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 Cs_2CO_3 (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 respectivly 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.

***p*-Anisidine (7a)**[S1]

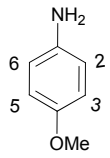


Table 1, Entry 1: Using a modification General procedure A, method 1; L-proline as ligand and DMF as solvent minus 4 Å molecular sieves: Acetamidine hydrochloride **1** (0.095 g, 1.00 mmol, 1.0 eq) afforded the title compound **7a** (0.0593 g, 0.479 mmol, 48%) as a light brown solid: Mp: 55-57 °C, Lit. [S1] 56-57 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47 (d, ^3J = 6.8 Hz, 2H, C3-H, C5-H), 6.60 (d, ^3J = 6.8 Hz, 2H, C2-H, C6-H) 3.68 (s, 3H, OCH_3); LRMS (ES^+): *m/z* (%) 124 (65) $[M+H]^+$.

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 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.

7a prepared by these additional routes was identical in all respects to that prepared as described above.

(*Z*)-*N'*-(4-methoxyphenyl)benzamidine (8a) [S2,3]

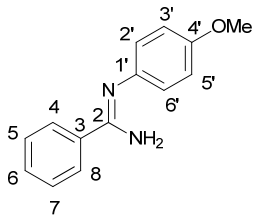


Table 1, Entry 4: Using General Procedure A method 1; L-proline as ligand and DMF as solvent; Benzamidine **2a** (0.157 g, 1.00 mmol, 1.00 eq) afforded the title compound **8a** (0.110 g, 0.48 mmol, 48 %) as a cream solid.

Mp: 116-117 °C, Lit. [S3] 114-116 °C; ^{1}H NMR (400 MHz, d_6-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, NH_2), 3.72 (s, 3H, OCH_3); 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)[S4]

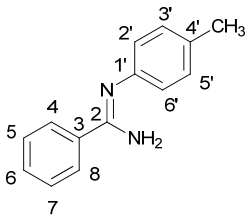


Table 1, Entry 7: Using General Procedure A method 1; L-proline as ligand and DMF as solvent: Benzamidine **2b** (0.661 g, 5.50 mmol, 1.00 eq) afforded the title compound **8b** (0.760 g, 3.614 mmol, 66 %) as a cream solid. Mp: 93-94 °C, Lit. [S4] 99-100 °C; ^{1}H NMR (400 MHz, d_6-DMSO): δ 7.94 (d, ^{3}J = 7.2 Hz, 2H, C4-H, C8-H), 7.47-7.39 (m, 3H, C5-H, C6-H, C7-H), 7.11 (d, ^{3}J = 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)

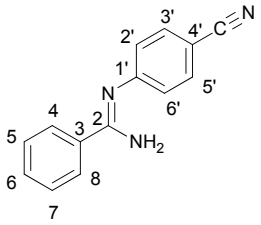


Table 1, Entry 15: Using General Procedure A method 2 with L-proline as ligand and toluene as solvent: Benzamidine **2b** (0.120 g, 1.00 mmol, 1.00 eq) afforded the title compound **8c** (0.081 g, 0.410 mmol, 41%) as a white solid. Mp: 149-150 °C; IR (KBr): ν_{max} = 3488, 3345 (s) (NH_2), 2217 (s) (CN), 1643 (s) cm^{-1}; ^1H NMR (400 MHz, d_6-DMSO): δ 7.90 (d, ^3J = 6.8 Hz, 2H, C4-H, C8-H), 7.70 (d, ^3J = 8.4 Hz, 2H, C3'-H, C5'-H), 7.50-7.40 (m, 3H, C5-H, C6-H, C7-H), 6.97 (d, ^3J = 5.2 Hz, 2H, C2'-H, C6'-H), 6.70 (br. s, 2H, NH_2); ^{13}C NMR (75.5 MHz, d_6-DMSO): ^{13}C 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 $C_{14}H_{14}N_3$ $[M+H]^+$: 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) [S5-7]

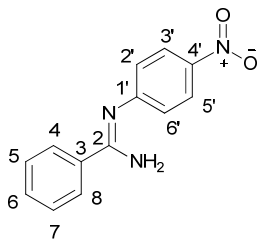


Table 1, Entry 16: Using General Procedure A method 2 with L-proline as ligand and toluene as solvent: Benzamidine **2b** (0.120 g, 1.00 mmol, 1.00 eq) afforded the title compound **8d** (0.040 g, 0.166 mmol, 17%) as a yellow solid. Mp: 163-164 °C, Lit. [S6-7]168 °C; ^{1}H NMR (400 MHz, d_6-DMSO): δ 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, NH_2); 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) [S3,S4]

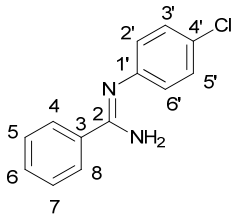


Table 1, Entry 17: Using General Procedure A method 2 with L-proline as ligand and toluene as solvent: Benzamidine **2b** (0.120 g, 1.00 mmol, 1.00 eq) afforded the title compound **8e** (0.116 g, 0.503 mmol, 50%) as a yellow solid. Mp: 114-115 °C, Lit. [S3] 114-115 °C; ^{1}H NMR (400 MHz, d_6-DMSO): 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, NH_2); 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) [S4,8]

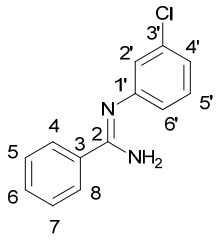


Table 1, Entry 18: Using General Procedure A method 2 with L-proline as ligand and toluene as solvent: Benzamidine **2b** (0.120 g, 1.00 mmol, 1.00 eq) afforded the title compound **8f** (0.123 g, 0.534 mmol, 53%) as a yellow solid. Mp: 106-107 °C, Lit. [S4] 106-107 °C; ^{1}H NMR (400 MHz, d_6-DMSO) 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, NH_2) ; LRMS (ES^+): *m/z* (%) 231 (100) $[M+H]^+$.

(*Z*)-*N'*-(3-trifluoromethyl)benzamidine (8g) [S9-10]

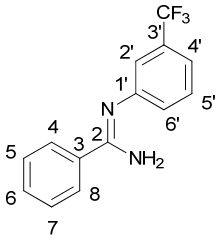


Table 1, Entry 19: Using General Procedure A method 2 with L-proline as ligand and toluene as solvent: Benzamidine **2b** (0.120 g, 1.00 mmol, 1.00 eq) afforded the title compound **8g** (0.096 g, 0.363 mmol, 36 %) as a yellow solid.

Mp: 100-101 °C; No literature melting point for **8g** can be found; ^{1}H NMR (400 MHz, d_6-DMSO) δ 7.97 (d, ^{3}J = 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, ^{3}J = 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 $C_{14}H_{12}N_2F_3$ $[M+H]^+$: 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)

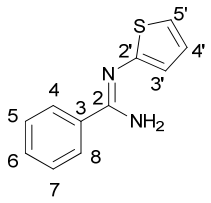


Table 1, Entry 20: Using General Procedure A method 2 with L-proline as ligand and toluene as solvent: Benzamidine **2b** (0.120 g, 1.00 mmol, 1.00 eq) afforded the title compound **8h** (0.074 g, 0.366 mmol, 37 %) as a brown oil. Mp:87-88 °C; ^{1}H NMR (400 MHz, d_6-DMSO) δ 7.94 (d, ^{3}J = 7.0 Hz, 2H, C4-H, C8-H), 7.51-7.43 (m, 3H, C5-H, C6-H, C7-H), 7.04 (d, ^{3}J = 5.5 Hz, 1H, C5'-H), 7.02 (br s, 2H, NH_2), 6.92 (dd, ^{3}J = 5.5 Hz, ^{4}J = 3.5 Hz, 1H, C4'-H), 6.56 (d, ^{3}J = 3.5 Hz, 1H, C3'-H), ^{13}C NMR (75.5 MHz, d_6-DMSO): δ 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 $C_{11}H_{11}N_2S$ $[M+H]^+$; 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]

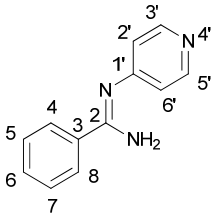


Table 1, Entry 21: Using General Procedure A method 2 with L-proline as ligand and toluene as solvent: Benzamidine **2b** (0.120 g, 1.00 mmol, 1.00 eq) afforded the title compound **8i** (0.103 g, 0. 522 mmol, 52 %) as a green solid. Mp: 166-167 °C; Lit.[S12] 147-149 °C; ^{1}H NMR (400 MHz, d_6-DMSO) δ 7.90 (d, ^3J = 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]

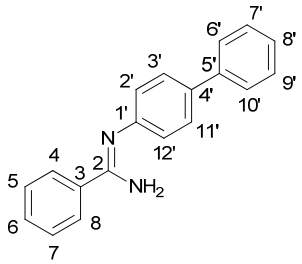


Table 1, Entry 22: Using General Procedure A method 2 with L-proline as ligand and toluene as solvent: Benzamidine **2b** (0.120 g, 1.00 mmol, 1.00 eq) afforded the title compound **8i** (0.057 g, 0. 210 mmol, 21 %) as a brown solid. Mp 176-177 °C, Lit.

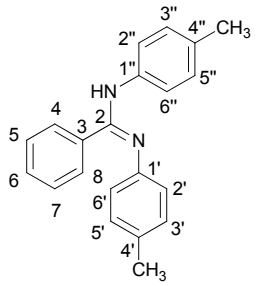
[S14] 126 °C; ^{1}H NMR (300MHz, d_6-DMSO) δ 7.98 (d, ^3J = 7.5 Hz, 2H, C4-H, C8-H), 7.68-7.60 (m, 4H, C2'-H, C6'-H, C10'-H, C12'-H), 7.45-7.41 (m, 5H, C5-H, C6-H, C7-H, C7'-H, C9'-H), 7.30 (t, ^3J = 7.5 Hz, 1H, , C8'-H), 6.97 (d, ^3J = 5.5 Hz, 2H, C3'-H, C11'-H), 6.42 (br. s, 2H, NH_2); LRMS (ES^+): *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.

(*E*)-*N*,*N'*-di-*p*-tolylbenzamidine (9b) [S15]

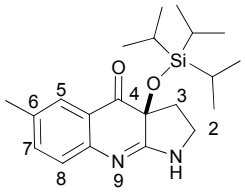


Using a modification of General Procedure A method 2 with ligand E as ligand, benzamidine **2b** (120 mg, 1.00 mmol, 1.00 eq), iodotoluene (0.785 g, 3.60 mmol, 3.60 eq), Cs_2CO_3 (1.63 g, 5.00 mmol, 5.00 eq), CuI (60.0 mg, 0.030 mmol, 30 mol%) and ligand F (90.0 mg, 0.600 mmol, 60 mol%) afforded the title compound **9b** (0.090 g, 0.20 mmol, 20%) as a white solid; Mp 132-133 °C, Lit. [S15] 134 -135 °C; ^{1}H NMR (400 MHz, d_6-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, CH_3), 2.12 (s, 3H, CH_3); 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

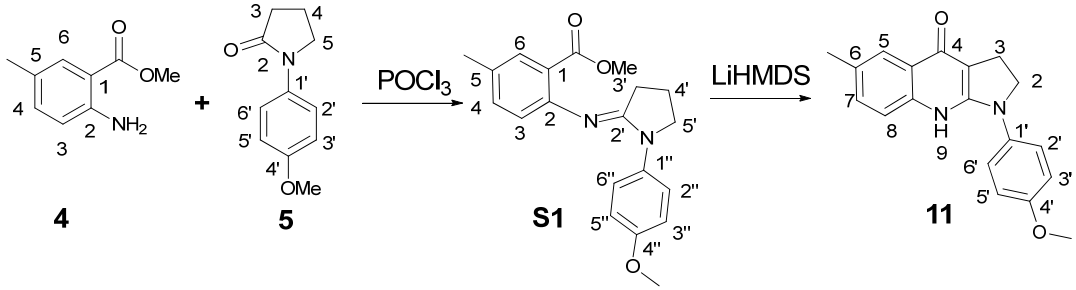
entry	Aryl iodide	CuI mol%	Ligand E mol%	Product	Yield (%)
S1	**6a**	5	10	**8a**	49
S2	**6b**	5	10	**8b**	49
S3	**6c**	5	10	**8c**	19
S4	**6d**	5	10	**8d**	17
S5	**6e**	5	10	**8e**	35
S6	**6g**	5	10	**8g**	28
S7	**6h**	5	10	**8h**	28
S8	**6i**	5	10	**8i**	5
S9	**6j**	5	10	**8j**	23

6-methyl-3a-((triisopropylsilyl)oxy)-3,3a-dihydro-1*H*-pyrrolo[2,3-*b*]quinolin-4(2*H*)-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 temparature for a further 4 hours before being absorbed onto Hydromatrix™ under reduced pressure. Purification on pre-packed Biotage® KP-NH™ silica cartriges (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_{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), 2.22 (s, 3H, CH_3), 0.82-0.78 (m, 21H, OSi-(*i*Pr)$_3$); ^{13}C NMR (100 MHz, THFd-8): 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 (CH_3), 15.7,15.5 (CH_3- OSi-*i*Pr), 11.1 (CH- OSi-*i*Pr); LRMS (ES^+): *m/z* (%) 373 (100) $[M+H]^+$; HRMS (ES^+): *m/z* calcd for $C_{21}H_{33}N_2O_2Si$ $[M+H]^+$: 373.5874; found 373.5698.

1-(4-methoxyphenyl)-6-methyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]quinolin-4(9*H*)-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, $CDCl_3$): δ 7.66 (s, 1H, C6-H), 7.10 (dd, ^3J = 8.4 Hz, ^4J = 2.4 Hz, 1H, C4-H), 6.63 (d, ^3J = 8.4 Hz, 1H, C3-H), 3.86 (s, 3H, OCH_3), 2.23 (s, 3H, CH_3); LRMS (ES^+): *m/z* (%) 165 (100) $[M+H]^+$.

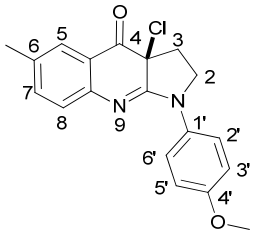
To a sealed Schlenk tube charged with *p*-iodo-anisole (20.1 g, 85.6 mmol, 1.10 eq), 2-pyrrolidinone (6.67 g 78.1 mmol, 1.00 eq), CuI (10 mol%), DiMED (20 mol%), K_3PO_4 (3.00 eq) and molecular sieves (4Å) at room temperature under an atmosphere of nitrogen was added toluene (67.0 mL). The resulting 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 pessure 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, $CDCl_3$)): δ 7.50 (d, ^3J = 9.0 Hz, 2H, C2'-H, C6'-H), 6.91 (d, ^3J = 9.0 Hz, 2H, C3'-H, C5'-H), 3.85-3.80 (m, 5H, C5-H_2, OCH_3), 2.60 (t, 2H, ^3J = 8.0 Hz, ^3J = 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): ν_{max} = 2950 (m), 1685 (C=O), 1240(s) (C-O) cm^{-1}; ^1H NMR (400 MHz, $CHCl_3$): δ 7.71 (d, ^3J = 8.9 Hz, 2H, C3''-H, C5''-H), 7.66 (d, ^4J = 1.5 Hz, 1H, C6-H), 7.19 (dd, ^3J = 8.1 Hz, ^4J = 1.8 Hz, 1H, C4-H), 6.93 (d, ^3J = 8.9 Hz, 2H, C2''-H, C6''-H), 6.74 (d, ^3J = 8.1 Hz, 1H, C3-H), 3.87-3.84 (m, 5H, $COOCH_3$, C5'-H_2), 3.81 (s, 3H, OCH_3), 2.47 (t, ^3J = 7.8 Hz, 2H, C3'-H_2), 2.33 (s, 3H, CH_3), 2.02-2.10 (m, 2H, C4'-H_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 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* calcd for $C_{20}H_{23}N_2O_3$ $[M+H]^+$: 339.1708; found 339.1709.

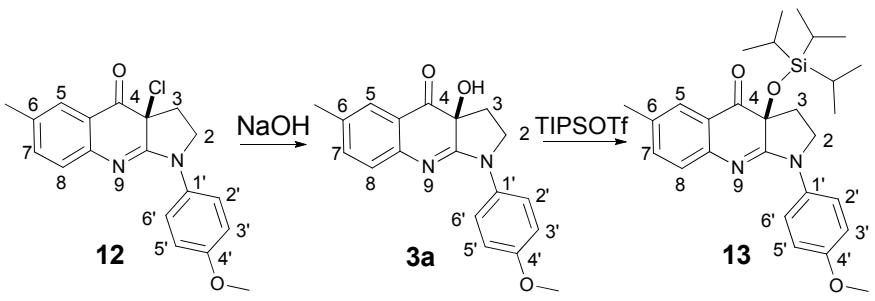
To a solution of methyl 2-((2-(4-methoxyphenyl)cyclopentylidene)amino)-5-methylbenzoate (**S1**) (7.70 g, 22.8 mmol, 1.00 eq) in anhydrous THF (20 mL) at -78 °C under an atmosphere of nitrogen, was added LiHMDS (1M solution in THF, 57 mL, 57.0 mmol, 2.50 eq). The resulting reaction mixture was allowed to warm up to 0 °C over 3 hours before being quenched at 0 °C by the addition of saturated $NH_4Cl_{(aq)}$ (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): ν_{max} = 3419 (m) (NH), 3039 (m) (Ar-H), 1628 (s) (C=O) cm^{-1}; ^1H NMR (400 MHz, THF_{d8}) : δ 7.84 (s, 1H, C5-H), 7.28-7.19 (m, 4H, C7-H, C8-H, C3'-H, C5'-H), 6.96 (d, ^3J = 9.0 Hz, 2H, C2'-H, C6'-H), 3.95 (t, ^3J = 8.5 Hz, 2H, C2-H_2), 3.74 (s, 3H, OCH_3), 3.03 (t, ^3J = 8.5 Hz, 2H, C3-H_2), 2.31 (s, 3H, CH_3); ^{13}C NMR (75.5 MHz, D_8-THF): δ 159.3 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* (%) 305.14 (100) [M-H]; HRMS (ES^+) *m/z* calc'd for $C_{19}H_{19}N_2O_2$ $[M+H]^+$: 307.1447; found: 307.1442.

3a-chloro-1-(4-methoxyphenyl)-6-methyl-3,3a-dihydro-1*H*-pyrrolo[2,3-*b*]quinolin-4(2*H*)-one (12)



To a solution of **11** (3.93 g, 12.8 mmol, 1.00 eq) in THF/H_2O (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:H_2O (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): ν_{max} = 3005 (m) (ArH), 1688(s) (C=O), 1247 (s) (C-O) cm^{-1}; ^{1}H 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-H_2), 4.03 (dd, ^3J = 10.0 Hz, ^4J = 8.0 Hz, 1H, 1 x C2-H_2), 3.79 (s, 3H, OCH_3), 2.72-1.61 (m, 2H, C3-H_2), 2.32 (s, 3H, CH_3); ^{13}C 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 (OCH_3), 47.5 (C2), 30.6 (C3), 20.0 (CH_3); LRMS (ES^+): *m/z* (%) 341.06 (25) $[M+H]^+$, 307.04 (100) $[M-^{35}Cl]^+$; HRMS (ES^+): *m/z* calcd for $C_{19}H_{17}{}^{35}ClN_2O_2$ $[M+H]^+$: 341.1052; found 341.1046.

(4-methoxy1-(4-methoxyphenyl)-6-methyl-3a-((triisopropylsilyl)oxy)-3,3a-dihydro-1*H*-pyrrolo[2,3-*b*]quinolin-4(2*H*)-one (13)

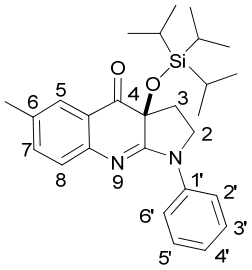


13 was prepared from **12** in 2 steps as follows: To a solution of **12** (4.14 g, 13.5 mmol, 1.00 eq) in THF/H_2O (1:1) (40 mL) was added 2 M $NaOH_{aq}$ (25 mL, 25.0 mmol, 1.85 eq) and the resulting reaction mixture stirred at room temperature for 18 hours. The reaction was then diluted with DCM (200 mL) and washed with saturated $NH_4Cl_{(aq)}$ (3 x 100 mL). The combined organic layers were dried ($MgSO_4$), filtered and absorbed onto Celite® (*w/w*) under reduced presure. Purification by flash chromatography on pre-packed Biotage® silica cartriges (5:1 to 1:1, hexane:ethyl acetate) afforded **3a-hydroxy-1-(4-methoxyphenyl)-6-methyl-3,3a-dihydro-1*H*-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): ν_{max} = 3429 (m) (OH), 3039 (m) (Ar-H), 1693 (s) (C=O), 1245 (s) (C=O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 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, OCH_3), 3.74-3.70 (m, 1H, 1 x C2-H_2), 3.65 (t, ^3J = 8.9 Hz, 1H, 1 x C2-H_2), 2.31 (dd, ^3J = 13.7 Hz, ^4J = 5.4 Hz, 1H, 1 x C3-H_2), 2.23 (s, 3H, CH_3), 2.09-2.17 (m, 1H, 1 x C3-H_2); ^{13}C NMR (100 MHz, $CHCl_3$): 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 (OCH_3), 48.7 (C2), 29.1 (C3), 20.6 (CH_3). LRMS (ES^+): *m/z* (%) 323 (100) $[M+H]^+$; HRMS (ES^+): *m/z* calcd for $C_{19}H_{19}N_2O_3$ $[M+H]^+$: 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 $NH_4Cl_{(aq)}$ (50 mL) and extracted with DCM (3 x 50 mL). The combined organic layers were dried ($MgSO_4$), 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 : ν_{max} = 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-H$_2$), 3.88-3.80 (m, 1H, 1 x C2-H$_2$), 3.72 (s, 3H, OCH$_3$), 2.42-2.38 (m, 1H, 1 x C3-H$_2$), 2.27-2.20 (m, 1H, 1 x C3-H$_2$), 2.21 (s, 3H, CH$_3$), 0.78-0.83 (m, 21H, OSi-*i*Pr); ^{13}C NMR (75.5 MHz, $CDCl_3$): 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 (OCH_3), 48.5 (C2), 30.4 (C3), 20.6 (CH_3), 17.9, 17.8 ($CHCH_3$), 13.2 (OSiCH); LRMS (ES^+): *m/z* (%) 479 (100) $[M+]^+$; HRMS (ES^+): *m/z* calcd for $C_{28}H_{39}N_2O_3Si$ $[M+H]^+$: 479.2730; found 479.2719.

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



To a sealed tube charged with Cs_2CO_3 (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 : ν_{max} = 2961 (m), 2857 (m), 1692 (m) (C=O), 1599 (s), 1480 (s), 1294 (m), 831 (w), 739 (w) cm^{-1}; ^{1}H 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 = 8.1 Hz, 1H, C7-H), 6.95 (t, ^3J = 7.30 Hz 1H, C4'-H), 4.03-3.98 (m, 1H, 1 x C2-H$_2$), 3.90-3.86 (m, 1H, 1 x C2-H$_2$) 2.33-2.22 (m, 2H, C3-H$_2$), 2.19 (s, 3H, CH$_3$), 0.78-0.84 (m, 21H, OSi-*i*Pr); ^{13}C NMR (75.5 MHz, $CDCl_3$): 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 (C3), 19.7 (CH_3), 16.9 (CH - OSi-*i*Pr), 13.0 (CH_3- OSi-*i*Pr); LRMS (ES^+): *m/z* (%) 449 (100) $[M+H]^+$, 471 (100) $[M+23]^+$; HRMS (ES^+): *m/z* calcd for $C_{27}H_{37}N_2O_2Si$ $[M+H]^+$: 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%).

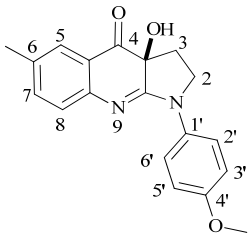
Table 2, Entry 8: Using general procedure C method 2 with ligand E, **10** (0.10 g, 0.27 mmol, 1.00 eq) afforded the title compound **14** (0.057 g, 0.127 mmol, 47%).

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.

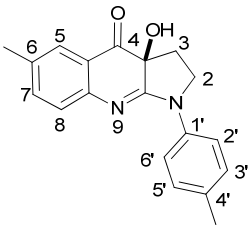
To a sealed tube charged with Cs_2CO_3 (3.00 eq), aryl iodide (1.20 eq), **10** (1.00 eq) and molecular sieves 4Å at room temperature and under an atmosphere of nitrogen was added either the catalyst ligand combination of [CuI (10 mol%) and ligand (20 mol%)], method 1 or [CuI (5 mol%) and ligand (10 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-1*H*-pyrrolo[2,3-*b*]quinolin-4(2*H*)-one (3a)



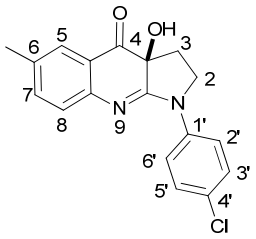
Using General Procedure B with CuI (10 mol%), ligand E (20 mol%) and **10** (80.0 mg, 0.210 mmol, 1.00 eq) afforded the title compound **3a** (40.0 mg, 0.139 mmol, 66 %) as a yellow solid; Spectroscopic analysis showed that the sample of **3a** prepared by this method was identical in all regards to that prepared from **12** as described above.

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



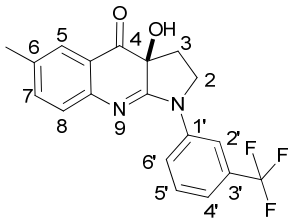
Using General Procedure B with CuI (10 mol%), ligand E (20 mol%) and **10** (80.0 mg, 0.210 mmol, 1.00 eq) afforded the title compound **3b** (40.0 mg, 0.132 mmol, 63 %) as a yellow solid; Mp: Decomp; > 190 °C; IR (KBr): ν_{max} = 3379 (m) (OH), 2926 (m) (Ar-H), 1670 (s) (C=O), 1600 (s), 1513 (s), 1471 (s), 1405 (m), 1292 (s) cm^{-1}; ^1H NMR (500 MHz, THF-d8): 8.01 (d, ^3J = 8.1 Hz, 2H, C3'-H, C5'-H), 7.58 (s, 1H, C5-H), 7.28 (dd, ^3J = 8.1 Hz, ^4J = 1.4 Hz H, C7-H,), 7.16 (d, ^3J = 8.1 Hz, 2H, C2'-H, C6'-H), 7.12 (d, ^3J = 7.5 Hz, 1H, C8-H), 5.85 (br. S, 1H, OH), 4.11-4.05 (m, 1H, 1 x NCH_2), 3.92 (t, ^3J = 7.5 Hz, 1H, 1 x NCH_2), 2.32-2.21 (m, 2H, NCH_2CH_2), 2.36 (s, 3H, Ar-CH_3), 2.32 (s, 3H, Ar-CH_3); ^{13}C NMR (75.5 MHz, CD_2Cl_2): δ 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) $[M+CH_3CN]^+$; HRMS (ES^+): *m/z* calcd for $C_{19}H_{19}N_2O_2$ $[M+H]^+$: 307.1447; found 307.1436.

1-(4-chlorophenyl)-3a-hydroxy-6-methyl-3,3a-dihydro-1*H*-pyrrolo[2,3-*b*]quinolin-4(2*H*)-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): ν_{max} = 3172 (m) (OH), 2916 (m) (Ar-H), 1690 (s) (C=O), 1606 (s), 1496 (s), 1476 (s), 1295 (s) cm^{-1}; ^1H NMR (400 MHz, THFd-8): 8.13 (d, ^3J = 7.0 Hz, 2H, C2'-H, C6'-H), 7.56 (d, ^3J = 2.0 Hz, 1H, C5-H), 7.31 (d, ^3J = 7.0 Hz, 2H, C3'-H, C5'-H), 7.27 (dd, ^3J = 7.5 Hz, ^4J = 2.0 Hz, 1H, C7-H), 7.10 (d, ^3J = 7.5 Hz, 1H, C8-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_2CH_2), 2.31 (s, 3H, Ar-CH_3); ^{13}C NMR (125 MHz, THF-d8): δ 192.1 (C4), 163.6 (C9a), 147.2 (C8a), 138.1 (C1'), 134.4 (C7), 130.9 (C4a), 126.5 (C3',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* calcd for $C_{18}H_{16}N_2O_2Cl$ $[M+H]^+$: 327.0895; found 327.0896.

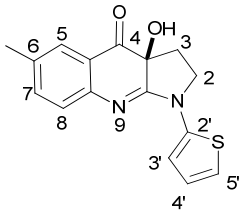
3a-hydroxy-6-methyl-1-(3-(trifluoromethyl)phenyl)-3,3a-dihydro-1*H*-pyrrolo[2,3-*b*]quinolin-4(2*H*)-one (3g)



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): ν_{max} = 3374 (m) (OH), 2924 (m) (Ar-H), 1697 (s) (C=O), 1629 (s), 1609 (s), 1459 (s), 1334(s), 1123 (s) cm^{-1}; ^1H NMR (400 MHz, DMSO-d6): 8.79 (s, 1H, C2'-H), 8.14 (dd, ^3J = 7.0 Hz, ^4J = 2.0 Hz, 1H, C4'-

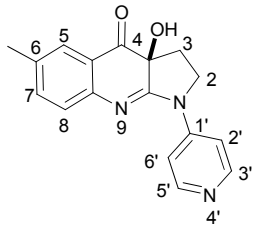
H), 7.65 (t, ^3J = 7.0 Hz, 1H, C5'-H), 7.55 (d, ^3J = 2.0 Hz, 1H, C5-H), 7.47 (d, ^3J = 7.5 Hz, 1H, C6'-H), 7.40 (dd, ^3J = 8.0 Hz, ^4J = 2.0 Hz, 1H, C7-H), 7.11 (1H, d, ^3J = 8.0 Hz, C8-H), 4.11-4.00(m, 2H, NCH_2), 2.31 (s, 3H, Ar-CH_3), 2.28-2.25 (m, 2H, NCH_2CH_2); ^{13}C NMR (125 MHz, DMSO-d6): δ 194.2 (C4), 165.5 (C9a), 148.3 (C8a), 141.5 (CF_3), 141.1 (C1'), 136.5 (C7), 132.9 (C4a), 129.9 (C5'), 129.4 (C3', q ^2J (C,F)=32.0Hz), 126.4 (C5), 125.9 (C8), 122.4 (C4'), 121.1 (C6), 119.4 (C6'), 115.9 (C2'), 72.7 (C3a), 47.3 (C2), 28.1 (C3), 20.2 (CH_3); LRMS (ES^+): *m/z* (%) 361 (70) $[M+H]^+$; HRMS (ES^+): *m/z* calcd for $C_{19}H_{16}N_2O_2F_3$ $[M+H]^+$: 361.1164.; found 361.1153.

3a-hydroxy-6-methyl-1-(thiophene-2-yl)-3,3a-dihydro-1*H*-pyrrolo[2,3-*b*]quinolin-4(2*H*)-one (3h)



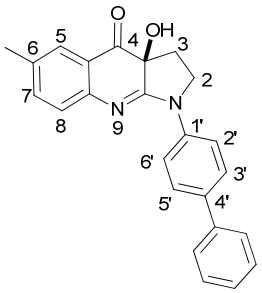
Using General Procedure B with CuI (10 mol%), ligand E (20 mol%) and **10** (80.0 mg, 0.210 mmol, 1.00 eq) afforded the title compound **3h** (30.0 mg, 0.110 mmol, 53%) as a yellow solid; Mp: Decomp; > 190 °C; IR (KBr): ν_{max} = 3433 (s) (OH), 3030 (m) (ArH), 2921 (m) (CH_2), 1687 (s) (C=O), 1616 (C=C) cm^{-1}; ^{1}H 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-H_2), 2.26 (s, 3H, CH_3). ^{13}C NMR (125 MHz, THFd-8): 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 (C3'), 72.3 (C3a), 48.4 (C2), 29.5 (C3), 19.9 (CH_3); LRMS (ES^+): *m/z* (%) 299 (50) $[M+H]^+$, 242 (100); HRMS (ES^+): *m/z* calcd for $C_{16}H_{14}N_2O_2S$ $[M+H]^+$: 299.0854; found 299.0862.

3a-hydroxy-6-methyl-1-(pyridine-4-yl)-3,3a-dihydro-1*H*-pyrrolo[2,3-*b*]quinolin-4(2*H*)-one (3i)



Using General Procedure B with CuI (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-CH_2), 3.90 (t, ^3J = 8.4 Hz, 1H, 1 x C2-CH_2), 2.31-2.22 (m, 2H, C3-CH_2), 2.26 (s, 3H, Ar-CH_3); ^{13}C 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 (CH_3); LRMS (ES^-): *m/z* (%) 292 (100) $[M-H]^-$; HRMS (ES^-): *m/z* calcd for $C_{17}H_{14}N_3O_2$ $[M-H]^-$: 292.1086; found 292.1078.

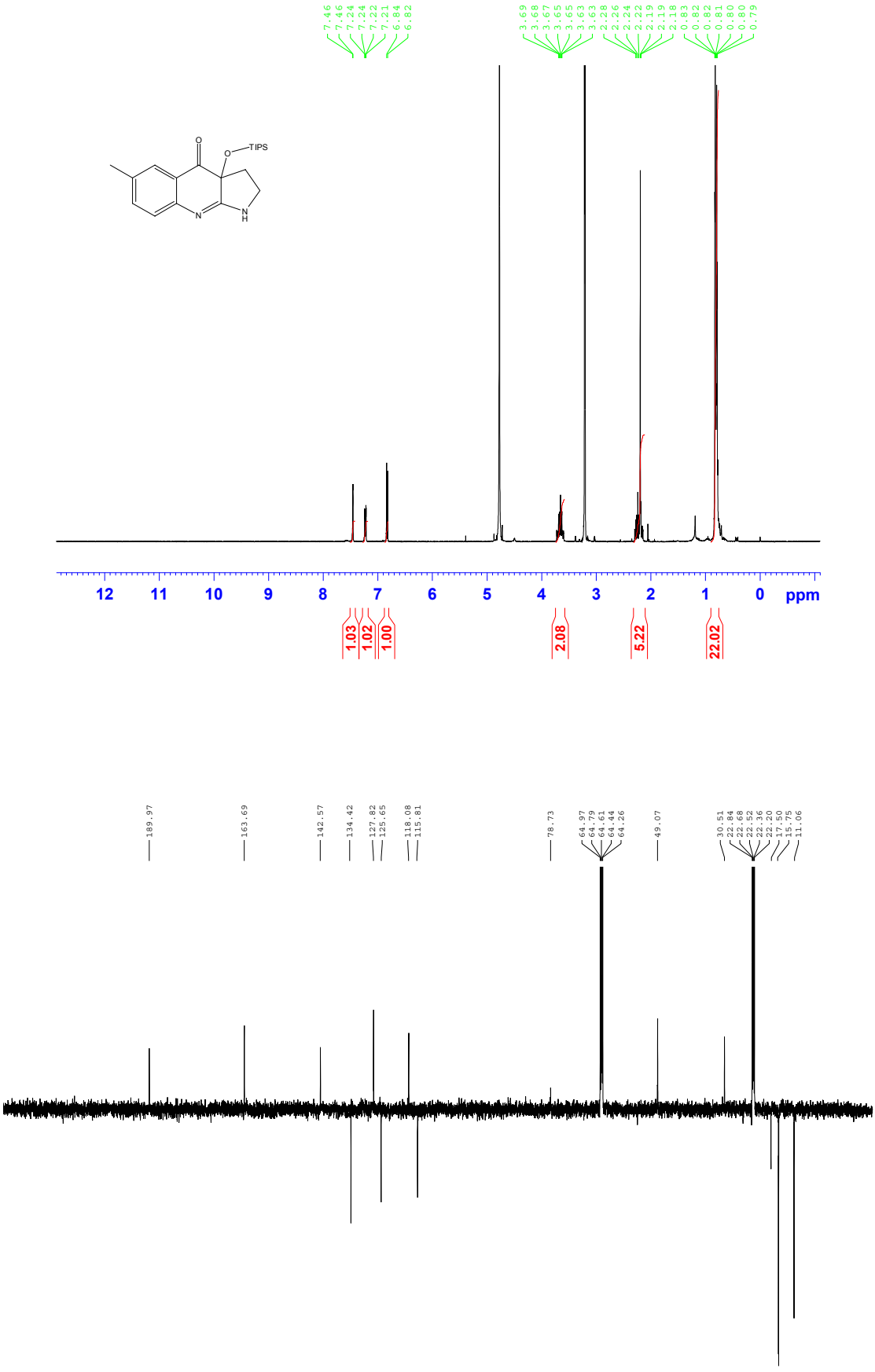
1-([1,1'-biphenyl]-4-yl)-3*a*-hydroxy-6-methyl-3,3a-dihydro-1*H*-pyrrolo[2,3-b]quino-lin-4(2*H*)-one (3j)



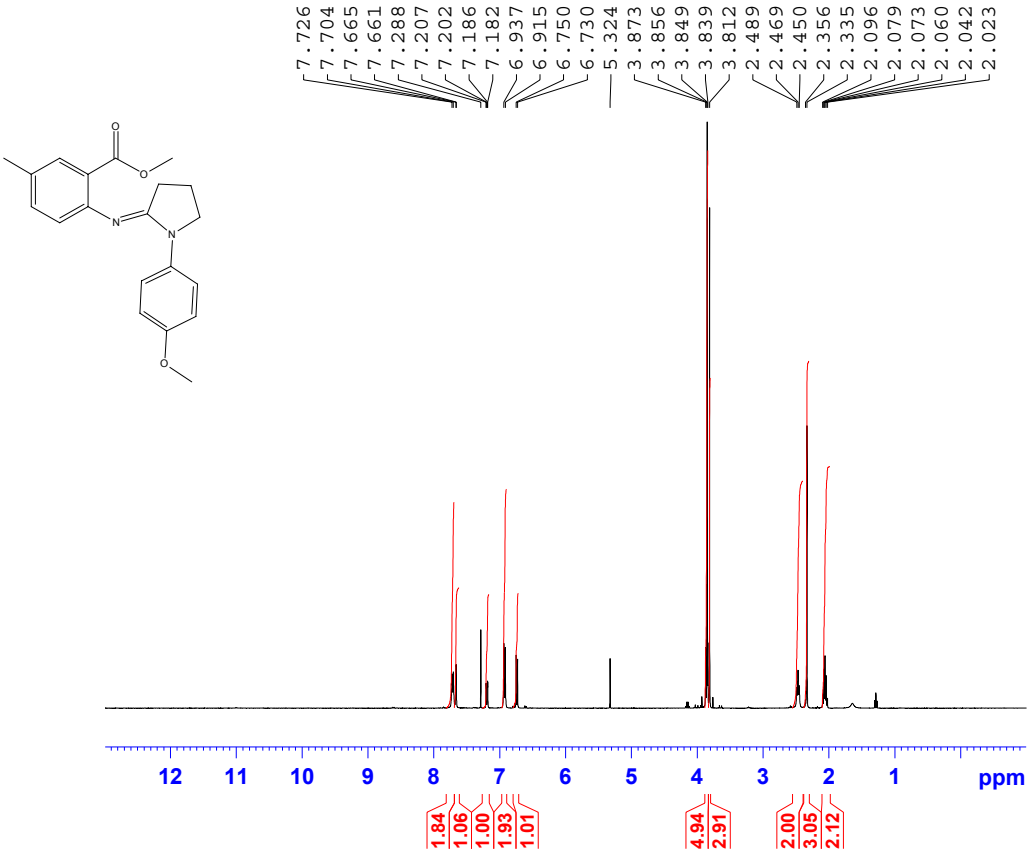
Using General Procedure with CuI (5 mol%), ligand F (10 mol%) and **10** (80.0 mg, 0.210 mmol, 1.00 eq) afforded the title compound **3j** (20.0 mg, 0.070 mmol, 34%) as a yellow solid; Mp: decomp. > 190 °C; IR (KBr): ν_{max} = 3364 (m) (OH), 2921 (m) (ArH), 1668 (s) (C=O), 1604 (s), 1501 (s), 1233 (s) 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-

$\underline{H}_2$), 2.26 (s, 3H, C$\underline{H}_3$), 2.09-1.99 (m, 2H, C3-$\underline{H}_2$); ^{13}C NMR (125 MHz, THFd-8): δ 193.1 (C$\underline{4}$), 170.4 (C$\underline{9a}$), 146.2 (C$\underline{1}$'), 139.7 (C$\underline{1}$"), 137.4 (C8a), 134.2 (C$\underline{7}$), 130.1 (C$\underline{4a}$), 127.0 (C4'), 126.5 (C$\underline{3}$', C$\underline{5}$'), 125.5 (C$\underline{3}$", C$\underline{5}$"), 125.3 (C$\underline{5}$), 123.6 (C$\underline{2}$", C$\underline{6}$"), 123. 4 (C$\underline{4}$"), 117.9 (C$\underline{6}$), 113.8 (C$\underline{8}$), 110.7 (C$\underline{2}$', C$\underline{6}$') 78.9 (C$\underline{3a}$), 36.9 (C$\underline{3}$), 36.2 (C$\underline{2}$), 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.

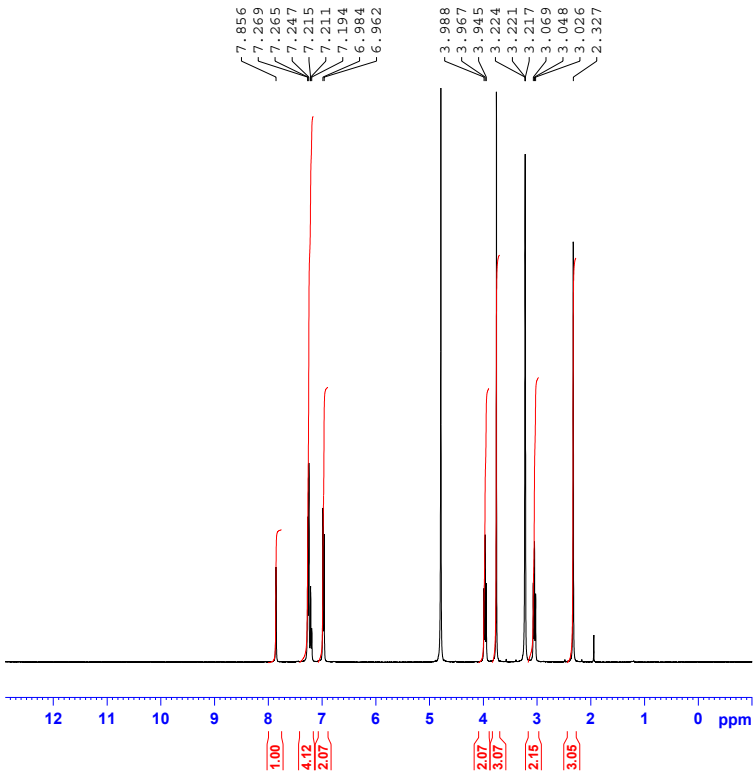
6-methyl-3a-((triisopropylsilyl)oxy)-3,3a-dihydro-1*H*-pyrrolo[2,3-*b*]quinolin-4(2*H*)-one (10)



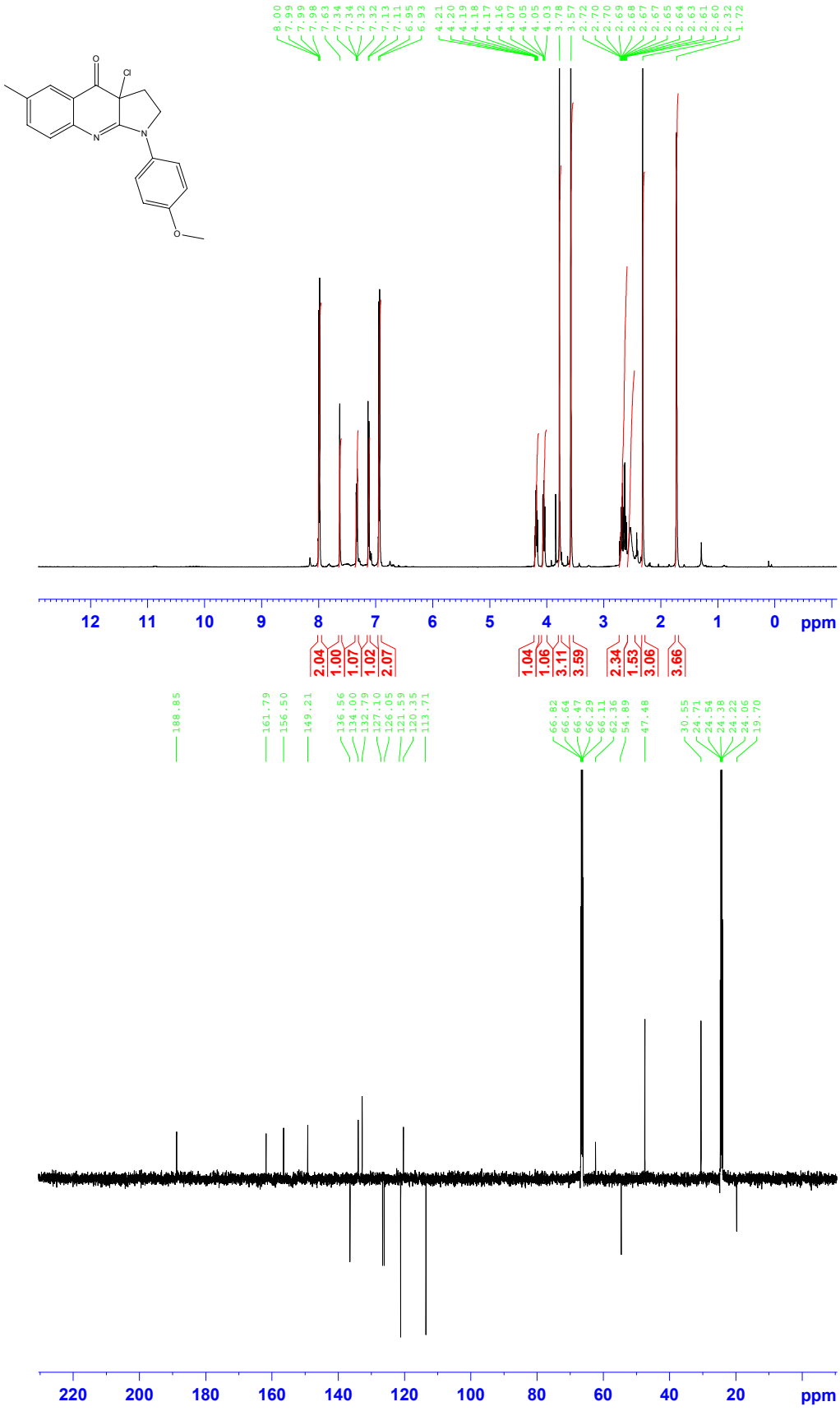
2-((2-(4-methoxyphenyl)cyclopentylidene)amino)-5-methylbenzoate (S1)



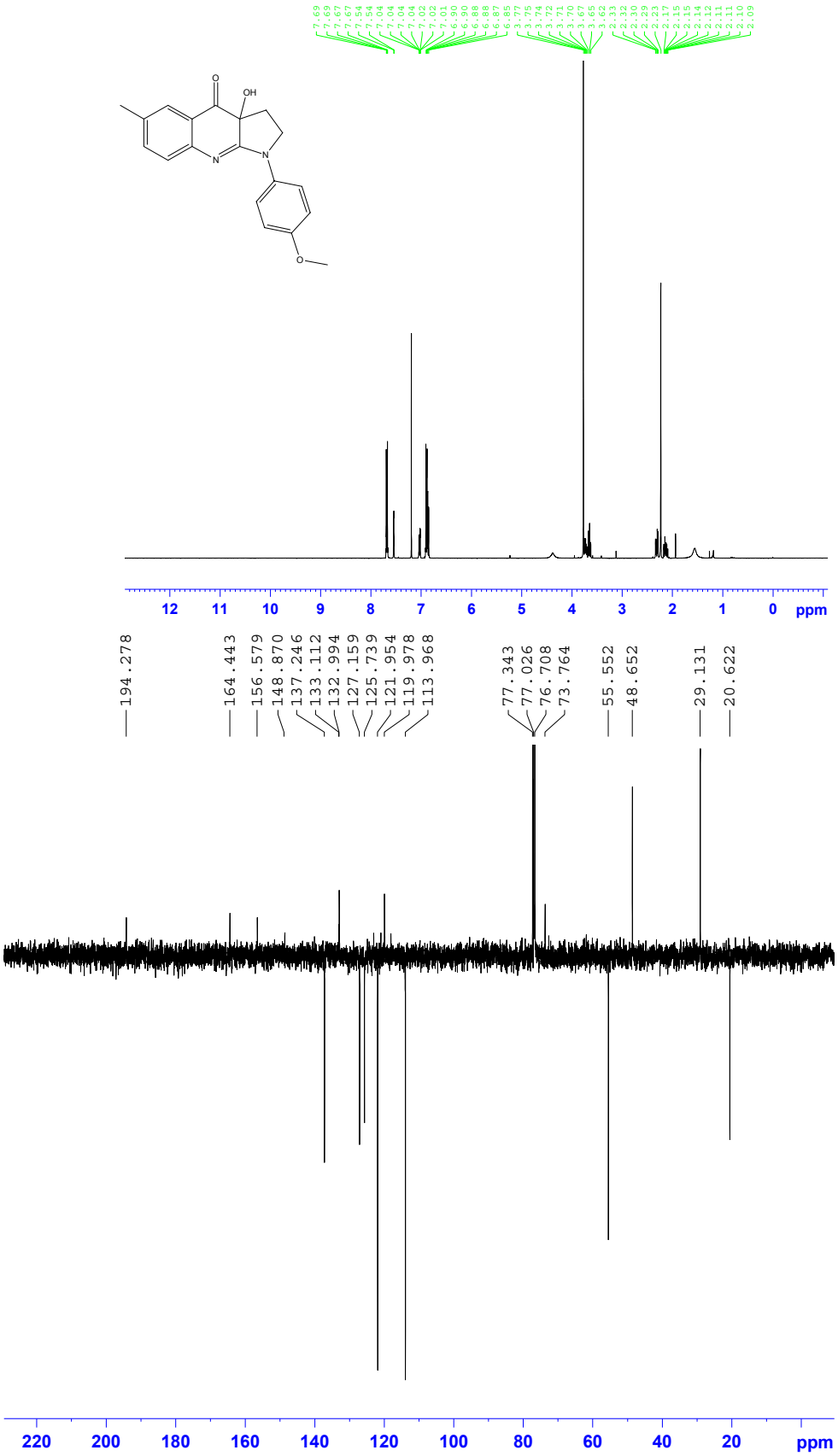
1-(4-methoxyphenyl)-6-methyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]quinolin-4(9*H*)-one (11)



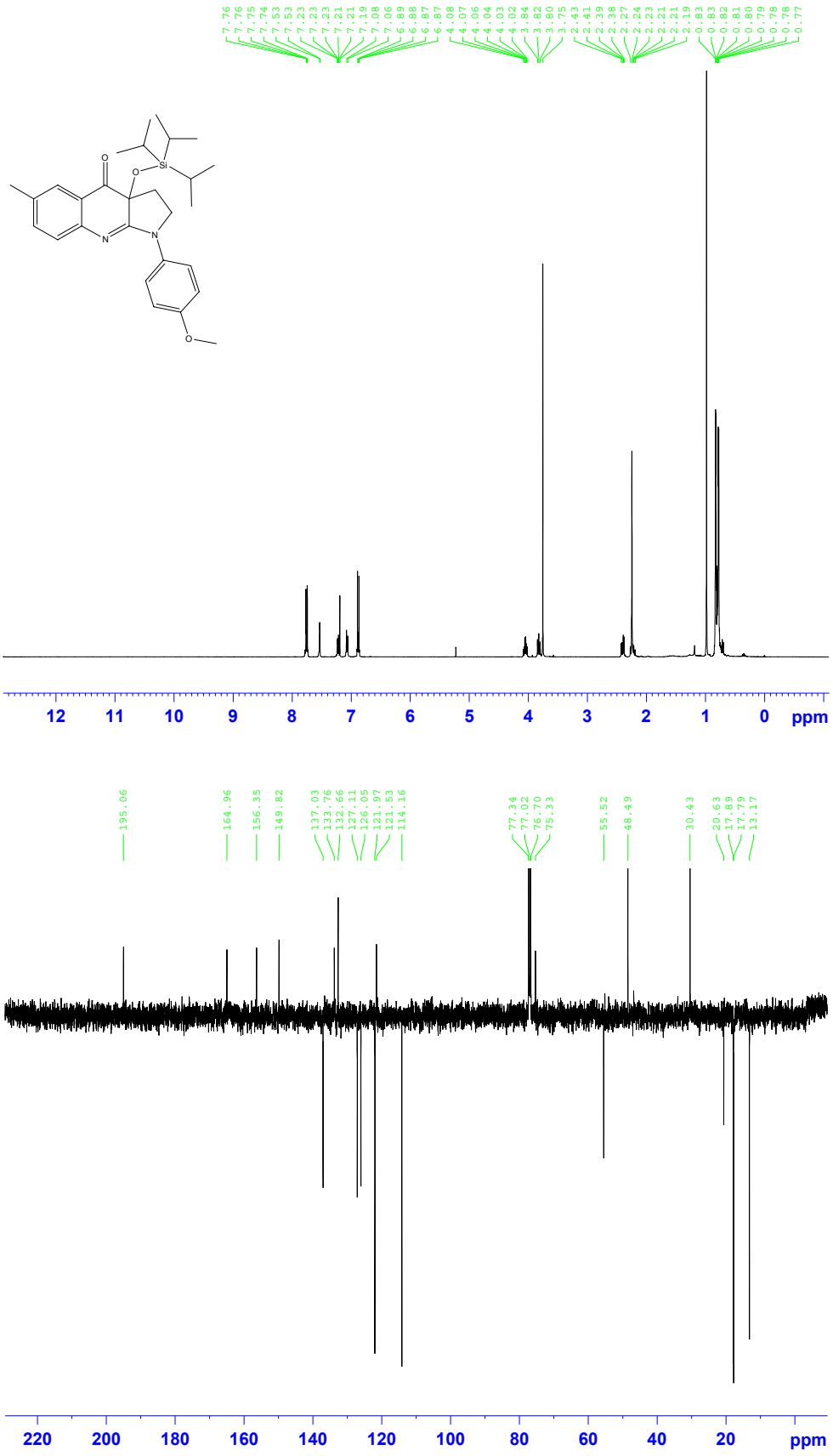
3a-chloro-1-(4-methoxyphenyl)-6-methyl-3,3a-dihydro-1*H*-pyrrolo[2,3-*b*]quinolin-4(2*H*)-one (12)



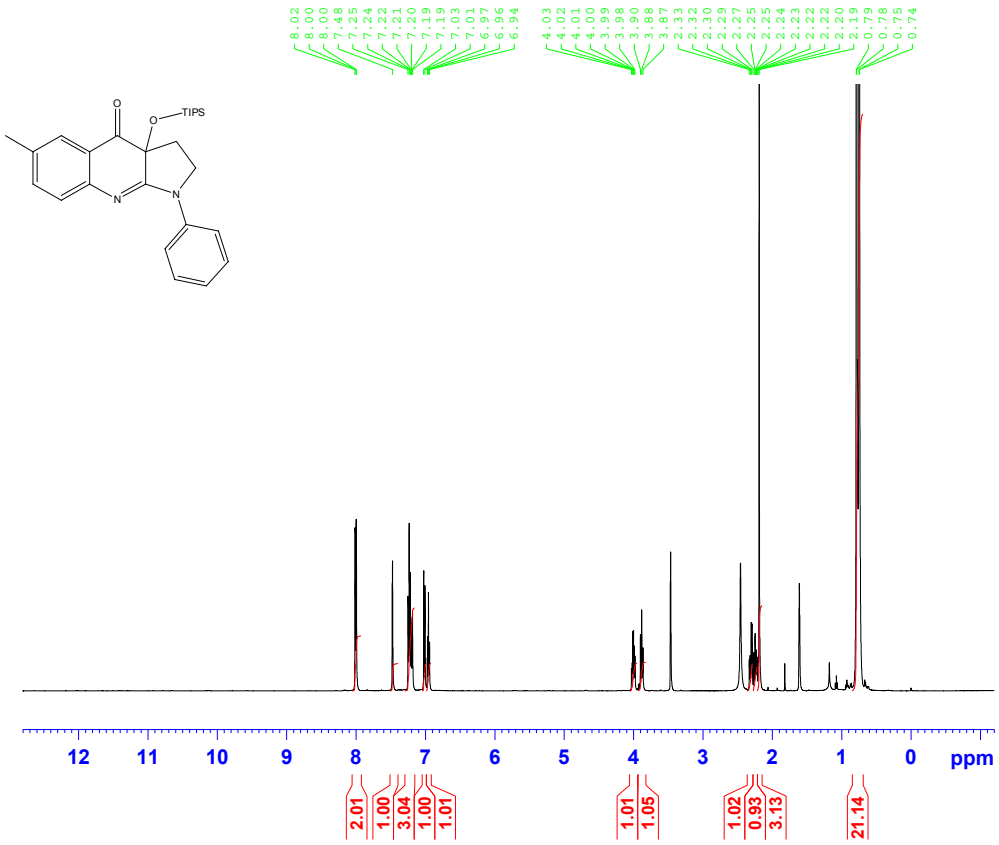
3a-hydroxy-1-(4-methoxyphenyl)-6-methyl-3,3a-dihydro-1*H*-pyrrolo[2,3-*b*]quinolin-4(2H)-one (3a)

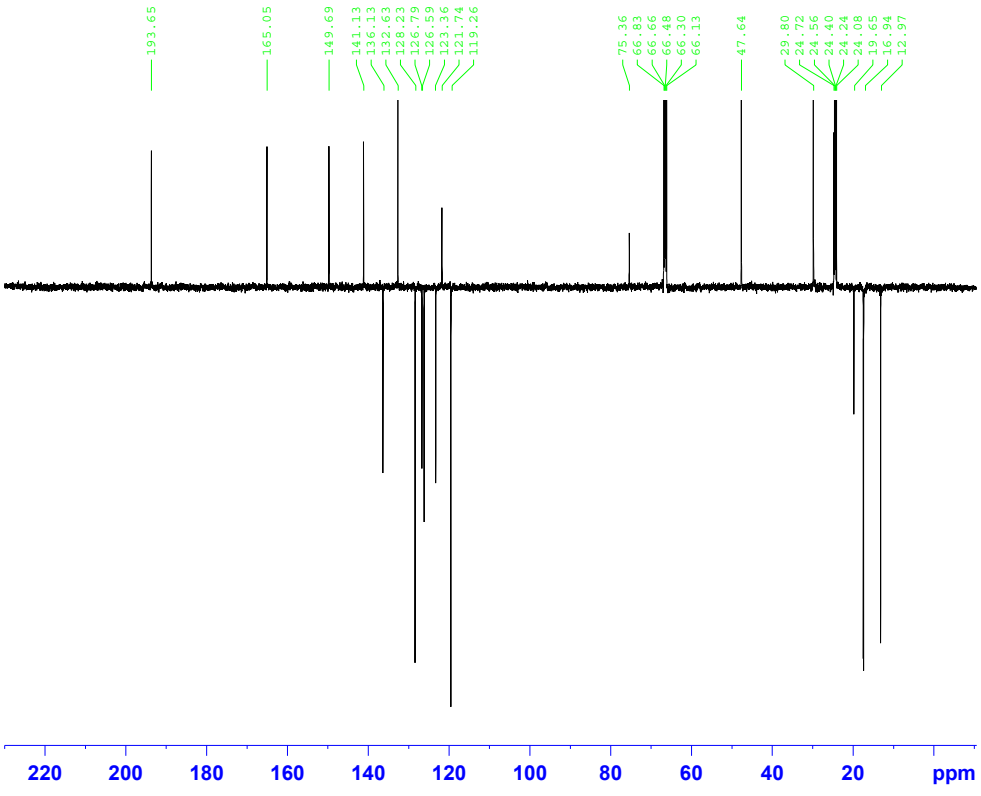


(4-methoxy1-(4-methoxyphenyl)-6-methyl-3a-((triisopropylsilyl)oxy)-3,3a-dihydro-1*H*-pyrrolo[2,3-*b*]quinolin-4(2*H*)-one (13)

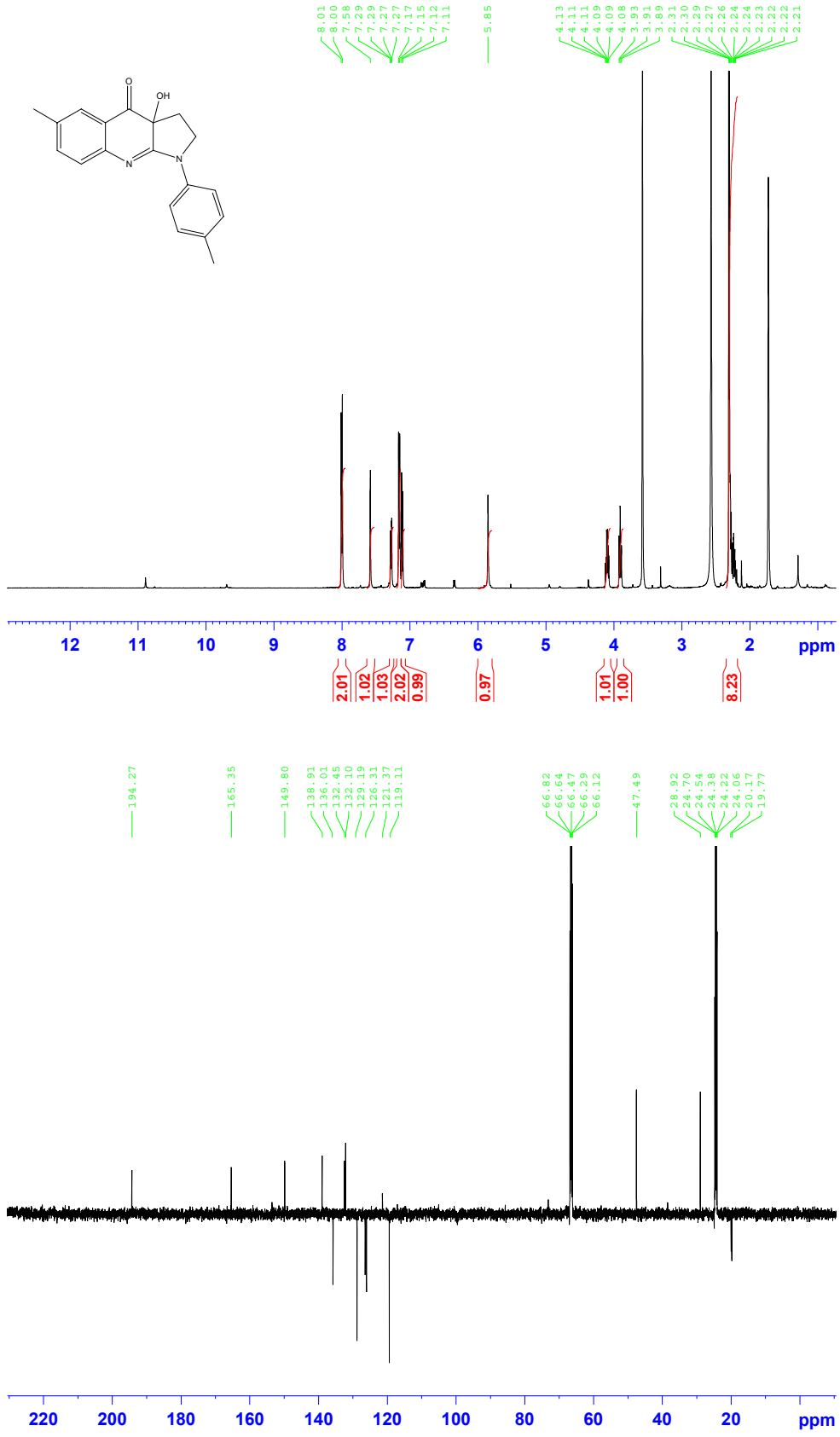


O-TIPS-blebbistatin (14)

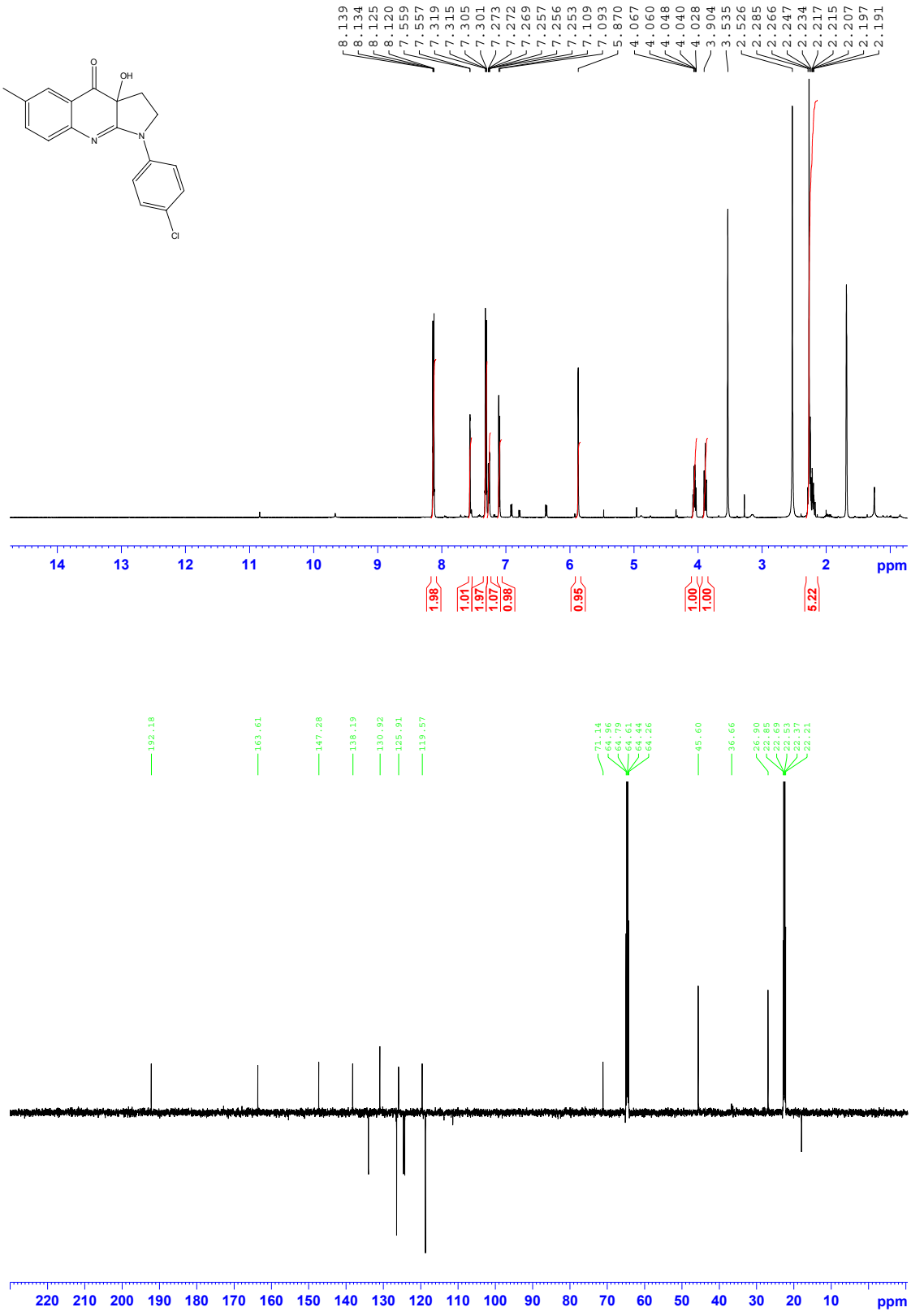




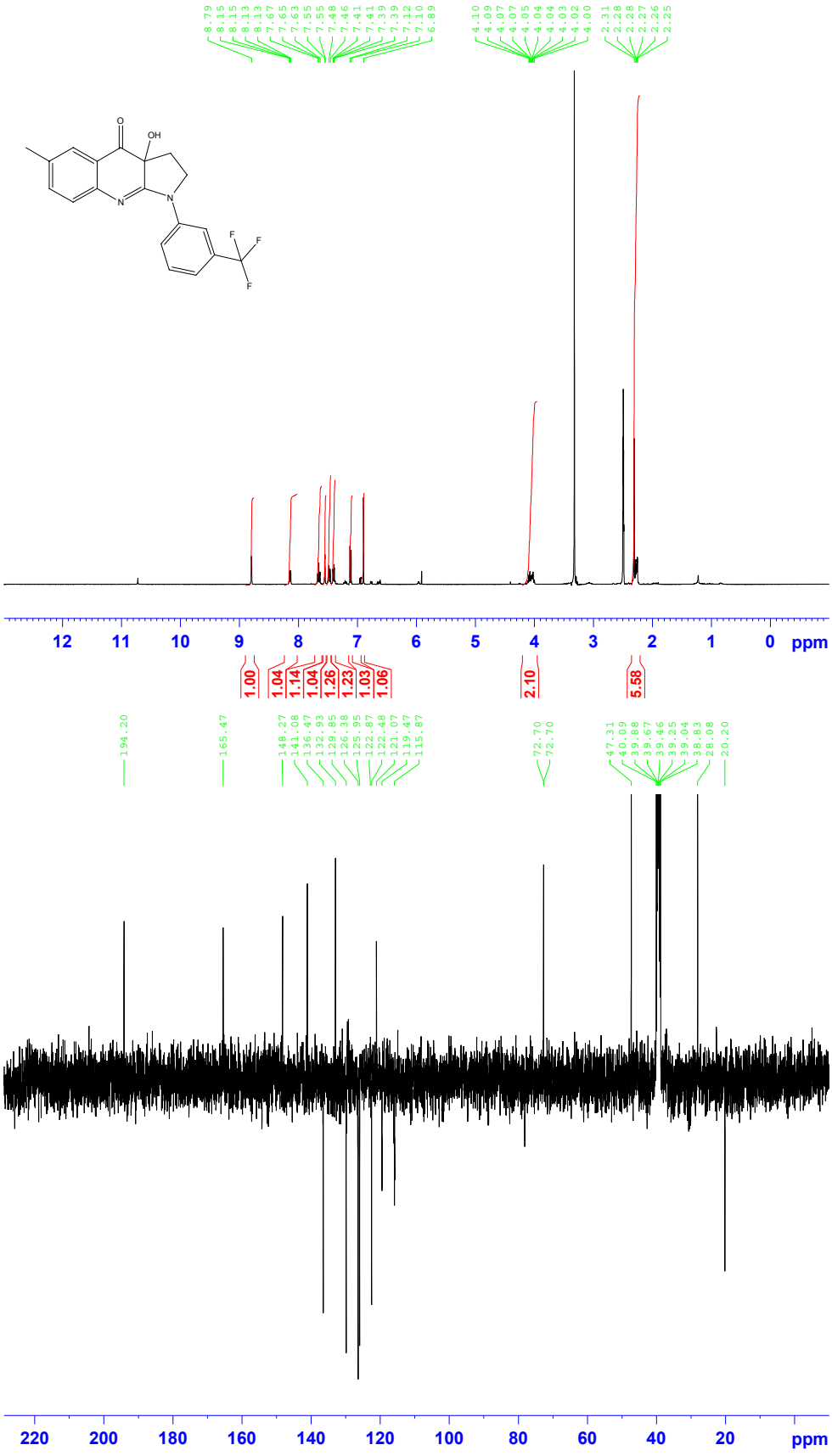
3a-hydroxy-6-methyl-1-(p-tolyl)-3,3a-dihydro-1*H*-pyrrolo[2,3-*b*]quinolin-4(2*H*)-one (3b)



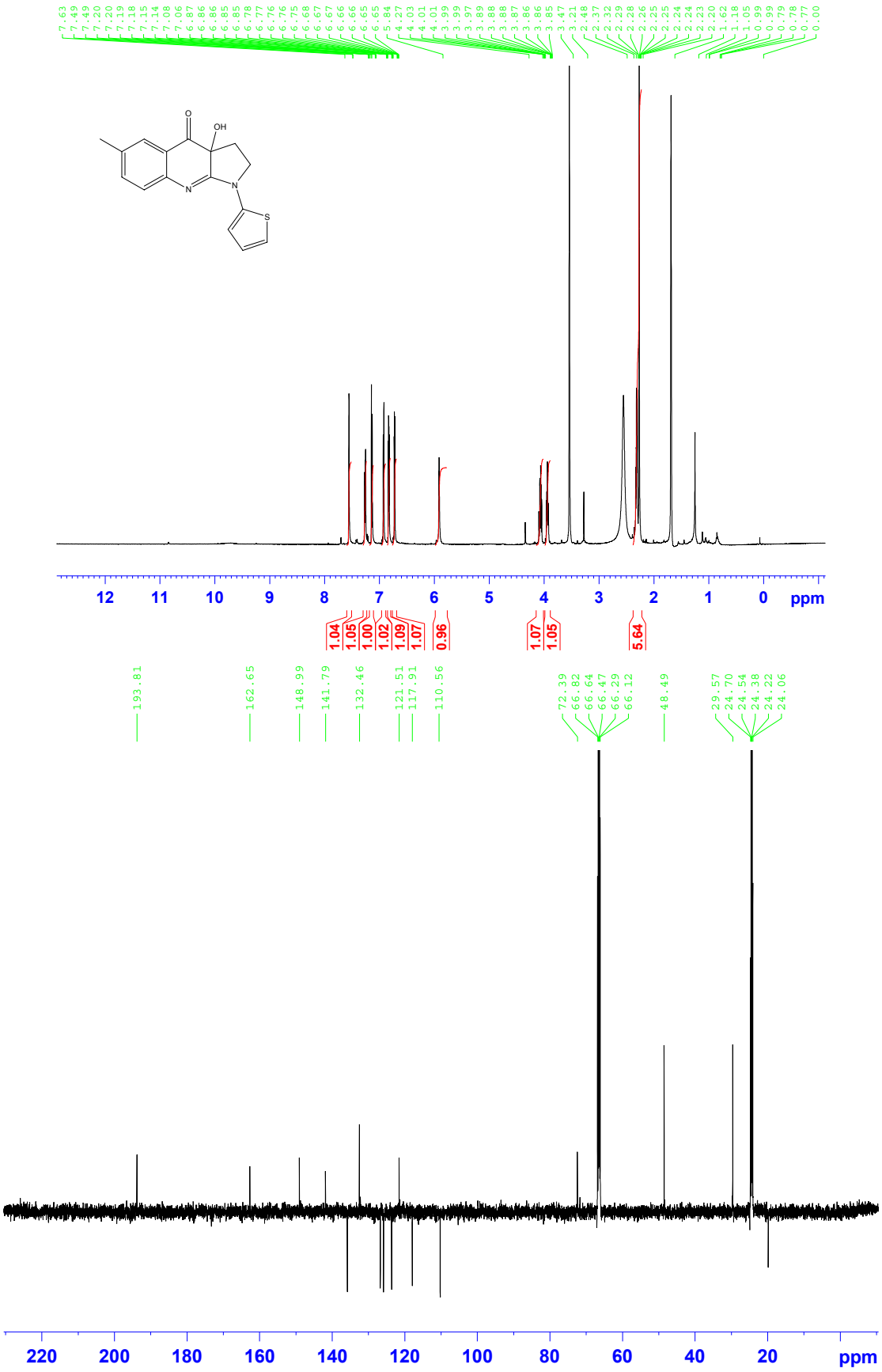
1-(4-chlorophenyl)-3a-hydroxy-6-methyl-3,3a-dihydro-1*H*-pyrrolo[2,3-*b*]quinolin-4(2*H*)-one (3e)



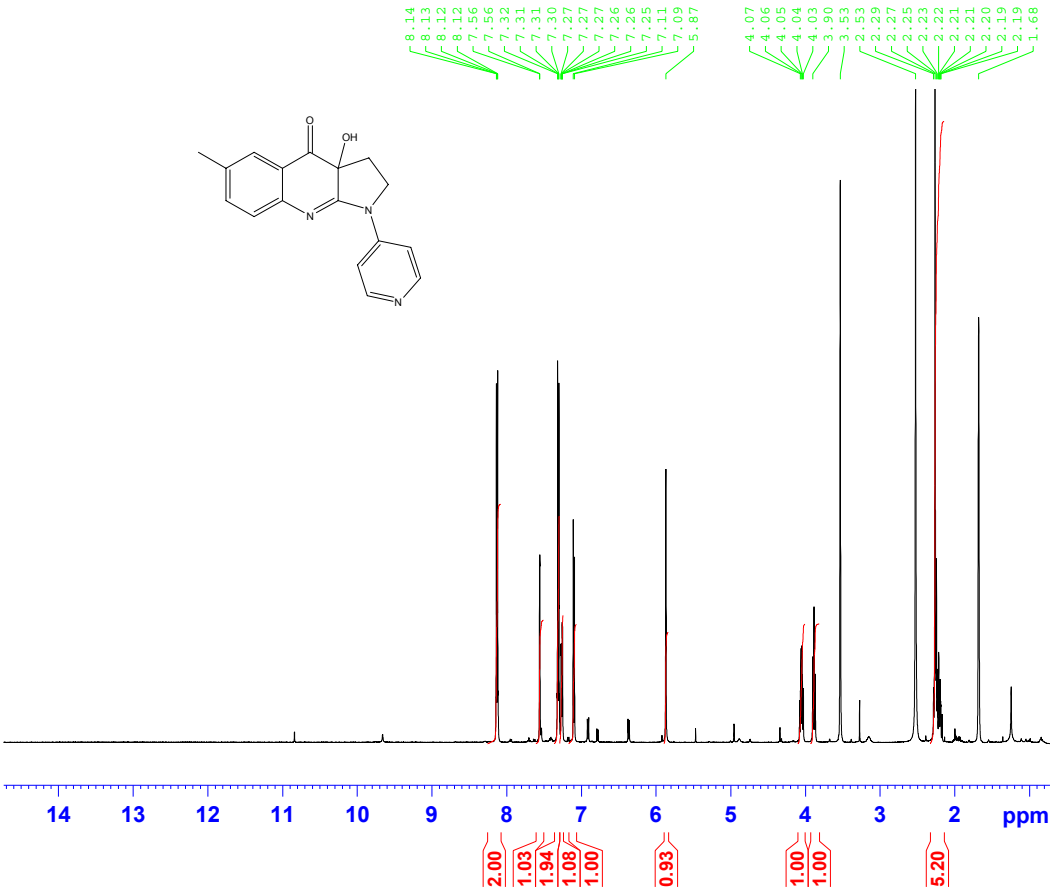
3a-hydroxy-6-methyl-1-(3-(trifluoromethyl)phenyl)-3,3a-dihydro-1*H*-pyrrolo[2,3-*b*]quinolin-4(2*H*)-one (3g)

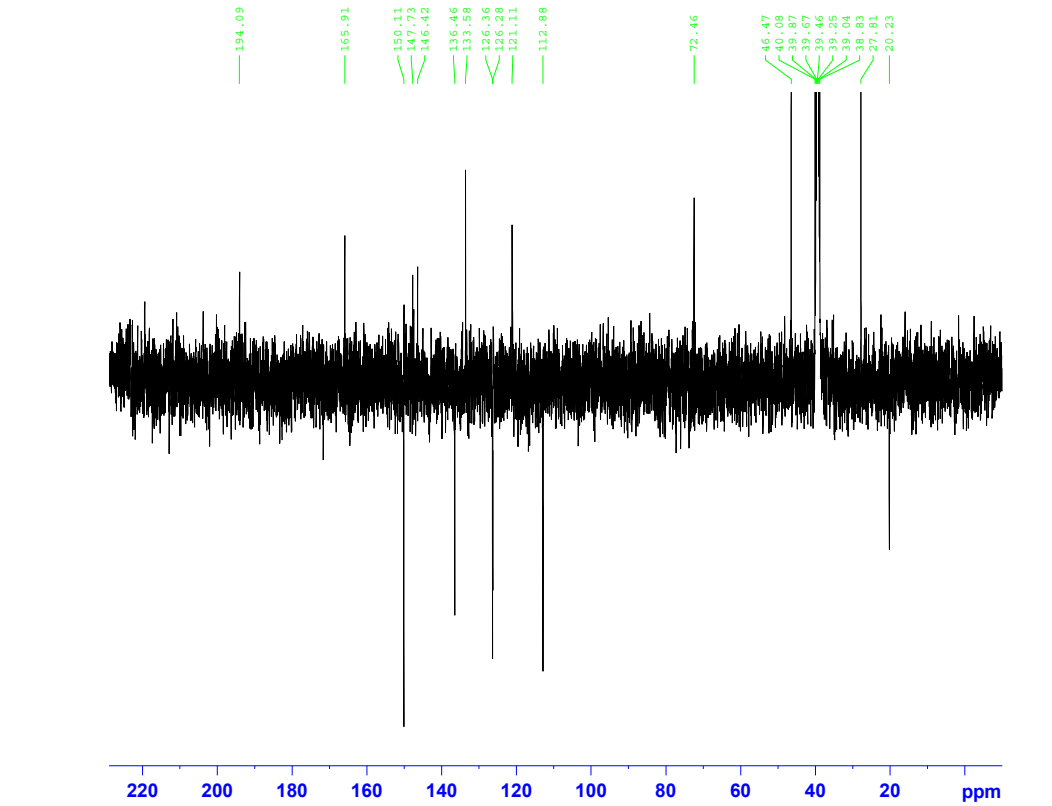


3a-hydroxy-6-methyl-1-(thiophene-2-yl)-3,3a-dihydro-1*H*-pyrrolo[2,3-*b*]quinolin-4(2*H*)-one (3h)

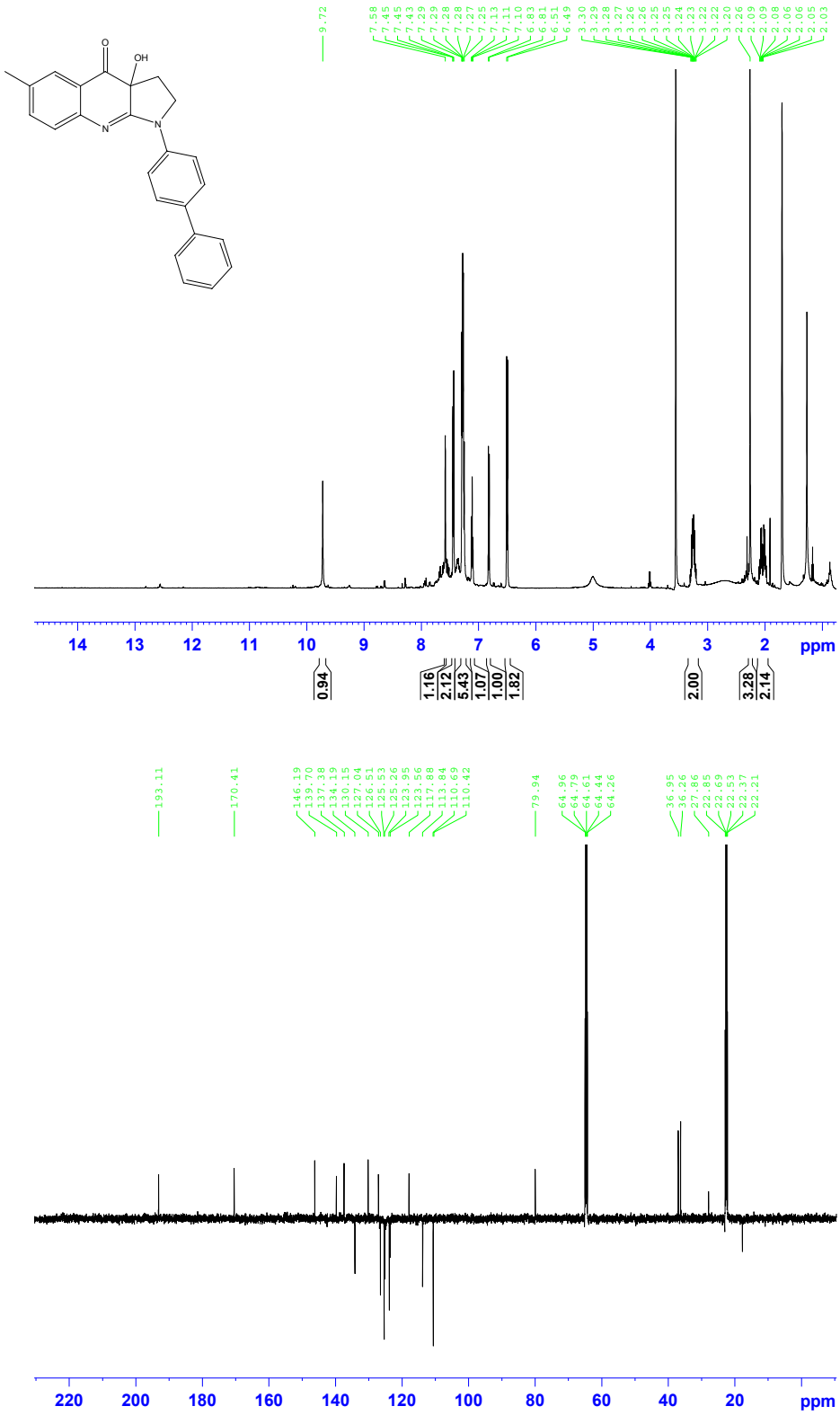


3a-hydroxy-6-methyl-1-(pyridine-4-yl)-3,3a-dihydro-1*H*-pyrrolo[2,3-*b*]quinolin-4(2*H*)-one (3i)

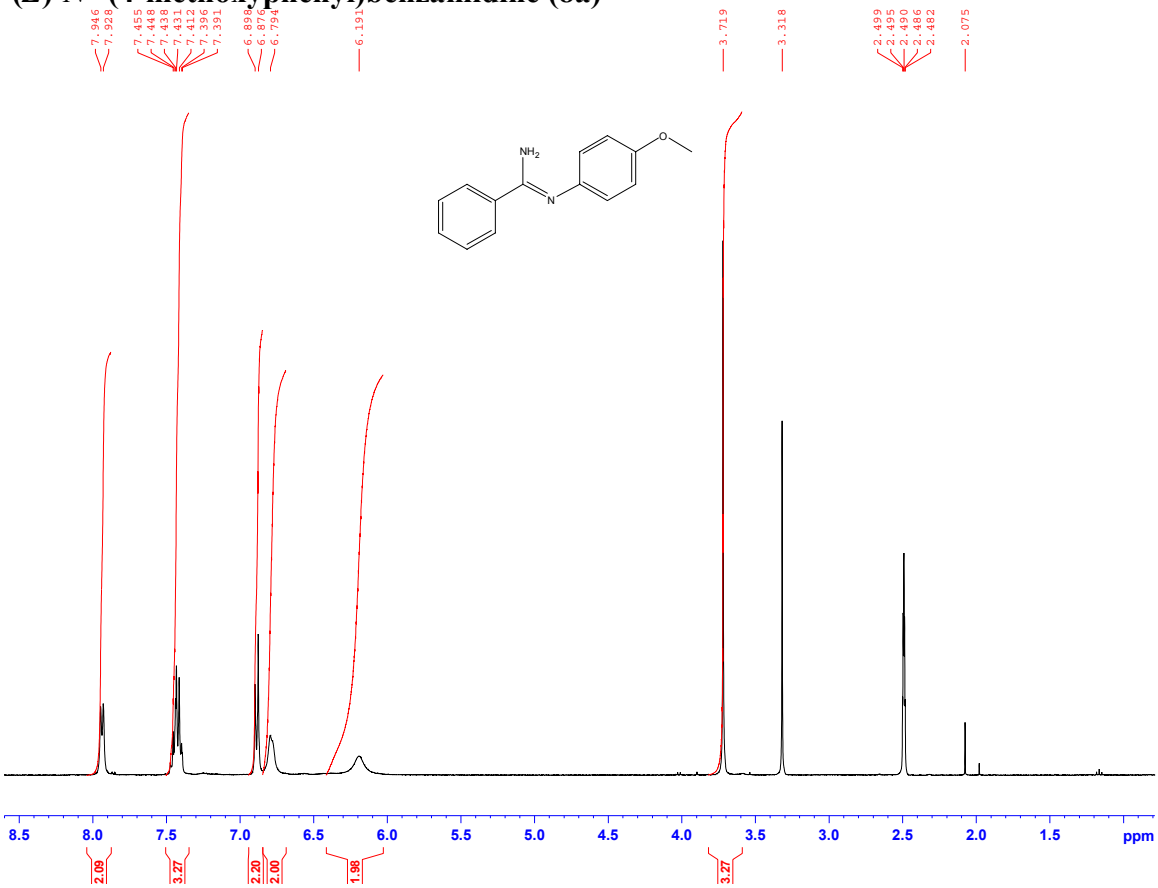




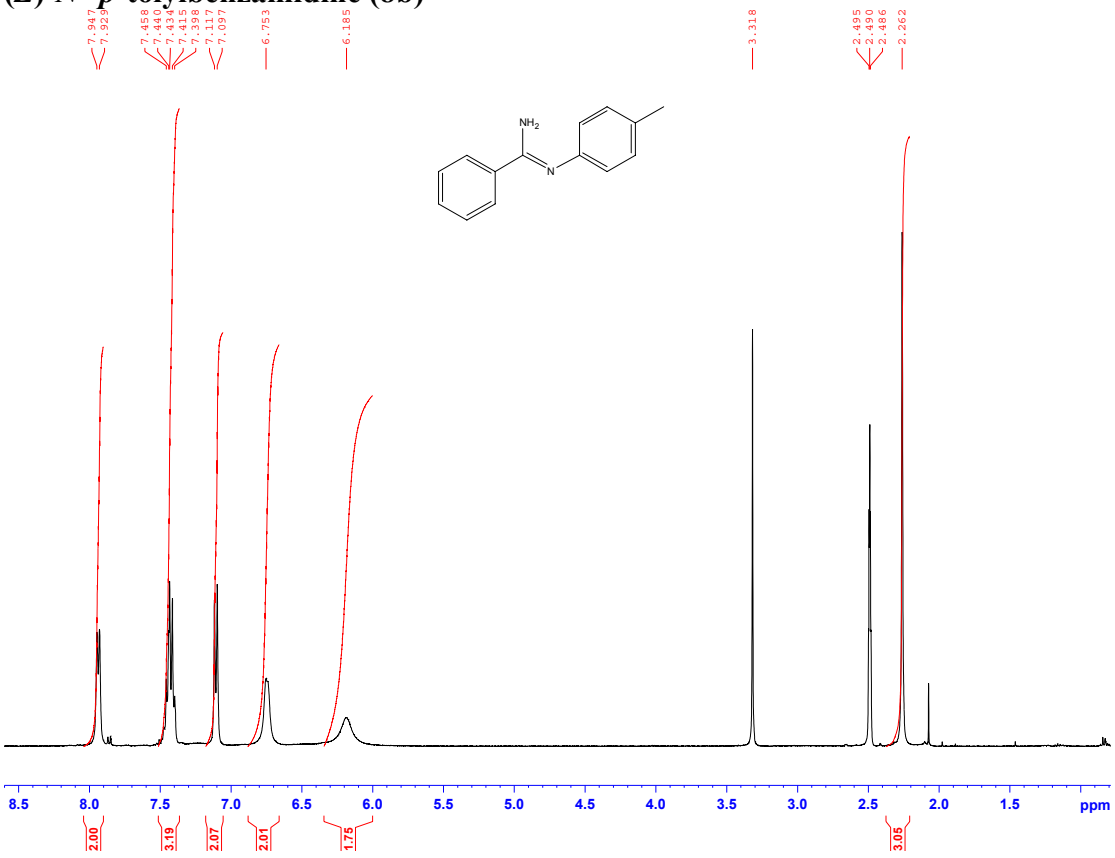
1-([1,1'-biphenyl]-4-yl)-3*a*-hydroxy-6-methyl-3,3a-dihydro-1*H*-pyrrolo[2,3-b]quino-lin-4(2*H*)-one (3j)



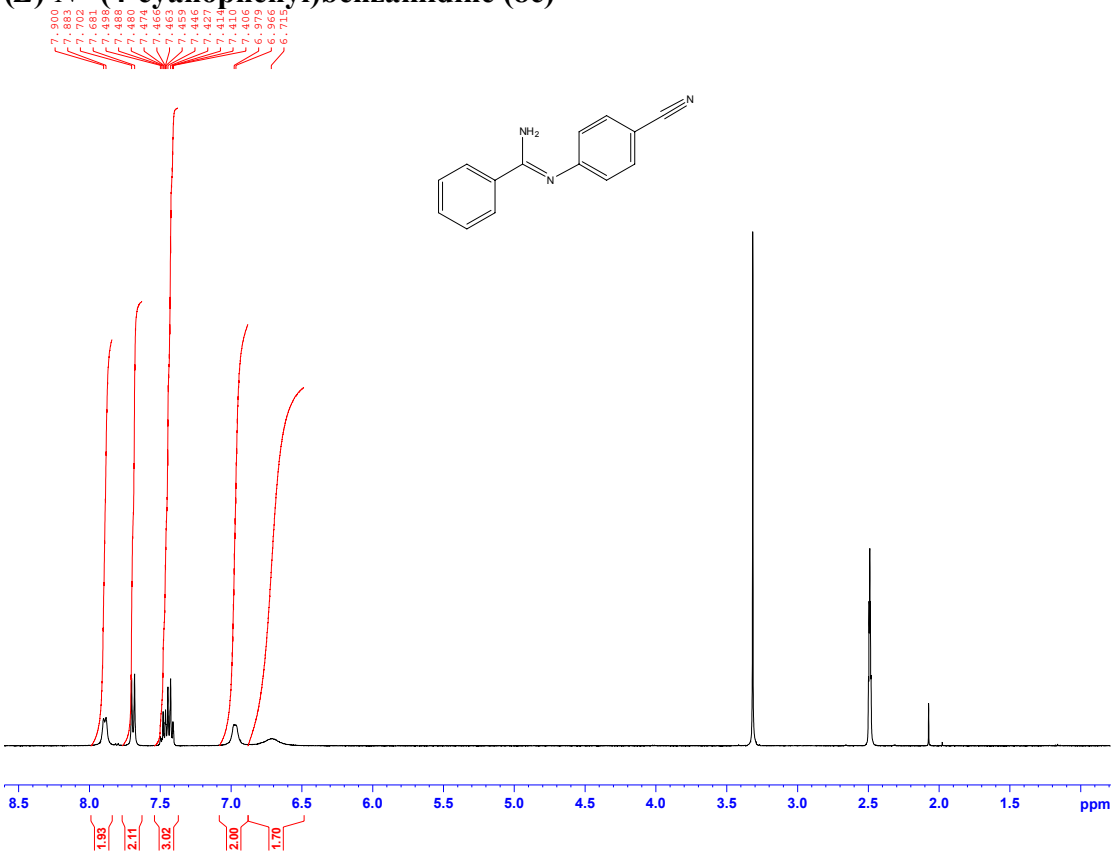
(*Z*)-*N'*-(4-methoxyphenyl)benzamidine (8a)

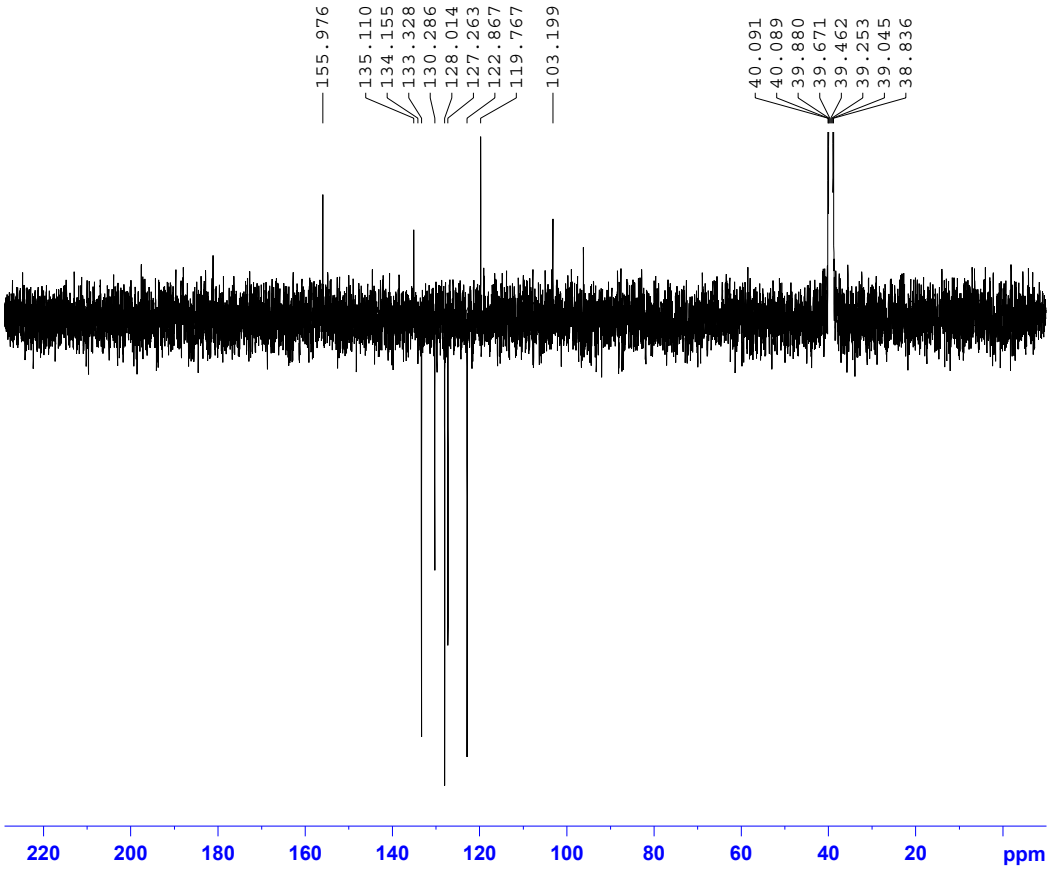


(*Z*)-*N'*-*p*-tolylbenzamidine (8b)

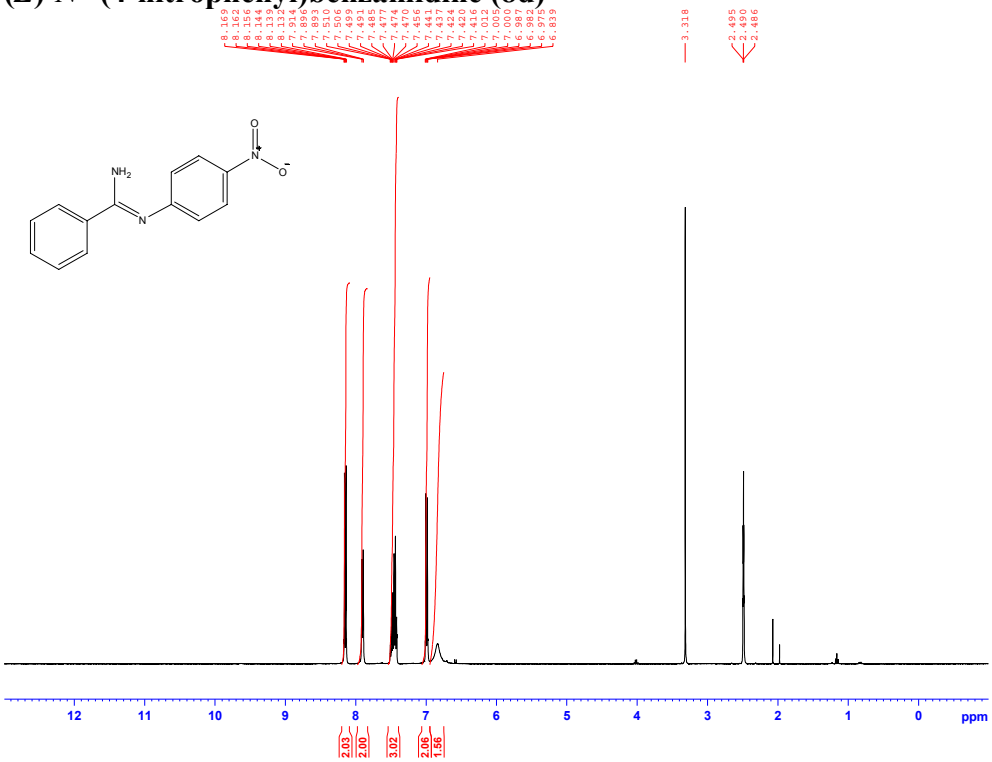


(*Z*)-*N*'-(4-cyanophenyl)benzamidine (8c)

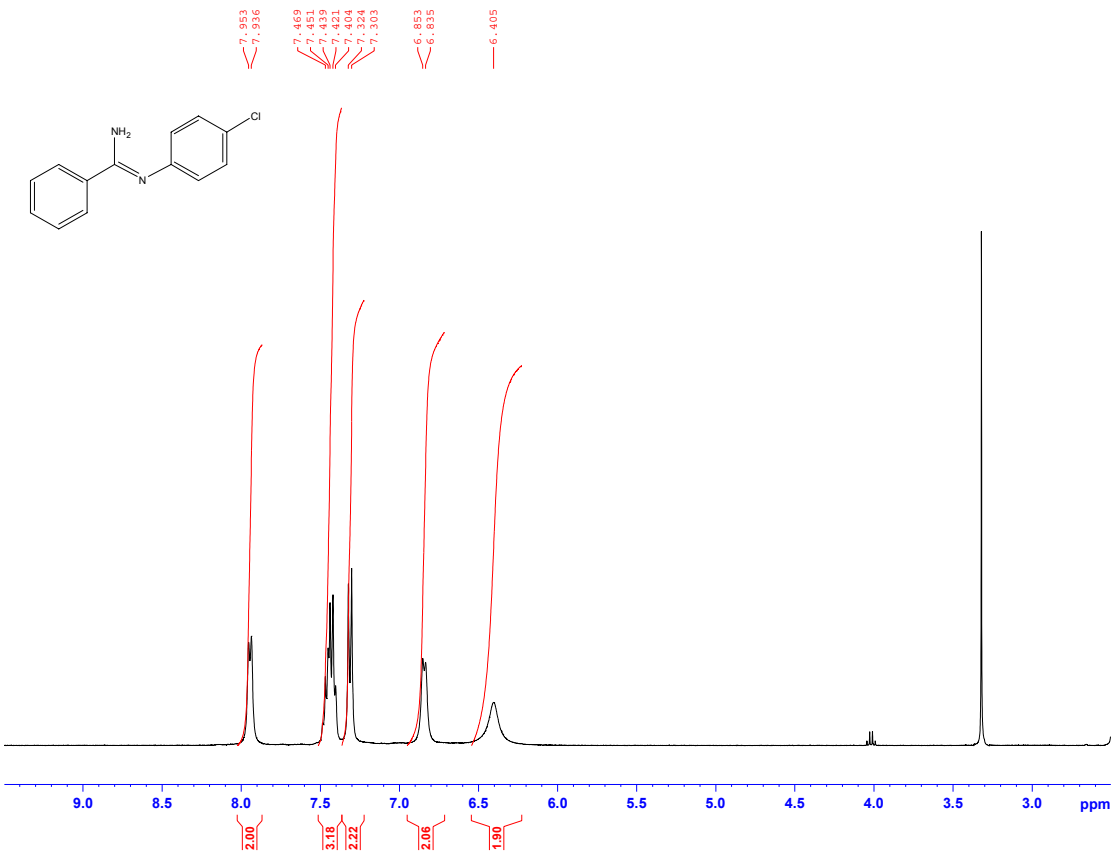




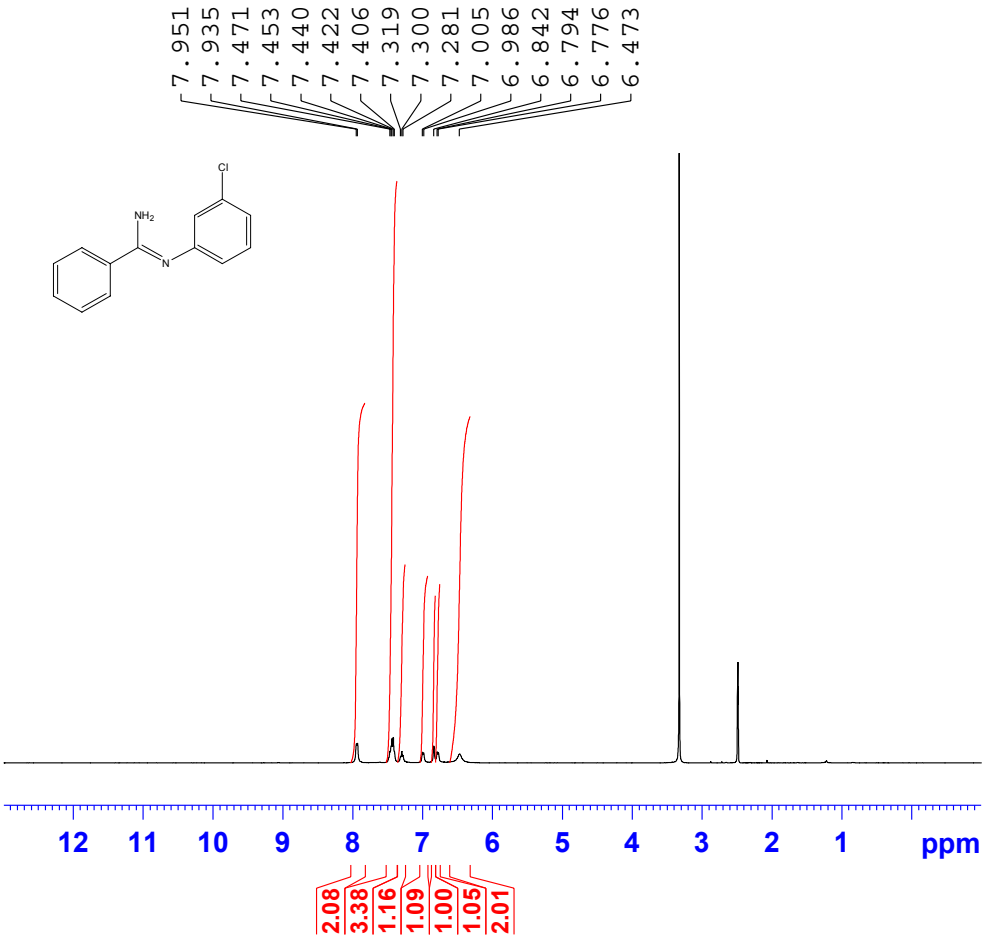
(*Z*)-*N*'-(4-nitrophenyl)benzamidine (8d)



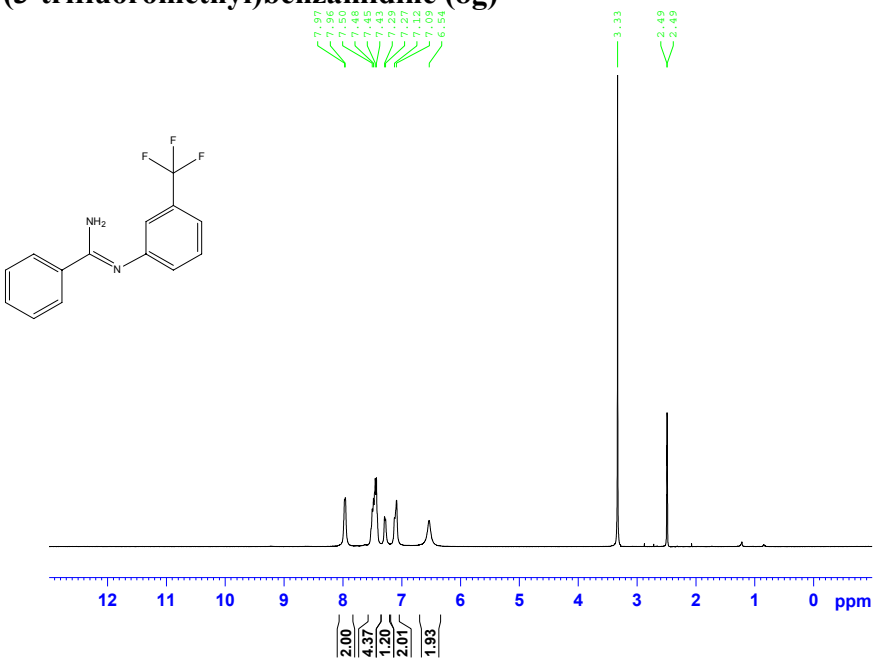
(*Z*)-*N*'-(4-chlorophenyl)benzamidine (8e)



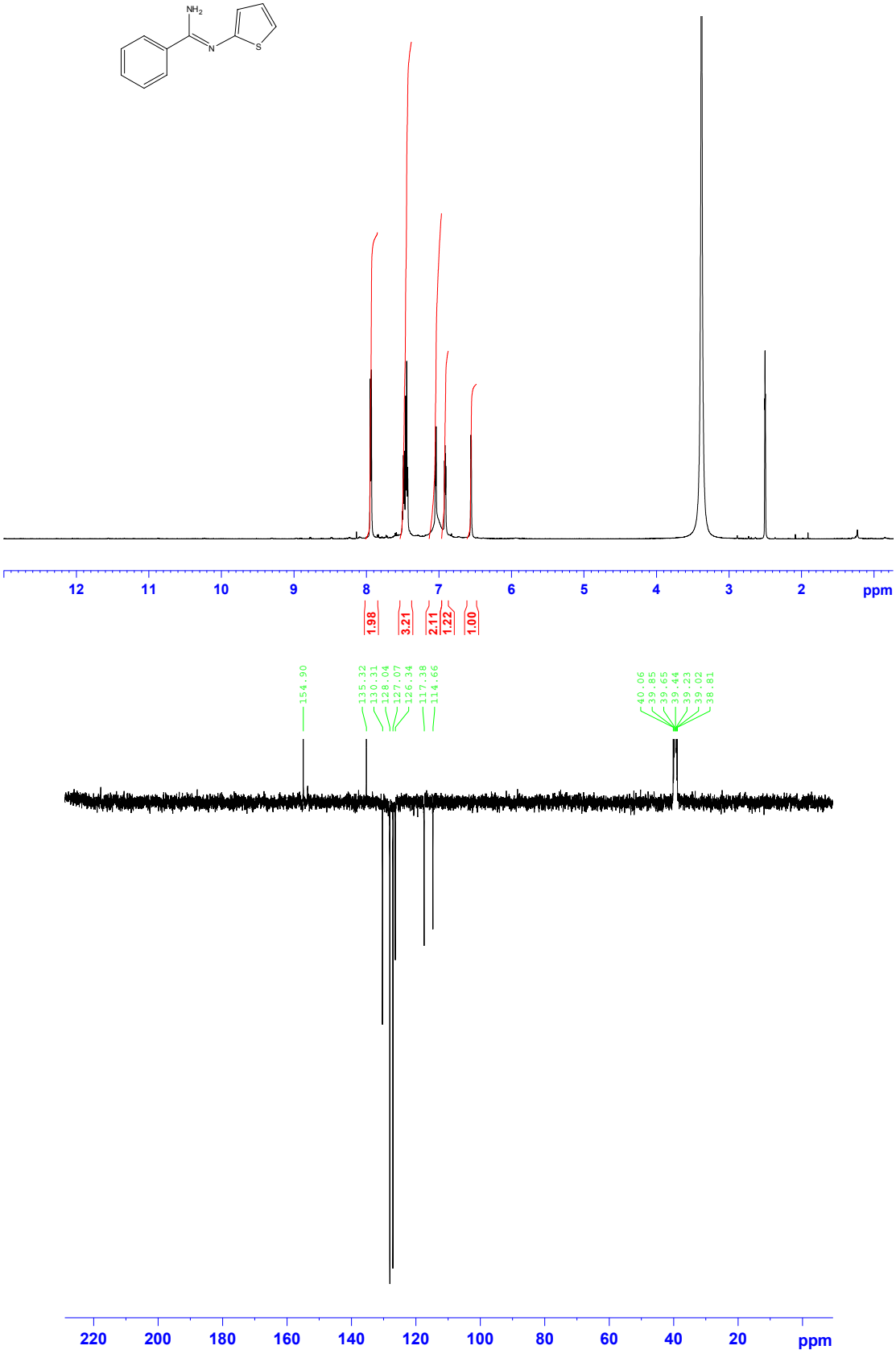
(*Z*)-*N*'-(3-chlorophenyl)benzamidine (8f)



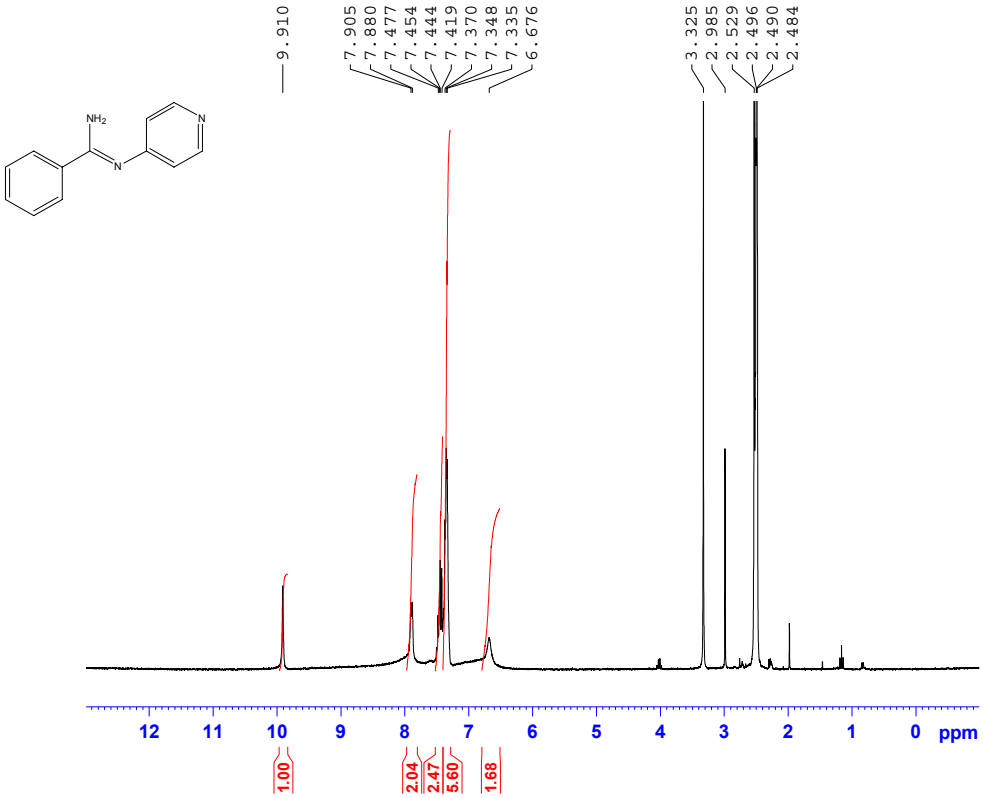
(*Z*)-*N*'-(3-trifluoromethyl)benzamidine (8g)



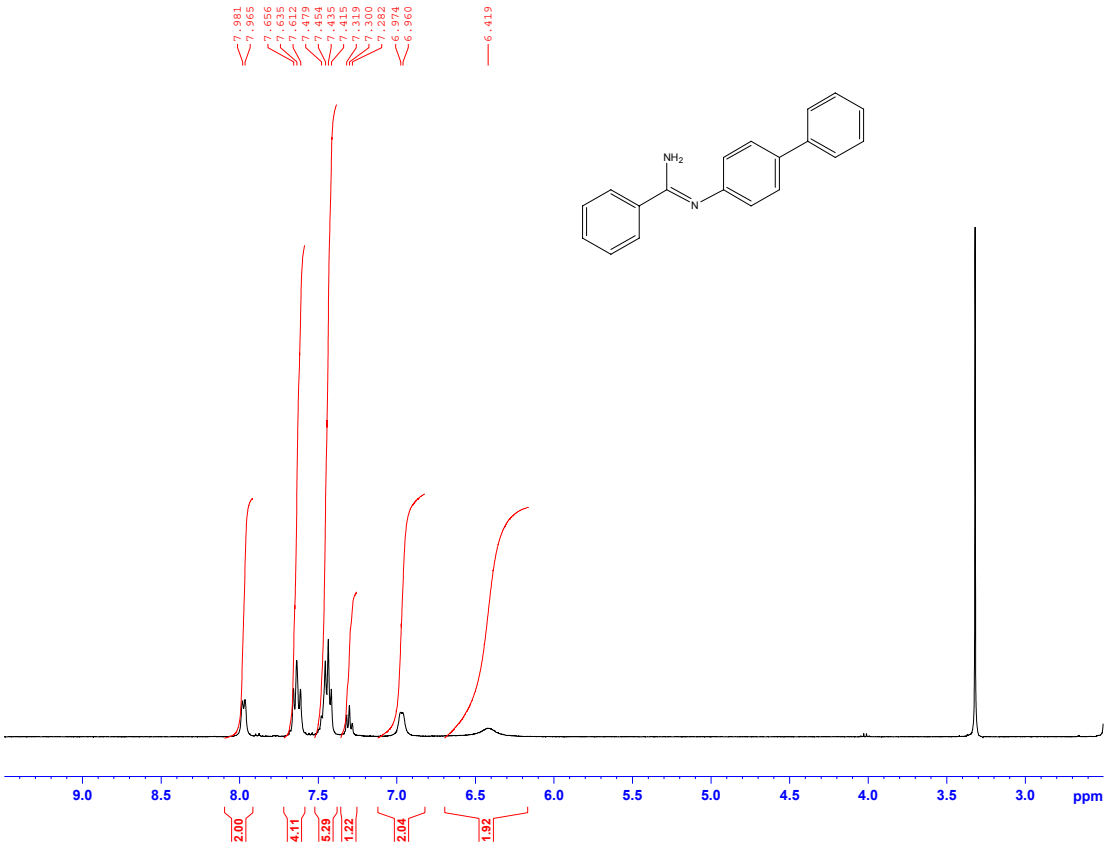
(*Z*)-*N*'-(thiophen-2-yl)benzamidine (8h)



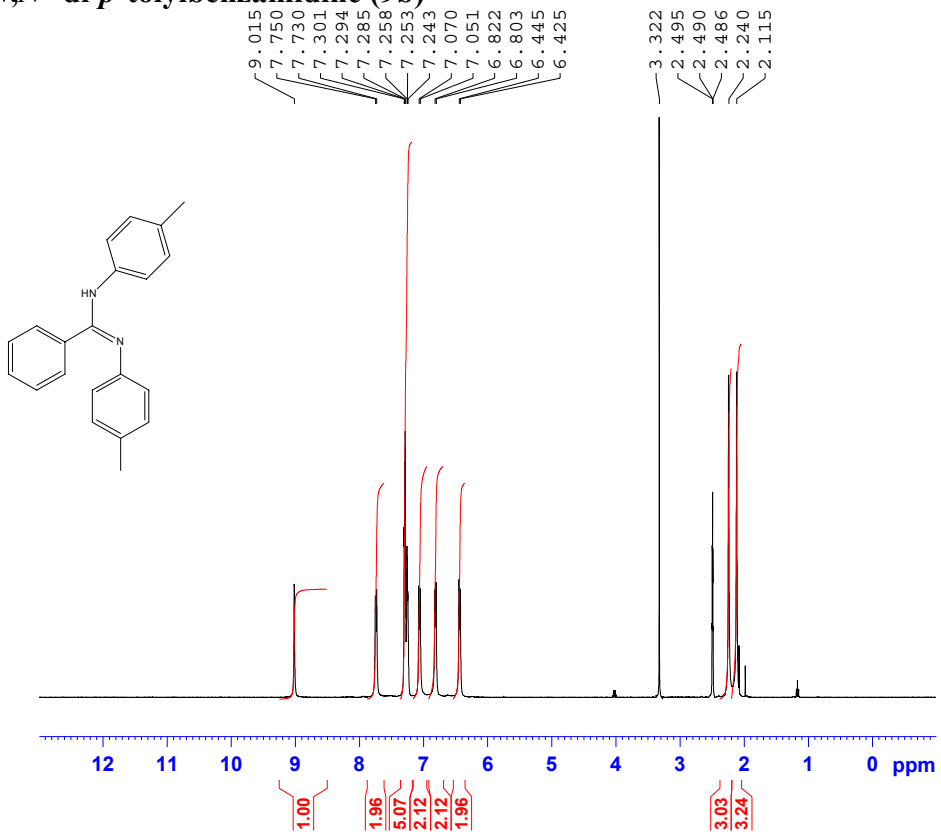
(*Z*)-*N*'-(pyridine-4-yl)benzamidine (8i)



(*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 fro several days prior to use. Thin-layer chromatography was performed using glassplates coated with silica gel (with fluorescent indicator UV_{254}). 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 ^{o}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 (^{1}H, 300.1 MHz; ^{13}C, 75.5 MHz), 400 (^{1}H, 400 MHz; ^{13}C, 100.1 MHz) or a 500 (^{1}H, 500 MHz; ^{13}C, 125 MHz) spectrometer and in the deuterated solvent stated. ^{13}C 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.

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