

LCMS Methods

Analytical LCMS

Analytical method employed Waters 2545 pumps, a Waters System fluidics organiser and a Waters 2998 diode array detector. The detection was performed between 210nm and 650nm. The mass spectrometer used was a Waters 3100 and a Waters Sunfire, 5µm pore size, C18 column of dimensions 50 x 4.6mm was used. The injection volume was 5µL.

The flow rate was 1.5 mL/min and the mobile phases of water and acetonitrile contained 0.1% formic acid. The elution was started at 95% water:5% acetonitrile ramping up to 5% water:95% acetonitrile over 5.5minutes. The eluent level was returned to the starting conditions of 95% water:5% acetonitrile over 0.1 minutes. These conditions were held for 1.4 minutes to allow equilibration of the column before the next sample was injected. The run lasted 7 minutes in total.

Preparatory LCMS

Samples purified by Mass Spectrometry directed High Performance Liquid Chromatography employed Waters 2545 and 515 pumps, a Waters System fluidics organiser and a Waters 2998 diode array detector. The detection was performed between 210nm and 650nm. The mass spectrometer used was a Waters 3100 and Waters Sunfire, 5µm pore size, C18 column of dimensions 50 x 19mm was used. The injection volume was up to 500 µL of solution at a maximum concentration of 50mg/mL.

The flow rate was 25 mL/min and the mobile phases of water and acetonitrile contained 0.1% formic acid. The elution was started at 95% water:5% acetonitrile ramping up to 5% water:95% acetonitrile over 5 minutes. The eluent level was returned to the starting conditions of 95% water:5% acetonitrile over 30 seconds.

NMR

Proton NMR spectra were recorded using a Bruker AMX-300 NMR machine at 300 MHz or a Bruker Avance-500 at 500 MHz or a Bruker AS-400 NMR machine at 400 MHz. Carbon NMR were ran using a Bruker AS-400 NMR machine at 101 MHz. Shifts were reported in ppm values relative to an internal standard of trimethylsilane (TMS) or residual protic solvent. The following abbreviations were used to describe the splitting patterns: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (double-doublet), dt (double-triplet), br (broad).

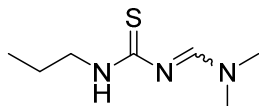
Purity

Purity of all final compounds was >95% as determined by HPLC with a Waters 2998 diode array detector and ¹H NMR analysis.

Microwave Reactor

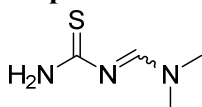
The microwave reactor used was a Biotage 30-Initiator 60.

Preparation of 1-[1-Dimethylamino-methylidene]-3-propyl-thiourea 10a



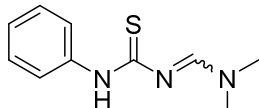
N-Propylthiourea (45 mmol, 5.32 g) was dissolved in ethanol (200 mL) and treated with dimethylformamide dimethylacetal (49.5 mmol, 6.6 g) and heated at reflux for 90 minutes. The reaction mixture was allowed to cool and then evaporated under reduced pressure. The residual oil was stirred vigorously in cyclohexane (60 mL) for 2 hours. The resultant white suspension was stirred, with cooling for 30 minutes and then filtered. The white precipitate was washed with cyclohexane and dried to give a white solid. Yield=7.45 g, 95%. LCMS m/z 174 [MI+H]. ^1H NMR (300 MHz, DMSO- d_6) δ 8.80 – 8.49 (2 H, m), 3.49 – 3.21 (3 H, m), 3.18 – 3.05 (3 H, m), 3.05 – 2.91 (2 H, m), 1.65 – 1.36 (2 H, m), 0.92 – 0.73 (3 H, m).

Preparation of [1-Dimethylamino-methylidene]-thiourea 10b



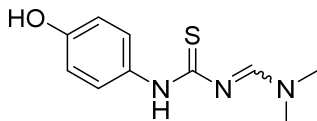
Dimethylformamide dimethylacetal (110 mmol, 14.54 g) was added to a solution of thiourea (100 mmol, 7.61 g) in ethanol (300 mL). This was heated to reflux for 3 hours. The reaction mixture was then evaporated and stirred in cyclohexane (30 mL) for 30 minutes. Then the precipitate was filtered off to yield the title compound as a yellow solid. Yield=13.10 g, 100%. ^1H NMR (300 MHz, DMSO- d_6) δ 8.61 (1 H, s), 8.20 (1 H, s), 7.93 (1 H, s), 3.12 (3 H, s), 2.97 (3 H, s).

Preparation of 1-[1-Dimethylamino-methylidene]-3-phenyl-thiourea 10c



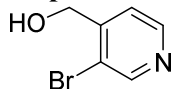
Synthesised from phenyl thiourea using the same method outlined for **10a**. Yield=6 g, 72%. LCMS m/z 207 [MI+H] $^+$. ^1H NMR (300 MHz, DMSO- d_6) δ 10.65 – 10.33 (1 H, m), 8.86 – 8.65 (1 H, m), 7.99 – 7.45 (2 H, m), 7.42 – 7.16 (2 H, m), 7.20 – 6.88 (1 H, m), 3.30 – 3.15 (3 H, m), 3.12 – 2.99 (3 H, m).

Preparation of 1-[1-Dimethylamino-methylidene]-3-(4-hydroxy-phenyl)-thiourea 10d



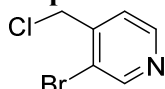
4-Hydroxyphenyl thiourea (10 mmol, 1.68 g) was dissolved in ethanol (60 mL) and treated with dimethyl formamide dimethylacetal (11 mmol, 1.31 g). The reaction mixture was heated at reflux for 2 hours and then cooled to room temperature. The solid precipitate was collected by filtration to provide the title compound as a mixture of *cis* and *trans* isomers as a cream coloured solid. Yield=1.4 g, 63%. LCMS m/z 224 [MI+H] $^+$. ^1H NMR (400 MHz, DMSO- d_6) δ 10.25 (1 H, s), 10.22 (1 H, s), 9.28 (1 H, s), 9.20 (1 H, s), 8.75 (1 H, s), 8.69 (1 H, s), 7.51 (1 H, s), 7.49 (1 H, s), 7.31 (1 H, d, J = 2.0 Hz), 7.30 (1 H, d, J = 2.0 Hz), 6.71 – 6.66 (2 H, m), 6.67 – 6.62 (2 H, m), 3.17 (3 H, s), 3.16 (3 H, s), 3.05 (3 H, s), 2.98 (3 H, s).

Preparation of (3-Bromo-pyridin-4-yl)-methanol **8**



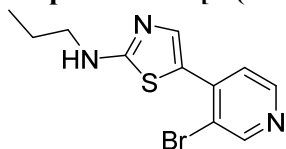
A solution of 3-bromo-pyridine-4-carbaldehyde (5 mmol, 0.93 g) in methanol (10 mL) was cooled to 0 °C under nitrogen. This was treated with sodium borohydride (5.5 mmol, 0.200 g) portionwise, and allowed to stir at 0 °C for 1 hour, then slowly allowed to return to room temperature overnight. The reaction was quenched by the addition of saturated ammonium chloride (5 mL), then evaporated under reduced pressure. The reaction mixture was then diluted with ethyl acetate (20 mL) and washed with water (20 mL). The organic layer was then separated and dried with MgSO₄, filtered and evaporated to yield the title compound as a white solid. Yield= 0.94 g, 100%. LCMS *m/z* 188/190 [MI+H]⁺. ¹H NMR (300 MHz, DMSO-d₆) δ 8.62 (1 H, m), 8.53 (1 H, d, *J* = 4.9 Hz), 7.53 (1 H, dd, *J* = 0.6, 4.9 Hz), 5.69 (1 H, t, *J* = 5.6 Hz), 4.51 (2 H, dd, *J* = 0.8, 5.6 Hz).

Preparation of 3-Bromo-4-chloromethyl-pyridine **9**



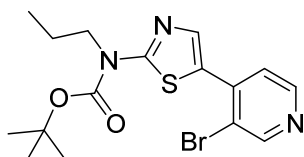
A solution of (3-bromo-pyridin-4-yl)-methanol **8** (3.5 mmol, 0.66 g) in anhydrous DCM (50 mL) and DMF (0.02 mL) was treated with thionyl chloride (7 mmol, 0.507 mL). The reaction mixture was refluxed for 4 hours and then allowed to cool to room temperature. The solvent was removed under reduced pressure and carefully treated with saturated sodium bicarbonate solution (20 mL). The aqueous layer was extracted into ethyl acetate (2x20 mL), dried with MgSO₄, filtered and evaporated to a dark red oil. This was purified by flash column chromatography eluting with 1:1 ethyl acetate: cyclohexane to yield the title compound as a dark red oil. Yield=0.550 g, 77%. LCMS *m/z* 205/207 [MI+H]⁺.

Preparation of [5-(3-Bromo-pyridin-4-yl)-thiazol-2-yl]-propyl-amine **11a**



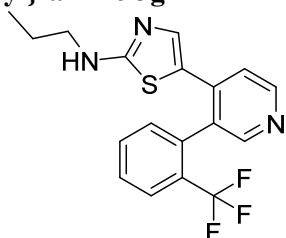
3-Bromo-4-chloromethyl-pyridine **9** (2.6 mmol, 0.54 g) and 1-[1-dimethylamino-methylidene]-3-propyl-thiourea **10a** (2.6 mmol, 0.45 g) were dissolved in acetonitrile (20 mL) and treated with triethylamine (5.2 mmol, 0.69 mL). The reaction mixture was heated at reflux for 2 hours and then allowed to cool to room temperature. The solvent was removed under reduced pressure and the residue was dissolved in DCM (20 mL) and washed with water (20 mL). The organics were passed through a phase separation cartridge and evaporated to a dark brown solid. The solid was purified by flash column chromatography eluting with 0-80% ethyl acetate in cyclohexane to yield the crude title compound as a dark orange solid. Yield=0.73 g, 94%. LCMS *m/z* 298/300 [MI+H]⁺.

Preparation of [5-(3-Bromo-pyridin-4-yl)-thiazol-2-yl]-propyl-carbamic acid *tert*-butyl ester **12**



5-(3-Bromo-pyridin-4-yl)-thiazol-2-yl-propyl-amine **11a** (2.4 mmol, 0.72 g) was dissolved in DCM (10 mL) with DMAP (0.50 mmol, 0.056 g) then di-*tert*-butyl dicarbonate (2.8 mmol, 0.62 g) was added, this was left to stir overnight. The reaction mixture was diluted with DCM (20 mL) washed with saturated sodium bicarbonate solution (50 mL), passed through a phase separator and the DCM layer was evaporated under reduced pressure. This was then purified by flash column chromatography, eluting with 0-40% ethyl acetate in cyclohexane. The fractions containing the product were evaporated to yield the title compound as a yellow gum. Yield=0.41 g, 44%. LCMS m/z 398/400 $[MI+H]^+$. 1H NMR (300 MHz, DMSO- d_6) δ 8.81 (1 H, s), 8.52 (1 H, d, $J = 5.1$ Hz), 8.09 (1 H, s), 7.71 (1 H, d, $J = 5.1$ Hz), 4.02 (2 H, m), 1.67 (2 H, m), 1.53 (9 H, s), 0.88 (3 H, t, $J = 7.4$ Hz).

Preparation of Propyl-{5-[3-(2-trifluoromethyl-phenyl)-pyridin-4-yl]-thiazol-2-yl}-amine **3g**



To a microwave tube were added [5-(3-bromo-pyridin-4-yl)-thiazol-2-yl]-propyl-carbamic acid *tert*-butyl ester **12** (0.13 mmol, 0.05 g), 2-trifluoromethylphenylboronic acid (0.15 mmol, 0.028 g), potassium carbonate (0.4 mmol, 0.055 g) and bis(triphenylphosphine) palladium(II)dichloride (0.01 mmol, 0.007 g), 1,4-dioxane (1.5 mL) and water (0.5 mL). The tube was capped and heated to 120 °C in a microwave reactor for 15 minutes. The reaction mixture was evaporated under reduced pressure then diluted with DCM (10 mL) and washed with water (10 mL). The organics were evaporated under reduced pressure re-dissolved in DCM (1 mL) and treated with TFA (1 mL) and left to stir for 15 hours at room temperature. The reaction was quenched by the addition of saturated sodium bicarbonate solution (10 mL). The aqueous was extracted into DCM (5 mL), passed through a phase separating cartridge and evaporated under reduced pressure. The residue was taken up in DMSO and purified by mass directed HPLC. The fractions were evaporated to yield the title compound as a white solid. Yield=0.010 g, 21%. LCMS m/z 364 $[MI+H]^+$. 1H NMR (300 MHz, DMSO- d_6) δ 8.50 (1 H, d, $J = 5.7$ Hz), 8.33 (1 H, s), 8.07 (1 H, s), 7.92 (1 H, m), 7.77 (3 H, t, $J = 3.8$ Hz), 7.43 (2 H, m), 3.07 (2 H, dd, $J = 6.9, 12.4$ Hz), 1.43 (2 H, dt, $J = 7.3, 14.4$ Hz), 0.81 (3 H, t, $J = 7.4$ Hz).

The following compounds were made by the same general procedure as **3g** using the appropriate boronic acid:

3a, {5-[3-(2-Chloro-phenyl)-pyridin-4-yl]-thiazol-2-yl}-propyl-amine (formic acid salt). LCMS m/z 330 $[MI+H]^+$. 1H NMR (300 MHz, DMSO- d_6) δ 8.48 (1 H, d, $J = 5.5$ Hz), 8.26 (1 H, d, $J = 0.7$ Hz), 8.14 (1 H, s), 7.91 (1 H, t, $J = 5.4$ Hz), 7.65 – 7.38 (5

H, m), 7.26 (1 H, s), 3.08 (2 H, td, $J = 7.0, 5.3$ Hz), 1.47 (2 H, h, $J = 7.3$ Hz), 0.83 (3 H, t, $J = 7.4$ Hz).

3b, {5-[3-(3-Chloro-phenyl)-pyridin-4-yl]-thiazol-2-yl}-propyl-amine LCMS m/z 330 [MI+H]⁺.

3c, {5-[3-(4-Chloro-phenyl)-pyridin-4-yl]-thiazol-2-yl}-propyl-amine LCMS m/z 330 [MI+H]⁺.

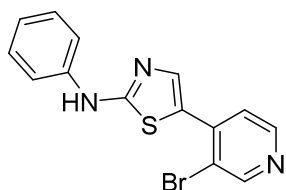
3d, [5-(3-Phenyl-pyridin-4-yl)-thiazol-2-yl]-propyl-amine LCMS m/z 296 [MI+H]⁺.

3e, Propyl-[5-(3-*o*-tolyl-pyridin-4-yl)-thiazol-2-yl]-amine LCMS m/z 310 [MI+H]⁺.

3f, {5-[3-(2-*Iso*-propyl-phenyl)-pyridin-4-yl]-thiazol-2-yl}-propyl-amine LCMS m/z 338 [MI+H]⁺.

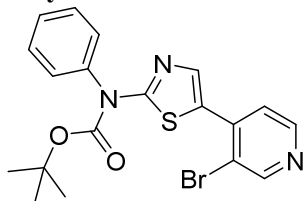
3h, {5-[3-(4-Methoxy-2-trifluoromethyl-phenyl)-pyridin-4-yl]-thiazol-2-yl}-propyl-amine LCMS m/z 394 [MI+H]⁺.

Preparation of [5-(3-Bromo-pyridin-4-yl)-thiazol-2-yl]-phenyl-amine **11c**.



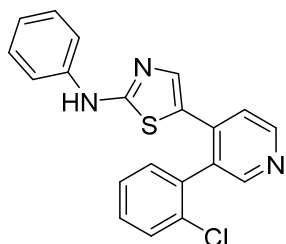
3-Bromo-4-chloromethyl-pyridine **9** (1 mmol, 0.21 g) and 1-[1-dimethylamino-methylidene]-3-phenyl-thiourea **10c** (1 mmol, 0.11 g) were weighed into a round bottom flask and treated with triethylamine (2 mmol, 0.28 mL) and acetonitrile (10 mL). The reaction mixture was heated at reflux for 2 hours. The solvent was removed under reduced pressure and then the residue was taken up in DCM (30 mL) and water (30 mL). The organics were separated in a phase extraction cartridge and evaporated to a gum. This was purified by flash column chromatography eluting with 1:4 ethyl acetate:cyclohexane to yield the title compound which was used crude in the next step. Yield=0.27 g, 82%. LCMS m/z 332/334 [MI+H]⁺.

Preparation of [5-(3-Bromo-pyridin-4-yl)-thiazol-2-yl]-phenyl-carbamic acid *tert*-butyl ester **19**



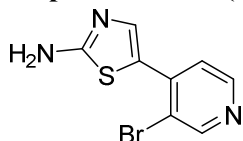
[5-(3-Bromo-pyridin-4-yl)-thiazol-2-yl]-phenyl-amine **11c** (1 mmol, 0.33 g) was weighed into a round bottomed flask and dissolved in DCM (10 mL), triethylamine (2 mmol, 0.28 mL) and DMAP (0.01 g) were added and then di-*tert*-butyl dicarbonate (1.4 mmol, 0.30 mL) was added. The reaction mixture was allowed to stir at room temperature for 15 hours. The reaction mixture was diluted with DCM (50 mL) and water (50 mL). The organic layer was separated, dried with MgSO₄ and evaporated under reduced pressure. The residue was purified by flash column chromatography 1:9 ethyl acetate:cyclohexane to yield the title compound as a gum which was used crude in the next step. Yield=0.17 g, 40%. LCMS m/z 376/378 [MI-*t*Bu]⁺.

Preparation of {5-[3-(2-Chloro-phenyl)-pyridin-4-yl]-thiazol-2-yl}-phenyl-amine **3n**.



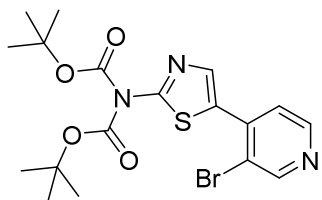
[5-(3-Bromo-pyridin-4-yl)-thiazol-2-yl]-phenyl-carbamic acid *tert*-butyl ester **19** (0.175 mmol, 0.08 g), 2-chloro phenyl boronic acid (0.175 mmol, 0.027 g), potassium carbonate (0.35 mmol, 0.048 g) and bis(triphenylphosphine) palladium(II)dichloride (0.009 mmol, 0.006 g) were weighed into a microwave vial and treated with dioxane (1 mL) and water (0.3 mL). The vial was sealed and heated at 150 °C for 15 minutes. The solvent was removed under reduced pressure and re-dissolved in DCM (20 mL) and washed with water (20 mL). The organics were separated using a phase separation cartridge. The organics were evaporated under reduced pressure to a brown oil. The residue was dissolved in DMSO and purified by mass directed LCMS. The fractions were evaporated to yield the title compound as a yellow solid. Yield=0.01 g, 17%. LCMS m/z 363 [MI+H]⁺. ¹H NMR, (300 MHz, DMSO-*d*₆) δ 10.31 (1 H, s), 8.56 (1 H, d, J = 5.4 Hz), 8.34 (1 H, s), 7.76 (1 H, d, J = 5.4 Hz), 7.53 (7 H, m), 7.26 (2 H, t, J = 7.7 Hz), 6.94 (1 H, t, J = 7.0 Hz).

Preparation of 5-(3-Bromo-pyridin-4-yl)-thiazol-2-ylamine **11b**



3-Bromo-4-chloromethyl-pyridine **9** (31.8 mmol, 6.55 g) was added to a solution of [1-dimethylamino-methylidene]-thiourea **10b** (31.8 mmol, 4.17 g) in acetonitrile (300 mL) with triethylamine (31.8 mmol, 4.2 mL). The reaction mixture was heated at reflux for 15 hours. The solvent was evaporated under reduced pressure and the reaction mixture was dissolved in DCM (200 mL) and then washed with saturated sodium bicarbonate solution (200 mL) then brine (200 mL). The organics were evaporated under reduced pressure to yield the title compound as a dark brown solid which was used crude in the next step. Yield=8 g, 98% LCMS m/z 256/258 [MI+H]⁺.

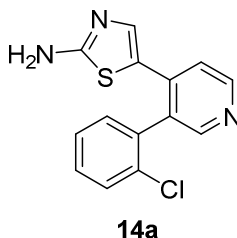
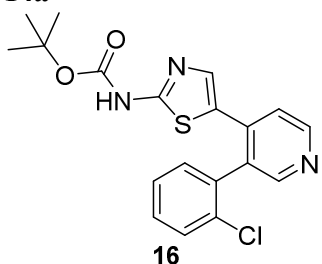
Preparation of 5-(3-Bromo-pyridin-4-yl)-thiazol-2-yl-dicarbamic acid *tert*-butyl ester **13**



A solution of 5-(3-bromo-pyridin-4-yl)-thiazol-2-ylamine **11b** (20 mmol, 5.12 g) was dissolved in THF (150 mL) with DMAP (0.002 g) and di-*tert*-butyl dicarbonate (70 mmol, 15.26 g) was added. The reaction mixture was heated at reflux for 6 hours, then allowed to cool to room temperature. The reaction mixture was diluted with

DCM (100 mL), then washed with saturated sodium bicarbonate solution (100 mL). The organics were separated and evaporated under reduced pressure. The residue was purified by flash column chromatography, eluting with 0-20% EtOAc: cyclohexane to yield the title compound as a yellow solid. Yield=1.6 g, 18%. LCMS m/z 456/458 $[MI+H]^+$. 1H NMR (300 MHz, DMSO- d_6) δ 8.85 (1 H, s), 8.57 (1 H, d, $J = 5.1$ Hz), 8.12 (1 H, s), 7.75 (1 H, d, $J = 5.1$ Hz), 1.52 (18 H, s).

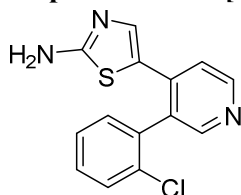
Preparation of {5-[3-(2-Chloro-phenyl)-pyridin-4-yl]-thiazol-2-yl}-carbamic acid *tert*-butyl ester **16 and 5-[3-(2-Chloro-phenyl)-pyridin-4-yl]-thiazol-2-ylamine **14a****



To a microwave tube were added [5-(3-bromo-pyridin-4-yl)-thiazol-2-yl]-dicarbamic acid *tert*-butyl ester **13** (1 mmol, 0.46 g), 2-chlorophenylboronic acid (1.5 mmol, 0.23 g), potassium carbonate (2 mmol, 0.27 g) and bis(triphenylphosphine) palladium(II)dichloride (0.1 mmol, 0.070 g) then 1,4-dioxane (8 mL) and water (2 mL) were added. The reaction mixture was heated to 150 °C in a microwave reactor for 30 minutes. The reaction mixture was diluted with DCM (100 mL) and washed with water (100 mL) and brine (100 mL). The organics were evaporated under reduced pressure and then purified by flash column chromatography eluting with 30-100% ethyl acetate:cyclohexane to yield {5-[3-(2-chloro-phenyl)-pyridin-4-yl]-thiazol-2-yl}-carbamic acid *tert*-butyl ester **16** as a cream solid. Yield=0.48 g, 18%. LCMS m/z 388 $[MI+H]^+$. 1H NMR (300 MHz, DMSO- d_6) δ 11.55 (1 H, s), 8.59 (1 H, d, $J = 5.3$ Hz), 8.39 (1 H, s), 7.52 (5 H, m), 7.32 (1 H, s), 1.43 (9 H, s). 5-[3-(2-Chloro-phenyl)-pyridin-4-yl]-thiazol-2-ylamine **14a** was also isolated as a brown gum. LCMS m/z 288 $[MI+H]^+$. 1H NMR (300 MHz, DMSO- d_6) δ 8.47 (1 H, d, $J = 5.4$ Hz), 8.25 (1 H, d, $J = 0.6$ Hz), 7.68 – 7.53 (5 H, m), 7.28 (2 H, s), 7.27 (1 H, s).

5-[3-(2-Chloro-phenyl)-pyridin-4-yl]-thiazol-2-ylamine **14a** could also be made by the following procedure.

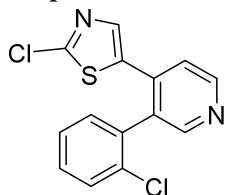
Preparation of 5-[3-(2-Chloro-phenyl)-pyridin-4-yl]-thiazol-2-ylamine **14a**



In a microwave vial 5-(3-bromo-pyridin-4-yl)-thiazol-2-yl]-dicarbamic acid *tert*-butyl ester **13** (1.13 mmol, 0.52 g) was dissolved in 1-4 dioxane (8 mL). 2-Chlorophenylboronic acid (1.4 mmol, 0.21 g), potassium carbonate (2.33 mmol, 0.32 g), bis(triphenylphosphine) palladium(II)dichloride (0.11 mmol, 0.081 g), and water (2 mL) were added. The vial was capped and heated to 80 °C in the microwave for 15 minutes. The reaction mixture was then diluted with DCM 100 mL and washed with water 100 mL, and brine 100 mL. The organics were evaporated and then purified by

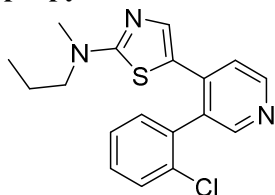
flash column chromatography eluting with 0-50% ethyl acetate: cyclohexane. The mixture of both mono and diboc material were combined and dissolved in DCM (15 mL), and TFA (5 mL) was added and allowed to stir overnight at room temperature. The reaction mixture was quenched by the slow addition of sodium bicarbonate, then left to stir for 1 hour. The reaction was diluted with DCM then washed with a saturated solution of sodium bicarbonate. The organics were evaporated to yield the title compound as a yellow solid. Yield=0.312 g, 94%. LCMS m/z 288 [MI+H]⁺. ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.47 (1 H, d, J = 5.4 Hz), 8.25 (1 H, d, J = 0.6 Hz), 7.68 – 7.53 (5 H, m), 7.28 (2 H, s), 7.27 (1 H, s).

Preparation of 3-(2-Chloro-phenyl)-4-(2-chloro-thiazol-5-yl)-pyridine 15



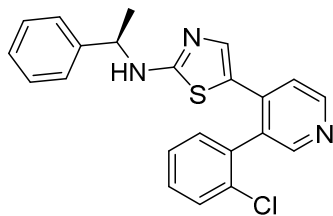
5-[3-(2-Chloro-phenyl)-pyridin-4-yl]-thiazol-2-ylamine **14a** (0.2 mmol, 0.06 g) was dissolved in 37% hydrochloric acid (2 mL) and cooled to 0 °C. The solution was treated with sodium nitrite (3 mmol, 0.20 g) and left to stir at 0 °C for 1 hour and then room temperature for 15 hours. The reaction mixture was added to NH₄OH (20 mL) and extracted with DCM (2x10 mL). The organics were passed through a phase separation cartridge and evaporated to a yellow oil which was used directly in the next step. Yield=0.06 g, 98%. LCMS m/z 307/309 [MI+H]⁺. ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.75 (1 H, d, J = 5.4 Hz), 8.56 (1 H, s), 8.13 (1 H, s), 7.96 (1 H, d, J = 5.4 Hz), 7.56 (4 H, m).

Preparation of {5-[3-(2-Chloro-phenyl)-pyridin-4-yl]-thiazol-2-yl}-methyl-propyl-amine 3i



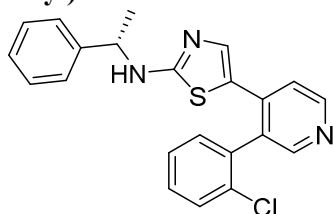
In a microwave vial was added 3-(2-chloro-phenyl)-4-(2-chloro-thiazol-5-yl)-pyridine **15** (0.2 mmol, 0.06 g), methanol (2 mL) and *N*-methyl propylamine (1 mmol, 0.072 g) and heated to 150 °C in a microwave reactor for 15 minutes. The reaction mixture was then diluted with DCM (5 mL) and washed with water (5 mL) and passed through a phase separator. The organic phase was then evaporated, dissolved in DMSO and purified by mass directed HPLC. Evaporation of the appropriate fractions provided the title compound. Yield=0.012 g, 17%. LCMS m/z 344 [MI+H]⁺. ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.49 (1 H, s), 8.28 (1 H, s), 7.50 (5 H, m), 7.20 (1 H, s), 3.27 (2 H, s), 2.91 (3 H, s), 1.50 (2 H, s), 0.79 (3 H, s).

Preparation of 5-[3-(2-Chloro-phenyl)-pyridin-4-yl]-thiazol-2-yl}-((*R*)-1-phenyl-ethyl)-amine 3m



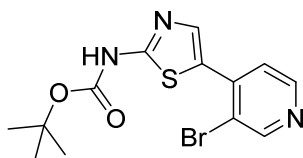
To a solution of {5-[3-(2-Chloro-phenyl)-pyridin-4-yl]-thiazol-2-yl}-carbamic acid *tert*-butyl ester **16** (0.15 mmol, 0.060 g) in THF (2 mL) cooled to 0 °C, triphenyl phosphine (0.15 mmol, 0.039 g) and (*S*)-1-phenylethanol (0.2 mmol, 0.024 g) were added followed by the slow addition of DIAD (0.15 mmol, 0.030 g). The reaction was left to warm to room temperature overnight. The reaction mixture was diluted with DCM (5 mL) then washed with water (5 mL), passed through a phase separating cartridge and evaporated under reduced pressure. The residue was then dissolved in DCM (1 mL) and treated with TFA (1 mL) and left to stir for 15 hours at room temperature. The reaction was quenched by the addition of saturated sodium bicarbonate solution (10 mL). The aqueous was extracted into DCM (5 mL), passed through a phase separating cartridge and evaporated under reduced pressure. The residue was taken up in DMSO and purified by mass directed HPLC. The fractions were evaporated to yield the title compound as a white solid. Yield=0.009 g, 15%. LCMS m/z 392 [MI+H]⁺. ¹H NMR (300 MHz, DMSO- d_6) δ 8.53 - 8.39 (2 H, m), 8.24 (1 H, s), 7.69 - 7.14 (11 H, m), 4.75 - 4.59 (1 H, m), 1.36 (3 H, d, J = 6.9 Hz).

Preparation of 5-[3-(2-Chloro-phenyl)-pyridin-4-yl]-thiazol-2-yl]-N-(*S*)-1-phenylethyl-amine **3l**



Prepared by an analogous procedure to **3m** using (*R*)-1-phenylethanol. LCMS m/z 392 [MI+H]⁺. ¹H NMR (300 MHz, DMSO- d_6) δ 8.53 - 8.39 (2 H, m), 8.24 (1 H, s), 7.69 - 7.14 (11 H, m), 4.75 - 4.59 (1 H, m), 1.36 (3 H, d, J = 6.9 Hz).

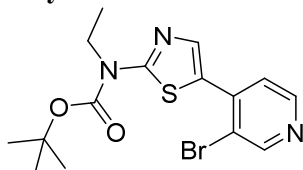
Preparation of 5-(3-Bromo-pyridin-4-yl)-thiazol-2-yl]-N-(*S*)-1-phenylethyl-amine **17**



5-(3-Bromo-pyridin-4-yl)-thiazol-2-ylamine **11b** (10 mmol, 2.56 g) was dissolved in DCM (100 mL) with DMAP (2 mmol, 0.224 g) and di-*tert*-butyl dicarbonate (24 mmol, 2.06 g) was added. This was left to stir at room temperature for 6 hours, then a further 2.4 equivalents of di-*tert*-butyl dicarbonate (24 mmol, 2.06 g) were added and the reaction was left to stir overnight. The reaction mixture was diluted with another 100 mL of DCM then washed with saturated sodium bicarbonate solution. The DCM layer was separated, dried with MgSO₄ and evaporated under reduced pressure. The residue was purified by column chromatography, eluting with 0-50%

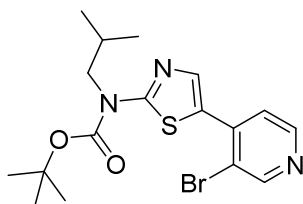
EtOAc:cyclohexane. The fractions were pooled and evaporated to provide the title compound. Yield=1.1 g, 30%. LCMS m/z 357 [MI+H]⁺. ¹H NMR (500 MHz, DMSO-d₆) δ 11.78 (1 H, s), 8.80 (1 H, s), 8.50 (1 H, d, J = 5.1 Hz), 8.03 (1 H, s), 7.70 (1 H, d, J = 5.2 Hz), 1.49 (9 H, s).

Preparation of [5-(3-Bromo-pyridin-4-yl)-thiazol-2-yl]-ethyl-carbamic acid *tert*-butyl ester **18a**



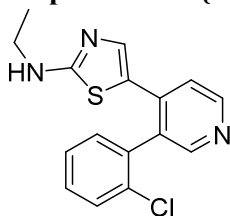
[5-(3-Bromo-pyridin-4-yl)-thiazol-2-yl]-carbamic acid *tert*-butyl ester **17** (0.2 mmol, 0.07g) was dissolved in THF (2 mL) and cooled to 0 °C, ethanol (0.3 mmol, 0.014g) and triphenyl phosphine (0.3 mmol, 0.079g) were added followed by DIAD (0.3 mmol, 0.06 g). This was left to stir overnight, then the reaction mixture was passed down an SCX cartridge, eluting first with methanol then 2 M triethylamine in methanol. This was then used crude in the next step assuming 100% yield. LCMS m/z 384/386 [MI+H]⁺.

[5-(3-Bromo-pyridin-4-yl)-thiazol-2-yl]-isobutyl-carbamic acid *tert*-butyl ester **18b**



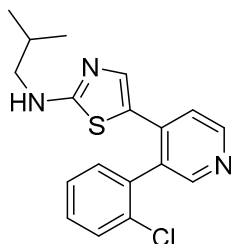
Prepared via an analogous procedure to **18a** using *iso*-butanol in place of ethanol. LCMS m/z 412/414 [MI+H]⁺.

Preparation of {5-[3-(2-Chloro-phenyl)-pyridin-4-yl]-thiazol-2-yl}-ethyl-amine **3j**



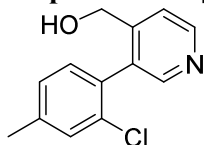
[5-(3-Bromo-pyridin-4-yl)-thiazol-2-yl]-ethyl-carbamic acid *tert*-butyl ester **18a** (2 mmol, 0.07 g) was dissolved in 1,4-dioxane (1.5 mL). 2-Chlorophenylboronic acid (2 mmol, 0.031 g), potassium carbonate (4 mmol, 0.055 g), and bis(triphenylphosphine) palladium(II)dichloride (0.02 mmol, 0.014 g) were added followed by water (0.5 mL). This was heated in the microwave to 150 °C for 15 minutes. The reaction mixture was then passed down an SCX column eluting with 2 M triethylamine in methanol. The basic fraction was evaporated then dissolved in DMSO and purified by mass directed HPLC. Evaporation of the appropriate fractions provided the title compound. Yield=0.005 g, 8%. LCMS m/z 316 [MI+H]⁺. ¹H NMR (300 MHz, DMSO-d₆) δ 8.47 (1 H, d, J = 5.5 Hz), 8.26 (1 H, s), 7.88 (1 H, t, J = 5.3 Hz), 7.74 – 7.34 (5 H, m), 7.27 (1 H, s), 3.14 (2 H, qd, J = 7.2, 5.2 Hz), 1.06 (3 H, t, J = 7.2 Hz).

Preparation of {5-[3-(2-Chloro-phenyl)-pyridin-4-yl]-thiazol-2-yl}-*iso*-butyl-amine 3k



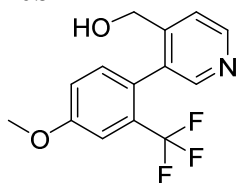
To a microwave tube were added [5-(3-bromo-pyridin-4-yl)-thiazol-2-yl]-isobutyl-carbamic acid *tert*-butyl ester **18b** (0.2 mmol, 0.082 g), 2-chlorophenylboronic acid (0.2 mmol, 0.031 g), potassium carbonate (0.4 mmol, 0.055 g) and bis(triphenylphosphine) palladium(II)dichloride (0.02 mmol, 0.014 g), 1,4-dioxane (1 mL) and water (0.5 mL). This was heated to 150 °C in a microwave reactor for 15 minutes. The reaction mixture was then passed down an SCX column, washing with methanol first then eluting with 2 M triethylamine in methanol. The solvent was evaporated under reduced pressure then dissolved in DMSO and purified by mass directed HPLC. The fractions were evaporated to yield the title compound. Yield=0.007 g, 7%. LCMS m/z 344 [MI+H]⁺. ¹H NMR (300 MHz, DMSO- d_6) δ 8.47 (1 H, d, $J = 5.4$ Hz), 8.25 (1 H, s), 7.93 (1 H, t, $J = 5.6$ Hz), 7.50 (5 H, m), 7.24 (1 H, s), 2.95 (2 H, m), 1.76 (1 H, dt, $J = 6.7, 13.4$ Hz), 0.82 (6 H, d, $J = 6.7$ Hz).

Preparation of [3-(2-Chloro-4-methyl-phenyl)-pyridin-4-yl]-methanol 20a



(3-Bromo-pyridin-4-yl)-methanol **8** (3.2 mmol, 0.61 g), 2-chloro-4-methyl phenyl boronic acid (3.5 mmol, 0.60 g), potassium carbonate (6.5 mmol, 0.89 g) and bis(triphenylphosphine)palladium(II)dichloride (0.16 mmol, 0.11 g) were weighed into a microwave vial and then treated with 1, 4-dioxane (9 mL) and water (3 mL). The vial was capped and heated at 130 °C for 15 minutes in a microwave reactor. The reaction mixture was evaporated under reduced pressure, taken up in DCM (20 mL), washed with water (20 mL) dried with MgSO₄, filtered and evaporated under reduced pressure to a cream coloured solid. Purified by flash column chromatography 1:1 ethyl acetate:cyclohexane to yield the title compound as a white solid. Yield=0.70 g, 92%. LCMS m/z 234 [MI+H]⁺. ¹H NMR (400 MHz, DMSO- d_6) δ 8.60 (1 H, d, $J = 5.1$ Hz), 8.25 (1 H, d, $J = 0.6$ Hz), 7.60 (1 H, dt, $J = 2.7, 5.1$ Hz), 7.44 (1 H, d, $J = 0.6$ Hz), 7.25 (2 H, m), 5.42 (1 H, dt, $J = 5.6, 11.0$ Hz), 4.26 (2 H, m), 2.38 (3 H, s).

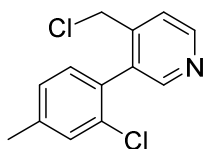
Preparation of 3-(4-Methoxy-2-trifluoromethyl-phenyl)-pyridin-4-yl]-methanol 20b



(3-Bromo-pyridin-4-yl)-methanol **8** (4 mmol, 0.75 g), 4-methoxy-2-(trifluoromethyl) phenylboronic acid (4.4 mmol, 0.96 g), potassium carbonate (8 mmol, 1.10 g) and

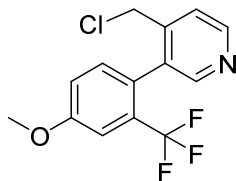
bis(triphenylphosphine)palladium(II)dichloride (0.2 mmol, 0.14 g) were weighed into a microwave vial and treated with water (0.5 mL) and 1,4-dioxane (1.5 mL). The vial was capped and heated to 130 °C in a microwave reactor for 15 minutes. The reaction mixture was evaporated under reduced pressure diluted with DCM (20 mL), washed with water (20 mL) and passed through a phase separating cartridge. The organics were evaporated under reduced pressure and the residue was purified by flash column chromatography eluting with 1:4 cyclohexane:ethyl acetate to yield the title compound as a white solid. Yield=0.58 g, 51%. LCMS m/z 284 [MI+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.59 (1 H, d, *J* = 5.1 Hz), 8.23 (1 H, s), 7.59 (2 H, m), 7.32 (2 H, m), 5.40 (1 H, t, *J* = 5.4 Hz), 4.26 (1 H, dd, *J* = 5.6, 15.5 Hz), 4.09 (1 H, dd, *J* = 5.3, 15.8 Hz), 3.90 (3 H, s).

Preparation of 4-Chloromethyl-3-(2-chloro-4-methyl-phenyl)-pyridine 21a



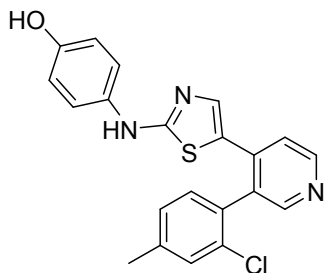
[3-(2-Chloro-4-methyl-phenyl)-pyridin-4-yl]-methanol **20a** (3 mmol, 0.7 g) was dissolved in DCM (40 mL) and DMF (0.01 mL) then treated with thionyl chloride (9 mmol, 0.65 mL). The reaction mixture was heated at reflux for 2 hours under nitrogen and then allowed to cool to room temperature overnight. The solution was evaporated under reduced pressure to a brown solid. This was dissolved in DCM (20 mL) and washed twice with saturated sodium bicarbonate solution (20 mL). The organics were dried with MgSO₄, filtered and evaporated under reduced pressure to a brown gum. This was used without further purification in the next step. Yield=0.76 g, 100%. LCMS m/z 252/254 [MI+H]⁺.

Preparation of 4-Chloromethyl-3-(4-methoxy-2-trifluoromethyl-phenyl)-pyridine 21b



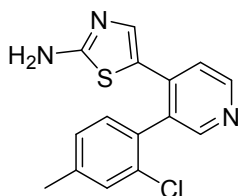
[3-(4-Methoxy-2-trifluoromethyl-phenyl)-pyridin-4-yl]-methanol **20b** (2 mmol, 0.57 g) was dissolved in DCM (25 mL) then treated with DMF (0.01 mL) and thionyl chloride (6 mmol, 0.43 mL). The reaction mixture was heated at reflux under nitrogen for 2 hours. The reaction mixture was left to cool and then evaporated under reduced pressure to a yellow solid. This was dissolved in DCM (10 mL) and washed with saturated sodium bicarbonate solution (10 mL). The organics were separated through a phase separation cartridge and evaporated under reduced pressure to a light brown oil. Yield=0.60 g, 100%. Used without further purification in the next step. LCMS m/z 302/304 [MI+H]⁺.

Preparation of 4-{5-[3-(2-Chloro-4-methyl-phenyl)-pyridin-4-yl]-thiazol-2-ylamino}-phenol 3o



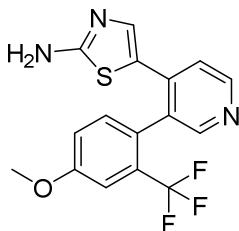
4-Chloromethyl-3-(2-chloro-4-methyl-phenyl)-pyridine (3 mmol, 0.76 g) **21a** was dissolved in acetonitrile (40 mL) and triethylamine (6 mmol, 0.84 mL) and then 1-[1-dimethylamino-methylidene]-3-(4-hydroxy-phenyl)-thiourea **10d** (3 mmol, 0.67 g) was added. The solution was heated at reflux for 4 hours and then allowed to cool to room temperature. The solvent was removed under reduced pressure to a red solid. The reaction mixture dissolved in DCM (100 mL) and washed with water (100 mL). The organics were dried with MgSO₄ filtered and evaporated to a dark red solid. This was purified by mass directed HPLC. Appropriate fractions were pooled and the solvent was evaporated to yield the title compound as a dark red solid. The solid was dissolved in DCM:methanol 1:1 and added to an SCX column which was washed with DCM (15 mL) and methanol (15 mL). The product was eluted with 2 M ammonia in methanol to yield the title compound as an orange solid. Yield=0.10 g, 8%. LCMS *m/z* 394/396 [MI+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 9.99 (1 H, s), 9.13 (1 H, s), 8.51 (1 H, d, *J* = 5.4 Hz), 8.28 (1 H, d, *J* = 0.5 Hz), 7.70 (1 H, dd, *J* = 0.5, 5.4 Hz), 7.47 (2 H, m), 7.30 (4 H, m), 6.69 (2 H, m), 2.41 (3 H, s). ¹³C NMR (101 MHz, DMSO-d₆) δ 166.28, 152.56, 150.80, 148.88, 140.72, 140.46, 138.47, 133.28, 133.12, 132.43, 131.95, 130.23, 129.83, 128.38, 120.75, 120.37, 119.46, 115.29, 20.53.

Preparation of 5-[3-(2-Chloro-4-methyl-phenyl)-pyridin-4-yl]-thiazol-2-ylamine **14b**.



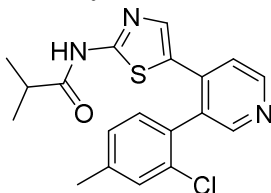
4-(Chloromethyl)-3-(2-chloro-4-methyl-phenyl)pyridine **21a** (2.06 mmol, 0.52 g) was dissolved in MeCN (20mL). [1-Dimethylamino-methylidene]-thiourea **10b** (2.06 mmol, 0.27 g) and triethylamine (5.15 mmol, 0.72 mL) were added. The reaction mixture was heated at reflux for 16 hours and then allowed to cool to room temperature. The solvent was removed under reduced pressure to provide a dark brown gum. This was re-dissolved in ethyl acetate and absorbed onto HMN resin before purification by flash column chromatography eluting with 1:1 ethyl acetate cyclohexane to 100% ethyl acetate. The fractions were evaporated to provide the title compound as an orange solid. Yield=0.15 g, 24%. LCMS *m/z* 302/304 [MI+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 8.80 (2 H, s), 8.54 (1 H, d, *J* = 5.4 Hz), 8.40 (1 H, s), 7.43 (1 H, d, *J* = 4.8 Hz), 7.31 (1 H, d, *J* = 2.6 Hz), 7.19 (1 H, d, *J* = 8.5 Hz), 7.11 (1 H, d, *J* = 2.6 Hz), 7.04 (1 H, s), 3.92 (3 H, s).

Preparation of 5-[3-(4-Methoxy-2-trifluoromethyl-phenyl)-pyridin-4-yl]-thiazol-2-ylamine **14c**



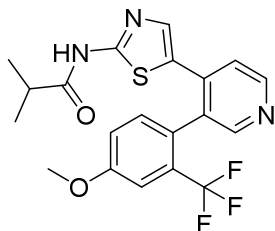
4-Chloromethyl-3-(4-methoxy-2-trifluoromethyl-phenyl)-pyridine **21b** (2.4 mmol, 0.73 g) was dissolved in acetonitrile (20 mL) and triethylamine (6.0 mmol, 0.84 mL) and then [1-dimethylamino-methylidene]-thiourea **10b** (2.4 mmol, 0.31 g) was added. The solution was heated at reflux for 15 hours and then allowed to cool to room temperature. The solvent was removed under reduced pressure to a brown oil. This was purified by flash column chromatography 100% ethyl acetate to elute the title compound as a red solid which was used crude in the next step. Yield=0.21 g, 24%. LCMS m/z 352 [MI+H]⁺.

Preparation of *N*-{5-[3-(2-Chloro-4-methyl-phenyl)-pyridin-4-yl]-thiazol-2-yl}-*iso*-butyramide **22c.**



5-[3-(2-Chloro-4-methyl-phenyl)-4-pyridyl]thiazol-2-amine **14b** (0.15 g, 0.497 mmol) was suspended in DCM (10 mL) and DIPEA (0.18 mL, 0.994 mmol) then treated with *iso*-butyryl chloride (0.06 mL, 0.596 mmol). The reaction mixture was allowed to stir for 3 days at room temperature under nitrogen. Saturated sodium bicarbonate solution (20 mL) was added and the flask was shaken before passing through a phase separation cartridge. The organics were absorbed onto silica and purified by flash column chromatography eluting with 50% ethyl acetate: cyclohexane then 100% ethyl acetate. Appropriate fractions were combined and evaporated under reduced pressure and the residue was dissolved in DMSO and purified by mass directed LCMS. The fractions were evaporated to a white solid which was dissolved in DCM and added to an SCX column which was washed with DCM then methanol and then eluted with 2 M ammonia in methanol. The solvent was evaporated under reduced pressure to provide the title compound as a white solid. Yield=0.015 g, 8%. LCMS m/z 372/374 [MI+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 11.81 (1 H, s), 8.63 (1 H, d, J = 5.2 Hz), 8.50 (1 H, s), 7.44 (1 H, dd, J = 5.3, 0.7 Hz), 7.31 – 7.27 (1 H, m), 7.23 – 7.13 (2 H, m), 6.94 (1 H, s), 2.46 (1 H, h, J = 6.9 Hz), 2.39 (3 H, s), 1.19 (6 H, d, J = 6.8 Hz). ¹³C NMR (101 MHz, CDCl₃) δ 175.06, 160.34, 151.52, 149.46, 140.42, 138.40, 136.13, 133.64, 133.52, 131.28, 130.38, 128.61, 128.13, 122.60, 77.24, 35.21, 21.12, 19.09.

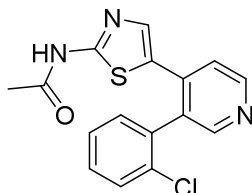
Preparation of *N*-{5-[3-(4-Methoxy-2-trifluoromethyl-phenyl)-pyridin-4-yl]-thiazol-2-yl}-*iso*-butyramide **22d**



5-[3-(4-Methoxy-2-trifluoromethyl-phenyl)-pyridin-4-yl]-thiazol-2-ylamine **14c** (0.9 mmol, 0.32 g) was dissolved in DCM (10 mL) and triethylamine (1.8 mmol, 0.25 mL). The solution was treated with *iso*-butryl chloride (0.9 mmol, 0.095 g) and allowed to stir for 15 hours at room temperature. The solution was washed with saturated sodium bicarbonate solution (20 mL). The organics were separated, dried with MgSO₄, filtered and evaporated under reduced pressure to a red solid. This was purified by flash column chromatography eluting with 100% ethyl acetate. The solid was dissolved in DCM and was added to an SCX column which was washed with DCM (5 mL) and methanol (5 mL). Then the product was eluted with 2 M ammonia in methanol to yield a pink solid which was further purified by mass directed HPLC. Appropriate fractions were pooled and the solvent was evaporated to yield the title compound as a white solid. Yield=0.03 g, 8%. LCMS *m/z* 422 [MI+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 12.12 (1 H, s), 8.58 (1 H, d, *J* = 5.3 Hz), 8.36 (1 H, s), 7.75 (1 H, dd, *J* = 0.5, 5.3 Hz), 7.57 (1 H, s), 7.41 (1 H, d, *J* = 2.2 Hz), 7.34 (2 H, m), 3.92 (3 H, s), 2.69 (1 H, m), 1.07 (6 H, d, *J* = 6.9 Hz). ¹³C NMR (101 MHz, CDCl₃) δ 175.18, 160.59, 159.63, 151.60, 149.54, 138.36, 136.30, 133.69, 131.65, 128.65, 128.05, 124.80, 122.45, 117.21, 77.24, 55.64, 35.15, 18.99, 18.96.

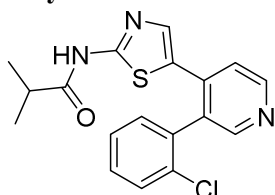
Compounds **22a** and **22b** were made using an analogous procedure to **22c**.

Preparation of *N*-{5-[3-(2-Chloro-phenyl)-pyridin-4-yl]-thiazol-2-yl}-acetamide **22a.**



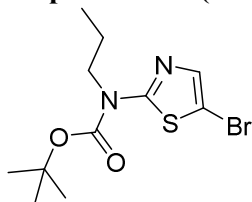
Prepared from **5-[3-(2-Chloro-phenyl)-pyridin-4-yl]-thiazol-2-ylamine 14a** and **acetyl chloride**. LCMS *m/z* 330/332 [MI+H]⁺.

Preparation of *N*-{5-[3-(2-Chloro-phenyl)-pyridin-4-yl]-thiazol-2-yl}-*iso*-butyramide **22b.**



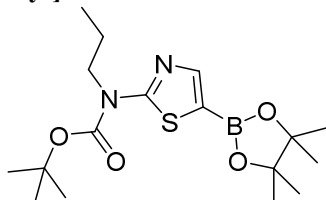
Prepared from **5-[3-(2-Chloro-phenyl)-pyridin-4-yl]-thiazol-2-ylamine 14a** and ***iso*-butryl chloride**. LCMS *m/z* 358/360 [MI+H]⁺. ¹H NMR (300 MHz, DMSO-d₆) δ 12.15 (1 H, s), 8.60 (1 H, d, *J* = 5.3 Hz), 8.39 (1 H, d, *J* = 0.6 Hz), 7.75 (1 H, dd, *J* = 5.3, 0.7 Hz), 7.63 – 7.40 (5 H, m), 2.67 (1 H, h, *J* = 6.8 Hz), 1.05 (6 H, dd, *J* = 6.8, 1.8 Hz).

Preparation of (5-Bromo-thiazol-2-yl)-propyl-carbamic acid *tert*-butyl ester **23**



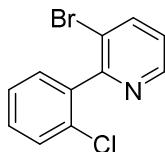
To a solution of 5-bromo-thiazol-2-yl)-carbamic acid *tert*-butyl ester (5.7 mmol, 1.6 g), propanol (8.6 mmol, 0.52 g), and triphenylphosphine (8.6 mmol, 2.26 g) in dry THF (50 mL) at room temperature was added, dropwise over a 5 minute period, diethyl azodicarboxylate (8.6 mmol, 1.5 g). After the addition, the rose coloured solution was left to stir at room temperature for 15 hours. The solvent was removed by evaporation under reduced pressure and the crude gum was adsorbed onto silica and purified by flash chromatography using 4:1 cyclohexane:ethyl acetate as eluent. Fractions were pooled together and evaporated to give the title compound as a brown oil. Yield=1.6 g, 86%. LCMS m/z 265/267 [MI- *t*-Bu]⁺. ¹H NMR (300 MHz, CDCl₃) δ 7.32 (1 H, s), 3.98 (2 H, q), 1.72 (2 H, m), 1.55 (9 H, s), 0.92 (3 H, t).

Preparation of Propyl-[5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-thiazol-2-yl]-carbamic acid *tert*-butyl ester **25**



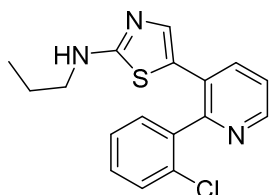
(5-Bromo-thiazol-2-yl)-propyl-carbamic acid *tert*-butyl ester **23** (10 mmol, 3.21 g) was weighed into a 3 neck round bottom flask. The flask was placed under a nitrogen atmosphere and THF (30 mL) was added. The reaction mixture was cooled to -78 °C and treated dropwise with *n*-butyl lithium 2.5 M in hexanes (11 mmol, 4.4 mL) keeping the temperature below -78° C. The reaction mixture was allowed to stir at -78° C for 1 hour and then treated with 2-*iso*-propoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (11 mmol, 2.04 g) dropwise. The reaction mixture was then allowed to warm to room temperature overnight. The reaction was quenched by the addition of 10 mL saturated ammonium chloride solution and then evaporated under reduced pressure. The residue was dissolved in ethyl acetate (100 mL) and washed with water (100 mL). The organics were separated, dried with MgSO₄, filtered and evaporated under reduced pressure. The residue was purified by flash column chromatography using a gradient elution 1:9 ethyl acetate:cyclohexane to 1:1 ethyl acetate:cyclohexane. The solvent was removed under reduced pressure to yield the title compound as a yellow solid which was used crude in subsequent reactions. Yield=1.7g, 46%.

Preparation of 3-Bromo-2-(2-chloro-phenyl)-pyridine **26**



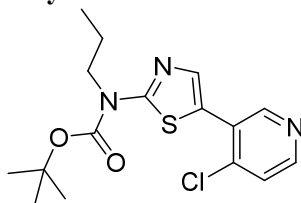
2,3-Dibromopyridine (1.0 mmol, 0.24 g), 2-chlorophenylboronic acid (1 mmol, 0.15 g), potassium phosphate (2 mmol, 0.42 g) and palladium tetrakis triphenyl phosphine (0.1 mmol, 0.42 g) were weighed into a microwave vial. *N,N*-dimethylacetamide (5 mL) and water (1.5 mL) were added, the vial was capped and heated at 130 °C for 15 minutes in a microwave reactor. The reaction mixture was allowed to cool, diluted with ethyl acetate (100 mL) and water (300 mL) and the layers were separated. The aqueous was extracted with another 100 mL portion of ethyl acetate, washed with water (200 mL), brine (200 mL), dried over MgSO₄, filtered and evaporated. The residue was purified by flash column chromatography. 1:9 ethyl acetate cyclohexane to yield the title compound as a clear oil. Yield=0.17 g, 63%. LCMS *m/z* 268 [MI+H]⁺. ¹H NMR (300 MHz, DMSO-d₆) δ 8.65 (1 H, d, *J* = 4.6 Hz), 8.22 (1 H, d, *J* = 8.1 Hz), 7.64 – 7.32 (5 H, m).

Preparation of {5-[2-(2-Chloro-phenyl)-pyridin-3-yl]-thiazol-2-yl}-propyl-amine **4**



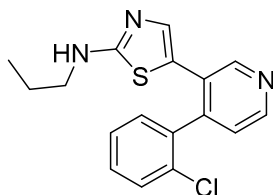
3-Bromo-2-(2-chloro-phenyl)-pyridine **26** (0.15 mmol, 0.04 g), 3-*tert*-butyl-1-propyl-1-[5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-thiazol-2-yl]-urea **25** (0.15 mmol, 0.55g), potassium carbonate (0.45 mmol, 0.062 g) and bis(triphenylphosphine) palladium(II) dichloride (0.007 mmol, 0.005 g) were weighed into a microwave vial 1,4-dioxane (1 mL) and water (0.3 mL) were added, the vial was capped and heated in a microwave reactor at 130 °C for 15 minutes. The reaction mixture was allowed to cool poured into water (10 mL) and DCM (5 mL) was added. The organics were separated, dried with MgSO₄ and evaporated under reduced pressure. DCM (0.5 mL) was added followed by of TFA (0.5 mL). The reaction mixture was allowed to stir at room temperature for 3 hours and then treated with a saturated solution of sodium bicarbonate and left to stir for a further 2 hours. The reaction mixture was passed through a phase separation cartridge and the organics were evaporated under reduced pressure. The residue was dissolved in DMSO (1 mL) and purified by mass directed LCMS. Appropriate fractions were evaporated under reduced pressure to yield the title compound. Yield=0.1 g, 20%. LCMS *m/z* 330 [MI+H]⁺. ¹H NMR (300 MHz, DMSO-d₆) δ 8.47 (1 H, dd, *J* = 1.5, 4.7 Hz), 7.99 (1 H, dd, *J* = 1.6, 8.0 Hz), 7.66 (1 H, t, *J* = 5.4 Hz), 7.58 – 7.30 (5 H, m), 6.95 (1 H, s), 3.06 (2 H, dd, *J* = 7.0, 12.5 Hz), 1.45 (2 H, dt, *J* = 7.2, 14.3 Hz), 0.83 (3 H, t, *J* = 7.4 Hz).

Preparation of [5-(4-Chloro-pyridin-3-yl)-thiazol-2-yl]-propyl-carbamic acid *tert*-butyl ester **27**



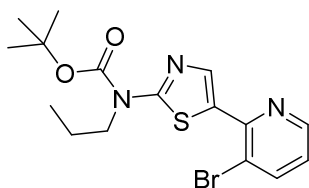
3-*tert*-Butyl-1-propyl-1-[5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-thiazol-2-yl]-urea **25** (1 mmol, 0.37 g), 3-bromo-4-chloropyridine (1 mmol, 0.19 g), potassium carbonate (2 mmol, 0.55 g), bis(triphenylphosphine) palladium(II)dichloride (0.05 mmol, 0.035 g) were weighed into a microwave vial. 1,4-Dioxane (3 mL) and water (1 mL) were added and the reaction mixture was heated at 120 °C for 15 minutes in a microwave reactor. The solvent was removed under reduced pressure and the residue was dissolved in DCM (50 mL) and washed with water (50 mL). The layers were separated and the solvent was removed under reduced pressure to a dark brown oil. This was purified by flash column chromatography using a gradient elution 0-100% ethyl acetate:cyclohexane. The solvent was removed under reduced pressure to yield the title compound as a yellow gum. Yield= 0.06 g, 17%. LCMS m/z 298 [MI-tBu]⁺. ¹H NMR (300 MHz, DMSO-d₆) δ 8.83 (1 H, s), 8.49 (1 H, d, J = 5.4), 7.91 (1 H, s), 7.67 (1 H, d, J = 5.3), 4.07 – 3.94 (2 H, m), 1.68 (2 H, dd, J = 7.3, 14.7), 1.53 (9 H, s), 0.89 (3 H, t, J = 7.4).

Preparation of {5-[4-(2-Chloro-phenyl)-pyridin-3-yl]-thiazol-2-yl}-propyl-amine **5**



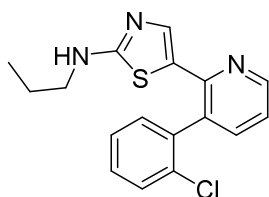
[5-(4-Chloro-pyridin-3-yl)-thiazol-2-yl]-propyl-carbamic acid *tert*-butyl ester **27** (0.16 mmol, 0.06 g), 2-chlorophenyl boronic acid (0.16 mmol, 0.025 g), potassium carbonate (0.32 mmol, 0.044 g) and bis(triphenylphosphine) palladium(II)dichloride (0.008 mmol, 0.005 g) were weighed into a microwave vial. 1,4-dioxane (1 mL) and water (0.3 mL) were added and the reaction mixture was heated at 150 °C for 15 minutes in a microwave reactor. The solvent was removed under reduced pressure, the residue was dissolved in DCM (10 mL) and washed with water (10 mL). The layers were separated and the organics were evaporated under reduced pressure to a dark brown oil. This was treated with DCM (1 mL) and trifluoroacetic acid (0.5 mL). The reaction mixture was allowed to stir at room temperature for 4 hours and then carefully treated with saturated sodium bicarbonate solution (10 mL). The mixture was diluted with DCM (10 mL) and the organics were separated using a phase separation cartridge, the solvent was evaporated under reduced pressure. The residue was then passed through a small silica plug eluting with ethyl acetate. After evaporation the residue was purified by mass directed LCMS. Evaporation of the appropriate fractions yielded the title compound as a yellow solid. Yield=0.015 g, 20%. LCMS m/z 330 [MI+H]⁺. ¹H NMR (300 MHz, DMSO-d₆) δ 8.80 (1 H, s), 8.46 (1 H, d, J = 5.0 Hz), 7.56 (4 H, m), 7.33 (1 H, dd, J = 1.9, 7.3 Hz), 7.21 (1 H, d, J = 5.0 Hz), 7.05 (1 H, s), 3.06 (2 H, dd, J = 6.9, 12.5 Hz), 1.46 (2 H, dd, J = 7.2, 14.4 Hz), 0.83 (3 H, t, J = 7.4 Hz).

Preparation of [5-(3-Bromo-pyridin-2-yl)-thiazol-2-yl]-propyl-carbamic acid *tert*-butyl ester **28**



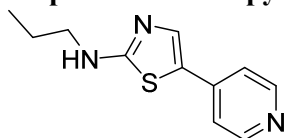
2,3-Dibromopyridine (1 mmol, 0.23 g), 3-*tert*-butyl-1-propyl-1-[5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-thiazol-2-yl]-urea **25** (1 mmol, 0.37 g), potassium phosphate (2 mmol, 0.42 g) and palladium tetrakis triphenyl phosphine (0.10 mmol, 0.11 g) were weighed into a microwave vial. Water (0.4 mL) and DMA (1.5 mL) were added and heated at 130 °C for 15 minutes. The reaction mixture was allowed to cool and poured into water (250 mL) and extracted with ethyl acetate (200 mL). The aqueous was extracted with ethyl acetate (2x200 mL) dried with MgSO₄, filtered and evaporated under reduced pressure to a brown oil. Purified by flash column chromatography eluting with 1:9 ethyl acetate:cyclohexane to yield a white solid. Yield=0.04 g, 10%. LCMS *m/z* 398/400 [MI+H]⁺.

Preparation of {5-[3-(2-Chloro-phenyl)-pyridin-2-yl]-thiazol-2-yl}-propyl-amine **6**



[5-(3-Bromo-pyridin-2-yl)-thiazol-2-yl]-propyl-carbamic acid *tert*-butyl ester **28** (0.15 mmol, 0.06 g), 2-chlorophenylboronic acid (0.15 mmol, 0.023 g), potassium phosphate (0.30 mmol, 0.063 g) and palladium tetrakis triphenyl phosphine (0.015 mmol, 0.017 g) were weighed into a microwave vial. Water (0.4 mL) and DMA (1.5 mL) were added, the vial was capped and heated at 150 °C for 15 minutes. The reaction mixture was allowed to cool and poured into water (50 mL) and extracted with DCM (2x10 mL). The aqueous was extracted with (2x200 mL) ethyl acetate dried with MgSO₄, filtered and evaporated under reduced pressure to a brown oil. The oil was dissolved up in DCM (0.5 mL) and trifluoroacetic acid (0.5 mL) and allowed to stir at room temperature for 4 hours. Saturated sodium bicarbonate (10 mL) was added and the reaction mixture was left to stir overnight. The aqueous was diluted with DCM (2x10 mL) and passed through a phase separation cartridge. The organics were then evaporated to a pale brown oil. The residue was dissolved in DMSO (1 mL) and purified by mass directed LCMS. Evaporation of the appropriate fractions provided the title compound. Yield=0.02 g, 20%. LCMS *m/z* 330/332 [MI+H]⁺.

Preparation of Propyl-(5-pyridin-3-yl-thiazol-2-yl)-amine **2**



4-(Chloromethyl)pyridine hydrochloride (0.2 mmol, 0.032 g) was dissolved in acetonitrile (2 mL) and triethylamine (0.4 mmol, 0.06 mL). 1-[1-Dimethylamino-methylidene]-3-propyl-thiourea **10a** (0.2 mmol, 0.30 g) was added and the mixture was heated to reflux overnight. The reaction mixture was then allowed to cool, diluted

with DCM, then washed with water. The organics were separated, evaporated under reduced pressure and then the residue was dissolved in DMSO and purified by mass directed HPLC. Evaporation of the appropriate fractions provided the title compound. LCMS m/z 219 $[M+H]^+$. 1H NMR (300 MHz, DMSO- d_6) δ 8.52 – 8.36 (2 H, m), 8.13 (1 H, s), 7.82 (1 H, d, $J = 0.7$ Hz), 7.47 – 7.26 (2 H, m), 3.22 (2 H, q, $J = 6.5$ Hz), 1.58 (2 H, h, $J = 7.2$ Hz), 0.91 (3 H, t, $J = 7.4$ Hz).