Supplementary Material:

Pyridylthiazole-Based Ureas as Inhibitors of Rho Associated Protein Kinases (ROCK1 and 2)

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Table S1: Crystallographic data collection and refinement statistics

Structure (PDB ID)	**Rock1-(*R*)-14f (3TV7)**
Data collection	
Space group	$C222_1$
Unit cell dimensions (Å)	a=151.0 b=150.9 c=185.6
Resolution range (Å)	20-2.75 (2.8-2.75)
Unique reflections	55041 (2851)
Completeness (%)	99.6 (100.0)
I/σI	19.9 (5.8)
R_{merge}[a](%)	7.0 (30.3)
Structure refinement	
Protein atoms **Average B-factor (Å^2)**	12860 (2 x dimer) 50
Ligand atoms **Average B-factor (Å^2)**	100 68
Solvent atoms **Average B-factor (Å^2)**	130 39
Rmsd[b] bond lengths (Å)	0.011
Rmsd bond angles (°)	1.32
R_{cryst} (%) [c]	20.6
R_{free} (%) [d]	25.3
R_{free} reflection set size	1101 (2.0 %)
Coordinate error: [e]	
- From Luzzati plot (Å)	0.42
- From SigmaA (Å)	0.53

[a] R_{merge} = quality of amplitudes (F) in the scaled data set (Diederichs & Karplus (1997), Nature Struct. Biol. 4, 269-275).
[b] r.m.s.d. = root mean square deviation from ideal values.
[c] $R_{cryst} = 100 \times \Sigma | F_{obs} - F_{model} | / F_{obs}$ where F_{obs} and F_{model} are observed and calculated structure factor amplitudes, respectively.
[d] R_{free} is R_{cryst} calculated for randomly chosen unique reflections, which were excluded from the refinement.
[e] Cross-validated coordinate error calculated by CNS (Brunger *et al*. Acta Crystallogr. D Biol. Crystallogr. 54, 905–921).

Figure S1

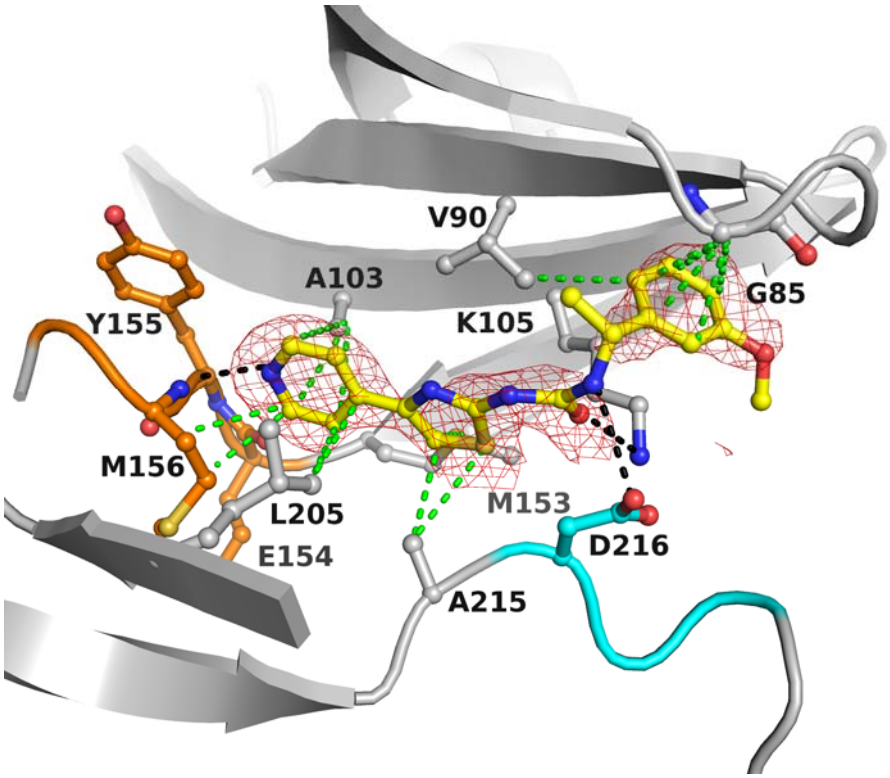
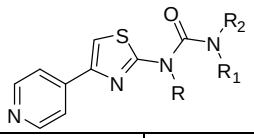
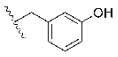
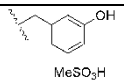
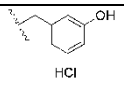
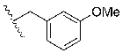
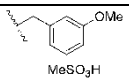
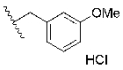
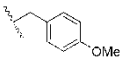
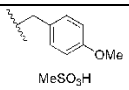
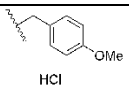


Fig. S1: Refinement of the Rock1-(*R*)-14f complex. Displayed in red is the Fo-Fc electron density map at 2.75 Å resolution and contoured at 2.5σ around the **(*R*)-14f** inhibitor, which was omitted during refinement.

Table S2. *In vitro* activity of the corresponding HCl and mesylate salts of compounds **5g**, **5b** and **5d**

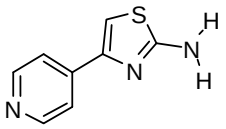


Compound	R	R_1	R_2	IC_{50} ± SD (μM) ROCK1	IC_{50} ± SD (μM) ROCK2
5g	H	H		0.008 ± 0.001, (10)	0.006 ± 0.001, (9)
5g-Mes	H	H		0.013 ± 0.00, (3)	0.008 ± 0.00, (3)
5g-HCl	H	H		0.009 ± 0.00, (3)	0.006 ± 0.00, (3)
5b	H	H		0.027 ± 0.005, (8)	0.011 ± 0.002, (6)
5b-Mes	H	H		0.03 ± 0.01, (3)	0.01 ± 0.00, (n = 3)
5b-HCl	H	H		0.023 ± 0.01, (3)	0.014 ± 0.01, (n = 3)
5d	H	H		ROCK1 % inhibition @ 50 μM: 9.1 ± 1.6	ND
5d-Mes	H	H		36.2 ± 10.0, (3)	7.4 ± 2.3, (3)
5d-HCl	H	H		ROCK1 % inhibition @ 50 μM: 15.3 ± 0.9	ND

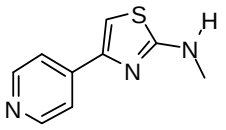
Key: number of repeats shown in parentheses

Chemistry Experimental

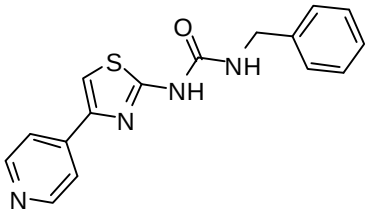
General. All reagents were purchased from commercial suppliers and used without further purification. Melting points were determined using a Barnstead international melting point apparatus and remain uncorrected. ^{1}H NMR spectra were recorded on a Varian Mercury 400 MHz spectrometer with $CDCl_3$ or DMSO-d_6 as the solvent. ^{13}C NMR spectra are recorded at 100 MHz. All coupling constants are measured in Hertz (Hz) and the chemical shifts (δ_H and δ_C) are quoted in parts per million (ppm) relative to TMS (δ 0), which was used as the internal standard. High resolution mass spectroscopy was carried out on an Agilent 6210 LC/MS (ESI-TOF). Microwave reactions were performed in CEM 908005 model and Biotage initiator 8 machines. HPLC analysis was performed using a JASCO HPLC system equipped with a PU-2089 Plus quaternary gradient pump and a UV-2075 Plus UV-VIS detector, using an Alltech Kromasil C-18 column (150 × 4.6 mm, 5 μm) and Agilent Eclipse XDB-C18 (150 × 4.6 mm, 5 μm). Melting points were recorded on an Optimelt automated melting point system (Stanford Research Systems). Thin layer chromatography was performed using silica gel 60 F254 plates (Fisher), with observation under UV when necessary. Anhydrous solvents (acetonitrile, dimethylformamide, ethanol, isopropanol, methanol and tetrahydrofuran) were used as purchased from Aldrich. Burdick and Jackson HPLC grade solvents (methanol, acetonitrile and water) were purchased from VWR for HPLC and mass analysis. HPLC grade TFA was purchased from Fisher.



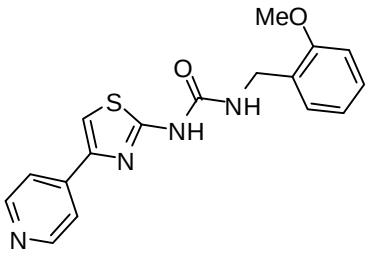
4-(Pyridin-4-yl)thiazol-2-amine (7). A mixture of 4-(bromoacetyl)pyridine hydrobromide (**6**) (6.097 g, 21.70 mmol), thiourea (1.65 g, 21.70 mmol) in anhydrous EtOH (30 ml) was stirred in a Biotage microwave reactor at 100 ºC for 30 min. After cooling to room temperature, the solvent precipitate mixture was filtered, and the precipitate dried under vacuum, suspended in sodium bicarbonate (aq. sat. 150 ml), filtered, washed with water (150 ml), and dried under vacuum. The pure aminothiazole **7** was obtained as a cream solid (3.732 g, 97%), m.p. > 213.2-246.3 ºC (decomposed) (lit.[1] mp 278-282 ºC). ^{1}H NMR (400 MHz, CD_3OD) δ 8.49 (dd, *J* = 1.6, 4.7 Hz, 2H), 7.79 (dd, *J* = 1.6, 4.7 Hz, 2H), 7.25 (s, 1H). HRMS (ESI +ve) *m/z* calculated for $C_8H_8N_3S$ $(M + H)^+$ 178.0433, found 178.0434.



***N*-Methyl-4-(pyridin-4-yl)thiazol-2-amine (8)**. A mixture of 4-(bromoacetyl)pyridine hydrobromide (**2**) (0.429 g, 1.53 mmol), *N*-methyl thiourea (0.138 g, 1.53 mmol) in anhydrous EtOH (3 ml) was stirred in a Biotage microwave reactor at 100 ºC for 30 min. After cooling to room temperature, the solvent precipitate was filtered, and the precipitate dried under vacuum, suspended in sodium bicarbonate (aq. sat. 5 ml), filtered, washed with water (5 ml), and dried under vacuum. The pure aminothiazole **8** was obtained as a cream solid (0.154 g, 53%). mp 168.7-170.1 ºC. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.53 (dd, *J* = 1.6, 4.5 Hz, 2H), 7.74 (dd, *J* = 1.6, 4.5 Hz, 2H), 7.70 (bd, *J* = 4.7 Hz, 1H), 7.43 (s, 1H), 2.87 (d, *J* = 4.7 Hz, 3H), HRMS (ESI +ve) *m/z* calculated for $C_9H_{10}N_3S$ $(M + H)^+$ 192.0589, found 192.0597.



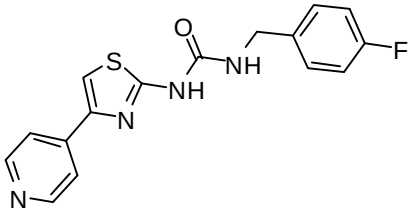
1-Benzyl-3-(4-(pyridin-4-yl)thiazol-2-yl)urea (5a). A mixture of (**7**) (0.251 g, 1.41 mmol), benzylisocyanate (0.357 g, 2.82 mmol) in anhydrous NMP (1.4 ml), was heated in a Biotage microwave reactor at 150 °C for 20 min. After cooling to room temperature, DCM (10 ml) was added and the organic layer washed with water (10 ml) and brine (10 ml), dried over Na_2SO_4 and the solvent removed under reduced pressure. Chromatography on silica gel performed using the FlashMaster 3 purification station afforded **(5a)** as an off-white solid (0.156 g, 35%), mp 219.0-220.9 ºC. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.82 (s, 1H), 8.56 (d, *J* = 5.8 Hz, 2H), 7.81 (s, 1H), 7.77 (d, *J* = 5.7 Hz, 2H), 7.34-7.22 (m, 5H), 7.01 (t, *J* = 5.6 Hz, 1H), 4.34 (d, *J* = 6.0 Hz, 2H); ^{13}C NMR (400 MHz, DMSO-d_6) δ 161.00, 154.63, 150.85, 146.80, 141.70, 140.18, 129.08, 127.82, 127.62, 120.48, 111.74, 43.57. HPLC purity 99.3% {t_R = 5.28 min, flow 1 ml/min, [(CH_3CN/(0.1% TFA in H_2O): 30/70]}; purity 99.3% {t_R = 17.13 min, flow 1 ml/min, [(MeOH/(0.1% TFA in H_2O):50/50]; HRMS (ESI +ve) *m/z* calculated for $C_{16}H_{14}N_4OS$ $(M + H)^+$ 311.0961, found 311.0970.



1-(2-Methoxybenzyl)-3-(4-(pyridin-4-yl)thiazol-2-yl)urea (5c). This was prepared from (**7**) (0.112 g, 0.632 mmol) and 2-methoxybenzyl isocyanate (0.206 g, 1.26 mmol) in the same manner as described for **5a**. Chromatography on silica gel performed using the FlashMaster 3 purification station, followed by trituration with ethyl acetate afforded **5c** as a white solid (0.066 g, 31%), mp 187.9-189.8 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.77 (s, 1H), 8.57 (d, *J* = 6.0, Hz, 2H), 7.81 (s, 1H), 7.77 (d, *J* = 6.1 Hz, 2H), 7.26 (t, *J* = 7.3

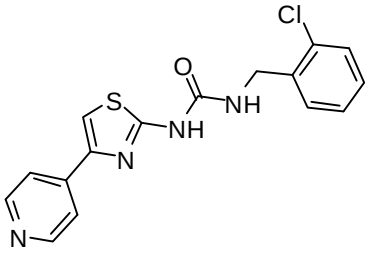
Hz, 1H), 7.20 (d, *J* = 6.5 Hz, 1H), 7.00 (d, *J* = 7.9 Hz, 1H), 6.92-6.88 (m 2H), 4.30 (d, *J* = 6.0 Hz, 2H), 3.82 (s, 3H); HPLC purity 99.4% {t_R = 6.84 min, flow 1 ml/min, [(CH_3CN/(0.1% TFA in H_2O):30/70]}; purity 97.4% {t_R = 8.40 min, flow 1 ml/min, [(MeOH/(0.1% TFA in H_2O):50/50]}; HRMS (ESI +ve) *m/z* calculated for $C_{17}H_{17}N_4O_2S$ $(M + H)^+$ 341.1066, found 341.1063.

1-(2-Fluorobenzyl)-3-(4-(pyridin-4-yl)thiazol-2-yl)urea (5r). This was prepared from **7** (0.113 g, 0.638 mmol) and 2-fluorobenzyl isocyanate (0.192 g, 1.27 mmol) in the same manner as described for **5a**. Chromatography on silica gel performed using the FlashMaster 3 purification station afforded urea **1ac** as a pale yellow solid (0.134 g, 64%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.84 (s, 1H), 8.57 (dd, *J* = 1.3, 4.7 Hz, 2H), 7.82 (s, 1H), 7.77 (dd, *J* = 1.4, 4.7 Hz, 2H), 7.37-7.28 (m, 2H), 7.20-7.15 (m, 2H), 7.04 (t, *J* = 6.2 Hz, 1H), 4.39 (d, *J* = 5.9 Hz, 2H); HPLC purity 99.0% {t_R = 5.98 min, flow 1 ml/min, [(CH_3CN/(0.1% TFA in H_2O):30/70]}; purity 97.8% {t_R = 6.83 min, flow 1 ml/min, [(MeOH/(0.1% TFA in H_2O):50/50]}; HRMS (ESI +ve) *m/z* calculated for $C_{16}H_{14}FN_4OS$ (M + H)+ 329.0866, found 329.0867.

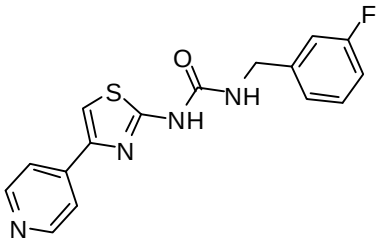


1-(4-Fluorobenzyl)-3-(4-(pyridin-4-yl)thiazol-2-yl)urea (5s). This was prepared from **7** (0.090 g, 0.508 mmol) and 4-fluorobenzylisocyanate (0.153 g, 1.01 mmol) in the same manner as described for **5a**. Chromatography on silica gel performed using the FlashMaster 3 purification station afforded **5s** as an off-white solid (0.026 g, 16%), mp >208 °C (decomposed). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.52 (s, 1H), 8.57 (d, *J* = 6.0 Hz, 2H), 7.80 (s, 1H), 7.76 (d, *J* = 6.1 Hz, 2H), 7.37-7.32 (m, 4H), 7.27-7.21 (m, 1H), 7.03 (d, *J* = 8.3 Hz, 1H), 4 .84 (p, *J* = 6.6 Hz, 1H), 1.41 (d, *J* = 6.9 Hz, 3H); HPLC purity 99.5% {t_R = 6.45 min, flow 1

ml/min, [(CH_3CN/(0.1% TFA in H_2O):30/70]}; purity 98.5% {t_R = 7.09 min, flow 1 ml/min, [(MeOH/(0.1% TFA in H_2O):50/50]; HRMS (ESI +ve) *m/z* calculated for $C_{16}H_{14}FN_4OS$ $(M + H)^+$ 329.0866, found 329.0866.

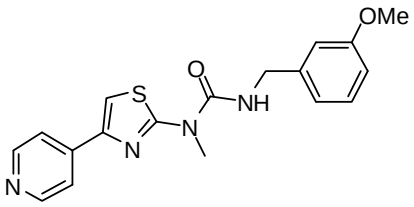


1-(2-Chlorobenzyl)-3-(4-(pyridin-4-yl)thiazol-2-yl)urea (5u). This was prepared from **7** (0.115 g, 0.649 mmol) and 2-chlorobenzylisocyanate (0.217 g, 1.29 mmol) in the same manner as described for **5a**. Chromatography on silica gel was performed twice using the FlashMaster 3 purification station, to afford urea **5u** as an off-white solid (0.027 g, 12%), mp > 196 °C (decomposed). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.92 (s, 1H), 8.57 (dd, *J* = 1.3, 4.7 Hz, 2H), 7.83 (s, 1H), 7.78 (dd, *J* = 1.4, 4.7 2Hz, 2H), 7.45 (dd, *J* = 1.4, 7.6 Hz, 1H), 7.33-7.27 (m, 3H), 7.11 (bt, *J* = 5.5 Hz, 1H), 4.42 (d, *J* = 6.0 Hz, 2H); HPLC purity 99.0% {t_R = 9.36 min, flow 1 ml/min, [(CH_3CN/(0.1% TFA in H_2O):30/70]}; purity 99.0% {t_R = 11.44 min, flow 1 ml/min, [(MeOH/(0.1% TFA in H_2O):50/50]}; HRMS (ESI +ve) *m/z* calculated for $C_{16}H_{14}ClN_4OS$ $(M + H)^+$ 345.0571, found 345.0570.

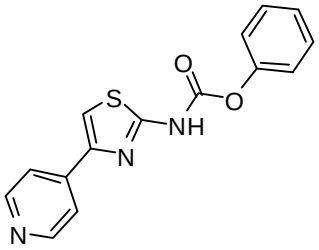


1-(3-Fluorobenzyl)-3-(4-(pyridin-4-yl)thiazol-2-yl)urea (5q). This was prepared from **7** (0.105 g, 0.593 mmol) and 3-fluorobenzylisocyanate (0.179 g, 1.18 mmol) in the same manner as described for **5a**. Chromatography on silica gel performed using the FlashMaster 3 purification station afforded urea **5q** as an off-white solid (0.019 g, 5%), mp > 186 ºC. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.90 (s, 1H, disappeared on

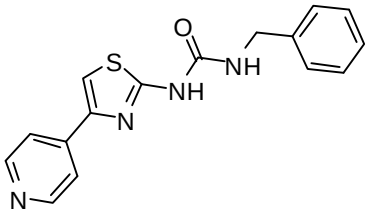
D_2O shake), 8.57 (dd, *J* = 1.5, 4.6 Hz, 2H), 7.82 (s, 1H), 7.78 (dd, *J* = 1.6, 4.6 Hz, 2H), 7.39-7.34 (m, 1H), 7.14-7.04 (m, 4H), 4.36 (d, *J* = 6.0 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.90 (d, *J* = 241.9 Hz, C-F), 160.98, 154.72, 150.85, 146.81, 143.39 (d, *J* = 7.0 Hz, C), 141.70, 131.02 (d, *J* = 8.25 Hz, CH), 123.74 (d, *J* = 2.67 Hz, CH), 120.49, 114.48 (d, *J* = 11.8 Hz, CH), 114.26 (d, *J* = 11.15 Hz, CH), 111.79, 43.10 (d, *J* = 1.4 Hz, CH_2); HPLC purity 99.3% {t_R = 6.40 min, flow 1 ml/min, [(CH_3CN/(0.1% TFA in H_2O):30/70]}; purity 99.1% {t_R = 7.13 min, flow 1 ml/min, [(MeOH/(0.1% TFA in H_2O):50/50]}; HRMS (ESI +ve) *m/z* calculated for $C_{16}H_{14}FN_4OS$ $(M + H)^+$ 329.0866, found 329.0870.



3-(3-Methoxybenzyl)-1-methyl-1-(4-(pyridin-4-yl)thiazol-2-yl)urea (5aa). This was prepared from **8** (0.086 g, 0.450 mmol) and 3-methoxybenzylisocyanate (0.146 g, 0.900 mmol) in the same manner as described for **5a**. After cooling to room temperature, the solvent was removed under reduced pressure. Chromatography on silica gel performed using the FlashMaster 3 purification station, followed by trituration with diethyl ether afforded the urea **5aa** as a white solid (0.085 g, 53%), mp 144.5-145.4 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.57 (dd, *J* = 1.4, 4.7 Hz, 2H), 8.17 (t, *J* = 5.8 Hz, 1H), 7.87 (s, 1H),), 7.83 (dd, *J* = 1.5, 4.6 Hz, 2H), 7.24 (t, *J* = 8.1 Hz, 1H), 6.88-6.90 (s, 2H), 6.81-6.79 (m, 1H), 4.35 (d, *J* = 5.7 Hz, 2H), 3.72 (s, 3H), 3.65 (s, 3H). HPLC purity 99.5% {t_R = 7.88 min, flow 1 ml/min, [(MeOH/(0.1% TFA in H_2O):50/50]}; HRMS (ESI +ve) *m/z* calculated for $C_{18}H_{19}N_4O_2S$ $(M + H)^+$ 355.1223, found 355.1215.

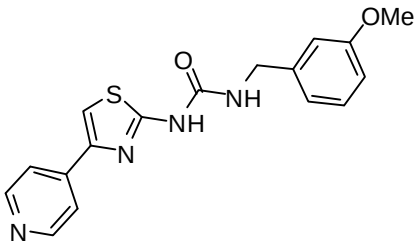


Phenyl 4-(pyridin-4-yl)thiazol-2-ylcarbamate (10). Phenyl chloroformate (2.10 g, 13.53 mmol) was added dropwise at 0 ºC, under Argon to a mixture of **7** (1.69 g, 9.59 mmol) in anhydrous pyridine (5 ml) and anhydrous DCM (5 ml). Further anhydrous pyridine (4 ml) was then added. After stirring at room temperature for 3h, the reaction mixture was quenched with sodium bicarbonate (aq. sat. 150 ml). The crude material was extracted with DCM (2 × 150 ml). The organic extracts were collected, dried over Na_2SO_4 and the solvent removed under reduced pressure. The solid residue was triturated with hexane/ethyl acetate (8:2, 30 ml), filtered and dried under vacuum. The pure carbamate **10** was obtained as a pale orange solid (2.15 g, 73%), mp 187.3-251.4 ºC (decomposed); ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.58 (s, 1H), 8.61 (d, *J* = 6.0 Hz, 2H), 8.02 (s, 1H), 7.82 (d, *J* = 6.1 Hz, 2H), 7.44 (t, *J* = 7.7 Hz, 2H), 7.30 (d, 1H, *J* = 7.5), 7.26 (d, 2H, *J* = 7.6); HRMS (ESI +ve) *m/z* calculated for $C_{15}H_{12}N_3O_2S$ $(M + H)^+$ 298.0644, found 298.0647.

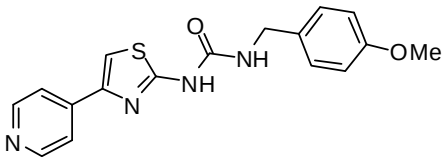


1-Benzyl-3-(4-(pyridin-4-yl)thiazol-2-yl)urea (5a). A mixture of **10** (0.110 g, 0.370 mmol), benzylamine (0.043 g, 0.407 mmol) in anhydrous THF (0.5 ml) and CH_3CN (0.3 ml) was stirred in a Biotage microwave at 80 ºC for 30 min. After cooling to room temperature, the precipitate was filtered, washed with a solution ethyl acetate and hexane (1:9, v:v), and dried under vacuum to afford pure urea **5a** as an off-white solid (0.079 g, 69%). White solid, ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.82 (s, 1H), 8.56 (d, *J* = 5.8 Hz, 2H), 7.81 (s, 1H), 7.77 (d, *J* = 5.7 Hz, 2H), 7.34-7.22 (m, 5H), 7.01 (t, 1H, *J* = 5.6 Hz), 4.34 (d, 2H, *J* = 6.0 Hz); HPLC purity

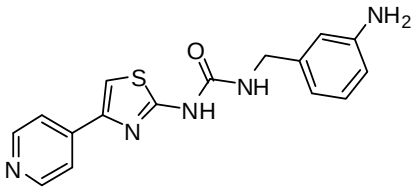
99.3% {t_R = 5.28 min, flow 1 ml/min, [(CH_3CN/(0.1% TFA in H_2O):30/70]}; purity 99.3% {t_R = 17.13 min, flow 1 ml/min, [(MeOH/(0.1% TFA in H_2O):40/60]}; HRMS (ESI +ve) *m/z* calculated for $C_{16}H_{14}N_4OS$ $(M + H)^+$ 311.0961, found 311.0963.



1-(3-Methoxybenzyl)-3-(4-(pyridin-4-yl)thiazol-2-yl)urea (5b). A mixture of **10** (0.112 g, 0.376 mmol), 3-methoxybenzylamine (0.062 g, 0.451 mmol) in anhydrous THF (0.6 ml) was stirred in a CEM microwave under the following conditions: power 150 W, ramp time 2 min, hold time 20 min, temperature 100 ºC, pressure 220 PSI. After cooling to room temperature, the precipitate was filtered, washed with THF, and dried *in vacuo* to afford pure urea **5b** as an off-white solid (0.081 g, 63%), mp 156.7-157.7 ºC; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.82 (s, 1H), 8.57 (dd, *J* = 1.6, 4.5 Hz, 2H), 7.82 (s, 1H), 7.77 (dd, *J* = 1.6, 4.5 Hz, 2H), 7.24 (t, *J* = 8.1 Hz, 1H), 7.00 (t, *J* = 6.0 Hz, 1H), 6.79-6.82 (m, 3H), 4.31 (d, *J* = 5.9 Hz, 1H), 3.72 (s, 3H); ^{13}C NMR (400 MHz, DMSO-d_6) δ 161.01, 160.01, 154.64, 150.84, 146.80, 141.79, 141.70, 130.18, 120.48, 119.91, 113.49, 112.90, 111.74, 55.66, 43.52; HPLC purity 98.9% {t_R = 5.67 min, flow 1 ml/min, [(CH_3CN/(0.1% TFA in H_2O):30/70]}; purity 98.0% {t_R = 6.33 min, flow 1 ml/min, [(MeOH/(0.1% TFA in H_2O):50/50]}; HRMS (ESI +ve) *m/z* calculated for $C_{17}H_{17}N_4O_2S$ $(M + H)^+$ 341.1066, found 341.1064.

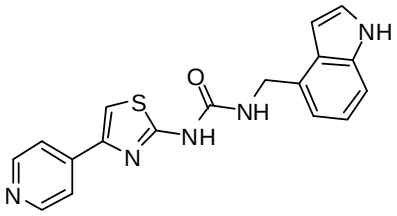


1-(4-Methoxybenzyl)-3-(4-(pyridin-4-yl)thiazol-2-yl)urea (5d). A mixture of **10** (0.102g, 0.349mmol), 4-methoxybenzylamine (0.057 g, 0.419 mmol) in anhydrous THF (0.6 ml) was stirred in a CEM microwave under the following conditions: power 150 W, ramp time 2 min, hold time 10 min, temperature 100 ºC, pressure 220 PSI. After cooling to room temperature, the precipitate was filtered, washed with THF, and dried under vacuum to afford pure urea **5d** as an off-white solid (0.088 g, 74%), mp 223.9-226.4 ºC. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.76 (bs, 1H, disappeared on D_2O shake), 8.56 (dd, *J* = 1.6, 4.5 Hz, 2H), 7.81 (s, 1H), 7.76 (dd, *J* = 1.6, 4.5 Hz, 2H), 7.21 (d, *J* = 8.7 Hz, 2H), 6.91 (bt, *J* = 5.6 Hz, 1H, disappeared on D_2O shake), 6.88 (d, *J* = 8.7 Hz, 2H), 4.25 (bd, *J* = 5.8 Hz, 2H), 3.71 (s, 3H).; HPLC purity 99.2% {t_R = 5.39 min, flow 1 ml/min, [(CH_3CN/(0.1% TFA in H_2O):30/70]}; purity 97.7% {t_R = 6.09 min, flow 1 ml/min, [(MeOH/(0.1% TFA in H_2O):50/50]}; HRMS (ESI +ve) *m/z* calculated for $C_{17}H_{17}N_4O_2S$ $(M + H)^+$ 341.1066, found 341.1062.

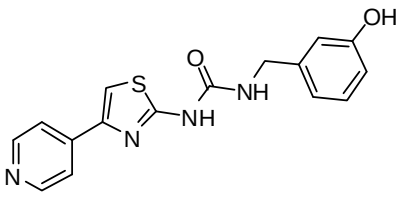


1-(3-Aminobenzyl)-3-(4-(pyridin-4-yl)thiazol-2-yl)urea (5e). This was obtained as an off-white solid (0.046 g, 0,141 mmol, 35%) from **10** (0.121 g, 0.406 mmol) and 3-aminobenzylamine (0.122 g, 0.487 mmol) in the same manner as described for **5b**. Mp 188.4-191.1 ºC. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.71 (s, 1H), 8.57 (dd, *J* = 1.5, 4.6 Hz, 2H), 7.81 (s, 1H), 7.77 (dd, *J* = 1.5, 4.6 Hz, 2H), 6.95 (t, *J* = 7.7 Hz, 1H), 6.89 (t, *J* = 5.2 Hz, 1H), 6.47 (s, 1H), 6.42 (t, *J* = 7.0 Hz, 2H), 5.06 (s, 2H), 4.19 (d, *J* = 5.8 Hz, 2H). HPLC purity 99.2% {t_R = 5.07 min, flow 1 ml/min, [(CH_3CN/(0.1% TFA in H_2O) 15/85]}; purity 99.2% {t_R = 18.35 min, flow 1

ml/min, [(MeOH/(0.1% TFA in H_2O) 20/80]}; HRMS (ESI +ve) *m/z* calculated for $C_{16}H_{16}N_5OS$ $(M + H)^+$ 326.1070, found 326.1063.

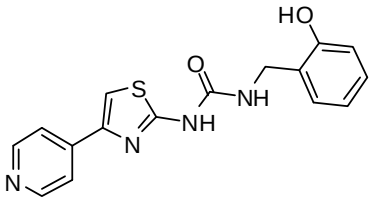


1-((1H-indol-4-yl)methyl)-3-(4-(pyridin-4-yl)thiazol-2-yl)urea (5f). This was prepared from **10** (0.103 g, 0.346 mmol) and 4-aminomethylindole (0.055 g, 0.376 mmol) in the same manner as described for **5b.** After cooling to room temperature, the precipitate was filtered and dried under vacuum. The pure urea **5f** was obtained as a white solid (0.099 g, 82%), mp 181.4-207.5 ºC (decomposed). ^{1}H NMR (400 MHz, DMSO-d_6) 11.17 (s, 1H), 10.63 (s, 1H), 8.56 (d, *J* = 6.1 Hz, 2H), 7.81 (s, 1H), 7.75 (d, *J* = 6.2 Hz, 2H), 7.35 (t, *J* = 2.8 Hz, 1H), 7.31 (d, *J* = 8.1 Hz, 1H), 7.05 (t, *J* = 7.7 Hz, 1H), 6.97 (bs, 1H), 6.92 (d, *J* = 7.2 Hz, 1H), 6.52-6.51 (m, 1H), 4.59 (d, *J* = 5.7 Hz, 2H,), HPLC purity 99.9% {t_R = 4.53 min, flow 1 ml/min, [(CH_3CN/(0.1% TFA in H_2O) 30/70]}; 98.5% {t_R = 4.31 min, flow 1 ml/min, [(MeOH/(0.1% TFA in H_2O) 50/50]}; HRMS (ESI +ve) *m/z* calculated for $C_{18}H_{16}N_5OS$ $(M + H)^+$ 350.1070, found 350.1069.

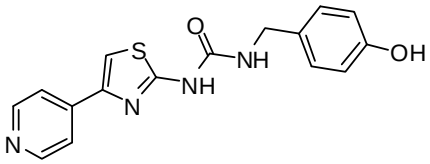


1-(3-Hydroxybenzyl)-3-(4-(pyridin-4-yl)thiazol-2-yl)urea (5g). This was prepared from **5b** (0.099 g, 0.332 mmol), 3-hydroxybenzylamine (0.078 g, 0.365 mmol), and Et_3N (0.1 ml) in the same manner as described for **10.** After cooling to room temperature, the precipitate was filtered, washed with water, and dried under vacuum. The pure urea **5a** was obtained as a white solid (0.064 g, 59%), mp 155.7-207.1 ºC (decomposed). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.37 (s, 1H), 8.57 (d, *J* = 6.1 Hz, 2H), 7.82 (s, 1H), 7.77 (d, *J* = 6.2 Hz,

2H), 7.11 (t, J = 8.0 Hz, 1H), 6.96 (bt, J = 5.6 Hz, 1H), 6.70-6.68 (m, 2H), 6.63-6.60 (m, 1H), 4.26 (d, J = 5.9 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.66, 153.21, 150.84, 48.20, 146.67, 141.65, 128.83, 126.90, 125.39, 120.47, 111.50, 55.46, 30.13; HPLC purity 99.8% {t_R = 8.51 min, flow 1 ml/min, [(CH_3CN/(0.1% TFA in H_2O) 20/80]}; purity 99.8% {t_R = 6.43 min, flow 1 ml/min, [(MeOH/(0.1% TFA in H_2O) 40/60]}; HRMS (ESI +ve) *m/z* calculated for $C_{16}H_{15}N_4O_2S$ $(M + H)^+$ 327.0910, found 327.0909.

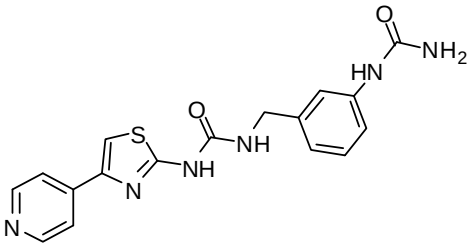


1-(2-Hydroxybenzyl)-3-(4-(pyridin-4-yl)thiazol-2-yl)urea (5h). This was prepared from **10** (0.103 g, 0.346 mmol) and 2-hydroxybenzylamine (0.042 g, 0.346 mmol) in the same manner as described for **5b**. After cooling to room temperature, the precipitate was filtered, and dried under vacuum. The pure urea **5h** was obtained as a white solid (0.087 g, 77%), mp 228.0-228.05 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.75 (s, 1H), 9.65 (s, 1H), 8.57 (d, J = 6.1 Hz, 2H), 7.80 (s, 1H), 7.77 (d, J = 6.2 Hz, 2H,), 7.13 (dd, J = 1.6, 7.4 Hz, 1H), 7.09-7.05 (m, 1H), 6.90 (s, 1H), 6.82-6.80 (m, 1H), 6.76-6.73 (m, 1H), 4.26 (d, J = 6.0 Hz, 2H); HPLC purity 99.9% {t_R = 14.57 min, flow 1 ml/min, [(CH_3CN/(0.1% TFA in H_2O):20/80]}; purity 99.9% {t_R = 10.40 min, flow 1 ml/min, [(MeOH/(0.1% TFA in H_2O):40/60]}; HRMS (ESI +ve) *m/z* calculated for $C_{16}H_{15}N_4O_2S$ $(M + H)^+$ 327.0910, found 327.0910.

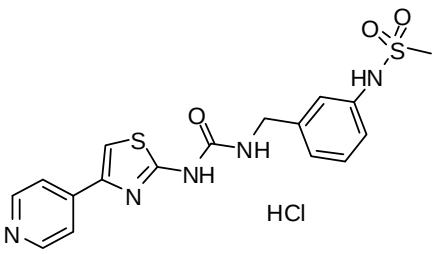


1-(4-Hydroxybenzyl)-3-(4-(pyridin-4-yl)thiazol-2-yl)urea (5i). This was obtained as an off-white solid (0.085 g, 74%) from **10** (0.105 g, 0.352 mmol) and 4-hydroxybenzylamine (0.052 g, 0.423 mmol) in the same

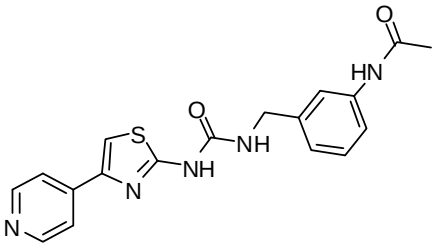
manner as described for **5b** mp 228.7-231.5 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.68 (s, 1H), 9.31 (s, 1H), 8.56 (d, *J* = 6.1 Hz, 2H), 7.80 (s, 1H), 7.76 (dd, *J* = 1.6, 4.6 Hz, 2H), 7.09 (d, *J* = 8.5 Hz, 2H), 6.87 (t, *J* = 5.4 Hz, 2H), 6.70 (d, J = 8.6 Hz, 2H), 4.21 (d, *J* = 5.8 Hz, 2H); HPLC purity 99.7% {t_R = 6.64 min, flow 1 ml/min, [(CH_3CN/(0.1% TFA in H_2O):20/80]}; purity 99.6% {t_R = 5.29 min, flow 1 ml/min, [(MeOH/(0.1% TFA in H_2O):40/60]}; HRMS (ESI +ve) *m/z* calculated for $C_{16}H_{15}N_4O_2S$ $(M + H)^+$ 327.0910, found 327.0905.



***N*-(3-((3-(4-(Pyridin-4-yl)thiazol-2yl)ureido)methyl)phenyl)acetamide (5j)**. A mixture of **10** (0.052 g, 0.174 mmol), 1-(3-(aminomethyl)phenyl)urea (0.030 g, 0.181 mmol), in anhydrous THF (0.5 ml) was stirred in a sealed tube at 159 °C for 4 h. After cooling to room temperature, THF (1 ml) was added and the precipitate was filtered, washed with THF (1 ml) and dried under vacuum. The pure urea **5j** was obtained as an off-white solid (0.058 g, 90%), mp 203.1-204.7 ºC. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.81 (s, 1H), 8.57 (dd, *J* = 1.5, 4.6, Hz, 2H), 8.53 (s, 1H), 7.82 (s, 1H), 7.77 (dd, *J* = 1.6, 4.5 HZ, 2H), 7.30-7.28 (m, 2H), 7.17-7.13 (m, 1H), 6.98 (s, 1H), 6.82 (d, *J* = 7.4 Hz, 1H), 5.80 (s, 2H), 4.28 (d, *J* = 5.9 Hz, 2H) HPLC purity 97.6% {t_R = 4.95 min, flow 1 ml/min, [(CH_3CN/(0.1% TFA in H_2O):30/70]}; purity 97.8% {t_R = 4.74 min, Flow 1 ml/min, [(MeOH/(0.1% TFA in H_2O):40/60]}; HRMS (ESI +ve) *m/z* calculated for $C_{17}H_{16}N_6O_2S$ $(M + H)^+$ 369.1128, found 369.1130.

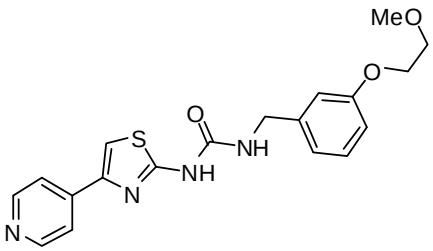


***N*-(3-((3-(4-(Pyridin-4-yl)thiazol-2-yl)ureido)methyl)phenyl)methanesulfonamide hydrochloride (5k)**. This was prepared from **10** (0.085 g, 0.285 mmol) and *N*-(3-(aminomethyl)phenyl)methanesulfonamide hydrochloride (0.067 g, 0.283 mmol) in presence of DIPEA (0.070 ml) in the same manner as described for **5b**. After cooling to room temperature, water (2 ml), NaOH (1 M, aq., 5 ml) and ethyl acetate (5 ml) were added. The aqueous phase was separated and acidified with HCl (1 M, aq., 10 ml). After standing at room temperature overnight, the precipitate was filtered, dried under vacuum. The pure urea **5k** was obtained as an off-white solid (0.055 g, 44%), mp 215.2-221.6 ºC. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.09 (s, 1H), 9.76 (s, 1H), 8.83 (d, J = 6.6 Hz, 2H), 8.32 (s, 1H), 8.29 (d, J = 6.6 Hz, 2H), 7.30-7.24 (m, 2H), 7.13 (s, 1H), 7.08 (d, J = 9.5 Hz,1H), 7.02 (d, J = 7.6 Hz, 1H), 4.32 (d, J = 5.9 Hz, 2H), 2.97 (s, 3H); HPLC purity 99.5% {t_R = 10.60 min, flow 1 ml/min, [(CH_3CN/(0.1% TFA in H_2O):20/80]}; purity 99.1% {t_R = 5.89 min, flow 1 ml/min, [(MeOH/(0.1% TFA in H_2O):40/60]}; HRMS (ESI +ve) *m/z* calculated for $C_{17}H_{17}N_5O_3S_2$ $(M + H)^+$ 404.0845, found 404.0842.

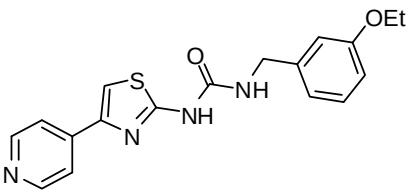


***N*-(3-((3-(4-(pyridin-4-yl)thiazol-2yl)ureido)methyl)phenyl)acetamide (5l)**. This was prepared from **10** (0.090 g, 0.302 mmol) and *N*-(3-(aminomethyl)phenyl)acetamide hydrochloride (0.072 g, 0.360 mmol) in presence of DIPEA (0.070 ml) in the same manner as described for **5b**. After cooling to room temperature, ethyl acetate (5 ml), MeOH (1 ml). The solvent was slowly evaporated at room temperature. When the volume of the solvent was evaporated to approximately 1 ml, the precipitate was filtered, washed with THF (2 ml), washed with ethanol (1 ml), and dried under vacuum. The pure urea **5l** was obtained as an off-white solid (0.025 g, 22%), mp > 215 ºC (decomposed). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.83 (s, 1H), 9.93 (s, 1H), 8.57 (d, J = 4.6 Hz, 2H), 7.82 (s, 1H), 7.77 (d, J = 6.1 Hz, 2H), 7.47-7.46 (m, 2H), 7.24 (t, J = 8.5 Hz,

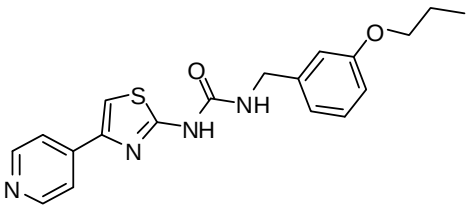
1H), 6.99 (bs, 1H), 6.95 (d, J = 7.5 Hz, 1H), 4.31 (d, J = 6.0 Hz, 2H), 2.00 (s, 3H) HPLC purity 98.4% {t_R = 7.15 min, flow 1 ml/min, [(CH_3CN/(0.1% TFA in H_2O):20/80]}; purity 98.0% {t_R = 6.37 min, flow 1 ml/min, [(MeOH/(0.1% TFA in H_2O):40/60]}; HRMS (ESI +ve) *m/z* calculated for $C_{17}H_{17}N_5O_2S$ $(M + H)^+$ 368.1175, found 368.1171.



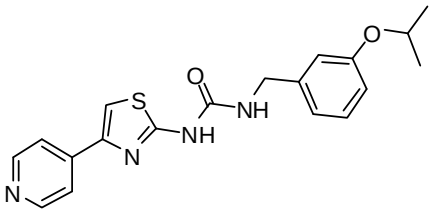
1-(3-(2-Methoxyethoxy)benzyl)-3-(4-(pyridin-4-yl)thiazol-2-yl)urea (5m). This was prepared from **10** (0.097 g, 0.325 mmol) and 1-[3-(2-methoxyethoxyl)phenyl]methanamine (0.043 g, 0.358 mmol) in the same manner as described for **5b**. After cooling to room temperature, the reaction mixture washed with NaOH (2 M, aq., 5 ml) and extracted with DCM (2 × 10 ml). The combined organic extracts were dried over Na_2SO_4 and the solvent removed under reduced pressure. The remaining solid was triturated with diethyl ether, filtered, and dried under vacuum. The pure urea **5m** was obtained as a white solid (0.053 g, 50%), mp 101.5-102.7 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.88 (s, 1H), 8.57 (d, J = 6.0 Hz, 2H), 7.81 (s, 1H), 7.78 (d, J = 6.1 Hz, 2H), 7.23 (t, J = 8.0 Hz, 1H), 7.07 (bs, 1H), 6.86-6.80 (m, 3H), 4.31 (d, J = 5.9 Hz, 2H), 4.05 (t, J = 4.6 Hz, 2H), 3.62 (t, J = 4.5 Hz, 2H), 3.28 (s, 3H); HPLC purity 99.6% {t_R = 15.53 min, flow 1 ml/min, [(MeOH/(0.1% TFA in H_2O):40/60]}; HRMS (ESI +ve) *m/z* calculated for $C_{19}H_{21}N_4O_3S$ $(M + H)^+$ 385.1328, found 385.1332.



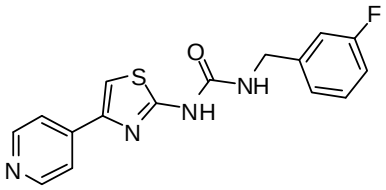
1-(3-ethoxybenzyl)-3-(4-(pyridin-4-yl)thiazol-2-yl)urea (5n). This was prepared from **10** (0.075 g, 0.0.252 mmol) and 3-ethoxybenzylamine (0.045 g, 0.302 mmol) in the same manner as described for **5b**. After cooling to room temperature, the solvent was removed under reduced pressure. The remaining solid was triturated with ether, filtered, washed with ether, and dried under vacuum. The pure urea **5n** was obtained as an off-white solid (0.078 g, 87%), mp 165.8-167.4 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.47 (s, 1H), 8.57 (dd, J = 1.6, 4.5 Hz, 2H), 7.82 (s, 1H), 7.77 (dd, J = 1.6, 4.5 Hz, 2H), 7.22 (t, J = 8.1 Hz, 1H), 7.00 (t, J = 6.4 Hz, 1H), 6.85-6.83 (m, 2H), 6.80-6.78 (m, 1H), 4.31 (d, J = 5.8 Hz, 2H), 3.99 (q, J = 7.0 Hz, 2H), 1.29 (t, J = 7.0 Hz, 3H); HPLC purity 99.5% {t_R = 9.59 min, flow 1 ml/min, [(CH_3CN/(0.1% TFA in H_2O):30/70]}; purity 99.2% {t_R = 10.74 min, flow 1 ml/min, [(MeOH/(0.1% TFA in H_2O):50/50]}; HRMS (ESI +ve) *m/z* calculated for $C_{18}H_{18}N_4O_2S$ $(M + H)^+$ 355.1223, found 355.1221.



1-(3-propoxybenzyl)-3-(4-(pyridin-4-yl)thiazol-2-yl)urea (5o). This was prepared from **10** (0.101 g, 0.339 mmol) and 3-propoxybenzylamine (0.082 g, 0.407 mmol), in presence of DIPEA (0.080 ml) in the same manner as described for **5b**. After cooling to room temperature, the reaction mixture washed with NaOH (1M, aq.) and extracted with DCM. The combined organic extracts were dried over Na_2SO_4 and the solvent removed under reduced pressure. The remaining solid was triturated with diethyl ether, filtered, and dried under vacuum. The pure urea **5o** was obtained as a white solid (0.100 g, 80%), mp 165.3-166.5 ºC. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.08 (s, 1H), 8.57 (d, J = 6.1 Hz, 2H), 7.85 (s, 1H), 7.82 (d, J = 4.6 Hz, 2H), 7.36-7.32 (m, 2H), 7.27-7.22 (m, 3H), 4.61 (s, 2H), 2.96 (s, 3H); HPLC purity 99.9% {t_R = 5.05 min, flow 1 ml/min, [(CH_3CN/(0.1% TFA in H_2O):40/60]}; purity 99.4% {t_R = 7.09 min, flow 1 ml/min, [(MeOH/(0.1% TFA in H_2O):60/40]}; HRMS (ESI +ve) *m/z* calculated for $C_{19}H_{20}N_4O_2S$ $(M + H)^+$ 369.1379, found 369.1377.

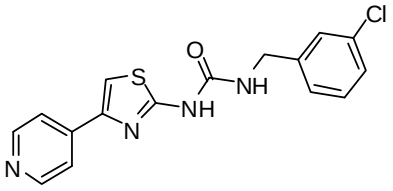


1-(3-*Iso*propoxybenzyl)-3-(4-(pyridin-4-yl)thiazol-2-yl)urea (5p). This was prepared from **10** (0.053 g, 0.178 mmol) and 3-*iso*propylbenzylamine (0.035 g, 0.213 mmol) in the same manner as described for **5b**. After cooling to room temperature, the solvent was removed under reduced pressure. The remaining solid was triturated diethyl ether, filtered and dried under vacuum. The pure urea **5p** was obtained as a white solid (0.055 g, 84%), mp 134.5-135.9 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.68 (s, 1H), 8.57 (dd, *J* = 1.6, 4.5 Hz, 2H), 7.82 (s, 1H), 7.77 (dd, *J* = 1.6, 4.5 Hz, 2H), 7.21 (t, *J* = 8.0 Hz, 1H), 6.99 (s, 1H), 6.82-6.77 (m, 3H), 4.57 (quin, *J* = 6.0 Hz, 1H), 4.30 (d, *J* = 5.9 Hz, 2H), 1.23 (d, *J* = 6.0 Hz, 6H); HPLC purity 99.8% {t_R = 14.88 min, flow 1 ml/min, [(CH_3CN/(0.1% TFA in H_2O):30/70]}; purity 97.7% {t_R = 15.87 min, flow 1 ml/min, [(MeOH/(0.1% TFA in H_2O):50/50]}; HRMS (ESI+ve) *m/z* calculated for $C_{19}H_{21}N_4O_2S$ $(M + H)^+$369.1379, found 369.1388.

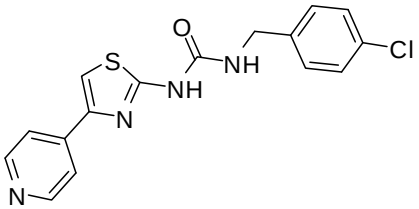


1-(3-Fluorobenzyl)-3-(4-(pyridin-4-yl)thiazol-2-yl)urea (5q). This was obtained as an off-white solid (0.072 g, 73%) from **10** (0.089 g, 0.299 mmol) and 3-fluorobenzylamine (0.044 g, 0.358 mmol) in the same manner as described for **5b**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.90 (s, 1H, disappeared on D_2O shake), 8.57 (dd, *J* = 1.5, 4.6 Hz, 2H), 7.82 (s, 1H), 7.78 (dd, *J* = 1.6, 4.6 Hz, 2H), 7.39-7.34 (m, 1H), 7.149-7.04 (m, 4H),

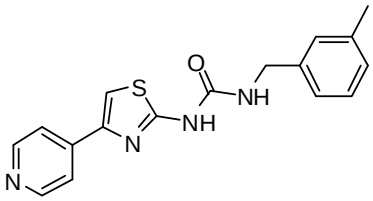
4.36 (d, J = 6.0 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.90 (d, J = 241.9 Hz, C-F), 160.98, 154.72, 150.85, 146.81, 143.39 (d, J = 7.0 Hz, C), 141.70, 131.02 (d, J = 8.25 Hz, CH), 123.74 (d, J = 2.67 Hz, CH), 120.49, 114.48 (d, J = 11.8 Hz, CH), 114.26 (d, J = 11.15 Hz, CH), 111.79, 43.10 (d, J = 1.4 Hz, CH_2); HPLC purity 99.2% {t_R = 6.51 min, flow 1 ml/min, [(CH_3CN/(0.1% TFA in H_2O):30/70]}; purity 98.5% {t_R = 7.12 min, flow 1 ml/min, [(MeOH/(0.1% TFA in H_2O):50/50]}; HRMS (ESI +ve) *m/z* calculated for $C_{16}H_{14}N_4FOS$ $(M + H)^+$ 329.0866, found 329.0868.



1-(3-Chlorobenzyl)-3-(4-(pyridin-4-yl)thiazol-2-yl)urea (5t). This was prepared from **10** (0.098 g, 0.329 mmol), 3-chlorobenzylamine (0.055g, 0.395 mmol) in the same manner as described for **5b**. After cooling to room temperature, the precipitate was filtered, washed with THF, and dried *in vacuo* to afford pure urea **5t** as an off-white solid (0.061 g, 54%), mp 211.9-214.3 ºC. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.93 (bs, 1H, disappeared on D_2O shake), 8.57 (dd, J = 1.5, 4.6 Hz, 2H), 7.82 (s, 1H), 7.77 (dd, J = 1.6, 4.6 Hz, 2H), 7.38-7.24 (m, 4H), 7.00 (bt, J = 5.5 Hz, 1H, disappeared on D_2O shake), 4.34 (bd, J = 6.0 Hz, 2H); ^{13}C NMR (400 MHz, DMSO-d_6) δ 160.96, 154.71, 150.85, 146.81, 143.01, 141.70, 133.67, 130.97, 127.59, 127.51, 126.48, 120.48, 111.80, 43.05; HPLC purity 98.6% {t_R = 12.07 min, flow 1 ml/min, [(CH_3CN/(0.1% TFA in H_2O):30/70]}; purity 97.4% {t_R = 13.17 min, flow 1 ml/min, [(MeOH/(0.1% TFA in H_2O):50/50]}; HRMS (ESI +ve) *m/z* calculated for $C_{16}H_{14}N_4OSCl$ $(M + H)^+$ 345.0571, found 345.0573.

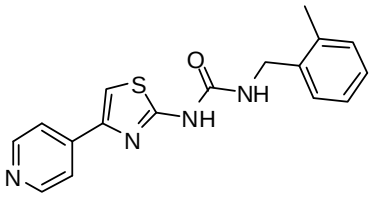


1-(4-Chlorobenzyl)-3-(4-(pyridin-4-yl)thiazol-2-yl)urea (5v). This was prepared from **10** (0.105 g, 0.352 mmol) and 4-chlorobenzylamine (0.054 g, 0.387 mmol) in the same manner as described for **5b**. After cooling to room temperature, the precipitate was filtered, washed with THF, and dried *in vacuo* to afford pure urea **5v** as an off-white solid (0.104 g, 86%), mp >180.7 °C (decomposed). ^{1}H NMR (DMSO-d_6) δ 10.89 (s, 1H), 8.56 (dd, *J* = 1.6, 4.6 Hz, 2H), 7.81 (s, 1H), 7.77 (dd, *J* = 1.6, 4.6 Hz, 2H), 7.38 (d, *J* = 8.4 Hz, 2H), 7.31 (d, *J* = 8.3 Hz, 2H), 7.04 (t, *J* = 7.0 Hz, 1H), 4.32 (d, *J* = 5.7 Hz, 2H); HPLC purity 99.52 % {t_R = 11.40 min, flow 1 ml/min, [(CH_3CN/(0.1% TFA in H_2O):30/70]}; purity 99.2% {t_R = 13.61 min, flow 1 ml/min, [(MeOH/(0.1% TFA in H_2O):50/50]}; HRMS (ESI +ve) *m/z* calculated for $C_{16}H_{14}FlN_4OS$ $(M + H)^+$ 345.0571, found 345.0570.

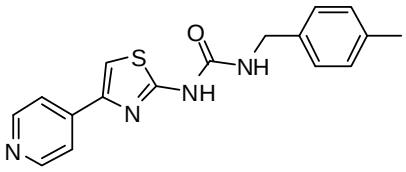


1-(3-Methylbenzyl)-3-(4-(pyridin-4-yl)thiazol-2-yl)urea (5w). This was prepared from **10** (0.111 g, 0.372 mmol) and 3-methylbenzylamine (0.054 g, 0.447 mmol) in the same manner as described for **5b**. After cooling to room temperature, THF (1.5–2 ml) and hexane (1.5–2 ml) were added. The precipitate was filtered, washed with a solution THF/hexane (1/9, 1 ml) and dried under vacuum. The pure urea **5w** was obtained as a white solid (0.071 g, 59%), mp 227.3-228.4 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.78 (s, 1H), 8.57 (dd, *J* = 1.6, 4.6 Hz, 2H), 7.81 (s, 1H), 7.77 (dd, *J* = 1.6, 4.5 Hz, 2H), 7.21 (t, *J* = 7.5 Hz, 2H), 7.09-7.04 (m, 3H), 6.98 (t, *J* = 5.4 Hz, 1H), 4.30 (d, *J* = 5.9 Hz, 2H), 2.27 (s, 3H); HPLC purity 97.7% {t_R = 11.63

min, flow 1 ml/min, [(MeOH/(0.1% TFA in H_2O):50/50]}; HRMS (ESI +ve) *m/z* calculated for $C_{16}H_{14}N_5O_3S$ $(M + H)^+$ 325.1117, found 325.1104.

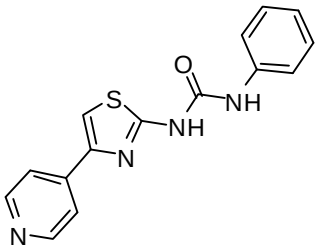


1-(2-Methylbenzyl)-3-(4-(pyridin-4-yl)thiazol-2-yl)urea (5x). This was prepared from **10** (0.086 g, 0.288 mmol) and 2-methylbenzylamine (0.038 g, 0.317 mmol) in the same manner as described for **5b**. After cooling to room temperature, the solvent was removed under reduced pressure. The remaining solid was triturated with diethyl ether, filtered and dried under vacuum. The pure urea **5x** was obtained as a white solid (0.045 g, 48%), mp. >195 ºC decomposed. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.19 (s, 1H), 8.57 (d, *J* = 6.0 Hz, 2H), 7.81 (s, 1H), 7.77 (d, *J* = 6.0 Hz, 2H), 7.23-7.21 (m, 1H), 7.16-7.14 (m, 3H), 6.93 (bs, 1H), 4.33 (d, *J* = 5.8 Hz, 2H), 2.28 (s, 3H); HPLC purity 98.5% {t_R = 6.08 min, flow 1 ml/min, [(MeOH/(0.1% TFA in H_2O):50/50]}; HRMS (ESI+ve) *m/z* calculated for $C_{17}H_{17}N_4OS$ $(M + H)^+$ 325.1117, found 325.1117.

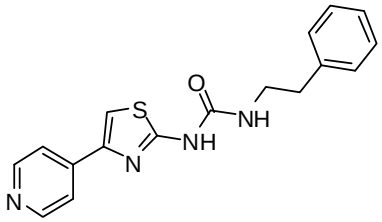


1-(4-Methylbenzyl)-3-(4-(pyridin-4-yl)thiazol-2-yl)urea (5y). This was obtained as a off-white solid (0.082 g, 77%) from **10** (0.097 g, 0.325 mmol) and 4-methylbenzylamine (0.047 g, 0.391 mmol) in the same manner as described for **5b,** mp 228.8-231.8 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.78 (s, 1H), 8.57 (d, *J* = 1.6, 4.5 Hz, 2H), 7.81 (s, 1H), 7.77 (dd, *J* = 1.6, 4.5 Hz, 2H), 7.18 (d, *J* = 8.1 Hz, 2H), 7.13 (d, *J* = 8.0 Hz, 2H), 6.95 (t, *J* = 6.0 Hz, 1H), 4.29 (d, *J* = 5.9 Hz, 2H), 2.26 (s, 3H); HPLC purity 98.5% {t_R = 11.71 min, flow 1 ml/min,

[(MeOH/(0.1% TFA in H_2O):50/50]}; HRMS (ESI +ve) *m/z* calculated for $C_{17}H_{17}N_4OS$ $(M + H)^+$ 325.1117, found 325.1110.

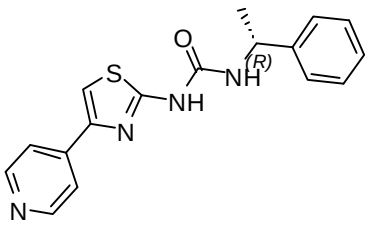


1-Phenyl-3-(4-(pyridin-4-yl)thiazol-2-yl)urea (12). A mixture of **7** (0.081 g, 0.457 mmol), phenyl isocyanate (0.065 g, 0.559 mmol) in anhydrous DMF (0.5 ml), was heated in a Biotage microwave at 150 ºC for 10 min. After cooling to room temperature, the solvent was removed under reduced pressure and chromatography on silica gel performed using the FlashMaster 3 purification station afforded the urea **12** as an off-white solid (0.072 g, 53%), mp > 174 °C (decomposed). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.77 (bs, 1H), 8.91 (bs, 1H), 8.60 (d, *J* = 6.0 Hz, 2H), 7.90 (s, 1H), 7.81 (d, *J* = 6.1 Hz, 2H), 7.47 (d, *J* = 8.3 Hz, 2H), 7.32 (t, *J* = 7.9 Hz, 2H), 7.04 (t, *J* = 7.4 Hz, 1H); HPLC purity 97.8 % {t_R = 5.87 min, flow 1 ml/min, [(MeOH/(0.1% TFA in H_2O):50/50]}; HRMS (ESI +ve) *m/z* calculated for $C_{15}H_{13}N_4OS$ $(M + H)^+$ 297.0804, found 297.0809.

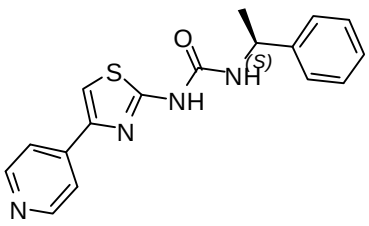


1-Phenethyl-3-(4-(pyridin-4-yl)thiazol-2-yl)urea (13). This was prepared from **10** (0.157 g, 0.527 mmol) and 2-phenylethylamine (0.076 g, 0.632 mmol) in the same manner as described for **5b**. After cooling to room temperature, DCM (3 ml) and hexane (3 ml) were added to the reaction mixture. The precipitate was filtered, dried under vacuum. The pure urea **13** was obtained as an off-white solid (0.142 g, 83%), mp > 184.5 °C (decomposed). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.69 (s, 1H), 8.56 (d, *J* = 6.1 Hz, 2H), 7.79 (s, 1H), 7.75

(d, J = 6.1 Hz, 2H), 7.30 (t, J = 6.6 Hz, 2H), 7.23-7.18 (m, 3H), 6.53 (t, J = 3.7 Hz, 1H), 3.38 (q, J = 6.4 Hz, 2H), 2.76 (t, J = 7.2 Hz, 2H); HPLC purity 99.0% {t_R = 7.33 min, flow 1 ml/min, [(CH_3CN/(0.1% TFA in H_2O):30/70]}; purity 97.4% {t_R = 9.50 min, flow 1 ml/min, [(MeOH/(0.1% TFA in H_2O):50/50]}; HRMS (ESI +ve) m/z calculated for $C_{17}H_{17}N_4OS$ $(M + H)^+$ 325.1117, found 325.1113.

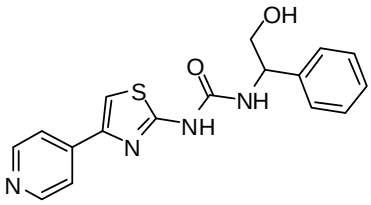


(R)-1-(1-Phenylethyl)-3-(4-(pyridin-4-yl)thiazol-2-yl)urea [(*R*)-14a]. This was obtained as an off-white solid (0.104 g, 67%) from **10** (0.142 g, 0.477 mmol) and (*R*)-(+)-alpha-methylbenzylamine (0.069 g, 0.572 mmol) in the same manner as described for **5b**, mp 196.4-197.4 ºC. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.51 (s, 1H), 8.56 (dd, J = 1.3, 4.7 Hz, 2H), 7.80 (s, 1H), 7.76 (dd, J = 1.5, 4.6Hz, 2H), 7.36-7.31 (m, 4H), 7.26-7.24 (m, 1H), 7.02 (d, J = 7.7 Hz, 1H), 4.84 (quint, J = 7.3 Hz, 1H), 1.40 (d, J = 6.9 Hz, 6H); ^{13}C NMR (400 MHz, DMSO-d_6) δ 160.80, 153.72, 150.84, 146.77, 145.01, 141.64, 129.14, 127.61, 126.47, 120.48, 111.71, 49.71, 23.54; HPLC purity 99.2% {t_R = 7.91 min, flow 1 ml/min, [(CH_3CN/(0.1% TFA in H_2O):30/70]}; purity 99.5% {t_R = 8.65 min, flow 1 ml/min, [(MeOH/(0.1% TFA in H_2O):50/50]}; HRMS (ESI +ve) *m/z* calculated for $C_{17}H_{17}N_4OS$ $(M + H)^+$ 3251117, found 325.1116. The enantiomeric excess was determined by HPLC using a Chiralcel OJ column [(*iso*-propanol/hexane:50/50), flow 1 ml/min], t_{R1} = 9.12 min, area% 0.37 (minor), t_{R2} = 14.47 min, area% 94.93 (major).

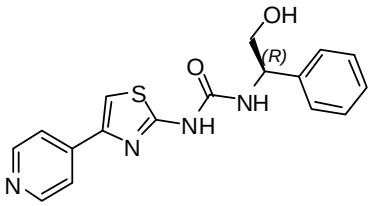


(*S*)-1-(1-Phenylethyl)-3-(4-(pyridin-4-yl)thiazol-2-yl)urea [(*S*)-14a]. This was obtained as an off-white solid (0.099 g, 0.305 mmol, 55%) from **10** (0.164 g, 0.551 mmol) and (*S*)-(-)-alpha-methylbenzylamine (0.080 g, 0.661 mmol) in the same manner as described for **5b**, mp 190.1-192.2 ºC. ^{1}H NMR (400 MHz, DMSO-d_6)δ 10.52 (s, 1H), 8.57 (dd, *J* = 1.5, 4.6 Hz, 2H), 7.80 (s, 1H), 7.76 (dd, *J* = 1.6, 4.5 Hz, 2H), 7.37-7.32 (m, 4H), 7.27-7.21 (m, 1H), 7.03 (d, *J* = 8.3 Hz, 1H), 4.84 (quin, *J* = 6.6 Hz, 1H), 1.41 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.79, 153.71, 150.85, 146.76, 145.01, 141.64, 129.14, 127.61, 126.47, 120.48, 111.72, 49.71, 23.54; HPLC purity 99.7% {t_R = 7.48 min, flow 1 ml/min, [(CH_3CN/(0.1% TFA in H_2O):30/70]}; purity 99.5% {t_R = 8.65 min, flow 1 ml/min, [(MeOH/(0.1% TFA in H_2O):50/50]}; HRMS (ESI +ve) *m/z* calculated for $C_{17}H_{17}N_4OS$ $(M + H)^+$ 3251117, found 325.1116. The enantiomeric excess was determined by HPLC using a Chiralcel OJ column [(*iso*-propanol/hexane:50/50), flow 1 ml/min], t_{R1} = 9.47 min , area% 99.24 (major).

(*S*)-1-(2-Hydroxy-1-phenylethyl)-3-(4-(pyridin-4-yl)thiazol-2-yl)urea [(*S*)-14b]. This was obtained as an off-white solid (0.090 g, 55%) from **10** (0.144 g, 0.483 mmol) and (*S*)-(+)-2-phenylglycinol (0.079 g, 0.580 mmol) in the same manner as described for **5b**, mp 191.3-193.5 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.71 (s, 1H), 8.57 (dd, *J* = 1.6, 4.5 Hz, 2H), 7.80 (s, 1H), 7.78 (dd, *J* = 1.6, 4.5 Hz, 2H,), 7.34-7.21 (m, 6H), 5.08 (t, *J* = 5.2 Hz, 1H), 4.77 (dd, *J* = 5.4, 12.4 Hz, 1H), 3.70-3.64 (s, 1H), 3.59-3.54 (m, 1H); HPLC purity 99.9% {t_R = 9.93 min, flow 1 ml/min, [(CH_3CN/(0.1% TFA in H_2O):20/80]}; purity 99.9% {t_R = 7.89 min, flow 1 ml/min, [(MeOH/(0.1% TFA in H_2O):40/60]}; HRMS (ESI +ve) *m/z* calculated for $C_{17}H_{17}N_4O_2S$ $(M + H)^+$ 341.1066, found 341.1067. The enantiomeric excess was determined by HPLC using a Chiralcel OJ column [(*iso*-propanol/hexane:70/30), flow 1 ml/min], t_{R1} = 5.47 min, area% 98.77.

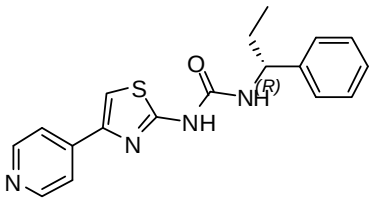


1-(2-Hydroxy-1-phenylethyl)-3-(4-(pyridin-4-yl)thiazol-2-yl)urea [(±)-14b]. This was obtained as a white solid (0.032 g, 27%) from **10** (0.105 g, 0.352 mmol) and racemic phenylglycinol (0.058 g, 0.423 mmol) in the same manner as described for **5b**, mp 195.6-197.5 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.71 (s, 1H), 8.57 (d, J = 5.9 Hz, 2H), 7.80 (s, 1H), 7.78 (d, J = 6.1 Hz, 2H), 7.28 (m, 6H), 5.08 (t, J = 5.1 Hz, 1H), 4.77 (dd, J = 5.5, 12.9 Hz, 1H), 3.70-3.63 (m, 1H), 3.58-3.54 (m, 1H). HPLC purity 99.8% {t_R = 9.97 min, flow 1 ml/min, [(CH_3CN/(0.1% TFA in H_2O):20/80]}; purity 99.7% {t_R = 7.97 min, flow 1 ml/min, [(MeOH/(0.1% TFA in H_2O):40/60]}; HRMS (ESI +ve) *m/z* calculated for $C_{17}H_{17}N_4O_2S$ $(M + H)^+$ 341.1066, found 341.1065. The enantiomeric excess was determined by HPLC using a Chiralcel OJ column [(*iso*-propanol/hexane:70/30), flow 1 ml/min], t_{R1} = 5.50 min, area% 52.58, t_{R2} = 11.73 min, area% 46.51.

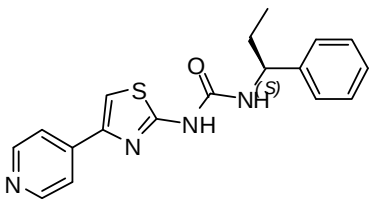


(*R*)-1-(2-Hydroxy-1-phenylethyl)-3-(4-(pyridin-4-yl)thiazol-2-yl)urea [(*R*)-14b]. This was obtained as an off-white solid (0.060 g, 39%) from **10** (0.134 g, 0.450 mmol) and (*R*)-(-)-2-amino-2-phenylethanol (0.074 g, 0.540 mmol) in the same manner as described for **5b**, mp 198.2-199.5 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.69 (s, 1H), 8.57 (dd, J = 1.6, 4.6 Hz. 2H), 7.80 (s, 1H), 7.78 (dd, J = 1.6, 4.6 Hz, 2H), 7.34-7.22 (m, 6H), 5.07 (t, J = 5.2 Hz, 1H), 4.77 (dd, J = 6.8, 12.1 Hz, 1H), 3.70-3.74 (m, 1H), 3.60-3.54 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.87, 154.14, 150.84, 146.78, 141.94, 141.64, 128.87, 127.57, 127.29, 120.50, 111.69, 65.34, 56.01; HPLC purity 99.9% {t_R = 9.96 min, flow 1 ml/min, [(CH_3CN/(0.1% TFA in H_2O):20/80]}; purity 99.8% {t_R = 7.94 min, flow 1 ml/min, [(MeOH/(0.1% TFA in H_2O):40/60]}; HRMS (ESI +ve) *m/z*

calculated for $C_{17}H_{17}N_4O_2S$ $(M + H)^+$ 341.1066, found 341.1074. The enantiomeric excess was determined by HPLC using a Chiralcel OJ column [(*iso*-propanol/hexane:70/30), flow 1 ml/min], t_{R1} = 5.45 min, area% 0.52 (minor), t_{R2} = 11.55 min, area% 98.55 (major).

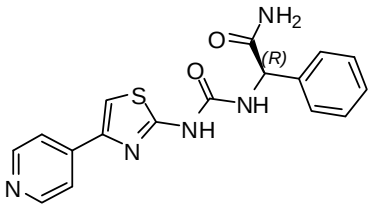


(*R*)-1-(1-Phenylpropyl)-3-(4-(pyridin-4-yl)thiazol-2-yl)urea [(*R*)-14c]. This was prepared from **10** (0.107 g, 0.359 mmol) and (*R*)-(+)-1-phenylpropylamine (0.071 g, 0.431 mmol) in the same manner as described for **5b**. After cooling to room temperature, the reaction mixture washed with NaOH (2 M, aq., 5 ml) and extracted with DCM (2 × 10 ml). The combined organic extracts were dried over Na_2SO_4 and the solvent removed under reduced pressure. The remaining solid was triturated with diethyl ether, filtered, and dried under vacuum. The pure **[(*R*)-14c]** was obtained as a white solid (0.045 g, 37%), mp 181.2-182.5 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.57 (d, *J* = 6.0 Hz, 2H), 7.80 (s, 1H), 7.76 (d, *J* = 6.0 Hz, 2H), 7.35-7.28 (m, 4H,), 7.26-7.21 (m, 1H), 7.04 (d, *J* = 7.4 Hz, 1H), 4.62 (q, *J* = 6.9 Hz, 1H), 1.73 (quin, *J* = 7.4 Hz, 2H), 0.83 (t, *J* = 7.3 Hz); HPLC purity 99.2% {t_R = 14.48 min, flow 1 ml/min, [(MeOH/(0.1% TFA in H_2O):50/50]}; HRMS (ESI +ve) *m/z* calculated for $C_{18}H_{19}N_4OS$ $(M + H)^+$ 339.1274, found 339.1272. The enantiomeric excess was determined by HPLC using a Chiralcel OJ column [(*iso*-propanol/hexane:30/70), flow 1 ml/min], t_{R1} = 16.60 min, area% 99.20.

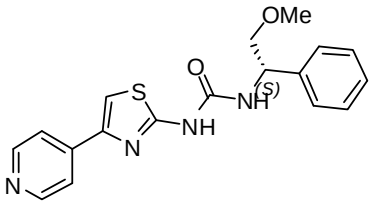


(*S*)-1-(1-Phenylpropyl)-3-(4-(pyridin-4-yl)thiazol-2-yl)urea [(*S*)-14c]. This was prepared from **10** (0.111 g, 0.372 mmol) and (*S*)-(-)-1-phenylpropylamine (0.073 g, 0.447 mmol) in the same manner as described for **5b**. After cooling to room temperature, the reaction mixture washed with NaOH (2 M, aq., 5 ml) and extracted with DCM (2 × 10 ml). The combined organic extracts were dried over Na_2SO_4 and the solvent removed under reduced pressure. The remaining solid was triturated with diethyl ether, filtered, and dried under vacuum. The pure urea **[(*S*)-14c]** was obtained as a white solid (0.082 g, 65%), mp 181.8-182.5 ºC.^{1}H NMR (400 MHz, DMSO-d_6) δ 8.57 (dd, *J* = 1.6, 4.6 Hz, 2H), 7.80 (s, 1H), 7.77 (dd, *J* = 1.6, 4.5 Hz, 2H), 7.32-7.29 (m, 4H), 7.26-7.21 (m, 1H), 7.04 (d, *J* = 6.7 Hz, 1H), 4.65-4.59 (m, 1H), 1.77-1.79 (m, 2H), 0.83 (t, *J* = 7.3 Hz, 3H); HPLC purity 99.3% {t_R = 14.47 min, flow 1 ml/min, [(MeOH/(0.1% TFA in H_2O):50/50]}; HRMS (ESI +ve) *m/z* calculated for $C_{18}H_{19}N_4OS$ $(M + H)^+$ 339.1274, found 339.1273. The enantiomeric excess was determined by HPLC using a Chiralcel OJ column [(*iso*-propanol/hexane:30/70), flow 1 ml/min], t_{R1} = 13.13 min, area% 99.32.

(*S*)-2-Phenyl-2-(3-(4-(pyridin-4-yl)thiazol-2-yl)ureido)acetamide [(*S*)-14d]. This was prepared from **10** (0.116 g, 0.389 mmol) and 2-phenylglycinamide hydrochloride salt (0.065 g, 0.346 mmol), in presence of DIPEA (0.050 ml) in the same manner as described for **5b**. After cooling to room temperature, the precipitate was filtered, washed with THF, and dried under vacuum to afford pure urea **[(*S*)-14d]** as an off-white solid (0.037 g, 30%), >189 ºC (decomposed). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.79 (s, 1H), 8.57 (d, *J* = 6.1 Hz, 2H), 7.86 (s, 1H), 7.81 (bs, 1H), 7.79 (d, *J* = 6.1 Hz, 2H), 7.68 (bs, 1H), 7.42-7.40 (m, 2H), 7.35 (t, *J* = 7.4 Hz, 2H), 7.29-7.26 (m, 1H), 5.29 (d, *J* = 7.4 Hz, 1H); HPLC purity 99.5% {t_R = 4.36 min, flow 1 ml/min, [(MeOH/(0.1% TFA in H_2O):40/60]}; purity 99.9% {t_R = 6.60 min, flow 1 ml/min, [(CH_3CN/(0.1% TFA in H_2O):20/80]}; HRMS (ESI +ve) *m/z* calculated for $C_{17}H_{16}N_5O_2S$ $(M + H)^+$ 354.1019, found 354.1019.

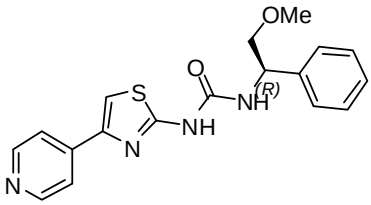


(*R*)-2-Phenyl-2-(3-(4-(pyridin-4-yl)thiazol-2-yl)ureido)acetamide [(*R*)-14d]. A mixture of **10** (0.108 g, 0.362 mmol), D-(-)-phenylglycinamide (0.065 g, 0.435 mmol) in anhydrous THF (0.5 ml) was heated in a CEM microwave reactor (power 150 W, ramp time 2 min, hold time 40 min, temperature 100 ºC, max. pressure 220 PSI). After cooling to room temperature, the precipitate was filtered, washed with acetone (2 ml), and dried *in vacuo*. The solid was further triturated with acetone, filtered, and dried under vacuum to afford pure urea **[(*R*)-14d]** as an off-white solid (0.070 g, 55%), mp > 192 °C (decomposed). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.77 (s, 1H), 8.57 (d, J = 6.0 Hz, 2H), 7.85 (s, 1H), 7.81 (s, 1H), 7.79 (d, J = 6.1 Hz, 2H), 7.66 (s, 1H), 7.41 (d, J = 7.2 Hz, 2H), 7.35 (t, J = 7.5 Hz, 2H), 7.29-7.25 (m, 2H), 5.29 (d, J = 7.5 Hz, 1H); HPLC purity 99.6% {t_R = 6.67 min, flow 1 ml/min, [(CH_3CN/(0.1% TFA in H_2O):20/80]}; purity 99.0% {t_R = 5.15 min, flow 1 ml/min, [(MeOH/(0.1% TFA in H_2O):40/60]}; HRMS (ESI +ve) *m/z* calculated for $C_{17}H_{16}N_5O_2S$ $(M + H)^+$ 354.1019, found 354.1022.

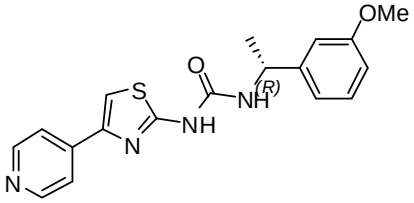


(*S*)-1-(2-Methoxy-1-phenylethyl)-3-(4-(pyridin-4-yl)thiazol-2-yl)urea [(*S*)-14e]. This was prepared from **10** (0.119 g, 0.339 mmol) and (*S*)-(+)-1-amino-1-phenyl-2-methoxyethane (0.075 g, 0.479 mmol) in the same manner as described for **5b**. After cooling to room temperature, the solvent was removed under reduced pressure. The remaining solid was triturated diethyl ether, filtered and dried under vacuum. The pure urea **[(*S*)-14e]** was obtained as a white solid (0.084 g, 70%), mp 149.9-151.2 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.66 (s, 1H), 8.57 (dd, J = 1.5, 4.6 Hz, 2H), 7.81 (s, 1H), 7.78 (dd, J = 1.6, 4.6 Hz, 2H), 7.34-7.30 (m, 5H),

7.24-7.22 (m, 1H), 4.96-4.91 (m, 1H,), 3.58 (d, J = 5.4 Hz, 2H), 3.26 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.82, 154.00, 150.85, 146.81, 141.61, 141.37, 128.96, 127.76, 127.24, 120.48, 111.73, 75.74, 59.00, 53.59; HPLC purity 99.4% {t_R = 5.83 min, flow 1 ml/min, [(CH_3CN/(0.1% TFA in H_2O):30/70]}; HRMS (ESI +ve) *m/z* calculated for $C_{18}H_{18}N_4O_2S$ $(M + H)^+$ 354.1223, found 354.1222.

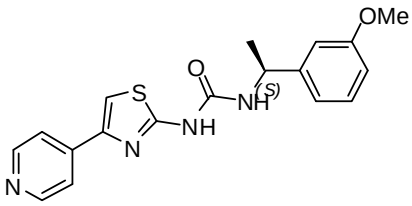


(*R*)-1-(2-Methoxy-1-phenylethyl)-3-(4-(pyridin-4-yl)thiazol-2-yl)urea [(*R*)-14e]. This was prepared from **10** (0.113 g, 0.379 mmol) and (*R*)-(-)-1-amino-1-phenyl-2-methoxyethane (0.068 g, 0.455 mmol) in the same manner as described for **5b**. After cooling to room temperature, the solvent was removed under reduced pressure. The remaining solid was triturated diethyl ether, filtered and dried under vacuum. The pure urea **[(*R*)-14e]** was obtained as a white solid (0.079 g, 59%), mp 150.4-151.6 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.66 (s, 2H), 8.57 (d, J = 6.1 Hz, 2H), 7.81 (s, 1H), 7.78 (d, J = 6.1 Hz, 2H), 7.37-7.30 (m, 5H), 7.28-7.22 (m, 1H), 4.96-4.89 (m, 1H), 3.58 (d, J = 5.2 Hz, 2H), 3.26 (s, 3H); HPLC purity 98.9% {t_R = 5.82 min, flow 1 ml/min, [(CH_3CN/(0.1% TFA in H_2O):30/70]}; HRMS (ESI +ve) *m/z* calculated for $C_{18}H_{19}N_4O_2S$ $(M + H)^+$ 355.1223, found 355.1226.



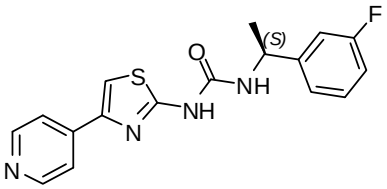
(*R*)-1-(1-(3-Methoxyphenyl)ethyl)-3-(4-(pyridin-4-yl)thiazol-2-yl)urea [(*R*)-14f]. This was prepared from **10** (0.100 g, 0.336 mmol) and (*R*)-(+)-1-(3-methoxylphenyl)ethylamine (0.060 g, 0.403 mmol) in the same manner as described for **5b**. After cooling to room temperature, the solvent was removed under reduced

pressure. The remaining solid was triturated diethyl ether, filtered and dried under vacuum. The pure urea **[(*R*)-14f]** was obtained as a white solid (0.060 g, 50%), mp 162.3-164.3 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.51 (s, 1H), 8.57 (dd, *J* = 1.6, 4.6 Hz, 2H), 7.80 (s, 1H), 7.76 (dd, 2H, *J* = 1.6, 4.5 Hz, 2H), 7.25 (t, *J* = 7.8 Hz, 1H), 7.02 (bd, *J* = 7.6 Hz, 1H), 6.90-6.88 (m, 2H), 6.81-6.79 (m, 1H), 4.80 (quin, *J* = 7.1 Hz, 1H), 1.39 (d, *J* = 6.9 Hz, 3H); HPLC purity 99.9% {t_R = 7.91 min, flow 1 ml/min, [(CH_3CN/(0.1% TFA in H_2O):30/70]}; purity 96.8% {t_R = 9.13 min, flow 1 ml/min, [(MeOH/(0.1% TFA in H_2O):50/50]}; HRMS (ESI +ve) *m/z* calculated for $C_{18}H_{19}N_4O_2S$ $(M + H)^+$ 355.1223, found 355.1220. The enantiomeric excess was determined by HPLC using a Chiralcel OJ column [(*iso*-propanol/hexane:40/60), flow 1 ml/min], t_{R1} = 24.70 min, area% 97.37.

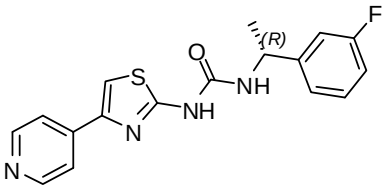


(*S*)-1-(1-(3-Methoxyphenyl)ethyl)-3-(4-(pyridin-4-yl)thiazol-2-yl)urea [(*S*)-14f]. This was prepared from **10** (0.109 g, 0.359 mmol) and (*S*)-(-)-1-(3-methoxylphenyl)ethylamine (0.065 g, 0.431 mmol) in the same manner as described for **5b**. After cooling to room temperature, the solvent was removed under reduced pressure. The remaining solid was triturated diethyl ether, filtered and dried under vacuum. The pure urea **[(*S*)-14f]**was obtained as a white solid (0.069 g, 54%), mp 161.6-163.4 ºC. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.52 (s, 1H), 8.57 (d, *J* = 6.0 Hz, 2H), 7.80 (s, 1H), 7.76 (d, *J* = 6.1 Hz, 2H), 7.25 (t, *J* = 7.9 Hz, 1H), 7.02 (d, *J* = 8.3 Hz, 1H), 6.90-6.88 (m, 2H), 6.81 (m, 1H), 4.80 (quin, *J* = 6.7 Hz, 1H), 1.39 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (400 MHz, DMSO-d_6) δ 160.79, 160.03, 153.70, 150.85, 146.75, 146.73, 141.64, 130.25, 120.47, 118.59, 112.77, 112.37, 111.74, 55.69, 49.71, 23.60. HPLC purity 99.7% {t_R = 7.90 min, flow 1 ml/min, [(CH_3CN/(0.1% TFA in H_2O):30/70]}; purity 96.3% {t_R = 9.24 min, flow 1 ml/min, [(MeOH/(0.1% TFA in H_2O):50/50]}; HRMS (ESI +ve) *m/z* calculated for $C_{18}H_{19}N_4O_2S$ $(M + H)^+$ 355.1223, found 355.1216. The

enantiomeric excess was determined by HPLC using a Chiralcel OJ column [(*iso*-propanol/hexane:40/60), flow 1 ml/min], t_{R1} = 15.40 min, area% 96.32.

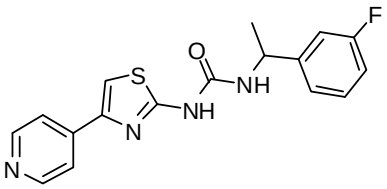


(*S*)-1-(1-(3-Fluorophenyl)ethyl)-3-(4-(pyridin-4-yl)thiazol-2-yl)urea [(*S*)-14g]. This was prepared from **10** (0.093 g, 0.312 mmol) and (*S*)-1-(3-fluorophenyl)ethylamine (0.050 g, 0.359 mmol) in the same manner as described for **5b**. After cooling to room temperature, the solvent was removed under reduced pressure. The remaining solid was triturated with ether (2 ml), filtered, washed with hexane (2 ml), and dried under vacuum. The pure urea **[(*S*)-14g]** was obtained as an off-white solid (0.085 g, 78%), mp 198.2-199.8 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.56 (s, 1H), 8.57 (d, *J* = 6.1 Hz, 2H), 7.80 (s, 1H), 7.77 (dd, *J* = 1.6, 4.5 Hz, 2H), 7.40-7.34 (m, 1H), 7.18-7.15 (m, 2H), 7.09-7.03 (s, 2H), 4.90-7.83 (m, 1H), 1.41 (d, *J* = 7.0 Hz, 3H); HPLC purity 98.4% {t_R = 9.40 min, flow 1 ml/min, [(CH_3CN/(0.1% TFA in H_2O):30/70]}; purity 98.4% {t_R = 10.12 min, flow 1 ml/min, [(MeOH/(0.1% TFA in H_2O):50/50]}; HRMS (ESI +ve) *m/z* calculated for $C_{17}H_{15}N_4FOS$ $(M + H)^+$ 343.1023, found 343.1051.

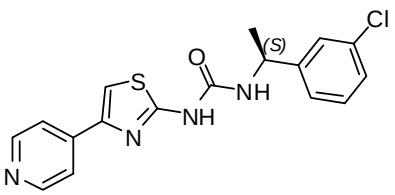


(*R*)-1-(1-(3-Fluorophenyl)ethyl)-3-(4-(pyridin-4-yl)thiazol-2-yl)urea [(*R*)-14g]. This was prepared from **10** (0.095 g, 0.319 mmol) and (*R*)-1-(3-fluorophenyl)ethylamine (0.053 g, 0.389 mmol) in the same manner as described for **5b**. After cooling to room temperature, the solvent was removed under reduced pressure. The remaining solid was triturated with ether (2 ml), filtered, washed with hexane (1.5 ml), and dried under

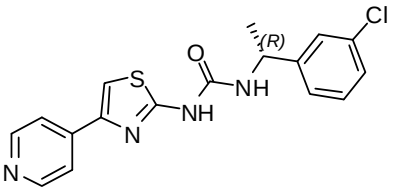
vacuum. The pure urea **[(*R*)-14g]** was obtained as an off-white solid (0.090 g, 83%), mp 198.0-200.0 ºC. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.58 (s, 1H), 8.57 (d, *J* = 6.1 Hz, 2H), 7.81 (s, 1H), 7.77 (dd, *J* = 1.6, 4.5 Hz, 2H), 7.40-7.33 (m, 1H), 7.18-7.15 (m, 2H,), 7.12 (bs, 1H), 7.08-7.03 (m, 1H), 4.87-7.81 (m, 1H), 1.40 (d, *J* = 7.0 Hz, 3H), HPLC purity 98.7% {t_R = 9.36 min, flow 1 ml/min, [(CH_3CN/(0.1% TFA in H_2O):30/70]}; purity 98.7% {t_R = 10.10 min, flow 1 ml/min, [(MeOH/(0.1% TFA in H_2O):50/50]}; HRMS (ESI +ve) *m/z* calculated for $C_{17}H_{15}N_4FOS$ $(M + H)^+$ 343.1023, found 343.1023.



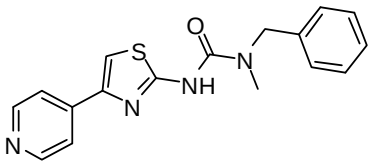
1-(1-(3-Fluorophenyl)ethyl)-3-(4-(pyridin-4-yl)thiazol-2-yl)urea [(±)-14g]. This was prepared from **10** (0.089 g, 0.299 mmol) and 1-(3-fluorophenyl)ethylamine (0.049 g, 0.358 mmol) in the same manner as described for **5b**. After cooling to room temperature, the solvent was removed under reduced pressure. The remaining solid was triturated with ether (3 ml), filtered, washed with hexane (1 ml), and dried under vacuum. The pure urea **[(±)-14g]** was obtained as an off-white solid (0.085 g, 83%), mp 201.7-203.7 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.57 (s, 1H), 8.57 (dd, *J* = 1.6, 4.5 HZ, 2H), 7.80 (s, 1H), 7.77 (dd, *J* = 1.6, 4.5 Hz, 2H), 7.40-7.32 (m, 1H), 7.18-7.15 (m, 2H), 7.11 (d, *J* = 7.2 Hz, 1H), 7.06 (m, 1H), 4.86 (quin *J* = 7.2 Hz, 1H), 1.40 (d, *J* = 7.0 Hz, 3H); HPLC purity 96.4% {t_R = 9.38 min, flow 1 ml/min, [(CH_3CN/(0.1% TFA in H_2O):30/70]}; purity 96.3% {t_R = 10.05 min, flow 1 ml/min, [(MeOH/(0.1% TFA in H_2O):50/50]}; HRMS (ESI +ve) *m/z* calculated for $C_{17}H_{15}N_4FOS$ $(M + H)^+$ 343.1023, found 343.1024.



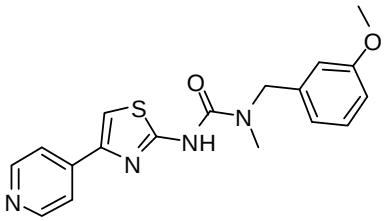
(*S*)-1-(1-(3-chlorophenyl)ethyl)-3-(4-(pyridin-4-yl)thiazol-2-yl)urea [(*S*)-14h]. This was prepared from **10** (0.093 g, 0.312 mmol) and (*S*)-1-(3-chlorophenyl)ethylamine (0.057 g, 0.364 mmol) in the same manner as described for **5b**. After cooling to room temperature, the solvent was removed under reduced pressure. The remaining solid was triturated with ether (3 ml), filtered, washed with hexane (2 ml), and dried under vacuum. The pure urea **[(*S*)-14h]** was obtained as an off-white solid (0.045 g, 40%), mp 206.6-208.2 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.58 (s, 1H), 8.57 (dd, J = 1.6, 4.6 Hz, 2H), 7.80 (s, 1H), 7.77 (dd, J = 1.6, 4.5 Hz, 2H), 7.40-7.35 (m, 2H), 7.31-7.28 (m, 2H), 7.10 (d, J = 8.7 Hz, 1H), 4.88-7.80 (m, 1H), 1.40 (d, J = 7.0 Hz, 3H), HPLC purity 99.5% {t_R = 16.02 min, flow 1 ml/min, [(CH_3CN/(0.1% TFA in H_2O):30/70]}; purity 99.5% {t_R = 18.66 min, flow 1 ml/min, [(MeOH/(0.1% TFA in H_2O):50/50]}; HRMS (ESI +ve) *m/z* calculated for $C_{17}H_{15}ClN_4OS$ $(M + H)^+$ 359.0727, found 359.0724.



(*R*)-1-(1-(3-Chlorophenyl)ethyl)-3-(4-(pyridin-4-yl)thiazol-2-yl)urea [(*R*)-14h]. This was prepared from **10** (0.090 g, 0.302 mmol) and (*R*)-1-(3-chlorophenyl)ethylamine (0.056 g, 0.362 mmol) in the same manner as described for **5b**. After storing the reaction mixture at –20 ºC overnight, the precipitate was filtered, washed with ether (2 ml), hexane (2 ml), and dried under vacuum. The pure urea **[(*R*)-14h]**was obtained as a white solid (0.070 g, 65%), mp 209.9-212.0 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.57 (s, 1H), 8.57 (dd, J = 1.6, 4.5 Hz, 2H), 7.81 (s, 1H), 7.77 (dd, J = 1.6, 4.5 Hz, 2H), 7.40-7.35 (m, 2H), 7.31-7.29 (m, 2H), 7.10 (d, J = 6.4 Hz, 1H), 4.87-7.80 (m, 1H), 1.40 (d, J = 7.0 Hz, 3H); HPLC purity 99.7% {t_R = 16.03 min, flow 1 ml/min, [(CH_3CN/(0.1% TFA in H_2O):30/70]}; purity 99.7% {t_R = 18.67 min, flow 1 ml/min, [(MeOH/(0.1% TFA in H_2O):50/50]}; HRMS (ESI +ve) *m/z* calculated for $C_{17}H_{15}ClN_4OS$ $(M + H)^+$ 359.0727, found 359.0726.



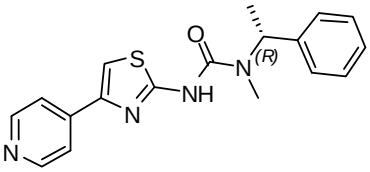
1-Benzyl-1-methyl-3-(4-(pyridin-4-yl)thiazol-2-yl)urea (5z). This was prepared from **10** (0.099 g, 0.332) and *N*-benzylmethylamine (0.048 g, 0.399 mmol) in the same manner as described for **5b**. After cooling to room temperature, the reaction mixture washed with NaOH (aq. 1 M, 10 ml) and extracted with DCM (10 ml). The combined organic extracts were dried over Na_2SO_4 and the solvent removed under reduced pressure. Chromatography on silica gel using a FlashMaster 3 purification station (EtOAc/hexane) afforded pure urea **(5z)** (0.068 g, 63%) as an off-white solid, mp 160.0 °C (decomposed). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.08 (s, 1H), 8.57 (dd, J = 1.5, 4.6 Hz, 2H), 7.85 (s, 1H), 7.82 (dd, J = 1.6, 4.6, 2H), 7.36-7.32 (m, 2H), 7.27-7.22 (m, 3H), 4.61 (s, 2H), 2.96 (s, 3H); HPLC purity 99.2% {t_R = 6.79 min, flow 1 ml/min, [(CH_3CN/(0.1% TFA in H_2O):30/70]}; purity 97.7% {t_R = 7.56 min, flow 1 ml/min, [(MeOH/(0.1% TFA in H_2O):50/50]}; HRMS (ESI +ve) *m/z* calculated for $C_{17}H_{17}N_4OS$ $(M + H)^+$ 325.1117, found 325.1112.



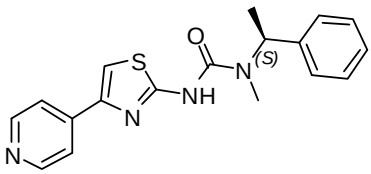
1-(3-Methoxybenzyl)-1-methyl-3-(4-(pyridin-4-yl)thiazol-2-yl)urea (5ab). A mixture of **10** (0.113 g, 0.379 mmol) and 3-methoxy-*N*-methylbenzylamine (0.068 g, 0.455 mmol) in anhydrous THF (0.5 ml) was stirred in a sealed tube at 112 °C for 1 h. After cooling to room temperature, the solvent was removed under reduced pressure. The remaining solid was triturated with diethyl ether, filtered, dried under vacuum. The pure urea **(5ab)** was obtained as a white solid (0.091 g, 68%), mp 153.1-154.3 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.05 (s, 1H), 8.58 (dd, J = 1.5, 4. Hz, 2H), 7.85 (s, 1H), 7.81 (dd, J = 1.6, 4.6 Hz, 2H), 7.26 (t, J = 7.9 Hz, 1H), 6.84-6.78 (m, 3H), 4.57 (s, 2H), 3.71 (s, 3H), 2.95 (s, 3H); ^{13}C NMR (400 MHz, DMSO-d_6) δ 162.16,

160.10, 155.33, 150.73, 146.73, 141.83, 140.06, 130.38, 120.54, 119.95, 113.65, 112.91, 112.22, 55.60, 51.92, 35.07; HPLC purity 99.6% {t_R = 7.21 min, flow 1 ml/min, [(CH_3CN/(0.1% TFA in H_2O):30/70]}; HRMS (ESI +ve) *m/z* calculated for $C_{18}H_{19}N_4O_2S$ $(M + H)^+$ 355.1223, found 355.1214.

[(*R*)-14i]

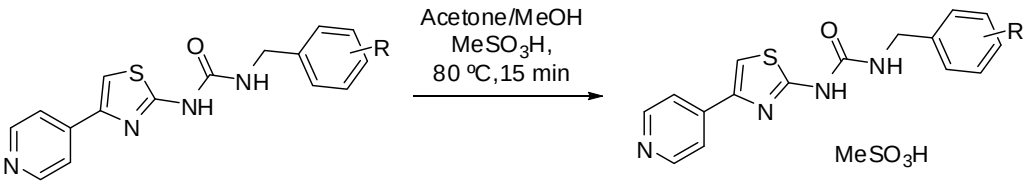


(*R*)-1-Methyl-1-(1-phenylethyl)-3-(4-(pyridin-4-yl)thiazol-2-yl)urea [(*R*)-14i]. This was prepared from **10** (0.104 g, 0.349 mmol) and (*R*)-(+)-*N*,α-dimethylbenzylamine (0.056 g, 0.419 mmol) in the same manner as described for **5aa**. After cooling to room temperature, the solvent was removed under reduced pressure. The remaining solid was triturated with diethyl ether, filtered, dried under vacuum. The pure urea **[(*R*)-14i]** was obtained as a white solid (0.089 g, 75%), mp 195.4-198.7 ºC. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.00 (s, 1H), 8.58 (dd, *J* = 1.5, 4.7 Hz, 2H), 7.85 (s, 1H), 7.82 (dd, *J* = 1.5, 4.7 Hz, 2H), 7.37-7.34 (m, 2H), 7.29-7.26 (m, 3H), 5.64 (q, *J* = 7.1 Hz, 1H), 2.70 (s, 3H), 1.49 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (400 MHz, DMSO-d_6) δ 162.16, 155.24, 150.84, 146.89, 141.92, 141.47, 129.14, 127.84, 127.53, 120.54, 112.40, 52.66, 29.34, 17.03; HPLC purity 99.0% {t_R = 10.49 min, flow 1 ml/min, [(CH_3CN/(0.1% TFA in H_2O):30/70]}; purity 97.9% {t_R = 11.86 min, flow 1 ml/min, [(MeOH/(0.1% TFA in H_2O):50/50]}; HRMS (ESI +ve) *m/z* calculated for $C_{18}H_{19}N_4OS$ $(M + H)^+$ 339.1274, found 339.1268. The enantiomeric excess was determined by HPLC using a Chiralcel OJ column [(*iso*-propanol/hexane:80/20), flow 1 ml/min], t_{R1} = 7.25 min, area% 97.02.



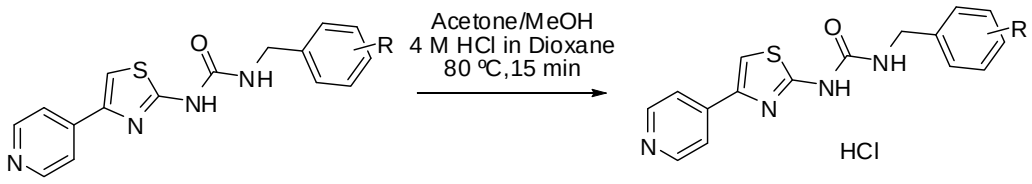
(*S*)-1-Methyl-1-(1-phenylethyl)-3-(4-(pyridin-4-yl)thiazol-2-yl)urea [(*S*)-14i]. This was prepared from **10** (0.106 g, 0.356 mmol) and (*S*)-(-)-*N*,α-dimethylbenzylamine (0.057 g, 0.427 mmol) in the same manner as described for **5aa**. After cooling to room temperature, the reaction mixture washed with NaOH (2 M, aq., 5 ml) and extracted with DCM (2 × 10 ml). The combined organic extracts were dried over Na_2SO_4 and the solvent removed under reduced pressure. The remaining solid was triturated with diethyl ether, filtered, and dried under vacuum. The pure urea **[(*S*)-14i]** was obtained as a white solid (0.070 g, 58%), mp 195.1-198.7 ºC. ^{1}H NMR (400 MHz, DMSO-d_6) δ; 11.01 (s, 1H), 8.58 (d, *J* = 4.8 Hz, 2H), 7.84 (s, 1H), 7.82 (dd, *J* = 1.5, 4.6 Hz, 2H), 7.36-7.33 (m, 2H,), 7.29-7.24 (m, 3H), 5.64 (q, *J* = 7.0 Hz,1H), 3.34 (s, 2H), 1.48 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (200 MHz, DMSO-d_6) δ 162.19, 155.24, 150.84, 146.85, 141.93, 141.47, 129.14, 127.83, 127.52, 120.54, 112.40, 52.66, 29.34, 17.03; HPLC purity 99.4% {t_R = 10.45 min, flow 1 ml/min, [(CH_3CN/(0.1% TFA in H_2O):30/70]}; HRMS (ESI +ve) *m/z* calculated for $C_{18}H_{19}N_4OS$ $(M + H)^+$ 339.1274, found 339.1269. The enantiomeric excess was determined by HPLC using a Chiralcel OJ column [(*iso*-propanol/hexane:80/20), Flow 1 ml/min], t_{R1} = 7.17 min, area% 0.50 (minor); t_{R2} = 33.00 min, area% 98.22 (major).

Synthesis of Mesylate salts of 5b, 5d and 5g.



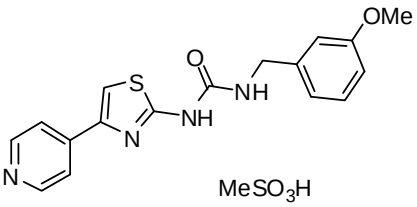
5g, R = 3-OH
5b, R = 3-OMe
5d, R = 4-OMe

5g-Mes, R = 3-OH
5b-Mes, R = 3-OMe
5d-Mes, R = 4-OMe

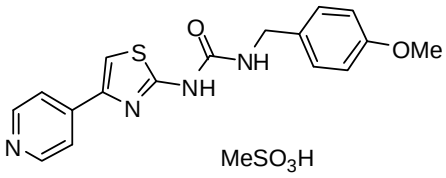


5g, R = 3-OH
5b, R = 3-OMe
5d, R = 4-OMe

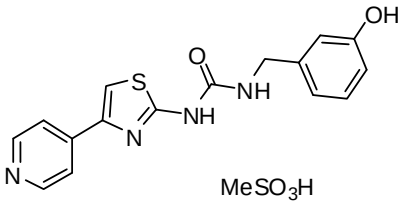
5g-HCl, R = 3-OH
5b-HCl, R = 3-OMe
5d-HCl, R = 4-OMe



1-(3-Methoxybenzyl)-3-(4-(pyridin-4-yl)thiazol-2-yl)urea methanesulfonate (5b-Mes). A solution of methanesulfonic acid (1.53 M in acetone, 0.250 ml, freshly prepared) was added to solution of **5b** (0.107 g, 0.314 mmol) in acetone (3 ml) at 80 ºC (oil bath T.) under Argon. The mixture was then stirred 80 ºC (oil bath temperature) under Argon for 15 min. After cooling to room temperature, acetone (1.5 ml) was added. The precipitate was filtered, washed with acetone (3 × 1.5 ml), hexane (5 ml), and dried under vacuum. The pure urea **5b-Mes** was obtained as an off-white solid (0.129 g, 94%), mp 191.5-193.2 ºC; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.99 (s, 1H), 8.86 (d, J = 8.2 Hz, 2H), 8.36-8.32 (m, 3H), 7.24 (t, J = 8.1 HZ, 1H), 7.17 (s, 1H), 6.87-6.85 (m, 2H), 6.82-6.79 (m, 1H), 4.32 (d, J = 6.0 Hz, 2H), 3.72 (s, 3H), 2.32-2.31 (m, 3H); HPLC purity 99.3% {t_R = 6.08 min, flow 1 ml/min, [(MeOH/(0.1% TFA in H_2O):50/50]}; HRMS (ESI +ve) calculated for $C_{17}H_{16}N_5O_2S$ $(M + H)^+$ 341.1066, found 341.1075.

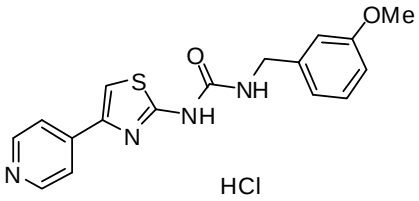


1-(4-Methoxybenzyl)-3-(4-(pyridin-4-yl)thiazol-2-yl)urea methanesulfonate (5d-Mes). A solution of methanesulfonic acid (1.53 M in acetone, 0.250 ml, freshly prepared) was added to mixture of **5d** (0.082 g, 0.241 mmol) in acetone (4 ml) and methanol (1 ml) at 80 ºC (oil bath temperature) under Argon. The solution was then stirred 80 ºC (oil bath T.) under Argon for 15 min. After cooling to room temperature, the precipitate was filtered, washed with acetone (3 × 1.5 ml), and dried under vacuum. The pure **5d-Mes** was obtained as an off-white solid (0.094 g, 89%), mp >216.7-219.0 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.88 (s, 1H), 8.80 (d, J = 5.8 Hz, 2H), 8.25-8.22 (m, 3H), 7.23 (d, J = 8.7 Hz, 2H), 7.00 (bs, 1H), 6.89 (d, J = 8.7 Hz, 2H), 4.27 (d, J = 5.7 Hz, 2H), 3.72 (s, 3H), 2.28 (s, 3H), HPLC purity 99.5% {t_R = 5.90 min, flow 1 ml/min, [(MeOH/(0.1% TFA in H_2O):50/50]}; HRMS (ESI +ve) *m/z* calculated for $C_{17}H_{16}N_5O_2S$ $(M + H)^+$ 354.1066, found 341.1070.

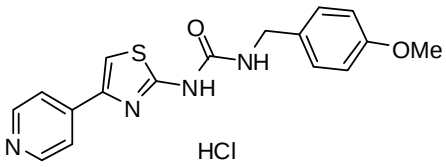


1-(3-Hydroxybenzyl)-3-(4-(pyridin-4-yl)thiazol-2-yl)urea methanesulfonate (5g-Mes). A solution of methanesulfonic acid (1.53 M in acetone, 0.200 ml, freshly prepared) was added to mixture of **5g** (0.091 g, 0.279 mmol) in acetone (3 ml) and methanol (1 ml) at 80 ºC (oil bath temperature) under Argon. The solution was then stirred 80 ºC (oil bath T.) under Argon for 15 min. After cooling to room temperature, acetone (5 ml) was added. The solution was stored in the fridge overnight. The precipitate was then filtered, washed with acetone (2 ml), hexane (5 ml), and dried under vacuum. The pure urea **5g-Mes** was obtained as an off-

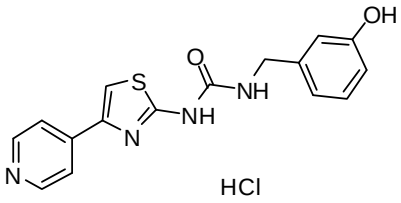
white solid (0.090 g, 76%), mp 208.2-209.0 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.96 (s, 1H), 9.36 (m, 1H), 8.86 (d, *J* = 6.8 Hz, 2H), 8.36 (s, 1H), 8.33 (d, *J* = 6.8 Hz, 2H), 7.11 (t, *J* = 7.9 Hz, 1H), 7.08 (s, 1H), 6.70-6.68 (m, 2H), 6.63-6.61 (m, 1H), 4.26 (d, *J* = 6.0 Hz, 2H), 2.31 (s, 3H); HPLC purity 99.7% {t_R = 6.56 min, flow 1 ml/min, [(MeOH/(0.1% TFA in H_2O):40/60]}; HRMS (ESI +ve) *m/z* calculated for $C_{16}H_{14}N_4O_2S$ $(M + H)^+$ 327.0910, found 327.0909.



1-(3-Methoxybenzyl)-3-(4-(pyridin-4-yl)thiazol-2-yl)urea hydrochloride (5b-HCl). A solution of HCl (4 M in dioxane, 0.090 ml) was added to a solution of **5b** (0.120 g, 0.329 mmol) in acetone (3 ml) at 80 ºC (oil bath T.) under Argon. The solution was then stirred 80 ºC (oil bath T.) under Argon for 15 min. After cooling to room temperature, the precipitate was then filtered, washed with acetone (4 × 1.5 ml), hexane (5 ml), and dried under vacuum. The pure urea **5b-HCl** was obtained as an off-white solid (0.124 g, 0.213 mmol, 93%), mp >215 °C (decomposed). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.10 (s, 1H), 8.82 (d, *J* = 4.9 Hz, 2H), 8.30-8.26 (m, 3H), 7.39 (t, *J* = 6.0 Hz, 1H), 7.24 (t, *J* = 8.1 Hz, 1H), 6.87-6.86 (m, 2H), 6.87-6.80 (m, 1H), 4.32 (d, *J* = 5.9 Hz, 2H), 3.72 (s, 1H); HPLC purity 99.1% {t_R = 6.03 min, flow 1 ml/min, [(MeOH/(0.1% TFA in H_2O):50/50]}; HRMS (ESI +ve) *m/z* calculated for $C_{17}H_{16}N_5O_2S$ $(M + H)^+$ 341.1066, found 341.1073.



1-(4-Methoxybenzyl)-3-(4-(pyridin-4-yl)thiazol-2-yl)urea hydrochloride (5d-HCl). A solution of HCl (4 M in dioxane, 0.050 ml) was added to mixture of **5d** (0.055 g, 0.161 mmol) in acetone (3 ml) and methanol (6 ml) under reflux under Argon. The solution was then stirred under reflux under Argon for 1 h. After cooling to room temperature, the solution was stored in the fridge for 24 h. The precipitate was then filtered, washed with cold methanol (1.5 ml), and dried under vacuum. The pure **5d-HCl** was obtained as an off-white solid (0.026 g, 43%), mp 214 °C (decomposed). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.01-10.99 (m, 1H), 8.83-8.80 (m, 2H), 8.32-8.27 (m, 3H,), 7.22 (d, J = 8.7 Hz, 2H), 7.17 (s, 1H), 6.88 (d, J = 8.7 Hz, 2H), 4.27 (d, J = 5.8 Hz, 2H), 3.71 (s, 3H); HPLC purity 99.7% {t_R = 5.82 min, flow 1 ml/min, [(MeOH/(0.1% TFA in H_2O):50/50]}; HRMS (ESI +ve) *m/z* calculated for $C_{17}H_{16}N_5O_2S$ $(M + H)^+$ 354.1066, found 341.1070.



1-(3-Hydroxybenzyl)-3-(4-(pyridin-4-yl)thiazol-2-yl)urea (5g-HCl). A solution of HCl (4 M in dioxane, 0.100 ml) was added to a solution of **5g** (0.115 g, 0.352 mmol) in acetone (3 ml) at 80 ° C (oil bath temperature) under Argon. The solution was then stirred 80 °C (oil bath T.) under Argon for 20 min. After cooling to room temperature, the precipitate was then filtered, washed with acetone (6 ml), hexane (6 ml), and dried under vacuum. The pure urea **5g-HCl** was obtained as a pale yellow solid (0.123 g, 96%), mp >219 °C. ^{1}H NMR (400 MHz, DMSO-d_6) 11.06-10.99 (m, 1H), 9.39 (bs, 1H), 8.82-8.84 (m, 2H), 8.32-8.28 (m, 3H), 7.23 (bs, 1H), 7.11 (t, J = 8.3 Hz, 1H), 6.70-6.78 (m, 2H), 6.64-6.61 (m, 1H), 4.27 (d, J = 5.9 Hz, 2H); HPLC purity 99.4% {t_R = 6.55 min, flow 1 ml/min, [(MeOH/(0.1% TFA in H_2O):40/60]}. HRMS (ESI +ve) *m/z* calculated for $C_{16}H_{14}N_4O_2S$ $(M + H)^+$ 327.0910, found 327.0919.

Table S2: HPLC purities of compounds **5-14**.

Compound	Method , purity (%)	Method , purity(%)	Comments
5a	A, 99.3	F, 99.3	From Method b
5e	A, 99.6	B, 97.4	
5r	B, 99.0	B, 99.4	
5u	A, 98.9	B, 99.0	
5q	A, 99.2	B, 99.1	From Method b
5q	A, 99.2	B, 98.5	
5s	A, 99.4	B, 98.5	
5b	A, 98.9	B, 97.9	
5d	A, 99.1	B, 97.7	
5e	C, 99.1	D, 99.1	
5f	A, 99.9	B, 98.5	
5g	E, 99.8	F, 99.8	
5h	E, 99.9	F, 99.8	
5i	E, 99.7	F, 99.5	
5j	A, 97.6	F, 97.7	
5k	E, 99.4	F, 99.0	
5l	E, 98.3	F, 98.0	
5m	F, 99.5		
5n	A, 99.4	B, 99.1	
5o	G, 99.9	H, 99.3	
5p	A, 99.8	B, 97.7	
5t	A, 98.6	B, 97.4	
5v	A, 99.5	B, 99.2	
5w		B, 97.7	
5x		B, 98.3	
5y		B, 98.4	
5z	A, 99.1	B, 97.6	
5aa		B, 99.4	
5ab	A, 99.5		
12		B, 97.8	
13	A, 98.5	B, 97.3	
(*R*)-14a	A, 99.2	B, 99.5	
(*S*)-14a	A, 99.7	B, 99.5	
(*R,S*)-14b	E, 99.9	F, 99.9	
(*S*)-14b	E, 99.8	F, 99.7	
(*R*)-14b	E, 99.8	F, 99.8	
(*R*)-14c		B, 99.2	
(*S*)-14c		B, 9.3	
(*S*)-14d	E, 99.9	G, 99.5	
(*R*)-14d	E, 99.6	G, 99.0	
(*R*)-14e	A, 99.3		
(S)-14e	A, 98.9		
(*R*)-14f	A, 99.9	B, 96.8	
(*S*)-14f	A, 99.9	B, 96.8	
(*R*)-14g	A, 98.6	B, 98.6	
(*S*)-14g	A, 98.4	B, 98.4	
(*R,S*)-14g	A, 96.4	B, 96.3	
(*R*)-14h	A, 99.6	B, 99.7	
(*S*)-14g	A, 99.4	B, 99.4	
(*R*)-14i	A, 98.6		
(*S*)-14i.	A, 99.4		
5b-Mes		B, 99.2	
5g-Mes	F, 99.1		
5d-Mes	B, 99.5		
5b-HCl	B, 99.1		
5g-HCl	F, 99.3		
5d-HCl	B, 99.6		

HPLC Methods

A: Flow 1 ml/min [(CH_3CN/(0.1% TFA in H_2O):30/70]

B; Flow 1 ml/min, [(MeOH/(0.1% TFA in H_2O):50/50]

C; Flow 1 ml/min, [(CH_3CN/(0.1% TFA in H_2O) 15/85]

D: Flow 1 ml/min, [(MeOH/(0.1% TFA in H_2O) 20/80]

E: Flow 1 ml/min, [(CH_3CN/(0.1% TFA in H_2O) 20/80]

F: Flow 1 ml/min, [(MeOH/(0.1% TFA in H_2O) 40/60]

G: Flow 1 ml/min, [(CH_3CN/(0.1% TFA in H_2O):40/60]

H: Flow 1 ml/min, [(MeOH/(0.1% TFA in H_2O):60/40]

References

1. M. P. Hay, S. Turcotte, J. U. Flanagan, M. Bonnet, D. A. Chan, P. D. Sutphin, P. Nguyen, A. J. Giaccia and W. A. Denny, *J. Med .Chem.*, 2009, **53**, 787-797.