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Chemistry & Drug Discovery

Supporting Information

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General. NMR spectra for identification of intermediates and final compoundswere recorded on Bruker instruments operating at 300 MHz or at 400 MHz. Chemical shifts are reported as δ values (ppm) relative to an internal standard of tetramethylsilane (TMS); s: singlet, d: doublet, t: triplet, q: quartet, b: broad. ESI mass spectra were determined on an API150 (Sciex) spectrometer. High resolution mass spectra (HR-MS) were recorded on a Fourier Transform (FT-MS) spectrometer (Thermo) with a 7 Tesla magnet. HPLC analysis was performed on a standard HPLC platform connected to a mass spectrometer and equipped with a multi-wavelenght UV detector and a light scattering detector. For purity assessment, two of the following 3 columns were evaluated, using a water/acetonitrile gradient (optionally with 0.1% formic acid) and considering either the 230 nm UV channel or the scattering channel: YMC Basic 50*4.0 mm; YMC Butyl, 120 Å, 5-3 μm, 4.6*50 mm; Agilent XDB C18, 3 μm, 3*30 mm.

All chemicals and solvents were of commercial quality and were used without further purification. Intermediate and end products were purified by either flash chromatography using Isolute SPE silica gel cartridges and an appropriate eluent.

2-Methyl-6-nitro-pyridin-3-ol (10)

3-Hydroxy-2-methyl pyridine **8** (10.0 g, 91.63 mmol) was added to concentrated sulfuric acid (65.0 mL) while maintaining a temperature of 0-5°C with external ice cooling. A mixture of nitric acid (6.5 g, 4.3 mL, 103.13 mmol) and sulfuric acid (8.5 mL) was then added over 2 hours. The mixture was poured onto crushed ice. Addition of few milliliters of concentrated ammonium hydroxide caused precipitation of crude 2-methyl-6-nitro-pyridin-3-ol **10**, which was filtered off and recrystallized from methanol/water to give pure **10** as a yellow solid (1.37 g, 9.7%). Addition of further ammonium hydroxide to the filtrate until pH 3-4 was reached caused precipitation of crude 2-methyl-4-nitro-pyridin-3-ol **9** (5.4 g, 34%). **10**: MS (70 eV): *m/z* = 154.1 [M^+]; ^{1}H NMR (400MHz, [D_6]DMSO, 300 K, TMS): δ= 8.09 (d, *J*= 8.4 Hz, 1H), 7.36 (d, *J*= 8.4 Hz, 1H), 2.40 ppm (s, 3H). **9**: ^{1}H NMR (400MHz, [D_6]DMSO, 300 K, TMS): δ= 8.03 (d, *J*= 5.6 Hz, 1H), 7.66 (d, *J*= 5.6 Hz, 1H), 2.50 ppm (s, 3H).

Acetic acid 2-methyl-6-nitro-pyridin-3-yl ester (11)

A solution of pyridin-ol **10** (0.77 g, 5.00 mmol) in acetone (50.0 mL) was treated with potassium carbonate (2.07 g, 15.00 mmol) and acetic anhydride (1.00 g, 9.80 mmol). The reaction mixture was stirred at room temperature for one hour, then filtered and washed with acetone. The filtrate was evaporated to yield crude **11** (0.75 g, 77%) as a white solid. MS (ESI): *m/z* = 197.3 [$M+H^+$]; ^{1}H NMR (400MHz, $CDCl_3$, 300 K, TMS): δ= 8.16 (d, *J*= 8.6 Hz, 1H), 7.73 (d, *J*= 8.6 Hz, 1H), 2.56 (s, 3H), 2.41 ppm (s, 3H).

Acetic acid 6-amino-2-methyl-pyridin-3-yl ester (12)

The nitropyridine **11** (0.30 g, 1.53 mmol) was dissolved in ethanol (60.0 mL) and flushed with argon. Pd/C 10% (0.04 g, 0.38 mmol) was added and the reaction was placed under an hydrogen atmosphere. After stirring at room temperature for 50 min, the catalyst was filtered off, and washed with ethanol. The filtrate was evaporated to yield crude **12** as a white solid (0.24 g, 95%). MS (70 eV): *m/z* = 166.2 [M^+];^{1}H NMR (400MHz, $CDCl_3$, 300 K, TMS): δ= 7.10 (d, *J*= 8.8 Hz, 1H), 6.33 (d, *J*= 8.8 Hz, 1H), 4.35 (bs, 2H), 2.29 (s, 3H), 2.24 ppm (s, 3H).

5-Bromo-2-methyl-thiazole-4-carboxylic acid (13)

A solution of 2-methyl-1,3-thiazole-4-carboxylic acid (2.48 g, 17.32 mmol) in tetrahydrofuran (200.0 mL) was cooled to -78°C under an argon atmosphere and a 1.6N solution of BuLi in hexanes was added dropwise (22.7 mL, 36.38 mmol). The reaction mixture was left to warm to 0°C and stirred at this temperature for 15 min, then cooled again to -78°C. A solution of bromine (3.04 g, 19.05 mmol) in hexane (2.0 mL) was added dropwise. The mixture was stirred for 15 min, then quenched with water and left to warm to room temperature. After treatment with 1N HCl, the slurry was extracted three times with dichloromethane. The combined organic phases were dried over sodium sulphate and evaporated. The residue was pure **13** (yellow solid, 3.79 g, 98%). MS (ESI): *m/z* = 220.0, 221.9 [*M-H*].

Acetic acid 6-[(5-bromo-2-methyl-thiazole-4-carbonyl)-amino]-2-methyl-pyridin-3-yl ester (14)

A solution of acid **13** (0.22 g, 1.00 mmol) in dichloromethane (10.0 mL) and dimethylformamide (0.1 mL) was treated with thionyl chloride (0.12 g, 1.05 mmol) and stirred at room temperature for 1.5 h. Amine **12** (0.17 g, 1.00 mmol) and DIPEA (0.26 g, 2.00 mmol) were then added. The mixture was stirred for 30 min, then the volatiles were removed under vacuum. The residue was purified by flash chromatography (heptane/ethyl acetate gradient) to yield the amide **14** as a white solid (0.18 g, 49%). MS (ESI): *m/z* = 370.0, 372.0 [$M+H^+$];^{1}H NMR (400MHz, $CDCl_3$, 300 K, TMS): δ= 9.79 (bs, NHCO, 1H), 3.26 (d, *J*= 8.8 Hz, 1h), 7.41 (d, *J*= 8.8 Hz, 1H), 2.69 (s, 3H), 2.36 (s, 3H), 2.34 ppm (s, 3H).

2-Methyl-5-(pyridin-3-ylamino)-thiazole-4-carboxylic acid (5-hydroxy-6-methyl-pyridin-2-yl)-amide (3)

A microwave vial was charged under an argon blanket with degassed dioxane (3.0 mL), $Pd_2(dba)_3$ (0.04 g, 0.04 mmol), xantphos (0.075 g, 0.13 mmol), amine **15** (0.04 g, 0.47 mmol), bromide **14** (0.16 g, 0.43 mmol) and Cs_2CO_3 (0.25 g, 1.29 mmol), then sealed. The mixture was irradiated in a microwave oven at 150°C for 15 min. The volatiles were evaporated and the residue purified by flash chromatography (heptane/ethyl acetate gradient) to yield acetic acid 2-methyl-6-{[2-methyl-5-(pyridin-3-ylamino)-thiazole-4-carbonyl]-amino}-pyridin-3-yl ester as a light yellow solid (0.07 g, 45%). MS (ESI): *m/z* = 384.4 [$M+H^+$]; ^{1}H-NMR ($CDCl_3$) δ: 10.24 (bs, NHCO, 1H), 9.44 (bs, NHAr, 1H), 8.57 (d, *J*= 2.8 Hz, 1H), 8.30 (dd, *J*= 1.1, 4.7 Hz, 1H), 8.17 (d, *J*= 8.8 Hz, 1H), 7.54 (m, 1H), 7.41 (1H, d, *J*= 8.8 Hz, 1H), 7.30 (dd, *J*= 4.7, 8.3 Hz, 1H), 2.61 (s, 3H), 2.37 (s, 3H), 2.35 ppm (s, 3H). A solution of acetic acid 2-methyl-6-{[2-methyl-5-(pyridin-3-ylamino)-thiazole-4-carbonyl]-amino}-pyridin-3-yl ester (0.07 g, 0.18 mmol) in methanol (20.0 mL) was treated with 2N NaOH (2.0 mL) and stirred at room temperature for 15 min. 2N HCl (2.0 mL) was then added and the volatiles evaporated. The residue was purified by flash chromatography (dichloromethane/MeOH gradient) to yield **3** as a white solid (0.04 g, 63%). MS (ESI): *m/z* = 342.1 [$M+H^+$]; HR-MS: 342.10177 [($C_{16}H_{15}N_5O_2S^+$; calc. 342.10192); ^{1}H NMR (400MHz, [D_6]DMSO, 300 K, TMS): δ= 9.93 (bs, OH, 1H), 9.60 (bs, NHCO, 1H), 9.18 (bs, NHAr, 1H), 8.61 (d, *J*= 2.7 Hz, 1H), 8.27 (m, 1H), 7.87 (d, *J*= 8.6 Hz, 1H), 7.78 (m, 1H), 7.41 (dd, 1H), 7.19 (d, *J*= 8.6 Hz, 1H), 2.61 (s, 3H), 2.29 ppm (s, 3H).

6-tert-Butoxycarbonylamino-pyridine-2-carboxylic acid ethyl ester (17)

A solution of pyridine-2,6-dicarboxylic acid monoethyl ester **16** (1.00 g, 5.12 mmol), TEA (1.04 g, 1.4 mL, 10.28 mmol), DPPA (1.93 g, 1.5 mL, 7.01 mmol) and tBuOH (3.0 mL) in toluene (30.0 mL) was heated at 100°C for 20 h. The mixture was then cooled to room temperature, diluted with ethyl acetate and washed with saturated $NaHCO_3$ and brine. The organic phase was dried over sodium sulphate and evaporated. The residue was purified by flash chromatography (ethyl acetate/heptane gradient) to yield **17** as an orange oil (1.06 g, 78%). MS (ESI): *m/z* = 267.3 [$M+H^+$];^{1}H NMR (400MHz, $CDCl_3$, 300 K, TMS): δ= 8.13 (dd, *J*= 3.0, 9.0 Hz, 1H), 7.79 (m, 2H), 4.45 (q, *J*= 7.3 Hz, 2H), 1.51 (*J*=s, 9H), 1.42 ppm (t, *J*= 7.3 Hz, 3H).

Acetic acid 6-tert-butoxycarbonylamino-pyridin-2-ylmethyl ester (18)

A solution of ester **17** (1.06 g, 3.99 mmol) in ethanol (30.0 mL) under argon was treated with finely powdered $CaCl_2$ (0.89 g, 7.80 mmol) and stirred at room temperature for 5 min. The reaction mixture was then cooled to 0°C and treated with $NaBH_4$ (0.77 g, 20.49 mmol). After stirring at 0°C for 2 h, the mixture was poured onto water and the resulting slurry extracted with chloroform. The combined organic phases were dried over sodium sulphate and evaporated. The residue (0.85 g) was dissolved in dichloromethane (30.0 mL) and treated with TEA (0.96 g, 1.32 mL, 9.48 mmol), DMAP (0.09 g, 0.76 mmol) and acetic anhydride (0.43 g, 4.17 mmol) and stirred at room temperature for 10 min. The reaction mixture was partitioned between water and dichloromethane, and the organic phase dried over sodium sulphate and evaporated. The residue was purified by flash chromatography (heptane/ethyl acetate gradient) to yield **18** (0.85 g, 80%) as a white solid. MS (ESI): *m/z* = 267.1 [$M+H^+$]; ^{1}H NMR (400MHz, $CDCl_3$, 300 K, TMS): δ= 7.85 (d, *J*= 8.2 Hz, 1H), 7.66 (t, *J*= 7.7 Hz, 1H), 7.20 (bs, 1H), 6.99 (d, *J*= 7.3 Hz, 1H), 5.07 (s, 2H), 2.15 (s, 3H), 1.52 ppm (*J*=s, 9H).

Acetic acid 6-[(5-bromo-2-methyl-thiazole-4-carbonyl)-amino]-pyridin-2-ylmethyl ester (19)

A solution of the protected pyridyl amine **18** (0.846 mg, 3.18 mmol) in dichloromethane (30.0 mL) was cooled to 0°C and treated dropwise with TFA (2.4 mL). After stirring at room temperature for 3 h, further TFA was added (1.5 mL). The mixture was stirred for further 2 h, then adjusted to pH 8 with 1N Na_2CO_3 (52 mL). The organic phase was separated and the aqueous phase extracted twice with dichloromethane. The combine organic phases were dried over sodium sulphate and evaporated. The residue (0.54 g, 100%) was pure acetic acid 6-amino-

pyridin-2-ylmethyl ester. A solution of 5-bromo-2-methylthiazole-4-carboxylic acid **13** (0.134 g, 0.60 mmol) in dichloromethane (5.0 mL) and dimethylformamide (0.10 mL) was treated with thionyl chloride (0.079 g, 0.66 mmol) and stirred at room temperature for 4.5 h. Acetic acid 6-amino-pyridin-2-ylmethyl ester (0.100 g, 0.060 mmol) and DIPEA (0.156 g, 1.20 mmol) were then added to the mixture. After stirring at room temperature for 30 min, the solvent was removed and the residue purified by flash chromatography (heptane/ethyl acetate gradient) to yield acetic acid 6-[(5-bromo-2-methyl-thiazole-4-carbonyl)-amino]-pyridin-2-ylmethyl ester **19** as a white solid (0.170 g, 76%). MS (ESI): *m/z* = 370.1, 372.0 [$M+H^+$]; ^{1}H NMR (400MHz, $CDCl_3$, 300 K, TMS): δ= 9.81 (bs, 1H), 8.33 (d, *J*= 8.3 Hz, 1H), 7.75 (t, *J*= 7.9 Hz, 1H), 7.26 (s, 1H), 7.12 (d, *J*= 7.5 Hz, 1H), 5.14 (s, 2H), 2.70 (s, 3H), 2.17 ppm (s, 3H).

2-Methyl-5-(pyridin-3-ylamino)-thiazole-4-carboxylic acid (6-hydroxymethyl-pyridin-2-yl)-amide (2)

A microwave vial was charged under argon with degassed dioxane (2.0 mL), $Pd_2dba_3.CHCl_3$ (0.043 g, 0.04 mmol), xantphos (0.073 g, 0.13 mmol), 3-aminopyridine **15** (0.039 g, 0.42 mmol), bromide **19** (0.155 g, 0.42 mmol) and Cs_2CO_3 (0.242 g, 1.26 mmol). The vial was sealed and irradiated in a microwave oven at 150°C for 15 min. The solvent was removed and the residue purified by flash chromatography (dichloromethane/methanol gradient) to yield acetic acid 6-{[2-methyl-5-(pyridin-3-ylamino)-thiazole-4-carbonyl]-amino}-pyridin-2-ylmethyl ester (0.046 g, 29%) as a white solid. This was dissolved in methanol (20.0 mL and treated with 2N NaOH (2.0 mL). The mixture was stirred at room temperature for 15 min, then quenched with 2N HCl (2.0 mL) and the solvent was removed. The crude was purified by flash chromatography (dichloromethane/methanol gradient) to yield **2** as a light yellow solid (0.035 g, 85%). MS (ESI): *m/z* = 342.1 [$M+H^+$]; HR-MS: 342.10180 ($C_{16}H_{15}N_5O_2S^+$; calc. 342.10192); ^{1}H NMR (400MHz, $CDCl_3$, 300 K, TMS): δ= 10.24 (bs, 1H), 9.44 (bs, 1H), 8.59 (d, *J*= 2.4 Hz, 1H), 8.32 (d, *J*= 3.8 Hz, 1H), 8.20 (d, *J*= 8.2 Hz, 1H), 7.74 (t, *J*= 7.8 Hz, 1H), 7.55 (dd, *J*= 1.4, 8.2 Hz, 1H), 7.29 (m, 1H), 6.99 (d, *J*= 7.5 Hz, 1H), 4.72 (s, 2H), 3.49 (bs, OH, 1H), 2.64 ppm (s, 3H).

5-Amino-2-methyl-thiazole-4-carboxylic acid ethyl ester (26)

A suspension of 2-acetylamino-cyanoacetic acid ethyl ester **25** (1.70 g, 10.00 mmol) and 2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane 2,4-disulfide (Lawesson's reagent) (2.02 g,

5.00 mmol) in toluene (25.00 ml) was heated under argon to 110°C and stirred for 22 h. The solvent was then evaporated, and the residue purified by flash chromatography (heptane/ethyl acetate 1:1) to yield 5-amino-2-methyl-thiazole-4-carboxylic acid ethyl ester **26** (0.94 g, 50.5%) as a yellow solid. MS (ESI): *m/z* = 187.3 [$M+H^+$]; ^{1}H NMR (400MHz, $CDCl_3$, 300 K, TMS): δ= 5.90 (bs, NH_2, 2H), 4.38 (q, *J*= 7.11 Hz, 2H), 2.54 (s, 3H), 1.40 ppm (t, *J*= 7.11 Hz, 3H).

2-Methyl-5-(pyridin-3-ylamino)-thiazole-4-carboxylic acid ethyl ester (27)

A microwave vial was charged with $Pd_2(dba)_3$ (0.20 g, 0.19 mmol), xanthphos (0.37 g, 0.65 mmol) and Cs_2CO_3 (2.17 g, 6.67 mmol), then sealed and flushed with argon. A solution of -amino-2-methyl-thiazole-4-carboxylic acid ethyl ester **26** (0.85 g, 4.56 mmol) and 3-bromopyridine (0.60 g, 3.80 mmol) in dioxane (15 mL) was degassed by sonication with contemporary argon bubbling for 5 min, then added to the microwave vial via syringe. The mixture was irradiated at 150°C for 10 min. After cooling, the mixture was diluted with tetrahydrofuran and filtered. The filtrate was evaporated and the residue purified by flash chromatography (ethyl acetate/methanol 0-10%) to yield 2-methyl-5-(pyridin-3-ylamino)-thiazole-4-carboxylic acid ethyl ester **27** (0.65 g, 65%) as an orange solid. MS (ESI): *m/z* = 264.0 [$M+H^+$]; ^{1}H NMR (400MHz, $CDCl_3$, 300 K, TMS): δ= 9.81 (bs, NH, 1H), 8.58 (d, J= 3 Hz, 1H), 8.31 (dd, *J*= 3, 4.8 Hz, 1H), 7.55 (ddd, *J*= 1.5, 3, 8.4 Hz, 1H), 7.30 (dd, *J*= 4.8, 8.4 Hz, 1H), 4.46 (q, *J*= 7.2 Hz, 2H), 2.64 (s, 3H), 1.45 ppm (t, *J*= 7.2 Hz, 3H).

2-Methyl-5-(pyrimidin-5-ylamino)-thiazole-4-carboxylic acid ethyl ester (28)

The compound **28** was prepared according to the method described for **27** starting from **26** (0.50 g, 2.68 mmol) and 5-bromo-pyrimidine (0.43 g, 2.68 mmol). The compound was obtained as an orange solid (0.43 g, 61%). MS (ESI): *m/z* = 265.1 [$M+H^+$]; ^{1}H NMR (400MHz, $CDCl_3$, 300 K, TMS): δ= 9.87 (bs, NH, 1H), 8.93 (s, 1H), 8.71 (s, 2H), 4.47 (q, *J*= 9.0 Hz, 2H), 2.67 (s, 3H), 1.46 ppm (t, *J*= 9.0 Hz, 3H).

2-Methyl-5-(pyridin-3-ylamino)-thiazole-4-carboxylic acid (29)

A solution of **27** (0.64 g, 2.44 mmol) in methanol (4.3 mL) was treated with a 2.55 N solution of KOH in water (2.9 mL, 7.40 mmol). The mixture was stirred at 55°C for 40 min. The volatiles were evaporated and the residue redissolved in water (5.4 mL) and acidified to pH 5-6 with 1N HCl. The mixture was stirred fro 45 min. The precipitated orange solid was filtered and the

filtrate acidified to pH 3 with 1N HCl. A light yellow solid forms, which is filtered and washed with water. After drying under high vacuum overnight, **29** was obtained (0.41 g, 72%) as a light yellow solid. MS (ESI): *m/z* = 234.1 [*M-H*]; ^{1}H NMR (400MHz, [D_6]DMSO, 300 K, TMS): δ= 12.69 (bs, 1H), 9.63 (bs, NH, 1H), 8.59 (d, *J*= 2.5 Hz, 1H), 8.27 (dd, *J*= 1.3, 4.6 Hz, 1H), 7.74 (ddd, *J*= 1.3, 2.8, 8.3 Hz, 1H), 7.39 ppm (dd, *J*= 4.6, 8.3 Hz, 1H).

2-Methyl-5-(pyridin-3-ylamino)-thiazole-4-carboxylic acid (6-methyl-pyridin-2-yl)-amide (1)

A solution of **29** (0.39 g, 1.66 mmol) in dimethylformamide (3.5 mL) at room temperature under argon was treated with TBTU (0.80 g, 2.50 mmol), DIPEA (0.64 g, 0.84 mL, 4.97 mmol) and 6-methyl-pyridin-2-ylamine (0.36 g, 3.32 mmoL). The mixture was stirred at room temperature for 18 hours, then partitioned between water and ethyl acetate. The organic phase was dried over sodium sulphate and evaporated. The residue was purified by flash chromatography (heptane/ethyl acetate gradient) to yield **1** as an off-white solid (0.28 g, 52%). MS (ESI): *m/z* = 326.4 [$M+H^+$]; MSMS (ESI, CE25eV): m/z (%): 326 (5), 218 (100) [C10H8N3OS]+, 192 (25) [C9H10N3S]+, 135 (30) [C7H7N2O]+, 109 (25) [C6H9N2]+; ^{1}H NMR (400MHz, $CDCl_3$, 300 K, TMS): δ= 10.27 (bs, NHCO, 1H), 9.42 (bs, NHAr, 1H), 8.58 (bs, 1H), 8.31 (d, *J*= 3.0 Hz, 1H), 8.09 (d, *J*= 9.0 Hz, 1H), 7.63 (t, *J*= 6.0 Hz, 1H), 7.55 (m, 1H), 7.30 (m, 1H), 6.91 (d, *J*= 6.0 Hz, 1H), 2.61 (s, 3H), 2.50 ppm (s, 3H). ^{13}C NMR (100MHz, $CDCl_3$, 300 K, TMS): δ= 169, 144, 140, 138, 123, 119, 110, 77, 26, 18 ppm.

2-Methyl-5-(pyridin-3-ylamino)-thiazole-4-carboxylic acid (2-methyl-pyridin-4-yl)-amide (20)

A solution of 4-amino-2-methyl pyridine (0.10 g, 0.91 mmol) in dioxane (2.0 mL) was treated at room temperature under argon with a 2N solution of trimethylaluminium in heptane (0.45 mL, 0.91 mmol). The mixture was stirred for 1 h at room temperature. The ester **27** was then added (0.08 g, 0.30 mmol) and the reaction mixture was irradiated in a microwave oven at 150°C for 15 min. The mixture was diluted with water (1.0 mL) and dichloromethane, dried over sodium sulphate and filtered. The solvent was removed and the residue purified by flash chromatography (dichloromethane/methanol gradient) to yield **20** as a yellow solid (0.04 g, 41%). MS (ESI): *m/z* = 326.1 [$M+H^+$] ^{1}H NMR (400MHz, $CDCl_3$, 300 K, TMS): δ= 10.17 (bs, NHCO, 1H), 8.93 (bs,

NHAr, 1H), 8.60 (d, *J*=2.7 Hz, 1H), 8.42 (d, *J*= 5.7 Hz, 1H), 8.33 (dd, *J*= 1.2, 4.8 Hz, 1H), 7.53 (m, 2H), 7.40 (dd, *J*= 1.8, 5.7 Hz, 1H), 7.31 (dd, *J*= 4.5, 8.1 Hz, 1H), 2.62 (s, 3H), 2.57 ppm (s, 3H).

2-Methyl-5-(pyridin-3-ylamino)-thiazole-4-carboxylic acid (5-fluoro-pyridin-2-yl)-amide (21)

Following the general procedure described for the synthesis of **20**, ester **27** (0.08 g, 0.30 mmol) was reacted with 2-amino-5-fluoropyridine (0.13 g, 1.15 mmol) to yield **21** as a light yellow solid (0.065 g, 68%). MS (ESI): *m/z* = 328.1 [*M-H*]; ^{1}H NMR (400MHz, $CDCl_3$, 300 K, TMS): δ= 10.20 (bs, NHCO, 1H), 9.49 (bs, NHAr, 1H), 8.58 (d, *J*= 2.8 Hz, 1H), 8.32 (m, 2H), 8.19 (d, *J*= 3.0 Hz, 1H), 7.54 (m, 1H), 7.48 (m, 1H), 7.29 (dd, *J*= 4.7, 8.3 Hz, 1H), 2.61 ppm (s, 3H).

2-Methyl-5-(pyrimidin-5-ylamino)-thiazole-4-carboxylic acid (6-methyl-pyridin-2-yl)-amide (22)

Following the general procedure described for the synthesis of **20**, ester **28** (0.15 g, 0.57 mmol) was reacted with 6-amino-2-picoline (0.24 g, 2.27 mmol) to yield **22** as a light yellow solid (0.092 g, 50%). MS (ESI): *m/z* = 327.3 [$M+H^+$]; ^{1}H NMR (400MHz, $CDCl_3$, 300 K, TMS): δ= 10.36 (bs, NHCO, 1H), 9.43 (bs, NHAr, 1H), 8.90 (s, 1H), 8.70 (s, 2H), 8.07 (d, *J*= 8.2 Hz, 1H), 7.63 (t, *J*= 7.9 Hz, 1H), 6.92 (d, *J*= 7.4 Hz, 1H), 2.64 (s, 3H), 2.50 ppm (s, 3H).

2-Methyl-5-(pyrimidin-5-ylamino)-thiazole-4-carboxylic acid (5-fluoro-pyridin-2-yl)-amide (23)

Following the general procedure described for the synthesis of **20**, ester **28** (0.05 g, 0.19 mmol) was reacted with 2-amino-5-fluoropyridine (0.08 g, 0.76 mmol) to yield **23** as a light yellow solid (0.023 g, 37%). MS (ESI): *m/z* = 331.1 [$M+H^+$]; ^{1}H NMR (400MHz, $CDCl_3$, 300 K, TMS): δ= 10.29 (bs, NHCO, 1H), 9.51 (bs, NHA, 1Hr), 8.92 (s, 1H), 8.71 (s, 2H), 8.30 (dd, *J*= 7.0, 12.1 Hz, 1H), 8.20 (d, *J*= 2.9 Hz, 1H), 7.48 (m, 1H), 2.65 ppm (s, 3H).

2-Methyl-5-(pyrimidin-5-ylamino)-thiazole-4-carboxylic acid (2-methyl-pyridin-4-yl)-amide (24)

Following the general procedure described for the synthesis of **20**, ester **28** (0.08 g, 0.30 mmol) was reacted with 4-amino-2-methyl pyridine (0.10 g, 0.91 mmol) to yield **24** as a light yellow

solid (0.051 g, 52%). MS (ESI): *m/z* = 327.1 [$M+H^+$]; ^{1}H NMR (400MHz, $CDCl_3$, 300 K, TMS): δ= 10.26 (bs, NHCO, 1H), 8.94 (bs, NHAr, 1H), 8.93 (s, 1H), 8.71 (s, 2H), 8.43 (d, *J*= 5.4 Hz, 1H), 7.51 (s, 1H), 7.40 (d, *J*= 5.4 Hz, 1H), 2.66 (s, 3H), 2.57 ppm (s, 3H).

2-Hydroxymethyl-5-(pyridin-3-ylamino)-thiazole-4-carboxylic acid (6-methyl-pyridin-2-yl)-amide (4)

^{1}H NMR (600MHz, [D_6]DMSO, 27°C): d=8.33 (s, 1H; CH), 8.12 (d,1H; CH), 7.86 (d, 1H; CH), 7.54 (t, 1H; CH), 7.39 (d, 1H; CH), 7.18 (dd, 1H; CH), 6.77 (d, 1H; CH), 4.44 (s, 2H; CH_2), 2.37 ppm (s, 3H; CH_3)

5-(6-Hydroxy-pyridin-3-ylamino)-2-methyl-thiazole-4-carboxylic acid (6-methyl-pyridin-2-yl)-amide (5)

^{1}H NMR (500MHz, [D_6]DMSO, 27°C): d=9.17 (s, 1H; NH), 9.01 (s,1H; NH), 8.00 (d, ^{3}J (H,H)=8.3 Hz, 1H; CH), 7.71 (t, ^{3}J (H,H)=8.0Hz, 1H; CH), 7.55 (m, 1H; CH), 7.54 (m, 1H; CH), 6.99 (d, ^{3}J (H,H)=7.6 Hz, 1H; CH), 6.41 (m, 1H; CH), 2.51 (s, 3H; CH_3), 2.41 ppm (s, 3H; CH_3)

5-(6-Hydroxy-pyridin-3-ylamino)-2-methyl-thiazole-4-carboxylic acid (5-hydroxy-6-methyl-pyridin-2-yl)-amide (6)

^{1}H NMR (500MHz, [D_3]Methanol, 27°C): d=7.85 (d, ^{3}J (H,H)= 8.8Hz, 1H; CH), 7.65 (dd, ^{3}J (H,H)=9,4Hz, 3.0Hz, 1H; CH), 7.58 (d, ^{3}J (H,H)=3.0Hz, 1H; CH), 7.15 (d, ^{3}J (H,H)=8.8 Hz, 1H; CH), 6.61 (d, ^{3}J (H,H)= 9,4 Hz, 1H; CH), 2.57 (s, 3H; CH_3), 2.38 ppm (s, 3H; CH_3),