

Supporting Information

Synthesis of Pyridopyrimidines by Palladium-Catalyzed Isocyanide Insertion

Verónica Estévez,^{†,§} Gitte Van Baelen,^{†,§,⊥} Babette H. Lentferink,[†] Tjøstil Vlaar,[†] Elwin Janssen,[†] Bert U. W. Maes,^{*,‡} Romano V. A. Orru^{*,†} and Eelco Ruijter^{*,†}

[†] Department of Chemistry & Pharmaceutical Sciences and Amsterdam Institute for Molecules, Medicines & Systems, VU University Amsterdam, De Boelelaan 1083, 1081 HV Amsterdam, the Netherlands

[‡] Organic Synthesis, Department of Chemistry, University of Antwerp, Groenenborgerlaan 171, B-2020, Antwerp, Belgium

* E-Mail: bert.maes@ua.ac.be; r.v.a.orr@vu.nl; e.ruijter@vu.nl

Contents

General information	S2
Experimental procedures and characterization data	S2
Synthesis of amidines 4a-f and 5a-b	S2
Synthesis of pyrido[3,2- <i>d</i>] pyrimidines 1a-i	S3
Synthesis of pyrido[2,3- <i>d</i>]pyrimidines 2a-d	S5
Synthesis of (<i>E</i>)- <i>N</i> -(<i>tert</i> -butyl)-2-phenyl-4 <i>H</i> -pyrido[1,2- <i>a</i>][1,3,5]triazin-4-imine (8)	S6

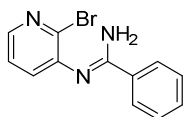
General information

All melting points were determined on a Stuart Scientific Melting Point Apparatus SMP3 with a heating rate of 1 °C/min. ¹H and ¹³C NMR spectra were recorded (at 400.13 or 500.23 MHz and 100.62 or 125.78 MHz, respectively) on a Bruker Avance 400 or 500 spectrometer in the solvent indicated and with the residual solvent resonance peak used as internal reference (CHCl₃, 1H: δ = 7.26 ppm; ¹³C{¹H}: δ = 77.0). All coupling constants are given in Hz and chemical shifts are reported in parts per million (ppm). The assignment of the ¹H NMR signals is based on 2D NMR techniques (COSY, NOESY, HSQC, HMBC). Infrared (IR) spectra were measured with ATR on a Shimadzu FTIR-8400S and wavenumbers (ν) are reported in cm⁻¹. Electrospray Ionization (ESI) mass spectrometry was carried out using a Bruker micrOTOF-Q instrument in positive ion mode (capillary potential of 4500 V). Flash column chromatography was performed on Silicycle silica gel (40-63 μm, 60 Å) using the indicated solvent. Thin Layer Chromatography was performed using silica plates (silica on aluminum with fluorescence indicator). Compounds on TLC were visualized by UV detection.

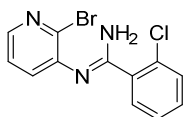
Experimental procedures and characterization data

Synthesis of amidines 4 and 5: *Method A:* A solution of **3a** (1.1 equiv.) and the appropriate nitrile (1.0 equiv.) in dry DMF was added at 0 °C to a suspension of NaH (1.5 equiv., washed with 30 mL pentane) in dry DMF. The mixture was stirred for 5 min at 0 °C and then overnight at room temperature. The reaction was quenched with ice-water. If a precipitate appeared, it was filtered and then dissolved in ethyl acetate. If there was not precipitate, the mixture was extracted with dichloromethane. In both cases, the organic phase was dried over anhydrous sodium sulphate. Removal of the solvent under reduced pressure and purification of the residue by column chromatography on silica gel, eluting with the corresponding mixture of CH₂Cl₂:EtOAc, afforded to the desired product **4**.

Method B: **3a** or **3b** (1.1 equiv.) was added at 0°C to a suspension of NaH (1.5 equiv., washed with pentane) in dry DMF and stirred at 0°C for 10 min, before the addition of a solution of the appropriate nitrile (1.0 equiv.) in dry DMF. The resulting mixture was stirred overnight at rt. The reaction was quenched with ice-water. If a precipitate appeared, it was filtered and then dissolved in ethyl acetate. If there was not precipitate, the mixture was extracted with dichloromethane. In both cases, the organic phase was dried over anhydrous sodium sulphate. Removal of the solvent under reduced pressure and purification of the residue by column chromatography on silica gel, eluting with the corresponding mixture of CH₂Cl₂:EtOAc, afforded to the desired amidine **4** or **5**.



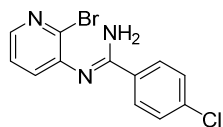
N-(2-Bromo-3-pyridyl)benzimidamide (4a). *Method A:* prepared from NaH (0.180 g, 4.50 mmol), 2-bromopyridin-3-amine **3a** (0.571 g, 3.30 mmol) and benzonitrile (0.411 g, 3.00 mmol); extracted with CH₂Cl₂; eluent: CH₂Cl₂:EtOAc, 98:2, 95:5, 9:1, 8:2; yield 549 mg (65%); yellow solid. mp: 74-77 °C; ¹H NMR (CDCl₃, 500 MHz): δ = 8.07 (s, 1H, H₆); 7.91 (s, 2H, H₂); 7.55-7.41 (m, 3H, H₃, H₄, H₅); 7.31 (s, 1H, H₄); 7.24 (s, 1H, H₅); 4.92 (br s, 2H, NH₂) ppm. ¹³C NMR (CDCl₃, 126 MHz): δ = 145.1, 144.2, 136.6, 134.8, 131.2, 130.7, 128.7, 128.4, 127.0, 123.5; IR: HRMS (ESI): *m/z* calcd for C₁₂H₁₁BrN₃ [M+H]⁺: 276.0131, found 276.0127.



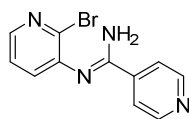
N-(2-Bromo-3-pyridyl)-2'-chlorobenzimidamide (4b). *Method A:* prepared from NaH (0.12 g, 3.00 mmol), 2-bromopyridin-3-amine **3a** (0.381 g, 2.20 mmol) and 2-chlorobenzonitrile (0.274 g, 2.00 mmol); eluent: CH₂Cl₂/EtOAc, 95:5, 9:1, 8:2; yield: 254 mg (41 %); orange solid. mp: 190-191 °C; ¹H NMR (CDCl₃, 500 MHz): δ = 8.11 (d, 1H, *J* = 3.2 Hz, H₆); 7.44 (d, 1H, *J* = 7.1 Hz, H₆); 7.41-7.35 (m, 3H, H₃, H₄, H₅); 7.32-7.31 (m, 1H, H₄); 7.28-7.27 (m, 1H, H₅); 5.00 (br s, 2H, NH₂) ppm; ¹³C NMR (CDCl₃, 126 MHz): δ = 155.1, 144.6, 144.3, 136.5, 134.8, 131.3, 131.2, 130.9, 130.7, 130.2, 127.3, 123.7 ppm; HRMS (ESI): *m/z* calcd for C₁₂H₁₀BrClN₃ [M+H]⁺: 309.9741, found 309.9730.



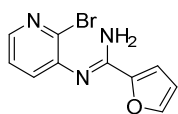
N-(2-Bromo-3-pyridyl)-3'-chlorobenzimidamide (4c). *Method A:* prepared from NaH (0.12 g, 3.00 mmol), 2-bromopyridin-3-amine **3a** (0.381 g, 2.20 mmol) and 3-chlorobenzonitrile (0.274 g, 2.00 mmol); extracted with CH₂Cl₂; eluent: CH₂Cl₂: EtOAc, 95:5, 9:1, 7:3; yield: 453 mg (73%); orange solid. mp: 126-128 °C; ¹H NMR (CDCl₃, 500 MHz): δ = 8.11 (d, 1H, *J* = 4.5 Hz, H₆); 7.92 (s, 1H, H₂); 7.79 (d, 1H, *J* = 8.7 Hz, H₆); 7.50 (d, 1H, *J* = 7.8 Hz, H₄); 7.42 (t, 1H, *J* = 7.8 Hz, H₅); 7.30 (d, 1H, *J* = 7.6 Hz, H₄); 7.27 (dd, 1H, *J* = 7.5, 4.6 Hz, H₅); 4.89 (br s, 2H, NH₂) ppm; ¹³C NMR (CDCl₃, 126 MHz) δ = 154.4, 144.8, 144.5, 136.6, 136.4, 134.8, 131.3, 130.6, 130.0, 127.4, 125.1, 123.6 ppm; HRMS (ESI): *m/z* calcd for C₁₂H₁₀BrClN₃ [M+H]⁺: 309.9741; found 309.9732.



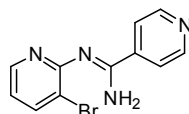
N-(2-Bromo-3-pyridyl)-4'-chlorobenzimidamide (4d). *Method A:* prepared from NaH (0.12 g, 3.00 mmol) 2-bromopyridin-3-amine (0.381 g, 2.20 mmol) and 4-chlorobenzonitrile (0.274 g, 2.00 mmol); yield: 347 mg (56%); light brown solid. mp: 160-161 °C; ¹H NMR (CDCl₃, 500 MHz): δ = 8.10 (s, 1H, H₆); 7.86 (d, 2H, *J* = 7.5 Hz, H₃); 7.45 (d, 2H, *J* = 7.8 Hz, H₂); 7.35 – 7.22 (m, 2H, H₄, H₅), 4.87 (br s, 2H, NH₂) ppm; ¹³C NMR (CDCl₃, 126 MHz) δ = 154.7, 144.8, 144.4, 137.4, 136.5, 133.3, 130.6, 128.9, 128.4, 123.6 ppm; HRMS (ESI): *m/z* calcd for C₁₂H₁₀BrClN₃ [M+H]⁺: 309.9741, found 309.9737.



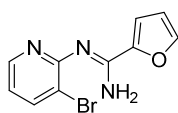
N-(2-Bromo-3-pyridyl)-isonicotinimidamide (4e). *Method A:* prepared from NaH (0.24 g, 6.00 mmol) 2-bromopyridin-3-amine (0.761 g, 4.40 mmol) and isonicotinonitrile (0.416 g, 4.00 mmol); eluent: CH₂Cl₂: EtOAc, 2:1, 1:1, EtOAc; yield: 1.00 g (90%); yellow solid. mp: 158-159 °C; ¹H NMR (CDCl₃, 500 MHz) δ = 8.76 (d, 2H, *J* = 5.9 Hz, H₃, H₅); 8.11 (dd, 1H, *J* = 4.3, 2.0 Hz, H₆); 7.79 (d, 2H, *J* = 5.9 Hz, H₂, H₆); 7.30 (dd, 1H, *J* = 7.7, 1.9 Hz, H₄); 7.28 (dd, 1H, *J* = 7.8, 2.8 Hz, H₅); 5.04 (br s, 2H, NH₂) ppm; ¹³C NMR (CDCl₃, 126 MHz) δ = 153.6, 150.5, 144.7, 144.4, 142.2, 136.2, 130.3, 123.6, 121.0 ppm; HRMS (ESI): *m/z* calcd for C₁₁H₁₀BrN₄ [M+H]⁺: 277.0083; found 277.0077.



N-(2-Bromo-3-pyridyl)-furan-2-carboximidamide (4f). *Method B:* prepared from NaH (0.30 g, 7.50 mmol), 2-bromopyridin-3-amine (0.952 g, 5.50 mmol) and furan-2-carbonitrile (0.44 mL, 5.00 mmol); yield: 1.08 g (81%); light orange solid. mp: 171-173 °C; ¹H NMR (CDCl₃, 500 MHz) δ = 8.08 (m, 1H, H₆); 7.51 (s, 1H, H₃); 7.31-7.17 (m, 3H, H₄, H₅, H₅); 6.56 (s, 1H, H₄); 5.04 (br s, 2H, NH₂) ppm; ¹³C NMR (CDCl₃, 126 MHz) δ = 148.1, 147.1, 144.3, 143.8, 136.9, 130.7, 123.4, 112.4 ppm; (ESI) *m/z* calcd for C₁₀H₉N₃O [M+H]⁺: 265.9924; found 265.9916.

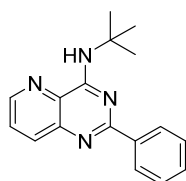


N-(3-Bromo-2-pyridyl)-isonicotinimidamide (5a). *Method B,* prepared from NaH (0.18 g, 4.50 mmol), 3-bromopyridin-2-amine (0.571 g, 3.30 mmol) and isonicotinonitrile (0.312 g, 3.00 mmol); yield: 0.598 g (72%); yellow solid. mp: 134-135 °C; ¹H NMR (CDCl₃, 500 MHz) δ = 8.75 (d, 2H, *J* = 6.1 Hz, H₃, H₅); 8.29 (dd, 1H, *J* = 4.8, 1.7 Hz, H₆); 7.96 (dd, 1H, *J* = 7.8, 1.7 Hz, H₄); 7.90 (d, 2H, *J* = 6.1 Hz, H₂, H₆); 6.86 (dd, 1H, *J* = 7.8, 4.8 Hz, H₅) ppm; ¹³C NMR (CDCl₃, 126 MHz) δ = 158.8, 156.3, 150.4, 145.0, 144.0, 141.4, 121.2, 119.3, 119.0 ppm; HRMS (ESI) *m/z* calcd for C₁₁H₁₀BrN₄ [M+H]⁺: 277.0083; found 277.0078.

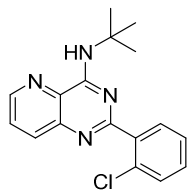


N-(3-Bromo-2-pyridyl)-furan-2-carboximidamide (5b). *Method B,* prepared from NaH (0.30 g, 7.50 mmol), 3-bromopyridin-2-amine (1.038 g, 6.00 mmol) and furan-2-carbonitrile (0.469 g, 5.00 mmol); eluent: CH₂Cl₂/EtOAc (95:5); yield: 0.997 g (75%); green oil. mp: 88-90°C; ¹H NMR (CDCl₃, 500 MHz) δ = 8.22 (dd, 1H, *J* = 4.5, 1.5 Hz, H₆); 7.90 (dd, 1H, *J* = 7.5, 1.5 Hz, H₄); 7.51 (s, 1H, H₃); 7.31 (d, 1H, *J* = 3.5 Hz, H₅); 6.76 (dd, 1H, *J* = 7.5, 4.5 Hz, H₅); 6.54 (dd, 1H, *J* = 3.5, 1.5 Hz, H₄) ppm; ¹³C NMR (CDCl₃, 126 MHz) δ = 159.5, 150.6, 149.9, 144.9, 144.0, 141.1, 118.2, 117.9, 113.0, 112.5 ppm; HRMS (ESI) *m/z* calcd for C₁₀H₉BrN₃O [M+H]⁺: 265.9850; found 265.9903.

Synthesis of pyrido[3,2-*d*] pyrimidines 1: A round-bottomed flask was charged with Pd(OAc)₂ (5 mol %) and Cy JohnPhos (10 mol %) followed by 5 mL of dry DMF. The mixture was flushed with N₂ for 10 min. In another round-bottomed flask, KOAc (3 equiv.), the appropriate amidine (1 equiv.) and isocyanide (1.5 equiv.) were weighed. To this mixture, the Pd catalyst solution was added and the flask was flushed with N₂. Then, the mixture was stirred and heated at 160 °C for 7 h. After cooling down to room temperature, the resulting mixture was filtered over a pad of Celite and rinsed with ethyl acetate. The solvent was removed under reduce pressure and the obtained residue was purified by flash column chromatography on silica gel using the appropriate mixture of solvents as the eluent.

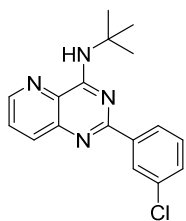


N-tert-Butyl-(2-phenyl)pyrido[3,2-*d*]pyrimidin-4-amine (1a). Prepared from Pd(OAc)₂ (0.011 g, 0.05 mmol), Cy JohnPhos (0.035 g, 0.10 mmol), N-(2-bromo-3-pyridyl)benzimidamide **4a** (0.276 g, 1 mmol), *tert*-butyl isocyanide (0.125 g, 1.5 mmol); eluent: CH₂Cl₂ (100%), then CH₂Cl₂/ EtOAc (95:5); yield 0.201 g (72%); yellow solid. mp: 93- 95 °C; ¹H NMR (CDCl₃, 500 MHz): δ = 8.61 (dd, 1H, *J* = 4.0, 1.5 Hz, H₆); 8.55 (dd, 2H, *J* = 8.5, 2.0 Hz, H₂, H₆); 8.12 (dd, 1H, *J* = 8.5, 1.5 Hz, H₈); 7.61 (dd, 1H, *J* = 8.5, 4.0 Hz, H₇); 7.50-7.47 (m, 3H, H₃, H₄, H₅); 7.20 (br s, 1H, NH); 1.70 (s, 9H, CCH₃) ppm; ¹³C NMR (CDCl₃, 126 MHz): δ = 160.9, 159.0, 147.1, 144.8, 138.9, 136.1, 131.5, 130.2, 128.5, 128.3, 127.3, 52.1, 28.7 ppm; HRMS (ESI): *m/z* calcd for C₁₇H₁₉N₄ [M+H]⁺: 279.1531; found 279.1608.

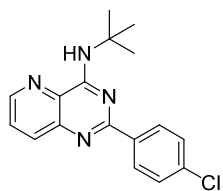


***N*-tert-Butyl-2-(2'-chloro-phenyl)pyrido[3,2-*d*]pyrimidin-4-amine (1b).**

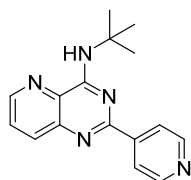
Prepared from Pd (OAc)₂ (0.011 g, 0.05 mmol), Cy JohnPhos (0.035 g, 0.10 mmol), *N*-(2-bromo-3-pyridyl)-2-chloro-benzimidamide **4b** (0.310 g, 1 mmol), *tert*-butyl isocyanide (0.125 g, 1.5 mmol); eluent: CH₂Cl₂/EtOAc (99:1), then CH₂Cl₂/EtOAc (95:5); yield: 0.090 g (29%); yellow paste. ¹H NMR (CDCl₃, 500 MHz): δ = 8.67 (dd, 1H, *J* = 4.5, 1.5 Hz, H₆); 8.13 (dd, 1H, *J* = 8.0, 1.5 Hz, H₈); 7.78- 7.76 (m, 1H, H₆); 7.63 (dd, 1H, *J* = 8.5, 4.0 Hz, H₇); 7.49- 7.47 (m, 1H, H₃); 7.36- 7.33 (m, 2H, H₄, H₅); 7.29 (br s, 1H, NH); 1.69 (s, 9H) ppm; ¹³C NMR (CDCl₃, 126 MHz): δ = 162.4, 158.9, 147.7, 144.3, 139.5, 136.1, 132.6, 131.4, 131.0, 130.3, 129.6, 127.4, 126.5, 52.3, 28.7 ppm; HRMS (ESI): *m/z* calcd for C₁₇H₁₈ClN₄ [M+H]⁺: 313.1141; found 313.1220.



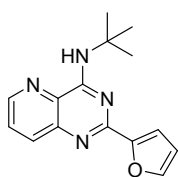
***N*-tert-Butyl-2-(3'-chloro-phenyl)pyrido[3,2-*d*]pyrimidin-4-amine (1c).** Prepared from Pd (OAc)₂ (0.011 g, 0.05 mmol), Cy JohnPhos (0.035 g, 0.10 mmol), *N*-(2-Bromo-3-pyridyl)-3-chlorobenzimidamide **4c** (0.310 g, 1 mmol), *tert*-butyl isocyanide (0.125 g, 1.5 mmol); eluent: CH₂Cl₂ (100%); yield 0.222 g (71%); light yellow solid. mp: 119-121 °C; ¹H NMR (CDCl₃, 500 MHz): δ = 8.62 (dd, 1H, *J* = 4.5, 1.5 Hz, H₆); 8.53 (d, 1H, *J* = 2.0 Hz, H₂); 8.43 (dt, 1H, *J* = 7.0, 1.5 Hz, H₄); 8.10 (dd, 1H, *J* = 8.5, 1.5 Hz, H₈); 7.61 (dd, 1H, *J* = 8.5, 4.0 Hz, H₇); 7.44-7.41 (m, 2H, H₅, H₆); 7.24 (br s, 1H, NH); 1.69 (s, 9H) ppm; ¹³C NMR (CDCl₃, 126 MHz): δ = 159.6, 159.1, 147.4, 144.6, 140.8, 136.1, 134.3, 131.5, 130.1, 129.5, 128.6, 127.4, 126.6, 52.2, 28.7 ppm; HRMS (ESI): *m/z* calcd for C₁₇H₁₈ClN₄ [M+H]⁺: 313.1141; found 313.1218.



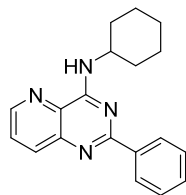
***N*-tert-Butyl-2-(4'-chloro-phenyl)pyrido[3,2-*d*]pyrimidin-4-amine (1d).** Prepared from Pd (OAc)₂ (0.011 g, 0.05 mmol), Cy JohnPhos (0.035 g, 0.10 mmol), *N*-(2-bromo-3-pyridyl)-4-chlorobenzimidamide **4d** (0.310 g, 1 mmol), *tert*-butyl isocyanide (0.125 g, 1.5 mmol); eluent: CH₂Cl₂/ EtOAc (98:2), then CH₂Cl₂/EtOAc (95:5); yield 0.207 g (66%); orange crystals. mp: 131-133 °C; ¹H NMR (CDCl₃, 500 MHz): δ = 8.62 (dd, 1H, *J* = 4.3, 1.6 Hz, H₆); 8.49 (d, 2H, *J* = 8.6 Hz, H₂, H₆); 8.10 (dd, 1H, *J* = 8.4, 1.5 Hz, H₈); 7.62 (dd, 1H, *J* = 8.4, 4.2 Hz, H₇); 7.45 (d, 2H, *J* = 8.7 Hz, H₃, H₅); 7.22 (br s, 1H, NH); 1.69 (s, 9H) ppm; ¹³C NMR (CDCl₃, 126 MHz): δ = 159.9, 159.0, 147.3, 144.7, 137.4, 136.3, 136.0, 131.5, 129.9, 129.8, 128.5, 128.4, 127.4, 52.1, 28.7 ppm; HRMS (ESI): *m/z* calcd for C₁₇H₁₈ClN₄ [M+H]⁺: 313.1141; found 313.1213.



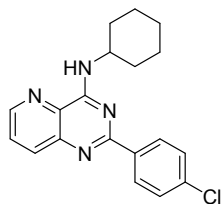
***N*-tert-Butyl-2-(pyridin-4'-yl)pyrido[3,2-*d*]pyrimidin-4-amine (1e).** Prepared from Pd (OAc)₂ (0.011 g, 0.05 mmol), Cy JohnPhos (0.035 g, 0.10 mmol), (*Z*)-*N*'-(2-bromo-3-pyridyl)-isonicotinimidamide **4e** (0.277 g, 1 mmol), *tert*-butyl isocyanide (0.125 g, 1.5 mmol); eluent: CH₂Cl₂/EtOAc (8:2), then CH₂Cl₂/EtOAc (1:1), CH₂Cl₂/EtOAc (1:2), then EtOAc (100%); yield 0.196 g (70%); reddish crystals. mp: 131-133 °C; ¹H NMR (CDCl₃, 500 MHz): δ = 8.76 (dd, 2H, *J* = 4.4, 1.2 Hz, H₃, H₅); 8.67 (dd, 1H, *J* = 4.0, 1.6 Hz, H₆); 8.36 (dd, 2H, *J* = 4.4, 1.6 Hz, H₂, H₆); 8.14 (dd, 1H, *J* = 8.4, 1.2 Hz, H₈); 7.65 (dd, 1H, *J* = 8.4, 4.4 Hz, H₇); 7.28 (br s, 1H, NH); 1.70 (s, 9H) ppm; ¹³C NMR (CDCl₃, 126 MHz): δ = 159.2, 158.8, 150.1, 148.0, 146.3, 144.5, 136.3, 133.0, 131.7, 127.6, 122.4, 52.3, 28.6 ppm; HRMS (ESI): *m/z* calcd for C₁₆H₁₈N₅ [M+H]⁺: 280.1484, found 280.1571.



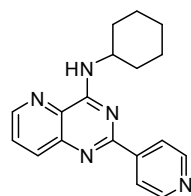
***N*-tert-Butyl-2-(furan-2'-yl)pyrido[3,2-*d*]pyrimidin-4-amine (1f).** Prepared from Pd (OAc)₂ (0.011 g, 0.05 mmol), Cy JohnPhos (0.035 g, 0.10 mmol), *N*-(2-bromo-3-pyridyl)-furan-2-carboximidamide **4f** (0.266 g, 1 mmol), *tert*-butyl isocyanide (0.125 g, 1.5 mmol); eluent: CH₂Cl₂/EtOAc (9:1); yield 0.094 g (35%); yellow paste. ¹H NMR (CDCl₃, 500 MHz): δ = 8.57 (dd, 1H, *J* = 4.0, 1.5 Hz, H₆); 8.15 (dd, 1H, *J* = 8.0, 1.5 Hz, H₈); 7.63 (d, 1H, *J* = 1.0 Hz, H₃); 7.58 (dd, 1H, *J* = 8.5, 4.5 Hz, H₇); 7.31 (d, 1H, *J* = 3.0 Hz, H₄); 7.18 (br s, 1H, NH); 6.55 (dd, 1H, *J* = 3.0, 1.5 Hz, H₅); 1.64 (s, 9H) ppm; ¹³C NMR (CDCl₃, 126 MHz): δ = 158.9, 154.0, 153.3, 147.0, 144.7, 144.5, 135.9, 133.6, 131.5, 127.5, 111.8, 52.2, 28.6 ppm; HRMS (ESI): *m/z* calcd for C₁₅H₁₇N₄O [M+H]⁺: 269.1324; found 269.1406.



***N*-cyclohexyl-2-phenylpyrido[3,2-*d*]pyrimidin-4-amine (1g).** Prepared from Pd(OAc)₂ (0.011 g, 0.05 mmol), Cy JohnPhos (0.035 g, 0.10 mmol), *N*-(2-bromo-3-pyridyl)benzimidamide **1a** (0.276 g, 1.00 mmol), cyclohexyl isocyanide (0.164 g, 1.50 mmol); eluent: CH₂Cl₂ (100%), then CH₂Cl₂/EtOAc (95:5); yield 0.107 g (35%); yellow powder. mp 129-131°C; ¹H NMR (CDCl₃, 500 MHz): δ = 8.63 (dd, 1H, *J* = 4.5, 1.5 Hz, H₆); 8.54 (dd, 2H, *J* = 8.0, 2.0 Hz, H₂, H₆); 8.13 (dd, 1H, *J* = 8.5, 1.5 Hz, H₈); 7.61 (dd, 1H, *J* = 8.5, 4.0 Hz, H₇); 7.52-7.46 (m, 3H, H₃, H₄, H₅); 7.07 (d, 1H, *J* = 8.0 Hz, NH); 4.39- 4.32 (m, 1H, Cy-H₁); 2.21 (dd, 2H, *J* = 12.0, 3.0 Hz, Cy), 1.86 (dt, 2H, *J* = 13.5, 4.0 Hz, Cy), 1.72 (dt, 1H, *J* = 9.0, 4.0 Hz, Cy-H₄); 1.59- 1.50 (m, 2H, Cy); 1.48- 1.40 (m, 2H, Cy); 1.36- 1.25 (m, 1H, Cy) ppm; ¹³C NMR (CDCl₃, 126 MHz): δ = 161.5, 158.9, 147.2, 145.1, 138.8, 135.9, 131.2, 130.2, 128.5, 128.3, 127.4, 49.4, 32.7, 25.7, 24.9 ppm; HRMS (ESI): *m/z* calcd for C₁₉H₂₁N₄ [M+H]⁺: 305.1688, found 305.1773.

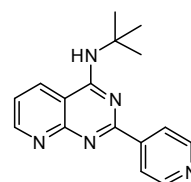


2-(4-chlorophenyl)-*N*-cyclohexylpyrido[3,2-*d*]pyrimidin-4-amine (1h). Prepared from Pd(OAc)₂ (0.011 g, 0.05 mmol), Cy JohnPhos (0.035 g, 0.10 mmol), *N*-(2-bromopyridin-3-yl)-4-chlorobenzimidamide (0.310 g, 1.00 mmol), cyclohexyl isocyanide (0.164 g, 1.50 mmol); eluent: CH₂Cl₂ (100%), then CH₂Cl₂/EtOAc (95:5, 9:1); yield 0.192 g (57%); yellow solid. mp: 141.5-146.6 °C; ¹H NMR (CDCl₃, 500 MHz): δ = 8.63 (dd, 1H, *J* = 4.3, 1.6 Hz, H₆); 8.48 (d, 2H, *J* = 8.7 Hz, H₂); 8.11 (dd, 1H, *J* = 8.5, 1.6 Hz, H₈); 7.62 (dd, 1H, *J* = 8.5, 4.3 Hz, H₇); 7.45 (d, 2H, *J* = 8.7, H₃); 7.09 (d, 1H, *J* = 7.9 Hz, NH); 4.37- 4.28 (m, 1H, Cy); 2.23- 2.15 (m, 2H, Cy); 1.90- 1.81 (m, 2H, Cy); 1.76- 1.68 (m, 1H, Cy); 1.62- 1.39 (m, 4H, Cy); 1.37- 1.26 (m, 1H, Cy) ppm; ¹³C NMR (CDCl₃, 126 MHz): δ = 160.4, 158.8, 147.4, 145.0, 137.2, 136.6, 135.9, 131.2, 129.9, 128.4, 127.5, 49.4, 32.7, 25.7, 24.9 ppm; HRMS (ESI): *m/z* calcd for C₁₉H₂₀ClN₄ [M+H]⁺: 339.1371, found 339.1358.

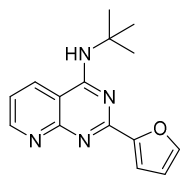


***N*-cyclohexyl-2-(pyridin-4-yl)pyrido[3,2-*d*]pyrimidin-4-amine (1i).** Prepared from Pd(OAc)₂ (0.011 g, 0.05 mmol), Cy JohnPhos (0.035 g, 0.10 mmol), *N*-(2-bromopyridin-3-yl)isonicotinimidamide (0.277 g, 1.00 mmol), KOAc (0.294 g, 3.00 mmol), cyclohexyl isocyanide (0.164 g, 1.50 mmol); eluent: CH₂Cl₂/EtOAc (95:5, 8:2, 7:3, 6:4, 1:1); yield 0.167 g (55%); orange solid. mp: 170.1-173.8 °C; ¹H NMR (CDCl₃, 500 MHz): δ = 8.70 (d, 2H, *J* = 6.1 Hz, H₃); 8.62 (dd, 1H, *J* = 4.3, 1.5 Hz, H₆); 8.29 (d, 2H, *J* = 6.1 Hz, H₂); 8.09 (dd, 1H, *J* = 8.5, 1.6 Hz, H₈); 7.59 (dd, 1H, *J* = 8.5, 4.3 Hz, H₇); 7.09 (d, 1H, *J* = 7.8 Hz, NH); 4.31- 4.22 (m, 1H, Cy); 2.17- 2.09 (m, 2H, Cy); 1.85- 1.74 (m, 2H, Cy); 1.70- 1.61 (m, 1H, Cy); 1.55- 1.33 (m, 4H, Cy); 1.32- 1.21 (m, 1H, Cy) ppm; ¹³C NMR (CDCl₃, 126 MHz): δ = 159.4, 159.0, 150.2, 148.1, 146.1, 144.8, 136.2, 131.5, 127.7, 122.4, 49.6, 32.7, 25.7, 24.9 ppm; HRMS (ESI): *m/z* calcd for C₁₈H₂₀N₅ [M+H]⁺: 306.1713, found 306.1706.

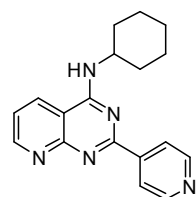
Synthesis of pyrido[2,3-*d*]pyrimidines 2: A round-bottomed flask was charged with Pd (OAc)₂ (3 mol %) and Cy JohnPhos (6 mol %) followed by 5 ml of dry DMF. The mixture was flushed with N₂ for 10 min. In another round-bottomed flask, KOAc (3 equiv.), the appropriate amidine (1 equiv.) and isocyanide (1.5 equiv.) were weighed. To this mixture, the Pd catalyst solution was added and the flask was flushed with N₂. Then, the mixture was stirred and heated at 120 °C for 7 h. After cooling down to room temperature, the resulting mixture was filtered over a pad of Celite and rinsed with ethyl acetate. The solvent was removed under reduce pressure and the obtained residue was purified by flash column chromatography on silica gel using the appropriate mixture of solvents as the eluent.



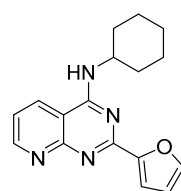
***N*-tert-Butyl-2-(4-pyridyl)pyrido[2,3-*d*]pyrimidin-4-amine (2a).** Prepared from Pd (OAc)₂ (0.0067 g, 0.03 mmol), Cy JohnPhos (0.021 g, 0.06 mmol), *N*-(3-bromo-2-pyridyl)isonicotinimidamide **5a** (0.277 g, 1.00 mmol), *tert*-butyl isocyanide (0.125 g, 1.5 mmol); eluent: CH₂Cl₂/EtOAc (8:2), then CH₂Cl₂/EtOAc (1:1), then EtOAc (100%); yield 0.260 g (93%); bordeaux solid. mp >250 °C; ¹H NMR (CDCl₃, 500 MHz): δ = 9.08 (dd, 1H, *J* = 4.4, 1.8 Hz, H₇); 8.78 (d, 2H, *J* = 6.1 Hz, H₂, H₆); 8.47 (d, 2H, *J* = 6.1 Hz, H₃, H₅); 8.07 (dd, 1H, *J* = 8.2, 1.8 Hz, H₈); 7.42 (dd, 1H, *J* = 8.1, 4.3 Hz, H₆); 5.73 (br s, 1H, NH); 1.70 (s, 9H) ppm; ¹³C NMR (CDCl₃, 126 MHz): δ = 161.5, 160.1, 159.2, 156.0, 150.2, 145.8, 130.1, 122.6, 121.2, 109.2, 53.4, 28.8 ppm; HRMS (ESI): *m/z* calcd for C₁₆H₁₈N₅ [M+H]⁺: 280.1484; found 280.1562.



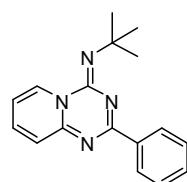
***N*-tert-Butyl-2-(2-furyl)pyrido[2,3-*d*]pyrimidin-4-amine (2b).** Prepared from Pd(OAc)₂ (0.0067 g, 0.03 mmol), Cy JohnPhos (0.021 g, 0.06 mmol), *N*-(3-bromo-2-pyridyl)furan-2-carboximidamide **5b** (0.264 g, 1.00 mmol), *tert*-butyl isocyanide (0.125 g, 1.5 mmol); eluent: CH₂Cl₂/EtOAc (95:5, 8:2, 1:1); yield 0.210 g (78%); orange solid. mp >250 °C; ¹H NMR (CDCl₃, 500 MHz): δ = 9.00 (dd, 1H, *J* = 4.4, 1.6 Hz, H₇); 7.96 (dd, 1H, *J* = 8.0, 1.6 Hz, H₅); 7.64 (s, 1H, H₃); 7.41 (d, 1H, *J* = 3.2 Hz, H₄); 7.29 (dd, 1H, *J* = 8.0, 4.4 Hz, H₆); 6.56 (dd, 1H, *J* = 3.2, 1.6 Hz, H₅); 5.58 (br s, 1H, NH); 1.66 (s, 9H) ppm; HRMS (ESI): *m/z* calcd for C₁₅H₁₇N₄O [M+H]⁺: 269.1324, found 269.1402.¹



***N*-cyclohexyl-2-(4-pyridyl)pyrido[2,3-*d*]pyrimidin-4-amine (2c).** Prepared from Pd(OAc)₂ (0.0067 g, 0.03 mmol), Cy JohnPhos (0.021 g, 0.06 mmol), *N*-(3-bromopyridin-2-yl)isonicotinimidamide (0.276 g, 1.00 mmol), cyclohexyl isocyanide (0.164 g, 1.5 mmol); eluent: CH₂Cl₂/EtOAc, 1:1, 1:2, then EtOAc (100%), then EtOAc/MeOH (98:2, 95:5); yield 0.296 g (97%); brown solid. mp: >250 °C; ¹H NMR (CDCl₃, 500 MHz): δ = 9.09 (dd, 1H, *J* = 4.4, 1.8 Hz, H₇); 8.78 (d, 2H, *J* = 6.0 Hz, H₃); 8.47 (d, 2H, *J* = 6.1 Hz, H₂); 8.12 (dd, 1H, *J* = 8.2, 1.8 Hz, H₅); 7.42 (dd, 1H, *J* = 8.2, 4.4 Hz, H₆); 5.76 (d, 1H, *J* = 7.1 Hz, NH); 4.45- 4.38 (m, 1H, Cy); 2.27- 2.20 (m, 2H, Cy); 1.91- 1.84 (m, 2H, Cy); 1.70- 1.50 (m, 2H, Cy); 1.44- 1.28 (m, 4H, Cy) ppm; ¹³C NMR (CDCl₃, 126 MHz): δ = 162.0, 160.0, 159.5, 156.1, 150.2, 145.7, 130.2, 122.6, 121.2, 108.8, 50.6, 32.8, 25.6, 25.0 ppm; HRMS (ESI): *m/z* calcd C₁₈H₂₀N₅ [M+H]⁺: 306.1713; found 306.1705.



***N*-cyclohexyl-2-(2-furyl)pyrido[2,3-*d*]pyrimidin-4-amine (2d).** Prepared from Pd(OAc)₂ (0.0067 g, 0.03 mmol), Cy JohnPhos (0.021 g, 0.06 mmol), *N*-(3-bromo-2-pyridyl)furan-2-carboximidamide **5b** (0.264 g, 1.00 mmol), cyclohexyl isocyanide (0.164 g, 1.5 mmol); eluent: CH₂Cl₂/EtOAc (8:2, 1:1), then EtOAc (100%); yield 0.212 g (72%); yellow solid. mp >250 °C; ¹H NMR (CDCl₃, 500 MHz): δ = 8.99 (dd, 1H, *J* = 4.0, 1.5 Hz, H₇); 8.07 (dd, 1H, *J* = 8.0, 2.0 Hz, H₅); 7.62 (dd, 1H, *J* = 1.5, 0.5 Hz, H₃); 7.42 (d, 1H, *J* = 3.5 Hz, H₄); 7.29 (dd, 1H, *J* = 8.0, 4.5 Hz, H₆); 6.55 (dd, 1H, *J* = 3.5, 2.0 Hz, H₅); 5.74 (d, 1H, *J* = 7.0 Hz, NH); 4.45- 4.38 (m, 1H, Cy-H₁); 2.20 (dd, 2H, *J* = 12.0, 3.0 Hz, Cy); 1.82 (dt, 2H, *J* = 13.5, 3.5 Hz, Cy), 1.72 (dt, 2H, *J* = 9.0, 3.5 Hz, Cy); 1.55-1.48 (m, 2H, Cy) ppm; ¹³C NMR (CDCl₃, 126 MHz): δ = 159.8, 159.5, 157.0, 155.9, 152.9, 145.0, 130.1, 120.2, 114.3, 112.0, 108.3, 50.2, 32.8, 25.7, 24.9 ppm; HRMS (ESI): *m/z* calcd for C₁₇H₁₉N₄O [M+H]⁺: 295.1480; found 295.1558.



(*E*)-*N*-(*tert*-butyl)-2-phenyl-4*H*-pyrido[1,2-*a*][1,3,5]triazin-4-imine (8): To a solution of *N*-arylamidine **7** (79 mg, 0.4 mmol), Pd(OAc)₂ (9.6 mg, 5.0 mol %) and Cs₂CO₃ (195 mg, 0.6 mmol, 1.5 equiv) in toluene (2.0 mL), *tert*-butyl isocyanide (130 μL, 1.2 mmol, 3.0 equiv) was added. The mixture was stirred at reflux temperature under balloon pressure of O₂. After 3 h, the consumption of amidine was complete (as monitored by TLC analysis), the mixture of reaction was cooled to room temperature and 20 mL EtOAc and 20 mL H₂O were added. The organic layer was separated, and the aqueous phase was further extracted with EtOAc (2 × 10 mL). The combined organic phase was washed with brine and dried over Na₂SO₄. After purification by flash column chromatography on silica gel, **8** was obtained in 95 % yield (105 mg). ¹H NMR (CDCl₃, 500 MHz): δ = 9.14 (d, 1H, *J* = 6.8 Hz, H₅); 8.44 (dd, 2H, *J* = 7.5, 1.4 Hz, H₂ and H₆); 7.72 (td, 1H, *J* = 8.5, 1.4 Hz, H₇); 7.50- 7.45 (m, 3H, H₃, H₄ and H₅); 7.30 (d, 1H, *J* = 8.7 Hz, H₈); 6.96 (t, 1H, *J* = 6.6 Hz, H₆); 1.51 (s, 9H) ppm; ¹³C NMR (CDCl₃, 126 MHz): δ = 162.3, 155.7, 142.9, 139.9, 137.3, 131.2, 130.4, 128.7, 128.2, 124.4, 115.3, 53.3, 29.5 ppm; HRMS (ESI): *m/z* calcd for C₁₇H₁₉N₄ [M+H]⁺: 279.1531, found 279.1593.

References

¹ Lavecchia, G.; Raboin, B.; Guillaumet, G. *Tetrahedron Lett.* **2005**, *46*, 5851.