) 160.5–162.5 °C]; 1H 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%).

***N*-(2-Methylphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (4). Method D.** Reaction of bromoketone hydrobromide **109** (291 mg, 1.0 mmol) and 2-methylphenylthiourea **113** (172 mg, 1.0 mmol) gave amine **4** (0.24 g, 87%) as a cream powder: mp (EtOAc/pet. ether) 158–160 °C; 1H 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%.

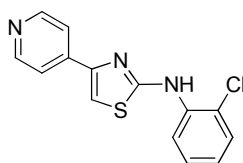
***N*-(2-Fluorophenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (5).**



***N*-(2-Fluorophenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (5). Method D.** Reaction of bromoketone hydrobromide **109** (0.37 g, 1.3 mmol) and *N*-(2-fluorophenyl)thiourea **114** (0.22 g, 1.3 mmol) gave amine **5** (0.31 g, 87%) as a cream powder: mp (EtOAc/pet. ether) 190–192 °C; 1H 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 $\text{C}_{14}\text{H}_{10}\text{FN}_3\text{S}$: C, 61.98; H, 3.72; N, 15.49. Found: C, 61.89; H, 3.37; N, 15.68%.

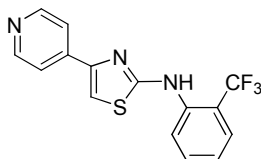
***N*-[2-Chlorophenyl]-4-(4-pyridinyl)-1,3-thiazol-2-amine (6).**



2-Chlorophenylthiourea (115). Method B. Reaction of NH_4SCN (3.12 g, 47.5 mmol) and 2-chloroaniline (6.07 g, 47.5 mmol) gave thiourea **115** (1.23 g, 14%) as a white powder: mp (EtOAc/pet. ether) 141–143 °C [lit.¹ mp (acetone) 144.5–146.5 °C]; ^1H 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%).

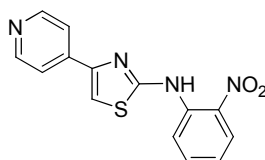
***N*-[2-Chlorophenyl]-4-(4-pyridinyl)-1,3-thiazol-2-amine (6). Method D.** Reaction of bromoketone hydrobromide **109** (0.30 g, 1.1 mmol) and 2-chlorophenylthiourea **115** (0.20 g, 1.1 mmol) gave amine **6** (0.27 g, 90%) as a cream powder: mp (EtOAc/pet. ether) 152–154 °C; ^1H NMR δ 9.79 (br s, 1 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 $\text{C}_{14}\text{H}_{10}\text{ClN}_3\text{S}$: C, 58.43; H, 3.50; N, 14.60. Found: C, 58.34; H, 3.62; N, 14.63%.

4-(4-Pyridinyl)-*N*-[2-(trifluoromethyl)phenyl]-1,3-thiazol-2-amine (7).

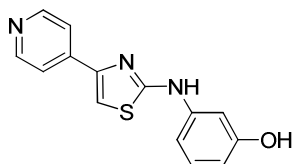


4-(4-Pyridinyl)-N-[2-(trifluoromethyl)phenyl]-1,3-thiazol-2-amine (7). Method D.

Reaction of bromoketone hydrobromide **109** (0.30 g, 1.1 mmol) and 2-trifluorophenylthiourea **116** (0.23 g, 1.1 mmol) gave amine **7** (0.31 g, 93%) as a cream powder: mp (EtOAc/pet. ether) 170–172 °C; ¹H 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'); ¹³C 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 C₁₅H₁₀F₃N₃S: C, 56.07; H, 3.14; N, 17.74. Found: C, 56.07; H, 3.27; N, 13.08%.

N-[2-Nitrophenyl]-4-(4-pyridinyl)-1,3-thiazol-2-amine (8).**N-[2-Nitrophenyl]-4-(4-pyridinyl)-1,3-thiazol-2-amine (8). Method D.**

Reaction of bromoketone hydrobromide **109** (0.32 g, 1.1 mmol) and 2-nitrophenylthiourea **117** (0.22 g, 1.1 mmol) gave amine **8** (0.32 g, 93%) as a cream powder: mp (EtOAc/pet. ether) 127–130 °C; ¹H 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''); ¹³C 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 C₁₄H₁₀N₄O₂S: C, 56.37; H, 3.38; N, 18.78. Found: C, 56.29; H, 3.39; N, 18.84%.

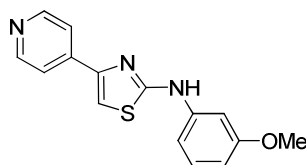
3-[[4-(4-Pyridinyl)-1,3-thiazol-2-yl]amino]phenol (9).

3-Hydroxyphenylthiourea (118). Method B. Reaction of NH₄SCN (3.54 g, 46.6 mmol) with 3-aminophenol (5.08 g, 46.6 mmol) gave thiourea **118** (0.64 g, 8%) as a white powder: mp (H₂O) 172–175 °C (lit.⁴ mp 183–184 °C); ¹H NMR δ 9.94 (s, 1 H, NH), 9.41 (br s, 1 H, OH), 7.34 (br s, 2 H, NH₂), 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).

3-[[4-(4-Pyridinyl)-1,3-thiazol-2-yl]amino]phenol (9). Method D. Reaction of bromoketone hydrobromide **109** (1.02 g, 3.63 mmol) and 3-hydroxyphenylthiourea **118** (0.61 g, 3.63 mmol) gave phenol **9** (0.98 g, 99%) as a cream powder: mp (H₂O) 228–231 °C; ¹H 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); ¹³C 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 C₁₄H₁₁N₃OS·1¼H₂O: C, 57.62; H, 4.66; N, 14.39. Found: C, 57.47; H, 4.14, N, 14.21%.

***N*-(3-Methoxyphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (10).**



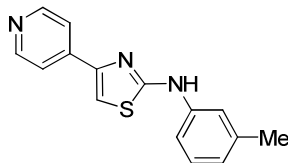
3-Methoxyphenylthiourea (119). Method B. Reaction of NH₄SCN (3.09 g, 40.6 mmol) and *m*-anisidine (5.00 g, 40.6 mmol) gave thiourea **119** (1.34 g, 18%) as a white powder: mp (H₂O) 154–157 °C [lit.¹ mp (MeOH) 157–159 °C]; ¹H NMR δ 9.65 (s, 1 H, NH), 7.42 (br s, 2 H, NH₂), 7.21 (dd, $J = 8.3, 7.9$ Hz, 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, OCH₃).

***N*-(3-Methoxyphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (10). Method D.**

Reaction of bromoketone hydrobromide **109** (1.02 g, 3.62 mmol) and 3-methoxyphenylthiourea **119** (0.66 g, 3.62 mmol) gave amine **10** (0.69 g, 68%) as a cream powder: mp (EtOAc/pet. ether) 176–178 °C; ¹H 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, OCH₃); ¹³C 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%.

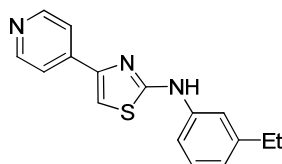
***N*-(3-Methylphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (11).**



3-Methylphenylthiourea (120). Method C. Reaction of benzoyl chloride (7.5 mL, 64.7 mmol) and NH_4SCN (5.28 g, 69.3 mmol) with *m*-toluidine (5.0 mL, 46.2 mmol) gave thiourea **120** (6.62 g, 86%) as a white powder: mp (EtOAc) 109–111 °C [lit.¹ mp (EtOH/water) 110–113 °C]; 1H 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).

***N*-(3-Methylphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (11). Method D.** Reaction of bromoketone hydrobromide **109** (1.13 g, 4.03 mmol) and 3-methylphenylthiourea **120** (0.67 g, 4.03 mmol) gave amine **11** (0.94 g, 87%) as a cream powder: mp (EtOAc/pet. ether) 158–160 °C; 1H 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 $C_{15}H_{13}N_3S \cdot \frac{1}{4}H_2O$: C, 66.27; H, 5.01; N, 15.46. Found: C, 66.48; H, 5.08; N, 15.08%.

***N*-(3-Ethylphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (12).**

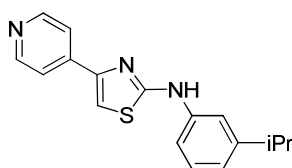


3-Ethylphenylthiourea (121). Method C. Reaction of benzoyl chloride (3.9 mL, 33.8 mmol) and NH_4SCN (2.76 g, 36.2 mmol) with 3-ethylaniline (3.0 mL, 24.1 mmol) gave thiourea **121** (2.73 g, 63%) as an white powder: mp (EtOAc) 82–83 °C; 1H NMR δ 9.60 (s, 1 H, NH), 7.42 (br s, 2 H, NH_2), 7.19–7.24 (m, 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, CH₂), 1.17 (t, $J = 7.4$ Hz, 3 H, CH₃); MS m/z 181.5 (MH⁺, 100%). Anal. calcd for C₉H₁₂N₂S: C, 59.96; H, 6.71; N, 15.54. Found: C, 60.09; H, 6.97; N, 15.59%.

***N*-(3-Ethylphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (12). Method D.** Reaction of bromoketone hydrobromide **109** (0.47 g, 1.7 mmol) and 3-ethylphenylthiourea **121** (0.30 g, 1.7 mmol) gave amine **12** (0.45 g, 95%) as a cream powder: mp (EtOAc/pet. ether) 172–174 °C; ¹H 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, CH₂), 1.22 (t, $J = 7.6$ Hz, 3 H, CH₃); ¹³C 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 C₁₆H₁₅N₃S: C, 68.30; H, 5.37; N, 14.93. Found: C, 68.53; H, 5.52; N, 14.92%.

***N*-(3-Isopropylphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (13).**



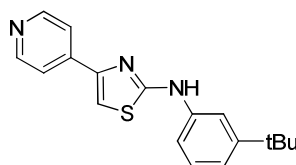
3-Isopropylphenylthiourea (122). Method B. Reaction of NH₄SCN (2.40 g, 31.7 mmol) and 3-isopropylaniline (4.28 g, 31.7 mmol) gave thiourea **122** (1.38 g, 22%) as an oil: ¹H NMR δ 9.60 (s, 1 H, NH), 7.35 (br s, 2 H, NH₂), 7.19–7.26 (m, 3 H, H-2, H-4, H-5), 7.00 (dt, $J = 4.5, 1.6$ Hz, 1 H, H-6), 2.86 (sept, $J = 6.9$ Hz, 1 H, CH), 1.19 (d, $J = 6.9$ Hz, 6 H, 2 × CH₃); MS m/z 195.5 (MH⁺, 100%). Anal. calcd for C₁₀H₁₄N₂S·¼H₂O: C, 60.42; H, 7.35; N, 14.09. Found: C, 60.41; H, 7.22; N, 13.85%.

***N*-(3-Isopropylphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (13). Method D.**

Reaction of bromoketone hydrobromide **109** (0.92 g, 3.3 mmol) and 3-isopropylphenylthiourea **122** (0.64 g, 3.3 mmol) gave amine **13** (0.81 g, 84%) as a cream powder: mp (EtOAc/pet. ether) 200–202 °C; ¹H 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, $2 \times \text{CH}_3$); ^{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 $\text{C}_{17}\text{H}_{17}\text{N}_3\text{S}$: C, 69.12; H, 5.80; N, 14.22. Found: C, 69.18; H, 5.92; N, 14.34%.

***N*-(3-*tert*-Butylphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (14).**

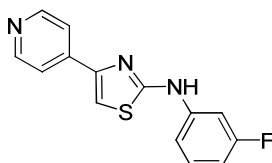


3-*tert*-Butylphenylthiourea (123). Method C. Reaction of benzoyl chloride (5.4 mL, 46.9 mmol) and NH_4SCN (3.83 g, 50.3 mmol) with 3-*tert*-butylaniline (5.0 g, 33.5 mmol) gave thiourea **123** (6.53 g, 94%) as a gum: ^1H NMR (CDCl_3) δ 7.95 (s, 1 H, NH), 7.35–7.38 (m, 2 H, H-4, H-5), 7.23–7.25 (m, 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, $\text{C}(\text{CH}_3)_3$]. Anal. calcd for $\text{C}_{11}\text{H}_{16}\text{N}_2\text{S}$: C, 63.42; H, 7.74; N, 13.45. Found: C, 63.83; H, 7.64; N, 12.81%.

***N*-(3-*tert*-Butylphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (14). Method D.**

Reaction of bromoketone hydrobromide **109** (0.56 g, 2.0 mmol) and 3-*tert*-butylphenylthiourea **123** (0.41 g, 2.0 mmol) gave amine **14** (0.50 g, 81%) as a cream powder: mp (EtOAc/pet. ether) 208–210 °C; ^1H 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, $\text{C}(\text{CH}_3)_3$]; ^{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 $\text{C}_{18}\text{H}_{19}\text{N}_3\text{S}$: C, 69.87; H, 6.19; N, 13.58. Found: C, 69.93; H, 6.07; N, 13.57%.

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

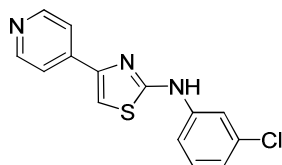


3-Fluorophenylthiourea (124). Method B. Reaction of NH_4SCN (0.53 g, 7.0 mmol) and benzoylchloride (0.82 mL, 7.2 mmol) with 3-chloroaniline (0.45 mL, 4.6 mmol)

gave thiourea **124** (0.49 g, 62%) as a white powder: mp (H₂O) 100–102 °C (lit.⁵ mp 113–114 °C); ¹H NMR δ 9.81 (s, 1 H, NH), 7.60 (br s, 2 H, NH₂), 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).

***N*-(3-Fluorophenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (15). Method D.** Reaction of bromoketone hydrobromide **109** (0.65 g, 2.3 mmol) and 3-fluorophenylthiourea **124** (0.39 g, 2.3 mmol) gave amine **15** (0.45 g, 71%) as a white powder: mp (EtOAc/pet. ether) 229–230 °C; ¹H 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''); ¹³C 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 C₁₄H₁₀FN₃S: C, 61.98; H, 3.72; N, 15.49. Found: C, 61.91; H, 3.79; N, 15.20%.

***N*-(3-Chlorophenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (16).**

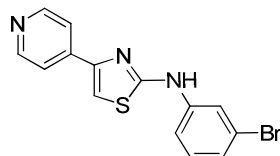


3-Chlorophenylthiourea (125). Method B. Reaction of NH₄SCN (2.98 g, 39.2 mmol) and 3-chloroaniline (5.00 g, 39.2 mmol) gave thiourea **125** (3.63 g, 50%) as a white powder: mp (H₂O) 139–142 °C [lit.¹ mp (acetone/H₂O) 140–140.5 °C]; ¹H NMR δ 9.78 (s, 1 H, NH), 7.78 (br s, 2 H, NH₂), 7.70 (br s, 1 H, H-2), 7.30–7.35 (m, 2 H, H-4, H-5), 7.17–7.16 (m, 1 H, H-6).

***N*-(3-Chlorophenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (16). Method D.** Reaction of bromoketone hydrobromide **109** (1.13 g, 4.02 mmol) and 3-chlorophenylthiourea **125** (0.75 g, 4.02 mmol) gave amine **16** (0.95 g, 82%) as a lemon powder: mp (EtOAc/pet. ether) 208–210 °C; ¹H 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''); ¹³C 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 $C_{14}H_{10}ClN_3S \cdot \frac{1}{4}EtOAc$: C, 58.16; H, 3.90; N, 13.56. Found: C, 58.21; H, 3.88; N, 13.78%

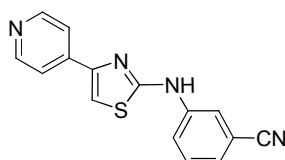
***N*-(3-Bromophenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (17).**



3-Bromophenylthiourea (126). Method C. Reaction of benzoyl chloride (4.5 mL, 38.6 mmol) and NH_4SCN (3.14 g, 41.3 mmol) with 3-bromoaniline (3.0 mL, 27.5 mmol) gave thiourea **126** (5.18 g, 82%) as a tan powder: mp (EtOAc/pet. ether) 151–152 °C [lit.⁶ mp (EtOH) 138 °C]; 1H 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).

***N*-(3-Bromophenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (17). Method D.** Reaction of bromoketone hydrobromide **109** (0.72 g, 2.6 mmol) and 3-bromophenylthiourea **126** (0.59 g, 2.6 mmol) gave amine **17** (0.62 g, 72%) as a cream powder: mp (EtOAc/pet. ether) 219–221 °C; 1H 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 $C_{14}H_{10}BrN_3S \cdot \frac{1}{4}CH_3CO_2CH_2CH_3$: C, 50.86; H, 3.41; N, 11.86. Found: C, 51.02; H, 3.41; N, 11.86%.

3-[[4-(4-Pyridinyl)-1,3-thiazol-2-yl]amino]benzonitrile (18).

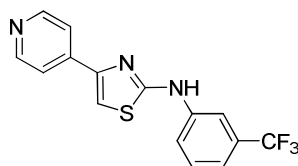


3-Cyanophenylthiourea (127). Method B. Reaction of 3-aminobenzonitrile (1.0 g, 8.5 mmol) and NH_4SCN (0.64 g, 8.5 mmol) gave thiourea **127** (0.22 g, 15%) as a tan powder: mp (EtOAc/DCM) 158–160 °C; 1H NMR δ 9.89 (s, 1 H, NH), 8.03 (br s, 1

H, H-2), 7.70 (dt, $J = 7.6, 2.0$ Hz, 1 H, H-4), 7.60 (br s, 2 H, NH₂), 7.48–7.55 (m, 2 H, H-5, H-6).

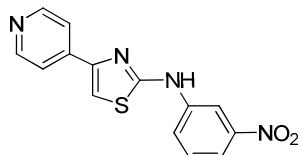
3-[[4-(4-Pyridinyl)-1,3-thiazol-2-yl]amino]benzonitrile (18). Method D. Reaction of bromoketone hydrobromide **109** (0.17 g, 0.62 mmol) and 3-cyanophenylthiourea **127** (0.11 g, 0.62 mmol) gave amine **18** (0.15 g, 90%) as a white powder: mp (MeOH/DCM) 252–253 °C; ¹H NMR δ 10.73 (s, 1 H, NH), 8.64 (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 C₁₅H₁₀N₄S·½H₂O: C, 63.70; H, 3.74; N, 19.81. Found: C, 63.63; H, 3.92; N, 19.72%.

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



4-(4-Pyridinyl)-N-[3-(trifluoromethyl)phenyl]-1,3-thiazol-2-amine (19). Method D. Reaction of bromoketone hydrobromide **109** (0.64 g, 2.27 mmol) and 3-trifluoromethylphenylthiourea **128** (0.50 g, 2.27 mmol) gave amine **19** (0.66 g, 90%) as a cream powder: mp (EtOAc/pet. ether) 239–241 °C; ¹H 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''); ¹³C 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 C₁₅H₁₀F₃N₃S: C, 56.07; H, 3.14; N, 13.08. Found: C, 55.67; H, 3.07; N, 12.85%.

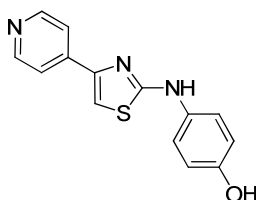
N-(3-Nitrophenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (20).



3-Nitrophenylthiourea (129). Method B. Reaction of NH_4SCN (2.89 g, 38.0 mmol) and m-nitroaniline (5.00 g, 36.2 mmol) gave thiourea **129** (0.45 g, 6%) as an orange powder: mp (EtOAc) 152–154 °C; ^1H 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).

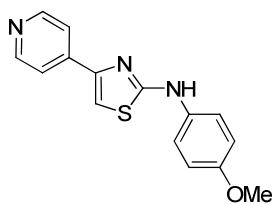
N-(3-Nitrophenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (20). Method D. Reaction of bromoketone hydrobromide **109** (0.58 g, 2.1 mmol) and 3-nitrophenylthiourea **129** (0.41 g, 2.1 mmol) gave amine **20** (0.43 g, 69%) as a orange powder: mp (EtOAc/pet. ether) 244–247 °C; ^1H NMR δ 10.89 (br s, 1 H, 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 $\text{C}_{14}\text{H}_{10}\text{N}_4\text{O}_2\text{S} \cdot \frac{1}{4}\text{CH}_3\text{OH}$: C, 55.87; H, 3.62; N, 18.29. Found: C, 55.85; H, 3.56; N, 18.21%.

4-[[4-(4-Pyridinyl)-1,3-thiazol-2-yl]amino]phenol (21).



4-[[4-(4-Pyridinyl)-1,3-thiazol-2-yl]amino]phenol (21). Method D. Reaction of bromoketone hydrobromide **109** (1.05 g, 3.74 mmol) and 4-hydroxyphenylthiourea **130** (0.63 g, 3.74 mmol) gave phenol **21** (0.82 g, 81%) as a cream powder: mp (H_2O) 269–272 °C; ^1H 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 $\text{C}_{14}\text{H}_{11}\text{N}_3\text{OS}$: C, 62.43; H, 4.12; N, 15.60. Found: C, 62.19; H, 4.24; N, 15.48%.

N-(4-Methoxyphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (22).

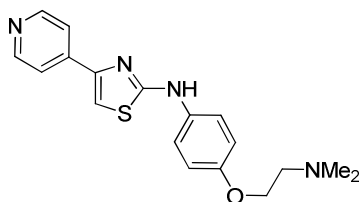


4-Methoxyphenylthiourea (131). Method B. Reaction of NH_4SCN (3.09 g, 40.6 mmol) and *p*-anisidine (5.00 g, 40.6 mmol) gave thiourea **131** (0.85 g, 11%) as a white powder: mp (H_2O) 206–209 °C [lit.¹ mp (MeOH) 212–214 °C]; ^1H NMR δ 9.44 (s, 1 H, NH), 7.15–7.30 (m, 4 H, NH_2 , H-3, H-5), 6.89 (ddd, $J = 9.0, 3.4, 2.2$ Hz, 2 H, H-2, H-6), 3.74 (s, 3 H, OCH_3).

***N*-(4-Methoxyphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (22). Method D.**

Reaction of bromoketone hydrobromide **109** (1.26 g, 4.50 mmol) and 4-methoxyphenylthiourea **131** (0.82 g, 4.50 mmol) gave amine **22** (0.76 g, 60%) as a cream powder: mp (EtOAc) 178–180 °C; ^1H 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 $\text{C}_{15}\text{H}_{13}\text{N}_3\text{OS}$: C, 63.58; H, 4.62; N, 14.83. Found: C, 63.45; H, 4.65; N, 14.82%.

***N*-[4-[2-(Dimethylamino)ethoxy]phenyl]-4-(4-pyridinyl)-1,3-thiazol-2-amine (23).**



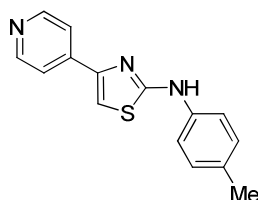
1-(4-(2-(Dimethylamino)ethoxy)phenyl)thiourea (132). Thiophosgene (0.95 mL, 12.45 mmol) was added dropwise to a stirred solution of 4-(2-(dimethylamino)ethoxy)aniline (2.04 g, 11.32 mmol) and $i\text{Pr}_2\text{NEt}$ (2.37 mL, 13.58 mmol) in dry THF (50 mL) at 0 °C and the solution stirred at 20 °C for 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 **132** (1.78 g, 66%) as a

gum: $^1\text{H NMR}$ 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, $\text{N}(\text{CH}_3)_2$]; MS m/z 240.4 (MH^+ , 100%).

***N*-{4-[2-(Dimethylamino)ethoxy]phenyl}-4-(4-pyridinyl)-1,3-thiazol-2-amine (23).**

Method D. Reaction of bromoketone hydrobromide **109** (0.63 g, 2.25 mmol) and 1-(4-(2-(dimethylamino)ethoxy)phenyl)thiourea **132** (0.54 g, 2.25 mmol) gave amine **23** (447 mg, 58%) as an oil: $^1\text{H NMR}$ 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, $\text{N}(\text{CH}_3)_3$]; $^{13}\text{C NMR}$ 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 $\text{C}_{18}\text{H}_{22}\text{Cl}_2\text{N}_4\text{OS}\cdot 1\frac{1}{4}\text{H}_2\text{O}$: C, 49.60; H, 5.66; N, 12.85. Found: C, 49.49; H, 5.75; N, 12.67%.

***N*-(4-Methylphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (24).**

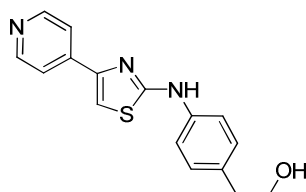


4-Methylphenylthiourea (133). Method B. Reaction of NH_4SCN (3.55 g, 46.7 mmol) and p-toluidine (5.00 g, 46.7 mmol) gave thiourea **133** (1.88 g, 24%) as a white powder: mp (H_2O) 181–183 °C [lit.¹ mp (MeOH) 194 °C]; $^1\text{H NMR}$ δ 9.45 (br s, 1 H, NH), 7.35 (br s, 2 H, NH_2), 7.24 (d, $J = 8.3$ 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).

***N*-(4-Methylphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (24). Method D.** Reaction of bromoketone hydrobromide **109** (0.72 g, 2.56 mmol) and 4-methylphenylthiourea **133** (0.43 g, 2.56 mmol) gave amine **24** (0.51 g, 74%) as a cream powder: mp (EtOAc) 230–233 °C; $^1\text{H NMR}$ 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, CH₃); ¹³C 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 C₁₅H₁₃N₃S: C, 67.39; H, 4.90; N, 15.72. Found: C, 67.53; H, 4.92; N, 15.50%.

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

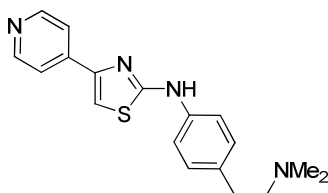


1-(4-(2-Hydroxyethyl)phenyl)thiourea (134). Method B. Reaction of NH₄SCN (2.91 g, 38.2 mmol) and 2-(4-aminophenyl)ethanol (5.24 g, 38.2 mmol) gave thiourea **134** (0.41 g, 5%) as a tan gum: ¹H NMR δ 9.56 (br s, 1 H, NH), 7.30 (br s, 2 H, NH₂), 7.26 (br d, $J = 8.4$ Hz, 2 H, H-3, H-5), 7.16 (br d, $J = 8.4$ 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%).

2-(4-{[4-(4-Pyridinyl)-1,3-thiazol-2-yl]amino}phenyl)ethanol (25). Method D.

Reaction of bromoketone hydrobromide **109** (0.58 g, 2.06 mmol) and thiourea **134** (0.41 g, 2.06 mmol) gave alcohol **25** (0.33 g, 54%) as a white powder: mp (EtOAc) 179–181 °C; ¹H 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); ¹³C NMR δ 163.6, 150.0 (2), 147.6, 141.0, 138.9, 132.5, 119.8 (2), 117.0 (2), 107.0, 62.2, 38.3; MS m/z 298.4 (MH⁺, 100%). Anal. calcd for C₁₆H₁₅N₃OS·¼CH₃OH: C, 63.91; H, 5.28; N, 13.76. Found: C, 63.94; H, 5.26; N, 14.03%.

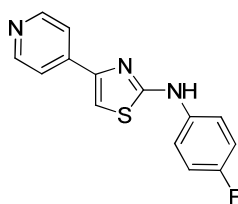
N-{4-[2-(Dimethylamino)ethyl]phenyl}-4-(4-pyridinyl)-1,3-thiazol-2-amine (26).



***N*-{4-[2-(Dimethylamino)ethyl]phenyl}-4-(4-pyridinyl)-1,3-thiazol-2-amine (26).**

Methanesulfonyl chloride (77 μ L, 1.00 mmol) was added dropwise to a stirred solution of alcohol **25** (270 mg, 0.91 mmol) and *i*Pr₂NEt (190 μ L, 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 KHCO₃ solution (20 mL), brine (10 mL), dried, and the solvent evaporated. The residue was dissolved in DMF (5 mL) and anhydrous Me₂NH 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 NH₃/20% MeOH/EtOAc, to give amine **26** (165 mg, 56%) as a oil: ¹H 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, CH₂), 2.44 (br dd, *J* = 8.2, 7.1 Hz, 2 H, CH₂N), 2.19 [s, 6 H, N(CH₃)₃]; ¹³C 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 C₁₈H₂₁ClN₄S·½CH₃OH: C, 58.95; H, 6.15; N, 14.86. Found: C, 58.96; H, 6.04; N, 15.06%.

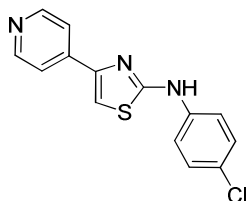
***N*-(4-Fluorophenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (27).**



***N*-(4-Fluorophenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (27). Method D.** Reaction of bromoketone hydrobromide **109** (0.83 g, 2.94 mmol) and 4-fluorophenylthiourea **135** (0.50 g, 2.94 mmol) gave amine **27** (0.76 g, 96%) as a cream powder: mp (EtOAc/pet. ether) 211–213 °C; ¹H 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''); ¹³C 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%.

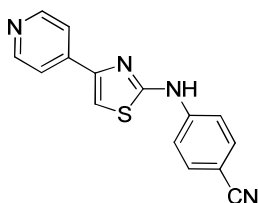
***N*-(4-Chlorophenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (28).**



4-Chlorophenylthiourea (136). Method B. Reaction of NH_4SCN (3.04 g, 40.0 mmol) and 4-chloroaniline (5.10 g, 40.0 mmol) gave thiourea **136** (3.28 g, 44%) as a white powder: mp (EtOAc/pet. ether) 172–172 °C [lit.¹ mp (iPrOH) 176–178 °C]; 1H 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).

***N*-(4-Chlorophenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (28). Method D.** Reaction of bromoketone hydrobromide **109** (1.24 g, 4.41 mmol) and 4-chlorophenylthiourea **136** (0.82 g, 4.41 mmol) gave amine **28** (0.49 g, 39%) as a cream powder: mp (EtOAc/pet. ether) 259–261 °C; 1H 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%.

4-[[4-(4-Pyridinyl)-1,3-thiazol-2-yl]amino]benzonitrile (29).

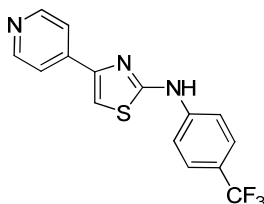


***N*-(4-Cyanophenyl)thiourea (137). Method B.** Reaction of NH_4SCN (3.83 g, 50.4 mmol) and 4-aminobenzonitrile (5.95 g, 50.4 mmol) gave thiourea **137** (3.58 g, 40%) as a white powder: mp (EtOAc/DCM) >310 °C [lit.⁷ mp 239 °C]; 1H NMR δ 10.06 (s,

1 H, NH), 7.70–7.80 (m, 6 H, NH₂, H-2', H-3', H-5', H-6'); MS *m/z* 178.4 (MH⁺, 100%).

4-[[4-(4-Pyridinyl)-1,3-thiazol-2-yl]amino]benzonitrile (29). Method D. Reaction of bromoketone hydrobromide **109** (0.31 g, 1.1 mmol) and *N*-(4-cyanophenyl)thiourea **137** (0.19 g, 1.1 mmol) gave amine **29** (0.27 g, 90%) as a cream powder: mp (EtOAc/pet. ether) >300 °C; ¹H 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); ¹³C 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 C₁₅H₁₀N₄S: C, 64.73; H, 3.62; N, 20.13. Found: C, 64.50; H, 3.80; N, 20.17%.

4-(4-Pyridinyl)-*N*-[4-(trifluoromethyl)phenyl]-1,3-thiazol-2-amine (30).

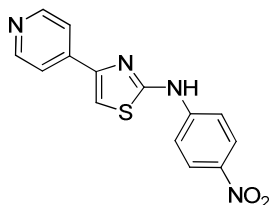


***N*-[4-(Trifluoromethyl)phenyl]thiourea (138). Method B.** Reaction of NH₄SCN (2.74 g, 36.0 mmol) and 4-trifluoromethylaniline (5.80 g, 36.0 mmol) gave thiourea **138** (0.98 g, 12%) as a white powder: mp (EtOAc/pet. ether) 122–125 °C [lit.¹ mp (toluene) 143.5–146 °C]; ¹H NMR δ 9.97 (s, 1 H, NH), 9.80 (br s, 2 H, NH₂), 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%).

4-(4-Pyridinyl)-*N*-[4-(trifluoromethyl)phenyl]-1,3-thiazol-2-amine (30). Method D. Reaction of bromoketone hydrobromide **109** (0.27 g, 1.0 mmol) and 4-trifluoromethylphenylthiourea **138** (0.22 g, 1.0 mmol) gave amine **30** (0.17 g, 54%) as a cream powder: mp (EtOAc/pet. ether) 238–241 °C; ¹H 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'); ¹³C 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%.

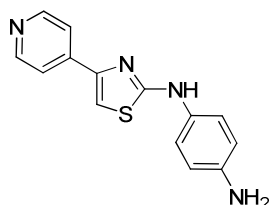
***N*-(4-Nitrophenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (31).**



4-Nitrophenylthiourea (139). Method B. Reaction of NH_4SCN (2.75 g, 36.2 mmol) and 4-nitroaniline (5.00 g, 36.2 mmol) gave thiourea **139** (2.16 g, 30%) as a tan powder: mp (EtOAc/pet. ether) 213–215 °C [lit.¹ mp (acetone) 220–242 °C (dec)]; 1H 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).

***N*-(4-Nitrophenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (31). Method D.** Reaction of bromoketone hydrobromide **109** (1.91 g, 6.80 mmol) and 4-nitrophenylthiourea **139** (1.34 g, 6.80 mmol) gave amine **31** (1.93 g, 95%) as a cream powder: mp (MeOH/EtOAc) >290 °C; 1H 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 $C_{14}H_{10}N_4O_2S \cdot \frac{1}{4}EtOAc$: C, 56.24; H, 3.78; N, 17.49. Found: C, 56.49; H, 4.08; N, 17.07%.

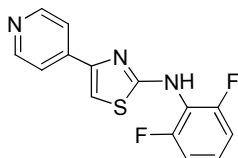
***N*¹-[4-(4-Pyridinyl)-1,3-thiazol-2-yl]-1,4-benzenediamine (32).**



A mixture of amine **31** (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 **32** (0.16 g, 90%) as a tan powder: mp (MeOH/EtOAc) 209–211 °C; 1H 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, NH₂); ¹³C 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 C₁₄H₁₂N₄S: C, 62.66; H, 4.51. Found: C, 62.64; H, 5.00%.

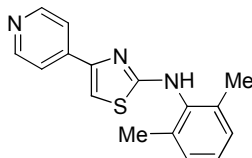
***N*-(2,6-Difluorophenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (33).**



***N*-(2,6-Difluorophenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (33). Method D.**

Reaction of bromoketone hydrobromide **109** (0.30 g, 1.1 mmol) and *N*-(2-fluorophenyl)thiourea **140** (0.20 g, 1.1 mmol) gave amine **33** (0.29 g, 91%) as a white powder: mp (EtOAc/pet. ether) 209–211 °C; ¹H 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''); ¹³C 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 C₁₄H₉F₂N₃S: C, 58.12; H, 3.14; N, 14.52. Found: C, 58.26; H, 3.42; N, 14.40%.

***N*-(2,6-Dimethylphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (34).**

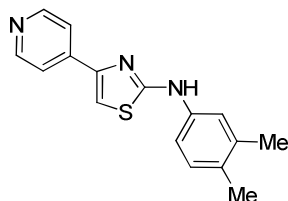


***N*-(2,6-Dimethylphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (34). Method D.**

Reaction of bromoketone hydrobromide **109** (0.30 g, 1.1 mmol) and *N*-(2,6-difluorophenyl)thiourea **141** (0.20 g, 1.1 mmol) gave amine **34** (0.28 g, 91%) as a white powder: mp (EtOAc/pet. ether) 208–210 °C; ¹H 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 × CH₃); ¹³C 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%.

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

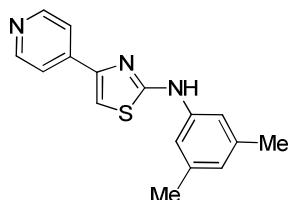


3,4-Dimethylphenylthiourea (142). Method B. Reaction of NH_4SCN (6.3 g, 83.3 mmol) and 3,4-dimethylaniline (10.1 g, 83.3 mmol) gave thiourea **142** (2.04 g, 14%) as a white powder: mp (H_2O) 181–182 °C [lit.¹ mp (DME/ Et_2O) 184–186 °C]; 1H NMR δ 9.48 (s, 1 H, NH), 7.05–7.25 (m, 5 H, H-2, H-5, H-6, NH_2), 2.18 (s, 6 H, 2 \times CH_3).

***N*-(3,4-Dimethylphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (35). Method D.**

Reaction of bromoketone hydrobromide **109** (0.70 g, 2.5 mmol) and 3,4-dimethylphenylthiourea **142** (0.45 g, 2.5 mmol) gave amine **35** (0.59 g, 85%) as a cream powder: mp (MeOH/ $EtOAc$) 177–179 °C; 1H 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%.

***N*-(3,5-Dimethylphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (36).**



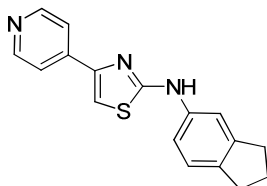
3,5-Dimethylphenylthiourea (143). Method B. Reaction of NH_4SCN (2.51 g, 33.0 mmol) and *m*-toluidine (4.00 g, 33.0 mmol) gave thiourea **143** (1.61 g, 17%) as a white powder: mp (H_2O) 174–176 °C [lit.¹ mp (iPrOH) 172–173 °C]; 1H NMR δ 9.52

(s, 1 H, NH), 7.36 (br s, 2 H, NH₂), 6.96 (s, 2 H, H-2, H-6), 6.76 (s, 1 H, H-4), 2.24 (s, 6 H, 2 × CH₃); 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%).

***N*-(3,5-Dimethylphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (36). Method D.**

Reaction of bromoketone hydrobromide **109** (842 mg, 3.0 mmol) and thiourea **143** (540 mg, 3.0 mmol) gave amine **36** (767 mg, 91%) as a cream powder: mp (EtOAc/pet. ether) 218–220 °C; ¹H 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 × CH₃); ¹³C 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 C₁₆H₁₅N₃S: C, 68.30; H, 5.37; N, 14.93. Found: C, 67.91; H, 5.20; N, 14.92%.

***N*-(2,3-Dihydro-1*H*-inden-5-yl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (37).**

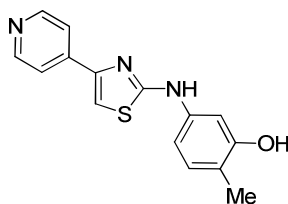


***N*-(2,3-Dihydro-1*H*-inden-5-yl)thiourea (144). Method C.** Reaction of benzoyl chloride (6.3 mL, 54.5 mmol) and NH₄SCN (4.44 g, 58.4 mmol) with 5-indanamine (5.18 g, 38.9 mmol) gave thiourea **144** (5.91 g, 79%) as cream needles: mp (EtOAc/pet ether) 175–177 °C [lit.¹ mp (acetone) 176–179 °C]; ¹H NMR δ 9.52 (s, 1 H, NH), 7.27 (br s, 2 H, NH₂), 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).

***N*-(2,3-Dihydro-1*H*-inden-5-yl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (37). Method D.** Reaction of bromoketone hydrobromide **109** (0.73 g, 2.60 mmol) and 1-(2,3-dihydro-1*H*-inden-5-yl)thiourea **144** (0.50 g, 2.60 mmol) gave amine **37** (0.66 g, 87%) as a tan powder: mp (MeOH/EtOAc) 190–192 °C; ¹H 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 $\text{C}_{17}\text{H}_{15}\text{N}_3\text{S}\cdot\frac{1}{2}\text{CH}_3\text{OH}$: C, 67.93; H, 5.53; N, 13.58. Found: C, 67.58; H, 5.21, N, 13.53%.

2-Methyl-5-[[4-(4-pyridinyl)-1,3-thiazol-2-yl]amino]phenol (38).

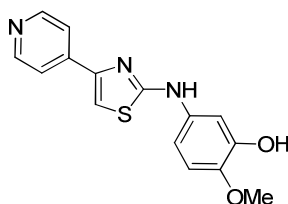


3-Hydroxy-4-methoxyphenylthiourea (145). Method B. Reaction of NH_4SCN (3.78 g, 49.6 mmol) and 3-hydroxy-4-methoxyaniline (6.11 g, 49.6 mmol) gave thiourea **145** (3.34 g, 37%) as a tan powder: ^1H NMR δ 9.46 (s, 1 H, NH), 9.34 (s, 1 H, OH), 7.25 (br s, 2 H, NH_2), 6.98 (d, $J = 8.0$ Hz, 1 H, H-5), 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).

2-Methyl-5-[[4-(4-pyridinyl)-1,3-thiazol-2-yl]amino]phenol (38). Method D.

Reaction of bromoketone hydrobromide **109** (1.23 g, 4.39 mmol) and 3-hydroxy-4-methylphenylthiourea **145** (0.80 g, 4.39 mmol) gave phenol **38** (0.94 g, 74%) as a white powder: mp (EtOAc/pet. ether) 213–215 °C; ^1H 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 $\text{C}_{15}\text{H}_{13}\text{N}_3\text{OS}$: C, 63.58; H, 4.62; N, 14.83. Found: C, 63.48; H, 4.71, N, 14.89%.

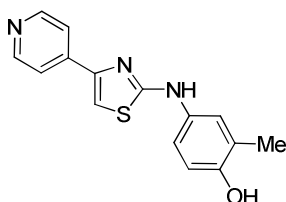
2-Methoxy-5-[[4-(4-pyridinyl)-1,3-thiazol-2-yl]amino]phenol (39).



3-Hydroxy-4-methoxyphenylthiourea (146). Method B. Reaction of NH_4SCN (2.65 g, 34.8 mmol) and 3-hydroxy-4-methoxyaniline (4.84 g, 34.8 mmol) gave thiourea **146** (3.10 g, 45%) as a tan powder: $^1\text{H NMR}$ 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).

2-Methoxy-5-[[4-(4-pyridinyl)-1,3-thiazol-2-yl]amino]phenol (39). Method D. Reaction of bromoketone hydrobromide **109** (1.40 g, 4.99 mmol) and 3-hydroxy-4-methoxyphenylthiourea **146** (0.96 g, 4.99 mmol) gave phenol **39** (1.06 g, 71%) as a white powder: mp (EtOAc) 230–232 °C; $^1\text{H NMR}$ 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); $^{13}\text{C NMR}$ 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 $\text{C}_{15}\text{H}_{13}\text{N}_3\text{O}_2\text{S} \cdot \frac{1}{4}\text{CH}_3\text{OH}$: C, 59.60; H, 4.59; N, 13.67. Found: C, 59.67; H, 4.51, N, 13.83%.

2-Methyl-4-[[4-(4-pyridinyl)-1,3-thiazol-2-yl]amino]phenol (40).

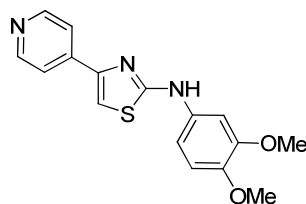


4-Hydroxy-3-methylphenylthiourea (147). Method B. Reaction of NH_4SCN (2.56 g, 33.6 mmol) and 4-hydroxy-3-methylaniline (4.14 g, 33.6 mmol) gave thiourea **147** (0.77 g, 13%) as a tan powder: mp (EtOAc/pet. ether) 168–170 °C; $^1\text{H NMR}$ δ 9.27 (s, 1 H, NH), 9.23 (s, 1 H, OH), 7.11 (br s, 2 H, 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 $\text{C}_8\text{H}_{10}\text{N}_2\text{OS}$: C, 52.72; H, 5.53; N, 15.37. Found: C, 52.71; H, 5.62, N, 15.19%.

2-Methyl-4-[[4-(4-pyridinyl)-1,3-thiazol-2-yl]amino]phenol (40). Method D. Reaction of bromoketone hydrobromide **109** (0.79 g, 2.81 mmol) and 1-(4-hydroxy-3-methylphenyl)thiourea **147** (0.51 g, 2.81 mmol) gave phenol **40** (0.64 g, 80%) as a

white powder: mp (EtOAc/pet. ether) 212–215 °C; ^1H 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, CH₃); ^{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 C₁₅H₁₃N₃OS: C, 63.58; H, 4.62; N, 14.83. Found: C, 63.88; H, 4.69, N, 14.85%.

***N*-(3,4-Dimethoxyphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (41).**

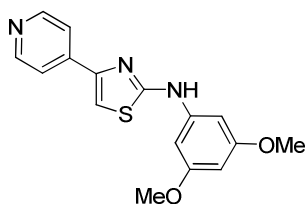


3,4-Dimethoxyphenylthiourea (148). Method B. Reaction of NH₄SCN (2.48 g, 32.6 mmol) and 3,4-dimethoxymethylaniline (5.00 g, 32.6 mmol) gave thiourea **148** (2.33 g, 34%) as a tan powder: ^1H NMR δ 9.48 (s, 1 H, NH), 7.25 (br s, 2 H, NH₂), 7.00 (br s, 1 H, H-2), 6.90 (d, $J = 8.6$ Hz, 1 H, H-5), 6.79 (dd, $J = 8.6, 2.3$ Hz, 1 H, H-6), 3.73 (s, 6 H, 2 \times OCH₃).

***N*-(3,4-Dimethoxyphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (41). Method D.**

Reaction of bromoketone hydrobromide **109** (1.08 g, 3.84 mmol) and 3,4-methoxyphenylthiourea **148** (0.82 g, 3.84 mmol) gave amine **41** (1.04 g, 87%) as a cream powder: mp (EtOAc/pet. ether) 192–194 °C; ^1H 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, OCH₃), 3.74 (s, 3 H, OCH₃); ^{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 C₁₆H₁₅N₃O₂S: C, 61.32; H, 4.82; N, 13.41. Found: C, 61.24; H, 4.79, N, 13.45%.

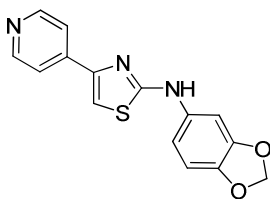
***N*-(3,5-Dimethoxyphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (42).**



3,5-Dimethoxyphenylthiourea (149). Method B. Reaction of NH_4SCN (2.51 g, 33.0 mmol) and 3,5-dimethoxyaniline (5.06 g, 33.0 mmol) gave thiourea **149** (2.92 g, 42%) as a white powder: mp (EtOAc/pet. ether) 173–175 °C; ^1H 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, $2 \times \text{OCH}_3$); ^{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 $\text{C}_9\text{H}_{12}\text{N}_2\text{O}_2\text{S}$: C, 50.92; H, 5.70; N, 13.20. Found: C, 51.02; H, 5.76; N, 13.24%.

***N*-(3,5-Dimethoxyphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (42). Method D.** Reaction of bromoketone hydrobromide **109** (842 mg, 3.0 mmol) and thiourea **149** (636 mg, 3.0 mmol) gave amine **42** (860 mg, 91%) as a cream powder: mp (EtOAc/pet. ether) 229–231 °C; ^1H 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, $2 \times \text{OCH}_3$); ^{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 $\text{C}_{16}\text{H}_{15}\text{N}_3\text{O}_2\text{S} \cdot \frac{1}{4}\text{H}_2\text{O}$: C, 60.46; H, 4.92; N, 13.22. Found: C, 60.65; H, 4.75; N, 13.51%.

***N*-(1,3-Benzodioxol-5-yl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (43).**

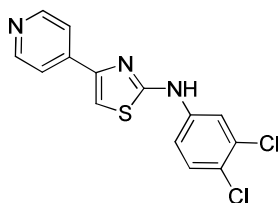


***N*-(1,3-Benzodioxol-5-yl)thiourea (150). Method B.** Reaction of NH_4SCN (2.78 g, 36.5 mmol) and benzo[*d*][1,3]dioxol-5-amine (5.00 g, 36.5 mmol) gave thiourea **150** (2.50 g, 35%) as a tan powder: mp (H_2O) 190–193 °C [lit.¹ mp (MeOH) 209–211 °C]; ^1H NMR δ 9.46 (s, 1 H, NH), 7.47 (br s, 2 H, NH_2), 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).

***N*-(1,3-Benzodioxol-5-yl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (43). Method D.**

Reaction of bromoketone hydrobromide **109** (0.73 g, 2.61 mmol) and 1-(benzo[*d*][1,3]dioxol-5-yl)thiourea **150** (0.51 g, 2.61 mmol) gave amine **43** (0.71 g, 92%) as a tan powder: mp (MeOH/EtOAc) 201–203 °C; ¹H 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''); ¹³C 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 C₁₅H₁₁N₃O₂S·¾H₂O: C, 57.96; H, 4.05; N, 13.51. Found: C, 58.03; H, 3.76, N, 13.16%.

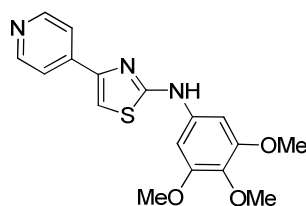
***N*-(3,4-Dichlorophenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (44).**



***N*-(3,4-Dichlorophenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (44). Method D.**

Reaction of bromoketone hydrobromide **109** (0.69 g, 2.44 mmol) and 3,4-dichlorophenylthiourea **151** (0.54 g, 2.44 mmol) gave amine **44** (0.77 g, 97%) as a cream powder: mp (EtOAc) 242–244 °C; ¹H 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''); ¹³C 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 C₁₄H₉Cl₂N₃S·¼EtOAc: C, 52.38; H, 3.27; N, 12.21. Found: C, 52.51; H, 3.51, N, 11.96%.

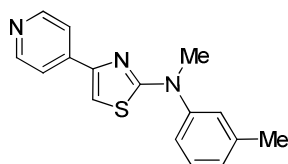
4-(4-Pyridinyl)-*N*-(3,4,5-trimethoxyphenyl)-1,3-thiazol-2-amine (45).



3,4,5-Trimethoxyphenylthiourea (152). Method B. Reaction of NH_4SCN (2.51 g, 33.0 mmol) and 3,4,5-trimethoxyaniline (6.04 g, 33.0 mmol) gave thiourea **152** (1.18 g, 15%) as a white powder: mp (EtOAc/pet. ether) 201–203 °C (lit.⁸ mp 203–205 °C); ^1H 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, $2 \times \text{OCH}_3$), 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 $\text{C}_{10}\text{H}_{14}\text{N}_2\text{O}_3\text{S}$: C, 49.57; H, 5.82; N, 11.56. Found: C, 49.84; H, 5.80; N, 11.57%.

4-(4-Pyridinyl)-*N*-(3,4,5-trimethoxyphenyl)-1,3-thiazol-2-amine (45). Method D. Reaction of bromoketone hydrobromide **109** (842 mg, 3.0 mmol) and 3,4,5-trimethoxyphenylthiourea **152** (726 mg, 3.0 mmol) gave amine **45** (215 mg, 21%) as a cream powder: mp (MeOH/EtOAc) 207–209 °C; ^1H 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, $2 \times \text{OCH}_3$), 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 $\text{C}_{17}\text{H}_{17}\text{N}_3\text{O}_3\text{S} \cdot \frac{1}{4}\text{CH}_3\text{OH}$: C, 58.96; H, 5.16; N, 11.96. Found: C, 58.79; H, 5.08; N, 11.95%.

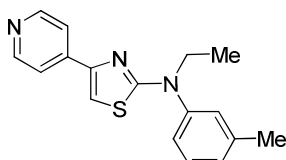
***N*-Methyl-*N*-(3-methylphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (46).**



***N*-Methyl-*N*-(3-methylphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (46).** NaH (216 mg, 5.4 mmol) was added to a stirred solution of amine **11** (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 **46** (0.69 g, 86%) as a colourless oil: ^1H 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

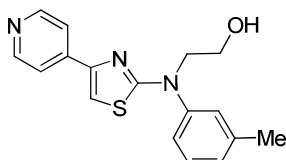
(m, 2 H, H-2'', H-6''), 7.11 (br d, $J = 7.6$ Hz, 1 H, H-4''), 6.90 (s, 1 H, H-5), 3.60 (s, 3 H, NCH₃), 2.39 (s, 3 H, CH₃); ¹³C NMR (CDCl₃) δ 170.1, 150.1 (2), 149.0, 146.1, 141.9, 139.9, 129.6, 127.5, 125.7, 122.1, 120.2 (2), 105.4, 40.4, 21.4; MS m/z 282.5 (MH⁺, 100%). Anal. calcd for C₁₆H₁₅N₃S: C, 68.30; H, 5.37; N, 14.93. Found: C, 67.97; H, 5.45; N, 14.86%.

***N*-Ethyl-*N*-(3-methylphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (47).**



***N*-Ethyl-*N*-(3-methylphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (47).** NaH (151 mg, 3.8 mmol) was added to a stirred solution of amine **11** (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 NH₄Cl solution (10 mL) and the mixture extracted with EtOAc (3 \times 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 **47** (0.55 g, 93%) as a colourless oil: ¹H NMR (CDCl₃) 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, CH₂N), 2.39 (s, 3 H, CH₃), 1.32 (t, $J = 7.1$ Hz, 3 H, CH₃); ¹³C NMR (CDCl₃) 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 C₁₇H₁₇N₃S: C, 69.12; H, 5.80; N, 14.22. Found: C, 68.90; H, 5.89; N, 14.28%.

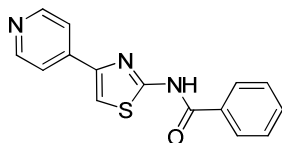
2-{3-Methyl[4-(4-pyridinyl)-1,3-thiazol-2-yl]anilino}ethanol (48).



2-{3-Methyl[4-(4-pyridinyl)-1,3-thiazol-2-yl]anilino}ethanol (48). NaH (107 mg, 2.7 mmol) was added to a stirred solution of amine **11** (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 NH₄Cl 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 **11** (0.22 g, 34%) and (ii) amine **48** (0.15 g, 19%) as a white powder: mp (EtOAc/pet. ether) 149–151 °C; ¹H 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, CH₃); ¹³C 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 C₁₇H₁₇N₃OS: C, 65.57; H, 5.50; N, 13.49. Found: C, 65.87; H, 5.43; N, 13.65%.

***N*-[4-(4-Pyridinyl)-1,3-thiazol-2-yl]benzamide (49).**

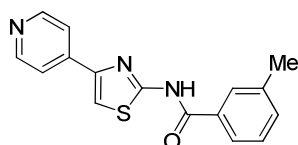


4-(4-Pyridinyl)-1,3-thiazol-2-amine (153). Method B. Reaction of bromoketone hydrobromide **109** (5.0 g, 17.8 mmol) and thiourea (1.36 g, 17.8 mmol) gave amine **153** (2.70 g, 86%) as a pink powder: mp (EtOH/H₂O) 278–282 °C [lit.³ mp (EtOH) 276–277 °C]; ¹H NMR [δ 8.53 (dd, *J* = 4.6, 1.6 Hz, 2 H, H-2', 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, NH₂); MS *m/z* 178.3 (MH⁺, 100%).

***N*-[4-(4-Pyridinyl)-1,3-thiazol-2-yl]benzamide (49).** Benzoyl chloride (0.44 mL, 3.8 mmol) was added to a stirred solution of amine **153** (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 **49** (448 mg, 61%) as a white powder: mp (MeOH/DCM) 241–243 °C; ¹H NMR δ 12.84 (s, 1 H, NHCO),

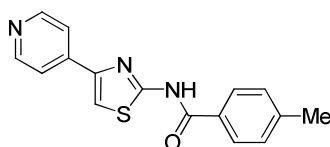
8.64 (dd, $J = 4.5, 1.6$ Hz, 2 H, H-2'', H-6''), 8.14 (br d, $J = 7.1$ Hz, 2 H, H-2, H-6), 8.04 (s, 1 H, H-5'), 7.90 (dd, $J = 4.5, 1.6$ Hz, 2 H, H-3'', H-5''), 7.56 (tt, $J = 7.4, 1.3$ Hz, 1 H, H-4), 7.35–7.39 (m, 2 H, H-3, H-5); ^{13}C NMR δ 165.3, 159.0, 150.1 (2), 146.6, 140.9, 132.6, 131.7, 128.5 (2), 128.1 (2), 119.9 (2), 112.6; MS m/z 282.4 (MH^+ , 100%). Anal. calcd for $\text{C}_{15}\text{H}_{11}\text{N}_3\text{OS}$: C, 64.04; H, 3.94; N, 14.94. Found: C, 63.75; H, 4.12, N, 14.93%.

3-Methyl-N-[4-(4-pyridinyl)-1,3-thiazol-2-yl]benzamide (50).



3-Methyl-N-[4-(4-pyridinyl)-1,3-thiazol-2-yl]benzamide (50). 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 **153** (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 **50** (110 mg, 19%) as a cream powder: mp (MeOH/EtOAc) 201–202 °C; ^1H 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 $\text{C}_{16}\text{H}_{13}\text{N}_3\text{OS}$: C, 65.06; H, 4.44; N, 14.23. Found: C, 65.19 H, 4.56; N, 14.31%.

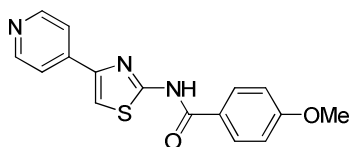
4-Methyl-N-[4-(4-pyridinyl)-1,3-thiazol-2-yl]benzamide (51).



4-Methyl-N-[4-(4-pyridinyl)-1,3-thiazol-2-yl]benzamide (51). 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

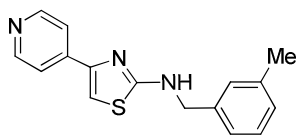
DMF (3 drops) in DCM (30 mL) and the solution stirred at 20 °C for 1 h. A solution of amine **153** (354 mg, 2.0 mmol) was added and the mixture stirred at 20 °C for 16 h. The solvent was evaporated and the residue partitioned between water (70 mL) and EtOAc (70 mL). The organic fraction was washed with 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 **51** (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, CH₃); ¹³C 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 C₁₆H₁₃N₃OS: C, 65.06; H, 4.44; N, 14.23. Found: C, 64.96; H, 4.62; N, 14.24%.

4-Methoxy-*N*-[4-(4-pyridinyl)-1,3-thiazol-2-yl]benzamide (52).



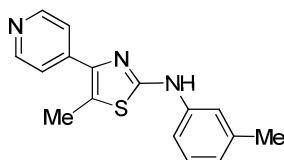
4-Methoxy-*N*-[4-(4-pyridinyl)-1,3-thiazol-2-yl]benzamide (52). 4-Methoxybenzoyl chloride (0.77 mL, 5.5 mmol) was added to a stirred solution of amine **153** (0.89 g, 5.0 mmol) and DMAP (60 mg, 0.5 mmol) in pyridine (30 mL) and the solution stirred at 20 °C for 16 h. The solvent was evaporated and the 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 **52** (448 mg, 61%) as a white powder: mp (MeOH/DCM) 271–274 °C; ¹H 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, OCH₃); ¹³C 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 C₁₆H₁₃N₃O₂S: C, 61.72; H, 4.21; N, 13.50. Found: C, 61.38; H, 4.48; N, 13.41%.

***N*-(3-Methylbenzyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (53).**



***N*-(3-Methylbenzyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (53).** A mixture of 2-aminothiazole **153** (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 NaBH₄ (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 **53** (0.11 g, 22%) as a cream powder: mp (MeOH/EtOAc) 192–194 °C; ¹H 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, CH₂N), 2.30 (s, 3 H, CH₃); MS *m/z* 282.5 (MH⁺, 100%). Anal. calcd for C₁₆H₁₅N₃S·¼CH₃OH: C, 67.87; H, 5.48; N, 14.72. Found: C, 67.78; H, 5.42; N, 14.92%.

5-Methyl-*N*-(3-methylphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (54).



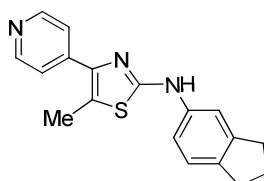
2-Bromo-1-(4-pyridinyl)-1-propanone Hydrobromide (154). Method A. Reaction of Br₂ (4.0 mL, 78.6 mmol) with 4-propionylpyridine (10.1 g, 74.9 mmol) in 30% HBr/HOAc (80 mL) gave the bromoketone hydrobromide salt **154** (21.21 g, 96%) as a white powder: mp (Et₂O/H₂O) 195–197 °C [lit.⁹ mp (HOAc) 188–190 °C]; ¹H 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).

5-Methyl-*N*-(3-methylphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (54). Method

D. Reaction of bromoketone hydrobromide **154** (0.92 g, 3.1 mmol) and 3-

methylphenylthiourea **120** (0.52 g, 3.1 mmol) gave amine **54** (0.82 g, 94%) as a cream powder: mp (EtOAc) 193–195 °C; ¹H 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 × CH₃); ¹³C 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 C₁₆H₁₅N₃S: C, 68.30; H, 5.37; N, 14.93. Found: C, 68.33; H, 5.51; N, 14.90%.

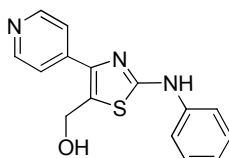
***N*-(2,3-Dihydro-1*H*-inden-5-yl)-5-methyl-4-(4-pyridinyl)-1,3-thiazol-2-amine (55).**



***N*-(2,3-Dihydro-1*H*-inden-5-yl)-5-methyl-4-(4-pyridinyl)-1,3-thiazol-2-amine (55).**

Method D. Reaction of bromide hydrobromide **154** (0.50 g, 1.7 mmol) and thiourea **144** (0.32 g, 1.7 mmol) gave amine **55** (0.47 g, 90%) as a tan powder: mp (EtOAc/Et₂O) 180–181 °C; ¹H 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 Hz, 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'''); ¹³C 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 C₁₈H₁₇N₃S·Et₂O: C, 70.02; H, 6.03; N, 12.89. Found: C, 70.47; H, 6.02; N, 12.88%.

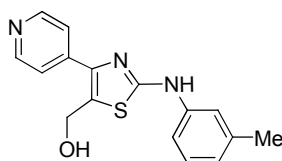
[2-(Phenylamino)-4-(4-pyridinyl)-1,3-thiazol-5-yl]methanol (56).



[2-(Phenylamino)-4-(4-pyridinyl)-1,3-thiazol-5-yl]methanol (56). A mixture of amine **1** (0.37 g, 1.46 mmol), 40% aqueous formaldehyde solution (5 mL) and Et₃N (1 mL) in THF (5 mL) was stirred in a glass pressure vessel at 130 °C for 1 h. The

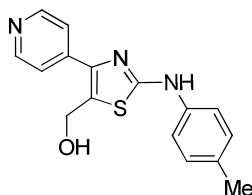
mixture was cooled to 20 °C, the reaction quenched with cNH₃ solution (2 mL) and the mixture diluted with water (50 mL). The mixture was extracted with EtOAc (3 × 20 mL), the combined organic fraction was dried and the solvent evaporated. The crude solid was purified by column chromatography, eluting with a gradient (0–5%) of MeOH/DCM, to give (i) starting material **1** (71 mg, 19%) and (ii) alcohol **56** (258 mg, 62%) as a white powder: mp (MeOH/DCM) 170–172 °C; ¹H 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); ¹³C 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 C₁₅H₁₃N₃OS·H₂O: C, 59.78; H, 5.01; N, 13.94. Found: C, 60.12; H, 4.57; N, 13.92%.

[2-[(3-Methylphenyl)amino]-4-(4-pyridinyl)-1,3-thiazol-5-yl]methanol (57).



[2-[(3-Methylphenyl)amino]-4-(4-pyridinyl)-1,3-thiazol-5-yl]methanol (57). A mixture of amine **11** (1.02 g, 1.87 mmol), 40% aqueous formaldehyde solution (10 mL) and Et₃N (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 cNH₃ 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 **11** (93 mg, 9%) and (ii) alcohol **57** (874 mg, 77%) as a white powder: mp (MeOH/DCM) 161–163 °C; ¹H 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, CH₃); ¹³C 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 C₁₆H₁₅N₃OS: C, 64.62; H, 5.08; N, 14.13. Found: C, 64.70; H, 5.18; N, 14.08%.

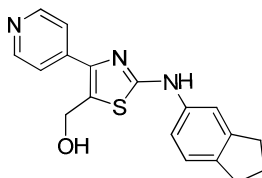
[2-[(4-Methylphenyl)amino]-4-(4-pyridinyl)-1,3-thiazol-5-yl]methanol (58).



[2-[(4-Methylphenyl)amino]-4-(4-pyridinyl)-1,3-thiazol-5-yl]methanol (58). A

mixture of amine **24** (0.25 g, 0.94 mmol), 40% aqueous formaldehyde solution (5 mL) and Et₃N (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 cNH₃ 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 **24** (95 mg, 38%) and (ii) alcohol **58** (162 mg, 58%) as a white powder: mp (MeOH/DCM) 208–212 °C (dec.); ¹H 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, CH₃); ¹³C NMR δ 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 C₁₆H₁₅N₃OS· $\frac{1}{3}$ CH₂Cl₂: C, 60.24; H, 4.85; N, 12.90. Found: C, 60.05; H, 4.94; N, 12.82%.

[2-(2,3-Dihydro-1*H*-inden-5-ylamino)-4-(4-pyridinyl)-1,3-thiazol-5-yl]methanol (59).

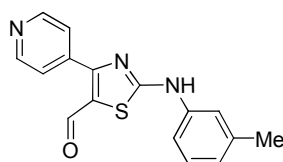


[2-(2,3-Dihydro-1*H*-inden-5-ylamino)-4-(4-pyridinyl)-1,3-thiazol-5-yl]methanol

(59). A mixture of amine **37** (0.25 g, 0.77 mmol), 40% aqueous formaldehyde solution (5 mL) and Et₃N (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 cNH₃ 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 **59** (172 mg, 69%) as a white powder: mp (MeOH/EtOAc) 185–187 °C; ¹H 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'''); ¹³C 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 C₁₈H₁₇N₃OS: C, 66.85; H, 5.30; N, 12.99. Found: C, 66.80; H, 5.30; N, 12.98%.

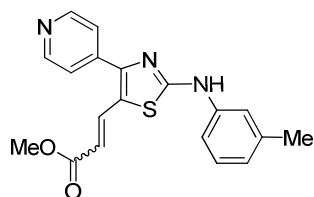
2-[(3-Methylphenyl)amino]-4-(4-pyridinyl)-1,3-thiazole-5-carbaldehyde (60).



2-[(3-Methylphenyl)amino]-4-(4-pyridinyl)-1,3-thiazole-5-carbaldehyde (60).

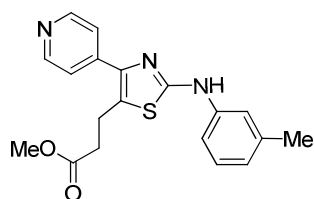
MnO₂ (1.23 g, 14.1 mmol) was added to a stirred solution of alcohol **57** (0.84 g, 2.8 mmol) in benzene (40 mL) at 80 °C and the mixture stirred at 80 °C for 2 h. The mixture was cooled to 20 °C, filtered through Celite, which was washed with benzene (2 × 40 mL). The solvent of combined organic fraction was evaporated. The crude solid was purified by column chromatography, eluting with a gradient (0–5%) of MeOH/DCM, to give aldehyde **60** (346 mg, 42%) as a white powder: mp (MeOH/EtOAc) 220–223 °C; ¹H 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, CH₃); ¹³C 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 C₁₆H₁₃N₃OS: C, 65.06; H, 4.44; N, 14.23. Found: C, 64.75; H, 4.56; N, 14.08%.

Methyl (2*E*)-3-[2-[(3-Methylphenyl)amino]-4-(4-pyridinyl)-1,3-thiazol-5-yl]-2-propenoate (61).



Methyl (2E)-3-[2-[(3-Methylphenyl)amino]-4-(4-pyridinyl)-1,3-thiazol-5-yl]-2-propenoate (61). A solution of aldehyde **60** (1.34 g, 4.54 mmol) and methyl (triphenylphosphoranylidene)acetate (1.82 g, 5.44 mmol) in DCM (60 mL) was stirred at 20 °C for 24 h. The solvent was evaporated and the crude solid was purified by column chromatography, eluting with 50% EtOAc/pet ether, to give ester **61** (1.11 g, 69%) as a white powder: mp (EtOAc/pet. ether) 205–207 °C; ¹H 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, OCH₃), 2.31 (s, 3 H, CH₃); ¹³C 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 C₁₉H₁₇N₃O₂S: C, 64.94; H, 4.88; N, 11.96. Found: C, 64.67; H, 5.12; N, 11.74%.

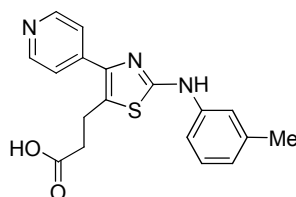
Methyl 3-[2-[(3-Methylphenyl)amino]-4-(4-pyridinyl)-1,3-thiazol-5-yl]propanoate (62).



Methyl 3-[2-[(3-Methylphenyl)amino]-4-(4-pyridinyl)-1,3-thiazol-5-yl]propanoate (62). A suspension of alkene **61** (1.06 g, 3.0 mmol) and Pd/C (100 mg) in EtOH/EtOAc (1:1, 100 mL) under H₂ (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 **62** (791 mg, 74%) as a yellow powder: mp (EtOAc/pet. ether) 121–123 °C; ¹H 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,

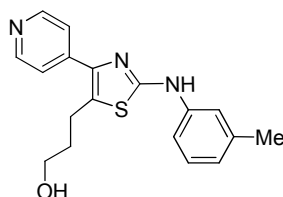
H-5'''), 6.77 (br d, $J = 7.4$ Hz, 1 H, H-4'''), 3.59 (s, 3 H, OCH₃), 3.25 (br t, $J = 7.3$ Hz, 2 H, H-3), 2.70 (br t, $J = 7.3$ Hz, 2 H, H-2), 2.29 (s, 3 H, CH₃); ¹³C NMR δ 171.9, 160.4, 149.8 (2), 143.2, 141.9, 140.9, 138.0, 128.7, 124.1, 122.4 (2), 122.0, 117.4, 114.0, 51.3, 34.9, 21.7, 21.2; MS m/z 354.6 (MH⁺, 100%). Anal. calcd for C₁₉H₁₉N₃O₂S: C, 64.57; H, 5.42; N, 11.89. Found: C, 64.55; H, 5.35; N, 11.97%.

3-[2-[(3-Methylphenyl)amino]-4-(4-pyridinyl)-1,3-thiazol-5-yl]propanoic Acid (63).



3-[2-[(3-Methylphenyl)amino]-4-(4-pyridinyl)-1,3-thiazol-5-yl]propanoic Acid (63). A solution of NaOH (2 M, 20 mL, 40 mM) was added to a stirred solution of ester **62** (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 **63** (674 mg, 99%) as a white powder: mp (H₂O) 235–239 °C; ¹H 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, CH₃), OH not observed; MS m/z 340.6 (MH⁺, 100%). Anal. calcd for C₁₈H₁₇N₃O₂S·1½H₂O: C, 59.50; H, 5.45; N, 11.56. Found: C, 59.18; H, 4.94; N, 11.35%.

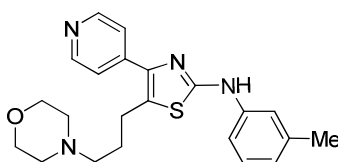
3-[2-[(3-Methylphenyl)amino]-4-(4-pyridinyl)-1,3-thiazol-5-yl]-1-propanol (64).



3-[2-[(3-Methylphenyl)amino]-4-(4-pyridinyl)-1,3-thiazol-5-yl]-1-propanol (64). LiAlH₄ (60 mg, 1.7 mmol) was added to a stirred solution of acid **63** (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 NH₃ 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 **64** (131 mg, 50%) as a white powder: mp (EtOAc) 150–152 °C; ¹H 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, CH₃), 1.75–1.82 (m, 2 H, H-2); ¹³C 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%).

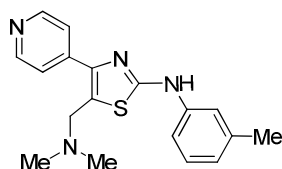
***N*-(3-Methylphenyl)-5-[3-(4-morpholinyl)propyl]-4-(4-pyridinyl)-1,3-thiazol-2-amine (65).**



***N*-(3-Methylphenyl)-5-[3-(4-morpholinyl)propyl]-4-(4-pyridinyl)-1,3-thiazol-2-amine (65).** MsCl (23 μL, 0.30 mmol) was added to a stirred solution of alcohol **64** (74 mg, 0.23 mmol) and *i*Pr₂NEt (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 NH₃ 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 **65** (64 mg, 70%) as a white powder: mp (MeOH/EtOAc) 128–131 °C; ¹H 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 × CH₂O), 2.93 (br t, *J* = 7.3 Hz, 2 H,

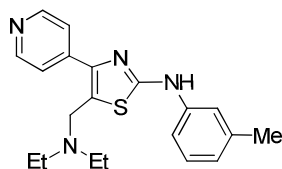
H-1"), 2.27–2.33 (m, 9 H, 3 × CH₂N, CH₃), 1.75–1.81 (m, 2 H, H-2"); ¹³C NMR δ 160.1, 149.7 (2), 142.6, 142.1, 140.9, 138.0, 128.7, 126.1, 122.3 (2), 121.9, 117.3, 114.0, 66.1 (2), 56.5, 53.1 (2), 27.7, 23.5, 21.2; MS *m/z* 367.7 (MH⁺, 100%).

5-[(Dimethylamino)methyl]-*N*-(3-methylphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (66).



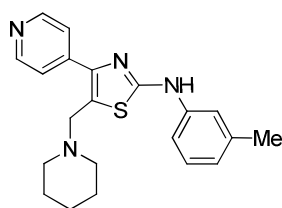
5-[(Dimethylamino)methyl]-*N*-(3-methylphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (66). MsCl (120 μL, 1.5 mmol) was added to a stirred solution of alcohol **57** (340 mg, 1.1 mmol) and *i*Pr₂NEt (300 μL, 1.7 mmol) in DCM (30 mL) at 0 °C and the mixture stirred at 20 °C for 3 h. The solvent was evaporated and the residue dissolved in DMF (3 mL) and 40% aqueous MeNH₂ 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 Na₂CO₃ 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 **66** (124 mg, 33%) as a white powder: mp (MeOH/DCM) 157–159 °C; ¹H 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, CH₃), 2.23 [s, 6 H, N(CH₃)₂]; ¹³C 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 C₁₈H₂₀N₄S: C, 66.63; H, 6.21; N, 17.27. Found: C, 66.51; H, 6.29; N, 17.04%.

5-[(Diethylamino)methyl]-*N*-(3-methylphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (67).



5-[(Diethylamino)methyl]-*N*-(3-methylphenyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (67). MsCl (105 μ L, 1.3 mmol) was added to a stirred solution of alcohol **57** (306 mg, 1.0 mmol) and *i*Pr₂NEt (270 μ L, 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 Et₂NH (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 Na₂CO₃ solution (5% w/v, 20 mL) and EtOAc (50 mL). The organic fraction was washed with water (2 \times 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 **67** (168 mg, 46%) as a white powder: mp (MeOH/EtOAc) 123–125 °C; ¹H 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 \times CH₂N), 2.29 (s, 3 H, CH₃), 0.98 (t, *J* = 7.1 Hz, 6 H, 2 \times CH₃); ¹³C 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 C₂₀H₂₄N₄S \cdot ½CH₃OH: C, 66.82; H, 7.11; N, 15.20. Found: C, 66.41; H, 7.09; N, 14.94%.

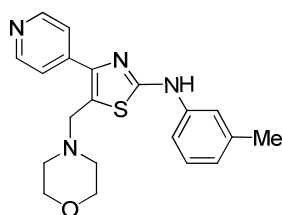
***N*-(3-Methylphenyl)-5-(1-piperidinylmethyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (68).**



***N*-(3-Methylphenyl)-5-(1-piperidinylmethyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (68).** MsCl (107 μ L, 1.4 mmol) was added to a stirred solution of alcohol **57** (311 mg, 1.0 mmol) and *i*Pr₂NEt (273 μ L, 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 Na₂CO₃ 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 **68** (208 mg, 54%) as a white powder: mp (MeOH/DCM) 150–151 °C; ¹H 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 × CH₂N), 2.29 (s, 3 H, CH₃), 1.47–1.53 (m, 4 H, 2 × CH₂), 1.36–1.42 (m, 2 H, CH₂); ¹³C 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 C₂₁H₂₄N₄S·½CH₃OH: C, 67.86; H, 6.89; N, 14.72. Found: C, 67.74; H, 6.72; N, 14.90%.

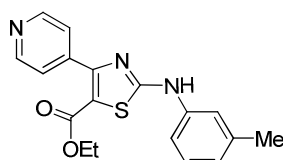
***N*-(3-Methylphenyl)-5-(4-morpholinylmethyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (69).**



***N*-(3-Methylphenyl)-5-(4-morpholinylmethyl)-4-(4-pyridinyl)-1,3-thiazol-2-amine (69).** MsCl (58 μL, 0.74 mmol) was added to a stirred solution of alcohol **57** (200 mg, 0.67 mmol) and *i*Pr₂NEt (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 Na₂CO₃ 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 **69** (153 mg, 62%) as a white powder: mp (MeOH/DCM) 160–161 °C; ¹H 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, $2 \times \text{CH}_2\text{N}$), 2.47 (br t, $J = 4.5$ Hz, 4 H, $2 \times \text{CH}_2\text{O}$), 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 $\text{C}_{20}\text{H}_{22}\text{N}_4\text{OS}$: C, 65.55; H, 6.05; N, 15.29. Found: C, 65.42; H, 6.02; N, 15.25%.

Ethyl 2-[(3-Methylphenyl)amino]-4-(4-pyridinyl)-1,3-thiazole-5-carboxylate (70).

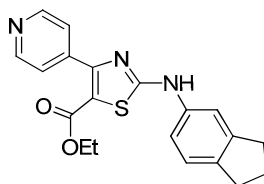


Ethyl 2-Bromo-3-oxo-3-(4-pyridinyl)propanoate Hydrobromide (155). Br_2 (1.4 mL, 27.7 mmol) was added dropwise to a stirred solution of ethyl isonicotinoyl acetate (5.09 g, 26.3 mmol) in CHCl_3 (100 mL) at 5°C . The mixture was stirred at 40°C for 1 h and then at 70°C for 1 h. The mixture was cooled to 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 **155** (8.19 g, 88%) as a white powder: mp ($\text{Et}_2\text{O}/\text{CHCl}_3$) $141\text{--}143^\circ\text{C}$; ^1H 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).

Ethyl 2-[(3-Methylphenyl)amino]-4-(4-pyridinyl)-1,3-thiazole-5-carboxylate (70)

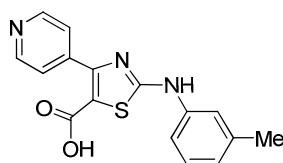
Method D. Reaction of bromide hydrobromide **155** (0.51 g, 1.4 mmol) and 3-methylphenylthiourea **120** (0.24 g, 1.4 mmol) gave ester **70** (0.25 g, 51%) as a yellow powder: mp (EtOH) $233\text{--}235^\circ\text{C}$; ^1H NMR δ 10.89 (s, 1 H, NH), 8.91 (dd, $J = 5.2, 1.4$ Hz, 2 H, H-2', H-6'), 7.67 (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, $J = 7.1$ Hz, 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%).

Ethyl 2-(2,3-Dihydro-1H-inden-5-ylamino)-4-(4-pyridinyl)-1,3-thiazole-5-carboxylate (71).



Ethyl 2-(2,3-Dihydro-1H-inden-5-ylamino)-4-(4-pyridinyl)-1,3-thiazole-5-carboxylate (71). Method D. Reaction of bromide hydrobromide **155** (1.80 g, 5.1 mmol) and *N*-(2,3-dihydro-1H-inden-5-yl)thiourea **144** (0.98 g, 5.1 mmol) gave ester **71** (0.50 g, 76%) as a yellow powder: mp (MeOH/DCM) 203–205 °C; ¹H 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 Hz, 2 H, CH₂O), 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, CH₃); ¹³C 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 C₂₀H₁₉N₃O₂S: C, 65.73; H, 5.24; N, 11.50. Found: C, 65.44; H, 5.27; N, 11.75%.

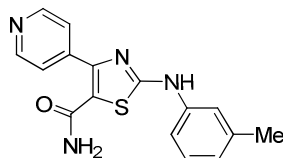
2-[(3-Methylphenyl)amino]-4-(4-pyridinyl)-1,3-thiazole-5-carboxylic acid (72).



2-[(3-Methylphenyl)amino]-4-(4-pyridinyl)-1,3-thiazole-5-carboxylic acid (72). A mixture of ester **70** (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 **72** (245 mg, 56%) as a yellow powder: mp (H₂O) 160–162 °C; ¹H NMR δ 13.0 (br s, 1 H, CO₂H), 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, CH₃); ¹³C 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%.

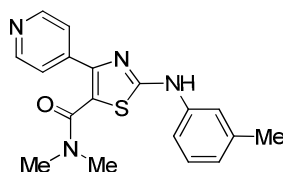
2-[(3-Methylphenyl)amino]-4-(4-pyridinyl)-1,3-thiazole-5-carboxamide (73).



2-[(3-Methylphenyl)amino]-4-(4-pyridinyl)-1,3-thiazole-5-carboxamide (73).

Oxalyl chloride (34 μ L, 0.40 mmol) was added dropwise to a stirred solution of acid **72** (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 was 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 **73** (6 mg, 7%) as a tan gum: 1H 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'', CONH₂), 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, CH₃); MS m/z 311.5 (MH^+ , 100%).

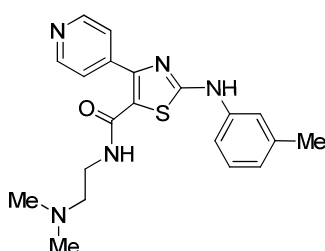
***N,N*-Dimethyl-2-[(3-methylphenyl)amino]-4-(4-pyridinyl)-1,3-thiazole-5-carboxamide (74).**



***N,N*-Dimethyl-2-[(3-methylphenyl)amino]-4-(4-pyridinyl)-1,3-thiazole-5-carboxamide (74).** Oxalyl chloride (34 μ L, 0.40 mmol) was added dropwise to a stirred solution of acid **72** (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 was 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

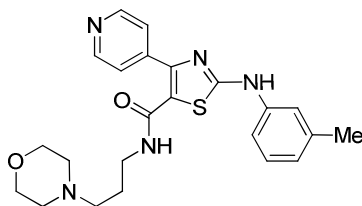
purified by column chromatography, eluting with a gradient (0–10%) of MeOH/DCM, to give carboxamide **74** (27 mg, 30%) as a tan solid: mp (MeOH/EtOAc) 193–196 °C; ¹H NMR δ 10.42 (s, 1 H, NH), 8.65 (dd, *J* = 4.5, 1.6 Hz, 2 H, H-2', H-6'), 7.57 (dd, *J* = 4.5, 1.6 Hz, 2 H, H-3', H-5'), 7.53 (br d, *J* = 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(CH₃)₂], 2.32 (s, 3 H, CH₃); MS *m/z* 339.6 (MH⁺, 100%).

***N*-[2-(Dimethylamino)ethyl]-2-[(3-methylphenyl)amino]-4-(4-pyridinyl)-1,3-thiazole-5-carboxamide (75).**



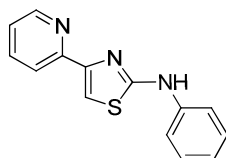
***N*-[2-(Dimethylamino)ethyl]-2-[(3-methylphenyl)amino]-4-(4-pyridinyl)-1,3-thiazole-5-carboxamide (75).** Oxalyl chloride (53 μL, 0.63 mmol) was added dropwise to a stirred solution of acid **72** (130 mg, 0.42 mmol) and DMF (1 drop) in DCM (5 mL) and the mixture was stirred at 20 °C for 2 h. The solvent was 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 NH₃ (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 **75** (39 mg, 24%) as a tan powder: mp (MeOH/DCM) 189–191 °C; ¹H 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, CH₂N), 2.40 (br t, *J* = 6.4 Hz, 2 H, CH₂N), 2.32 (s, 3 H, CH₃), 2.20 [s, 6 H, N(CH₃)₂]; ¹³C 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 C₂₀H₂₃N₅OS·¼CH₂Cl₂: C, 60.39; H, 5.88; N, 17.39. Found: C, 60.04; H, 5.95; N, 17.06%.

2-[(3-Methylphenyl)amino]-N-[3-(4-morpholinyl)propyl]-4-(4-pyridinyl)-1,3-thiazole-5-carboxamide (76).



2-[(3-Methylphenyl)amino]-N-[3-(4-morpholinyl)propyl]-4-(4-pyridinyl)-1,3-thiazole-5-carboxamide (76). Oxalyl chloride (41 μ L, 0.48 mmol) was added dropwise to a stirred solution of acid **72** (100 mg, 0.32 mmol) and DMF (1 drop) in DCM (5 mL) and the mixture was stirred at 20 $^{\circ}$ C for 2 h. The solvent was evaporated and the residue suspended in DCM (5 mL) and 3-(4-morpholinyl)propylamine (140 μ L, 0.96 mmol) was added and the mixture stirred at 20 $^{\circ}$ 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 **76** (30 mg, 21%) as a tan powder: mp (MeOH/EtOAc) 190–192 $^{\circ}$ C; ^1H 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, $2 \times \text{CH}_2\text{O}$), 3.20 (dt, $J = 6.7, 5.9$ Hz, 2 H, CH_2N), 2.25 (m, 9 H, $3 \times \text{CH}_2\text{N}$, 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 $\text{C}_{23}\text{H}_{27}\text{N}_5\text{O}_2\text{S} \cdot \text{H}_2\text{O}$: C, 60.64; H, 6.42; N, 15.37. Found: C, 60.70; H, 6.27; N, 15.18%.

N-Phenyl-4-(2-pyridinyl)-1,3-thiazol-2-amine (77).

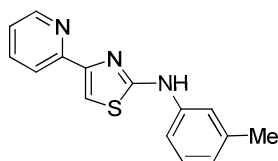


2-Bromo-1-(pyridin-2-yl)ethanone hydrobromide (156). Method A. Reaction of Br_2 (4.1 mL, 80.6 mmol) and 2-acetylpyridine (9.30 g, 76.8 mmol) gave the bromoketone hydrobromide salt **156** (19.46 g, 90%) as a cream powder: mp 200–205 $^{\circ}$ C (dec) (lit.² mp 203–205 $^{\circ}$ C); ^1H NMR δ 8.74 (ddd, $J = 4.5, 1.5, 1.0$ 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).

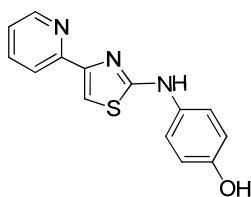
***N*-Phenyl-4-(2-pyridinyl)-1,3-thiazol-2-amine (77). Method D.** Reaction of bromoketone hydrobromide **156** (0.29 g, 1.0 mmol) and phenylthiourea **110** (0.16 g, 1.0 mmol) gave amine **77** (0.21 g, 81%) as a white powder: mp (MeOH/DCM) 142–144 °C; ^1H NMR [(CD₃)₂SO] δ 10.28 (br s, 1 H, NH), 8.58 (ddd, $J = 4.7, 1.7, 0.9$ Hz, 1 H, H-6'), 8.01 (br t, $J = 7.9, 0.9$ Hz, 1 H, H-3'), 7.80 (ddd, $J = 7.8, 7.6, 1.8$ Hz, 1 H, H-4'), 7.74 (br d, $J = 8.6$ Hz, 2 H, H-2'', H-6''), 7.55 (s, 1 H, H-5), 7.31–7.38 (m, 3 H, H-5', H-3'', H-5''), 6.97 (tt, $J = 7.4, 1.0$ Hz, 1 H, H-4''); MS m/z 254.4 (MH⁺, 100%). Anal. calcd for C₁₄H₁₁N₃S: C, 66.38; H, 4.38; N, 16.59. Found: C, 66.24; H, 4.28; N, 16.79.

***N*-(3-Methylphenyl)-4-(2-pyridinyl)-1,3-thiazol-2-amine (78).**



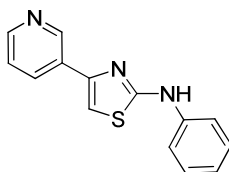
***N*-(3-Methylphenyl)-4-(2-pyridinyl)-1,3-thiazol-2-amine (78). Method D.** Reaction of bromoketone hydrobromide **156** (0.96 g, 3.4 mmol) and 3-methylphenylthiourea **120** (0.57 g, 3.4 mmol) gave amine **78** (0.74 g, 81%) as a cream powder: mp (EtOAc) 164–166 °C; ^1H NMR δ 10.20 (br s, 1 H, NH), 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, CH₃); ^{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 C₁₅H₁₃N₃: C, 67.39; H, 4.90; N, 15.72. Found: C, 67.13; H, 5.10; N, 15.67%.

4-[[4-(2-Pyridinyl)-1,3-thiazol-2-yl]amino]phenol (79).



4-[[4-(2-Pyridinyl)-1,3-thiazol-2-yl]amino]phenol (79). Method D. Reaction of bromoketone hydrobromide **156** (0.78 g, 2.8 mmol) and 1-(4-hydroxyphenyl)thiourea **130** (0.46 g, 2.8 mmol) gave phenol **79** (0.67 g, 90%) as a cream powder: mp (EtOAc) 185–186 °C; $^1\text{H NMR}$ 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); $^{13}\text{C NMR}$ 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 $\text{C}_{14}\text{H}_{11}\text{N}_3\text{OS}$: C, 62.43; H, 4.12; N, 15.60. Found: C, 62.30; H, 4.37; N, 15.69%.

***N*-Phenyl-4-(3-pyridinyl)-1,3-thiazol-2-amine (80).**

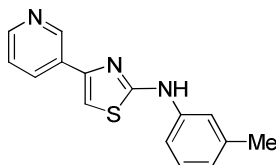


2-Bromo-1-(pyridin-3-yl)ethanone hydrobromide (157). Method A. Reaction of Br_2 (2.0 mL, 38.6 mmol) and 3-acetylpyridine (4.45 g, 36.7 mmol) gave bromoketone **157** as the hydrobromide salt (9.79 g, 95%) as a cream powder: mp 195–198 °C [lit.¹⁰ mp (MeOH/ether) 185–188 °C]; $^1\text{H NMR}$ δ 9.23 (dd, $J = 2.2, 0.7$ 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, $\text{N}\cdot\text{HBr}$), 5.02 (s, 2 H, H-2).

***N*-Phenyl-4-(3-pyridinyl)-1,3-thiazol-2-amine (80). Method D.** Reaction of bromoketone hydrobromide **157** (0.30 g, 1.1 mmol) and phenylthiourea **110** (0.16 g, 1.1 mmol) gave amine **80** (0.25 g, 93%) as a white powder: mp (MeOH/DCM) 200–202 °C; $^1\text{H NMR}$ δ 10.31 (br s, 1 H, NH), 9.14 (t, $J = 1.7$ Hz, 1 H, H-2'), 8.41 (dd, $J = 4.7, 1.6$ Hz, 1 H, H-6'), 8.25 (dt, $J = 7.9, 1.9$ Hz, 1 H, H-4'), 7.72 (br d, $J = 8.6$ Hz, 2 H, H-2'', H-6''), 7.51 (s, 1 H, H-5), 7.46 (ddd, $J = 7.9, 4.7, 0.7$ Hz, 1 H, H-5'), 7.35 (br dd, $J = 8.5, 7.4$ Hz, 2 H, H-3'', H-5''), 6.98 (br t, $J = 7.4$ Hz, 1 H, H-4''); MS m/z 254.4

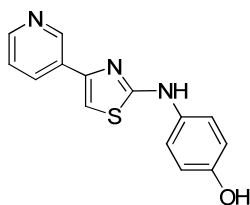
(MH⁺, 100%). Anal. calcd for C₁₄H₁₁N₃S: C, 66.38; H, 4.38; N, 16.59. Found: C, 66.57; H, 4.42; N, 16.78.

***N*-(3-Methylphenyl)-4-(3-pyridinyl)-1,3-thiazol-2-amine (81).**



***N*-(3-Methylphenyl)-4-(3-pyridinyl)-1,3-thiazol-2-amine (81). Method D.** Reaction of bromoketone hydrobromide **157** (1.17 g, 4.2 mmol) and 3-methylphenylthiourea **120** (0.64 g, 4.2 mmol) gave amine **81** (0.86 g, 77%) as a cream powder: mp (EtOAc) 171–173 °C; ¹H 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, CH₃); ¹³C 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 C₁₅H₁₃N₃: C, 67.39; H, 4.90; N, 15.72. Found: C, 67.20; H, 5.07; N, 15.77%.

4-[[4-(3-Pyridinyl)-1,3-thiazol-2-yl]amino]phenol (82).

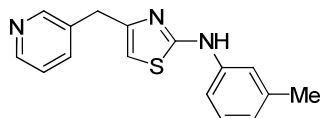


4-[[4-(3-Pyridinyl)-1,3-thiazol-2-yl]amino]phenol (82). Method D. Reaction of bromoketone hydrobromide **157** (0.84 g, 3.0 mmol) and 1-(4-hydroxyphenyl)thiourea **130** (0.50 g, 3.0 mmol) gave phenol **82** (0.77 g, 95%) as a cream powder: mp (H₂O) 275–278 °C; ¹H NMR δ 9.95 (br s, 1 H, NH), 9.10 (m, 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); ¹³C 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 C₁₄H₁₁N₃OS·¼H₂O: C, 61.41; H, 4.23; N, 15.34.

Found: C, 61.66; H, 4.45; N, 15.46%.

***N*-(3-Methylphenyl)-4-(3-pyridinylmethyl)-1,3-thiazol-2-amine (83).**



***N*-Methyl-*N*-methoxy-2-(3-pyridinyl)acetamide (158). Method E.** Reaction of 3-pyridinylacetic acid (5.12 g, 29.4 mmol), EDCI (6.22 g, 32.4 mmol), HOBT·H₂O (4.38 g, 32.4 mmol), MeNHOMe·HCl (4.30 g, 44.1 mmol) and Et₃N (16.4 mL, 118 mmol) in dry DCM (150 mL), gave amide **158** (3.55 g, 67%) as an oil: ¹H NMR (CDCl₃) δ 8.52 (d, *J* = 1.6 Hz, 1 H, H-2'), 8.50 (dd, *J* = 4.5, 1.6 Hz, 1 H, H-6'), 7.67 (dt, *J* = 7.9, 1.9 Hz, 1 H, H-4'), 7.26 (dd, *J* = 7.9, 4.5 Hz, 1 H, H-5'), 3.77 (s, 2 H, H-2), 3.68 (s, 3 H, OCH₃), 3.21 (s, 3 H, NCH₃); MS *m/z* 181.4 (MH⁺, 100%). Anal. calcd for C₉H₁₂N₂O₂·¼H₂O: C, 58.52; H, 6.82; N, 15.17. Found: C, 58.40; H, 6.62; N, 15.65%.

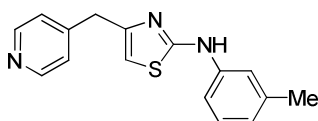
1-(3-Pyridinyl)-2-propanone (159). Method F. Reaction of MeMgBr (3 M in hexanes, 10.0 mL, 29.5 mmol) and amide **158** (3.54 g, 19.7 mmol) in dry THF (100 mL) gave ketone **159** (2.50 g, 94%) as an oil: ¹H NMR (CDCl₃) δ 8.53 (dd, *J* = 4.8, 1.5 Hz, 1 H, H-6'), 8.46 (d, *J* = 1.5 Hz, 1 H, H-2'), 7.54 (dt, *J* = 7.9, 1.9 Hz, 1 H, H-4'), 7.27 (br dd, *J* = 7.9, 4.85 Hz, 1 H, H-5'), 3.72 (s, 2 H, H-1), 2.22 (s, 3 H, CH₃); MS *m/z* 181.4 (MH⁺, 100%).

1-Bromo-3-(3-pyridinyl)-2-propanone Hydrobromide (160). Method A. Reaction of Br₂ (1.90 mL, 37.0 mmol) ketone **159** (2.50 g, 18.5 mmol) followed by addition of acetone (40 mL) and stirring for 5 h and subsequent precipitation with Et₂O (150 mL) gave the crude hydrobromide salt **160** (4.35 g, 80%) as a white powder: ¹H NMR δ 8.80 (br d, *J* = 5.2 Hz, 1 H, H-6'), 8.73 (br s, 1 H, H-2'), 8.32 (br d, *J* = 8.0 Hz, 1 H, H-4'), 7.96 (br dd, *J* = 8.0, 5.2 Hz, 1 H, H-5'), 4.54 (s, 2 H, H-1), 4.13 (s, 3 H, CH₃); MS *m/z* 214.4/216.4 (MH⁺, 100%).

***N*-(3-Methylphenyl)-4-(3-pyridinylmethyl)-1,3-thiazol-2-amine (83). Method D.** Reaction of bromoketone **160** (0.43 g, 1.4 mmol) and 3-methylphenylthiourea **120** (0.24 g, 1.4 mmol) in EtOH (30 mL) gave amine **83** (0.39 g, 96%) as a tan gum: ¹H

NMR δ 10.01 (s, 1 H, NH), 8.55 (d, $J = 1.8$ Hz, 1 H, H-2'), 8.43 (dd, $J = 4.8, 1.6$ Hz, 1 H, H-6'), 7.71 (dt, $J = 7.9, 1.9$ Hz, 1 H, H-4'), 7.38 (br s, 1 H, H-2''), 7.31–7.36 (m, 2 H, H-5', H-6''), 7.15 (br t, $J = 7.8$ Hz, 1 H, H-5''), 6.70 (br d, $J = 7.4$ Hz, 1 H, H-4''), 6.49 (s, 1 H, H-5), 3.91 (s, 2 H, CH₂), 2.26 (s, 3 H, CH₃); ¹³C NMR δ 163.4, 150.4, 149.8, 147.2, 141.0, 137.3, 136.2, 135.0, 128.6, 123.2, 121.7, 117.2, 113.8, 102.9, 34.4, 21.2; MS m/z 282.6 (MH⁺, 100%). Anal. calcd for C₁₆H₁₅N₃S: C, 68.30; H, 5.37; N, 14.93. Found: C, 67.91; H, 5.41; N, 14.79%.

***N*-(3-Methylphenyl)-4-(4-pyridinylmethyl)-1,3-thiazol-2-amine (84).**



***N*-Methyl-*N*-methoxy-2-(4-pyridinyl)acetamide (161). Method D.** Reaction of 4-pyridinylacetic acid (2.53 g, 15.2 mmol), EDCI (3.19 g, 16.7 mmol), HOBT·H₂O (2.24 g, 16.7 mmol), MeNHOMe·HCl (2.22 g, 22.7 mmol) and Et₃N (8.5 mL, 60.6 mmol) in dry DCM (140 mL), gave amide **161** (1.33 g, 49%) as an oil: ¹H NMR (CDCl₃) δ 8.54 (dd, $J = 4.5, 1.6$ Hz, 2 H, H-2', H-6'), 7.22 (br d, $J = 4.5, 1.6$ Hz, 2 H, H-3', H-5'), 3.77 (s, 2 H, H-2), 3.65 (s, 3 H, OCH₃), 3.21 (s, 3 H, NCH₃); MS m/z 181.4 (MH⁺, 100%).

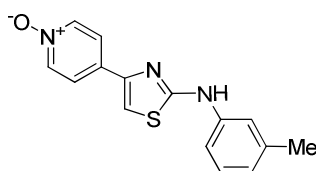
1-(4-Pyridinyl)-2-propanone (162). Method F. Reaction of MeMgBr (3 M in hexanes, 2.8 mL, 8.3 mmol) and amide **161** (1.0 g, 5.6 mmol) in dry THF (50 mL) gave ketone **162** (0.48 g, 64%) as an oil: ¹H NMR (CDCl₃) δ 8.57 (dd, $J = 4.4, 1.6$ Hz, 2 H, H-2', H-6'), 7.14 (br d, $J = 4.5, 1.6$ Hz, 2 H, H-3', H-5'), 3.72 (s, 2 H, H-1), 2.21 (s, 3 H, H-3); MS m/z 136.3 (MH⁺, 100%). Also recovered: starting material (0.09 g, 9%).

1-Bromo-3-(4-pyridinyl)-2-propanone Hydrobromide (163). Method A. Reaction of Br₂ (0.40 mL, 7.7 mmol) and ketone **162** (0.52 g, 3.8 mmol) followed by addition of acetone (40 mL) and stirring for 5 h and subsequent precipitation with Et₂O (150 mL) gave the crude hydrobromide salt **163** (0.90 g, 79%) as a white powder: ¹H NMR δ 8.88 (d, $J = 6.6$ Hz, 2 H, H-2', H-6'), 7.92 (d, $J = 6.6$ Hz, 2 H, H-3', H-5'), 4.38 (s, 2 H, H-1), 4.29 (s, 2 H, H-3); MS m/z 214.4/216.4 (MH⁺, 100%).

***N*-(3-Methylphenyl)-4-(4-pyridinylmethyl)-1,3-thiazol-2-amine (84). Method D.**

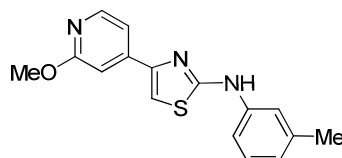
Reaction of bromoketone **163** (0.90 g, 3.0 mmol) and 3-methylphenylthiourea **120** (0.51 g, 3.0 mmol) gave amine **84** (0.80 g, 93%) as a tan gum: $^1\text{H NMR}$ δ 10.03 (br s, 1 H, NH), 8.48 (dd, $J = 4.4, 1.5$ Hz, 2 H, H-2', H-6'), 7.33–7.38 (m, 2 H, H-2'', H-6''), 7.31 (dd, $J = 4.4, 1.5$ Hz, 2 H, H-3', H-5'), 7.15 (br t, $J = 7.7$ Hz, 1 H, H-5''), 6.74 (br d, $J = 7.5$ Hz, 1 H, H-4''), 6.54 (s, 1 H, H-5), 3.91 (s, 2 H, CH₂), 2.26 (s, 3 H, CH₃); $^{13}\text{C NMR}$ δ 163.4, 149.4, 149.3 (2), 148.3, 141.0, 137.9, 128.6, 124.1 (2), 121.8, 117.2, 113.8, 103.4, 36.5, 21.1; MS m/z 282.5 (MH⁺, 100%). Anal. calcd for C₁₆H₁₅N₃S: C, 68.30; H, 5.37; N, 14.93. Found: C, 68.08; H, 5.57; N, 14.60%.

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



***N*-(3-Methylphenyl)-4-(1-oxido-4-pyridinyl)-1,3-thiazol-2-amine (85).** MCPBA (50–55%, 710 mg, 2.1 mmol) was added to a solution of amine **11** (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. NaHCO₃ solution (50 mL), washed with sat. aq. Na₂S₂O₅ 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 **85** (240 mg, 45%) as a yellow powder: mp (EtOAc/pet.ether) 162–164 °C; $^1\text{H NMR}$ 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, H-5''), 6.81 (d, $J = 7.5$ Hz, H-4''), 2.32 (s, 3 H, CH₃); $^{13}\text{C NMR}$ 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 C₁₅H₁₃N₃OS: C, 63.58; H, 4.62; N, 14.83. Found: C, 63.08; H, 4.59; N, 14.86%.

***N*-{4-[2-(Methoxy)-4-pyridinyl]-1,3-thiazol-2-yl}-*N*-(3-methylphenyl)amine (86).**

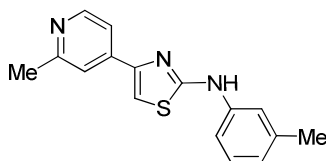


2-Bromo-1-[2-(methoxy)-4-pyridinyl]ethanone (164). Oxalyl chloride (3.6 mL, 42.4 mmol) was added to a stirred suspension of 2-methoxy-4-pyridinecarboxylic acid (1.30 g, 8.5 mmol) and DMF (3 drops) in DCM (30 mL) and the mixture was stirred at 20 °C for 3 days. The solvent was evaporated and the residue dissolved in THF (20 mL) and added to a stirred solution of TMSCH₂N₂ (2 M in pet. ether) (10. 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 KHCO₃ 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 **164** (1.08 g, 55%) as a cream powder: ¹H 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, OCH₃); MS *m/z* 230.4/232.4 (MH⁺, 100%). The HBr salt was a cream solid: mp 116 °C (dec.). Anal. calcd for C₈H₉BrNO₂: C, 30.90; H, 2.92; N, 4.50. Found: C, 31.16; H, 3.05; N, 4.43%.

***N*-{4-[2-(Methoxy)-4-pyridinyl]-1,3-thiazol-2-yl}-*N*-(3-methylphenyl)amine (86).**

Method D. Reaction of bromoketone **164** (0.21 g, 0.9 mmol) and 3-methylphenylthiourea **120** (0.15 g, 0.9 mmol) gave amine **86** (0.20 g, 87%) as a cream powder: mp (EtOAc/pet. ether) 131–133 °C; ¹H 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, OCH₃), 2.32 (s, 3 H, CH₃); ¹³C 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 C₁₆H₁₅N₃OS: C, 64.62; H, 5.08; N, 14.13. Found: C, 64.71; H, 5.13; N, 14.22%.

***N*-(3-Methylphenyl)-4-(2-methyl-4-pyridinyl)-1,3-thiazol-2-amine (87).**



2-Methyl-4-pyridinecarbonitrile (165). Me₂SO₄ (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 CHCl₃ (3 × 50 mL), the combined organic fraction washed with brine (50 mL) and dried. The solvent was evaporated and the residue purified by column chromatography, eluting with 20% EtOAc/pet. ether, to give nitrile **165** as an oil: ¹H NMR (CDCl₃) 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, CH₃); MS *m/z* 119.3 (MH⁺, 100%).

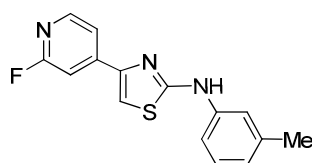
1-(2-Methyl-4-pyridinyl)ethanone (166). A solution of MeMgBr (3 M in hexanes, 6.0 mL, 17.9 mmol) was added slowly to a stirred solution of nitrile **165** (1.76 g, 14.9 mmol) in dry THF (100 mL) at 0 °C and the mixture was stirred at reflux temperature for 16 h. The mixture was cooled to 20 °C and the 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 cNH₃ solution. The mixture was extracted with CHCl₃ (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 **166** (0.50 g, 25%) as an oil: ¹H NMR (CDCl₃) 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, CH₃); MS *m/z* 136.5 (MH⁺, 100%).

2-Bromo-1-(2-methyl-4-pyridinyl)ethanone (167). Method A. Reaction of Br₂ (0.2 mL, 3.9 mmol) and ketone **166** (0.50 g, 3.3 mmol) gave the hydrobromide **167** (0.98 g, 90%) as a white powder: mp (Et₂O/H₂O) 183–186 °C; ¹H 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, CH₃). Anal. calcd for C₈H₉BrNO: C, 32.57; H, 3.08; N, 4.75. Anal. calcd for C₈H₉BrNO·1¼HBr: C, 30.49; H, 2.96; N, 4.44. Found: C, 30.65; H, 3.39; N, 4.34%.

N-(3-Methylphenyl)-4-(2-methyl-4-pyridinyl)-1,3-thiazol-2-amine (87). Method D. Reaction of bromide **167** (0.45 g, 1.5 mmol) and 3-methylphenylthiourea **120** (0.25

g, 1.5 mmol) gave amine **87** (0.37 g, 87%) as a cream powder: mp (EtOAc/pet. ether) 198–200 °C; $^1\text{H NMR}$ 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, CH₃), 2.33 (s, 3 H, CH₃); $^{13}\text{C NMR}$ 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 C₁₆H₁₅N₃S: C, 68.30; H, 5.37; N, 14.93. Found: C, 67.99; H, 5.25; N, 14.95%.

4-(2-Fluoro-4-pyridinyl)-N-(3-methylphenyl)-1,3-thiazol-2-amine (88).



2-Fluoro-N-methyl-N-(methoxy)-4-pyridinecarboxamide (168). Method E.

Reaction 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), MeNHOMe·HCl (2.1 g, 21.3 mmol) and Et₃N (7.9 mL, 57 mmol) in dry DCM (55 mL), gave amide **168** (1.68 g, 64%) a colourless oil: $^1\text{H NMR}$ (CDCl₃) δ 8.30 (d, $J = 5.1$ Hz, 1 H, H-6), 7.41 (dt, $J = 5.1, 1.7, 1.4$ Hz, 1 H, H-5), 7.20 (br s, 1 H, H-3), 3.56 (s, 3 H, OCH₃), 3.38 (s, 3 H, NCH₃); MS m/z 185.5 (MH⁺, 100%).

1-(2-Fluoro-4-pyridinyl)ethanone (169). Method F. Reaction of MeMgBr (3 M in Et₂O, 3.8 mL, 11.4 mmol) and amide **168** (1.4 g, 7.6 mmol) in dry THF (40 mL) gave ketone **169** (1.01 g, 96%) as a colourless liquid: $^1\text{H NMR}$ (CDCl₃) 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, CH₃); MS m/z 140.5 (MH⁺), 172.5 (MH⁺ + MeOH, 100%).

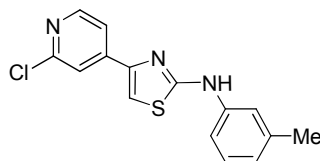
2-Fluoro-1-(2-bromo-4-pyridinyl)ethanone Hydrobromide (170). Method A.

Reaction of Br₂ (0.39 mL, 7.5 mmol) and 1-(2-fluoro-4-pyridinyl)ethanone (**169**) (938 mg, 6.74 mmol) gave the crude bromoketone **170** (941 mg) as white solid which was used in the next step without further purification.

4-(2-Fluoro-4-pyridinyl)-N-(3-methylphenyl)-1,3-thiazol-2-amine (88). Method D.

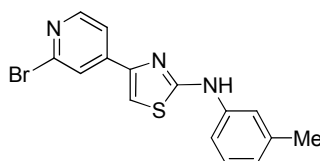
Reaction of crude bromoketone hydrobromide **170** (941 mg, 3.15 mmol) and 3-methylphenylthiourea **120** (524 mg, 3.15 mmol) in EtOH (25 mL) gave amine **88** (25 mg, 3 %) as a white solid: (CH₃CN/H₂O/CF₃CO₂H) = 162–164 °C; ¹H NMR (CD₃OD) δ 8.19 (d, *J* = 5.4 Hz, 1 H, H-6'), 7.78 (dt, *J* = 5.4, 1.8 Hz, 1 H, H-5'), 7.52–7.50 (m, 3 H, H-2', 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 Hz, 1 H, H-4''), 2.34 (s, 3 H, CH₃), NH not observed; ¹³C NMR (CD₃OD) 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 C₁₅H₁₂FN₃S·½H₂O: C, 63.14; H, 4.24; N, 14.73. Found: C, 61.21; H, 4.45; N, 14.28%.

4-(2-Chloro-4-pyridinyl)-N-(3-methylphenyl)-1,3-thiazol-2-amine (89).



4-(2-Chloro-4-pyridinyl)-N-(3-methylphenyl)-1,3-thiazol-2-amine (89). Method D. Reaction of 2-bromo-1-(2-chloro-4-pyridinyl)ethanone (0.51 g, 2.2 mmol) and 3-methylphenylthiourea **120** (0.36 g, 2.2 mmol) gave amine **89** (0.62 g, 94%) as a white powder: mp (EtOAc/pet. ether) 195–197 °C; ¹H 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, CH₃); ¹³C 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 C₁₅H₁₂ClN₃S: C, 59.70; H, 4.01; N, 13.92. Found: C, 59.75; H, 4.07; N, 13.82%.

4-(2-Bromo-4-pyridinyl)-N-(3-methylphenyl)-1,3-thiazol-2-amine (90).



2-Bromo-*N*-methyl-*N*-(methoxy)-4-pyridinecarboxamide (171). Method E.

Reaction 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), MeNHOMe·HCl (3.91 g, 40.0 mmol) and Et₃N (14.9 mL, 107 mmol) in dry DCM (100 mL) gave amide **171** (4.56 g, 70%) as an oil: ¹H NMR (CDCl₃) 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, OCH₃), 3.67 (s, 3 H, NCH₃); MS *m/z* 244.3/246.3 (MH⁺, 100%).

1-(2-Bromo-4-pyridinyl)ethanone (172). Method F. Reaction of MeMgBr (3 M in hexanes, 9.3 mL, 27.9 mmol) and amide **171** (4.56 g, 18.6 mmol) in dry THF (100 mL) gave ketone **172** (3.51 g, 94%) as an oil: ¹H NMR (CDCl₃) 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 C₇H₆BrNO·¼CH₃CO₂CH₂CH₃: C, 42.68; H, 3.34; N, 6.63. Found: C, 42.62; H, 3.06; N, 6.97%.

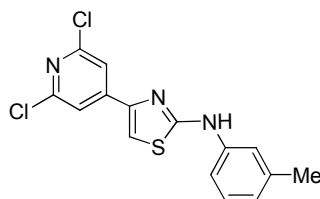
2-Bromo-1-(2-bromo-4-pyridinyl)ethanone Hydrobromide (173). Method A.

Reaction of Br₂ (0.81 mL, 15.9 mmol) and ketone **172** (3.02 g, 15.1 mmol) gave the crude hydrobromide **173** (5.28 g, 97%) as a white powder: mp (HOAc/ether) >295 °C; ¹H 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* 280.4 (MH⁺, 100%).

4-(2-Bromo-4-pyridinyl)-*N*-(3-methylphenyl)-1,3-thiazol-2-amine (90). Method

D. Reaction of bromoketone hydrobromide **173** (0.62 g, 1.7 mmol) and 3-methylphenylthiourea **120** (0.25 g, 1.7 mmol) gave amine **90** (0.50 g, 84%) as a cream powder: mp (EtOAc/pet. ether) 202–204 °C; ¹H 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, CH₃); ¹³C 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 C₁₅H₁₂BrN₃S: C, 52.03; H, 3.49; N, 12.14. Found: C, 52.21; H, 3.51; N, 12.13%.

4-(2,6-Dichloro-4-pyridinyl)-N-(3-methylphenyl)-1,3-thiazol-2-amine (91).



2,6-Dichloro-N-methyl-N-(methoxy)-4-pyridinecarboxamide (174). Method E.

Reaction 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), MeNHOMe·HCl (1.52 g, 15.6 mmol) and Et₃N (5.8 mL, 41.6 mmol) in dry DCM (50 mL) gave amide **174** (2.01 g, 83 %) as a colourless oil: ¹H NMR (CDCl₃) δ 7.51 (s, 2 H, H-2, H-6), 3.59 (s, 3 H, OCH₃), 3.38 (s, 3 H, NCH₃); MS *m/z* 235.4, 237.4 (MH⁺, 100%).

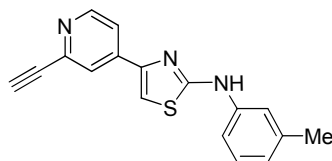
1-(2,6-Dichloro-4-pyridinyl)ethanone (175). Method F. Reaction of A solution of MeMgBr (3 M in Et₂O, 4.3 mL, 12.8 mmol) and amide **174** (2.0 g, 8.5 mmol) in dry THF (40 mL) gave ketone **175** (1.61 g, 99%) as white crystals: mp (EtOAc) 50–51 °C; ¹H NMR (CDCl₃) δ 7.68 (s, 2 H, H-3', H-5'), 2.61 (s, 3 H, CH₃); MS *m/z* 190.4, 192.4 (MH⁺), 222.4, 224.4 (MH⁺ + MeOH, 100%).

2-Bromo-1-(2,6-dichloro-4-pyridinyl)ethanone (176). Method A. Reaction of Br₂ (0.24 mL, 4.66 mmol) and ketone **175** (653 mg, 4.2 mmol) gave the crude bromoketone **176** (1.32 g) as a pale yellow solid which was used without further purification.

4-(2,6-Dichloro-4-pyridinyl)-N-(3-methylphenyl)-1,3-thiazol-2-amine (91).

Method D. Reaction of bromoketone **176** (1.32 g, 3.8 mmol) and 3-methylphenylthiourea **120** (632 mg, 3.8 mmol) gave amine **91** (904 mg, 71 %) as a beige solid: mp (EtOAc/pet. ether) = 204–206 °C; ¹H 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, CH₃); ¹³C 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%). Anal. calcd for C₁₅H₁₁Cl₂N₃S: C, 53.58; H, 3.30; N, 12.50. Found: C, 53.55; H, 3.25; N, 12.28%.

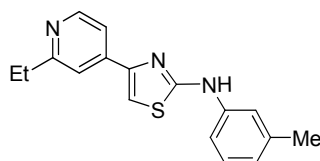
4-(2-Ethynyl-4-pyridinyl)-N-(3-methylphenyl)-1,3-thiazol-2-amine (92).



4-(2-Ethynyl-4-pyridinyl)-N-(3-methylphenyl)-1,3-thiazol-2-amine (92).

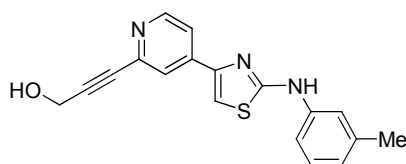
PdCl₂(PPh₃)₂ (35 mg, 0.05 mmol) was added to a purged mixture of 4-(2-bromo-4-pyridinyl)-N-(3-methylphenyl)-1,3-thiazol-2-amine (**90**) (346 mg, 1.0 mmol), trimethylsilylacetylene (0.15 mL, 1.1 mmol), CuI (10 mg, 0.05 mmol) in Et₃N (3 mL) and DMF (3 mL) and the mixture was stirred at 50 °C for 16 h 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 **92** (0.18 g, 62%) as a tan powder: mp (EtOAc/pet. ether) 192–194 °C; ¹H 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, CH₃); ¹³C 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 C₁₇H₁₃N₃S·¼CH₃OH: C, 69.21; H, 4.71; N, 14.04. Found: C, 69.44; H, 4.57; N, 13.86%.

4-(2-Ethyl-4-pyridinyl)-N-(3-methylphenyl)-1,3-thiazol-2-amine (93).



4-(2-Ethyl-4-pyridinyl)-N-(3-methylphenyl)-1,3-thiazol-2-amine (93). A mixture of amine **92** (120 mg, 0.41 mmol) and Pd/C (25 mg) in EtOH (20 mL) was stirred under H₂ (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 **93** (45 mg, 37%) as a white powder: mp (EtOAc/pet. ether) 206–209 °C; ¹H 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, CH₂), 2.32 (s, 3 H, CH₃), 1.27 (t, *J* = 7.6 Hz, 3 H, CH₃); ¹³C 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 C₁₇H₁₇N₃S: C, 69.12; H, 5.80; N, 14.22. Found: C, 69.14; H, 5.87; N, 14.22%.

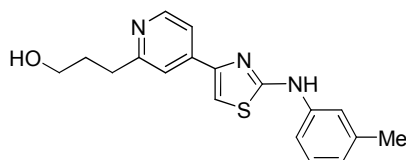
3-(4-{2-[(3-Methylphenyl)amino]-1,3-thiazol-4-yl}-2-pyridinyl)-2-propyn-1-ol (94).



3-(4-{2-[(3-Methylphenyl)amino]-1,3-thiazol-4-yl}-2-pyridinyl)-2-propyn-1-ol (94). PdCl₂(PPh₃)₂ (108 mg, 0.15 mmol) was added to a purged mixture of 4-(2-bromo-4-pyridinyl)-N-(3-methylphenyl)-1,3-thiazol-2-amine **90** (1.07 g, 3.1 mmol), propargyl alcohol (0.20 mL, 3.4 mmol), CuI (29 mg, 0.15 mmol) in Et₃N (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 **94** (0.81 g, 81%) as a tan powder: mp (EtOAc/pet. ether) 143–145 °C; ¹H 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, CH₃);

^{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 $\text{C}_{18}\text{H}_{15}\text{N}_3\text{OS}$: C, 67.27; H, 4.70; N, 13.07. Found: C, 67.05; H, 4.81; N, 12.62%.

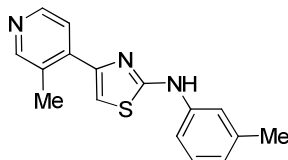
3-(4-{2-[(3-Methylphenyl)amino]-1,3-thiazol-4-yl}-2-pyridinyl)-1-propanol (95).



3-(4-{2-[(3-Methylphenyl)amino]-1,3-thiazol-4-yl}-2-pyridinyl)-1-propanol (95).

A mixture of amine **94** (700 mg, 2.17 mmol) and Pd/C (100 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 50% EtOAc/pet. ether, to give amine **95** (470 mg, 67%) as a yellow foam: ^1H 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 $\text{C}_{18}\text{H}_{19}\text{N}_3\text{OS} \cdot \frac{1}{4}\text{CH}_3\text{OH}$: C, 65.74; H, 6.05; N, 12.60. Found: C, 65.72; H, 6.20; N, 12.58%.

***N*-(3-Methylphenyl)-4-(3-methyl-4-pyridinyl)-1,3-thiazol-2-amine (96).**



***N*,3-Dimethyl-*N*-(methoxy)-4-pyridinecarboxamide (177). Method D.** Reaction 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), MeNHOMe·HCl (1.08 g, 11.0 mmol) and Et_3N (4.1 mL, 29.4 mmol) in dry DCM (80 mL) gave amide **177** (0.84 g, 63%) as an oil: ^1H 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,

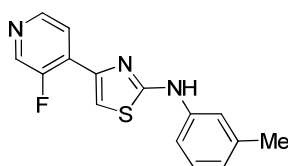
H-5), 3.45 (s, 3 H, OCH₃), 3.35 (s, 3 H, NCH₃), 2.32 (s, 3 H, CH₃); MS *m/z* 181.4 (MH⁺, 100%).

1-(3-Methyl-4-pyridinyl)ethanone (178). Method F. Reaction of MeMgBr (3 M in hexanes, 1.7 mL, 5.1 mmol) and amide **177** (0.84 g, 4.6 mmol) in dry THF (30 mL) gave ketone **178** (0.49 g, 78%) as an oil: ¹H NMR (CDCl₃) 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, CH₃); MS *m/z* 136.5 (MH⁺, 100%).

2-Bromo-1-(3-methyl-4-pyridinyl)ethanone Hydrobromide (179). Method A. Reaction of Br₂ (0.21 mL, 4.0 mmol) and ketone **178** (0.49 g, 3.7 mmol) gave the crude hydrobromide salt **179** (0.75 g, 69%) as a tan powder: ¹H 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%).

***N*-(3-Methylphenyl)-4-(3-methyl-4-pyridinyl)-1,3-thiazol-2-amine (96). Method D.** Reaction of bromoketone hydrobromide **179** (0.53 g, 1.8 mmol) and 3-methylphenylthiourea **120** (0.30 g, 1.8 mmol) gave amine **96** (0.42 g, 83%) as a tan powder: mp (EtOAc/pet. ether) 170–172 °C; ¹H 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, CH₃), 2.30 (s, 3 H, CH₃); ¹³C 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 C₁₆H₁₅N₃S: C, 68.30; H, 5.37; N, 14.93. Found: C, 68.09; H, 5.43; N, 14.67%.

4-(3-Fluoro-4-pyridinyl)-*N*-(3-methylphenyl)-1,3-thiazol-2-amine (97).



3-Fluoro-*N*-methyl-*N*-(methoxy)-4-pyridinecarboxamide (180). Method E.

Reaction of 3-fluoro-4-pyridinecarboxylic acid (2.0 g, 14.2 mmol), EDCI (3.0 g, 15.6

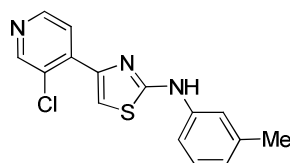
mmol), HOBt (2.1 g, 15.6 mmol) and MeNHOMe·HCl (2.1 g, 21.3 mmol) and Et₃N (7.9 mL, 57 mmol) in dry DCM (55 mL) gave amide **180** (1.60 g, 62%) as a colourless oil: ¹H NMR (CDCl₃) δ 8.55 (s, 1 H, H-2), 8.50 (dd, *J* = 4.8, 1.1 Hz, 1 H, H-6), 7.35 (t, *J* = 5.1 Hz, 1 H, H-5); 3.54 (br s, 3 H, OCH₃), 3.38 (br s, 3 H, NCH₃); MS *m/z* 185.5 (MH⁺, 100%).

1-(3-Fluoro-4-pyridinyl)ethanone (181). Method F. Reaction of MeMgBr (3 M in Et₂O, 4.1 mL, 12.2 mmol) and amide **180** (1.5 g, 8.14 mmol) gave ketone **181** (1.00 g, 88%) as a colourless liquid: ¹H NMR (CDCl₃) (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, CH₃), 2.68 (s, 1.5 H, CH₃); MS *m/z* 140.5 (MH⁺, 100%), 172.5 (MH⁺ + MeOH).

3-Fluoro-1-(2-bromo-4-pyridinyl)ethanone Hydrobromide (182). Method A. Reaction of Br₂ (0.36 mL, 7.0 mmol) and ketone **181** (880 mg, 6.33 mmol) gave crude bromoketone hydrobromide **182** (1.65 g) as a pale yellow solid which was used without further purification.

4-(3-Fluoro-4-pyridinyl)-*N*-(3-methylphenyl)-1,3-thiazol-2-amine (97). Method D. Reaction of bromoketone hydrobromide **182** (1.5 g, 5.0 mmol) and 3-methylphenylthiourea **120** (831 mg, 5.0 mmol) in EtOH (20 mL) gave amine **97** (1.02 g, 72%) as a beige solid: mp (EtOAc/pet. ether) = 159–161 °C; ¹H NMR (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* = 5.0 Hz, 0.5 H, H-5''), 8.01 (d, *J* = 5.0 Hz, 0.5 H, H-5''), 7.60–7.754 (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, CH₃); ¹³C 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 C₁₅H₁₂FN₃S (MH⁺) *m/z* 286.0814, found 286.0813.

4-(3-Chloro-4-pyridinyl)-*N*-(3-methylphenyl)-1,3-thiazol-2-amine (98).



3-Chloro-*N*-methyl-*N*-(methoxy)-4-pyridinecarboxamide (183). Method E.

Reaction 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), MeNHOMe·HCl (1.86 g, 19.0 mmol) and Et₃N (7.1 mL, 50.8 mmol) gave amide **183** (1.46 g, 58%) as a white solid: mp (EtOAc/pet. ether) = 54–56 °C; ¹H NMR (CDCl₃) 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, OCH₃), 3.39 (s, 3 H, NCH₃); MS *m/z* 201.4/203.4 (MH⁺, 100%).

1-(3-Chloro-4-pyridinyl)ethanone (184). Method F. Reaction of MeMgBr (3 M in Et₂O, 3.2 mL, 9.6 mmol) and amide **183** (1.28 g, 6.4 mmol) in dry THF (40 mL) at 0 °C gave ketone **184** (883 mg, 89%) as a colourless liquid: ¹H NMR (CDCl₃) 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, CH₃); MS *m/z* 156.4 (MH⁺, 100%), 188.4 (MH⁺ + MeOH).

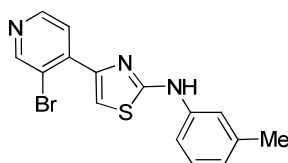
3-Chloro-1-(2-bromo-4-pyridinyl)ethanone Hydrobromide (185). Method A.

Reaction of Br₂ (0.24 mL, 4.66 mmol) and ketone **184** (653 mg, 4.2 mmol) gave the crude bromoketone hydrobromide **185** (1.27 g) as a pale yellow solid which was used in the next step without further purification.

4-(3-Chloro-4-pyridinyl)-*N*-(3-methylphenyl)-1,3-thiazol-2-amine (98). Method

D. Reaction of bromoketone hydrobromide **185** (1.23 g, 4 mmol) and 3-methylphenylthiourea **120** (651 mg, 4 mmol) in EtOH (25 mL) gave amine **98** (340 mg, 28%) as beige crystals: mp (EtOAc) 161–163 °C; ¹H NMR (CDCl₃) δ 10.31 (s, 1 H, NH), 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, CH₃); ¹³C NMR (CDCl₃) 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 (MH⁺, 100%); HRMS calcd for C₁₅H₁₃³⁵ClN₃S *m/z* 302.05187, found 302.05141.

4-(3-Bromo-4-pyridinyl)-*N*-(3-methylphenyl)-1,3-thiazol-2-amine (99).



3-Bromo-N-methyl-N-(methoxy)-4-pyridinecarboxamide (186). Method E.

Reaction 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), MeNHOMe·HCl (1.55 g, 15.9 mmol) and Et₃N (5.9 mL, 42.4 mmol) in dry DCM (100 mL) gave amide **186** (1.74 g, 67%) as an oil: ¹H NMR (CDCl₃) 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, OCH₃), 3.28 (s, 3 H, NCH₃); MS *m/z* 245.3/247.3 (MH⁺, 100%).

1-(3-Bromo-4-pyridinyl)ethanone (187). Method F. Reaction of MeMgBr (3 M in hexanes, 3.5 mL, 10.5 mmol) and amide **186** (1.72 g, 7.0 mmol) in dry THF (50 mL) gave ketone **187** (0.91 g, 65%) as an oil: ¹H NMR (CDCl₃) 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%).

2-Bromo-1-(3-bromo-4-pyridinyl)ethanone Hydrobromide (188). Method A.

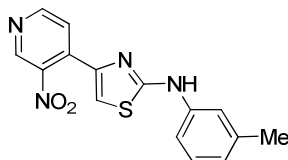
Reaction of Br₂ (0.26 mL, 5.0 mmol) and ketone **187** (0.90 g, 4.5 mmol) gave crude bromoketone **188** (0.31 g, 25%) as an oil: ¹H NMR δ 8.94 (br s, 1 H, H-2'), 8.75 (d, *J* = 4.9 Hz, 1 H, H-5'), 7.83 (dd, *J* = 4.9, 0.4 Hz, 1 H, H-6'), 4.88 (s, 2 H, H-2); MS *m/z* 280.3 (MH⁺, 100%).

4-(3-Bromo-4-pyridinyl)-N-(3-methylphenyl)-1,3-thiazol-2-amine (99). Method

D. Reaction of bromoketone hydrobromide **188** (0.30 g, 1.1 mmol) and 3-methylphenylthiourea **120** (0.18 g, 1.1 mmol) gave amine **99** (0.29 g, 77%) as a tan powder: mp (EtOAc/pet. ether) 180–182 °C; ¹H 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, CH₃); ¹³C 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%.

***N*-(3-Methylphenyl)-4-(3-nitro-4-pyridinyl)-1,3-thiazol-2-amine (100).**



1-(3-Nitro-4-pyridinyl)ethanone (189).¹¹ 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 **189** (1.66 g, 55%) as an oil: 1H 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%).

2-Bromo-1-(3-nitro-4-pyridinyl)ethanone Hydrobromide (190). Method A.

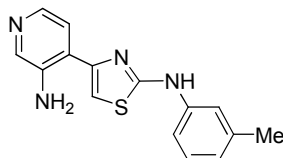
Reaction of Br_2 (0.53 mL, 10.4 mmol) and ketone **189** (1.64 g, 9.9 mmol) gave the crude hydrobromide salt **190** (2.76 g, 86%) as a white powder: 1H NMR δ 9.48 (s, 1 H, H-2'), 9.10 (d, $J = 4.9$ Hz, 1 H, H-6'), 7.81 (dd, $J = 4.9, 0.4$ Hz, 1 H, H-5'), 4.86 (s, 2 H, H-2) $N \cdot HBr$ not observed; MS m/z 277.4/279.4 (MH^+ , 100%).

***N*-(3-Methylphenyl)-4-(3-nitro-4-pyridinyl)-1,3-thiazol-2-amine (100). Method D.**

Reaction of bromoketone hydrobromide **190** (2.00, 6.1 mmol) and 3-methylphenylthiourea **120** (1.02 g, 6.1 mmol) in EtOH (50 mL) gave amine **100** (1.74 g, 91%) as an orange powder: mp (EtOAc/pet. ether) 198–200 °C; 1H 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''), 2.32 (s, 3 H, CH_3); ^{13}C NMR δ 163.4, 152.1, 144.7,

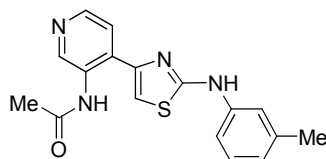
144.3, 143.1, 140.5, 138.3, 133.8, 128.6, 122.8, 122.3, 117.3, 114.1, 111.5, 21.1; MS m/z 313.6 (MH^+ , 100%). Anal. calcd for $C_{15}H_{12}N_4O_2S$: C, 57.68; H, 3.87; N, 17.94. Found: C, 57.81; H, 3.92; N, 18.00%.

***N*-[4-(2-Amino-4-pyridinyl)-1,3-thiazol-2-yl]-*N*-(3-methylphenyl)amine (101).**



***N*-[4-(2-Amino-4-pyridinyl)-1,3-thiazol-2-yl]-*N*-(3-methylphenyl)amine (101).** A mixture of nitropyridine **100** (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 **101** (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 $C_{15}H_{14}N_4S$: C, 63.80; H, 5.00; N, 19.84. Found: C, 64.09; H, 5.21; N, 19.54%.

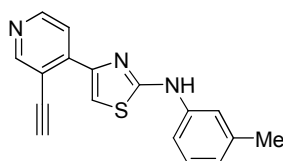
***N*-(4-{2-[(3-Methylphenyl)amino]-1,3-thiazol-4-yl}-2-pyridinyl)acetamide (102).**



***N*-(4-{2-[(3-Methylphenyl)amino]-1,3-thiazol-4-yl}-2-pyridinyl)acetamide (102).** Ac_2O (0.23 mL, 2.4 mmol) was added to a stirred solution of amine **101** (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 \times 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 **102** (148 mg, 56%) as a tan powder: mp (EtOAc/pet. ether) 189–

191 °C; ^1H 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, CH₃), 1.99 (s, 3 H, CH₃); ^{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 C₁₇H₁₆N₄OS: C, 62.94; H, 4.97; N, 17.27. Found: C, 62.98; H, 4.90; N, 17.03%.

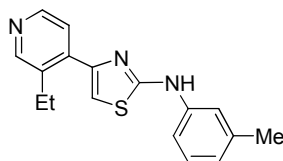
4-(3-Ethynyl-4-pyridinyl)-N-(3-methylphenyl)-1,3-thiazol-2-amine (103).



4-(3-Ethynyl-4-pyridinyl)-N-(3-methylphenyl)-1,3-thiazol-2-amine (103).

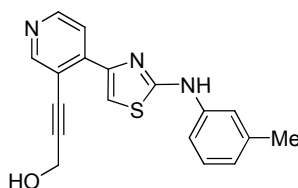
PdCl₂(PPh₃)₂ (52 mg, 0.07 mmol) was added to a purged mixture of bromide **99** (517 mg, 1.5 mmol), trimethylsilylacetylene (0.23 mL, 1.6 mmol), CuI (14 mg, 0.07 mmol) in Et₃N (3 mL) and DMF (3 mL) and the mixture was stirred at 50 °C for 16 h in a sealed tube. The mixture was cooled to 20 °C, diluted 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 **103** (0.39 g, 89%) as a tan powder: mp (EtOAc/pet. ether) 158–160 °C; ^1H 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, CH₃); ^{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 C₁₇H₁₃N₃S: C, 69.12; H, 5.80; N, 14.22. Found: C, 68.70; H, 5.83; N, 14.13%.

4-(3-Ethyl-4-pyridinyl)-N-(3-methylphenyl)-1,3-thiazol-2-amine (104).



4-(3-Ethyl-4-pyridinyl)-N-(3-methylphenyl)-1,3-thiazol-2-amine (104). A mixture of amine **103** (233 mg, 0.80 mmol) and Pd/C (25 mg) in EtOH (20 mL) was stirred under H₂ (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 **104** (47 mg, 20%) as a cream powder: mp (EtOAc/pet. ether) 151–153 °C; ¹H 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, CH₂), 2.29 (s, 3 H, CH₃), 1.18 (t, *J* = 7.5 Hz, 3 H, CH₃); ¹³C 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 C₁₇H₁₇N₃S: C, 69.12; H, 5.80; N, 14.22. Found: C, 68.70; H, 5.83; N, 14.13%.

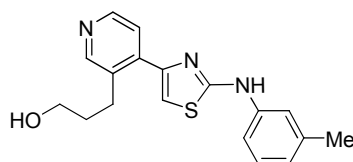
3-(4-{2-[(3-Methylphenyl)amino]-1,3-thiazol-4-yl}-3-pyridinyl)-2-propyn-1-ol (105).



3-(4-{2-[(3-Methylphenyl)amino]-1,3-thiazol-4-yl}-3-pyridinyl)-2-propyn-1-ol (105). PdCl₂(PPh₃)₂ (101 mg, 0.15 mmol) was added to a purged mixture of bromide **99** (1.00 g, 2.9 mmol), propargyl alcohol (0.19 mL, 3.2 mmol), CuI (28 mg, 0.15 mmol) in Et₃N (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 **105** (0.34 g, 34%) as a tan powder: mp (EtOAc/pet. ether) 155–158 °C; ^1H 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, CH₃); ^{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 C₁₈H₁₅N₃OS·¼CH₃OH: C, 66.54; H, 4.90; N, 12.76. Found: C, 66.87; H, 5.02; N, 12.42%.

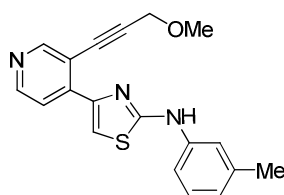
3-(4-{2-[(3-Methylphenyl)amino]-1,3-thiazol-4-yl}-3-pyridinyl)-1-propanol (106).



3-(4-{2-[(3-Methylphenyl)amino]-1,3-thiazol-4-yl}-3-pyridinyl)-1-propanol (106).

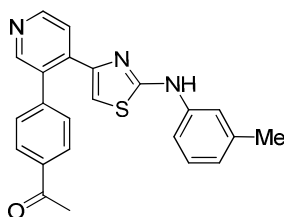
A mixture of amine **105** (205 mg, 0.64 mmol) and Pd/C (40 mg) in EtOH (50 mL) was stirred under H₂ (60 psi) for 16 h. The mixture was filtered through Celite, washed with EtOH. The solvent was evaporated and the crude solid was purified by column chromatography, eluting with EtOAc, to give amine **106** (78 mg, 37%) as a tan gum: ^1H 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, CH₃), 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 C₁₈H₁₉N₃OS: C, 66.43; H, 5.88; N, 12.91. Found: C, 66.03; H, 6.04; N, 12.58%.

4-[3-(3-Methoxy-1-propynyl)-4-pyridinyl]-N-(3-methylphenyl)-1,3-thiazol-2-amine (107).



4-[3-(3-Methoxy-1-propynyl)-4-pyridinyl]-N-(3-methylphenyl)-1,3-thiazol-2-amine (107). PdCl₂(PPh₃)₂ (55 mg, 0.08 mmol) was added to a purged mixture of bromide **99** (542 mg, 1.6 mmol), methylpropargyl ether (0.15 mL, 1.7 mmol), CuI (15 mg, 0.08 mmol) in Et₃N (2 mL) and DMF (2 mL) and the mixture was stirred at 80 °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 10% EtOAc/pet. ether, to give amine **107** (60 mg, 11%) as a cream powder powder: mp (EtOAc/pet. ether) 112–114 °C; ¹H NMR δ 10.27 (s, 1 H, NH), 8.70 (s, 1 H, H-2''), 8.62 (d, *J* = 5.2 Hz, 1 H, H-6''), 7.97–8.00 (m, 2 H, H-5, H-5''), 7.59 (br d, *J* = 8.0 Hz, 1 H, H-6'), 7.45 (br s, 1 H, H-2'), 7.24 (br t, *J* = 7.8 Hz, 1 H, H-5'), 6.91 (br d, *J* = 7.5 Hz, 1 H, H-4'), 4.45 (s, 2 H, CH₂O), 3.36 (s, 3 H, OCH₃), 2.32 (s, 3 H, CH₃); ¹³C NMR δ 162.6, 154.0, 149.4, 145.9, 141.3, 140.9, 138.2, 129.9, 122.3, 121.8, 117.6, 114.6, 114.2, 110.6, 93.4, 83.3, 59.7, 57.2, 21.3; MS *m/z* 336.4 (MH⁺, 100%). Anal. calcd for C₁₉H₁₇N₃OS·¼hexane: C, 68.98; H, 5.79; N, 11.77. Found: C, 68.62; H, 5.53; N, 11.55%.

1-[4-(4-{2-[(3-methylphenyl)amino]-1,3-thiazol-4-yl}-3-pyridinyl)phenyl]ethanone (108).



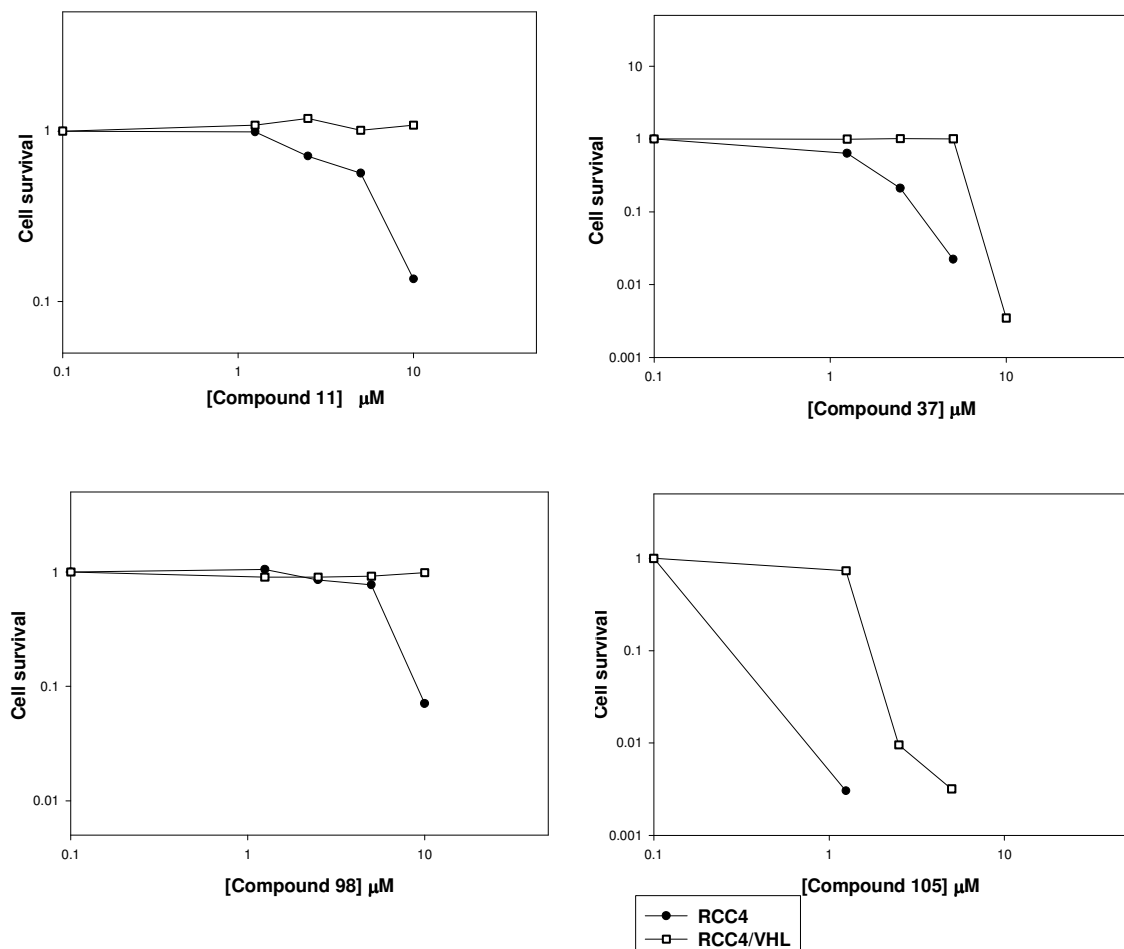
A solution of bromide **99** (100 mg, 0.29 mmol), 4-acetylphenylboronic acid (74 mg, 0.45 mmol) and K₂CO₃ (415 mg, 3.0 mmol) in a mixture of toluene/ethanol/H₂O/DMF (5 mL/3 mL/1.5 mL/4 mL) was purged with N₂ for 1 h. PdCl₂(dppf) (24 mg, 0.03 mmol) was added to the reaction mixture and it was heated at 90 °C for 16 h. The mixture was cooled to 20 °C and partitioned between EtOAc (200 mL) and H₂O (100 mL). The organic phase was dried, filtered and the solvent

evaporated. The residue was purified by column chromatography, eluting with 40% EtOAc/pet. ether, followed by recrystallization from EtOAc to give ketone **108** (24 mg, 22%) as a pale yellow solid: mp (EtOAc) 151–153 °C; ¹H NMR δ 10.03 (s, 1 H, NH), 8.67 (d, *J* = 5.1 Hz, 1 H, H-6''), 8.55 (s, 1 H, H-2''), 7.99 (d, *J* = 8.2 Hz, 2 H, H-2', H-6'), 7.78 (d, *J* = 5.1 Hz, 1 H, H-5''), 7.47 (d, *J* = 8.1 Hz, 2 H, H-3', H-5'), 7.02–6.95 (m, 3 H, H-5''', H-5'''' , H-6''''), 6.83 (s, 1 H, H-2''''), 6.68 (br d, *J* = 5.1 Hz, 1 H, H-4''''), 2.55 (s, 3 H, COCH₃), 2.20 (s, 3 H, CH₃); ¹³C NMR δ 197.4, 162.5, 150.6, 149.2, 147.4, 143.2, 140.6, 140.3, 137.7, 135.6, 133.7, 129.3 (2), 128.4, 128.2 (2), 123.1, 121.8, 117.1, 113.8, 109.1, 26.6, 21.1; MS *m/z* 386.8 (MH⁺, 100%). Anal. calcd for C₂₃H₁₉N₃OS· $\frac{1}{6}$ EtOAc: C, 70.95; H, 5.07; N, 10.56. Found: C, 70.93; H, 4.92; N, 10.91%.

Compounds used in 3D-QSAR analysis:

1, 2, 3, 5, 6, 9, 10, 11, 12, 13, 16, 17, 21, 22, 24, 27, 28, 35, 36, 37, 38, 40, 41, 44, 46, 47, 54, 55, 56, 87, 88, 89, 90, 91, 92, 96, 97, 98, 99, 103, 105

Table 1. Clonogenic survival curves for selected PAT compounds **11**, **37**, **98** and **105**.



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