

# **TMP-Magnesium and TMP-Zinc Bases for the Regioselective Metalation of the Cinnoline Scaffold**

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**Supporting Information**  
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#### **1) General considerations**

All reactions were carried out under an argon atmosphere in dried glassware. Syringes and needles were flushed with argon three times before use. THF was continuously refluxed and freshly distilled from sodium benzophenone ketyl under nitrogen and kept over 4 Å molecular sieves. Yields refer to isolated yields of compounds estimated to be of >95 % purity as determined by <sup>1</sup>H-NMR and capillary-GC analysis. NMR spectra were recorded in solutions in deuterated chloroform (CDCl<sub>3</sub>) with residual chloroform (δ 7.26 ppm for <sup>1</sup>H NMR and δ 77.16 ppm for <sup>13</sup>C NMR) or deuterated benzene (C<sub>6</sub>D<sub>6</sub>) with residual benzene (7.16 ppm for <sup>1</sup>H NMR and δ 128.06 ppm for <sup>13</sup>C NMR). Abbreviations for signal coupling are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Column chromatography was performed using SiO<sub>2</sub> (0.040 – 0.063 mm, 230 – 400 mesh ASTM) from Merck if not indicated otherwise.

#### **2) Experimental Procedures and Analytical Data**

##### **Preparation of ZnCl<sub>2</sub> in THF (1.0 M)**

ZnCl<sub>2</sub> (27.3 g, 200 mmol) was placed in a 250 mL Schlenk tube equipped with a magnetic stirring bar and a septum. The salt is heated at 150 °C in an oil bath for 4 h under high vacuum. Then, after cooling to 25 °C absolute THF was added till a total volume of 200 mL was reached. Afterwards, the septum was replaced by a glass stopper and the suspension was left stirring over night at 25 °C. After 12 h, the salts had completely dissolved, the stirring was stopped and the solution was left for some more time to become completely clear (little particles and insoluble impurities were allowed to settle down by that way). The solution was stored under argon upon use.

### **Preparation of TMPMgCl·LiCl**

A dry and argon flushed 250 mL Schlenk flask was charged with *i*-PrMgCl·LiCl (100 mL, 1.2 M in THF, 120 mmol). Freshly distilled 2,2,6,6-tetramethylpiperidine (TMPH) (17.8 g, 126 mmol, 1.05 equiv) was added dropwise at 25 °C. The reaction mixture was stirred at room temperature until gas evolution ceased (ca. 48 h). The fresh TMPMgCl·LiCl (**1**) solution was titrated at 25 °C with benzoic acid using 4-(phenylazo)diphenylamine as indicator

### **Preparation of the reagent TMP<sub>2</sub>Mg·2LiCl (**2**) from TMPMgCl·LiCl and TMPLi**

In an argon flushed Schlenk flask, 2,2,6,6-tetramethylpiperidine (TMPH, 5.07 mL, 30.0 mmol) was dissolved in THF (30 mL). This solution was cooled to -40 °C and *n*-BuLi (2.4 M in hexane, 12.5 mL, 30.0 mmol) was added dropwise. After the addition was complete, the reaction mixture was warmed to 0 °C and stirred at this temperature for 30 min. Freshly titrated TMPMgCl·LiCl (1.45 M in THF, 20.7 mL, 30.0 mmol) was then added dropwise to the LiTMP solution, the reaction mixture was stirred at 0 °C for 30 min, warmed to 25 °C and stirred for 1 h. The solvents were then removed *in vacuo* without heating, affording a yellowish solid. Freshly distilled THF was then slowly added under vigorous stirring, until a complete dissolution of the salts was observed. The fresh TMP<sub>2</sub>Mg·2LiCl solution was titrated prior to use at 0 °C against benzoic acid using 4-(phenylazo)-diphenylamine as indicator. A concentration of 0.7 M in THF was obtained.

### **General procedures for the preparation of CuCN·2LiCl (1 M solution in THF)**

A Schlenk flask was charged with LiCl (16.96 g, 0.40 mol) and CuCN (17.95 g, 0.20 mol) and dried for 6 h at 150 °C under high vacuum ( $5 \cdot 10^{-2}$  mbar; dry stirring). Careful addition of THF (200 mL) and stirring overnight furnishes a slightly yellowish to greenish solution which is kept over molecular sieves (4 Å).

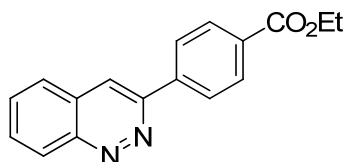
### **Typical Procedure A for the magnesiation of cinnoline (TP 1)**

A dry, argon-flushed 25 mL Schlenk flask was charged with cinnoline **1** (130 mg, 1.0 mmol) and dry THF (4 mL). The solution was cooled to 0 °C, where dry BF<sub>3</sub>·Et<sub>2</sub>O (0.14 mL, 1.1 mmol) was added dropwise. The reaction mixture was stirred for 15 min, then cooled to -78 °C, where TMP<sub>2</sub>Mg·2LiCl (1.1 mmol) was added dropwise. The completion of the metalation was checked by using GC analysis of reaction aliquots quenched with a solution of I<sub>2</sub> in THF (reaction was >95% conversion in 5 min).

### Typical Procedure B for the Zincation of cinnoline (TP 2)

A dry, argon-flushed 25 mL Schlenk flask was charged with cinnoline **1** (130 mg, 1.0 mmol) and dry THF (4 mL). A 1.0 M solution of ZnCl<sub>2</sub> (1.0 mL, 1.0 mmol) in THF was added at room temperature, followed by the immediate addition of TMPMgCl·LiCl (2.0 mmol). The reaction mixture was then heated at 50 °C. The completion of the metalation was checked by using GC analysis of reaction aliquots quenched with a solution of I<sub>2</sub> in THF (reaction was complete in 3 h).

### Synthesis of Ethyl 4-(cinnolin-3-yl)benzoate (5a)



According to **TP 1**, the metalation of cinnoline (**1**; 100 mg, 0.77 mmol) was completed within 5 min at -78 °C. Then, a 1.0 M solution of ZnCl<sub>2</sub> (0.77 mL, 0.77 mmol) was added dropwise to the reaction mixture and it was stirred for 10 min at -78 °C. A solution of Pd(PPh<sub>3</sub>)<sub>4</sub> (45 mg, 0.04 mmol), and ethyl 4-bromobenzoate (141 mg, 0.62 mmol) in THF (1.0 mL) was added dropwise. The reaction mixture was stirred at 50 °C overnight. Then, the reaction mixture was quenched with sat. aq. NH<sub>4</sub>Cl solution (5 mL), extracted with EtOAc (3 x 15 mL) and dried over MgSO<sub>4</sub>. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography (CH<sub>2</sub>Cl<sub>2</sub>:EtOAc = 7:3) to give **5a** as a yellow solid (127 mg, 74 %).

**m.p. (°C):** 178.

**<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>):** δ / ppm = 8.50 (m, 1 H), 8.36 - 8.32 (m, 2 H), 8.21 - 8.18 (m, 2 H), 7.35 (d, *J* = 0.78 Hz, 1 H), 7.21 - 7.18 (m, 2 H), 7.12 - 7.08 (m, 1 H), 4.21 - 4.15 (q, *J* = 7.1 Hz, 2 H), 1.08 - 1.04 (t, *J* = 7.2 Hz, 3 H).

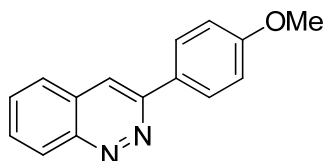
**<sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>):** δ / ppm = 166.1, 152.3, 150.5, 141.6, 131.8, 130.8, 130.5, 130.3, 130.3, 127.6, 127.1, 126.1, 118.7, 61.0, 14.3.

**IR (Diamond-ATR, neat):**  $\tilde{\nu}$  / cm<sup>-1</sup> = 3062, 2985, 2947, 2899, 2229, 1719, 1712, 1620, 1610, 1584, 1478, 1416, 1396, 1366, 1354, 1293, 1269, 1241, 1187, 1179, 1123, 1114, 1105, 1020, 963, 911, 861, 851, 793, 772, 752, 699, 675.

**MS (EI, 70 eV):**  $m/z$  (%) = 279 (22), 278 (100), 251 (13), 250 (68), 233 (18), 223 (10), 222 (58), 205 (15), 178 (12), 177 (40), 176 (45), 151 (19), 150 (12), 88 (29), 44 (10).

**HRMS (EI)** for  $C_{17}H_{14}N_2O_2$  (278.1055): 278.1044 ( $M^+$ ).

### Synthesis of 3-(4-Methoxyphenyl)cinnoline (5b)



According to **TP 1**, the metalation of cinnoline (**1**; 100 mg, 0.77 mmol) was completed within 5 min at  $-78$  °C. Then, a 1.0 M solution of  $ZnCl_2$  (0.77 mL, 0.77 mmol) was added dropwise to the reaction mixture and it was stirred for 10 min at  $-78$  °C. A solution of  $Pd(dba)_2$  (8.9 mg, 0.02 mmol),  $P(o\text{-furyl})_3$  (7.2 mg, 0.03 mmol) and 4-iodoanisole (144 mg, 0.62 mmol) in THF (1.0 mL) was added dropwise. The reaction mixture was allowed to warm to 25 °C and stirred overnight. Then, the reaction mixture was quenched with sat. aq.  $NH_4Cl$  solution (5 mL), extracted with EtOAc (3 x 15 mL) and dried over  $MgSO_4$ . After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography ( $CH_2Cl_2$ :EtOAc = 8:2) to give **5b** as a brown solid (109 mg, 75 %).

**m.p.** (°C): 107.

**$^1H$ -NMR (300 MHz,  $CDCl_3$ ):**  $\delta$  / ppm = 8.53 (d,  $J$  = 8.3 Hz, 1 H), 8.25 - 8.18 (m, 2 H), 8.09 (s, 1 H), 7.86 - 7.69 (m, 3 H), 7.12 - 7.05 (m, 2 H), 3.90 (s, 3 H).

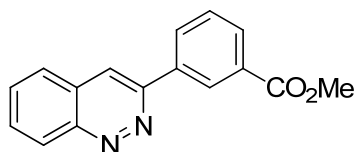
**$^{13}C$ -NMR (75 MHz,  $CDCl_3$ ):**  $\delta$  / ppm = 161.0, 153.4, 149.7, 131.3, 130.0 (2), 129.6, 128.7, 127.0, 126.8, 117.8, 114.6, 55.6.

**IR (Diamond-ATR, neat):**  $\tilde{\nu}$  /  $cm^{-1}$  = 2836, 1603, 1510, 1438, 1257, 1243, 1172, 1119, 1034, 1019, 896, 830, 745, 752, 675.

**MS (EI, 70 eV):**  $m/z$  (%) = 237 (18), 236 (100), 209 (13), 208 (79), 193 (16), 166 (12), 165 (79), 164 (12), 163 (12), 104 (13).

**HRMS (EI)** for  $C_{15}H_{12}N_2O$  (236.0950): 236.0936 ( $M^+$ ).

### Synthesis of Methyl 3-(cinnolin-3-yl)benzoate (**5c**)



According to **TP 1**, the metalation of cinnoline (**1**; 100 mg, 0.77 mmol) was completed within 5 min at  $-78\text{ }^{\circ}\text{C}$ . Then, a 1.0 M solution of  $\text{ZnCl}_2$  (0.77 mL, 0.77 mmol) was added dropwise to the reaction mixture and it was stirred for 10 min at  $-78\text{ }^{\circ}\text{C}$ . A solution of  $\text{Pd}(\text{PPh}_3)_4$  (45 mg, 0.04 mmol), and methyl 3-bromobenzoate (132 mg, 0.62 mmol) in THF (1.0 mL) was added dropwise. The reaction mixture was stirred at  $50\text{ }^{\circ}\text{C}$  overnight. Then, the reaction mixture was quenched with sat. aq.  $\text{NH}_4\text{Cl}$  solution (5 mL), extracted with EtOAc (3 x 15 mL) and dried over  $\text{MgSO}_4$ . After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography ( $\text{CH}_2\text{Cl}_2$ :EtOAc = 7:3) to give **5c** as a yellow solid (110 mg, 69 %).

**m.p.** ( $^{\circ}\text{C}$ ): 105-107.

**$^1\text{H-NMR}$  (300 MHz,  $\text{CDCl}_3$ ):**  $\delta$  / ppm = 8.84 - 8.79 (m, 1 H), 8.58 - 8.51 (m, 2 H), 8.22 (s, 1 H), 8.14 (dd,  $J = 7.7, 1.4$  Hz, 1 H), 7.88 (d,  $J = 8.0$  Hz, 1 H), 7.85 - 7.71 (m, 2 H), 7.62 (t,  $J = 7.9$  Hz, 1 H), 3.96 (s, 3 H).

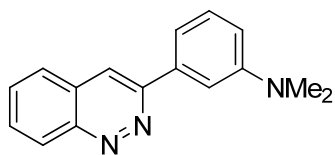
**$^{13}\text{C-NMR}$  (75 MHz,  $\text{CDCl}_3$ ):**  $\delta$  / ppm = 166.9, 152.5, 150.1, 137.3, 131.8, 131.6, 131.1, 130.7, 130.5, 129.9, 129.3, 128.2, 127.1, 126.5, 119.2, 52.4.

**IR (Diamond-ATR, neat):**  $\tilde{\nu}$  /  $\text{cm}^{-1}$  = 3032, 2945, 2924, 2846, 1720, 1605, 1582, 1446, 1429, 1335, 1288, 1263, 1214, 1179, 1136, 1106, 1087, 1050, 967, 912, 829, 804, 797, 778, 751, 738, 692.

**MS (EI, 70 eV):**  $m/z$  (%) = 265 (38), 264 (100), 237 (13), 236 (76), 233 (15), 207 (10), 206 (63), 205 (16), 178 (16), 177 (65), 176 (80), 165 (15), 151 (29), 150 (14), 127 (12), 102 (17), 89 (15), 88 (58), 75 (13), 69 (13), 57 (19), 55 (18), 43 (16), 43 (16), 43 (42), 41 (16).

**HRMS (EI) for  $\text{C}_{16}\text{H}_{12}\text{N}_2\text{O}_2$  (264.0899):** 264.0886 ( $\text{M}^+$ ).

### Synthesis of 3-(Cinnolin-3-yl)-*N,N*-dimethylaniline (5d)



According to **TP 1**, the metalation of cinnoline (**1**; 100 mg, 0.77 mmol) was completed within 5 min at  $-78\text{ }^{\circ}\text{C}$ . Then, a 1.0 M solution of  $\text{ZnCl}_2$  (0.77 mL, 0.77 mmol) was added dropwise to the reaction mixture and it was stirred for 10 min at  $-78\text{ }^{\circ}\text{C}$ . A solution of  $\text{Pd}(\text{dba})_2$  (8.9 mg, 0.02 mmol),  $\text{P}(o\text{-furyl})_3$  (7.2 mg, 0.03 mmol) and 3-iodo-*N,N*-dimethylaniline (152 mg, 0.62 mmol) in THF (1.0 mL) was added dropwise. The reaction mixture was allowed to warm to  $25\text{ }^{\circ}\text{C}$  and stirred overnight. Then, the reaction mixture was quenched with sat. aq.  $\text{NH}_4\text{Cl}$  solution (5 mL), extracted with EtOAc (3 x 15 mL) and dried over  $\text{MgSO}_4$ . After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography ( $\text{CH}_2\text{Cl}_2\text{:EtOAc} = 6\text{:}4$ ) to give **5d** as a brown solid (112 mg, 73 %).

**m.p.** ( $^{\circ}\text{C}$ ): 108-110.

**$^1\text{H-NMR}$  (300 MHz,  $\text{CDCl}_3$ ):**  $\delta$  / ppm = 8.55 - 8.50 (m, 1 H), 8.12 (s, 1 H), 7.83 (d,  $J = 8.9$  Hz, 1 H), 7.80 - 7.66 (m, 3 H), 7.48 - 7.43 (m, 1 H), 7.39 (t,  $J = 7.7$  Hz, 1 H), 6.86 (m, 1 H), 3.05 (s, 6 H).

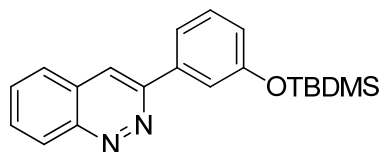
**$^{13}\text{C-NMR}$  (75 MHz,  $\text{CDCl}_3$ ):**  $\delta$  / ppm = 154.1, 151.2, 149.9, 137.7, 131.1, 130.1, 129.8, 129.7, 127.1, 126.6, 118.9, 115.5, 113.7, 111.6, 40.8.

**IR (Diamond-ATR, neat):**  $\tilde{\nu}$  /  $\text{cm}^{-1}$  = 3062, 2916, 2851, 2804, 1601, 1586, 1566, 1500, 1434, 1363, 1348, 1229, 1133, 1097, 1062, 991, 952, 913, 871, 835, 801, 794, 767, 699, 688, 684.

**MS (EI, 70 eV):**  $m/z$  (%) = 249 (100), 248 (17), 235 (22), 234 (68), 206 (23), 205 (26), 178 (39), 177 (17), 177(18), 176 (30), 165 (24), 110 (27), 102 (16), 97 (45), 77 (18), 71 (17), 69 (25), 57 (60), 56 (22), 55 (22), 44 (75), 43 (31), 43 (54), 42 (51).

**HRMS (EI) for  $\text{C}_{16}\text{H}_{15}\text{N}_3$**  (249.1266): 249.1256 ( $\text{M}^+$ ).

### Synthesis of 3-(3-((*tert*-Butyldimethylsilyl)oxy)phenyl)cinnoline (5e)



According to **TP 1**, the metalation of cinnoline (**1**; 100 mg, 0.77 mmol) was completed within 5 min at  $-78\text{ }^{\circ}\text{C}$ . Then, a 1.0 M solution of  $\text{ZnCl}_2$  (0.77 mL, 0.77 mmol) was added dropwise to the reaction mixture and it was stirred for 10 min at  $-78\text{ }^{\circ}\text{C}$ . A solution of  $\text{Pd}(\text{dba})_2$  (8.9 mg, 0.02 mmol),  $\text{P}(o\text{-furyl})_3$  (7.2 mg, 0.03 mmol) and *tert*-butyl(3-iodophenoxy)dimethylsilane (206 mg, 0.62 mmol) in THF (1.0 mL) was added dropwise. The reaction mixture was allowed to warm to  $25\text{ }^{\circ}\text{C}$  and stirred overnight. Then, the reaction mixture was quenched with sat. aq.  $\text{NH}_4\text{Cl}$  solution (5 mL), extracted with EtOAc (3 x 15 mL) and dried over  $\text{MgSO}_4$ . After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography ( $\text{CH}_2\text{Cl}_2:\text{EtOAc} = 8:2$ ) to give **5e** as a yellow solid (131 mg, 63 %).

**m.p.** ( $^{\circ}\text{C}$ ): 87-88.

**$^1\text{H-NMR}$  (300 MHz,  $\text{CDCl}_3$ ):**  $\delta$  / ppm = 8.55 (d,  $J = 8.6$  Hz, 1 H), 8.13 (s, 1 H), 7.87 (d,  $J = 9.1$  Hz, 1 H), 7.84 - 7.70 (m, 4 H), 7.41 (t,  $J = 8.0$  Hz, 1 H), 6.97 (dt,  $J = 8.6, 1.5$  Hz, 1 H), 1.09 - 0.94 (m, 9 H), 0.35 - 0.19 (m, 6 H).

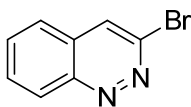
**$^{13}\text{C-NMR}$  (75 MHz,  $\text{CDCl}_3$ ):**  $\delta$  / ppm = 156.5, 153.4, 150.0, 138.5, 131.4, 130.4, 130.1, 129.9, 127.1, 126.7, 121.3, 120.3, 119.2, 119.0, 25.9, 18.4, -4.2.

**IR (Diamond-ATR, neat):**  $\tilde{\nu}$  /  $\text{cm}^{-1}$  = 3039, 2955, 2927, 2892, 2855, 1621, 1601, 1580, 1487, 1481, 1471, 1462, 1449, 1428, 1402, 1389, 1360, 1356, 1329, 1313, 1287, 1253, 1246, 1227, 1183, 1178, 1166, 1131, 1099, 1010, 1006, 999, 979, 960, 943, 895, 869, 853, 836, 825, 810, 797, 776, 741, 696, 683, 662.

**MS (EI, 70 eV):**  $m/z$  (%) = 336 (13), 281 (9), 280 (31), 279 (100), 265 (5), 176 (5), 125 (6).

**HRMS (EI) for  $\text{C}_{20}\text{H}_{24}\text{N}_2\text{OSi}$  (336.1658):** 336.1650 ( $\text{M}^+$ ).

### Synthesis of 3-Bromocinnoline (5f)



According to **TP 1**, the metalation of cinnoline (**1**; 130 mg, 1.0 mmol) was completed within 5 min at  $-78\text{ }^{\circ}\text{C}$ . The metalated species was then cannulated into a solution of dibromotetrachloroethane (651 mg, 2 mmol) in dry THF (2 mL), pre-cooled to  $-78\text{ }^{\circ}\text{C}$ . The reaction mixture was allowed to warm to  $25\text{ }^{\circ}\text{C}$  overnight. Then, the reaction mixture was quenched with sat. aq.  $\text{NaHCO}_3$  solution (10 mL), extracted with EtOAc (3 x 15 mL) and dried over  $\text{Na}_2\text{SO}_4$ . After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography (isohexane:EtOAc = 9:1) to give **5f** as an off-white solid (116 mg, 55 %).

**m.p.** ( $^{\circ}\text{C}$ ): 92.

**$^1\text{H-NMR}$  (300 MHz,  $\text{CDCl}_3$ ):**  $\delta$  / ppm = 8.48 (d,  $J = 8.6$  Hz, 1 H), 8.07 (s, 1 H), 7.88 - 7.81 (m, 1 H), 7.79 - 7.72 (m, 2 H).

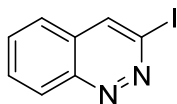
**$^{13}\text{C-NMR}$  (75 MHz,  $\text{CDCl}_3$ ):**  $\delta$  / ppm = 150.0, 141.2, 132.3, 131.2, 129.9, 127.8, 126.3, 125.8.

**IR (Diamond-ATR, neat):**  $\tilde{\nu}$  /  $\text{cm}^{-1}$  = 3033, 1568, 1554, 1529, 1471, 1418, 1295, 1178, 1137, 1100, 1045, 964, 926, 916, 854, 788, 749.

**MS (EI, 70 eV):**  $m/z$  (%) = 210 (39), 208 (38), 182 (20), 180 (19), 101 (49), 84 (16), 75 (17), 70 (13), 61 (18), 45 (15), 44 (20), 43 (100).

**HRMS (EI) for  $\text{C}_8\text{H}_5\text{BrN}_2$  (207.9636):** 207.9624 ( $\text{M}^+$ ).

### Synthesis of 3-Iodocinnoline (5g)



According to **TP1**, the metalation of cinnoline (**1**; 130 mg, 1.0 mmol) was completed within 5 min at  $-78\text{ }^{\circ}\text{C}$ . The metalated species was then cannulated into a solution of  $\text{I}_2$  (518 mg, 2 mmol) in dry THF (2 mL), pre-cooled to  $-78\text{ }^{\circ}\text{C}$ . The reaction mixture was allowed to warm to  $25\text{ }^{\circ}\text{C}$  overnight. Then, the reaction mixture was quenched with aq.  $\text{Na}_2\text{S}_2\text{O}_3$  solution (10 mL), extracted with EtOAc (3 x 15 mL) and dried over  $\text{Na}_2\text{SO}_4$ . After filtration, the

solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography (isohexane:EtOAc = 9:1) to give **5g** as an off-white solid (132 mg, 51 %).

**m.p. (°C):** 109.

**<sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>):** δ / ppm = 8.47 (dd, *J* = 8.5, 1.0 Hz, 1 H), 8.30 (d, *J* = 0.9 Hz, 1 H), 7.89 - 7.83 (m, 1 H), 7.79 - 7.68 (m, 2 H)

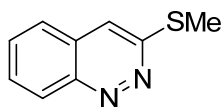
**<sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>):** δ / ppm = 149.7, 132.6, 132.1, 131.3, 129.9, 127.5, 125.5, 116.9.

**IR (Diamond-ATR, neat):**  $\tilde{\nu}$  / cm<sup>-1</sup> = 3060, 1563, 1539, 1523, 1468, 1413, 1292, 1262, 1174, 1138, 1097, 1026, 959, 906, 848, 788, 748.

**MS (EI, 70 eV):** *m/z* (%) = 257 (14), 256 (100), 228 (23), 102 (13), 101 (91), 76 (14), 75 (37), 74 (12), 50 (11), 44 (13).

**HRMS (EI) for C<sub>8</sub>H<sub>5</sub>IN<sub>2</sub> (255.9497):** 255.9479 (M<sup>+</sup>).

### Synthesis of 3-(Methylthio)cinnoline (**5h**)



According to **TP1**, the metalation of cinnoline (**1**; 130 mg, 1.0 mmol) was completed within 5 min at -78 °C. The metalated species was then cannulated into a solution of MeSO<sub>2</sub>SMe (379 mg, 3 mmol) in dry THF (10 mL), pre-cooled to -78 °C. The reaction mixture was allowed to warm to 25 °C overnight. Then, the reaction mixture was quenched with sat. aq. NH<sub>4</sub>Cl solution (10 mL), extracted with EtOAc (3 x 15 mL) and dried over MgSO<sub>4</sub>. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography (isohexane:EtOAc = 9:1) to give **5h** as brown solid (90 mg, 51 %).

**m.p. (°C):** 81-83.

**<sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>):** δ / ppm = 8.40 - 8.33 (m, 1 H), 7.70 - 7.59 (m, 4 H), 2.78 (s, 3 H).

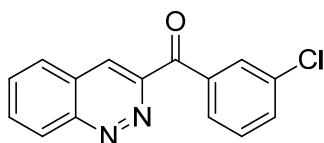
**<sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>):** δ / ppm = 156.9, 148.9, 131.6, 129.8, 129.5, 126.3, 125.6, 119.2, 14.2.

**IR (Diamond-ATR, neat):**  $\tilde{\nu}$  / cm<sup>-1</sup> = 3010, 2925, 1567, 1548, 1421, 1302, 1178, 1144, 1097, 1068, 963, 918, 870, 789, 747.

**MS (EI, 70 eV):**  $m/z$  (%) = 177 (12), 176 (100), 175 (12), 148 (18), 147 (26), 89 (47).

**HRMS (EI) for C<sub>9</sub>H<sub>8</sub>N<sub>2</sub>S** (176.0408): 176.0404 (M<sup>+</sup>).

### Synthesis of (3-Chlorophenyl)(cinnolin-3-yl)methanone (**5i**)



According to **TP 1**, the metalation of cinnoline (**1**; 100 mg, 0.77 mmol) was completed within 5 min at  $-78$  °C. Then, a 1.0 M solution of ZnCl<sub>2</sub> (1.92 mL, 1.92 mmol) was added dropwise to the reaction mixture and it was stirred for 10 min at  $-78$  °C. The reaction mixture was allowed to warm to  $-40$  °C, then a 1.0 M solution of CuCN·2LiCl (0.85 mL, 0.85 mmol) and 3-chlorobenzoyl chloride (135 mg, 0.77 mmol) were added. The resulting mixture was allowed to warm to 25 °C and stirred overnight. Then, the reaction mixture was quenched with sat. aq. NH<sub>4</sub>Cl solution (5 mL), extracted with EtOAc (3 x 15 mL) and dried over MgSO<sub>4</sub>. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography (CH<sub>2</sub>Cl<sub>2</sub>:EtOAc = 8:2) to give **5i** as a yellow solid (110 mg, 53 %).

**m.p. (°C):** 126-127.

**<sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>):**  $\delta$  / ppm = 8.68 (t,  $J$  = 3.9 Hz, 2 H), 8.26 (t,  $J$  = 1.9 Hz, 1 H), 8.18 (d,  $J$  = 7.7 Hz, 1 H), 8.08 - 7.99 (m, 2 H), 7.89 (t,  $J$  = 7.6 Hz, 1 H), 7.62 (m, 1 H), 7.48 (t,  $J$  = 7.9 Hz, 1 H).

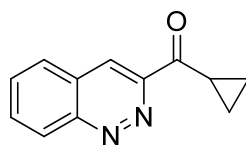
**<sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>):**  $\delta$  / ppm = 191.2, 151.6, 151.2, 137.9, 134.7, 133.3, 133.1, 132.2, 131.4, 130.2, 129.9, 129.7, 128.2, 126.1, 125.6.

**IR (Diamond-ATR, neat):**  $\tilde{\nu}$  / cm<sup>-1</sup> = 3057, 2924, 1664, 1615, 1568, 1487, 1415, 1394, 1372, 1319, 1246, 1219, 1186, 1080, 954, 941, 891, 859, 805, 784, 751, 742, 737, 681, 669.

**MS (EI, 70 eV):**  $m/z$  (%) = 270 (31), 269 (32), 268 (95), 267 (59), 241 (12), 240 (24), 239 (23), 233 (36), 212 (12), 206 (17), 205 (100), 178 (11), 177 (19), 141 (14), 139 (43), 116 (13), 110 (60), 75 (33).

**HRMS (EI) for C<sub>15</sub>H<sub>9</sub>ClN<sub>2</sub>O** (268.0403): 268.0400 (M<sup>+</sup>).

### Synthesis of Cinnolin-3-yl(cyclopropyl)methanone (**5j**)



According to **TP 1**, the metalation of cinnoline (**1**; 100 mg, 0.77 mmol) was completed within 5 min at  $-78\text{ }^{\circ}\text{C}$ . Then, a 1.0 M solution of  $\text{ZnCl}_2$  (1.92 mL, 1.92 mmol) was added dropwise to the reaction mixture and it was stirred for 10 min at  $-78\text{ }^{\circ}\text{C}$ . The reaction mixture was allowed to warm to  $-40\text{ }^{\circ}\text{C}$ , then a 1.0 M solution of  $\text{CuCN}\cdot 2\text{LiCl}$  (0.85 mL, 0.85 mmol) and cyclopropanecarbonyl chloride (80 mg, 0.77 mmol) were added. The resulting mixture was allowed to warm to  $25\text{ }^{\circ}\text{C}$  and stirred overnight. Then, the reaction mixture was quenched with sat. aq.  $\text{NH}_4\text{Cl}$  solution (5 mL), extracted with EtOAc (3 x 15 mL) and dried over  $\text{MgSO}_4$ . After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography ( $\text{CH}_2\text{Cl}_2$ :EtOAc = 9:1) to give **5j** as a yellow solid (89 mg, 58 %).

**m.p.** ( $^{\circ}\text{C}$ ): 109-110.

**$^1\text{H-NMR}$  (300 MHz,  $\text{CDCl}_3$ ):**  $\delta$  / ppm = 8.65 (d,  $J = 8.0$  Hz, 1 H), 8.56 (s, 1 H), 8.04 - 7.94 (m, 2 H), 7.83 (t,  $J = 7.6$  Hz, 1 H), 4.00 - 3.91 (m, 1 H), 1.44 - 1.37 (m, 2 H), 1.27 - 1.22 (m, 2 H).

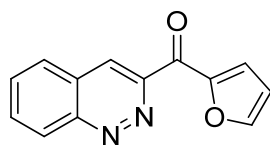
**$^{13}\text{C-NMR}$  (75 MHz,  $\text{CDCl}_3$ ):**  $\delta$  / ppm = 200.6, 151.6, 150.3, 132.7, 131.9, 130.0, 128.6, 126.0, 122.3, 17.1, 13.5.

**IR (Diamond-ATR, neat):**  $\tilde{\nu}$  /  $\text{cm}^{-1}$  = 3070, 3052, 3009, 2924, 2853, 1677, 1617, 1555, 1538, 1488, 1387, 1362, 1308, 1238, 1182, 1169, 1129, 1098, 1036, 964, 942, 894, 874, 796, 776, 756, 746, 717.

**MS (EI, 70 eV):**  $m/z$  (%) = 200 (11), 199 (49), 198 (38), 197 (73), 170 (30), 169 (100), 131 (38), 130 (17), 115 (17), 103 (11), 102 (12), 101 (25), 75 (16), 71 (10), 69 (10), 69 (49), 57 (15), 42 (16), 40 (49).

**HRMS (EI) for  $\text{C}_{12}\text{H}_{10}\text{N}_2\text{O}$  (198.0793):** 198.0810 ( $\text{M}^+$ ).

### Synthesis of Cinnolin-3-yl(furan-2-yl)methanone (**5k**)



According to **TP 1**, the metalation of cinnoline (**1**; 100 mg, 0.77 mmol) was completed within 5 min at  $-78\text{ }^{\circ}\text{C}$ . Then, a 1.0 M solution of  $\text{ZnCl}_2$  (1.92 mL, 1.92 mmol) was added dropwise to the reaction mixture and it was stirred for 10 min at  $-78\text{ }^{\circ}\text{C}$ . The reaction mixture was allowed to warm to  $-40\text{ }^{\circ}\text{C}$ , then a 1.0 M solution of  $\text{CuCN}\cdot 2\text{LiCl}$  (0.85 mL, 0.85 mmol) and furan-2-carbonyl chloride (101 mg, 0.77 mmol) were added. The resulting mixture was allowed to warm to  $25\text{ }^{\circ}\text{C}$  and stirred overnight. Then, the reaction mixture was quenched with sat. aq.  $\text{NH}_4\text{Cl}$  solution (5 mL), extracted with EtOAc (3 x 15 mL) and dried over  $\text{MgSO}_4$ . After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography ( $\text{CH}_2\text{Cl}_2$ :EtOAc = 8:2) to give **5k** as a yellow solid (92 mg, 53 %).

**m.p.** ( $^{\circ}\text{C}$ ): 174-176.

**$^1\text{H-NMR}$  (300 MHz,  $\text{CDCl}_3$ ):**  $\delta$  / ppm = 8.77 (s, 1 H), 8.65 (d,  $J = 8.6$  Hz, 1 H), 8.39 (d,  $J = 3.6$  Hz, 1 H), 8.07 - 7.98 (m, 2 H), 7.91 - 7.82 (m, 2 H), 6.71 (dd,  $J = 4.0, 2.1$  Hz, 1 H).

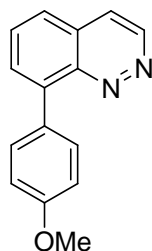
**$^{13}\text{C-NMR}$  (75 MHz,  $\text{CDCl}_3$ ):**  $\delta$  / ppm = 177.6, 151.4, 151.3, 151.0, 148.5, 132.9, 132.0, 130.0, 128.3, 126.1, 125.8, 124.7, 113.0.

**IR (Diamond-ATR, neat):**  $\tilde{\nu}$  /  $\text{cm}^{-1}$  = 3159, 3131, 3111, 3057, 1643, 1633, 1557, 1485, 1463, 1389, 1324, 1262, 1163, 1117, 1106, 1098, 1081, 1024, 1013, 992, 950, 935, 897, 817, 800, 782, 773, 765, 750, 657.

**MS (EI, 70 eV):**  $m/z$  (%) = 225 (10), 224 (47), 197 (15), 196 (100), 169 (12), 168 (80), 141 (13), 140 (17), 139 (43), 114 (10), 101 (11), 75 (12).

**HRMS (EI) for  $\text{C}_{13}\text{H}_8\text{N}_2\text{O}_2$  (224.0586):** 224.0581 ( $\text{M}^+$ ).

### Synthesis of 8-(4-Methoxyphenyl)cinnoline (6a)



According to **TP 2**, the metalation of cinnoline (**1**; 100 mg, 0.77 mmol) was completed within 3 h at 50 °C. Then, a solution of Pd(dba)<sub>2</sub> (8.9 mg, 0.02 mmol), P(*o*-furyl)<sub>3</sub> (7.2 mg, 0.03 mmol) and 4-iodoanisole (144 mg, 0.62 mmol) in THF (1.0 mL) was added to the reaction mixture dropwise and it was stirred overnight. Then, the reaction mixture was quenched with sat. aq. NH<sub>4</sub>Cl solution (5 mL), extracted with EtOAc (3 x 15 mL) and dried over MgSO<sub>4</sub>. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography (CH<sub>2</sub>Cl<sub>2</sub>:EtOAc = 8:2) to give **6a** as a brown solid (153 mg, 84 %).

**m.p.** (°C): 121-122.

**<sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>):** δ / ppm = 9.33 (d, *J* = 5.8 Hz, 1 H), 7.92 - 7.69 (m, 6 H), 7.10 - 7.01 (m, 2 H), 3.88 (s, 3 H).

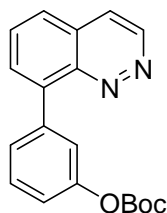
**<sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>):** δ / ppm = 159.8, 148.9, 145.0, 141.3, 132.3, 131.2, 130.8, 130.2, 126.5, 125.7, 122.6, 113.9, 55.5.

**IR (Diamond-ATR, neat):**  $\tilde{\nu}$  / cm<sup>-1</sup> = 2831, 1737, 1602, 1508, 1454, 1423, 1371, 1308, 1290, 1271, 1244, 1177, 1099, 1028, 852, 832, 805, 782.

**MS (EI, 70 eV):** *m/z* (%) = 237 (13), 236 (68), 235 (55), 221 (32), 220 (18), 206 (17), 205 (100), 193 (10), 192 (20).

**HRMS (EI) for C<sub>15</sub>H<sub>12</sub>N<sub>2</sub>O (236.0950):** 236.0938 (M<sup>+</sup>).

### Synthesis of *tert*-Butyl (3-(cinnolin-8-yl)phenyl) carbonate (**6b**)



According to **TP 2**, the metalation of cinnoline (**1**; 100 mg, 0.77 mmol) was completed within 3 h at 50 °C. Then, a solution of Pd(dba)<sub>2</sub> (8.9 mg, 0.02 mmol), P(*o*-furyl)<sub>3</sub> (7.2 mg, 0.03 mmol) and *tert*-butyl (3-iodophenyl) carbonate (198 mg, 0.62 mmol) in THF (1.0 mL) was added to the reaction mixture dropwise and it was stirred overnight. Then, the reaction mixture was quenched with sat. aq. NH<sub>4</sub>Cl solution (5 mL), extracted with EtOAc (3 x 15 mL) and dried over MgSO<sub>4</sub>. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography (isoHexane:EtOAc = 8:2) to give **6b** as a dark oil (140 mg, 70 %).

**<sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>):** δ / ppm = 9.39 (d, *J* = 5.9 Hz, 1H), 8.03 (d, *J* = 5.9 Hz, 1H), 7.93 - 7.85 (m, 3H), 7.65 (ddd, *J* = 7.7, 1.6, 1.1 Hz, 1H), 7.62 - 7.59 (m, 1H), 7.51 (t, *J* = 7.9 Hz, 1H), 7.31 - 7.26 (m, 1H), 1.56 (s, 9H).

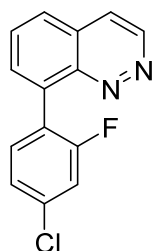
**<sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>):** δ / ppm = 151.8, 150.9, 148.3, 143.9, 140.8, 138.6, 132.0, 132.0, 129.1, 128.5, 127.0, 126.6, 123.9, 123.7, 121.0, 83.5, 27.7 (3C).

**IR (Diamond-ATR, neat):**  $\tilde{\nu}$  / cm<sup>-1</sup> = 2977, 2930, 1751, 1581, 1393, 1368, 1270, 1246, 1131, 1100, 1002, 914, 853, 743, 693, 672.

**MS (EI, 70 eV):** *m/z* (%) = 322 (15), 221 (100), 205 (95), 192 (15), 166 (15), 139 (20).

**HRMS (EI) for C<sub>19</sub>H<sub>18</sub>N<sub>2</sub>O<sub>3</sub> (322.1317):** 322.1322 (M<sup>+</sup>).

### Synthesis of 8-(4-Chloro-2-fluorophenyl)cinnoline (**6c**)



According to **TP 2**, the metalation of cinnoline (**1**; 100 mg, 0.77 mmol) was completed within 3 h at 50 °C. Then, a solution of Pd(dba)<sub>2</sub> (8.9 mg, 0.02 mmol), P(*o*-furyl)<sub>3</sub> (7.2 mg,

0.03 mmol) and 4-chloro-2-fluoro-1-iodobenzene (158 mg, 0.62 mmol) in THF (1.0 mL) was added to the reaction mixture dropwise and it was stirred overnight. Then, the reaction mixture was quenched with sat. aq. NH<sub>4</sub>Cl solution (5 mL), extracted with EtOAc (3 x 15 mL) and dried over MgSO<sub>4</sub>. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography (isoHexane:EtOAc = 8:2) to give **6c** as a dark solid (104 mg, 65 %).

**m.p.** (°C): 127-129.

**<sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>):** δ / ppm = 9.39 (d, *J* = 5.9 Hz, 1H), 8.02 (d, *J* = 5.9 Hz, 1H), 7.98 – 7.90 (m, 1H), 7.90 – 7.85 (m, 2H), 7.56 – 7.47 (m, 1H), 7.33 – 7.24 (m, 2H).

**<sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>):** δ / ppm = 161.8, 158.5, 148.5, 145.1 (d, *J* = 1 Hz), 135.1 (d, *J* = 1 Hz), 134.9 (d, *J* = 10 Hz), 133.3 (d, *J* = 4 Hz), 132.0 (d, *J* = 2 Hz), 130.8, 126.2, 124.3 (d, *J* = 16 Hz), 124.3 (d, *J* = 4 Hz), 122.5, 116.5 (d, *J* = 26 Hz).

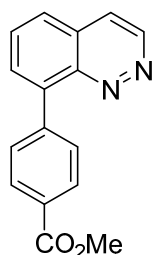
**<sup>19</sup>F-NMR (282 MHz, CDCl<sub>3</sub>):** δ / ppm = -110.90.

**IR (Diamond-ATR, neat):**  $\tilde{\nu}$  / cm<sup>-1</sup> = 3064, 2926, 1708, 1613, 1569, 1485, 1361, 1219, 1191, 1161, 1115, 1100, 1076, 980, 853, 823, 803, 768, 724, 706, 675.

**MS (EI, 70 eV):** *m/z* (%) = 257 (45), 239 (35), 223 (100), 194 (35), 169 (10).

**HRMS (EI) for C<sub>14</sub>H<sub>8</sub>ClFN<sub>2</sub> (258.0360):** 258.0360 (M<sup>+</sup>).

### Synthesis of Methyl 4-(cinnolin-8-yl)benzoate (**6d**)



According to **TP 2**, the metalation of cinnoline (**1**; 100 mg, 0.77 mmol) was completed within 3 h at 50 °C. Then, a solution of Pd(dba)<sub>2</sub> (8.9 mg, 0.02 mmol), P(*o*-furyl)<sub>3</sub> (7.2 mg, 0.03 mmol) and methyl 4-iodobenzoate (162 mg, 0.62 mmol) in THF (1.0 mL) was added to the reaction mixture dropwise and it was stirred overnight. Then, the reaction mixture was quenched with sat. aq. NH<sub>4</sub>Cl solution (5 mL), extracted with EtOAc (3 x 15 mL) and dried over MgSO<sub>4</sub>. After filtration, the solvents were evaporated *in vacuo*. The crude product was

purified by flash column chromatography (isoHexane:EtOAc = 8:2) to give **6d** as a brownish solid (98 mg, 60 %).

**m.p.** (°C): 165-170.

**<sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>):** δ / ppm = 9.37 (d, *J* = 5.8 Hz, 1H), 8.20 – 8.15 (m, 2H), 7.94 (d, *J* = 5.8 Hz, 1H), 7.90 – 7.82 (m, 5H), 3.95 (s, 3H).

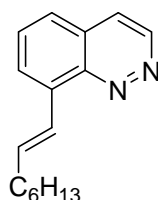
**<sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>):** δ / ppm = 167.0, 148.5, 148.4, 144.9, 142.3, 140.6, 131.4, 131.2, 131.0, 129.6, 129.4, 129.4, 127.0, 126.5, 122.9, 52.2.

**IR (Diamond-ATR, neat):**  $\tilde{\nu}$  / cm<sup>-1</sup> = 3178, 1718, 1607, 1426, 1289, 1185, 1101, 1021, 849, 778, 721, 703.

**MS (EI, 70 eV):** *m/z* (%) = 263 (20), 249 (22), 233 (5), 205 (100), 176 (5), 151 (5), 88 (7).

**HRMS (EI) for C<sub>16</sub>H<sub>12</sub>N<sub>2</sub>O<sub>2</sub> (264.0899):** 264.0898 (M<sup>+</sup>).

#### Synthesis of (*E*)-8-(Oct-1-en-1-yl)cinnoline (**6e**)



According to **TP 2**, the metalation of cinnoline (**1**; 100 mg, 0.77 mmol) was completed within 3 h at 50 °C. Then, a solution of Pd(dba)<sub>2</sub> (8.9 mg, 0.02 mmol), P(*o*-furyl)<sub>3</sub> (7.2 mg, 0.03 mmol) and methyl (*E*)-1-iodooctene (148 mg, 0.62 mmol) in THF (1.0 mL) was added to the reaction mixture dropwise and it was stirred overnight. Then, the reaction mixture was quenched with sat. aq. NH<sub>4</sub>Cl solution (5 mL), extracted with EtOAc (3 x 15 mL) and dried over MgSO<sub>4</sub>. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography (isoHexane:EtOAc = 8:2) to give **6e** as a thick oil (97 mg, *E:Z* > 99:1, 65 %).

**<sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>):** δ / ppm = 9.31 (d, *J* = 5.8 Hz, 1H), 8.01 – 7.92 (m, 2H), 7.80 (d, *J* = 5.8 Hz, 1H), 7.74 – 7.61 (m, 2H), 6.61 (dt, *J* = 15.9 and 7.0 Hz, 1H), 2.44 – 2.34 (m, 2H), 1.61 – 1.52 (m, 2H), 1.42 – 1.25 (m, 6H), 0.93 – 0.84 (m, 3H).

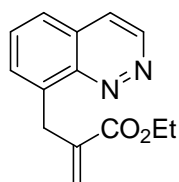
**<sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>):** δ / ppm = 148.1, 144.8, 137.5, 135.8, 131.4, 126.2, 125.8, 124.9, 124.4, 122.6, 33.6, 31.7, 29.3, 29.0, 22.6, 14.1.

**IR (Diamond-ATR, neat):**  $\tilde{\nu}$  /  $\text{cm}^{-1}$  = 3392, 2953, 2852, 1734, 1641, 1605, 1582, 1545, 1487, 1455, 1378, 1304, 1157, 1101, 1086, 966, 852, 808, 760, 724, 664.

**MS (EI, 70 eV):**  $m/z$  (%) = 240 (20), 211 (5), 169 (100), 155 (60), 141 (5), 128 (4), 115 (5).

**HRMS (EI) for  $\text{C}_{16}\text{H}_{20}\text{N}_2$  (240.1626):** 240.1622 ( $\text{M}^+$ ).

### Synthesis of Ethyl 2-(cinnolin-8-ylmethyl)acrylate (**6f**)



According to **TP 2**, the metalation of cinnoline (**1**; 100 mg, 0.77 mmol) was completed within 3 h at 50 °C. The reaction mixture was cooled to -40 °C, then a 1.0 M solution of  $\text{CuCN}\cdot 2\text{LiCl}$  (0.85 mL, 0.85 mmol) and ethyl 2-(bromomethyl)acrylate (223 mg, 1.16 mmol) were added. The resulting mixture was allowed to warm to 25 °C and stirred overnight. Then, the reaction mixture was quenched with sat. aq.  $\text{NH}_4\text{Cl}$  solution (5 mL), extracted with EtOAc (3 x 15 mL) and dried over  $\text{MgSO}_4$ . After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography ( $\text{CH}_2\text{Cl}_2$ :EtOAc = 7:3) to give **6f** as a brown oil (114 mg, 61 %).

**$^1\text{H-NMR}$  (300 MHz,  $\text{CDCl}_3$ ):**  $\delta$  / ppm = 9.32 (d,  $J$  = 5.8 Hz, 1 H), 7.83 (d,  $J$  = 5.8 Hz, 1 H), 7.76 - 7.64 (m, 3 H), 5.63 - 5.59 (m, 1 H) 6.31 (s, 1 H), 4.59 (s, 2 H), 4.22- 4.145(m, 2 H), 1.22 (t,  $J$  = 7.1 Hz, 3 H).

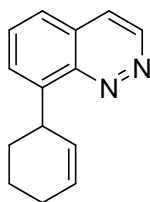
**$^{13}\text{C-NMR}$  (75 MHz,  $\text{CDCl}_3$ ):**  $\delta$  / ppm = 167.1, 149.3, 145.1, 139.5, 139.3, 131.3, 130.8, 127.5, 126.4, 125.5, 122.8, 60.9, 32.7, 14.3.

**IR (Diamond-ATR, neat):**  $\tilde{\nu}$  /  $\text{cm}^{-1}$  = 2979, 2924, 2853, 1710, 1629, 1590, 1561, 1388, 1366, 1248, 1229, 1203, 1178, 1138, 1095, 1022, 947, 852, 765, 695.

**MS (EI, 70 eV):**  $m/z$  (%) = 242 (5), 213 (12), 170 (17), 169 (100), 168 (25), 85 (14), 71 (19), 57 (27), 43 (18).

**HRMS (EI) for  $\text{C}_{14}\text{H}_{14}\text{N}_2\text{O}_2$  (242.1055):** 242.1056 ( $\text{M}^+$ ).

### Synthesis of 8-(Cyclohex-2-en-1-yl)cinnoline (6g)



According to **TP 2**, the metalation of cinnoline (**1**; 100 mg, 0.77 mmol) was completed within 3 h at 50 °C. The reaction mixture was cooled to -40 °C, then a 1.0 M solution of CuCN·2LiCl (0.85 mL, 0.85 mmol) and 3-bromocyclohex-1-ene (186 mg, 1.16 mmol) were added. The resulting mixture was allowed to warm to 25 °C and stirred overnight. Then, the reaction mixture was quenched with sat. aq. NH<sub>4</sub>Cl solution (5 mL), extracted with EtOAc (3 x 15 mL) and dried over MgSO<sub>4</sub>. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography (CH<sub>2</sub>Cl<sub>2</sub>:EtOAc = 8:2) to give **6g** as a yellow oil (86 mg, 53 %).

**<sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>):** δ / ppm = 9.31 (d, *J*=5.80 Hz, 1 H), 7.83 (d, *J* = 5.8 Hz, 1 H), 7.71 - 7.66 (m, 3 H), 6.08 - 6.03 (m, 1 H), 5.87 - 5.81 (m, 1 H), 5.26 - 5.20 (m, 1 H), 2.38 - 2.31 (m, 1 H), 2.16 (dq, *J* = 5.8, 2.8 Hz, 2 H), 1.78 - 1.66 (m, 3 H).

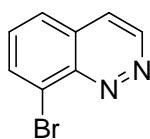
**<sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>):** δ / ppm = 148.8, 146.2, 144.9, 131.4, 129.8, 129.5, 129.0, 126.4, 124.7, 123.0, 34.9, 31.8, 25.4, 21.1.

**IR (Diamond-ATR, neat):**  $\tilde{\nu}$  / cm<sup>-1</sup> = 3016, 2923, 2856, 2833, 1612, 1582, 1550, 1445, 1423, 1388, 1294, 1158, 1103, 981, 849, 762, 723, 683, 674.

**MS (EI, 70 eV):** *m/z* (%) = 210 (57), 209 (29), 207 (15), 195 (14), 182 (42), 181 (100), 169 (58), 168 (20), 155 (16), 154 (14), 115 (12).

**HRMS (EI) for C<sub>14</sub>H<sub>14</sub>N<sub>2</sub> (210.1157):** 210.1141 (M<sup>+</sup>).

### Synthesis of 8-Bromocinnoline (6h)



According to **TP 2**, the metalation of cinnoline (**1**; 130 mg, 1.0 mmol) was completed within 3 h at 50 °C. The reaction was allowed to cool to 25 °C, then a 1.0 M solution of ZnCl<sub>2</sub> (1.0 mL, 1.0 mmol) was added. The reaction mixture was then cooled to -78 °C, where, it

was cannulated to a flask containing equimolar amounts of bromine (0.15 mL, 3.0 mmol) and dry dioxane (0.26 mL, 3.0 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (3 mL). The reaction mixture was allowed to warm to 25 °C overnight. Then, the reaction mixture was quenched with sat. aq. NaHCO<sub>3</sub> solution (10 mL), extracted with EtOAc (3 x 15 mL) and dried over Na<sub>2</sub>SO<sub>4</sub>. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography (isohexane:EtOAc = 8:2) to give **6h** as an off-white solid (97 mg, 46 %).

**m.p.** (°C): 80.

**<sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>):** δ / ppm = 9.41 (d, *J* = 6.1 Hz, 1 H), 8.15 (dd, *J* = 7.5, 1.1 Hz, 1 H), 7.85 (d, *J* = 5.8 Hz, 1 H), 7.81 (dd, *J* = 8.4, 1.2 Hz, 1 H), 7.62 - 7.56 (m, 1 H).

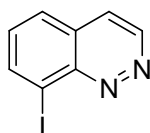
**<sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>):** δ / ppm = 147.8, 145.9, 134.6, 131.6, 127.8, 126.8, 125.9, 122.7.

**IR (Diamond-ATR, neat):**  $\tilde{\nu}$  / cm<sup>-1</sup> = 3077, 3051, 1608, 1571, 1528, 1480, 1404, 1282, 1214, 1096, 978, 967, 848, 803, 778, 761, 669.

**MS (EI, 70 eV):** *m/z* (%) = 210 (54), 208 (65), 182 (17), 180 (17), 101 (100), 100 (18), 75 (66), 74 (39), 50 (28).

**HRMS (EI) for C<sub>8</sub>H<sub>5</sub>BrN<sub>2</sub> (207.9636):** 207.9614 (M<sup>+</sup>).

### Synthesis of 8-Iodocinnoline (6i)



According to **TP 2**, the metalation of cinnoline (**1**; 130 mg, 1.0 mmol) was completed within 3 h at 50 °C. The reaction mixture was then cooled to 0 °C and cannulated into a solution of I<sub>2</sub> (518 mg, 2 mmol) in dry THF (2 mL), pre-cooled to 0 °C. The reaction mixture was stirred at 0 °C for 30 min, then at rt for 1 h. The reaction was quenched with a saturated aqueous solution of Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (10 mL) and extracted with EtOAc (3\*15 mL) and dried over Na<sub>2</sub>SO<sub>4</sub>. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography (isohexane:EtOAc = 8:2) to give **6j** as an off-white solid (133 mg, 52 %).

**m.p.** (°C): 82.

**<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>):** δ / ppm = 9.38 (d, *J* = 5.9 Hz, 1 H), 8.44 (dd, *J* = 7.4, 1.2 Hz, 1 H), 7.82 (dd, *J* = 8.2, 1.2 Hz, 1 H), 7.74 (d, *J* = 5.9 Hz, 1 H), 7.44 (dd, *J* = 8.2, 7.4 Hz, 1 H).

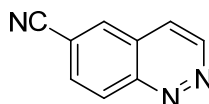
**<sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>):** δ / ppm = 149.0, 146.0, 141.6, 132.1, 127.8, 127.3, 122.6, 103.4.

**IR (Diamond-ATR, neat):**  $\tilde{\nu}$  / cm<sup>-1</sup> = 3070, 3059, 1602, 1569, 1477, 1412, 1398, 1280, 1254, 1212, 1163, 1115, 1095, 965, 847, 800, 774, 760, 662.

**MS (EI, 70 eV):** *m/z* (%) = 257 (3), 256 (37), 228 (23), 102 (13), 101 (19), 58 (39), 43 (100).

**HRMS (EI) for C<sub>8</sub>H<sub>5</sub>N<sub>2</sub> (255.9497):** 255.9493 (M<sup>+</sup>).

### Synthesis of Cinnoline-6-carbonitrile (7a)



Cinnoline-6-carbonitrile (**7a**) was synthesized according to a known procedure<sup>1</sup> and was obtained as a brown solid.

**m.p. (°C):** 129-131

**<sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>):** δ / ppm = 9.50 (d, *J* = 5.8 Hz, 1 H), 8.69 (d, *J* = 8.9 Hz, 1 H), 8.30 (d, *J* = 1.1 Hz, 1 H), 8.01 - 7.92 (m, 2 H).

**<sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>):** δ / ppm = 150.1, 146.4, 133.7, 131.8, 131.1, 125.2, 122.3, 117.5, 115.2.

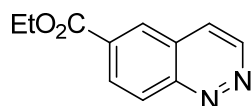
**IR (Diamond-ATR, neat):**  $\tilde{\nu}$  / cm<sup>-1</sup> = 3069, 3041, 2924, 2858, 2229, 1958, 1827, 1621, 1574, 1476, 1452, 1394, 1369, 1325, 1289, 1252, 1174, 1168, 1159, 1091, 1081, 970, 912, 907, 898, 846, 777, 686, 684, 660.

**MS (EI, 70 eV):** *m/z* (%) = 156 (11), 155 (100), 128 (10), 127 (95), 101 (12), 100 (39), 97 (12), 76 (19), 74 (17), 71 (13), 70 (11), 69 (14), 63 (10), 61 (16), 57 (21), 55 (13), 50 (31), 45 (15), 43 (13), 43 (90).

**HRMS (EI) for C<sub>9</sub>H<sub>5</sub>N<sub>3</sub> (155.0483):** 155.0476 (M<sup>+</sup>).

(1) Kimball, D. B.; Weakley, T. J. R.; Haley, M. M. *The J. Org. Chem.* **2002**, *67*, 6395.

### Synthesis of Ethyl cinnoline-6-carboxylate (**7b**)



Ethyl cinnoline-6-carboxylate (**7b**) was synthesized according to a known procedure<sup>1</sup> and was obtained as a yellow solid.

**m.p.** (°C): 112-113.

**<sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>):**  $\delta$  / ppm = 9.42 (d,  $J$  = 5.8 Hz, 1 H), 8.61 (dd,  $J$  = 5.7, 3.5 Hz, 2 H), 8.42 (dd,  $J$  = 9.1, 1.7 Hz, 1 H), 7.97 (d,  $J$  = 5.8 Hz, 1 H), 4.48 (q,  $J$  = 7.2 Hz, 2 H), 1.46 (t,  $J$  = 7.2 Hz, 3 H).

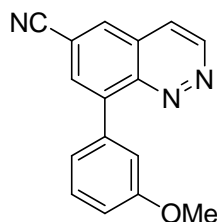
**<sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>):**  $\delta$  / ppm = 165.3, 151.5, 145.9, 132.7, 130.4, 130.1, 130.0, 125.3, 123.5, 62.1, 14.4.

**IR (Diamond-ATR, neat):**  $\tilde{\nu}$  / cm<sup>-1</sup> = 3039, 2986, 2952, 2923, 2905, 2875, 2852, 1961, 1827, 1719, 1485, 1454, 1443, 1373, 1366, 1302, 1281, 1267, 1250, 1229, 1166, 1146, 1120, 1091, 1022, 985, 966, 916, 869, 853, 842, 795, 779, 746, 738.

**MS (EI, 70 eV):**  $m/z$  (%) = 203 (13), 202 (100), 174 (12), 157 (28), 146 (13), 129 (51), 101 (20), 75 (20).

**HRMS (EI) for C<sub>11</sub>H<sub>10</sub>N<sub>2</sub>O<sub>2</sub> (202.0742):** 202.0736 (M<sup>+</sup>).

### Synthesis of 8-(3-Methoxyphenyl)cinnoline-6-carbonitrile (**8a**)



According to **TP 2**, the metalation of cinnoline-6-carbonitrile (**7a**; 100 mg, 0.64 mmol) was completed within 1 h at 25 °C. Then, a solution of Pd(dba)<sub>2</sub> (7.4 mg, 0.01 mmol), P(*o*-furyl)<sub>3</sub> (5.9 mg, 0.03 mmol) and 1-iodo-3-methoxybenzene (120 mg, 0.51 mmol) in THF (1.0 mL) was added to the reaction mixture dropwise and it was stirred overnight. Then, the reaction mixture was quenched with sat. aq. NH<sub>4</sub>Cl solution (5 mL), extracted with EtOAc (3 x 15 mL) and dried over MgSO<sub>4</sub>. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography (CH<sub>2</sub>Cl<sub>2</sub>:EtOAc = 7:3) to give **8a** as a yellow solid (96 mg, 72 %).

**m.p. (°C):** 183-184.

**<sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>):** δ / ppm = 9.52 (d, *J* = 5.9 Hz, 1 H), 8.25 (d, *J* = 1.7 Hz, 1 H), 7.98 (d, *J* = 1.7 Hz, 1 H), 7.95 (d, *J* = 5.9 Hz, 1 H), 7.46 (t, *J* = 7.9 Hz, 1 H), 7.35 - 7.28 (m, 2 H), 7.06 (m, 1 H), 3.88 (s, 3 H).

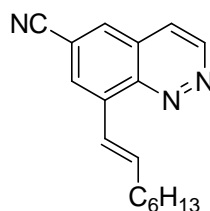
**<sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>):** δ / ppm = 159.6, 148.3, 146.2, 143.8, 137.2, 132.6, 131.3, 129.6, 125.7, 123.5, 122.4, 117.6, 116.8, 115.1, 114.8, 55.6.

**IR (Diamond-ATR, neat):**  $\tilde{\nu}$  / cm<sup>-1</sup> = 3038, 2955, 2921, 2834, 2232, 1604, 1570, 1470, 1457, 1451, 1436, 1407, 1376, 1322, 1289, 1276, 1252, 1229, 1136, 1093, 1045, 1005, 928, 899, 877, 842, 812, 778, 739, 699, 674.

**MS (EI, 70 eV):** *m/z* (%) = 261 (42), 260 (30), 246 (10), 231 (18), 230 (100), 218 (10), 217 (13).

**HRMS (EI) for C<sub>16</sub>H<sub>11</sub>N<sub>3</sub>O (261.0902):** 261.0897 (M<sup>+</sup>).

### Synthesis of (*E*)-8-(Oct-1-en-1-yl)cinnoline-6-carbonitrile (**8b**)



According to **TP 2**, the metalation of cinnoline-6-carbonitrile (**7a**; 100 mg, 0.64 mmol) was completed within 1 h at 25 °C. Then, a solution of Pd(dba)<sub>2</sub> (7.4 mg, 0.01 mmol), P(*o*-furyl)<sub>3</sub> (5.9 mg, 0.03 mmol) and (*E*)-1-iodooct-1-ene (122 mg, 0.45 mmol) in THF (1.0 mL) was added to the reaction mixture dropwise and it was stirred overnight. Then, the reaction mixture was quenched with sat. aq. NH<sub>4</sub>Cl solution (5 mL), extracted with EtOAc (3 x 15 mL) and dried over MgSO<sub>4</sub>. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography (CH<sub>2</sub>Cl<sub>2</sub>:EtOAc = 7:3) to give **8b** as a brown solid (92 mg, 68 %).

**m.p. (°C):** 71-73.

**<sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>):** δ / ppm = 9.46 (d, *J* = 6.1 Hz, 1 H), 8.05 (d, *J* = 6.4 Hz, 2 H), 7.94 (d, *J* = 16.31 Hz, 1 H), 7.86 (d, *J* = 5.8 Hz, 1 H), 6.70 (dt, *J* = 16.0, 7.1 Hz, 1 H), 2.42 (q, *J* = 7.1 Hz, 2 H), 1.62 - 1.52 (m, 2 H), 1.44 - 1.28 (m, 6 H), 0.89 (t, *J* = 6.6 Hz, 3 H).

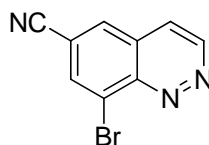
**<sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>):**  $\delta$  / ppm = 147.4, 146.2, 139.7, 138.9, 130.8, 126.0, 125.4, 123.1, 122.4, 117.8, 115.3, 33.8, 31.8, 29.2, 29.1, 22.7, 14.2.

**IR (Diamond-ATR, neat):**  $\tilde{\nu}$  / cm<sup>-1</sup> = 3080, 3043, 2944, 2928, 2882, 2866, 2845, 2231, 1642, 1611, 1550, 1469, 1395, 1170, 1106, 977, 968, 953, 901, 887, 836, 801, 718, 659.

**MS (EI, 70 eV):** m/z (%) = 265 (27), 208 (10), 195 (31), 194 (100), 193 (19), 182 (12), 181 (19), 180 (47), 169 (12), 43 (15).

**HRMS (EI) for C<sub>17</sub>H<sub>19</sub>N<sub>3</sub> (265.1579):** 265.1571 (M<sup>+</sup>).

### Synthesis of 8-Bromocinnoline-6-carbonitrile (**8c**)



According to **TP 2**, the metalation of cinnoline-6-carbonitrile (**7a**; 250 mg, 1.61 mmol) was completed within 1 h at 25 °C. The reaction was then cooled to -78 °C, where, it was cannulated to a flask containing equimolar amounts of bromine (772 mg, 4.83 mmol) and dry dioxane (426 mg, 4.83 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL). The reaction mixture was allowed to warm to 25 °C overnight. Then, the reaction mixture was quenched with sat. aq. NH<sub>4</sub>Cl solution (30 mL), extracted with EtOAc (3 x 30 mL) and dried over MgSO<sub>4</sub>. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography (isohexane:EtOAc = 8:2) to give **8c** as a yellow solid (222 mg, 59 %).

**m.p. (°C):** 189.

**<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>):**  $\delta$  / ppm = 9.60 (d, *J* = 5.9 Hz, 1 H), 8.30 (d, *J* = 1.5 Hz, 1 H), 8.26 (d, *J* = 1.5 Hz, 1 H), 7.93 (d, *J* = 5.9 Hz, 1 H).

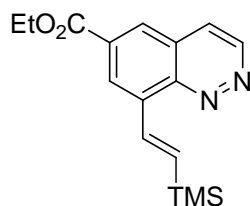
**<sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>):**  $\delta$  / ppm = 147.4, 147.2, 134.3, 133.2, 128.1, 126.6, 122.4, 116.3, 115.7.

**IR (Diamond-ATR, neat):**  $\tilde{\nu}$  / cm<sup>-1</sup> = 3071, 3043, 2920, 2848, 2234, 1611, 1461, 1413, 1392, 1366, 1284, 1224, 1168, 1140, 1092, 1075, 994, 918, 908, 887, 881, 877, 840, 798, 736.

**MS (EI, 70 eV):** m/z (%) = 235 (72), 233 (70), 207 (37), 205 (37), 127 (11), 126 (100), 125 (20), 100 (51), 99 (55), 98 (12), 76 (18), 75 (39), 74 (37), 63 (16), 62 (13), 61 (10), 50 (23), 43 (11).

**HRMS (EI) for C<sub>9</sub>H<sub>4</sub>BrN<sub>3</sub> (232.9589):** 232.9579 (M<sup>+</sup>).

### Synthesis of (*E*)-Ethyl 8-(2-(trimethylsilyl)vinyl)cinnoline-6-carboxylate (**8d**)



According to **TP 2**, the metalation of ethyl cinnoline-6-carboxylate (**7b**; 100 mg, 0.49 mmol) was completed within 1 h at 25 °C. Then, a solution of Pd(dba)<sub>2</sub> (5.6 mg, 0.01 mmol), P(*o*-furyl)<sub>3</sub> (4.6 mg, 0.02 mmol) and (*E*)-(2-iodovinyl)trimethylsilane (78 mg, 0.34 mmol) in THF (1.0 mL) was added to the reaction mixture dropwise and it was stirred overnight. Then, the reaction mixture was quenched with sat. aq. NH<sub>4</sub>Cl solution (5 mL), extracted with EtOAc (3 x 15 mL) and dried over MgSO<sub>4</sub>. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography (CH<sub>2</sub>Cl<sub>2</sub>:EtOAc = 7:3) to give **8d** as a yellow solid (59 mg, 57 %).

**m.p. (°C):** 135-137.

**<sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>):** δ / ppm = 9.43 (d, *J* = 5.9 Hz, 1 H), 8.59 (m, 1 H), 8.47 (m, 1 H), 7.93 (d, *J* = 5.9 Hz, 1 H), 7.02 (d, *J* = 19.4 Hz, 1 H), 4.50 (q, *J* = 7.2 Hz, 2 H), 2.16 (s, 1 H), 1.48 (t, *J* = 7.1 Hz, 3 H), 0.26 (s, 9 H).

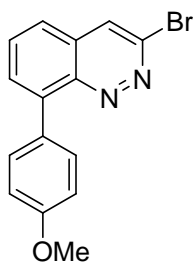
**<sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>):** δ / ppm = 165.6, 148.5, 145.7, 138.3, 137.4, 136.8, 132.7, 128.8, 125.7, 125.5, 123.6, 62.1, 14.5, -1.0.

**IR (Diamond-ATR, neat):**  $\tilde{\nu}$  / cm<sup>-1</sup> = 2986, 2951, 2899, 1721, 1716, 1575, 1473, 1397, 1312, 1275, 1240, 1234, 1225, 1212, 1164, 1096, 1026, 990, 862, 851, 836, 766, 760, 746, 722, 693.

**MS (EI, 70 eV):** *m/z* (%) = 300 (2), 272 (20), 271 (100), 199 (8), 154 (21), 73 (32).

**HRMS (EI) for C<sub>16</sub>H<sub>20</sub>N<sub>2</sub>O<sub>2</sub>Si (300.1294):** 300.1280 (M<sup>+</sup>).

### Synthesis of 3-Bromo-8-(4-methoxyphenyl)cinnoline (8e)



According to **TP 2**, the metalation of **5f** (105 mg, 0.5 mmol) was completed within 4 h at 50 °C. Then, a solution of Pd(dba)<sub>2</sub> (8.6 mg, 0.02 mmol), P(*o*-furyl)<sub>3</sub> (7.0 mg, 0.03 mmol) and 4-iodoanisole (140 mg, 0.6 mmol) in THF (1.0 mL) was added to the reaction mixture dropwise and it was stirred overnight. Then, the reaction mixture was quenched with sat. aq. NH<sub>4</sub>Cl solution (5 mL), extracted with EtOAc (3 x 15 mL) and dried over Na<sub>2</sub>SO<sub>4</sub>. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography (isohexanes:EtOAc = 8:2) to give **8e** as a yellow solid (102 mg, 65 %).

**m.p.** (°C): 151-153.

**<sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>):** δ / ppm = 8.10 (s, 1 H), 7.87 - 7.79 (m, 2 H), 7.76 - 7.68 (m, 3 H), 7.08 - 7.083 (m, 2 H), 3.89 (s, 3 H).

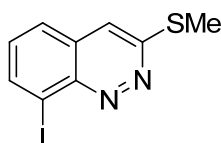
**<sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>):** δ / ppm = 160.0, 148.1, 141.6, 141.5, 132.5, 132.4, 131.0, 129.6, 128.5, 126.2, 124.7, 113.9, 55.5.

**IR (Diamond-ATR, neat):**  $\tilde{\nu}$  / cm<sup>-1</sup> = 3005, 2960, 2930, 1607, 1570, 1507, 1372, 1307, 1290, 1268, 1246, 1178, 1144, 1107, 1063, 1028, 973, 887, 840, 818, 807, 783.

**MS (EI, 70 eV):** m/z (%) = 317 (11), 314 (72), 301 (26), 299 (31), 285 (100), 283 (94), 235 (10), 192 (31), 191 (15), 164 (35), 163 (38), 58 (12), 44 (29), 43 (34).

**HRMS (EI) for C<sub>15</sub>H<sub>11</sub>BrN<sub>2</sub>O (314.0055):** 314.0044 (M<sup>+</sup>).

### Synthesis of 8-Iodo-3-(methylthio)cinnoline (8f)



A dry, argon-flushed 25 mL Schlenk flask was charged with **5h** (70 mg, 0.4 mmol) and dry THF (2 mL). The solution was cooled to 0 °C, where TMPMgCl·LiCl (0.8 mmol) was added

dropwise. The reaction mixture was stirred at 0 °C for 3 h and cannulated into a solution of I<sub>2</sub> (202 mg, 08 mmol) in dry THF (2 mL), pre-cooled to 0 °C. The reaction mixture was allowed to warm to room temperature and then quenched with a saturated aqueous solution of Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (10 mL) and extracted with EtOAc (3\*15 mL) and dried over Na<sub>2</sub>SO<sub>4</sub>. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography (isohexane:EtOAc = 8:2) to give **8f** as a brown oil (58 mg, 48 %).

**<sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>):** δ / ppm = 8.29 (d, *J* = 7.2 Hz, 1 H), 7.62 (d, *J* = 8.6 Hz, 1 H), 7.56 (s, 1 H), 7.33 (t, *J* = 7.7 Hz, 1 H), 2.86 (s, 3 H).

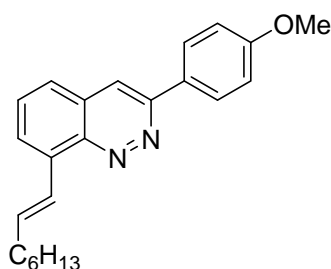
**<sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>):** δ / ppm = 158.1, 147.1, 140.4, 132.4, 127.3, 126.6, 119.5, 103.2, 14.1.

**IR (Diamond-ATR, neat):**  $\tilde{\nu}$  / cm<sup>-1</sup> = 3058, 2988, 2921, 2894, 2852, 1718, 1711, 1597, 1558, 1510, 1493, 1444, 1411, 1384, 1365, 1358, 1291, 1281, 1269, 1240, 1182, 1179, 1104, 1066, 1020, 966, 907, 872, 861, 851, 798, 792, 772, 752, 699, 688, 684, 675, 655.

**MS (EI, 70 eV):** *m/z* (%) = 303 (12), 302 (100), 274 (11), 259 (16), 147 (8), 132 (40).

**HRMS (EI) for C<sub>9</sub>H<sub>7</sub>IN<sub>2</sub>S (301.9375):** 301.9371 (M<sup>+</sup>).

### Synthesis of (*E*)-3-(4-Methoxyphenyl)-8-(oct-1-en-1-yl)cinnoline (**8g**)



According to **TP 1**, the metalation of cinnoline (**6e**; 51 mg, 0.21 mmol) was completed within 5 min at -78 °C. Then, a 1.0 M solution of ZnCl<sub>2</sub> (0.25 mL, 0.25 mmol) was added dropwise to the reaction mixture dropwise and it was stirred for 10 min at -78 °C. A solution of Pd(dba)<sub>2</sub> (2.4 mg, 0.0042 mmol), P(*o*-furyl)<sub>3</sub> (2.4 mg, 0.0084 mmol) and 4-iodoanisole (39 mg, 0.17 mmol) in THF (0.5 mL) was added to the reaction dropwise. The reaction mixture was allowed to warm to 25 °C and stirred overnight. Then, the reaction mixture was quenched with sat. aq. NH<sub>4</sub>Cl solution (2 mL), extracted with EtOAc (3 x 5 mL) and dried over MgSO<sub>4</sub>. After filtration, the solvents were evaporated *in vacuo*. The crude product was

purified by flash column chromatography (isoHexane:EtOAc = 9:1) to give **8g** as a yellowish thick oil (40 mg, *E:Z* > 99:1, 68 %).

**<sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>):**  $\delta$  / ppm = 8.27 – 8.22 (m, 2H), 8.05 (s, 1H), 7.99 (d, *J* = 16.1 Hz, 1H), 7.87 (dd, *J* = 5.7, 2.8 Hz, 1H), 7.67 (s, 1H), 7.70 – 7.63 (m, 1H), 7.11 – 7.06 (m, 2H), 6.64 (dt, *J* = 15.9, 6.9 Hz, 1H), 3.90 (s, 3H), 2.40 (td, *J* = 8.6, 1.6 Hz, 2H), 1.62 – 1.53 (m, 2H), 1.45 – 1.37 (m, 2H), 1.36 – 1.29 (m, 4H), 0.93 – 0.87 (m, 3H).

**<sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>):**  $\delta$  / ppm = 160.9, 152.8, 146.8, 137.4, 135.7, 131.4, 129.2, 128.4, 126.8, 125.2, 125.0, 124.4, 117.8, 114.5, 55.4, 33.7, 31.8, 29.3, 29.0, 22.6, 14.1.

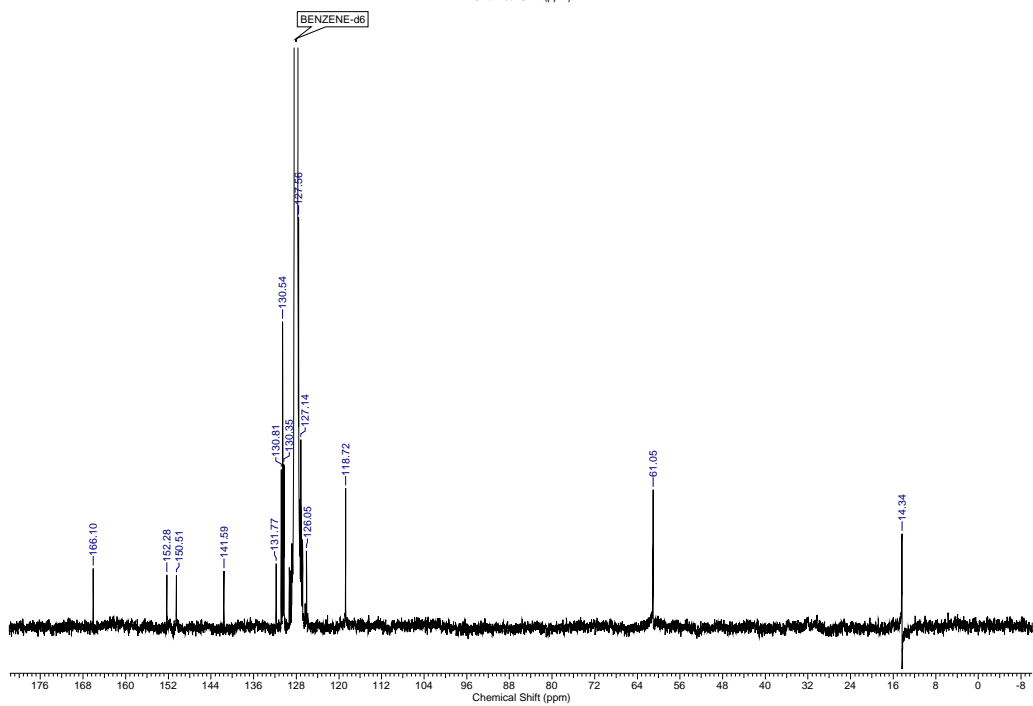
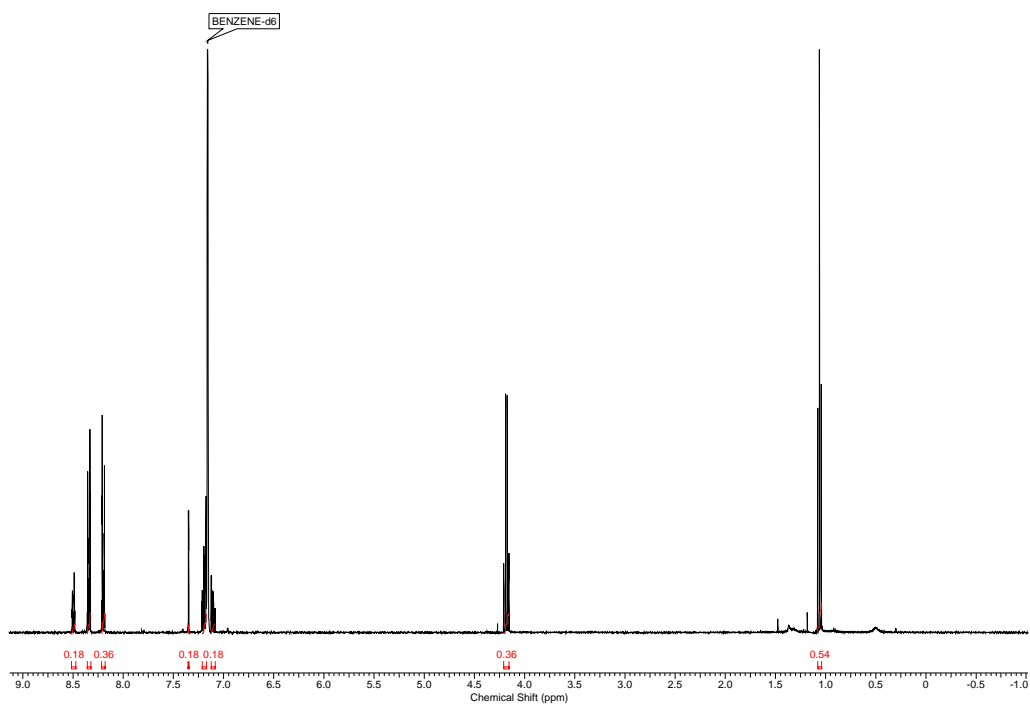
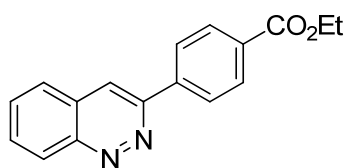
**IR (Diamond-ATR, neat):**  $\tilde{\nu}$  / cm<sup>-1</sup> = 2953, 2922, 2851, 1642, 1603, 1513, 1462, 1336, 1173, 1115, 1030, 967, 891, 831, 794, 680.

**MS (EI, 70 eV):** *m/z* (%) = 346 (40), 275 (30), 275 (100), 133 (13), 44 (61).

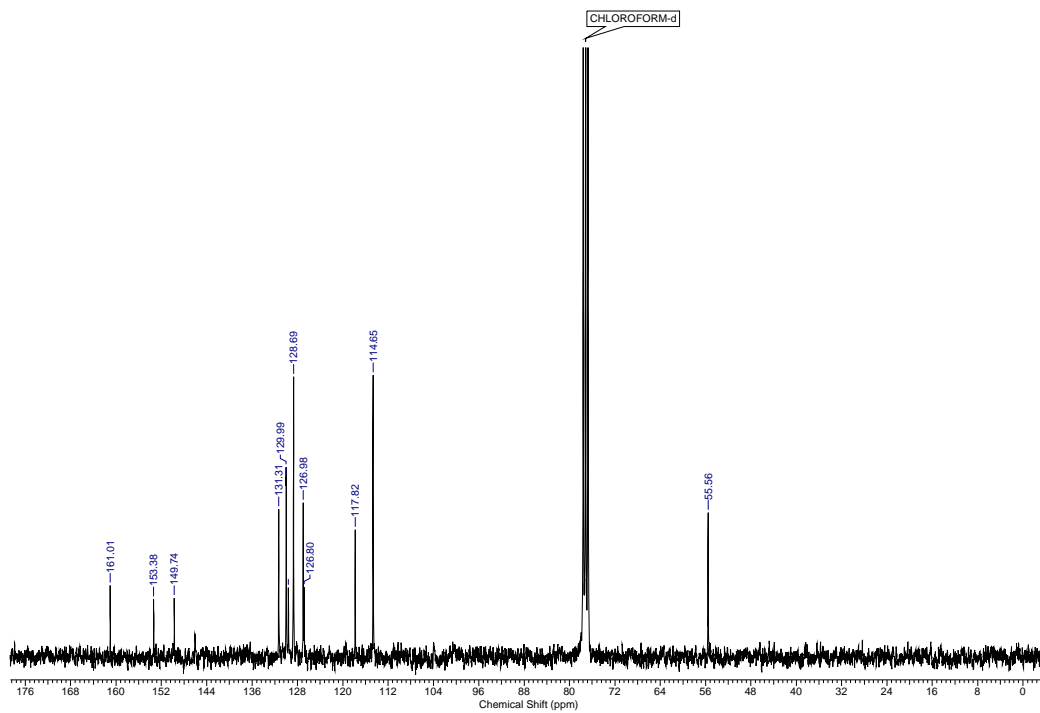
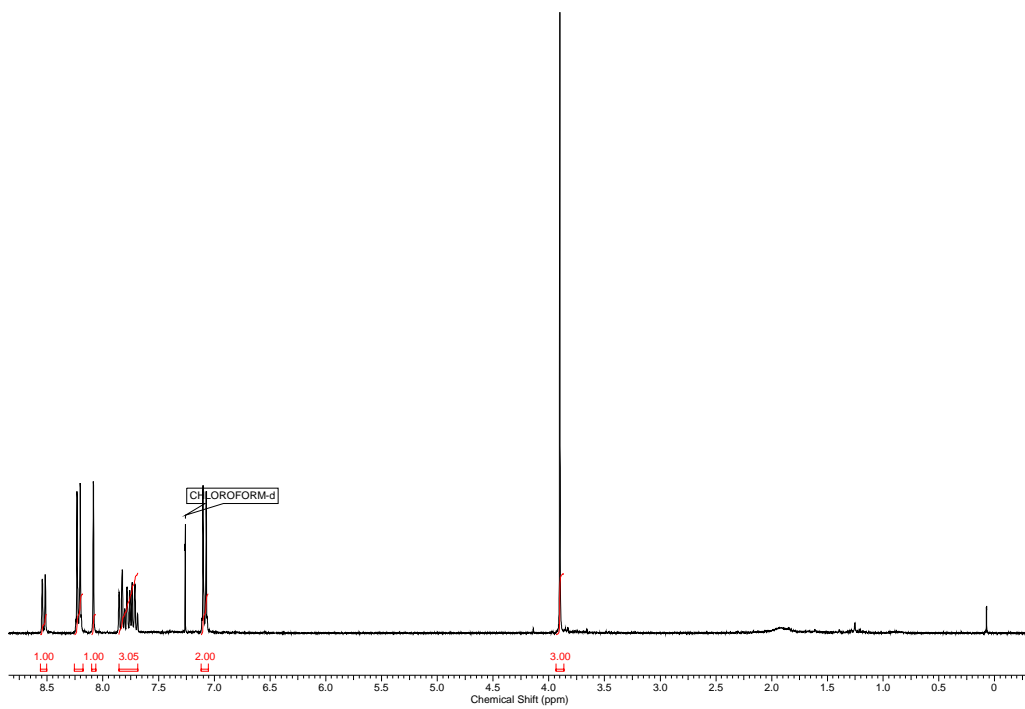
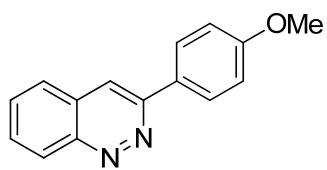
**HRMS (EI) for C<sub>23</sub>H<sub>26</sub>N<sub>2</sub>O (346.2045):** 346.2038 (M<sup>+</sup>).

# NMR:

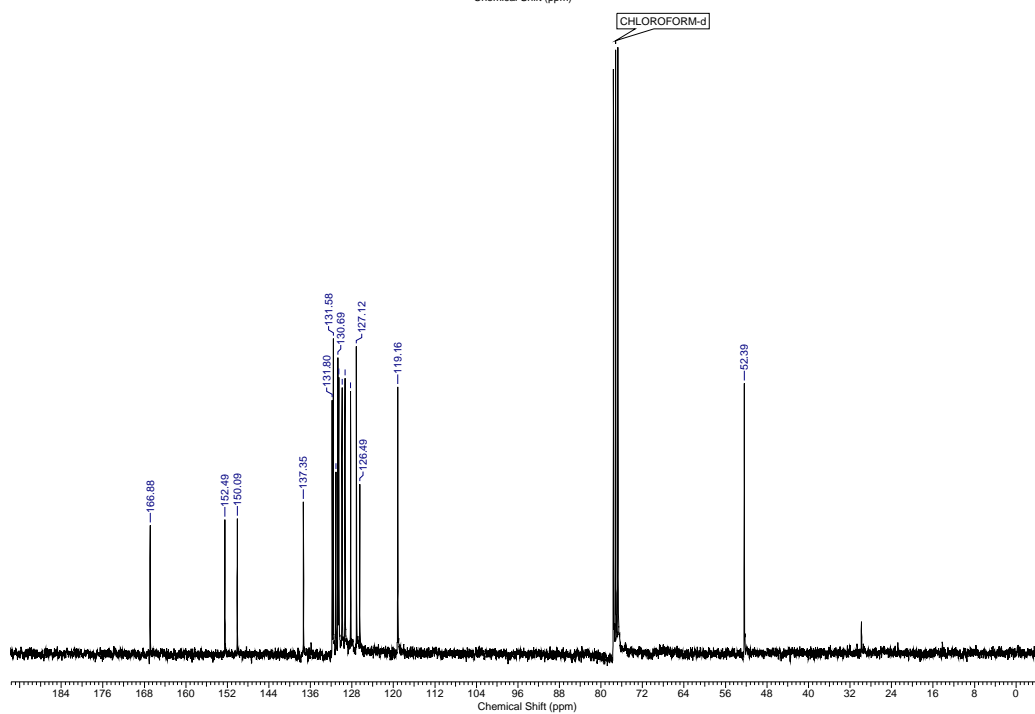
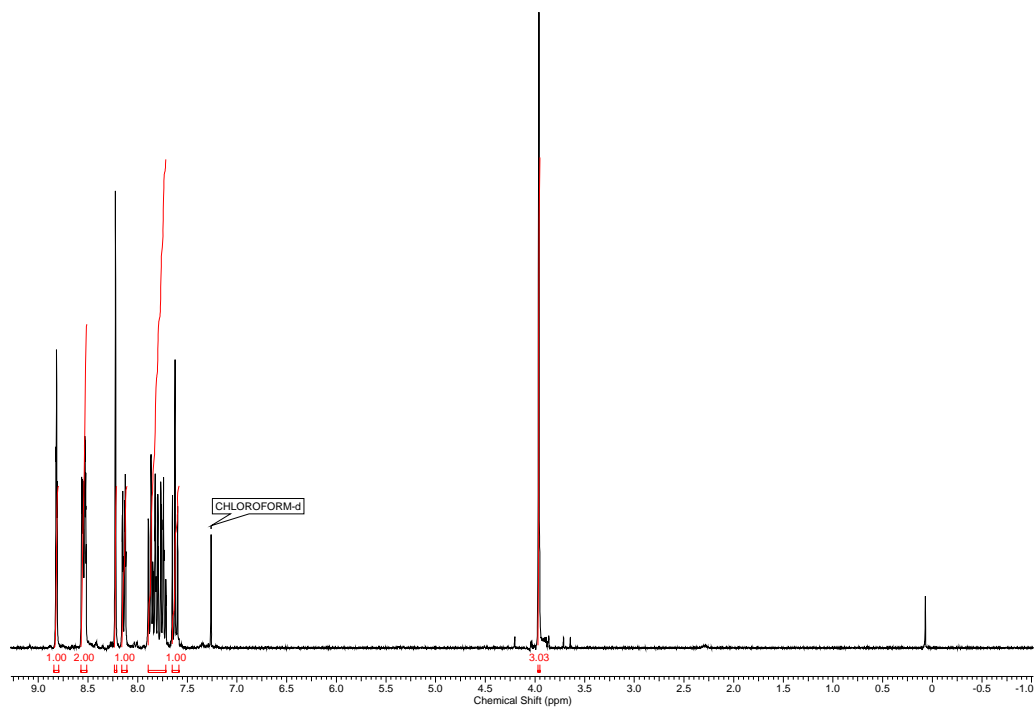
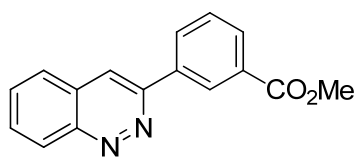
## Ethyl 4-(cinnolin-3-yl)benzoate (5a)



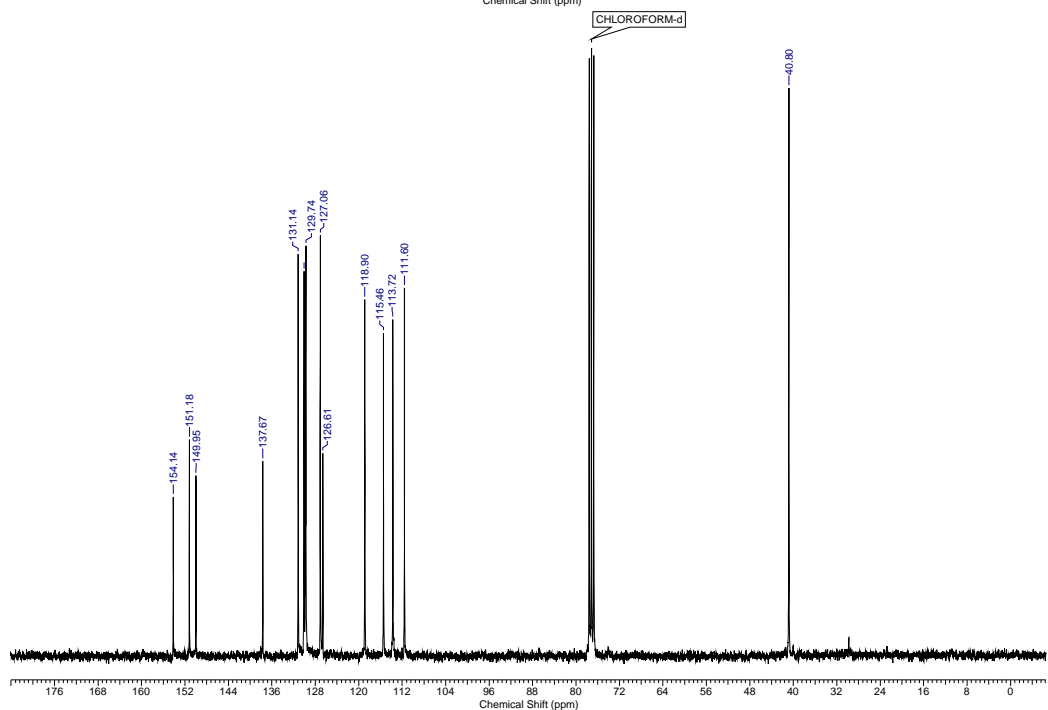
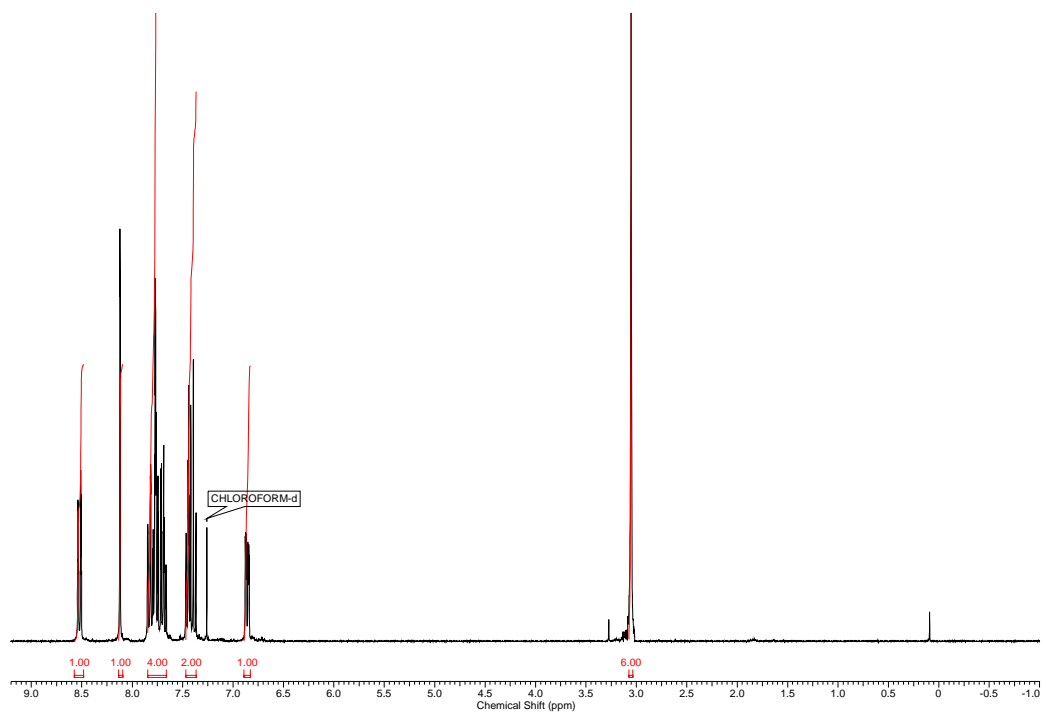
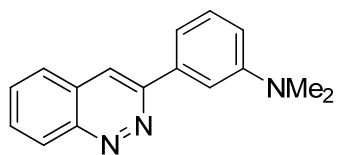
### 3-(4-Methoxyphenyl)cinnoline (5b)



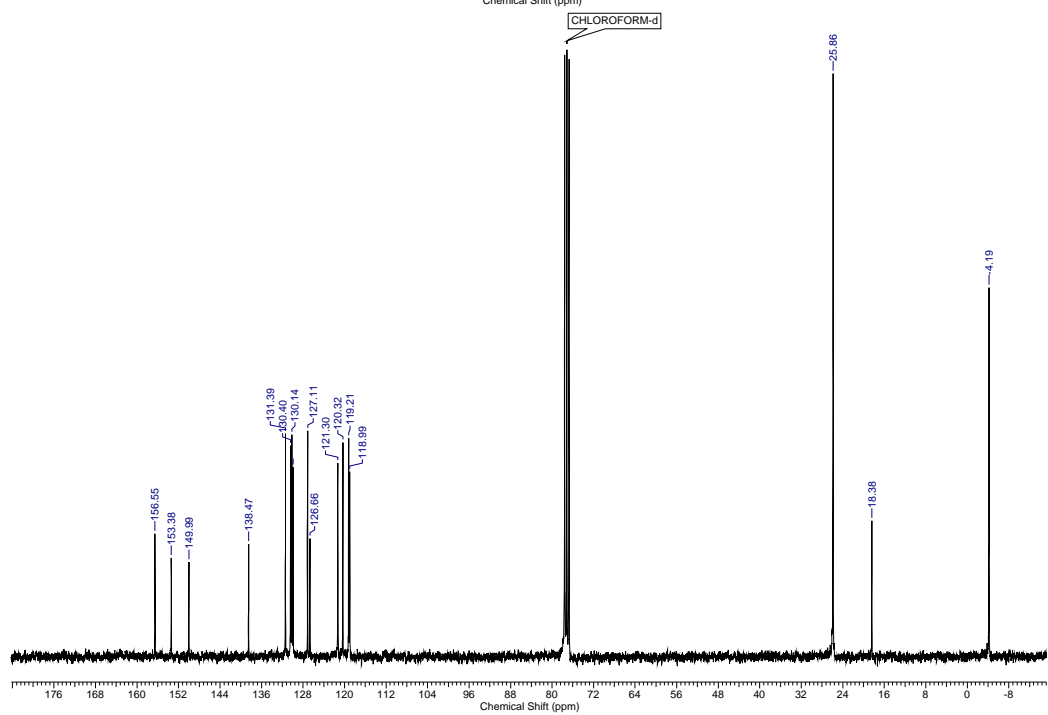
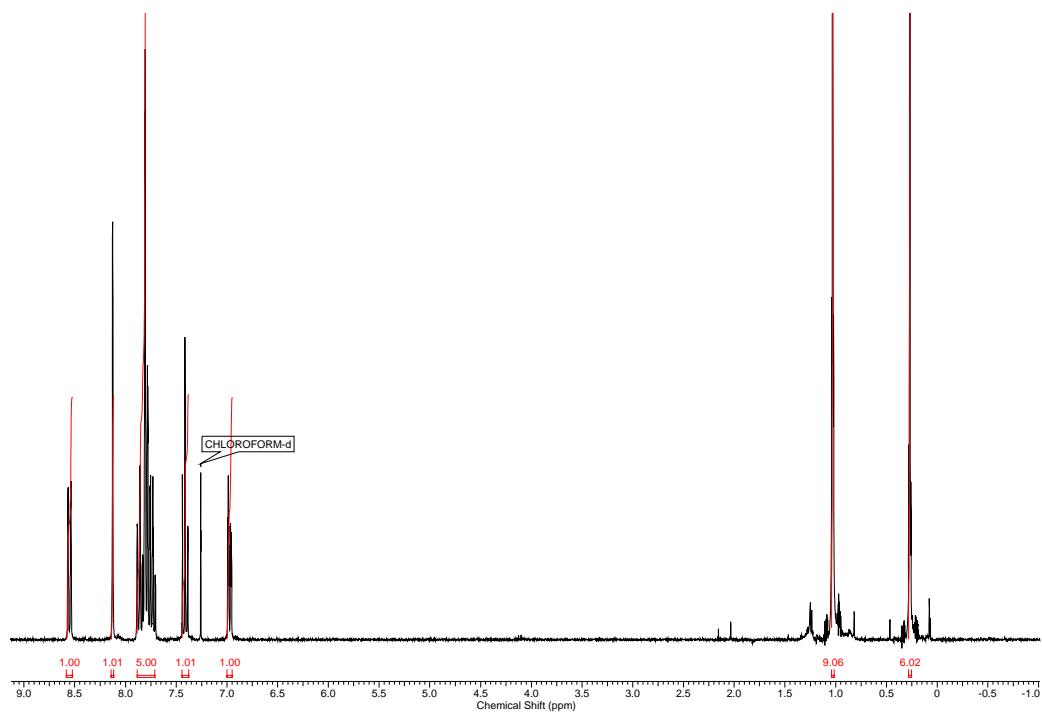
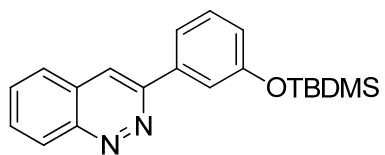
# Methyl 3-(cinnolin-3-yl)benzoate (5c)



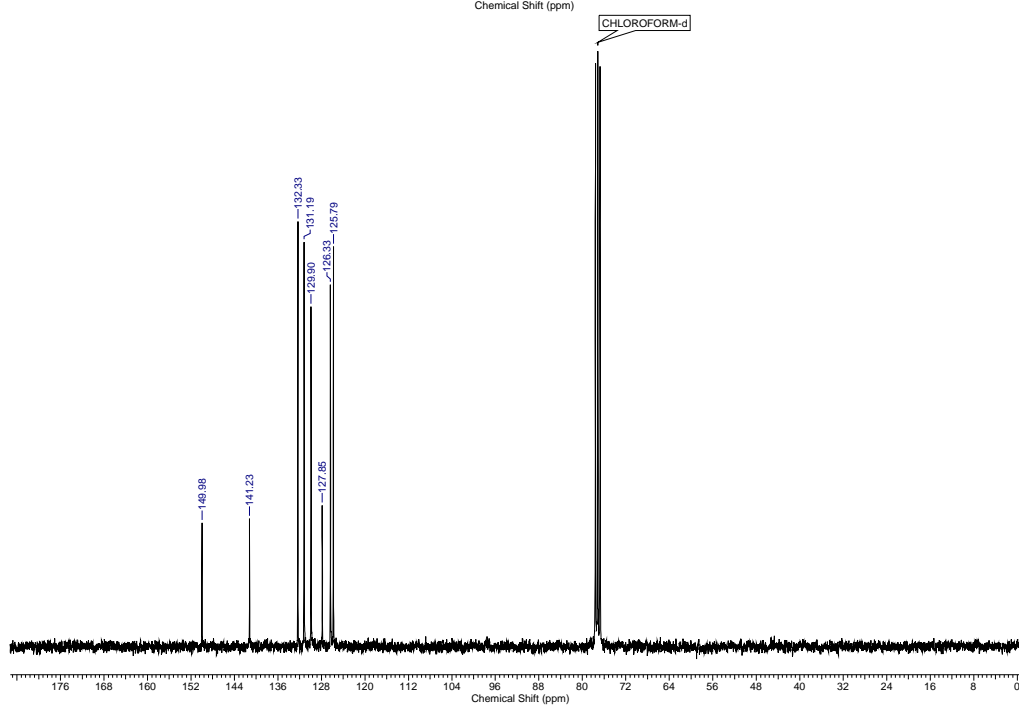
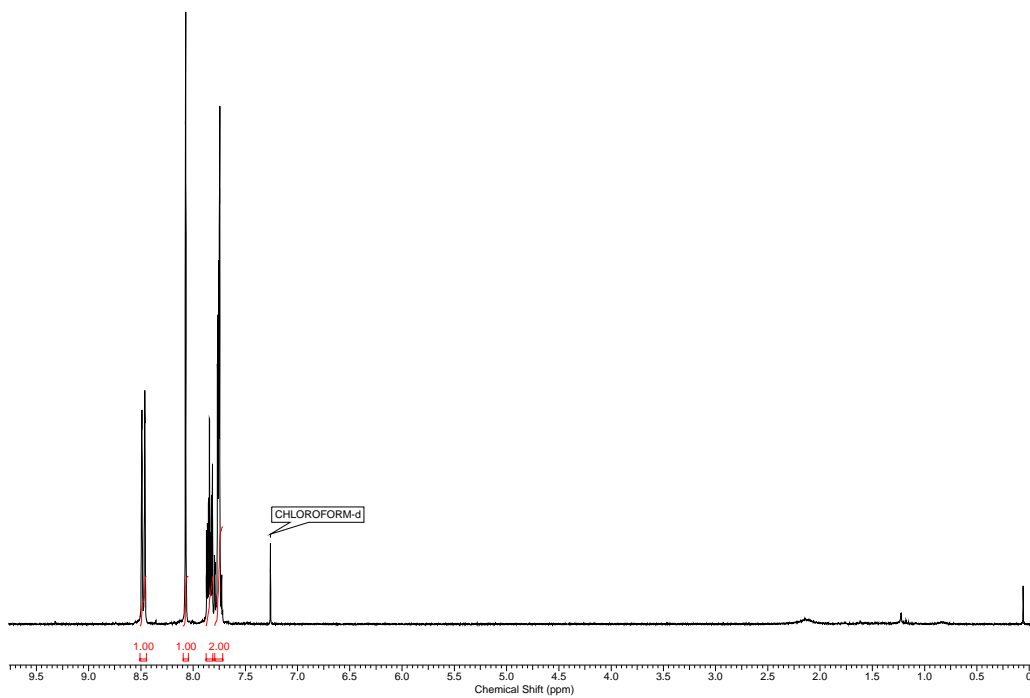
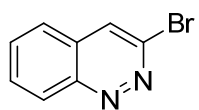
### 3-(Cinnolin-3-yl)-*N,N*-dimethylaniline (5d)



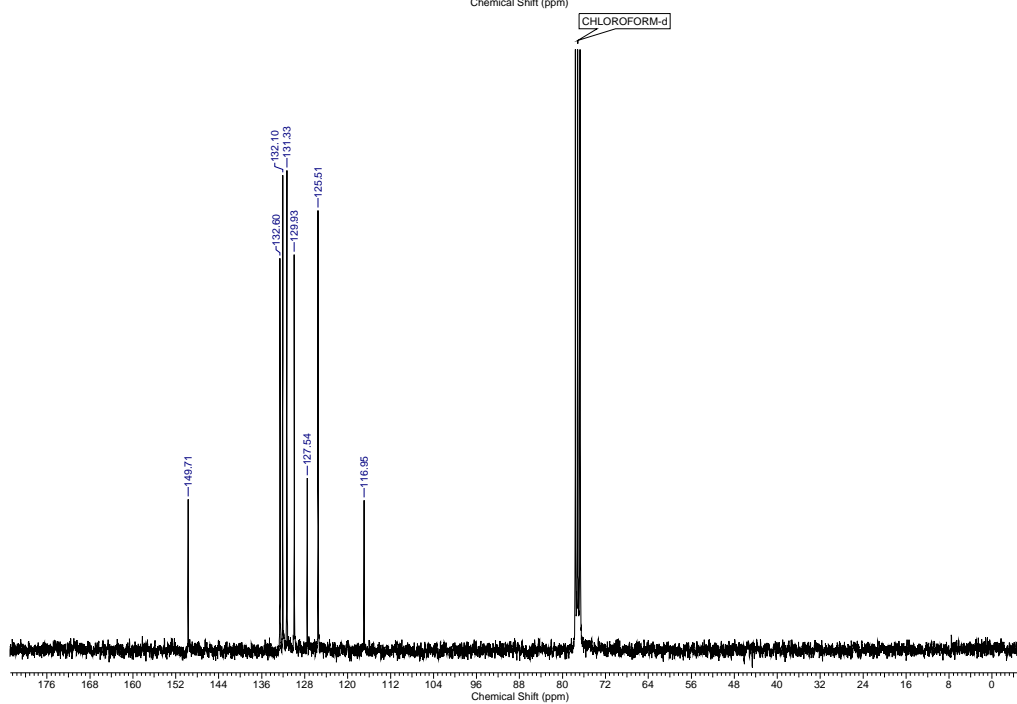
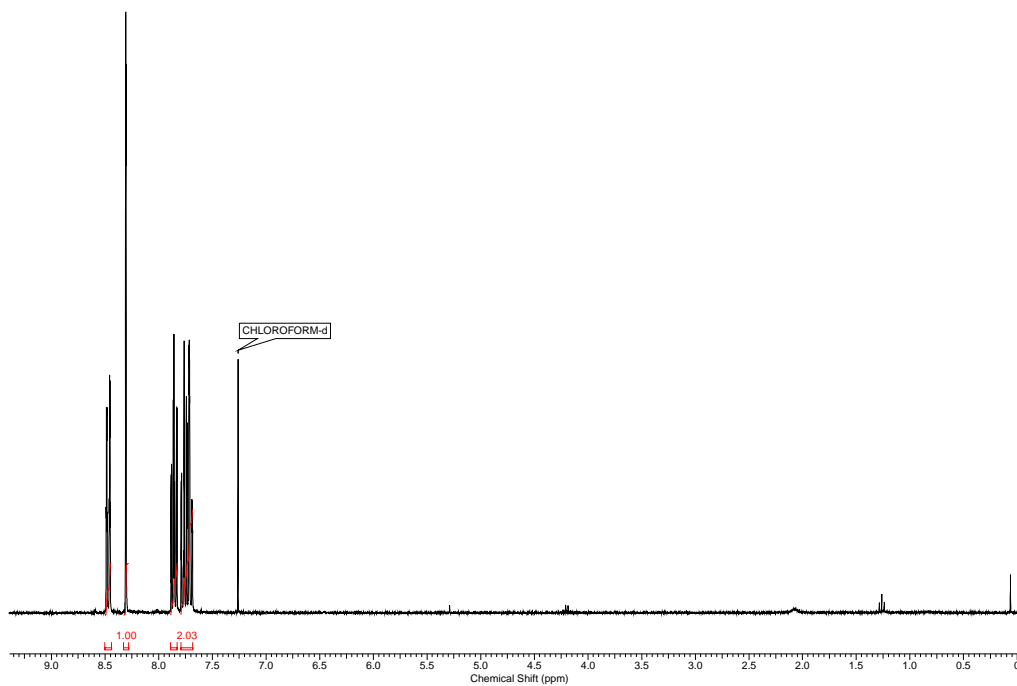
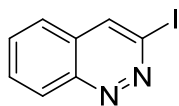
### 3-(3-((*tert*-Butyldimethylsilyl)oxy)phenyl)cinnoline (5e)



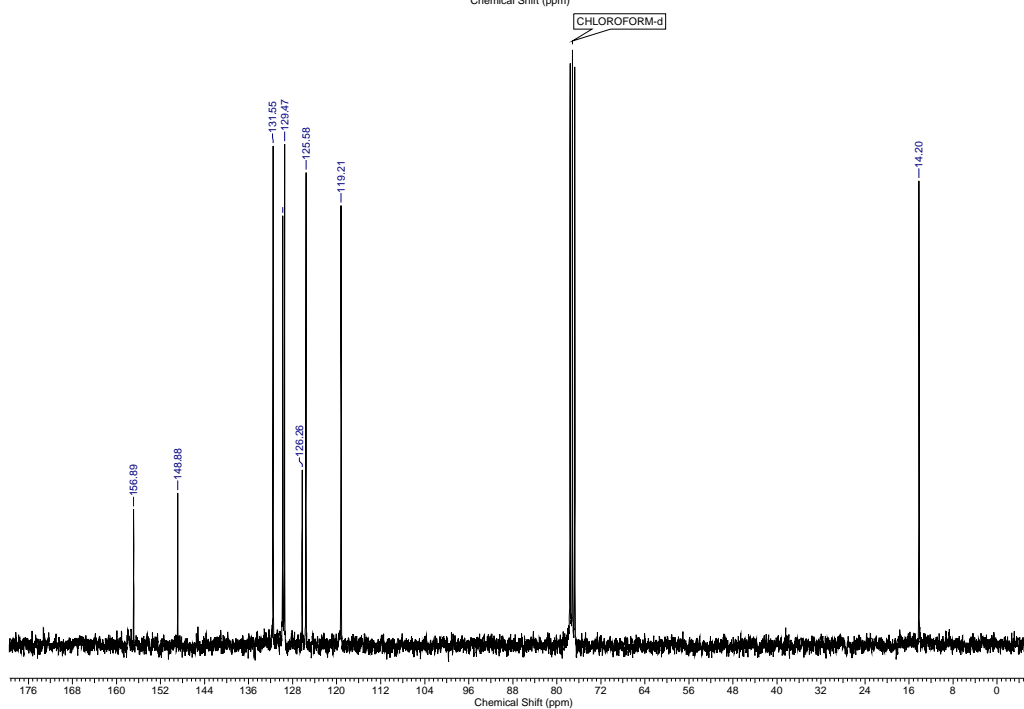
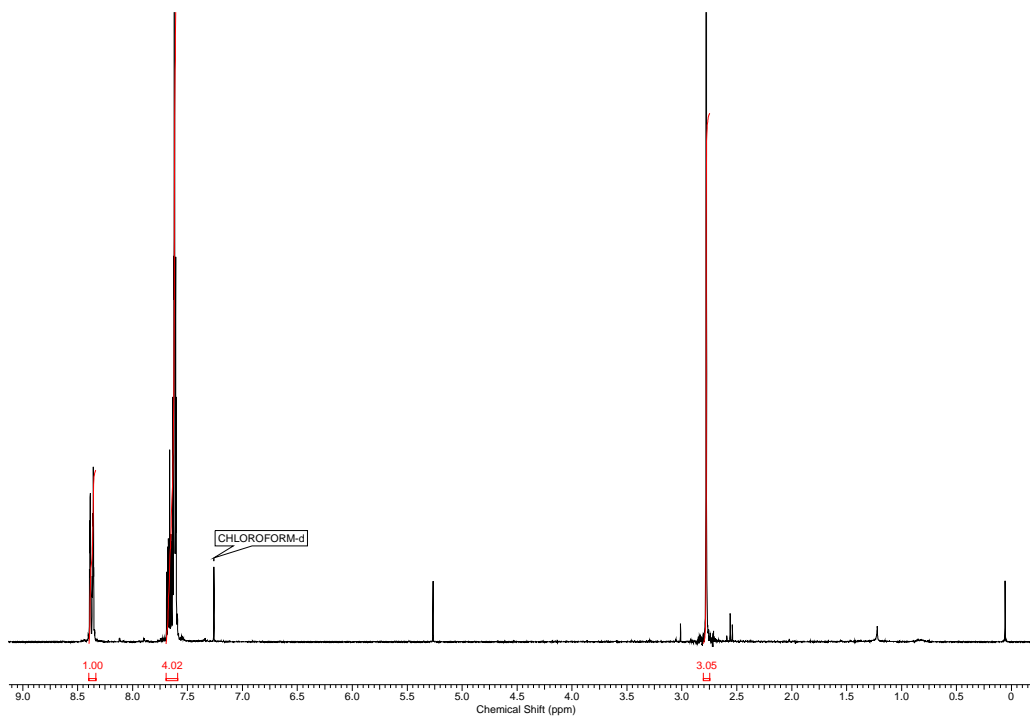
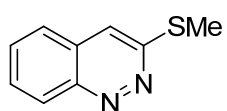
### 3-Bromocinnoline (5f)



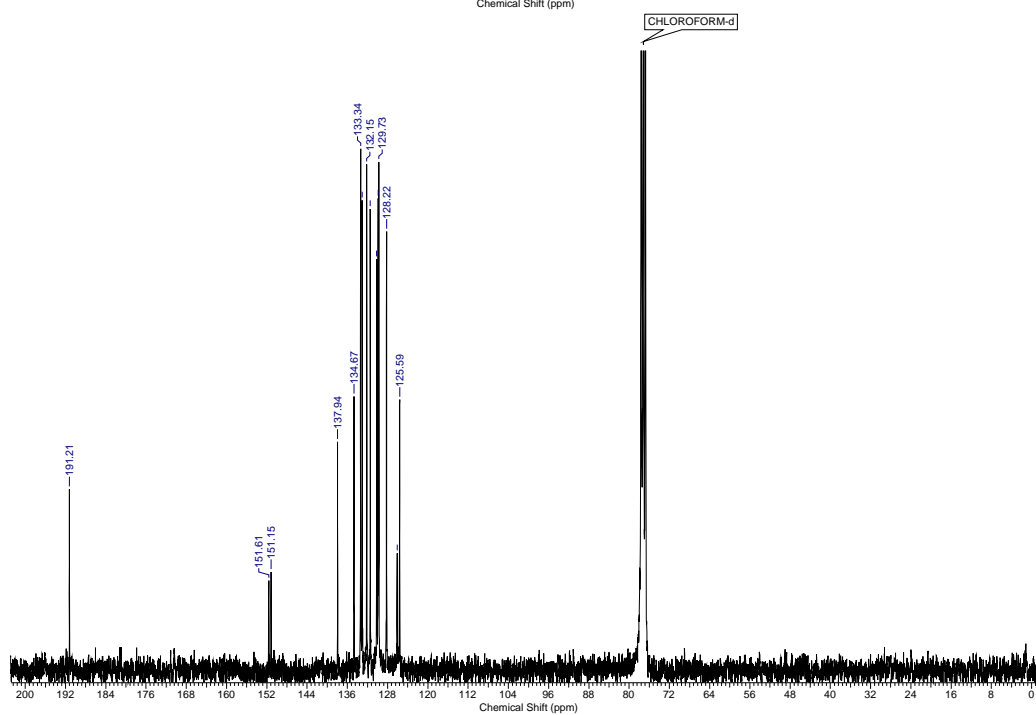
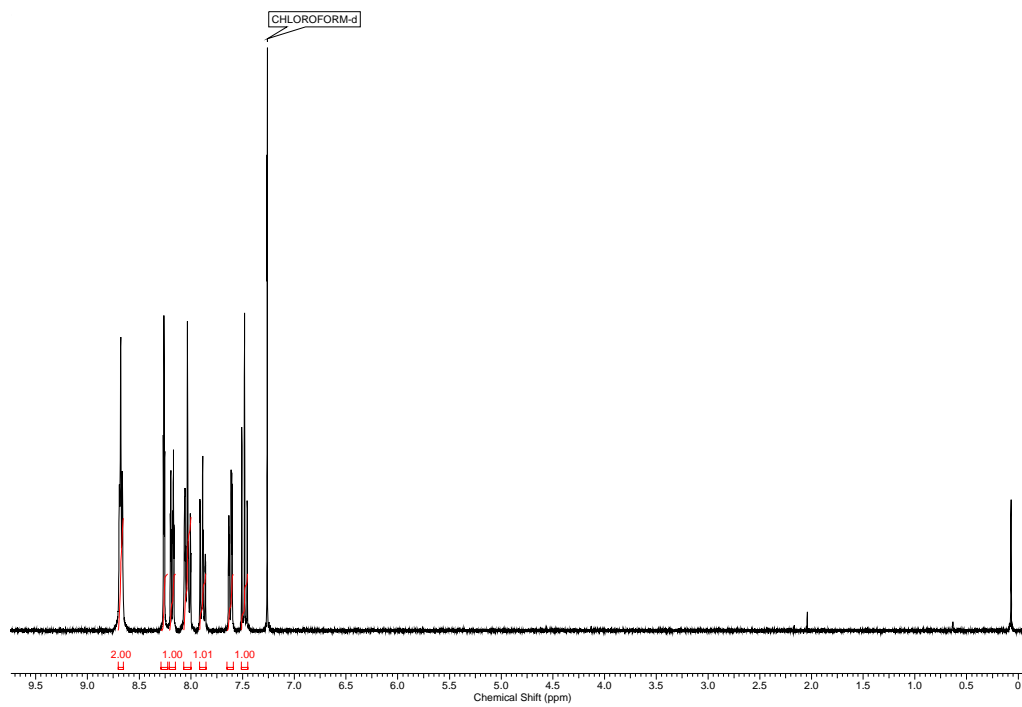
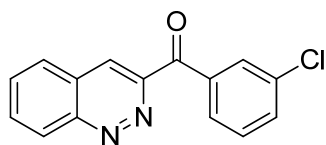
### 3-Iodocinnoline (5g)



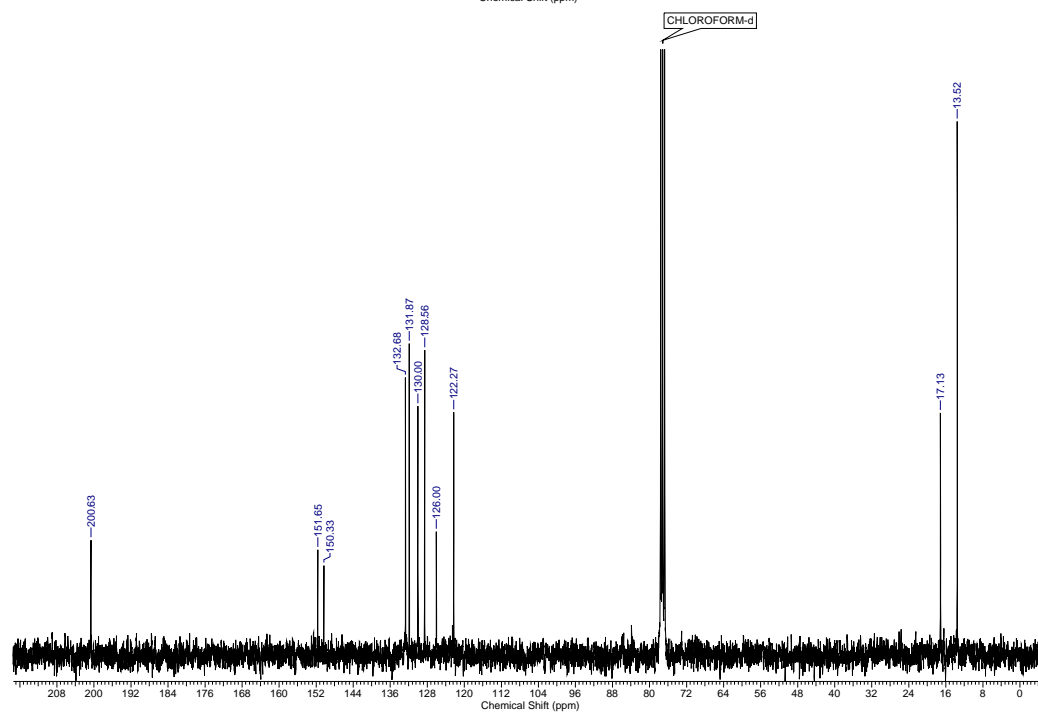
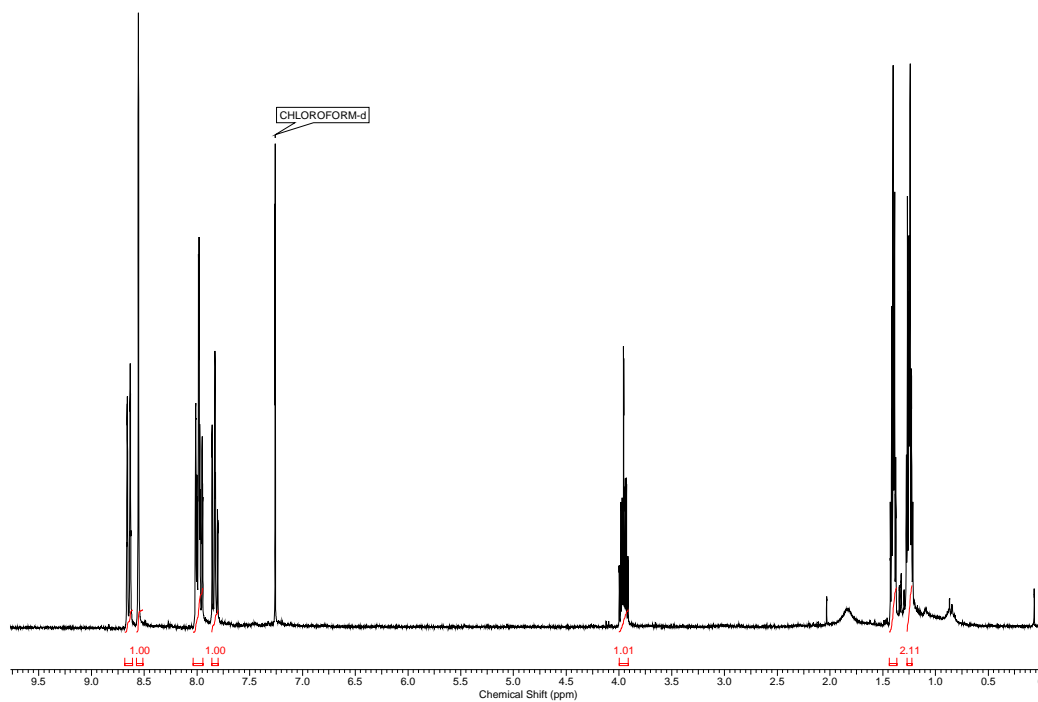
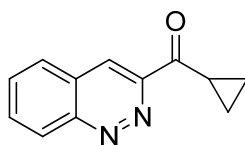
### 3-(Methylthio)cinnoline (5h)



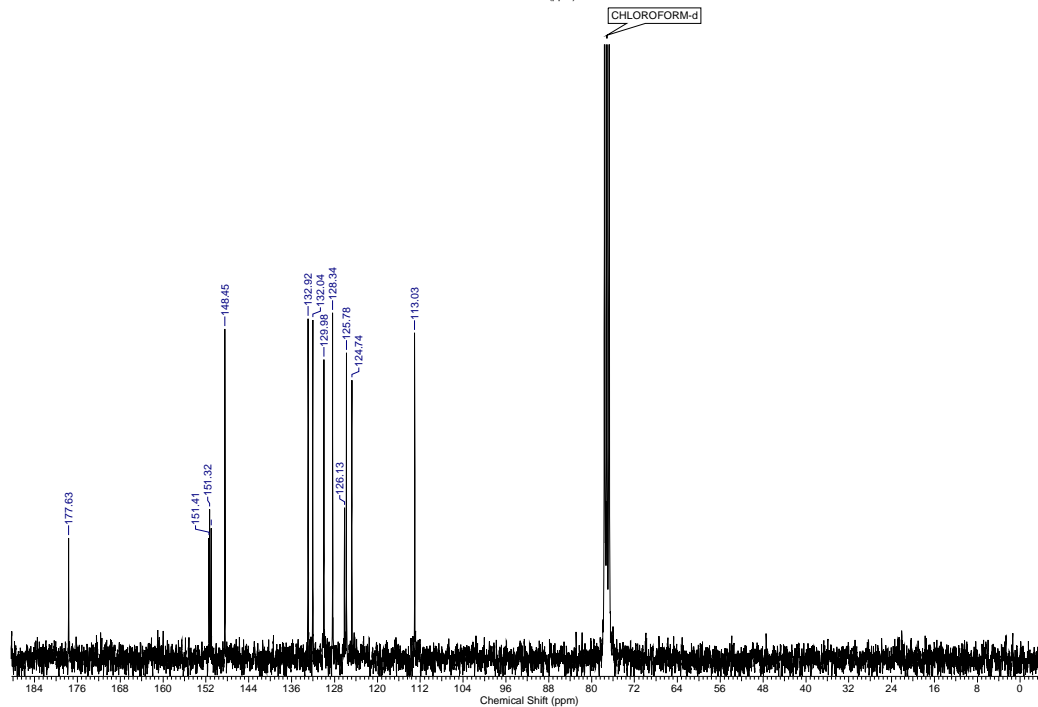
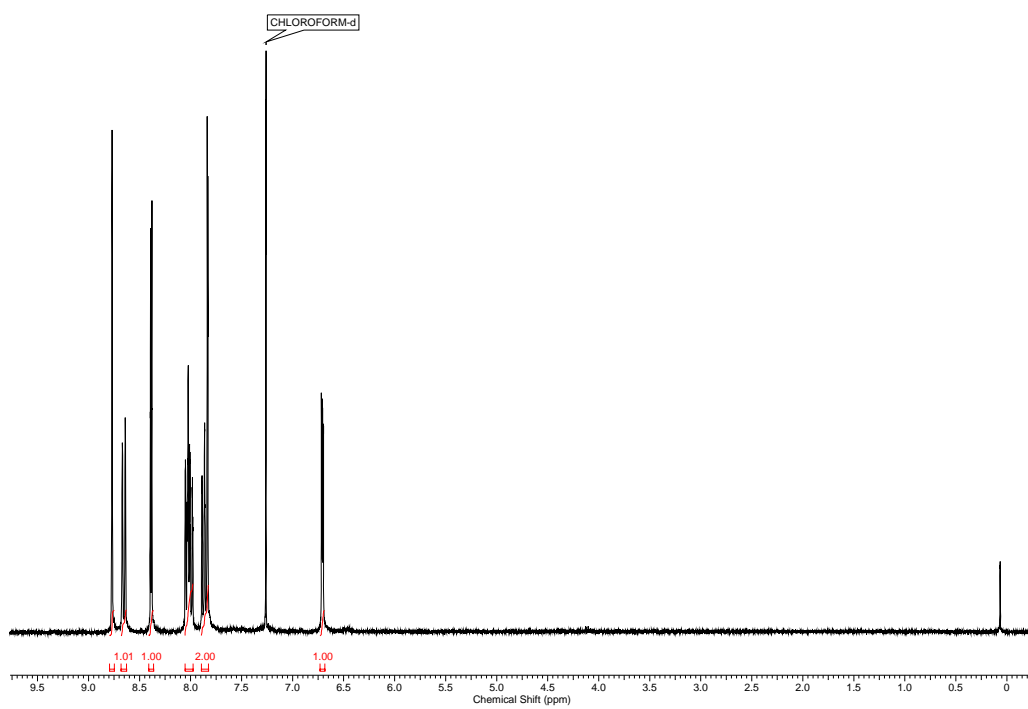
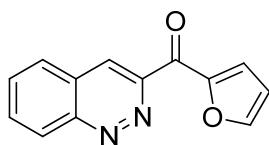
### (3-Chlorophenyl)(cinnolin-3-yl)methanone (5i)



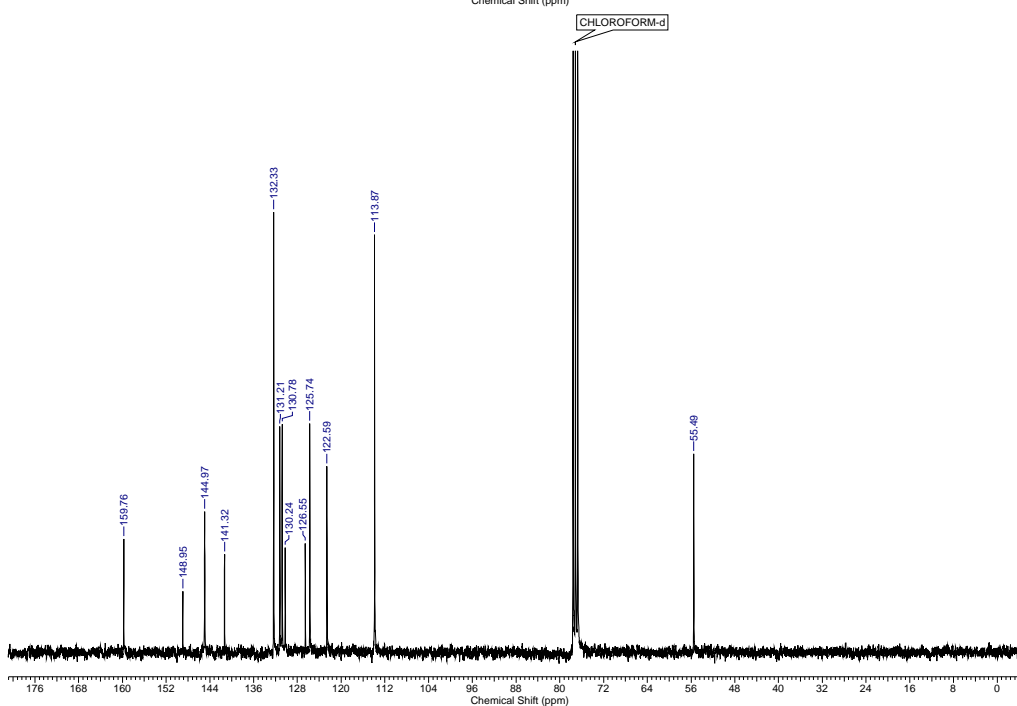
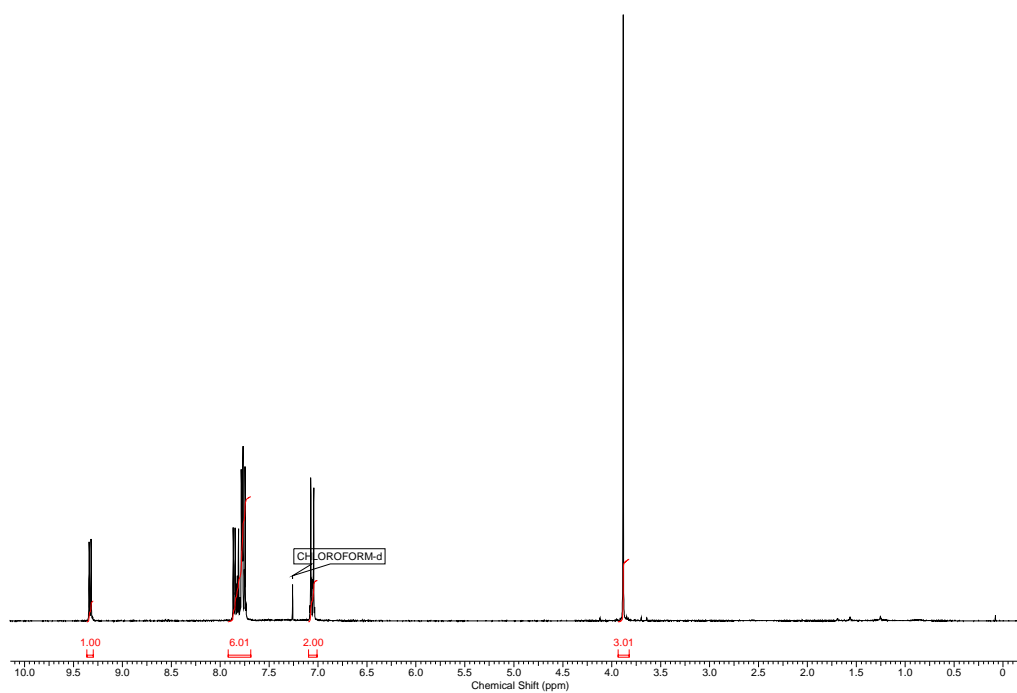
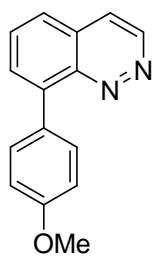
# Cinnolin-3-yl(cyclopropyl)methanone (5j)



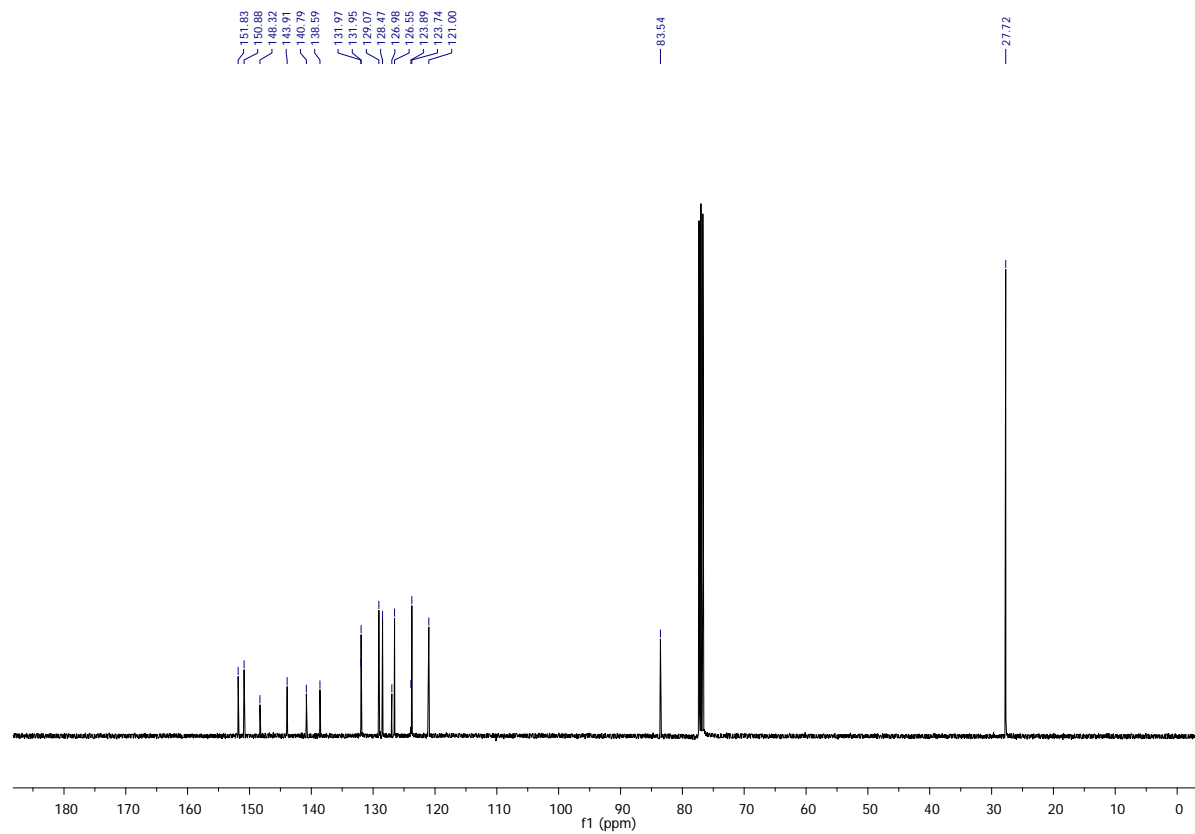
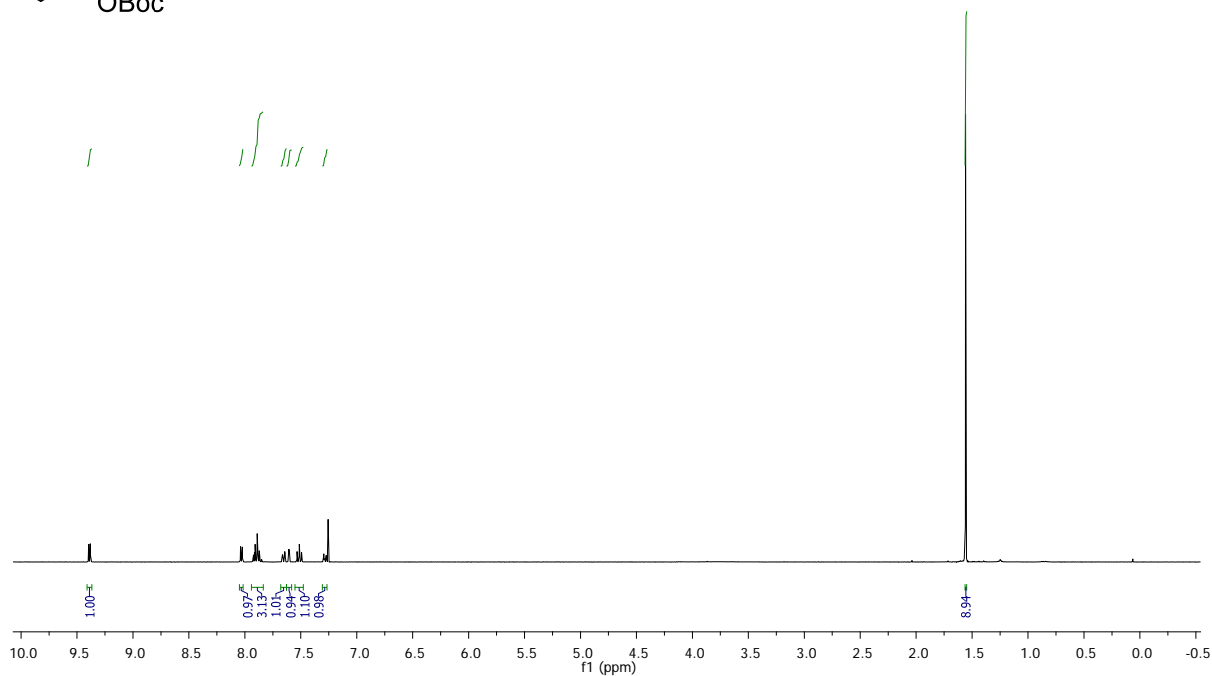
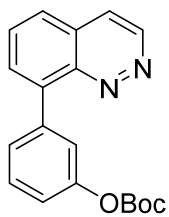
# Cinnolin-3-yl(furan-2-yl)methanone (5k)



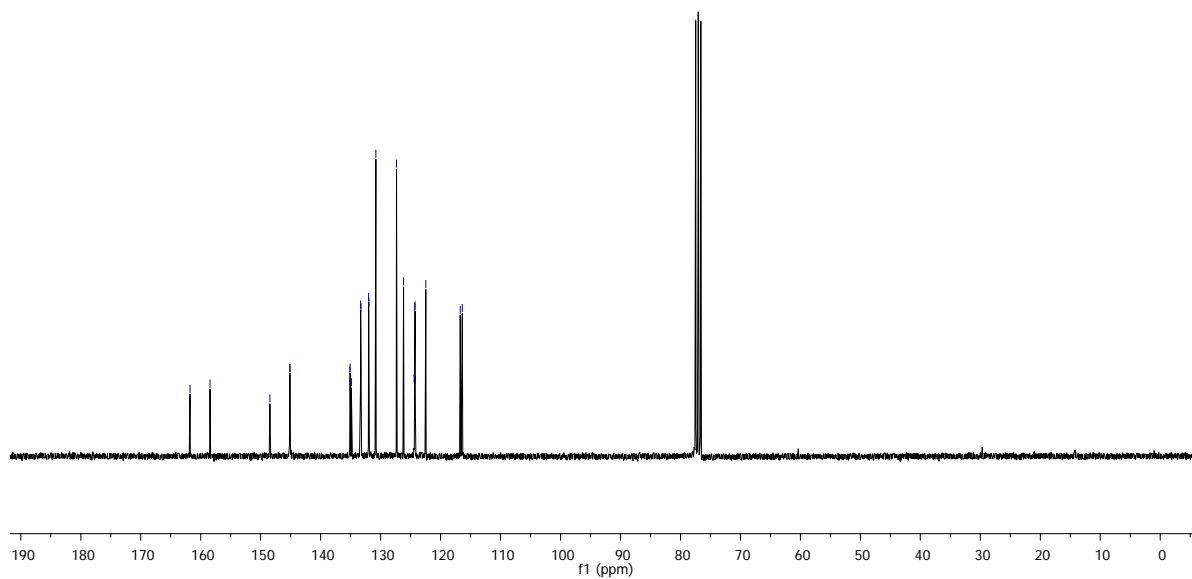
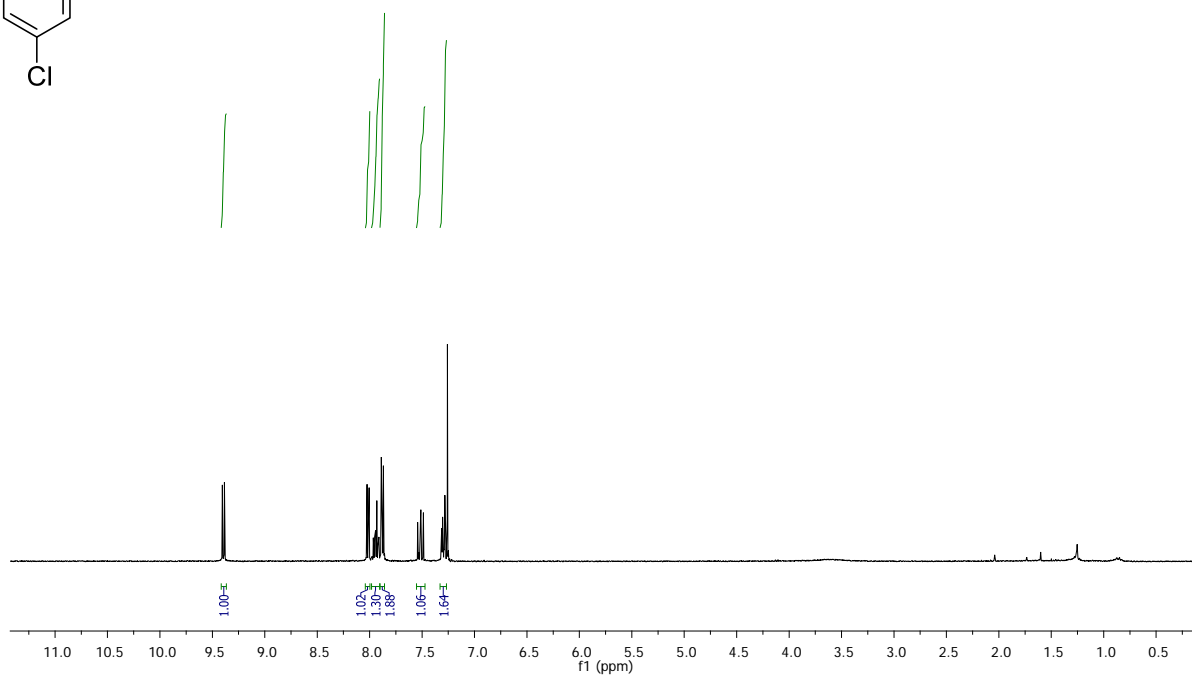
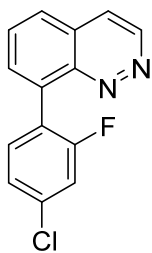
# 8-(4-Methoxyphenyl)cinnoline (6a)



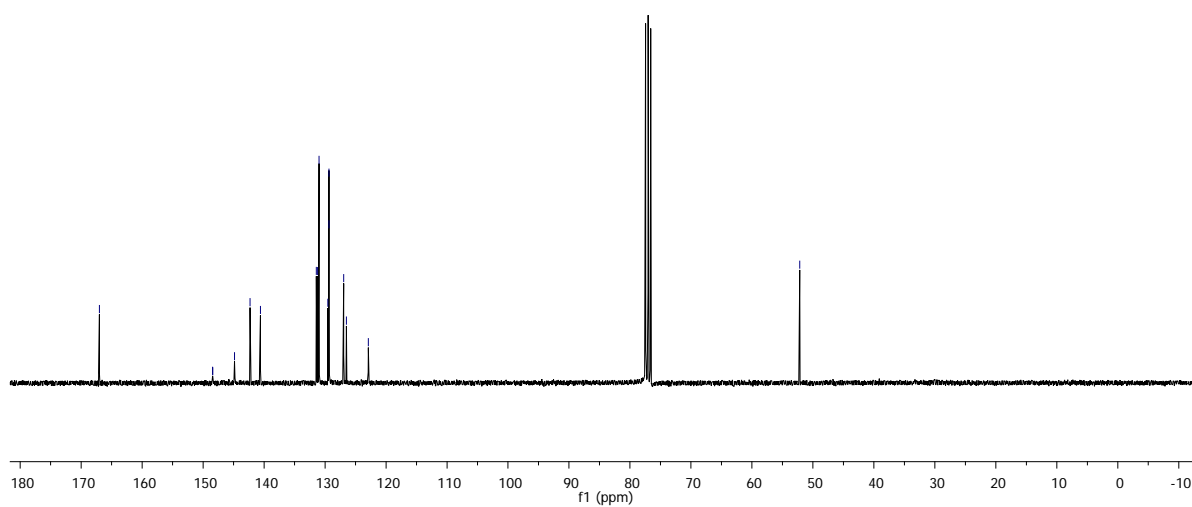
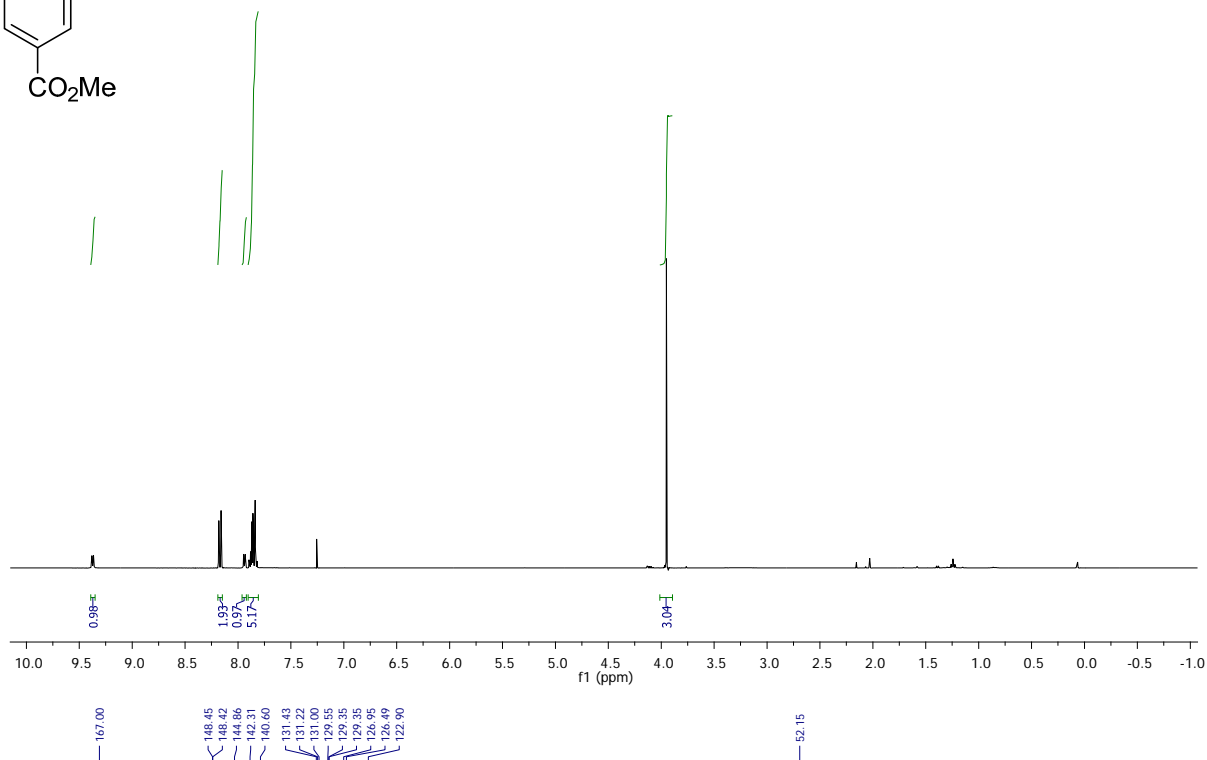
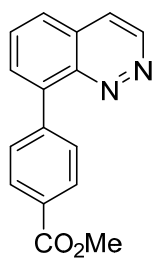
**tert-Butyl (3-(cinnolin-8-yl)phenyl) carbonate (6b)**



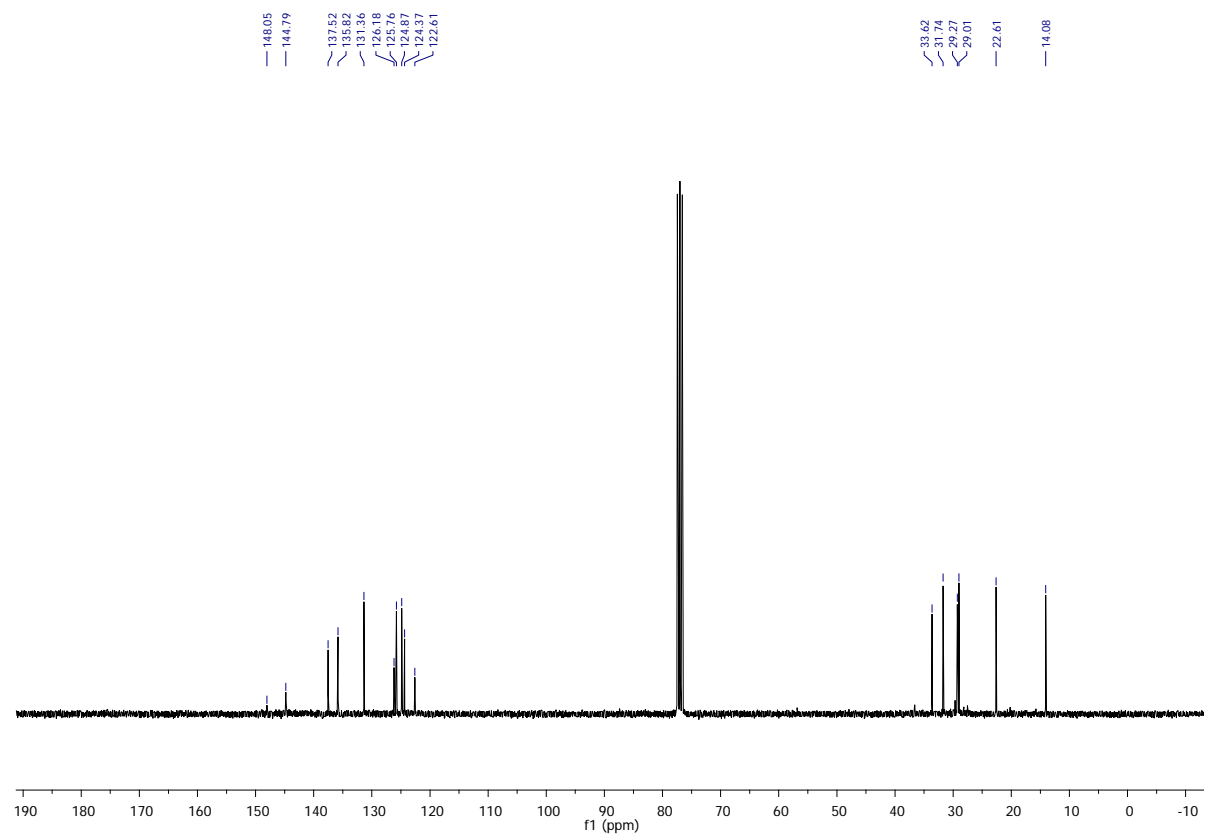
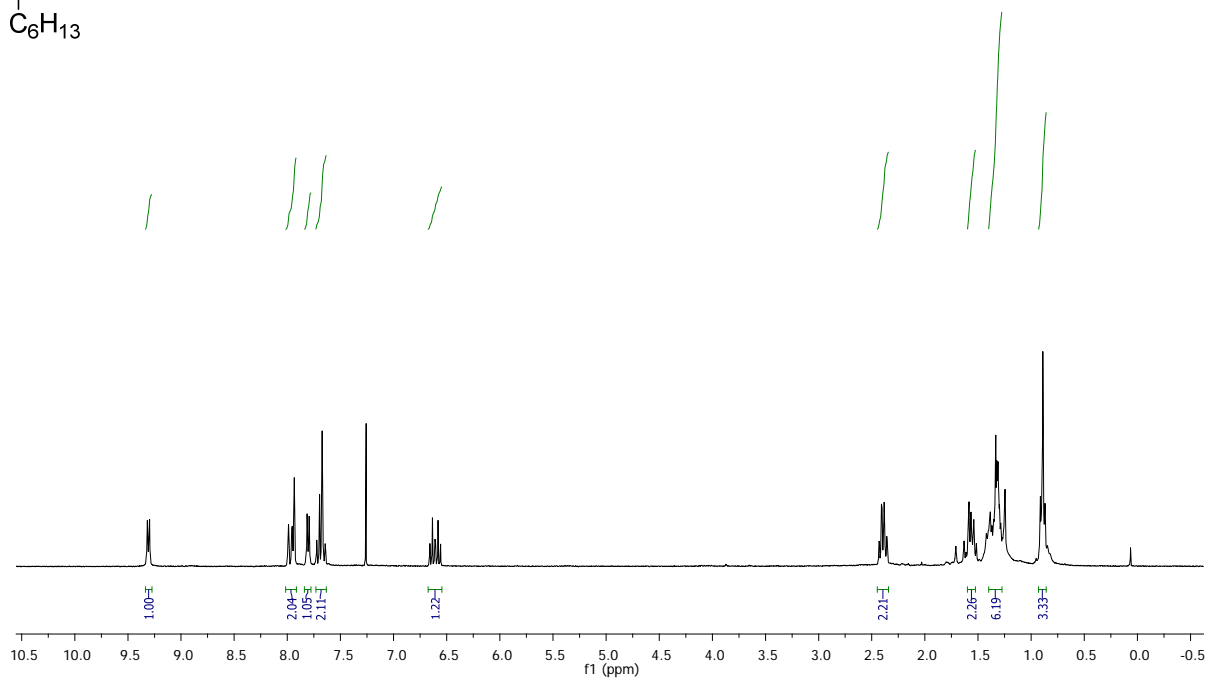
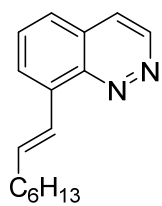
### 8-(4-Chloro-2-fluorophenyl)cinnoline (6c)



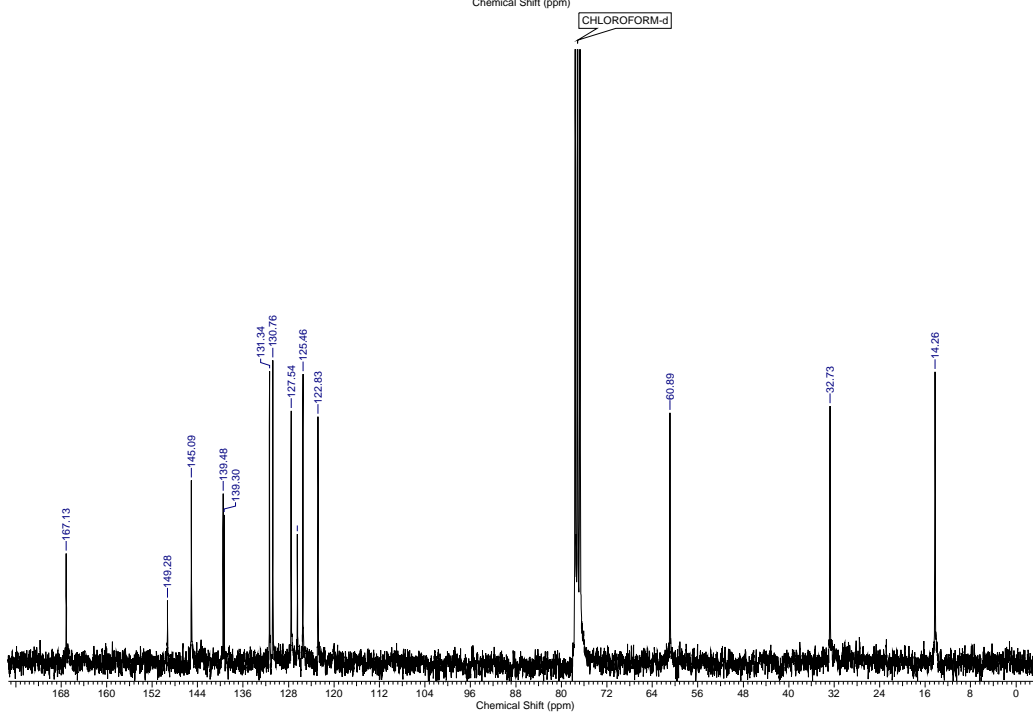
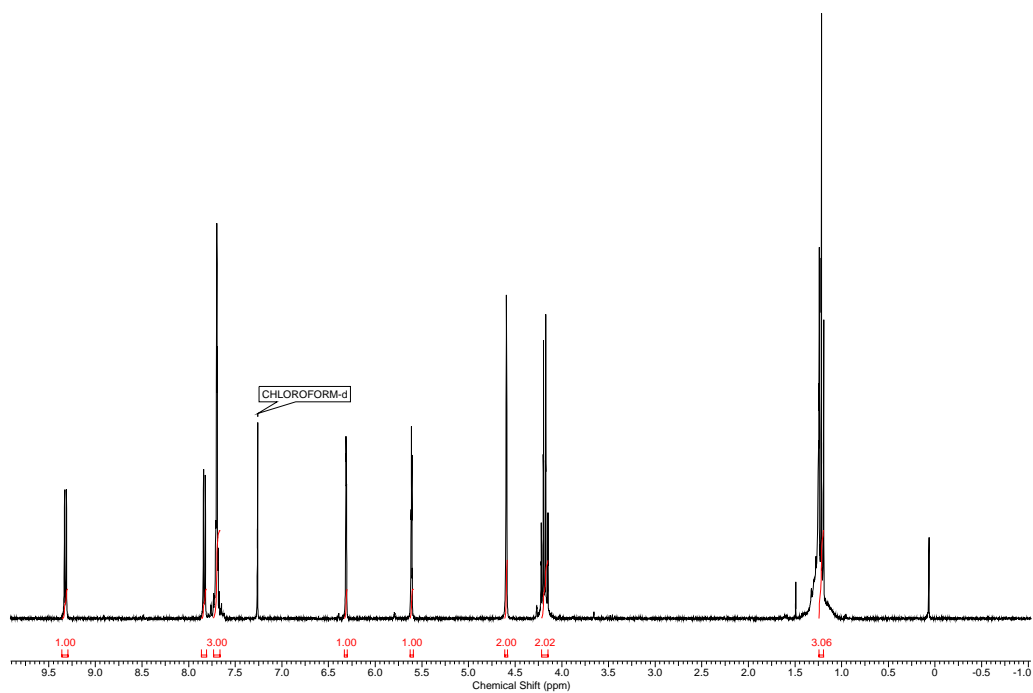
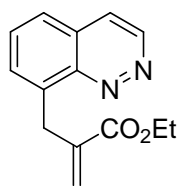
# Methyl 4-(cinnolin-8-yl)benzoate (6d)



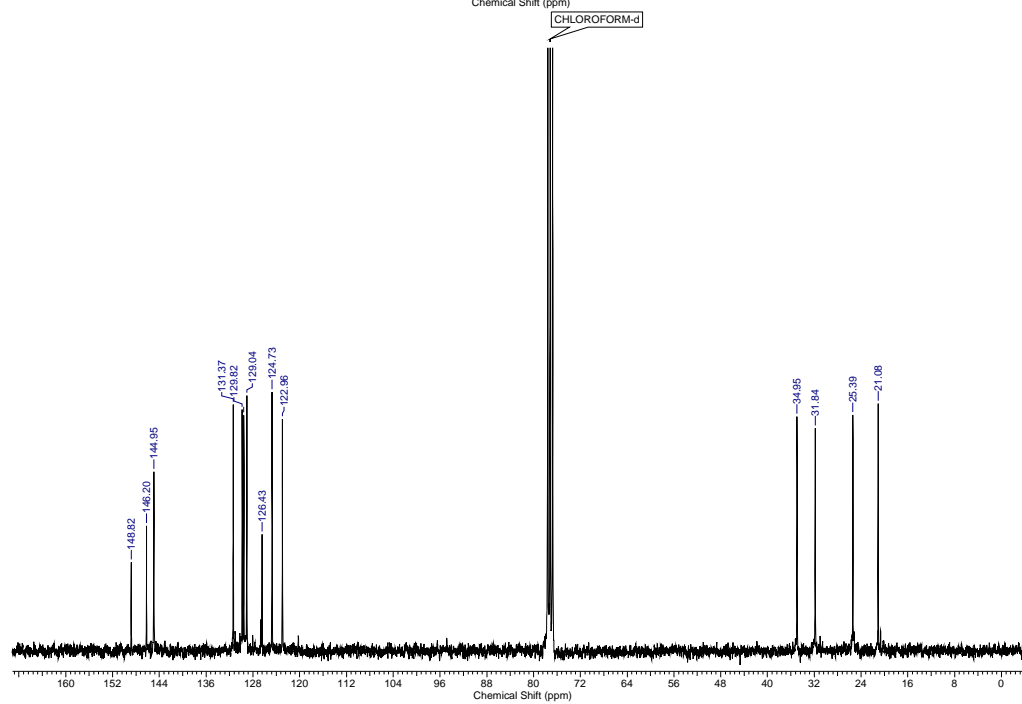
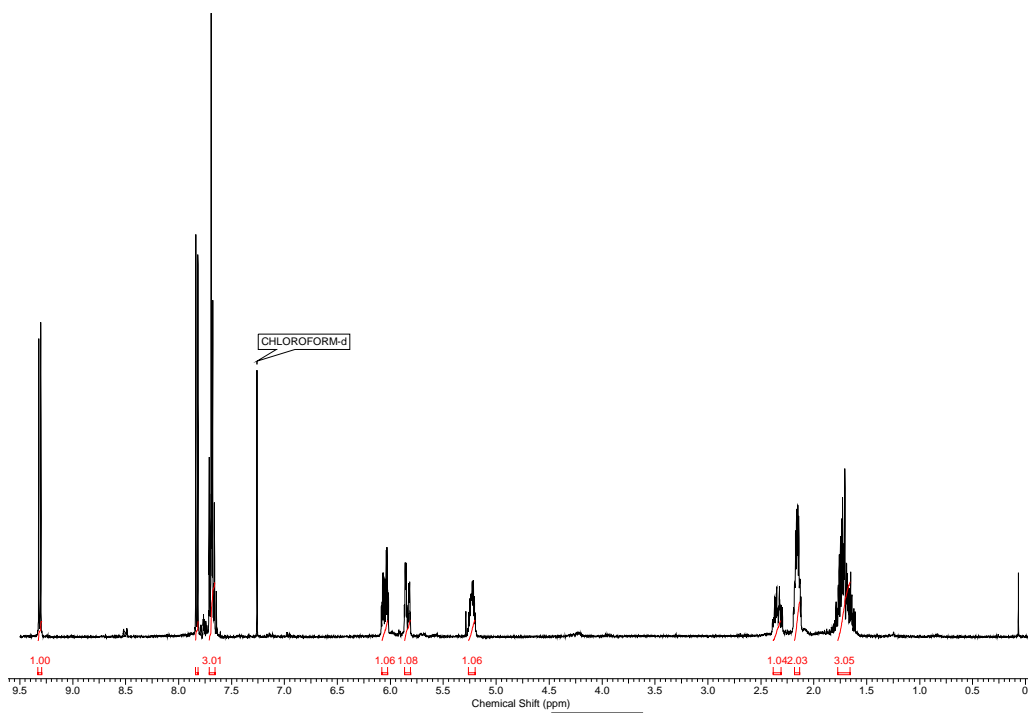
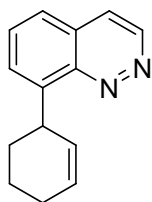
**(E)-8-(Oct-1-en-1-yl)cinnoline (6e)**



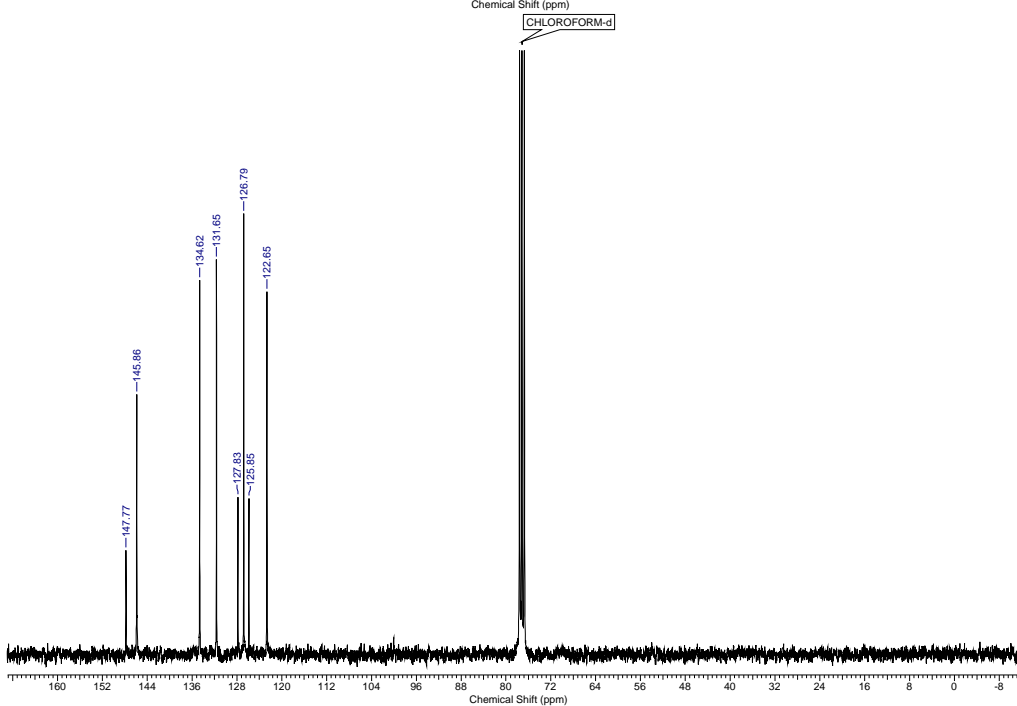
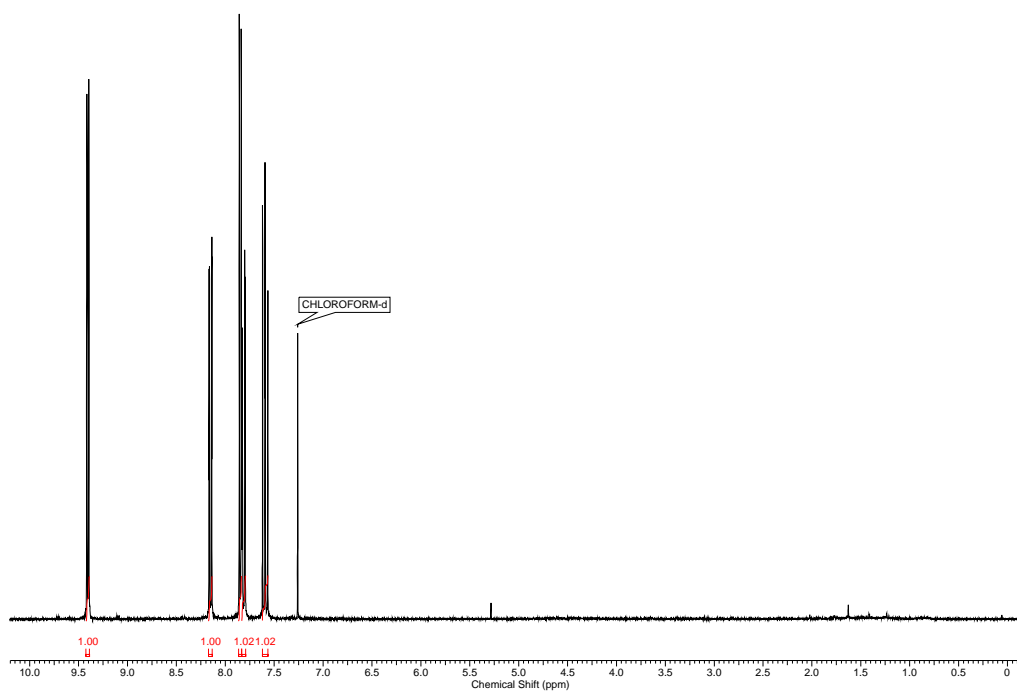
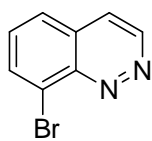
# Ethyl 2-(cinnolin-8-ylmethyl)acrylate (6f)



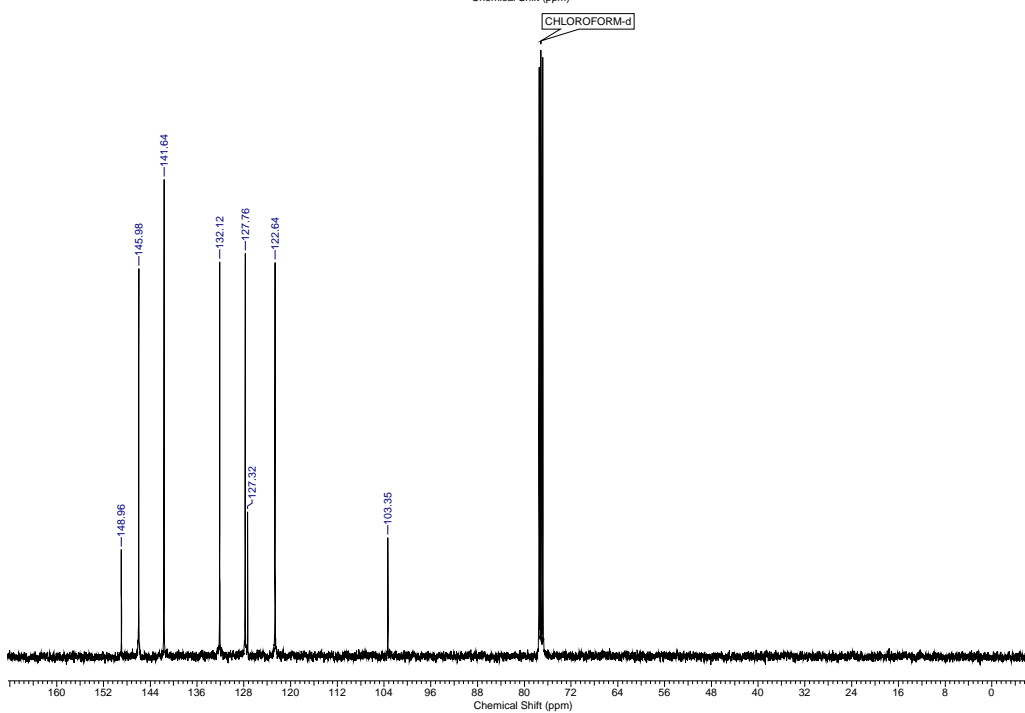
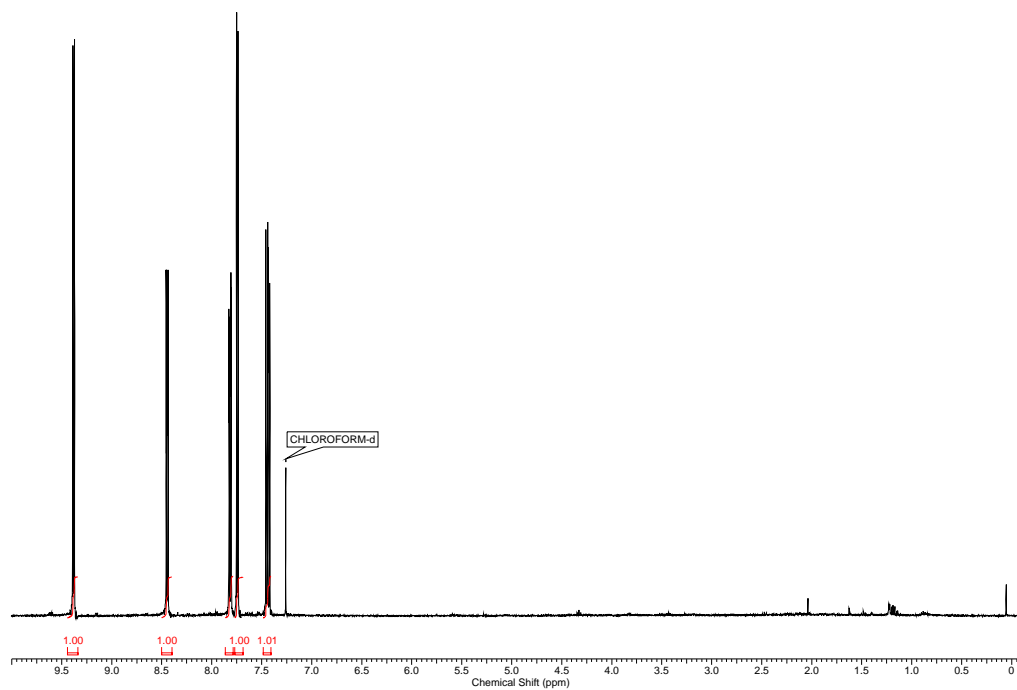
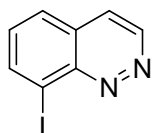
# 8-(Cyclohex-2-en-1-yl)cinnoline (6g)



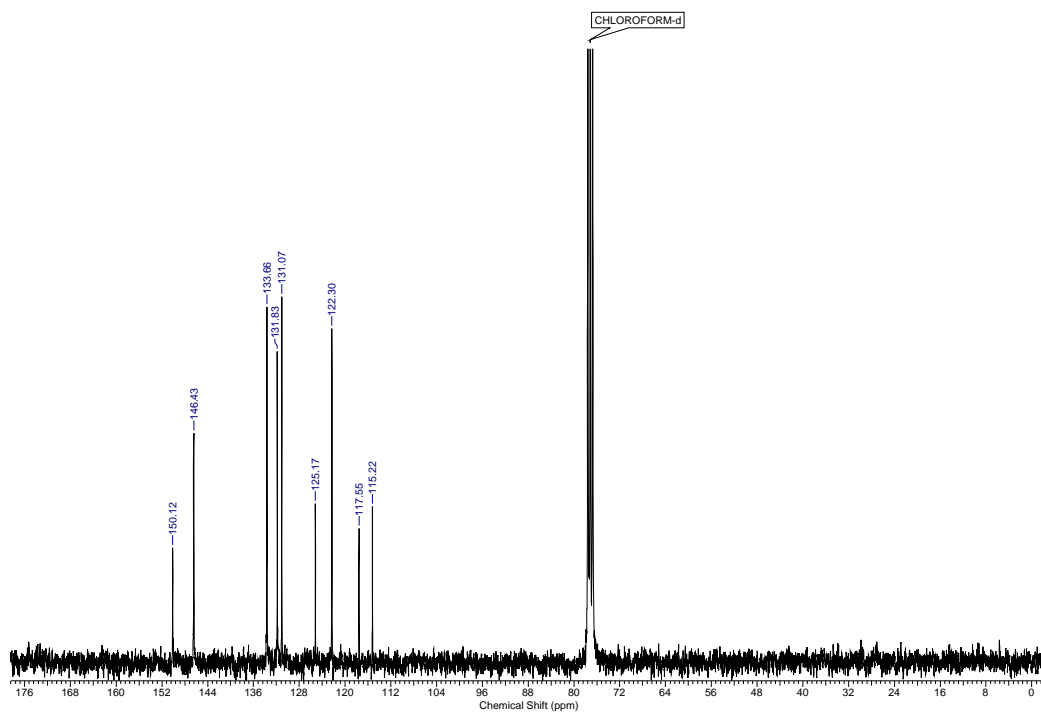
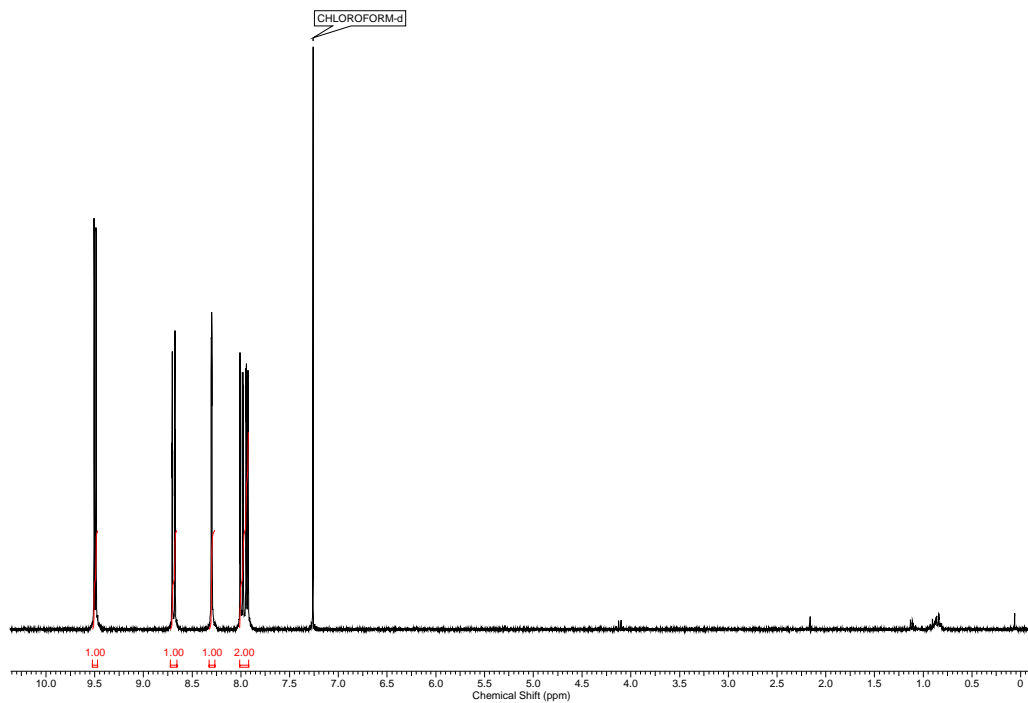
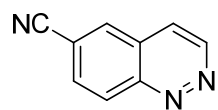
## 8-Bromocinnoline (6h)



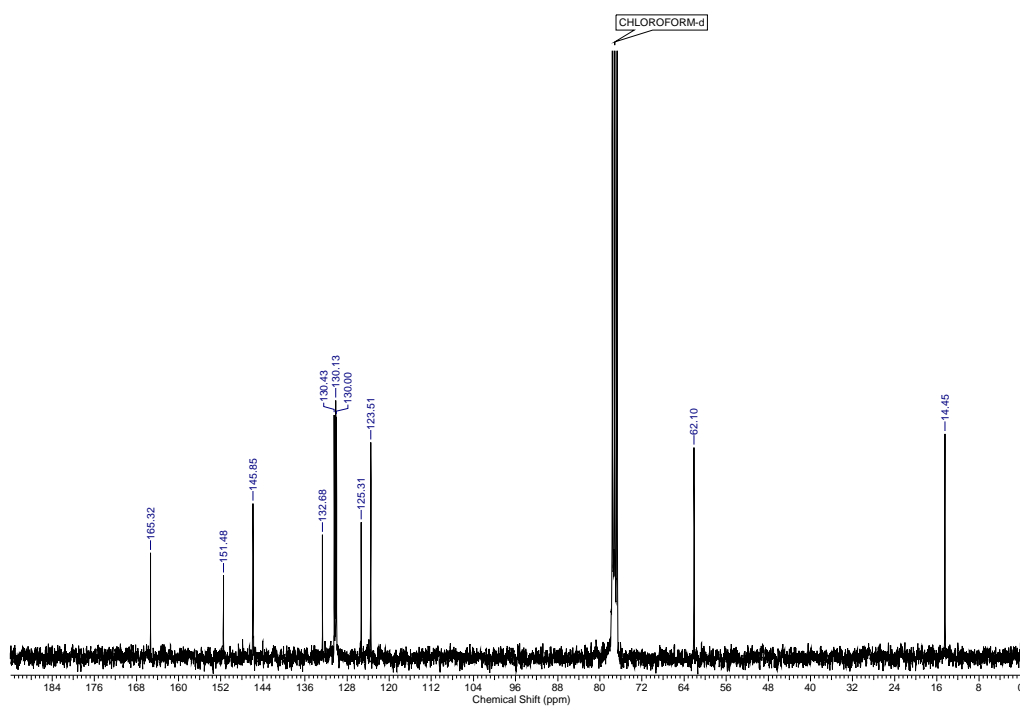
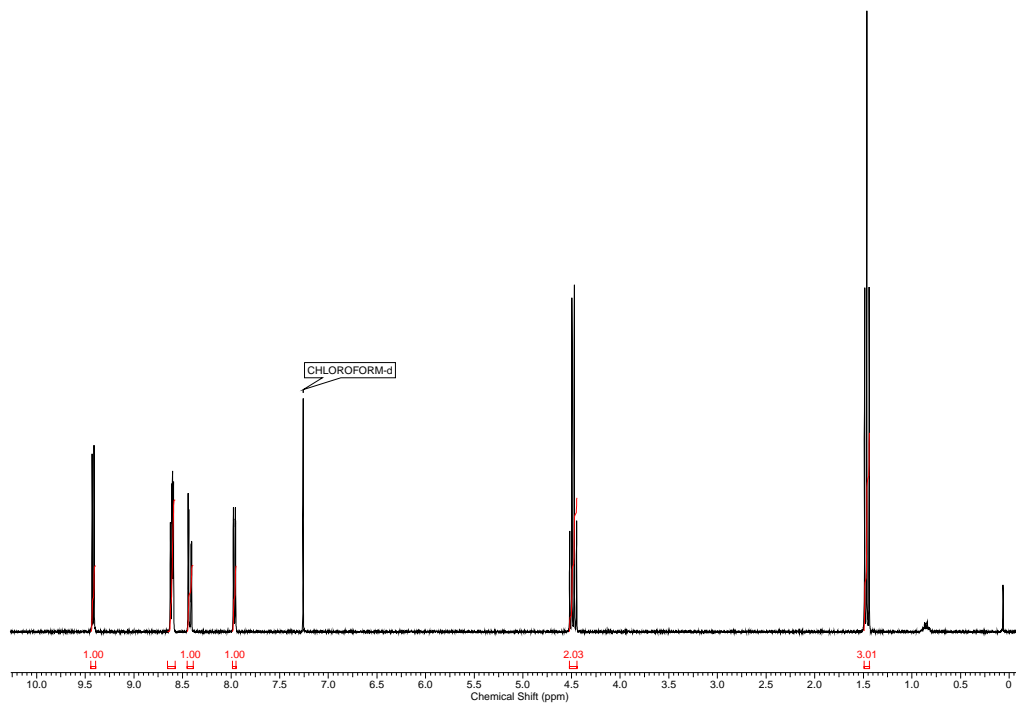
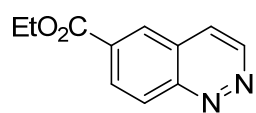
# 8-Iodocinnoline (6i)



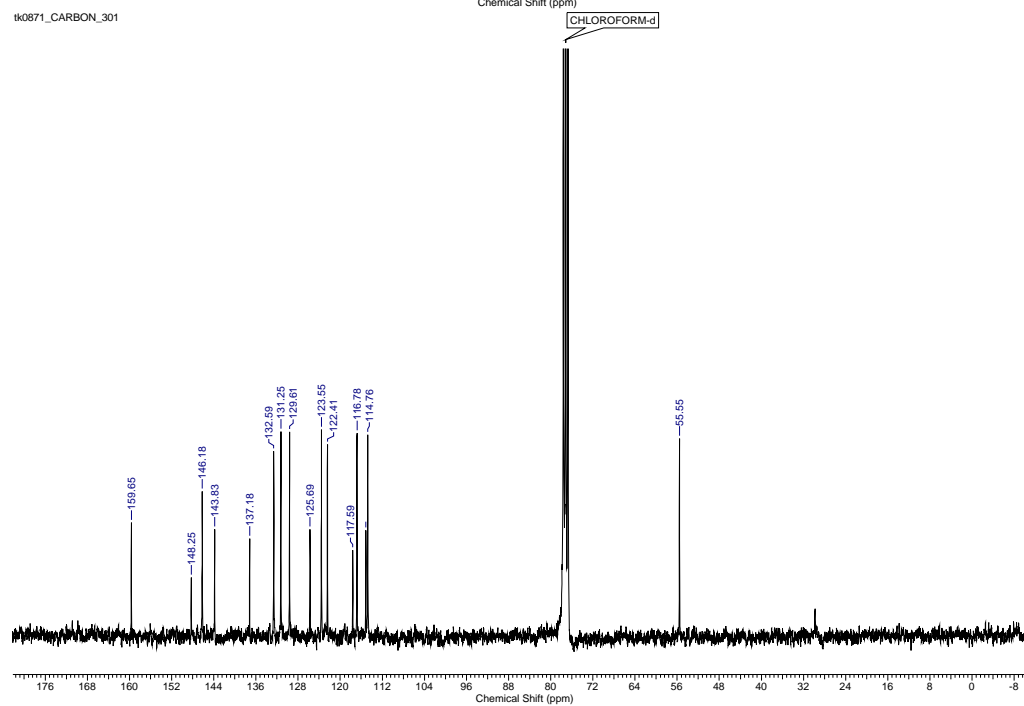
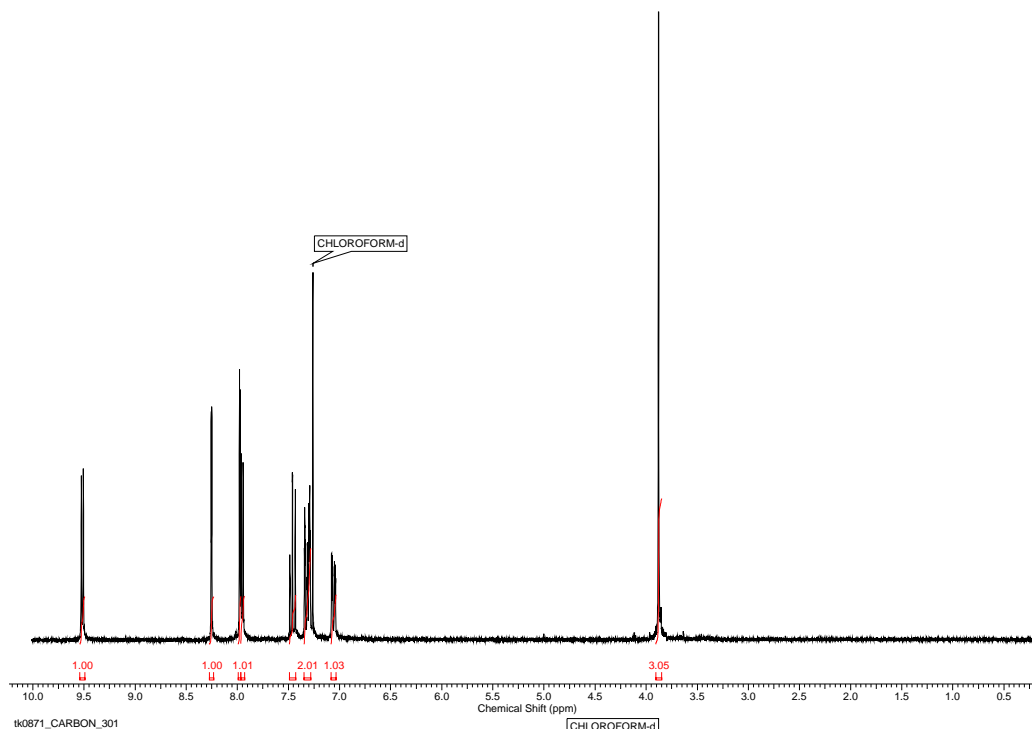
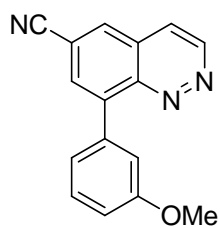
# Cinnoline-6-carbonitrile (7a)



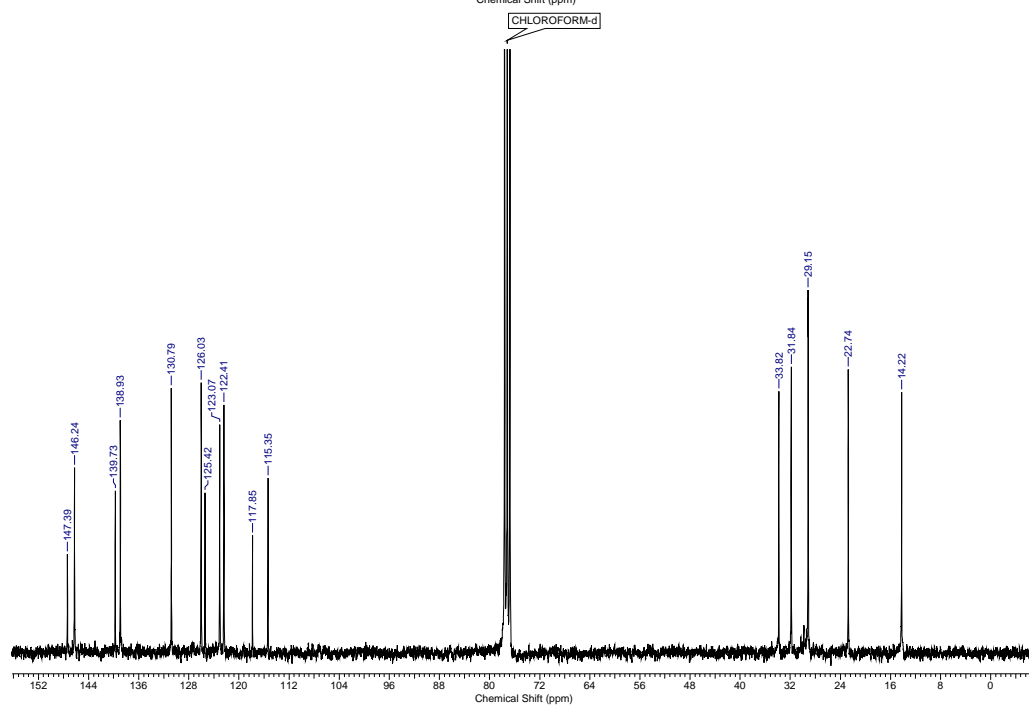
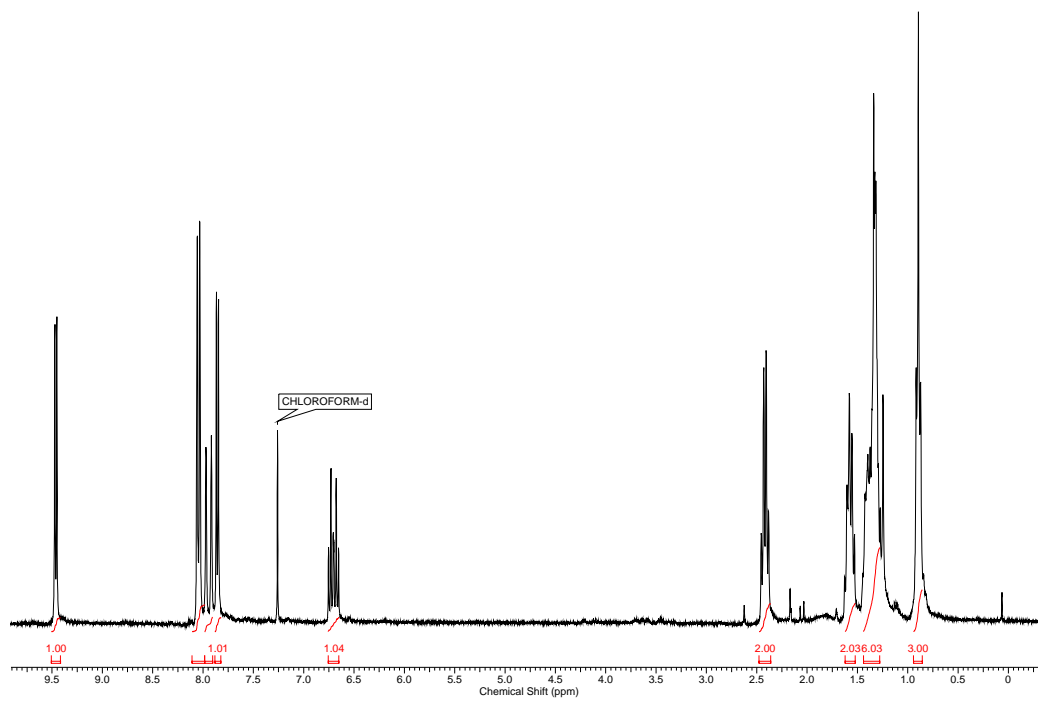
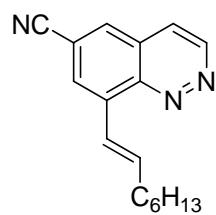
# Ethyl cinnoline-6-carboxylate (7b)



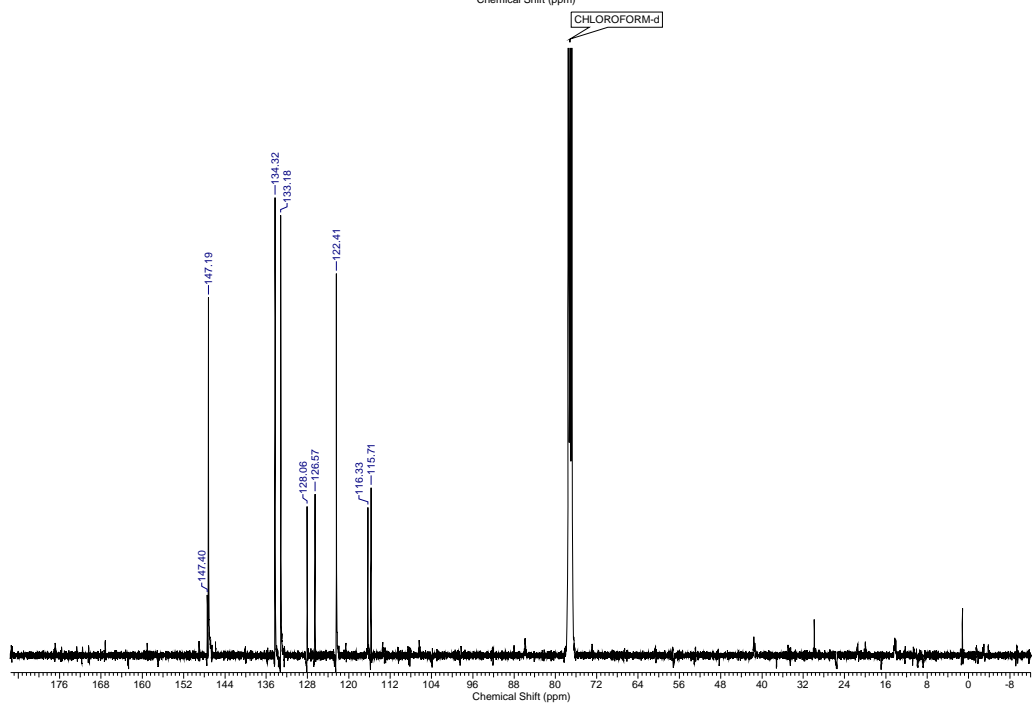
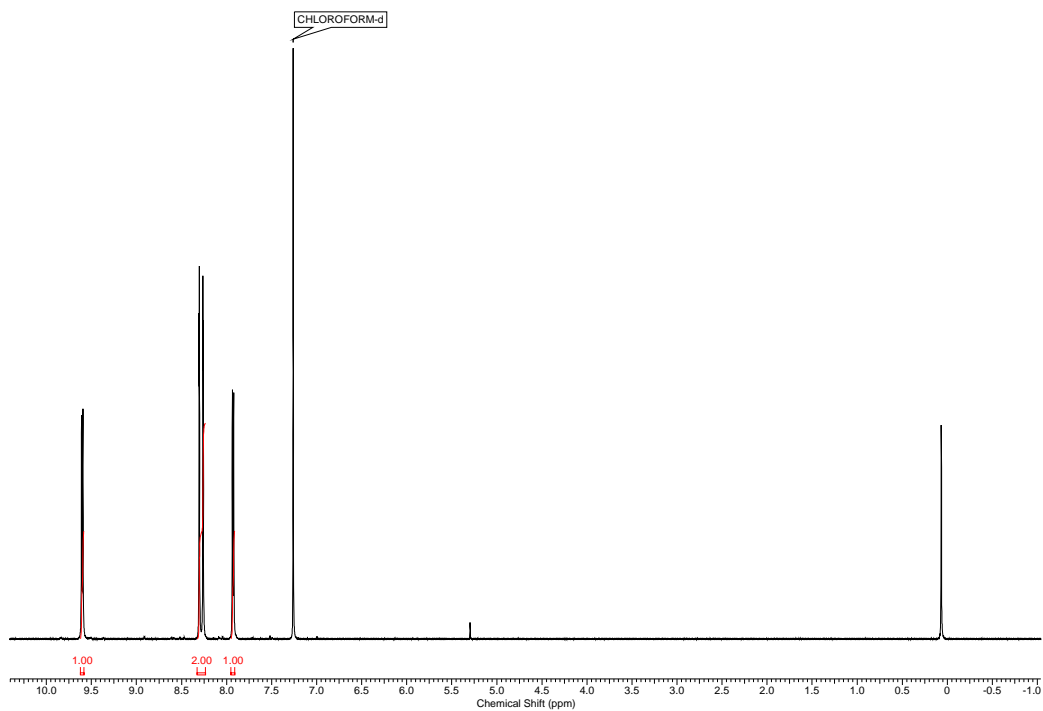
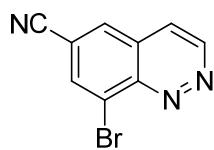
# 8-(3-Methoxyphenyl)cinnoline-6-carbonitrile (8a)



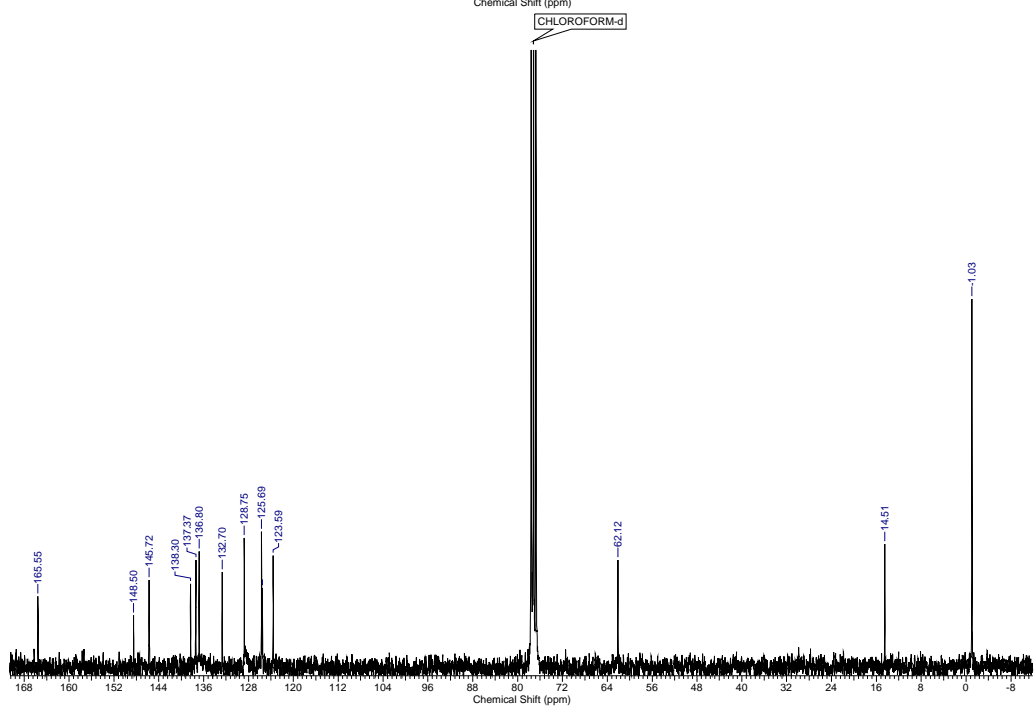
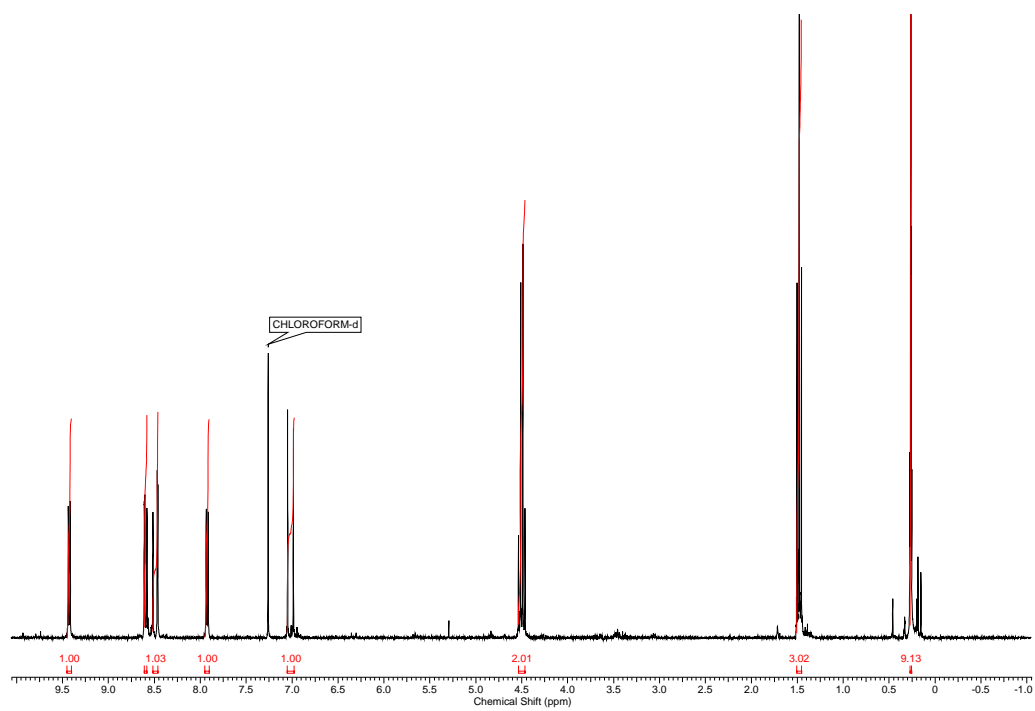
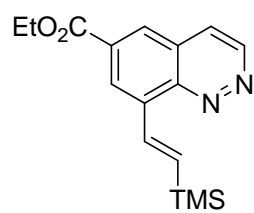
**(E)-8-(Oct-1-en-1-yl)cinnoline-6-carbonitrile (8b)**



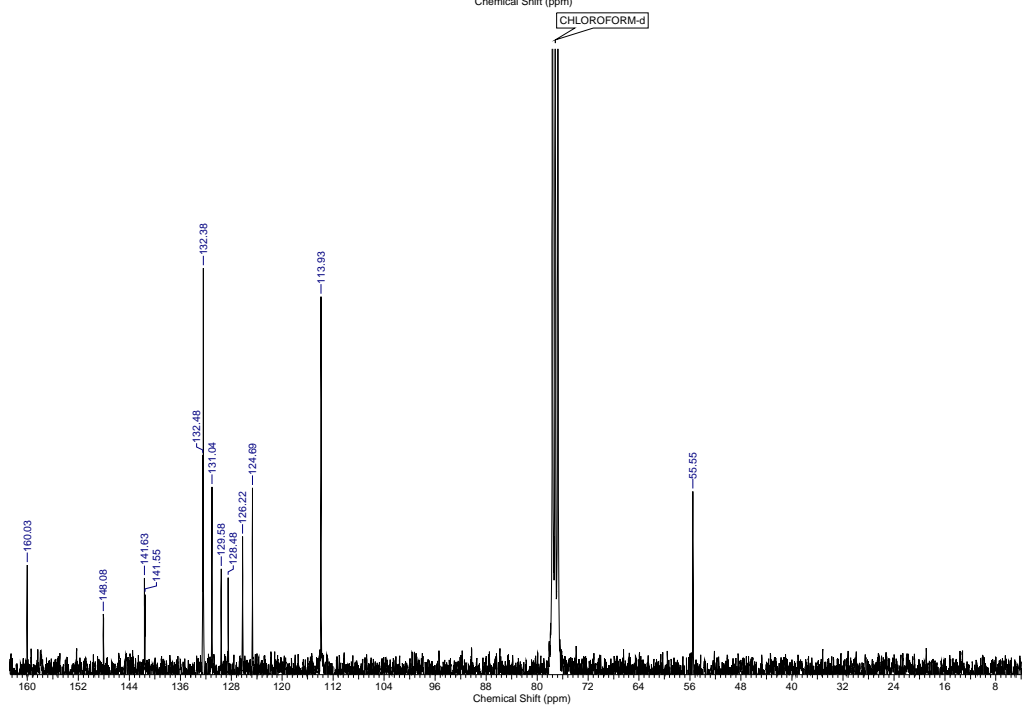
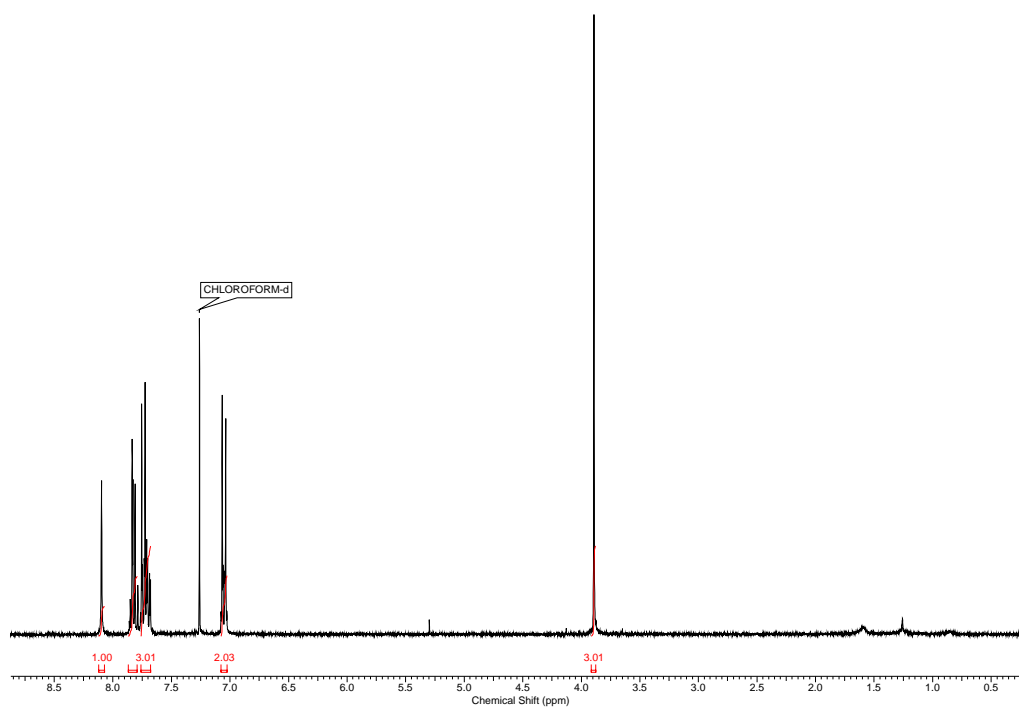
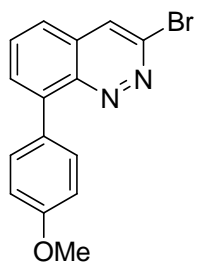
# 8-Bromocinnoline-6-carbonitrile (8c)



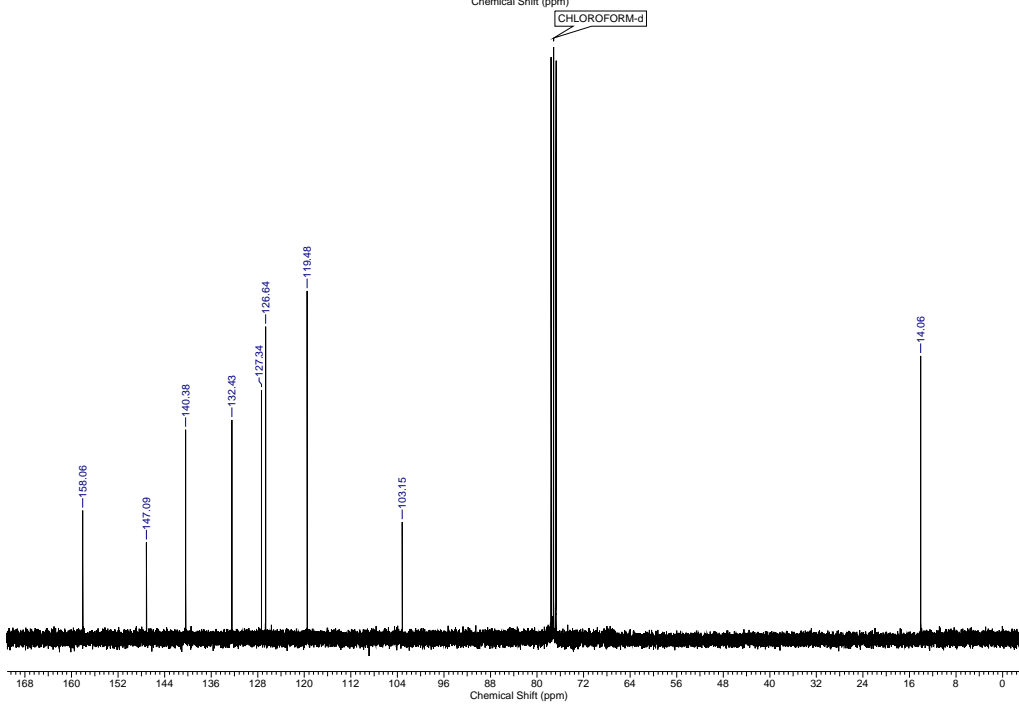
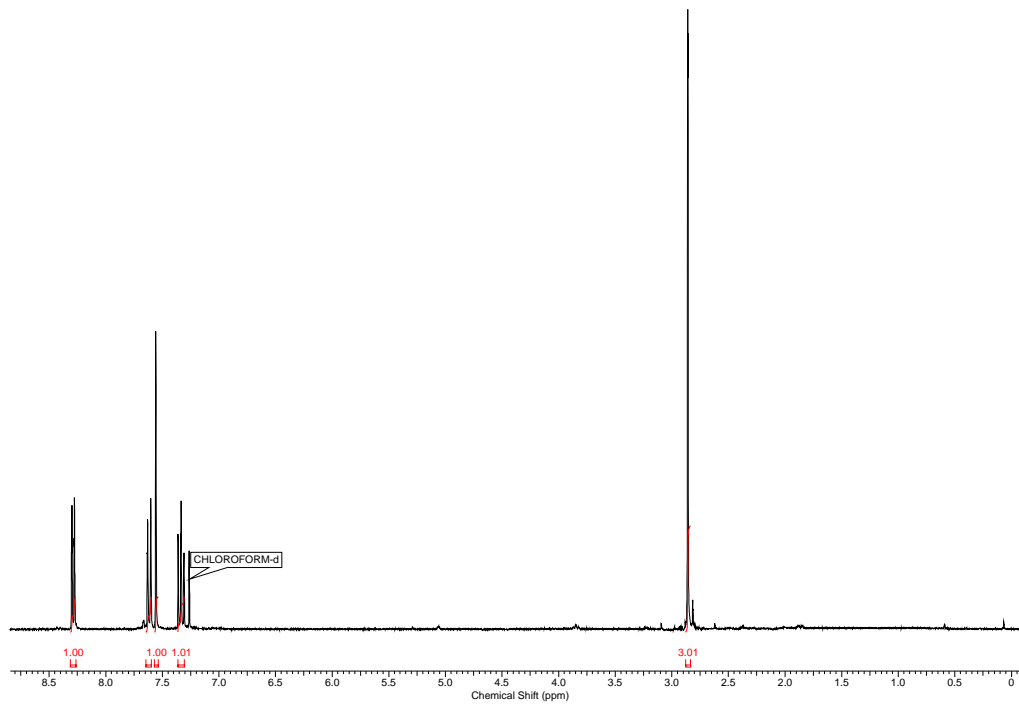
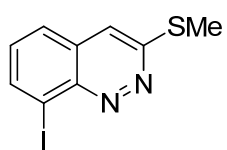
**(E)-Ethyl 8-(2-(trimethylsilyl)vinyl)cinnoline-6-carboxylate (8d)**



### 3-Bromo-8-(4-methoxyphenyl)cinnoline (8e)



# 8-Iodo-3-(methylthio)cinnoline (8f)



**(E)-3-(4-Methoxyphenyl)-8-(oct-1-en-1-yl)cinnoline (8g)**

