A Concise Synthesis of Fused Tricyclic Pyrrolo[3,2-d]pyrimidines

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Experimental procedures and spectroscopic characterization of products

General:

Anhydrous solvents were purchased from Sigma-Aldrich and used without further purification. Reagents and starting materials were purchased from commercial sources. Purification was performed by flash silica gel chromatography, using pre-packed columns from Grace or Biotage and run on an Isco Companion. Where a microwave reactor has been used, this refers to a Biotage ‘Initiator Robot 60’, voltage 100-120/220-240V, frequency 50-60 Hz, power 100 VA. All new compounds were characterized by $^1$H and $^{13}$C NMR, HRMS and LCMS or UPLC/MS and are of ≥ 95% purity unless otherwise stated.

Analytical Methods:

$^1$H and $^{13}$C NMR spectra were obtained either from a 400 MHz ($^1$H: 400 MHz, $^{13}$C: 101 MHz) or 500 MHz ($^1$H: 500 MHz, $^{13}$C: 126MHz) spectrometer. $^1$H and $^{13}$C shifts are given in ppm, and are measured relative to solvent.

Accurate mass and MSMS fragmentation data were obtained using a Thermo Scientific hybrid LTQ-FT Mass Spectrometer with an Agilent 1100 Quaternary pump with PDA and Autosampler. 5μL of sample dissolved in 50:50 Acetonitrile:water 0.1% formic acid was injected onto a Thermo Scientific Hypersil Gold 50 x 2.1mm 5μm particle LC Column. The gradient was 5 to 100% B over 17 min with 3 min re-equilibration time at 5% B. The flow rate is 0.5 mL/min with A being 0.1% formic acid in water and B 0.1% formic acid in acetonitrile. The MS and MSMS spectra were obtained in ESI +ve mode in both the ion trap and Ion Cyclotron Resonance (ICR) cell using helium as the collision gas at a normalised collision energy of 35eV. The ICR cell was run at resolution settings of 25000 in MS mode and 12500 in MSMS mode.

All compounds were further analysed by either LCMS or UPLC systems as described below.

The LCMS system used consists of a Waters 2790/95 LC system with a 2996 PDA and a 2000 amu ZQ single quadrupole mass spectrometer. The solvents used are A= Water, B= Acetonitrile, C= 50:50 acetonitrile:water 0.1% formic acid and D= 50:50 acetonitrile:water 0.1% ammonium hydroxide. At a flow rate of 1.1 mL/min 5μL of sample is injected onto a 50 x 2.1 5μm Phenomenex Gemini NX column. The gradient runs from 95% A to 95% B for 4.0 mins with a constant 5% infusion of C (for acid analysis, D is used for base analysis). The flow is held at 95% B for 0.5 mins before returning to start conditions. Data is acquired from 150 to 850 amu in both positive and negative mode on the Mass Spectrometer and 220 -320 nm on the PDA.

The UPLC system utilises a Waters Aquity Binary pump with sample manager, Aquity PDA and SQD Mass spectrometer. The solvents used are A1= 0.1% formic acid (aq), B1 0.1% formic acid in acetonitrile, A2 = 0.1% ammonium hydroxide (aq) and B2 0.1% ammonium hydroxide in acetonitrile. At a flow rate of 1 mL/min 1 μL of sample is injected onto a 50 x 2.1
1.7µm Waters BEH column (at 40°C). The gradient runs from 97% A1 to 97% B1 over 1.30mins before being held for 0.2 min and returning to start conditions (substitute A1 and B1 for A2 and B2 for base analysis). Data is acquired from 150 – 1000 amu in positive and negative ion mode on the mass spectrometer and 245 -320 amu on the PDA

Experimental procedures:

4-Chloro-6,7,8,9-tetrahydropyrimido[4,5-b]indolizine 10b

(E)-Diisopropyl diazene-1,2-dicarboxylate (0.499 mL, 2.53 mmol) was added to a stirred solution of 4-(4-chloro-5H-pyrrolo[3,2-d]pyrimidin-6-yl)butan-1-ol 12b (520 mg, 2.30 mmol) and triphenylphosphine (665 mg, 2.53 mmol) in THF (20 mL), at 0 °C under nitrogen. Stirring was continued for 45 minutes. The reaction mixture was purified directly by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 1M NH₃ in MeOH and pure fractions were adsorbed onto silica. The crude product was further purified by flash silica chromatography, elution gradient 20 to 100% EtOAc in heptane. Pure fractions were evaporated to dryness to afford 4-chloro-6,7,8,9-tetrahydropyrimido[4,5-b]indolizine 10b (360 mg, 75%) as a white solid, mp 125-127 °C. ¹H NMR (400 MHz, DMSO) 1.69 - 1.95 (m, 2H), 1.95 - 2.16 (m, 2H), 3.04 (t, J = 6.2 Hz, 2H), 4.50 (t, J = 6.2 Hz, 2H), 6.46 (s, 1H), 8.51 (s, 1H); ¹³C NMR (101 MHz, DMSO) 18.9, 22.4, 24.2, 45.1, 99.1, 123.0, 140.0, 147.8, 149.1, 151.4; HRMS (ESI): Anal cald for C₁₀H₁₀ClN₃ [M+H⁺]: 208.06360, Found: 208.06358.

4-Chloro-7,8,9,10-tetrahydro-6H-pyrimido[4′,5′:4,5]pyrrolo[1,2-a]azepine 10c

10c was prepared from 12c according to the procedure shown for 10b, to afford 10c (110 mg, 84%) as a pale yellow oil which solidified on standing, mp 126-129 °C. ¹H NMR (400 MHz, DMSO) 1.62 – 1.86 (m, 6H), 2.99 – 3.06 (m, 2H), 4.70 (s, 2H), 6.57 (s, 1H), 8.52 (s, 1H); ¹³C NMR (101 MHz, DMSO) 26.5, 27.7, 28.2, 29.5, 45.5, 100.5, 123.2, 139.4, 148.6, 151.3, 154.0; Anal cald for C₁₁H₁₂ClN₃ [M+H⁺]: 222.0798, found: 222.0809.

4-Chloro-7,8,9,10-tetrahydro-6H-pyrido[2′,3′:4,5]pyrrolo[1,2-a]azepine 10d

10d was prepared from 12d according to the procedure shown for 10b. The reaction mixture was stirred at room temperature for 2 hours, after which time the reaction was incomplete, therefore further portions of triphenylphosphine (1.1 eq) and (E)-diisopropyl diazene-1,2-dicarboxylate (1.1 eq) were added and stirring was continued for a further 1 hour.
Purification was carried out as for 10b, to afford 10d as a colourless gum. $^1$H NMR (400 MHz, DMSO) 1.63 – 1.84 (m, 6H), 2.93 – 3.00 (m, 2H), 4.66 – 4.74 (m, 2H), 6.46 (s, 1H), 7.11 (d, $J = 5.1$ Hz, 1H), 8.14 (d, $J = 5.1$ Hz, 1H); $^{13}$C NMR (101 MHz, DMSO) 27.2, 27.5, 28.8, 29.6, 45.2, 100.8, 117.2, 123.4, 124.4, 142.2, 148.3, 149.6; Anal cald for C$_{12}$H$_{13}$ClN$_2$ [M+H$^+$]: 221.08400, Found: 221.08415.

7,8,9,10-Tetrahydro-6H-pyrido[2',3':4,5]pyrrolo[1,2-a]azepine

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\begin{align*}
J &= 8.2 \\
J &= 4.7
\end{align*}
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10% Pd on C (60 mg, 0.36 mmol) was added to 1-chloro-7,8,9,10-tetrahydro-6H-pyrido[4',3':4,5]pyrrolo[1,2-a]azepine 10d (80 mg, 0.36 mmol) and ammonium formate (45.7 mg, 0.72 mmol) in methanol (5 mL) at room temperature under nitrogen. The resulting mixture was heated at 55 °C for 16 hours, then allowed to cool and filtered through celite. The filtrate was adsorbed onto silica and the crude product was purified by flash silica chromatography, elution gradient 5 to 100% EtOAc in heptane. Pure fractions were evaporated to dryness to afford 7,8,9,10-tetrahydro-6H-pyrido[2',3':4,5]pyrrolo[1,2-a]azepine (50 mg, 74%) as a pale yellow solid. $^1$H NMR (400 MHz, CDCl$_3$) 1.71 – 1.82 (m, 4H), 1.83 – 1.92 (m, 2H), 2.91 – 2.99 (m, 2H), 4.09 – 4.16 (m, 2H), 6.45 (s, 1H), 7.02 (dd, $J = 4.7$, 8.2 Hz, 1H), 7.50 (d, $J = 8.2$ Hz, 1H), 8.36 (dd, $J = 1.3$, 4.7 Hz, 1H); $^{13}$C NMR (101 MHz, CDCl$_3$) 27.7, 28.9, 30.9, 44.7, 100.3, 115.1, 115.2, 129.9, 142.3, 146.3, 147.1; Anal cald for C$_{12}$H$_{14}$N$_2$ [M+H$^+$]: 187.1235, Found: 187.1246.

6-(5-Amino-6-chloropyrimidin-4-yl)hex-5-yn-1-ol 11b

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\begin{align*}
\end{align*}
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Triethylamine (42.5 mL, 304.89 mmol) was added to a stirred solution of 4,6-dichloropyrimidin-5-amine (5 g, 30.49 mmol), copper(I) iodide (0.116 g, 0.61 mmol) and (PPh$_3$)$_2$PdCl$_2$ (0.856 g, 1.22 mmol) in THF (80 mL) under nitrogen. The solution was degassed with a stream of nitrogen. A solution of hex-5-yn-1-ol (3.36 mL, 30.49 mmol) in THF (3 mL) was added in one portion and the mixture was then heated at 65 °C for 2 hours. The reaction mixture was adsorbed onto silica and the crude product was purified by flash silica chromatography, elution gradient 30 to 100% EtOAc in heptane. Pure fractions were evaporated to dryness to afford 6-(5-amino-6-chloropyrimidin-4-yl)hex-5-yn-1-ol 11b (3.50 g, 51%) as a yellow gum. $^1$H NMR (400 MHz, DMSO) 1.51 – 1.69 (m, 4H), 2.53 – 2.6 (m, 2H), 3.41 – 3.48 (m, 2H), 4.40 (t, $J = 5.2$ Hz, 1H), 5.85 (s, 2H), 8.13 (s, 1H); $^{13}$C NMR (101 MHz, DMSO) 18.5, 24.3, 31.7, 60.1, 75.5, 102.0, 133.6, 140.3, 143.1, 145.0; HRMS (ESI): Anal cald for C$_{10}$H$_{12}$ClN$_3$O [M+H$^+$]: 226.07417, Found: 226.07442.
7-(5-Amino-6-chloropyrimidin-4-yl)hept-6-yn-1-ol 11c

11c was prepared from 4,6-dichloropyrimidin-5-amine and hept-6-yn-1-ol according to the method shown for 11b, to afford 11c as an orange gum (1.68 g, 56%). $^1$H NMR (400 MHz, DMSO) 1.38 – 1.51 (m, 4H), 1.56 – 1.66 (m, 2H), 2.55 (t, $J = 7.1$ Hz, 2H), 3.37 – 3.44 (m, 2H), 4.33 (t, $J = 5.1$ Hz, 1H), 5.84 (s, 2H), 8.13 (s, 1H). $^{13}$C NMR (101 MHz, DMSO) 19.1, 25.0, 27.6, 31.9, 60.5, 75.4, 101.9, 133.6, 140.3, 143.0, 145.0; HRMS (ESI): Anal cald for C$_{11}$H$_{14}$ClN$_3$O [M+H$^+$]: 240.0904, Found: 240.0920.

7-(3-Amino-4-chloropyridin-2-yl)hept-6-yn-1-ol 11d

Triethylamine (14.11 mL, 101.23 mmol) was added to a stirred solution of 2,4-dichloropyridin-3-amine (1.65 g, 10.12 mmol), copper(I) iodide (39 mg, 0.20 mmol) and bis(triphenylphosphine)palladium(II) dichloride (0.284 g, 0.40 mmol) in THF (70 mL) under nitrogen and the solution was degassed with a stream of nitrogen. A solution of hept-6-yn-1-ol (1.135 g, 10.12 mmol) in THF (3 mL) was added in one portion. The reaction solution was stirred at 65 °C for 2 hours. The solution was adsorbed onto silica and the crude product was purified by flash silica chromatography, elution gradient 0 to 4% MeOH in DCM. Pure fractions were evaporated to dryness to afford 7-(3-amino-4-chloropyridin-2-yl)hept-6-yn-1-ol 11d (1.20 g, 50%) as an yellow gum (~85% purity, remainder hept-6-yn-1-ol dimer). $^1$H NMR (400 MHz, DMSO) 1.41 – 1.50 (m, 4H), 1.54 – 1.64 (m, 2H), 2.50 – 2.54 (m, 2H) partially obscured by DMSO peak, 3.38 – 3.44 (m, 2H), 4.33 (t, $J = 5.1$ Hz, 1H), 5.49 (s, 2H), 7.26 (d, $J = 5.1$ Hz, 1H), 7.68 (d, $J = 5.1$ Hz, 1H); $^{13}$C NMR (101 MHz, DMSO) 18.9, 25.0, 27.8, 32.0, 60.6, 76.9, 96.9, 123.5, 125.1, 129.0, 137.4, 142.3; Anal cald for C$_{12}$H$_{15}$ClN$_2$O [M+H$^+$]: 239.09457, Found: 239.09450.

4-(4-Chloro-5H-pyrrolo[3,2-d]pyrimidin-6-yl)butan-1-ol 12b

Method A:
6-(5-Amino-6-chloropyrimidin-4-yl)hex-5-yn-1-ol 11b (135 mg, 0.60 mmol) was dissolved in DMF (5 mL) and the solution was degassed with a stream of nitrogen. Copper(I) iodide (17.1 mg, 0.09 mmol) was added and the mixture was stirred at 110 °C for 35 minutes, then allowed to cool to room temperature. The crude product was purified by ion exchange
chromatography, using an SCX column. The desired product was eluted from the column using 10% NH₃ (1M solution in MeOH) in DCM and product fractions were evaporated to dryness to afford a brown gum. The crude product was purified by flash silica chromatography, elution gradient 0 to 15% MeOH in DCM. Pure fractions were evaporated to dryness to afford 4-(4-chloro-5H-pyrrolo[3,2-d]pyrimidin-6-yl)butan-1-ol 12b (80 mg, 59%) as a gum. Analysis was consistent with that from material prepared according to Method B.

**Method B:**
Potassium tert-butoxide (716 mg, 6.38 mmol) was added to 6-(5-amino-6-chloropyrimidin-4-yl)hex-5-yn-1-ol 11b (960 mg, 4.25 mmol) in NMP (12 mL) at 0 °C under nitrogen. The resulting mixture was stirred at 0 °C for 1.5 hours. The crude product was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 10% NH₃ (1M in MeOH) in DCM and pure fractions were adsorbed onto silica. The crude product was purified by flash silica chromatography, elution gradient 0 to 15% MeOH in DCM. Pure fractions were evaporated to dryness to afford 4-(4-chloro-5H-pyrrolo[3,2-d]pyrimidin-6-yl)butan-1-ol 12b (650 mg, 68%) as a yellow gum. 

$^1$H NMR (400 MHz, DMSO) 1.44 – 1.53 (m, 2H), 1.71 – 1.81 (m, 2H), 2.84 (t, $J = 7.6$ Hz, 2H), 3.40 – 3.47 (m, 2H), 4.37 (t, $J = 5.2$ Hz, 1H), 6.49 (s, 1H), 8.53 (s, 1H), 12.14 (s, 1H); $^{13}$C NMR (101 MHz, DMSO) 25.0, 27.7, 32.0, 60.3, 99.9, 123.9, 134.0, 149.1, 150.9, 151.7; HRMS (ESI) [M+H$^+$]: Anal cald for C$_{10}$H$_{12}$ClN$_3$O: 226.07417, Found: 226.07420.

5-(4-Chloro-5H-pyrrolo[3,2-d]pyrimidin-6-yl)pentan-1-ol 12c

![Structure of 5-(4-Chloro-5H-pyrrolo[3,2-d]pyrimidin-6-yl)pentan-1-ol 12c]

**Method A:**
12c was prepared from 11c according to the procedure shown for compound 12b. Final purification was carried out by silica chromatography, elution gradient 0 to 10% MeOH in EtOAc, to afford 12c (720 mg, 60%) as a pale yellow solid. $^1$H NMR (400 MHz, DMSO) 1.29 – 1.51 (m, 4H), 1.67 – 1.78 (m, 2H), 2.82 (t, $J = 7.6$ Hz, 2H), 3.36 – 3.42 (m, 2H), 4.37 (t, $J = 5.1$ Hz, 1H), 6.49 (d, $J = 1.9$ Hz, 1H), 8.53 (s, 1H), 12.18 (s, 1H); $^{13}$C NMR (101 MHz, DMSO) 25.2, 27.9, 28.3, 32.1, 60.5, 99.9, 123.9, 140.0, 149.1, 150.9, 151.6; Anal cald for C$_{11}$H$_{14}$ClN$_3$O [M+H$^+$]: 240.0904, Found: 240.0920.

**Method B:**
12c was prepared from 11c according to the procedure shown for compound 12b, stirring at 0 °C for 20 minutes before work-up. Final purification was carried out by silica chromatography, elution gradient 0 to 10% MeOH in DCM, to afford 12c (100 mg, 67%) as a pale yellow solid. Analysis was consistent with that from material prepared according to Method A.
5-(7-Chloro-1H-pyrrolo[3,2-b]pyridin-2-yl)pentan-1-ol 12d

Method A:
12d was prepared from 11d according to the procedure shown for compound 12b, to afford 12d (120 mg, 83%) as a pale yellow gum that solidified on standing. $^1$H NMR (400 MHz, DMSO) 1.31 – 1.52 (m, 4H), 1.66 – 1.77 (m, 2H), 2.78 (t, $J = 7.6$ Hz, 2H), 3.35 – 3.44 (m, 2H), 4.31 (t, $J = 5.1$ Hz, 1H), 6.37 (d, $J = 2.0$ Hz, 1H), 7.12 (d, $J = 5.0$ Hz, 1H), 8.16 (d, $J = 5.0$ Hz, 1H), 11.53 (s, 1H); $^{13}$C NMR (101 MHz, DMSO) 25.2, 27.8, 28.5, 32.2, 60.6, 100.1, 123.5, 142.4, 146.3, 148.5; Anal cald for C$_{12}$H$_{15}$ClN$_2$O $[$M+H$]^+$: 239.09457, Found: 239.09465.

Method B:
12d was prepared from 11d according to the procedure shown for compound 12b, to afford 12d (580 mg, 79%) as a cream solid. Analysis was consistent with that from material prepared according to Method A.

4-Isopropoxy-7,8-dihydro-6H-pyrimido[4,5-b]pyrrolizine 13

Method C: Sodium hydride (207 mg, 5.16 mmol) was added in one portion to $^1$PrOH (5 mL), stirred at room temperature under nitrogen. Stirring was continued for 1 hour, before addition of 4-chloro-7,8-dihydro-6H-pyrimido[4,5-b]pyrrolizine 10a (100 mg, 0.52 mmol). The reaction mixture was heated at 60 °C for 1.5 hours, then allowed to cool to room temperature. The crude reaction mixture was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 1M NH$_3$ in MeOH and pure fractions were evaporated to dryness to afford 13 (98 mg, 87%) as a cream solid, mp 95-96 °C. $^1$H NMR (400 MHz, DMSO) 1.38 (d, $J = 6.2$ Hz, 6H), 2.47 – 2.56 (m, 2H) partially obscured by DMSO peak, 2.96 – 3.03 (m, 2H), 4.19 – 4.26 (m, 2H), 5.47 (hept, $J = 6.2$ Hz, 1H), 6.21 (t, $J = 0.9$ Hz, 1H), 8.27 (s, 1H); $^{13}$C NMR (101 MHz, DMSO) 21.9, 24.4, 26.6, 46.5, 68.3, 93.3, 111.8, 148.8, 149.4, 154.1, 154.1; Anal cald for C$_{12}$H$_{15}$N$_3$ $[$M+H$]^+$: 218.12879, Found: 218.12880.
4-(4-Methoxyphenoxy)-7,8-dihydro-6H-pyrimidino[4,5-b]pyrrolizine 14

Method D: 4-Chloro-7,8-dihydro-6H-pyrimidino[4,5-b]pyrrolizine 10a (80 mg, 0.41 mmol), 4-methoxyphenol (56.4 mg, 0.45 mmol) and cesium carbonate (269 mg, 0.83 mmol) were suspended in NMP (4 mL). The reaction was stirred and heated at 100 °C for 1 hour. The crude reaction mixture was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 1M NH₃ in MeOH and pure fractions were evaporated to dryness to afford 14 (110 mg, 95%) as a beige solid. ¹H NMR (400 MHz, DMSO) 2.53 – 2.63 (m, 2H), 3.07 (t, J = 7.3 Hz, 2H), 3.79 (s, 3H), 4.36 (t, J = 7.1 Hz, 2H), 6.33 (s, 1H), 6.96 – 7.03 (m, 2H), 7.17 – 7.24 (m, 2H), 8.21 (s, 1H); ¹³C NMR (101 MHz, DMSO) 24.5, 26.6, 46.8, 55.5, 93.7, 111.6, 114.5, 122.8, 145.7, 148.5, 150.9, 154.1, 155.3, 156.6; Anal cald for C₁₆H₁₅N₃O₂ [M+H⁺]: 282.12370, Found: 282.12381.

N-(2-Methoxyethyl)-7,8-dihydro-6H-pyrimidino[4,5-b]pyrrolizin-4-amine 15

Method E: 4-Chloro-7,8-dihydro-6H-pyrimidino[4,5-b]pyrrolizine 10a (60 mg, 0.31 mmol), 2-methoxyethan-1-amine (81 μL, 0.93 mmol) and 4M HCl in dioxane (39 μL, 0.15 mmol) were suspended in PrOH (2 mL) and sealed into a microwave tube. The reaction was heated to 140 °C for 2 hours in the microwave reactor and cooled to room temperature. The crude product was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 1M NH₃ in MeOH and pure fractions were adsorbed onto silica. The crude product was purified by flash silica chromatography, elution gradient 0 to 10% MeOH in DCM. Pure fractions were evaporated to dryness to afford 15 (51 mg, 71%) as a cream solid, mp 122-123 °C. ¹H NMR (400 MHz, DMSO) 2.45 – 2.55 (m, partially obscured by DMSO peak), 2.93 (t, J = 7.3 Hz, 2H), 3.28 (s, 3H), 3.54 (t, 2H), 3.59 – 3.67 (m, 2H), 4.32 (t, J = 7.0 Hz, 2H), 6.05 (s, 1H), 6.47 (t, J = 5.4 Hz, 1H), 8.08 (s, 1H); ¹³C NMR (101 MHz, CDCl₃) 24.4, 27.3, 40.3, 46.6, 58.9, 71.3, 94.4, 112.1, 147.4, 149.2, 150.7, 152.2; Anal cald for C₁₂H₁₆N₄O [M+H⁺]: 233.13969, Found: 233.13979.
Method F: 4-Chloro-7,8-dihydro-6H-pyrrolo[4,5-b]pyrrolizine (60 mg, 0.31 mmol) and 4-fluoroaniline (32 μL, 0.34 mmol) were suspended in iPrOH (2 mL). 4M HCl in dioxane (39 μL, 0.15 mmol) was added and the reaction was heated at 140 °C in a microwave reactor for 1 hour. The crude product was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 1M NH₃ in MeOH and product fractions were adsorbed onto silica. The crude product was purified by flash silica chromatography, elution gradient 0 to 10% MeOH in DCM. Pure fractions were evaporated to dryness to afford N-(4-fluorophenyl)-7,8-dihydro-6H-pyrrolo[4,5-b]pyrrolizine 13 (63 mg, 76%) as a cream solid, mp 223-226 °C (decomp.). ¹H NMR (400 MHz, DMSO) 2.46 – 2.58 (m, 2H) partially obscured by DMSO peak, 3.00 (t, J = 7.3 Hz, 2H), 4.46 (t, J = 7.0 Hz, 2H), 6.19 (s, 1H), 7.11 – 7.2 (m, 2H), 7.62 – 7.69 (m, 2H), 8.20 (s, 1H), 8.30 (s, 1H); ¹³C NMR (101 MHz, DMSO) 24.2, 26.6, 46.7, 93.6, 112.1, 114.9 (d), 123.1 (d), 136.4, 146.2, 149.06, 149.11, 153.0, 157.8 (d); Anal cald for C₁₅H₁₃FN₄ [M+H⁺]: 269.11970, Found: 269.11960.

4-(7,8-Dihydro-6H-pyrrolo[4,5-b]pyrrolizin-4-yl)morpholine 17

17 was prepared from 10a and morpholine according to Method E, as described for compound 15 above, to afford 17 (60 mg, 79%) as a cream solid, mp 147-149 °C. ¹H NMR (400 MHz, DMSO) 2.44 – 2.55 (m, 2H) partially obscured by DMSO peak, 2.96 – 3.03 (m, 2H), 3.35 – 3.4 (m, 4H), 3.75 – 3.81 (m, 4H), 4.28 (t, J = 6.9 Hz, 2H), 6.24 (t, J = 0.8 Hz, 1H), 8.30 (s, 1H); ¹³C NMR (101 MHz, DMSO) 24.4, 27.1, 47.9, 49.8, 66.0, 94.2, 115.5, 149.0, 149.8, 152.2, 154.2; Anal cald for C₁₃H₁₆N₆O [M+H⁺]: 245.13969, Found: 245.13986.

4-(Cyclohexylthio)-7,8-dihydro-6H-pyrrolo[4,5-b]pyrrolizine 18
**Method G:** Sodium hydride (18.6 mg, 0.46 mmol) was added in one portion to cyclohexanethiol (45 μL, 0.37 mmol) in THF (7 mL) under nitrogen and the mixture was stirred at room temperature for 1 hour. 4-Chloro-7,8-dihydro-6H-pyrimido[4,5-b]pyrrolizine 10a (60 mg, 0.31 mmol) was added and the mixture allowed to stir at 60 °C for 2 hours. The reaction was quenched with methanol and adsorbed onto silica. The crude product was purified by flash silica chromatography, elution gradient 0 to 10% MeOH in DCM. Pure fractions were evaporated to dryness to afford 18 (67 mg, 79%) as a white solid, mp 116-117 °C. ¹H NMR (400 MHz, DMSO) 1.25 – 1.66 (m, 6H), 1.68 – 1.78 (m, 2H), 2.02 – 2.12 (m, 2H), 2.49 – 2.58 (m, 2H), 2.97 – 3.06 (m, 2H), 4.11 – 4.22 (m, 1H), 4.35 (t, J = 7.1 Hz, 2H), 6.26 (t, J = 0.9 Hz, 1H), 8.51 (s, 1H); ¹³C NMR (101 MHz, DMSO) 24.4, 25.2, 25.5, 26.6, 32.8, 41.3, 47.2, 93.4, 121.9, 148.6, 149.2, 151.2, 151.4; Anal cald for C₁₅H₁₉N₃S [M+H⁺]: 274.13724, Found: 274.13715.

**N-(2-Methoxyethyl)-6,7,8,9-tetrahydropyrimido[4,5-b]indolizin-4-amine 19**

![Diagram of 19](image)

19 was prepared from 10b according to Method E, as shown for compound 15 above, to afford 19 (80 mg, 96 %) as a cream solid, mp 152-154 °C. ¹H NMR (400 MHz, DMSO) 1.73 – 1.82 (m, 2H), 1.95 – 2.05 (m, 2H), 2.88 (t, J = 6.3 Hz, 2H), 3.28 (s, 3H), 3.49 – 3.56 (m, 2H), 3.59 – 3.67 (m, 2H), 4.35 (t, J = 6.2 Hz, 2H), 6.05 (s, 1H), 6.43 (t, J = 5.3 Hz, 1H), 8.08 (s, 1H); ¹³C NMR (101 MHz, CDCl₃) 19.9, 23.6, 24.5, 40.5, 45.3, 58.8, 71.3, 99.5, 114.8, 140.5, 148.4, 149.8, 150.8.; Anal cald for C₁₃H₁₈N₄O [M+H⁺]: 247.15534, Found: 247.15543.

**N-(2-Methoxyethyl)-7,8,9,10-tetrahydro-6H-pyrimido[4',5':4,5]pyrrolo[1,2-a]azepin-4-amine 20**

![Diagram of 20](image)

20 was prepared from 10c according to Method E, as shown for compound 15 above, to afford 20 (50 mg, 71 %) as a yellow solid. ¹H NMR (400 MHz, DMSO) 1.57 – 1.83 (m, 6H), 2.83 – 2.91 (m, 2H), 3.28 (s, 3H), 3.50 – 3.57 (m, 2H), 3.64 (q, J = 5.5 Hz, 2H), 4.29 – 4.39 (m, 2H), 6.16 (s, 1H), 6.55 (t, J = 5.5 Hz, 1H), 8.09 (s, 1H); ¹³C NMR (101 MHz, CDCl₃) 27.3, 28.5, 29.4, 30.5, 40.8, 47.7, 58.8, 71.2, 101.3, 115.8, 147.7, 148.2, 149.3, 150.2; Anal cald for C₁₄H₂₀N₄O [M+H⁺]: 261.17099, Found: 261.17111.
N-(2-Methoxyethyl)-7,8,9,10-tetrahydro-6H-pyrido[2',3':4,5]pyrrolo[1,2-a]azepin-4-amine

21 was prepared from 10d according to Method E, as shown for compound 15 above, to afford 21 (70 mg, 85%) as a cream solid, mp 113-116 °C. 1H NMR (400 MHz, DMSO) 1.59 – 1.82 (m, 6H), 2.81 – 2.89 (m, 2H), 3.31 (s, 3H), 3.34 (q, J = 6.0 Hz, 2H), 3.57 (t, J = 6.0 Hz, 2H), 4.33 – 4.43 (m, 2H), 5.52 (t, J = 5.5 Hz, 1H), 6.16 (s, 1H), 6.31 (d, J = 5.4 Hz, 1H), 7.89 (d, J = 5.4 Hz, 1H); 13C NMR (101 MHz, DMSO) 27.5, 27.7, 29.43, 29.9, 42.5, 46.2, 58.1, 70.2, 99.5, 100.6, 119.0, 140.6, 143.1, 145.7, 146.0; Anal cald for C15H21N4O [M+H]+: 260.17574, Found: 260.17581.