Expedient parallel synthesis of 2-amino-4-heteroaryl pyrimidines

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Supporting Information.

General procedures.

All water-sensitive reactions were carried out under an atmosphere of nitrogen using oven dried glassware. All commercially available solvents and reagents were used without purification. NMR spectra were recorded on Bruker AM-400 (400 MHz). Chemical shifts were reported in ppm (δ units) downfield from DMSO-D₆ where solvent peaks were used as the internal standard. Crude and isolated final products were analyzed via Agilent 1100 LCMS system. Compounds were purified as noted via SiO₂ gel column chromatography or preparative HPLC was carried out on C-18 reverse-phase columns using a Gilson semi-prep HPLC system consisting of a 215 autosampler, 322 solvent pump, 307 make-up pump, and 155 UV/VIS detector with acetonitrile/water gradients containing 0.1% trifluoroacetic acid for elution.

Specific Procedures.

2-chloro-4-(1,3-thiazol-2-yl)pyrimidine (6a). To a $-45\text{ }^{\circ}\text{C}$ suspension of 2-bromothiazole (0.95 mL, 10.66 mmol, 1.08 eq) in 20 ml of Et₂O was added dropwise nBuLi (4.26 mL, 2.5 M in hexanes, 10.66 mmol, 1.08 eq). The resulting suspension was stirred for 30 min and allowed to warm to $-30\text{ }^{\circ}\text{C}$. A suspension of 2-chloropyrimidine (1.12 g, 9.84 mmol, 1 equiv.) in 25 ml Et₂O was added in 5 mL portions over 15 min. The resulting suspension was stirred for 30 min at $-30\text{ }^{\circ}\text{C}$ and allowed to warm to $0\text{ }^{\circ}\text{C}$ for 1 hr. The reaction was quenched with H₂O (0.27 mL, 1.5 equiv.) in THF (3 mL) and then DDQ (2.95 g, 10.66 mmol, 1.08 equiv.) in THF (15 mL) was added. The resulting suspension was stirred at 23

°C for 15 min, and then cooled to 0 °C. Hexanes (10 ml) was added followed by a 0 °C solution of NaOH (10 ml, 3N). The suspension was stirred for 5 min at 0 °C, 100 ml of H₂O was added and the layers were separated. The organic layer was dried (Na₂SO₄) and concentrated in vacuo to afford 1.76 g (91%) **6a**. ¹H NMR (400 MHz, DMSO-D₆) δ ppm 8.14 (d, *J*=5.2 Hz, 1 H) 8.16 (d, *J*=3.2 Hz, 1 H) 8.19 (d, *J*=3.2 Hz, 1 H) 8.92 (d, *J*=5.29 Hz, 1 H). HPLC: *R*_t = 1.63 min; MS (ESI) *m/z* 198.

2-chloro-4-(thiophen-2-yl)pyrimidine (6b). To a 0 °C mixture of thiophene (1.98 mL, 25 mmol, 2 eq) in 25 mL of Et₂O at was added dropwise nBuLi (5.2 mL, 2.5 M in hexanes, 13 mmol, 1.08 eq). The resulting mixture was stirred for 15 min and cooled to –30 °C. A suspension of 2-chloropyrimidine (1.4 g, 12 mmol, 1 equiv.) in 30 ml Et₂O was added in 5 mL portions over 15 min. The resulting suspension was stirred for 30 min at –30 °C and allowed to warm to 0 °C for 1 hr. The reaction was quenched with H₂O (0.27 ml, 1.5 equiv.) in THF (3 ml) and then DDQ (2.99 g, 13 mmol, 1.08 equiv.) in THF (15 ml) was added. The resulting suspension was stirred at 23 °C for 15 min, and then cooled to 0 °C. Hexanes (10 ml) was added followed by a 0 °C solution of NaOH (10 ml, 3N). The suspension was stirred for 5 min at 0 °C, 100 ml of H₂O was added and the layers were separated. The organic layer was dried (Na₂SO₄) and concentrated in vacuo. Purification via SiO₂ gel column chromatography afforded 2.17 g (90%) **6b**. ¹H NMR (400 MHz, DMSO-D₆) δ ppm 7.29 (dd, *J*=4.95, 1.08 Hz, 1 H) 7.95 (dd, *J*=5.04, 1.01 Hz, 1 H) 8.04 (d, *J*=5.29 Hz, 1 H) 8.16 (dd, *J*=3.90, 1.13 Hz, 1 H) 8.73 (d, *J*=5.54 Hz, 1 H). HPLC: *R*_t = 2.17 min; MS (ESI) *m/z* 197.

2-chloro-4-(pyridin-3-yl)pyrimidine (6c). To a –78 °C solution nBuLi (13.5 mL, 2.5 M in hexanes, 34 mmol, 1.08 eq) in 50 mL of Et₂O was added 3-bromo pyridine (3 mL, 31 mmol, 1 eq) over 10 min. The resulting mixture was stirred at –75 °C for 1 hr. A suspension of 2-chloropyrimidine (3.6 g, 31 mmol, 1 equiv.) in 30 ml Et₂O was added in 5 mL portions over 15 min. The resulting suspension was stirred for 30 min at –30 °C and allowed to warm to 0 °C for 1 hr. The reaction was quenched with H₂O (1 ml, 1.5 equiv.) in THF (10 ml) and then DDQ (7.6 g, 34 mmol, 1.08 equiv.) in THF (25 ml) was added. The resulting suspension was stirred at 23 °C for 15 min, and then cooled to 0 °C. Hexanes (25 ml) was added followed by a 0 °C solution of NaOH (25 ml, 3N). The suspension was stirred for 5 min at 0 °C, 100 ml of H₂O was added and the layers were separated. The organic layer was dried (Na₂SO₄) and concentrated in vacuo. Purification via SiO₂ gel column chromatography afforded 5.6 g (94%) **6c**. ¹H

NMR (400 MHz, DMSO-D₆) δ ppm 7.62 (dd, J =8.0, 4.8 Hz, 1 H) 8.27 (d, J =5.29 Hz, 1 H) 8.54 (dt, J =8.0, 2.0 Hz, 1 H) 8.79 (dd, J =4.78, 1.76 Hz, 1 H) 8.90 (d, J =5.29 Hz, 1 H) 9.35 (d, J =2.0 Hz, 1 H). HPLC: R_t = 1.50 min; MS (ESI) m/z 192.

Synthesis of 2-anilino-4-heteroaryl pyrimidines (7). To a vial containing the mixture of the desired 2-chloro-4-heteroaryl pyrimidines (0.25 mmol, 1 eq.) and the desired aniline (0.31 mmol, 1.25 eq.) was added a solution of TsOH-H₂O (0.20 mmol, 0.8 eq) in 2.5 mL dioxane. The mixture was heated to 100°C and allowed to stir overnight. The solution was allowed to cool to room temperature, analyzed via LC/MS and concentrated via speedvac. SiO₂ gel column chromatography or C-18 reverse-phase HPLC column on a Gilson HPLC using acetonitrile/water gradients containing 0.1% trifluoroacetic acid for elution afforded the desired product.

N-phenyl-4-(1,3-thiazol-2-yl)pyrimidin-2-amine (7a). To a vial containing the mixture of **6a** (50 mg, 0.25 mmol, 1 eq.) and aniline (29 mg, 0.31 mmol, 1.25 eq.) was added a solution of TsOH-H₂O (38 mg, 0.20 mmol, 0.8 eq) in 2.5 mL dioxane. The mixture was heated to 100°C and allowed to stir overnight. The solution was allowed to cool to room temperature, analyzed via LC/MS and concentrated via speedvac. SiO₂ gel column chromatography afforded 87 mg (68%) **7a**. ¹H NMR (400 MHz, DMSO-D₆) δ ppm 6.98-7.02 (m, 1 H) 7.33 (t, J = 8.4 Hz, 2 H) 7.47 (d, J =5.0 Hz, 1 H) 7.84 (d, J =8.4 Hz, 2 H) 8.03 (d, J =3.2 Hz, 1 H) 8.10 (d, J =3.2 Hz, 1 H) 8.65 (d, J =5.0 Hz, 1 H) 9.86 (m, 1 H); ¹³C NMR (101 MHz, DMSO-D₆) δ ppm 106.11, 118.57 (2 C), 121.18, 128.15, 128.32 (2 C), 128.59, 130.49, 140.41, 142.54, 158.62, 159.79; HPLC: R_t = 2.67 min; MS [M+H] (m/z) 255; MS (ESI) m/z 255.1.

N-(4-methoxyphenyl)-4-(1,3-thiazol-2-yl)pyrimidin-2-amine (7b). To a vial containing the mixture of **6a** (50 mg, 0.25 mmol, 1 eq.) and 4-methoxyaniline (38 mg, 0.31 mmol, 1.25 eq.) was added a solution of TsOH-H₂O (38 mg, 0.20 mmol, 0.8 eq) in 2.5 mL dioxane. The mixture was heated to 100°C and allowed to stir overnight. The solution was allowed to cool to room temperature, analyzed via LC/MS and concentrated via speedvac. SiO₂ gel column chromatography afforded 87 mg (61%) **7b**. ¹H NMR (400 MHz, DMSO-D₆) δ ppm 3.75 (s, 3 H) 6.92 (d, J =9.06 Hz, 2 H) 7.40 (d, J =4.78 Hz, 1 H) 7.70 (d, J =9.06 Hz, 2 H) 8.01 (d, J =3.02 Hz, 1 H) 8.09 (d, J =3.02 Hz, 1 H) 8.60 (d, J =4.78 Hz, 1 H) 9.68 (s, 1 H); ¹³C NMR (101 MHz, DMSO-D₆) δ ppm 55.55, 106.08, 114.11 (2 C), 121.16 (2 C), 124.54,

133.61, 145.23, 154.83, 160.29, 160.36, 167.30; HPLC: R_t = 2.60 min; MS [M+H] (m/z) 285; MS (ESI) m/z 285.2.

N-(4-chlorophenyl)-4-(1,3-thiazol-2-yl)pyrimidin-2-amine (7c). To a vial containing the mixture of **6a** (50 mg, 0.25 mmol, 1 eq.) and 4-chloroaniline (30 mg, 0.31 mmol, 1.25 eq.) was added a solution of TsOH-H₂O (38 ms, 0.20 mmol, 0.8 eq) in 2.5 mL dioxane. The mixture was heated to 100°C and allowed to stir overnight. The solution was allowed to cool to room temperature, analyzed via LC/MS and concentrated via speedvac. SiO₂ gel column chromatography afforded 108 mg (75%) **7c**. ¹H NMR (400 MHz, DMSO-D₆) δ ppm 7.36 - 7.40 (m, 2 H) 7.50 (d, J =4.78 Hz, 1 H) 7.84 - 7.88 (m, 2 H) 8.04 (d, J =3.02 Hz, 1 H) 8.11 (d, J =3.27 Hz, 1 H) 8.67 (d, J =5.04 Hz, 1 H) 10.02 (s, 1 H); ¹³C NMR (101 MHz, DMSO-D₆) δ ppm 106.59, 120.39 (2 C), 124.30, 125.16, 128.29 (2 C), 139.10, 144.91, 157.24, 159.57, 159.94, 166.50; HPLC: R_t = 2.98 min; MS [M+H] (m/z) 289, 291; MS (ESI) m/z 289.

Characterization of 2-anilino-4-heteroaryl pyrimidines 7a-7z^{a,b}

Compound	X-substituent	Y-substituent	HPLC (Min), MS (M+H)
7a	thiazole	phenyl	2.67, 255
7b	thiazole	p-methoxyphenyl	2.60, 285
7c	thiazole	p-chlorophenyl	2.98, 289, 291
7d	thiazole	p-nitrophenyl	2.77, 300
7e	thiazole	o-methylphenyl	2.71, 269
7f	thiazole	m-trifluoromethylphenyl	3.06, 323
7g	thiazole	p-sulfonamidephenyl	2.08, 334
7h	thiazole	p-N-acetylphenyl	2.14, 312
7i	thiazole	p-morpholinophenyl	2.29, 340
7j	thiophene	phenyl	2.87, 254
7k	thiophene	p-methoxyphenyl	2.73, 284
7l	thiophene	p-chlorophenyl	3.19, 288, 290
7m	thiophene	p-nitrophenyl	3.05, 299
7n	thiophene	o-methylphenyl	2.82, 268
7o	thiophene	m-trifluoromethylphenyl	3.25, 322
7p	thiophene	p-sulfonamidephenyl	2.34, 333
7q	thiophene	p-N-acetylphenyl	2.29, 311
7r	thiophene	p-morpholinophenyl	2.46, 339
7s	3-pyridyl	phenyl	2.04, 249
7t	3-pyridyl	p-methoxyphenyl	2.02, 279
7u	3-pyridyl	p-chlorophenyl	2.48, 283, 285
7v	3-pyridyl	p-nitrophenyl	2.29, 294
7w	3-pyridyl	o-methylphenyl	2.08, 263
7x	3-pyridyl	m-trifluoromethylphenyl	2.69, 317
7y	3-pyridyl	p-N-acetylphenyl	1.65, 306

7z	3-pyridyl	p-morpholinophenyl	1.89, 334
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^a **HPLC Conditions:** Instrument - Agilent 1100; Column: Xterra C18 MS, 30 mm x 2.1 mm, 3.5 μ ; Mobile Phase A: 0.1% formic acid in water; Mobile Phase B: 0.1% formic acid in acetonitrile; Flow Rate: 1 ml/min; Column Temperature: 50°C; Injection Volume: 5 μ l; UV: monitor 220, 254.

Gradient Table:

<u>Time(min)</u>	<u>%B</u>
0.0	5
3.5	90
5	90

^b **MS Conditions:** Instrument: Agilent MSD; Ionization Mode: API-ES; Gas Temperature: 350 C; Drying Gas: 12.0 L/min.; Nebulizer Pressure: 60psig; Polarity: 50% positive, 50% negative; VCap: 4500V (positive), 4500V (negative); Fragmentor: 140 (positive), 170 (negative); Mass Range: 110 – 1000m/z; Threshold: 150; Step size: 0.15; Gain: 1; Peak width: 0.15min.

***N*-(4-nitrophenyl)-4-(1,3-thiazol-2-yl)pyrimidin-2-amine (7d).** ¹H NMR (400 MHz, DMSO-D₆) δ ppm 7.64 (d, *J*=5.04 Hz, 1 H) 8.08 (d, *J*=2.01 Hz, 1 H) 8.09 - 8.11 (m, 2 H) 8.14 (d, *J*=3.02 Hz, 1 H) 8.23 - 8.27 (m, 2 H) 8.78 (d, *J*=5.04 Hz, 1 H) 10.67 (s, 1 H); MS (ESI) *m/z* 298.1

***N*-(2-methylphenyl)-4-(1,3-thiazol-2-yl)pyrimidin-2-amine (7e).** ¹H NMR (400 MHz, DMSO-D₆) δ ppm 2.25 (s, 3 H) 7.09 (t, *J*=7.30 Hz, 1 H) 7.20 (t, *J*=7.18 Hz, 1 H) 7.24 (d, *J*=7.55 Hz, 1 H) 7.38 (d, *J*=5.04 Hz, 1 H) 7.50 (d, *J*=7.81 Hz, 1 H) 7.96 (d, *J*=3.02 Hz, 1 H) 8.06 (d, *J*=3.02 Hz, 1 H) 8.53 (d, *J*=5.04 Hz, 1 H) 9.08 (s, 1 H); MS (ESI) *m/z* 269.2.

4-(1,3-thiazol-2-yl)-*N*-[3-(trifluoromethyl)phenyl]pyrimidin-2-amine (7f). ¹H NMR (400 MHz, DMSO-D₆) δ ppm 7.33 (d, *J*=7.6 Hz, 1 H) 7.56 (m, 2 H) 7.94 (d, *J*=8.0 Hz, 1 H) 8.10 (dd, *J*=3.2, 16 Hz, 2 H) 8.50 (s, 1 H) 8.72 (d, *J*=4.8 Hz, 1 H) 10.26 (s, 1 H); MS (ESI) *m/z* 323.1.

4-[[4-(1,3-thiazol-2-yl)pyrimidin-2-yl]amino]benzenesulfonamide (7g). ¹H NMR (400 MHz, DMSO-D₆) δ ppm 7.21 (s, 2 H) 7.56 (d, *J*=5.2 Hz, 1 H) 7.78 (d, *J*=8.8 Hz, 2 H) 7.99 (d, *J*=8.8 Hz, 2 H) 8.06 (d, *J*=2.8 Hz, 1 H) 8.12 (d, *J*=2.8 Hz, 1 H) 8.72 (d, *J*=5.2 Hz, 1 H) 10.28 (s, 1 H); MS (ESI) *m/z* 332.1.

N-(4-[[4-(1,3-thiazol-2-yl)pyrimidin-2-yl]amino}phenyl)acetamide (7h). ¹H NMR (400 MHz, DMSO-D₆) δ ppm 2.03 (s, 3 H) 7.42 (d, *J*=5.2 Hz, 1 H) 7.52 (d, *J*=9.2 Hz, 2 H) 7.71 (d, *J*=8.8 Hz, 2 H) 8.01 (d, *J*=3.2 Hz, 1 H) 8.09 (d, *J*=3.2 Hz, 1 H) 8.62 (d, *J*=5.2 Hz, 1 H) 9.77 (s, 1 H) 9.84 (s, 1 H); MS (ESI) *m/z* 312.2.

N-(4-morpholin-4-ylphenyl)-4-(1,3-thiazol-2-yl)pyrimidin-2-amine (7i). ¹H NMR (400 MHz, DMSO-D₆) δ ppm 3.1 (m, 4 H) 3.77 (m, 4 H) 7.00 (d, *J*=8.81 Hz, 2 H) 7.40 (d, *J*=5.04 Hz, 1 H) 7.69 (d, *J*=9.06 Hz, 2 H) 8.02 (d, *J*=3.02 Hz, 1 H) 8.09 (d, *J*=3.02 Hz, 1 H) 8.59 (d, *J*=5.04 Hz, 1 H) 9.68 (s, 1 H); MS (ESI) *m/z* 340.2.

N-phenyl-4-(2-thienyl)pyrimidin-2-amine (7j). ¹H NMR (400 MHz, DMSO-D₆) δ ppm 6.96 (t, *J*=7.30 Hz, 1 H) 7.24 (dd, *J*=4.91, 3.65 Hz, 1 H) 7.31 (dd, *J*=8.56, 7.30 Hz, 2 H) 7.34 (d, *J*=5.29 Hz, 1 H) 7.81 (dd, *J*=5.04, 1.26 Hz, 1 H) 7.84 (d, *J*=7.55 Hz, 2 H) 8.00 (dd, *J*=3.78, 1.26 Hz, 1 H) 8.49 (d, *J*=5.29 Hz, 1 H) 9.64 (s, 1 H); ¹³C NMR (101 MHz, DMSO-D₆) δ ppm 106.18, 118.74 (2 C) 121.28, 128.20, 128.37 (2 C) 128.63, 130.52, 140.42, 142.48, 158.58, 158.64, 159.75; MS (ESI) *m/z* 254.1.

N-(4-methoxyphenyl)-4-(2-thienyl)pyrimidin-2-amine (7k). ¹H NMR (400 MHz, DMSO-D₆) δ ppm 3.74 (s, 3 H) 6.90 (d, *J*=9.2, 2 H) 7.23 (dd, *J*=5.04, 3.78 Hz, 1 H) 7.27 (d, *J*=5.29 Hz, 1 H) 7.72 (d, *J*=9.06 Hz, 2 H) 7.80 (dd, *J*=4.91, 1.13 Hz, 1 H) 7.97 (dd, *J*=3.65, 1.13 Hz, 1 H) 8.43 (d, *J*=5.29 Hz, 1 H) 9.46 (s, 1 H); ¹³C NMR (101 MHz, DMSO-D₆) δ ppm 55.54, 106.07, 114.05 (2 C), 120.86 (2 C), 128.48, 129.02, 130.80, 134.01, 143.06, 154.53, 159.04, 160.28; MS (ESI) *m/z* 284.1.

N-(4-chlorophenyl)-4-(2-thienyl)pyrimidin-2-amine (7l). ¹H NMR (400 MHz, DMSO-D₆) δ ppm 7.25 (dd, *J*=5.04, 3.78 Hz, 1 H) 7.33 - 7.37 (m, 3 H) 7.82 (dd, *J*=5.04, 1.01 Hz, 1 H) 7.85 - 7.89 (m, 2 H) 8.01 (dd, *J*=3.78, 1.01 Hz, 1 H) 8.50 (d, *J*=5.04 Hz, 1 H) 9.81 (s, 1 H); ¹³C NMR (101 MHz, DMSO-D₆) δ ppm 106.57, 120.15 (2 C), 124.73, 128.21 (2 C), 128.38, 128.69, 130.63, 139.43, 142.28, 158.67, 158.71, 159.51; MS (ESI) *m/z* 288.1.

N-(4-nitrophenyl)-4-(2-thienyl)pyrimidin-2-amine (7m). ¹H NMR (400 MHz, DMSO-D₆) δ ppm 7.27 (dd, *J*=4.91, 3.90 Hz, 1 H) 7.53 (d, *J*=5.29 Hz, 1 H) 7.87 (dd, *J*=4.78, 4.0 Hz, 1 H) 8.07 (s, 1 H)

8.10 (d, $J=9.57$ Hz, 2 H) 8.23 (d, $J=9.32$ Hz, 2 H) 8.61 (d, $J=5.29$ Hz, 1 H) 10.48 (s, 1 H); MS (ESI) m/z 299.1.

***N*-(2-methylphenyl)-4-(2-thienyl)pyrimidin-2-amine (7n).** ^1H NMR (400 MHz, DMSO- D_6) δ ppm 2.25 (s, 3 H) 7.06 (td, $J=7.43, 1.26$ Hz, 1 H) 7.16 - 7.24 (m, 3 H) 7.25 (d, $J=5.29$ Hz, 1 H) 7.53 (d, $J=7.30$ Hz, 1 H) 7.76 (dd, $J=4.91, 1.13$ Hz, 1 H) 7.94 (dd, $J=3.78, 1.01$ Hz, 1 H) 8.36 (d, $J=5.29$ Hz, 1 H) 8.82 (s, 1 H); MS (ESI) m/z 268.2.

4-(2-thienyl)-*N*-[3-(trifluoromethyl)phenyl]pyrimidin-2-amine (7o). ^1H NMR (400 MHz, DMSO- D_6) δ ppm 7.26 (m, 2 H) 7.44 (d, $J=6.0$ Hz, 1 H) 7.53 (t, $J=7.2$ Hz, 1 H) 7.86 (d, $J=4.8$ Hz, 1 H) 7.93 (d, $J=8.4$ Hz, 1 H) 8.04 (d, $J=4.0$ Hz, 1 H) 8.52 (s, 1 H) 8.55 (d, $J=5.2$ Hz, 1 H) 10.06 (s, 1 H); MS (ESI) m/z 322.1.

4-[(4-thien-2-yl)pyrimidin-2-yl]amino]benzenesulfonamide (7 p). ^1H NMR (400 MHz, DMSO- D_6) δ ppm 7.18 (s, 2 H) 7.26 (dd, $J=5.2, 4.0$ Hz, 1 H) 7.44 (d, $J=4.8$ Hz, 1 H) 7.75 (m, 2 H) 7.84 (dd, $J=4.8, 0.8$ Hz, 1 H) 7.99 (m, 2 H) 8.04 (dd, $J=3.6, 0.8$ Hz, 1 H) 8.56 (d, $J=5.2$ Hz, 1 H) 10.08 (s, 1 H); MS (ESI) m/z 331.1.

***N*-(4-[[4-(2-thienyl)pyrimidin-2-yl]amino]phenyl)acetamide (7q).** ^1H NMR (400 MHz, DMSO- D_6) δ ppm 2.02 (s, 3 H) 7.24 (dd, $J=5.04, 3.78$ Hz, 1 H) 7.30 (d, $J=5.29$ Hz, 1 H) 7.50 (d, $J=9.06$ Hz, 2 H) 7.72 (d, $J=9.06$ Hz, 2 H) 7.80 (dd, $J=5.04, 1.01$ Hz, 1 H) 7.99 (dd, $J=3.78, 1.01$ Hz, 1 H) 8.45 (d, $J=5.04$ Hz, 1 H) 9.57 (s, 1 H) 9.82 (s, 1 H); MS (ESI) m/z 311.2.

***N*-(4-morpholin-4-ylphenyl)-4-(2-thienyl)pyrimidin-2-amine (7r).** ^1H NMR (400 MHz, DMSO- D_6) δ ppm 3.05 (m, 4 H) 3.75 (m, 4 H) 6.93 (d, $J=9.06$ Hz, 2 H) 7.23 (dd, $J=5.04, 3.78$ Hz, 1 H) 7.26 (d, $J=5.29$ Hz, 1 H) 7.68 (d, $J=9.06$ Hz, 2 H) 7.79 (dd, $J=4.91, 1.13$ Hz, 1 H) 7.97 (dd, $J=3.78, 1.01$ Hz, 1 H) 8.42 (d, $J=5.29$ Hz, 1 H) 9.42 (s, 1 H); MS (ESI) m/z 339.2.

***N*-(4-methoxyphenyl)-4-pyridin-3-ylpyrimidin-2-amine (7s).** ^1H NMR (400 MHz, DMSO- D_6) δ ppm 6.98 (t, $J=7.6$ Hz, 1 H) 7.33 (dd, $J=7.2, 0.8$ Hz, 2 H) 7.50 (d, $J=5.2$ Hz, 1 H) 7.59 (ddd, $J=7.6, 4.4, 0.4$

Hz, 1 H) 7.82 (dd, $J=8.8$, 1.2 Hz, 2 H) 8.50 (m, 1 H) 8.61 (d, $J=5.2$ Hz, 1 H) 8.73 (dd, $J=4.8$, 1.6 Hz, 1 H) 9.34 (s, 1 H) 9.75 (s, 1 H); MS (ESI) m/z 249.1.

N-(4-methoxyphenyl)-4-pyridin-3-ylpyrimidin-2-amine (7t). ^1H NMR (400 MHz, DMSO- D_6) δ ppm 3.75 (s, 3 H) 6.93 (m, 2 H) 7.43 (d, $J=5.2$ Hz, 1 H) 7.58 (ddd, $J=8.4$, 4.8, 0.8 Hz, 1 H) 7.70 (m, 2 H) 8.48 (m, 1 H) 8.55 (d, $J=4.8$ Hz, 1 H) 8.73 (dd, $J=4.8$, 1.6 Hz, 1 H) 9.33 (d, $J=1.6$ Hz, 1 H) 9.57 (s, 1 H); MS (ESI) m/z 279.1.

N-(4-chlorophenyl)-4-pyridin-3-ylpyrimidin-2-amine (7u). ^1H NMR (400 MHz, DMSO- D_6) δ ppm 7.38 (m, 2 H) 7.54 (d, $J=5.2$ Hz, 1 H) 7.59 (ddd, $J=8.4$, 4.8, 0.8 Hz, 1 H) 7.86 (m, 2 H) 8.50 (ddd, $J=8.31$, 2.01, 1.76 Hz, 1 H) 8.63 (d, $J=5.29$ Hz, 1 H) 8.74 (dd, $J=4.78$, 1.51 Hz, 1 H) 9.34 (d, $J=1.51$ Hz, 1 H) 9.92 (s, 1 H); MS (ESI) m/z 283.

N-(4-nitrophenyl)-4-pyridin-3-ylpyrimidin-2-amine (7v). ^1H NMR (400 MHz, DMSO- D_6) δ ppm 7.62 (dd, $J=8.0$, 4.8, 0.8 Hz, 1 H) 7.70 (d, $J=5.3$ Hz, 1 H) 8.08-8.12 (m, 2 H) 8.24-8.27 (m, 2 H) 8.54-8.57 (m, 1 H) 8.74 (d, $J=5.2$ Hz, 1 H) 8.77 (dd, $J=4.8$, 1.8 Hz, 1 H) 9.39 (d, $J=1.8$ Hz, 1 H) 10.59 (s, 1 H); MS (ESI) m/z 294.1.

N-(2-methylphenyl)-4-pyridin-3-ylpyrimidin-2-amine (7w). ^1H NMR (400 MHz, DMSO- D_6) δ ppm 2.26 (s, 3 H) 7.19-7.26 (m, 2 H) 7.41 (d, $J=5.2$ Hz, 1 H) 7.52-7.57 (m, 2 H) 8.38-8.42 (m, 1 H) 8.50 (d, $J=5.0$ Hz, 1 H) 8.70 (dd, $J=4.8$, 1.8 Hz, 1 H) 8.94 (s, 1 H) 9.25 (dd, $J=2.3$, 0.7 Hz, 1 H); MS (ESI) m/z 263.1.

4-pyridin-3-yl-N-[3-(trifluoromethyl)phenyl]pyrimidin-2-amine (7x). ^1H NMR (400 MHz, DMSO- D_6) δ ppm 7.32 (d, $J=7.8$ Hz, 1 H) 7.57 (t, $J=8.0$ Hz, 1 H) 7.63 (d, $J=5.2$ Hz, 1 H) 7.70 (dd, $J=8.0$, 5.0 Hz, 1 H) 8.02 (d, $J=8.7$ Hz, 1 H) 8.43 (s, 1 H) 8.62 (m, 1 H) 8.71 (d, $J=5.0$ Hz, 1 H) 8.81 (dd, $J=5.0$, 1.4 Hz, 1 H) 9.40 (d, $J=1.8$ Hz, 1 H) 10.18 (s, 1 H); MS (ESI) m/z 317.2.

N-(4-morpholin-4-ylphenyl)-4-pyridin-3-ylpyrimidin-2-amine (7z). ^1H NMR (400 MHz, DMSO- D_6) δ ppm 3.14-3.17 (m, 4 H) 3.78-3.80 (m, 4 H) 7.07 (d, $J=8.9$ Hz, 2 H) 7.48 (d, $J=4.8$ Hz, 1 H) 7.70-7.75 (m, 3 H) 8.59 (d, $J=5.1$ Hz, 1 H) 8.64-8.67 (m, 1 H) 8.81 (dd, $J=4.8$, 1.4 Hz, 1 H) 9.37 (d, $J=2.2$ Hz, 1 H) 9.67 (s, 1 H); MS (ESI) m/z 334.3.

Synthesis of 2-amino acid-4-heteroaryl pyrimidines (8). To a vial containing a solution of the desired 2-chloro-4-heteroaryl pyrimidines (0.25 mmol, 1 eq.) and the desired amino acid (0.38 mmol, 1.5 eq.) in 2.5 ml DMSO was added NaH (1 mmol, 4 eq). The mixture was heated to 90°C and allowed to stir overnight. The solution was allowed to cool to room temperature, analyzed via LC/MS, 500 uL water added and concentrated via speedvac. C-18 reverse-phase HPLC column on a Gilson HPLC using acetonitrile/water gradients containing 0.1% trifluoroacetic acid for elution afforded the desired product.

Characterization of 2-amino acid-4-heteroaryl pyrimidines 8a-8d^{a,b}

Compound	X-substituent	Y-substituent	HPLC (Min), MS (M+H)
8a	thiazole	leucine	2.40, 293
8b	thiazole	serine	1.27, 267
8c	3-pyridyl	leucine	1.94, 287
8d	3-pyridyl	serine	0.25, 261

^a HPLC Conditions: Instrument - Agilent 1100; Column: Xterra C18 MS, 30 mm x 2.1 mm, 3.5 µ; Mobile Phase A: 0.1% formic acid in water; Mobile Phase B: 0.1% formic acid in acetonitrile; Flow Rate: 1 ml/min; Column Temperature: 50°C; Injection Volume: 5 ul; UV: monitor 220, 254.

Gradient Table:

<u>Time(min)</u>	<u>%B</u>
0.0	5
3.5	90
5	90

^b MS Conditions: Instrument: Agilent MSD; Ionization Mode: API-ES; Gas Temperature: 350 C; Drying Gas: 12.0 L/min.; Nebulizer Pressure: 60psig; Polarity: 50% positive, 50% negative; VCap: 4500V (positive), 4500V (negative); Fragmentor: 140 (positive), 170 (negative); Mass Range: 110 – 1000m/z; Threshold: 150; Step size: 0.15; Gain: 1; Peak width: 0.15min.

2-leucine-4-(1,3-thiazol-2-yl)pyrimidine (8a). ¹H NMR (400 MHz, DMSO-D₆) δ ppm 0.89 (s, 3 H) 0.94 (d, *J*=6.30 Hz, 3 H) 1.58 (s, 1 H) 1.73 - 1.83 (m, 2 H) 4.40 (s, 1 H) 7.27 (s, 1 H) 7.67 (s, 1 H) 7.97 (s, 1 H) 8.05 (s, 1 H) 8.46 (s, 1 H). MS [M+H] (ESI) 293.2.

2-serine-4-(1,3-thiazol-2-yl)pyrimidine (8b). ¹H NMR (400 MHz, DMSO-D₆) δ ppm 0.89 (d, *J*=6.04 Hz, 3 H) 0.94 (d, *J*=6.30 Hz, 3 H) 1.59 (d, *J*=5.29 Hz, 1 H) 1.74 - 1.83 (m, 2 H) 4.40 (s, 2 H) 7.33 (s, 1 H) 7.52-7.72 (m, 2 H) 8.45 (s, 1 H) 8.579 (dt, *J*=8 Hz, 1.8 Hz, 1 H) 8.76 (d, *J*=3.78 Hz, 1 H) 9.32 (d, *J*=1.76 Hz, 1 H). MS [M+H]⁺ (ESI) 267.1.

2-leucine-4-(pyridin-3-yl)pyrimidine (8c). ¹H NMR (400 MHz, DMSO-D₆) δ ppm 3.40 (s, 1 H) 3.88 (d, *J*=7.55 Hz, 2 H) 6.59 (d, *J*=4.28 Hz, 1 H) 7.22 (d, *J*=5.04 Hz, 1 H) 7.96 (d, *J*=3.02 Hz, 1 H) 8.04 (d, *J*=3.02 Hz, 1 H) 8.45 (d, *J*=5.04 Hz, 1 H). MS [M+H]⁺ (ESI) 287.2.

2-serine-4-(pyridin-3-yl)pyrimidine (8d). ¹H NMR (400 MHz, DMSO-D₆) δ ppm 3.40 (s, 1 H) 3.54 (m, 2 H) 6.693 (d, *J*=5.5 Hz, 1 H) 7.27 (d, *J*=5 Hz, 1 H) 7.544 (ddd, *J*=8.0 Hz, 5.0 Hz, 0.5 Hz, 1 H) 8.41 (d, *J*=5 Hz, 1 H) 8.44 (dt, *J*=8.0 Hz, 1.8 Hz, 1 H) 8.694 (dd, *J*=5.0 Hz, 1.8 Hz, 1 H) 9.268 (d, *J*=1.8 Hz, 1 H). MS [M-H]⁻ (ESI) 258.9.

2-glycine-4-(2-thienyl)pyrimidine (9). To Fmoc-glycine Wang resin (0.17 g, 0.75 mmol/g, 0.13 mmol, 1 eq.) was added a 10 mL of 25% solution of piperidine in DMF. The mixture was agitated for 30 min, filtered and washed with DMF (2x5ml), MeOH (2x5ml), and then DCM (2x5ml). To the resin was added NaH (13 mg, 0.32 mmol, 2.5 eq), 2-chloro-4-(1,3-thiazol-2-yl)pyrimidine (**6a**) (25 mg, 0.32 mmol, 2.5 eq) and 3 ml DMSO. The mixture was agitated and heated to 100 °C for 12 hr. The resin was allowed to cool, filtered and washed with DMSO (2x5ml), DMF (2x5ml), MeOH (2x5ml), and then DCM (2x5ml). To the resin was added 10 mL of a 20% solution of TFA in DCM. The mixture was agitated for 45 min, filtered and washed with DCM (2x5ml), MeOH (2x5ml), and then DCM (2x5ml). Concentration of the solution followed by preparative HPLC was carried out on C-18 reverse-phase columns using a Gilson semi-prep HPLC system yielded 20 mg (45%) **9**. ¹H NMR (400 MHz, DMSO-D₆) δ ppm 3.98 (s, 2 H) 7.18-7.23 (m, 2 H) 7.80 (d, *J*=4.9 Hz, 1 H) 7.97 (d, *J*=3.4 Hz, 1 H) 8.33 (d, *J*=5.2 Hz, 1 H); HPLC: *R*_t = 1.31 min; MS [M+H]⁺ (*m/z*) 236; MS (ESI) *m/z* 236.1.