Application of the copper-catalysed N-arylation of amidines in the synthesis of analogues of the chemical tool, Blebbistatin.

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General Procedure A: Synthesis of N-arylbenzamidines 8a-8j.
To a sealed tube charged with Cs2CO3 (3.00 eq), aryl iodide (1.20 eq), amidine (1.00 eq) and 4Å molecular sieves at room temperature was added either the catalyst ligand combination of [CuI (10 mol%) and ligand (20 mol%)], method 1 or [CuI (5 mol%) and ligand (10 mol%)], method 2 respectively under an atmosphere of nitrogen. The reaction solvent (2 mL per mmol of amidine) was then added and, after standing for 5-10 minutes, the resulting mixture was stirred at 120 °C for 18 hours. The reaction was allowed to cool to room temperature, filtered through a pad of Celite® and washed with ethyl acetate (3 x 30 mL). The filtrate was subsequently absorbed onto Celite® (w/w) under reduced pressure. Purification by flash chromatography on silica gel afforded the title compounds.

\[ \text{p-Anisidine (7a)} \]

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| 6 | H \\
| 5 | | OMe \\
| 2 | H \\
| 3 | H \\
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Table 1, Entry 1: Using a modification General procedure A, method 1; L-proline as ligand and DMF as solvent minus 4 Å molecular sieves: Acetamidine hydrochloride 1 (0.095 g, 1.00 mmol, 1.0 eq) afforded the title compound 7a (0.0593 g, 0.479 mmol, 48%) as a light brown solid: Mp: 55-57 °C, Lit. S1 56-57 °C; \( ^1 \text{H NMR (400 MHz, CDCl3): } \delta \text{ 7.47 (d, }^3 J = 6.8 \text{ Hz, 2H, C3-H, C5-H), 6.60 (d, }^3 J = 6.8 \text{ Hz, 2H, C2-H, C6-H) 3.68 (s, 3H, OCH}_3); \) LRMS (ES⁺): \( m/z (%) 124 (65) [M+H]^+ \).

\text{7a} was also prepared using the following protocols:

Table 1, Entry 2: Using General procedure A method 1; L-proline as ligand, DMF as solvent: Acetamidine hydrochloride 1 (0.095 g, 1.00 mmol, 1.0 eq) afforded 0.0345 g, 0.280 mmol, 28%) as a light brown solid.

Table 1, Entry 3: Benzamidine hydrochloride 2a (0.156 g, 1.00 mmol, 1.0 eq) afforded the title compound 7a (0.036 g, 0.292 mmol, 29%) as a light brown solid.

\text{7a} prepared by these additional routes was identical in all respects to that prepared as described above.
**Table 1, Entry 4:** Using General Procedure A method 1; L-proline as ligand and DMF as solvent; Benzamidine 2a (0.157 g, 1.00 mmol, 1.00 eq) afforded the title compound 8a (0.110 g, 0.48 mmol, 48%) as a cream solid.

Mp: 116-117 °C, Lit. S3 114-116 °C; 1H NMR (400 MHz, d6-DMSO): δ 7.94 (d, 3 J = 7.2 Hz, 2H, C4-H, C8-H), 7.47-7.39 (m, 3H, C5-H, C6-H, C7-H), 6.89 (d, 3 J = 8.8 Hz, 2H, C2’-H, C6’-H), 6.79 (br. m, 2H, C3’-H, C5’-H), 6.19 (br. s, 2H, NH2), 3.72 (s, 3H, OCH3); LRMS (ES⁺): m/z (%) 227 (100) [M+H]+. An analytic sample of 8a suitable for small molecule X-ray crystallographic analysis was obtained by recrystallisation from ethyl acetate:hexane (1:5).

8a was also prepared using the following protocols:

**Table 1, Entry 5:** Using a modification General procedure A, method 1; L-proline as ligand and DMF as solvent minus 4 Å molecular sieves: Benzamidine 2b (0.661 g, 5.50 mmol, 1.00 eq) afforded the title compound 8a (0.466 g, 2.06 mmol, 37%) as a cream solid.

**Table 1, Entry 6:** Using General Procedure A method 1; L-proline as ligand and DMF as solvent: Benzamidine 2b (0.661 g, 5.50 mmol, 1.00 eq) afforded the title compound 8a (0.557 g, 2.46 mmol, 45%) as a cream solid.

**Table 1, Entry 9:** Using a modification General procedure A, method 1; L-proline as ligand and DMF as solvent minus ligand: Benzamidine 2b (0.120 g, 1.00 mmol, 1.0 eq) afforded the title compound 8a (0.054 g, 0.238 mmol, 24%) as a light brown solid.

**Table 1, Entry 10:** Using General Procedure A method 1 with L-proline as ligand and toluene as solvent: Benzamidine 2b (0.661 g, 5.50 mmol, 1.00 eq) afforded the title compound 8a (0.907 g, 4.01 mmol, 73%) as a cream solid.
Table 1, Entry 12: Using General Procedure A method 1 with L-proline as ligand and DMSO as solvent: Benzamidine 2b (120 mg, 1.00 mmol, 1.00 eq) afforded the title compound 8a (0.11 g, 0.49 mmol, 49 %) as a light brown solid.

Table 1, Entry 13: Using General Procedure A method 2 with L-proline as ligand and toluene as solvent: Benzamidine 2b (0.120 g, 1.00 mmol, 1.00 eq) afforded the title compound 8a (0.137 g, 0.605 mmol, 60 %) as a cream solid.

Table S1, Entry S1: Using General Procedure A method 2 with ligand E as ligand and toluene as solvent: Benzamidine 2b (0.120 g, 1.00 mmol, 1.00 eq) afforded the title compound 8a (0.112 g, 0.494 mmol, 49 %) as a cream solid.

8a prepared by these additional routes was identical in all respects to that prepared as described above.

(Z)-N’-p-tolylbenzamidine (8b)

Table 1, Entry 7: Using General Procedure A method 1; L-proline as ligand and DMF as solvent: Benzamidine 2b (0.661 g, 5.50 mmol, 1.00 eq) afforded the title compound 8b (0.760 g, 3.614 mmol, 66 %) as a cream solid. Mp: 93-94 °C, Lit.\(^{S4}\) 99-100 °C; \(^1\)H NMR (400 MHz, \(d_6\)-DMSO): \(\delta\) 7.94 (d, \(^3J = 7.2\) Hz, 2H, C4-H, C8-H), 7.47-7.39 (m, 3H, C5-H, C6-H, C7-H), 7.11 (d, \(^3J = 8.0\) Hz, 2H, C3’-H, C5’-H), 6.75 (br. m, 2H, C2’-H, C6’-H), 6.18 (br. s, 2H, NH\(_2\)), 2.26 (s, 3H, CH\(_3\)); LRMS (ES\(^{+}\)): m/z (%) 211 (100) [M+H]\(^+\). An analytic sample of 8b suitable for small molecule X-ray crystallographic analysis was obtained by recrystallisation from ethyl acetate:hexane (1:5).

8b was also prepared using the following protocols:

Table 1, Entry 11: Using General Procedure A method 1 with L-proline as ligand and toluene as solvent: Benzamidine 2b (0.661 g, 5.50 mmol, 1.00 eq) afforded the title compound 8b (0.913 g, 4.342 mmol, 79%) as a cream solid.
Table 1, Entry 14: Using General Procedure A method 2 with L-proline as ligand and toluene as solvent: Benzamidine 2b (0.120 g, 1.00 mmol, 1.00 eq) afforded the title compound 8b (0.146 g, 0.694 mmol, 69 %) as a cream solid.

Table 1, Entry 23: Using a modification General procedure A, method 2; L-proline as Ligand and toluene as solvent: 4-bromo-toluene (0.205 g, 1.2 mmol, 1.20 eq) and benzamidine 2b (0.120 g, 1.00 mmol, 1.00 eq) afforded the title compound 8b (0.097 g, 0.462 mmol, 46 %) as a cream solid.

Table S1, Entry S2: Using General Procedure A method 2 with ligand E as ligand and toluene as solvent: Benzamidine 2b (0.120 g, 1.00 mmol, 1.00 eq) afforded the title compound 8b (0.104 g, 0.494 mmol, 49 %) as a cream solid. 8b prepared by these additional routes was identical in all respects to that prepared as described above.

(Z)-N’-(4-cyanophenyl)benzamidine (8c)

Table 1, Entry 15: Using General Procedure A method 2 with L-proline as ligand and toluene as solvent: Benzamidine 2b (0.120 g, 1.00 mmol, 1.00 eq) afforded the title compound 8c (0.081 g, 0.410 mmol, 41%) as a white solid. Mp: 149-150 °C; IR (KBr): ν_max = 3488, 3345 (s) (NH_2), 2217 (s) (CN), 1643 (s) cm⁻¹; ¹H NMR (400 MHz, d_6-DMSO): δ 7.90 (d, 3 J = 6.8 Hz, 2H, C4-H, C8-H), 7.70 (d, 3 J = 8.4 Hz, 2H, C3’-H, C5’-H), 7.50-7.40 (m, 3H, C5-H, C6-H, C7-H), 6.97 (d, 3 J = 5.2 Hz, 2H, C2’-H, C6’-H), 6.70 (br. s, 2H, NH₂); ¹³C NMR (75.5 MHz, d_6-DMSO): ¹³C NMR (75.5 MHz, d_6-DMSO): δ 156.4 (C1’), 156.0 (C2), 135.1 (C3), 133.3 (C3’, C5’), 130.3 (C6), 128.0 (C5, C7), 127.3 (C4, C8), 122.8 (C2’, C6’), 119.7 (CN), 103.2 (C4’); LRMS (ES⁺): m/z (%) 222 (50) [M+H⁺], 244 (100) [M+23]⁺; HRMS (ES⁺): m/z calcd for C_{14}H_{13}N_{3}[M+H]^+: 222.1031; found 222.1028.

8c was also prepared using the following protocol:

Table S1, Entry S3: Using General Procedure A method 2 with ligand E as ligand and toluene as solvent: Benzamidine 2b (0.120 g, 1.00 mmol, 1.00 eq) afforded the title compound 8c (0.038 g, 0.193 mmol, 19 %) as a white solid.
8c prepared by this additional route was identical in all respects to that prepared as described above.

(Z)-N’-(4-nitrophenyl)benzamidine (8d)

![Chemical structure of (Z)-N’-(4-nitrophenyl)benzamidine (8d)](image)

**Table 1, Entry 16:** Using General Procedure A method 2 with L-proline as ligand and toluene as solvent: Benzamidine 2b (0.120 g, 1.00 mmol, 1.00 eq) afforded the title compound 8d (0.040 g, 0.166 mmol, 17%) as a yellow solid. Mp: 163-164 °C, Lit. S6-7168 °C; ¹H NMR (400 MHz, d₆-DMSO): δ 8.13-8.17 (m, 2H, C3’-H, C5’-H), 7.89-7.91 (m, 2H, C4-H, C8-H), 7.51-7.41 (m, 3H, C5-H, C6-H, C7-H), 7.01-6.97 (m, 2H, C2’-H, C6’-H), 6.84 (br. s, 2H, NH₂); LRMS (ES⁺): m/z (%) 242 (100) [M+H]⁺, (ES⁻): m/z (%) 240 (100) [M-H]⁻.

8d was also prepared using the following protocol:

**Table S1, Entry S4:** Using General Procedure A method 2 with ligand E as ligand and toluene as solvent: Benzamidine 2b (0.120 g, 1.00 mmol, 1.00 eq) afforded the title compound 8d (0.040 g, 0.166 mmol, 17%) as a yellow solid.

8d prepared by this additional route was identical in all respects to that prepared as described above.

(Z)-N’-(4-chlorophenyl)benzamidine (8e)

![Chemical structure of (Z)-N’-(4-chlorophenyl)benzamidine (8e)](image)

**Table 1, Entry 17:** Using General Procedure A method 2 with L-proline as ligand and toluene as solvent: Benzamidine 2b (0.120 g, 1.00 mmol, 1.00 eq) afforded the title compound 8e (0.116 g, 0.503 mmol, 50%) as a yellow solid. Mp: 114-115 °C, Lit. S3 114-115 °C; ¹H NMR (400 MHz, d₆-DMSO): δ 7.94 (d, 3J = 7.0 Hz, 2H, C4-H, C8-
H), 7.40-7.47 (m, 3H, C5-H, C6-H, C7-H), 7.31 (d, 3J = 8.4 Hz, 2H, C3’-H, C5’-H), 6.84 (d, 3J = 7.2 Hz, 2H, C2’-H, C6’-H), 6.41 (br. s, 2H, NH2); LRMS (ES+): m/z (%) 231 (100) [M+H]+.

8e was also prepared using the following protocol:

**Table S1, Entry S5:** Using General Procedure A method 2 with ligand E as ligand and toluene as solvent: Benzamidine 2b (0.120 g, 1.00 mmol, 1.00 eq) afforded the title compound 8e (0.082 g, 0.355 mmol, 35 %) as a yellow solid. 8e prepared by this additional route was identical in all respects to that prepared as described above.

(Z)-N’-(3-chlorophenyl)benzamidine (8f)

![Z-N’-(3-chlorophenyl)benzamidine (8f)](image)

**Table 1, Entry 18:** Using General Procedure A method 2 with L-proline as ligand and toluene as solvent: Benzamidine 2b (0.120 g, 1.00 mmol, 1.00 eq) afforded the title compound 8f (0.123 g, 0.534 mmol, 53%) as a yellow solid. Mp: 106-107 °C, Lit. S4 106-107 °C; 1H NMR (400 MHz, d6-DMSO) δ 7.95 (d, 3J = 6.4 Hz, 2H, C4-H, C8-H), 7.48-7.41 (m, 3H, C5-H, C6-H, C7-H), 7.30 (t, 1H, 3J = 7.6 Hz, C5’-H), 6.99 (d, 3J = 7.6 Hz, 1H, C4’-H), 6.85 (s, 1H, C2’-H), 6.78 (d, 3J = 7.6 Hz, 1H, C6’-H), 6.47 (br. s, 2H, NH2); LRMS (ES+): m/z (%) 231 (100) [M+H]+.

(Z)-N’-(3-trifluoromethyl)benzamidine (8g)

![Z-N’-(3-trifluoromethyl)benzamidine (8g)](image)

**Table 1, Entry 19:** Using General Procedure A method 2 with L-proline as ligand and toluene as solvent: Benzamidine 2b (0.120 g, 1.00 mmol, 1.00 eq) afforded the title compound 8g (0.096 g, 0.363 mmol, 36%) as a yellow solid.
Supplementary Information

Mp: 100-101 °C; No literature melting point for 8g can be found; $^1$H NMR (400 MHz, $d_6$-DMSO) $\delta$ 7.97 (d, $^3J$ = 5.2 Hz, 2H, C4-H, C8-H), 7.50-7.43 (m, 4H, C5-H, C6-H, C7-H, C5'-H), 7.29 (d, $^3J$ = 6.4 Hz, 1H, C4'-H), 7.12-7.08 (m, 2H, C2'-H, C6'-H), 6.53 (br. s, 2H, NH$_2$); LRMS (ES$^+$): m/z (%) 265 (100) [M+H]$^+$; HRMS (ES$^+$): m/z calcd for C$_{14}$H$_{12}$N$_2$F$_3$ [M+H]$^+$: 265.0953; found 265.0945.

8g was also prepared using the following protocol:

**Table S1, Entry S6:** Using General Procedure A method 2 with ligand E as ligand and toluene as solvent: Benzamidine 2b (0.120 g, 1.00 mmol, 1.00 eq) afforded the title compound 8g (0.074 g, 0.280 mmol, 28 %) as a yellow solid.

8g prepared by this additional route was identical in all respects to that prepared as described above.

(Z)-N'-(thiophen-2-yl)benzamidine (8h)

![Chemical structure of (Z)-N'-(thiophen-2-yl)benzamidine (8h)](image)

**Table 1, Entry 20:** Using General Procedure A method 2 with L-proline as ligand and toluene as solvent: Benzamidine 2b (0.120 g, 1.00 mmol, 1.00 eq) afforded the title compound 8h (0.074 g, 0.366 mmol, 37 %) as a brown oil. Mp: 87-88 °C; $^1$H NMR (400 MHz, $d_6$-DMSO) $\delta$ 7.94 (d, $^3J$ = 7.0 Hz, 2H, C4-H, C8-H), 7.51-7.43 (m, 3H, C5-H, C6-H, C7-H), 7.04 (d, $^3J$ = 5.5 Hz, 1H, C5'-H), 7.02 (br s, 2H, NH$_2$), 6.92 (dd, $^3J$ = 5.5 Hz, $^4J$ = 3.5 Hz, 1H, C4'-H), 6.56 (d, $^3J$ = 3.5 Hz, 1H, C3'-H), $^{13}$C NMR (75.5 MHz, $d_6$-DMSO): $\delta$ 155.0 (C2), 153.5 (C2'), 135.2 (C3), 130.4 (C6), 128.0 (C5, C7), 127.1 (C4, C8), 126.3 (C4'), 117.5 (C5'), 114.8 (C3'); LRMS (ES$^+$): m/z (%) 203 (100) [M+H]$^+$, HRMS (ES$^+$): m/z calcd for C$_{11}$H$_{11}$N$_2$S [M+H]$^+$: 203.0643; found 203.0639.

8h was also prepared using the following protocol:

**Table S1, Entry S7:** Using General Procedure A method 2 with ligand F as ligand and toluene as solvent; Benzamidine 2b (0.120 g, 1.00 mmol, 1.00 eq) afforded the title compound 8h (0.057 g, 0.282 mmol, 28 %) as a brown oil.
8h prepared by this additional route was identical in all respects to that prepared as described above.

(Z)-N’-(pyridine-4-yl)benzamidine (8i) \(^{S11-S12}\)

Table 1, Entry 21: Using General Procedure A method 2 with L-proline as ligand and toluene as solvent: Benzamidine 2b (0.120 g, 1.00 mmol, 1.00 eq) afforded the title compound 8i (0.103 g, 0.522 mmol, 52 %) as a green solid. Mp: 166-167 °C; Lit.\(^{S12}\) 147-149 °C; \(^1\)H NMR (400 MHz, d\(_6\)-DMSO) \(\delta\) 7.90 (d, \(J = 8.0\) Hz, 2H, C3’-H, C5’-H), 7.88 (m, 2H, C4-H, C8-H), 7.48-7.41 (m, 5H, C5-H, C6-H, C7-H, C2’-H, C6’-H), 6.67 (br. s, 2H, NH\(_2\)).

8i was also prepared using the following protocol:

Table S1, Entry S8: Using General Procedure A method 2 with ligand E as ligand and toluene as solvent; Benzamidine 2b (0.120 g, 1.00 mmol, 1.00 eq) afforded the title compound 8i (0.010 g, 0.051 mmol, 5 %) as a green solid.

8i prepared by this additional route was identical in all respects to that prepared as described above.

(Z)-N’-(biphenyl-4-yl)benzamidine (8j) \(^{S13-S14}\)

Table 1, Entry 22: Using General Procedure A method 2 with L-proline as ligand and toluene as solvent: Benzamidine 2b (0.120 g, 1.00 mmol, 1.00 eq) afforded the title compound 8i (0.057 g, 0.210 mmol, 21 %) as a brown solid. Mp 176-177 °C, Lit.
Supplementary Material (ESI) for Chemical Communications
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Supplementary Information

S14 126 °C; ¹H NMR (300MHz, d₆-DMSO) δ 7.98 (d, ³J = 7.5 Hz, 2H, C4-H, C8-H), 7.68-7.60 (m, 4H, C2’-H, C6’-H, C10’-H, C12’-H), 7.45-7.41 (m, 5H, C5-H, C6-H, C7-H, C7’-H, C9’-H), 7.30 (t, ³J = 7.5 Hz, 1H, C8’-H), 6.97 (d, ³J = 5.5 Hz, 2H, C3’-H, C11’-H), 6.42 (br. s, 2H, NH₂); LRMS (ES⁺): m/z (%) 273 (100) [M+H]⁺.

8j was also prepared using the following protocol:

**Table S1, Entry S9:** Using General Procedure A method 2 with ligand E as ligand and toluene as solvent; Benzamidine 2b (0.120 g, 1.00 mmol, 1.00 eq) afforded the title compound 8j (0.062 g, 0.227 mmol, 23 %) as a brown solid.

8j prepared by this additional route was identical in all respects to that prepared as described above.

(⁴N,N’-di-p-tolylbenzamidine (9b) S15

[Chemical structure image]

Using a modification of General Procedure A method 2 with ligand E as ligand, benzamidine 2b (120 mg, 1.00 mmol, 1.00 eq), iodotoluene (0.785 g, 3.60 mmol, 3.60 eq), Cs₂CO₃ (1.63 g, 5.00 mmol, 5.00 eq), CuI (60.0 mg, 0.030 mmol, 30 mol%) and ligand F (90.0 mg, 0.600 mmol, 60 mol%) afforded the title compound 9b (0.090 g, 0.20 mmol, 20%) as a white solid; Mp 132-133 °C, Lit. S15 134 -135 °C; ¹H NMR (400 MHz, d₆-DMSO): δ 9.01 (br. s,1H, NH), 7.74 (d, ³J = 8.0 Hz, 2H, C3’-H, C5’-H), 7.30-7.28 (m, 3H, C5-H, C6-H, C7-H), 7.25-7.23 (m, 2H, C4-H, C8-H), 7.06 (d, ³J = 7.6 Hz, 2H, C2’-H, C6’-H), 6.81 (d, ³J = 7.6 Hz, 2H, C3’-H, C5’-H), 6.43 (d, ³J = 8.0 Hz, 2H, C2’-H, C6’-H), 2.24 (s, 3H, CH₃), 2.12 (s, 3H, CH₃); LRMS (ES⁺): m/z (%) 301 (100) [M+H]⁺. An analytic sample of 9b suitable for small molecule X-ray crystallographic analysis was obtained by recrystallisation from ethyl acetate:hexane (1:5).
**Table S1. Synthesis of N-arylbenzamidines using CuI and Ligand E**

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6-methyl-3a-((triisopropylsilyl)oxy)-3,3a-dihydro-1H-pyrrolo[2,3-b]quinolin-4(2H)-one (10)

To a solution of 13 (232 mg, 0.484 mmol, 1.00 eq) in acetonitrile/water (1:1) (15 mL) at 0 °C was added CAN (1.19 g, 2.18 mmol, 4.50 eq) portionwise over a period of 4 hours and the resulting reaction mixture stirred at this temperature for a further 4 hours before being absorbed onto Hydromatrix™ under reduced pressure. Purification on pre-packed Biotage® KP-NH™ silica cartridges (1:0 to 10:1, DCM:MeOH) afforded the title compound 10 (90.0 mg, 0.242 mmol, 50%) as a yellow solid; Mp: 189-191°C; IR : ν \text{max} = 2943 (m), 2866 (m), 1696 (m) (C=O), 1664 (s), 1498 (s), 831 (w), 668 (w) cm⁻¹; ¹H NMR (400 MHz, MeOD): 7.45 (d, 3J = 1.6 1H, C5-H), 7.24 (dd, 3J = 7.8 Hz, 4J = 3.1 Hz, 1H, C8-H), 6.83 (d, 3J = 7.84 Hz, 1H, C7-H), 3.72-3.60 (m, 2H, C2-H), 2.29-2.14 (m, 2H, C3-H), 2.22 (s, 3H, CH3), 0.82-0.78 (m, 21H, OSi-(iPr)3); ¹³C NMR (100 MHz, THF-d8): 190.0 (C4), 163.7 (C9a), 142.6 (C8a), 134.4 (C7), 127.8 (C6), 125.7 (C5), 118.1 (C4a), 115.8 (C8), 78.7 (C3a), 49.1 (C2), 30.51 (C3), 17.5 (CH3), 15.7,15.5 (CH3-Osi-iPr), 11.1 (CH-Osi-iPr); LRMS (ES⁺): m/z (%) 373 (100) [M+H]+; HRMS (ES⁺): m/z calcd for C21H33N2O2Si [M+H]+: 373.5874; found 373.5698.

1-(4-methoxyphenyl)-6-methyl-2,3-dihydro-1H-pyrrolo[2,3-b]quinolin-4(9H)-one (11)
11 was prepared in 4 steps from methyl 2-amino-5-methylbenzoate (4) and 1-(4-methoxyphenyl)pyrrolin-2-one (5) as follows:

To a solution of 5-methyl-2-aminobenzoic acid (10.0 g, 66.2 mmol, 1.00 eq) in methanol (150 mL) was added concentrated sulphuric acid (15 mL) and the resulting mixture heated under reflux for 72 hours. The reaction mixture was then cooled and concentrated under reduced pressure. The resulting residue was washed with saturated NaHCO$_3$ (aq) (pH adjusted to 8) and extracted with ethyl acetate (3 x 100 mL). The combined organic layers were dried (MgSO$_4$), filtered and concentrated under reduced pressure to afford 4 (10.0 g, 60.6 mmol, 92%) as a brown solid. Mp: 69-70 °C (lit. S16 71 °C); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.66 (s, 1H, C6-H), 7.10 (dd, $^3$J = 8.4 Hz, $^4$J = 2.4 Hz, 1H, C4-H), 6.63 (d, $^3$J = 8.4 Hz, 1H, C3-H), 3.86 (s, 3H, OCH$_3$), 2.23 (s, 3H, CH$_3$); LRMS (ES$^+$): m/z (%) 165 (100) [M+H]$^+$.  

To a sealed Schlenk tube charged with p-iodo-anisole (20.1 g, 85.6 mmol, 1.10 eq), 2-pyrrolidinone (6.67 g 78.1 mmol, 1.00 eq), CuI (10 mol%), DiMED (20 mol%), K$_3$PO$_4$ (3.00 eq) and molecular sieves (4Å) at room temperature under an atmosphere of nitrogen was added toluene (67.0 mL). The resulting mixture was heated under reflux for 18 hours. The reaction mixture was then cooled, filtered through a pad of Celite® and washed with ethyl acetate (3 x 100 mL). Removal of solvent under reduced pressure afforded the crude product. Purification by flash chromatography on silica gel (1:20 to 1:1, hexane:ethyl acetate) afforded 5 (13.2 g, 69.1 mmol, 88%) as a white crystalline solid. Mp: 113-114 °C (lit. S17 112-114 °C); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.50 (d, $^3$J = 9.0 Hz, 2H, C2'-H, C6'-H), 6.91 (d, $^3$J = 9.0 Hz, 2H, C3'-H, C5'-H), 3.85-3.80 (m, 5H, C5-H$_2$, OCH$_3$), 2.60 (t, 2H, $^3$J = 8.0 Hz, C3-H$_2$), 2.20-2.14 (m, 2H, C4-H$_2$); LRMS (ES$^+$): m/z (%) 192 (100) [M+H]$^+$.  

To a solution of 5 (7.18 g, 37.5 mmol, 1.20 eq) in anhydrous DCM (72.0 mL) under a nitrogen atmosphere was added POCl$_3$ (5.75 g, 3.50 mL, 37.5 mmol, 1.20 eq) and the resulting mixture stirred at room temperature for 3 hours. A solution of 4 (5.16 g, 31.3 mmol, 1.00 eq) in dry DCM (10 mL) was then added to the reaction mixture and then heated under reflux for 18 hours. The reaction mixture was cooled, then diluted with DCM (50 mL) and washed with saturated NaHCO$_3$ (aq) (3 x 100 mL). The combined organic layers were dried (MgSO$_4$), filtered and absorbed onto celite® ($w/w$) under
reduced pressure. Purification by flash chromatography on pre-packed Biotage® KP-NH™ silica cartridges (1:0 to 10:1, DCM:MeOH) afforded methyl 2-((2-(4-methoxyphenyl)cyclopentylidene)amino)-5-methylbenzoate (S1) (9.67 g, 28.6 mmol, 91%) as a light brown oil; IR (KBr): \( \nu_{\text{max}} = 2950\ \text{m}, 1685\ \text{C=O}, 1240\ \text{s}\ \text{cm}^{-1} \); 

\[ \begin{align*}
1^H \text{NMR (400 MHz, CHCl}_3) & : \delta 7.71 \ (d, \ 3^J = 8.9 \ \text{Hz}, 2\ H, \ C3''-H, \ C5''-H), \ 7.66 \ (d, \ 4^J = 1.5 \ \text{Hz}, 1\ H, \ C6-H), \ 7.19 \ (dd, \ 3^J = 8.1 \ \text{Hz}, 1\ H, \ C3-H), \ 6.93 \ (d, \ 3^J = 8.9 \ \text{Hz}, 2\ H, \ C2''-H, \ C6''-H), \ 6.74 \ (d, \ 3^J = 8.1 \ \text{Hz}, 1\ H, \ C3-H), \ 3.87-3.84 \ (m, 5H, \ COOCH_3, \ C5'-H_2), \ 3.81 \ (s, 3H, \ OCH_3), \ 2.47 \ (t, \ 3^J = 7.8 \ \text{Hz}, 2\ H, \ C3'-H_2), \ 2.33 \ (s, 3H, \ CH_3), \ 2.02-2.10 \ (m, 2H, \ C4'-H_2); \ 13^C \text{NMR (100 MHz, CDCl}_3) : \delta 167.9 \ (C=O), \ 160.5 \ (C2'), \ 156.0 \ (C4'') \ 149.8 \ (C2), \ 134.2 \ (C1''), \ 133.6 \ (C4), \ 131.3 \ (C5), \ 131.0 \ (C6), \ 123.6 \ (C3), \ 122.8 \ (C2''), \ 122.0 \ (C1), \ 114.1 \ (C3''), \ 55.5 \ (OCH_3), \ 52.3 \ (4''-OCH_3), \ 51.6 \ (C5'), \ 29.2 \ (C3'), \ 20.6 \ (CH_3), \ 19.9 \ (C4'); \ LRMS (ES^+): m/z \ (% 339.22 (100) [M+H]^+, 361.22 (35) [M+Na]; HRMS (ES^+): m/z calec'd for C20H23N2O3 [M+H]^+: 339.1708; found 339.1709.
\end{align*} \]

To a solution of methyl 2-((2-(4-methoxyphenyl)cyclopentylidene)amino)-5-methylbenzoate (S1) (7.70 g, 22.8 mmol, 1.00 eq) in anhydrous THF (20 mL) at -78 °C under an atmosphere of nitrogen, was added LiHMDS (1M solution in THF, 57 mL, 57.0 mmol, 2.50 eq). The resulting reaction mixture was allowed to warm up to 0 °C over 3 hours before being quenched at 0 °C by the addition of saturated NH₄Cl (aq) (100 mL). The resulting mixture was then allowed to warm up to room temperature over 1 hour and the resultant precipitate was filtered off and washed with ice cold ethyl acetate (20 mL) affording the title compound 11 (6.16 g, 20.1 mmol, 89%) as a cream coloured solid. Mp: 254-255 °C; IR (KBr): \( \nu_{\text{max}} = 3419\ \text{m} (NH), 3039\ \text{m} (Ar-H), 1628\ \text{s} (C=O) \ \text{cm}^{-1} \); 

\[ \begin{align*}
1^H \text{NMR (400 MHz, THF}_d8) & : \delta 7.84 \ (s, 1H, \ C5-H), \ 7.28-7.19 \ (m, 4H, \ C7-H, \ C8-H, \ C3'-H, \ C5'-H), \ 6.96 \ (d, \ 3^J = 9.0 \ \text{Hz}, 2H, \ C2'-H, \ C6'-H), \ 3.95 \ (t, \ 3^J = 8.5 \ \text{Hz}, 2H, \ C2-H_2), \ 3.74 \ (s, 3H, \ OCH_3), \ 3.03 \ (t, \ 3^J = 8.5 \ \text{Hz}, 2H, \ C3-H_2), \ 2.31 \ (s, 3H, \ CH_3); \ 13^C \text{NMR (75.5 MHz, D}_8-\text{THF}) : \delta 159.3 \ \text{ppm (C4)}, \ 157.9 \ (C9a), \ 155.0 \ (C4'), \ 146.9 \ (C8a), \ 136.4 \ (C1'), \ 130.8 \ (C6), \ 130.3 \ (C7), \ 125.4 \ (C8), \ 121.4 \ (C5), \ 120.0 \ (C2', \ C4a), \ 113.9 \ (C3'), \ 105.6 \ (C3a), \ 55.0 \ (4'-OCH_3), \ 49.9 \ (C2), \ 22.5 \ (C3), \ 21.3 \ (CH_3); \ LRMS (ES^+): m/z \ (% 307.17 (100) [M+H]^+, LRMS (ES^+) m/z calc’d for C19H19N2O2 [M+H]^+: 307.1447; found: 307.1442.
\end{align*} \]
3a-chloro-1-(4-methoxyphenyl)-6-methyl-3,3a-dihydro-1H-pyrrolo[2,3-b]quinolin-4(2H)-one (12)

To a solution of 11 (3.93 g, 12.8 mmol, 1.00 eq) in THF/H2O (1:1) (40 mL) was added sodium dichloroisocyanurate (1.41 g 6.41 mmol, 0.50 eq) and the resulting reaction mixture stirred at room temperature for 4 hours. The resultant precipitate was filtered off and washed with ice cold THF:H2O (1:1) (10 mL) affording the title compound 12 (4.00 g, 11.7 mmol, 91%) as a red solid. Mp: Decomp. > 190 °C; IR (KBr): νmax = 3005 (m) (ArH), 1688(s) (C=O), 1247 (s) (C-O) cm⁻¹; ¹H NMR (500MHz, THF-d8): δ 7.99 (d, 3J = 7.0 Hz, 4J = 2.2 Hz, 2H, C3'-H, C5'-H), 7.63 (s, 1H, C5-H), 7.33 (dd, 3J = 8.1 Hz, 4J = 2.0 Hz, 1H, C7-H), 7.13 (d, 3J = 8.0 Hz, 1H, C8-H), 6.94 (dd, 2H, 3J = 7.0 Hz, 4J = 2.1 Hz, C2'-H, C6'-H), 4.20 (td, 3J = 10.0 Hz, 4J = 5.5 Hz, 1H, 1 x C2-H2), 4.03 (dd, 3J = 10.0 Hz, 4J = 8.0 Hz, 1H, 1 x C2-H2), 3.79 (s, 3H, OCH₃), 2.72-1.61 (m, 2H, C3-H2), 2.32 (s, 3H, CH₃); ¹³C NMR (75.5 MHz, THF-d8): 188.9 (C4), 161.8 (C9a), 156.5 (C4'), 149.2 (C8a), 136.6 (C7), 134.8 (C6), 134.0 (C1'), 126.5 (C5), 126.3 (C8), 121.3 (C3', C5'), 120.4, (C4a), 113.7 (C2', C6'), 62.4 (C3a), 54.9 (OCH₃), 47.5 (C2), 30.6 (C3), 20.0 (CH₃); LRMS (ES⁺): m/z (%) 341.06 (25) [M+H]+, 307.04 (100) [M-35Cl]+; HRMS (ES⁺): m/z calcd for C₁₉H₁₇ClN₂O₂ [M+H]+: 341.1052; found 341.1046.

(4-methoxy-1-(4-methoxyphenyl)-6-methyl-3a-((triisopropylsilyl)oxy)-3,3a-dihydro-1H-pyrrolo[2,3-b]quinolin-4(2H)-one (13)
13 was prepared from 12 in 2 steps as follows: To a solution of 12 (4.14 g, 13.5 mmol, 1.00 eq) in THF/H2O (1:1) (40 mL) was added 2 M NaOHaq (25 mL, 25.0 mmol, 1.85 eq) and the resulting reaction mixture stirred at room temperature for 18 hours. The reaction was then diluted with DCM (200 mL) and washed with saturated NH4Cl(aq) (3 x 100 mL). The combined organic layers were dried (MgSO4), filtered and absorbed onto Celite® (w/w) under reduced pressure. Purification by flash chromatography on pre-packed Biotage® silica cartridges (5:1 to 1:1, hexane:ethyl acetate) afforded 3a-hydroxy-1-(4-methoxyphenyl)-6-methyl-3,3a-dihydro-1H-pyrrolo[2,3-b]quinolin-4(2H)-one (3a) (2.30 g, 7.13 mmol, 52%) as a bright orange solid; Mp: 207-209 °C; IR (KBr): νmax = 3429 (m) (OH), 3039 (m) (Ar-H), 1693 (s) (C=O), 1245 (s) (C=O) cm⁻¹; 1H NMR (400 MHz, CDCl3): δ 7.66-7.70 (m, 2H, C3'-H, C5'-H), 7.54 (d, 4J = 2.0 Hz, 1H, C5-H), 7.03 (dd, 3J = 8.0 Hz, 4J = 2.0 Hz, 1H, C7-H), 6.91-6.88 (m, 2H, C2'-H, C6'-H), 6.86 (d, 3J = 8.0 Hz, 1H, C8-H), 4.38 (br. s, 1H, OH), 3.77 (s, 3H, OCH3), 3.74-3.70 (m, 1H, 1 x C2-H2), 3.65 (t, 3J = 8.9 Hz, 1H, 1 x C2-H2), 2.31 (dd, 3J = 13.7 Hz, 4J = 5.4 Hz, 1H, 1 x C3-H2), 2.23 (s, 3H, CH3), 2.09-2.17 (m, 1H, 1 x C3-H2); 13C NMR (100 MHz, CDCl3): δ 194.3 (C4), 164.4 (C9a), 156.6 (C4'), 148.8 (C8a), 137.3 (C7), 133.1 (C1'), 133.0 (C6), 127.2 (C5), 125.8 (C8), 122.0 (C2'), 120.0 (C4a), 114.0 (C3'), 73.8 (C3a), 55.6 (OCH3), 48.7 (C2), 29.1 (C3), 20.6 (CH3). LRMS (ES⁺): m/z (%) 323 (100) [M+H]⁺; HRMS (ES⁺): m/z calcd for C19H19N2O3 [M+H]⁺: 332.1396; found 323.1397.

To a solution of 3a (1.10 g, 3.41 mmol, 1.00 eq) in anhydrous DCM (20 mL) under an atmosphere of nitrogen was added anhydrous DIPEA (1.76 g, 2.37 mL, 13.7 mmol, 4.00 eq) followed by TIPS-OTf (3.13 g, 2.76 mL, 10.2 mmol, 3.00 eq). The resulting reaction mixture was then heated under reflux for 6 hours then cooled and quenched by addition of saturated NH4Cl(aq) (50 mL) and extracted with DCM (3 x 50 mL). The combined organic layers were dried (MgSO4), filtered and absorbed onto Celite® (w/w) under reduced pressure. Purification by flash chromatography on silica gel (1:0 to 3:1, hexane:ethyl acetate) afforded the title compound 13 (1.31 g, 2.73 mmol, 80%) as a bright orange solid; Mp: 138-140 °C; IR : νmax = 2961 (m), 2857 (m), 1692 (m) (C=O), 1599 (s), 1480 (s), 1294 (m), 831 (w), 739 (w) cm⁻¹; 1H NMR (400 MHz, MeOD): 7.75 (dd, 3J = 6.5 Hz, 4J = 2.5 Hz, 2H, C3'-H, C5'-H), 7.54 (d, 4J = 1.5 Hz, 1H, C5-H), 7.23 (dd, 3J = 8.5 Hz, 4J = 2.0 Hz, 1H, C7-H), 7.08 (d, 3J = 8.5 Hz, 1H, C8-H), 6.90 (dd, 3J = 6.5 Hz, 4J = 2.5 Hz, 2H, C2'-H, C6'-H), 4.05-3.98 (m, 1H, 1 x
C2-H2, 3.88-3.80 (m, 1H, 1 x C2-H2), 3.72 (s, 3H, OCH3), 2.42-2.38 (m, 1H, 1 x C3-H2), 2.27-2.20 (m, 1H, 1 x C3-H2), 2.21 (s, 3H, CH3), 0.78-0.83 (m, 21H, OSi-iPr);
13C NMR (75.5 MHz, CDCl3): δ 195.1 (C4), 165.0 (C9a), 156.3 (C4'), 149.8 (C8a), 137.0 (C7), 133.8 (C1'), 132.7 (C6), 127.1 (C5), 126.0 (C8), 122.0 (C4a), 121.5 (C2'), 114.2 (C3'), 75.3 (C3a), 55.5 (OCH3), 48.5 (C2), 30.4 (C3), 20.6 (CH3), 17.9, 17.8 (CHCH3), 13.2 (OSiCH); LRMS (ES+): m/z (%) 479 (100) [M+]+; HRMS (ES+): m/z calcd for C28H39N2O3Si [M+H]+ : 479.2730; found 479.2719.

**General Procedure C:** The CuI Mediated synthesis of O-TIPS-blebbistatin (14).

To a sealed tube charged with Cs2CO3 (3.00 eq), aryl iodide (1.20 eq), 10 (1.00 eq) and molecular sieves 4Å at room temperature and under an atmosphere of nitrogen was added the catalyst ligand combination of [CuI (10 mol%) and ligand (20 mol%)], for each respective ligand under an atmosphere of nitrogen. Toluene (2 mL) was then added and the resulting mixture was heated at 120 °C for 24 hours. The crude reaction mixture was cooled, filtered through a pad of Celite® and absorbed onto Celite® under reduced pressure. Purification by flash column chromatography using pre-packed Biotage® 10 g silica gel cartridges (1:0 to 1:2, hexane:ethyl acetate) afforded the title compound.

**Table 2, Entry 5:** Using general procedure C with ligand E and aryl iodide 6k, 10 (0.10 g, 0.27 mmol, 1.00 eq) afforded the title compound 14 (0.008 g, 1.872 exp-5 mmol, 7%). Mp: 88-89 °C; IR : νmax = 2961 (m), 2857 (m), 1692 (m) (C=O), 1599 (s), 1480 (s), 1294 (m), 831 (w), 739 (w) cm⁻¹; 1H NMR (500 MHz, THF-d8): 8.01 (d, 3J = 7.8 Hz, 2H, C6'-H, C2'-H), 7.47 (s, 1H, C5-H), 7.25-7.18 (m, 3H, C3'-H, C5'-H, C8-H), 7.02 (d, 3J = 7.30 Hz 1H, C4'-H), 4.03-3.98 (m, 1H, 1 x C2-H2), 3.70-3.86 (m, 1H, 1 x C2-H2) 2.33-2.22 (m, 2H, C3-H2), 2.19 (s, 3H, CH3), 0.78-0.84 (m, 21H, OSi-iPr); 13C NMR (75.5 MHz, CDCl3): δ 193.7 (C4),
165.1 (C9a), 149.7 (C8a), 141.1 (C4a), 136.1 (C7), 132.6 (C1'), 128.2 (2',6'), 126.8 (C5), 126.6 (C8), 121.7 (C6), 119.3 (C3',C5'), 75.4 (C3a), 47.6 (C2), 29.8 (C5), 126.6 (C8), 121.7 (C6), 119.3 (C3',C5'), 75.4 (C3a), 47.6 (C2), 29.8 (C3), 19.7 (CH3), 16.9 (CH - OSi-Pr), 13.0 (CH3- OSi-Pr); LRMS (ES⁺): m/z (%) 449 (100) [M+H]+, 471 (100) [M+23]+; HRMS (ES⁺): m/z calcd for C27H37N2O2Si [M+H]+: 449.2631; found 479.2624.

14 was also prepared using the following protocols:

**Table 2, Entry 6:** Using general procedure C with ligand D, 10 (0.10 g, 0.27 mmol, 1.00 eq) afforded the title compound 14 (0.031 g, 0.067 mmol, 25%).

**Table 2, Entry 7:** Using general procedure C method 1 with ligand E, 10 (0.10 g, 0.27 mmol, 1.00 eq) afforded the title compound 14 (0.096 g, 0.218 mmol, 80%).

**Table 2, Entry 8:** Using general procedure C method 2 with ligand E, 10 (0.10 g, 0.27 mmol, 1.00 eq) afforded the title compound 14 (0.057 g, 0.127 mmol, 47%).

14 prepared by these additional routes was identical in all respects to that prepared as described above.

**General Procedure B: The CuI Mediated synthesis of N-Aryl Blebbistatin Analogues.**

To a sealed tube charged with Cs2CO3 (3.00 eq), aryl iodide (1.20 eq), 10 (1.00 eq) and molecular sieves 4Å at room temperature and under an atmosphere of nitrogen was added either the catalyst ligand combination of [CuI (10 mol%) and ligand (20 mol%)], method 1 or [CuI (5 mol%) and ligand (10 mol%)], method 2 respectively. Toluene (2 mL per mmol) was then added and the resulting mixture was heated at 120 °C for 24 hours. The reaction was cooled, filtered through a pad of silica and concentrated under reduced pressure. The resulting residue was redissolved in THF (1 mL) and treated with TBAF (3.00 eq) for a further 2 hours and then absorbed onto Celite® under reduced pressure. Purification by flash column chromatography using pre-packed Biotage® 10 g silica gel cartridges (1:0 to 1:2, hexane:ethyl acetate) afforded the title compounds.

3a-hydroxy-1-(4-methoxyphenyl)-6-methyl-3,3a-dihydro-1H-pyrrolo[2,3-b]quinolin-4(2H)-one (3a)
Using General Procedure B with CuI (10 mol%), ligand E (20 mol%) and 10 (80.0 mg, 0.210 mmol, 1.00 eq) afforded the title compound 3a (40.0 mg, 0.139 mmol, 66 %) as a yellow solid; Spectroscopic analysis showed that the sample of 3a prepared by this method was identical in all regards to that prepared from 12 as described above.

3a-hydroxy-6-methyl-1-(p-tolyl)-3,3a-dihydro-1H-pyrrolo[2,3-b]quinolin-4(2H)-one (3b)

Using General Procedure B with CuI (10 mol%), ligand E (20 mol%) and 10 (80.0 mg, 0.210 mmol, 1.00 eq) afforded the title compound 3b (40.0 mg, 0.132 mmol, 63 %) as a yellow solid; Mp: Decomp; > 190 °C; IR (KBr): \( \nu_{\text{max}} = 3379 \) (m) (OH), 2926 (m) (Ar-H), 1670 (s) (C=O), 1600 (s), 1513 (s), 1471 (s), 1405 (m), 1292 (s) cm\(^{-1}\); \(^1\)H NMR (500 MHz, THF-d8): 8.01 (d, \( J = 8.1 \) Hz, 2H, C3'-H, C5'-H), 7.58 (s, 1H, C5-H), 7.28 (dd, \( J = 8.1 \) Hz, \( J = 1.4 \) Hz H, C7-H), 7.16 (d, \( J = 8.1 \) Hz, 2H, C2'-H, C6'-H), 7.12 (d, \( J = 7.5 \) Hz, 1H, C8-H), 5.85 (br. S, 1H, OH), 4.11-4.05 (m, 1H, \( \text{NCH}_2 \)), 3.92 (t, \( J = 7.5 \) Hz, 1H, 1 x NCH\(_2\)), 2.32-2.21 (m, 2H, NCH\(_2\)CH\(_2\)), 2.36 (s, 3H, Ar-CH\(_3\)), 2.32 (s, 3H, Ar-CH\(_3\)); \(^{13}\)C NMR (75.5 MHz, CD\(_2\)Cl\(_2\)): \( \delta \) 194.2 (C4), 165.3 (C9a), 149.8 (C8a), 138.9 (C1'), 136.0 (C7), 132.4 (C4a), 132.0 (C4'), 129.2 (C2', 6'), 126.3 (C8), 126.3 (C5), 121.3 (C6), 119.1 (C3', 5'), 73.2 (C3a), 47.4 (C2), 28.9 (C3), 20.1 (C4'-CH\(_3\)), 19.7 (C6-CH\(_3\)); LRMS (ES\(^+\)) : m/z (%) 307 (14) [M+H\(^+\)], 329 (100) [M+Na\(^+\)], 347 (90) [M+CH\(_3\)CN\(^+\)]; HRMS (ES\(^+\)) : m/z calcd for C\(_{19}\)H\(_{19}\)N\(_2\)O\(_2\) [M+H\(^+\)]\(^+\): 307.1447; found 307.1436.
1-(4-chlorophenyl)-3a-hydroxy-6-methyl-3,3a-dihydro-1H-pyrrolo[2,3-b]quinolin-4(2H)-one (3e)

Using General Procedure B with CuI (10 mol%), ligand E (20 mol%) and 10 (80.0 mg, 0.210 mmol, 1.00 eq) afforded the title compound 3e (40.0 mg, 0.139 mmol, 66%) as a yellow solid; Mp: Decomp; > 190 °C; IR (KBr): $\nu_{\text{max}} = 3172$ (m) (OH), $2916$ (m) (Ar-H), $1690$ (s) (C=O), $1606$ (s), $1496$ (s), $1476$ (s), $1295$ (s) cm$^{-1}$; $^1$H NMR (400 MHz, THF-d8): $8.13$ (d, $^3J = 7.0$ Hz, 2H, C2'-H, C6'-H), $7.27$ (s, 1H, C4'-H), $7.10$ (d, $^3J = 7.5$ Hz, 1H, C5-H), $4.07-4.03$ (m, 1H, 1 x NCH$_2$), $3.90$ (t, $^3J = 7.5$ Hz, 1H, 1 x NCH$_2$), $2.29-2.19$ (m, 2H, NCH$_2$CH$_2$), $2.31$ (s, 3H, Ar-CH$_3$); $^{13}$C NMR (125 MHz, THF-d8): $\delta$ 192.1 (C4), 163.6 (C9a), 147.2 (C8a), 138.1 (C1'), 134.4 (C7), 130.9 (C4a), 126.5 (C2', 5'), 125.9 (C4'), 124.5 (C8), 124.4 (C5), 119.5 (C6), 118.5 (C2', 6'), 71.1 (C3a), 44.6 (C2), 26.9 (C3), 17.8 (CH$_3$); LRMS (ES$^+$): m/z (%) 327 (100) [M+H]$^+$; HRMS (ES$^+$): m/z calcld for C$_{18}$H$_{16}$N$_2$O$_2$Cl [M+H]$^+$: 327.0895; found 327.0896.

3a-hydroxy-6-methyl-1-(3-(trifluoromethyl)phenyl)-3,3a-dihydro-1H-pyrrolo[2,3-b]quinolin-4(2H)-one (3g)

Using General Procedure B with CuI (5 mol%), ligand E (10 mol%) and 10 (80.0 mg, 0.210 mmol, 1.00 eq) afforded the title compound 3g (10.0 mg, 0.040 mmol, 19%) as a yellow solid; Mp: 208-209 °C; IR (KBr): $\nu_{\text{max}} = 3374$ (m) (OH), $2924$ (m) (Ar-H), $1697$ (s) (C=O), $1629$ (s), $1609$ (s), $1459$ (s), $1334$ (s), $1123$ (s) cm$^{-1}$; $^1$H NMR (400 MHz, DMSO-d6): $8.79$ (s, 1H, C2'-H), $8.14$ (dd, $^3J = 7.0$ Hz, $^4J = 2.0$ Hz, 1H, C4'-
3a-hydroxy-6-methyl-1-(thiophene-2-yl)-3,3a-dihydro-1H-pyrrolo[2,3-b]quinolin-4(2H)-one (3h)

Using General Procedure B with CuI (10 mol%), ligand E (20 mol%) and 10 (80.0 mg, 0.210 mmol, 1.00 eq) afforded the title compound 3h (30.0 mg, 0.110 mmol, 53%) as a yellow solid; Mp: Decomp; > 190 °C; IR (KBr): νmax = 3433 (s) (OH), 3030 (m) (ArH), 2921 (m) (CH2), 1687 (s) (C=O), 1616 (C=C) cm⁻¹; ¹H NMR (500 MHz, THF-d8): 7.55 (d, 3J = 2.5 Hz, 1H, C5'-H), 7.27 (dd, 3J = 7.5 Hz, 4J = 2.5 Hz, 1H, C7-H), 7.14 (d, 3J = 7.2 Hz, 1H, C8-H), 6.93-6.92 (m, 1H, C5'-H), 6.84-6.82 (m, 1H, C4'-H), 6.73-6.72 (m, 1H, C3'-H), 5.89 (br. s, 1H, OH), 4.09-4.04 (m, 1H, 1 x C2-H), 3.95-3.92 (m, 1H, 1 x C2-H), 2.33-2.30 (m, 2H, C3-H2), 2.26 (s, 3H, CH3). ¹³C NMR (125 MHz, THF-d8): δ 193.8 (C4), 162.6 (C9a), 148.9 (C8a), 141.7 (C2'), 136.0 (C7), 132.4 (C4a), 126.8 (C5), 125.9 (C8), 123.6 (C4'), 121.5 (C6), 117.9 (C5'), 110.5 (C2'), 72.3 (C3a), 48.4 (C2), 29.5 (C3), 19.9 (CH3); LRMS (ES⁺): m/z (%) 299 (50) [M+H⁺], 242 (100); HRMS (ES⁺): m/z calcld for C16H14N2O2S [M+H⁺]: 299.0854; found 299.0862.

3a-hydroxy-6-methyl-1-(pyridine-4-yl)-3,3a-dihydro-1H-pyrrolo[2,3-b]quinolin-4(2H)-one (3i)
Using General Procedure B with Cul (10 mol%), ligand F (20 mol%) and 10 (80.0 mg, 0.210 mmol, 1.00 eq) afforded the title compound 3i (40.0 mg, 0.140 mmol, 71%) as a yellow solid; Mp: decomp. > 255 °C; (KBr): ν max = 3438 (m) (OH), 2921 (m) (ArH), 1700 (s) (C=O), 1631 (m), 1587 (s), 1405 (m) cm⁻¹; ¹H NMR (500 MHz, THF d-8): 8.13-8.12 (dd, 3J = 7.1 Hz, 4J = 1.9 Hz, 2H, C3'-H, C5'-H), 7.56 (d, 3J = 1.2 Hz, 1H, C5-H), 7.31 (dd, 3J = 7.1 Hz, 4J = 1.9 Hz 2H, C2'-H, C6'-H), 7.27 (dd, 3J = 8.2 Hz, 4J = 2.0 Hz, 1H, C7-H), 7.10 (d, 3J = 8.2 Hz, 1H, C8-H), 4.06-4.02 (m, 1H, 1 x C2-CH₂), 3.90 (t, 3J = 8.4 Hz, 1H, 1 x C2-CH₂), 2.31-2.22 (m, 2H, C3-CH₂), 2.26 (s, 3H, Ar-CH₃); ¹³C NMR (125 MHz, DMSO d-6): δ 194.1 (C4), 165.9 (C9a), 150.1 (C5', C3') 147.7 (C8a), 146.4 (C1'), 136.4 (C7), 133.5 (C4a), 126.4 (C5), 126.2 (C8), 121.1(C6), 112.8 (C2', 6'), 72.5 (C3a), 46.5 (C2), 27.8 (C3), 20.2 (CH₃); LRMS (ES⁻): m/z (%) 292 (100) [M-H]⁻; HRMS (ES⁻): m/z calcd for C₁₇H₁₄N₃O₂ [M-H]⁻: 292.1086; found 292.1078.

1-([1,1'-biphenyl]-4-yl)-3α-hydroxy-6-methyl-3,3α-dihydro-1H-pyrrolo[2,3-b]quinolin-4(2H)-one (3j)

Using General Procedure with Cul (5 mol%), ligand F (10 mol%) and 10 (80.0 mg, 0.210 mmol, 1.00 eq) afforded the title compound 3j (20.0 mg, 0.070 mmol, 34%) as a yellow solid; Mp: decomp. > 190 °C; IR (KBr): ν max = 3364 (m) (OH), 2921 (m) (ArH), 1668 (s) (C=O), 1604 (s), 1501 (s), 1233 (s) cm⁻¹; ¹H NMR (500 MHz, THF-d8): 9.7 (s, H, OH), 7.58 (s, H, C5-H), 7.44 (d, 3J = 8.0 Hz, 2H, C-2''H, C-6''H), 7.29-7.25 (m, 5H, 3'-H, 3''-H, 5'-H, 5''-H, 7-H), 7.11 (t, 3J = 7.5 Hz, H, C4'-H), 6.82 (d, 4J = 8.0 Hz H, C8-H), 6.50 (d, 3J = 8.5 Hz, 2H, C2'-H, C6'-H), 3.30-3.20 (m, 2H, C2-
H_2), 2.26 (s, 3H, CH_3), 2.09-1.99 (m, 2H, C3-H_2); ^13^C NMR (125 MHz, THF-d8): δ 193.1 (C4), 170.4 (C9a), 146.2 (C1'), 139.7 (C1''), 137.4 (C8a), 134.2 (C7), 130.1 (C4a), 127.0 (C4'''), 126.5 (C3', C5'''), 125.5 (C3'', C5''), 125.3 (C5), 123.6 (C2'', C6''), 123.4 (C4''), 117.9 (C6), 113.8 (C8), 110.7 (C2', C6') 78.9 (C3a), 36.9 (C3), 36.2 (C2), 17.9 (CH_3); LRMS (ES^+): m/z (%) 369 (80) [M+H]^+; HRMS (ES^+): m/z calcd for C_{24}H_{21}N_2O_2 [M+H]^+: 369.1603; found 369.1609.
6-methyl-3a-((triisopropylsilyl)oxy)-3,3a-dihydro-1H-pyrrolo[2,3-b]quinolin-4(2H)-one (10)
2-((2-(4-methoxyphenyl)cyclopentylidene)amino)-5-methylbenzoate (S1)

1-(4-methoxyphenyl)-6-methyl-2,3-dihydro-1H-pyrrolo[2,3-b]quinolin-4(9H)-one (11)
3a-chloro-1-(4-methoxyphenyl)-6-methyl-3a-dihydro-1H-pyrrolo[2,3-b]quinolin-4(2H)-one (12)
3a-hydroxy-1-(4-methoxyphenyl)-6-methyl-3,3a-dihydro-1H-pyrrolo[2,3-b]quinolin-4(2H)-one (3a)
(4-methoxy-1-(4-methoxyphenyl)-6-methyl-3a-((triisopropylsilyl)oxy)-3,3a-
dihydro-1H-pyrrolo[2,3-b]quinolin-4(2H)-one (13)
O-TIPS-blebbistatin (14)
3a-hydroxy-6-methyl-1-(p-tolyl)-3,3a-dihydro-1H-pyrrolo[2,3-b]quinolin-4(2H)-one (3b)
1-(4-chlorophenyl)-3a-hydroxy-6-methyl-3,3a-dihydro-1H-pyrrolo[2,3-b]quinolin-4(2H)-one (3e)
3a-hydroxy-6-methyl-1-(3-(trifluoromethyl)phenyl)-3,3a-dihydro-1H-pyrrolo[2,3-b]quinolin-4(2H)-one (3g)
3a-hydroxy-6-methyl-1-(thiophene-2-yl)-3,3a-dihydro-1H-pyrrolo[2,3-b]quinolin-4(2H)-one (3h)
3a-hydroxy-6-methyl-1-(pyridine-4-yl)-3,3a-dihydro-1H-pyrrolo[2,3-b]quinolin-4(2H)-one (3i)
1-(1,1'-biphenyl)-4-yl)-3a-hydroxy-6-methyl-3,3a-dihydro-1H-pyrrolo[2,3-b]quinolin-4(2H)-one (3j)
(Z)-N’-(4-methoxyphenyl)benzamidine (8a)

(Z)-N’-p-tolylbenzamidine (8b)
(Z)-N'-{(4-cyanophenyl)benzamidine (8c)
(Z)-N'(3-chlorophenyl)benzamidine (8f)

\[
\begin{align*}
\text{NH}_2 & \quad \text{N} \\
\text{Cl} & \quad \text{NH}_2 \\
\end{align*}
\]

(Z)-N'(3-trifluoromethyl)benzamidine (8g)

\[
\begin{align*}
\text{NH}_2 & \quad \text{N} \\
\text{F} & \quad \text{F} \\
\end{align*}
\]
(Z)-N'-(thiophen-2-yl)benzamidine (8h)
(Z)-N’-(pyridine-4-yl)benzamidine (8i)

(Z)-N’-(biphenyl-4-yl)benzamidine (8j)
(E)-N,N'-di-p-tolylbenzamidine (9b)
General experimental

Chemicals and reagents were used as received unless otherwise stated. All reactions involving moisture sensitive reagents were performed in oven dried glassware under a positive pressure of argon. Toluene were obtained dry from a solvent purification system. DMSO and DMF were dried by standing over molecular sieves for several days prior to use. Thin-layer chromatography was performed using glassplates coated with silica gel (with fluorescent indicator UV254). Developed plates were air-dried and analysed under a UV lamp. Flash column chromatography was performed using silica gel (40-63 μm). Melting points were recorded in open capillaries. Values are quoted to the nearest 1 °C and are uncorrected. Infrared spectra were recorded using either thin films on NaCl plates (NaCl) or KBr discs (KBr) as stated. Absorption maxima are reported as wavenumbers (cm⁻¹) and intensities are quoted as strong (s), medium (m), weak (w) and broad (br). Low resolution (LR) and high resolution (HR) electrospray mass spectral (ES-MS) analyses were acquired by electrospray ionisation (ESI), electron impact (EI) or chemical ionisation (CI). Low and high resolution ESI MS were carried out on a Micromass LCT spectrometer and low and high resolution CI MS were recorded on a high performance orthogonal acceleration reflecting TOF mass spectrometer, coupled to a HPLC. Only the major peaks are reported and intensities are quoted as percentages of the base peak. Nuclear magnetic resonance (NMR) spectra were acquired on either a 300 (¹H, 300.1 MHz; ¹³C, 75.5 MHz), 400 (¹H, 400 MHz; ¹³C, 100.1 MHz) or a 500 (¹H, 500 MHz; ¹³C, 125 MHz) spectrometer and in the deuterated solvent stated. ¹³C NMR spectra were acquired using the PENDANT or DEPTQ pulse sequences. All NMR spectra were acquired using the deuterated solvent as the lock. Coupling constants (J) are quoted in Hz and are recorded to the nearest 0.5 Hz.
References

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