Supporting Information

Catalytic dearomatization approach to quinolizidine alkaloids: Five step total synthesis of (±)-lasubine II

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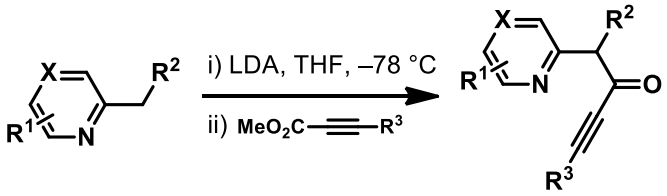
General information

Except where stated, all reagents were purchased from commercial sources and used without further purification. Anhydrous THF was obtained by distillation over sodium benzophenone ketyl immediately before use. ^{1}H NMR and ^{13}C NMR spectra were recorded on a JEOL ECX400 or JEOL ECS400 spectrometer, operating at 400 MHz and 100 MHz, respectively. All spectral data was acquired at 295 K. Chemical shifts (δ) are quoted in parts per million (ppm). The residual solvent peaks, δ_H 7.27 and δ_C 77.0 for $CDCl_3$ were used as reference. Coupling constants (*J*) are reported in Hertz (Hz) to the nearest 0.5 Hz. The multiplicity abbreviations used are: s singlet, d doublet, t triplet, q quartet, m multiplet. Signal assignment was achieved by analysis of DEPT, COSY, HMBC and HSQC experiments where required. Infrared (IR) spectra were recorded on a PerkinElmer UATR 2 spectrometer, either as a compressed solid or a thin film dispersed from CH_2Cl_2 or $CDCl_3$. High-resolution mass-spectra were obtained by the University of York Mass Spectrometry Service, using electrospray ionisation (ESI) on a Bruker Daltonics, Micro-tof spectrometer. Melting points were determined using Gallenkamp apparatus. Thin layer chromatography was carried out on Merck silica gel $60F_{254}$ pre-coated aluminium foil sheets and were visualised using UV light (254 nm) and stained with basic aqueous potassium permanganate. Column chromatography and silica gel mediated reactions were carried out using Fluka silica gel (SiO_2), 35–70 μm, 60 Å; column chromatography was carried out under a light positive pressure, eluting with the specified solvent system.

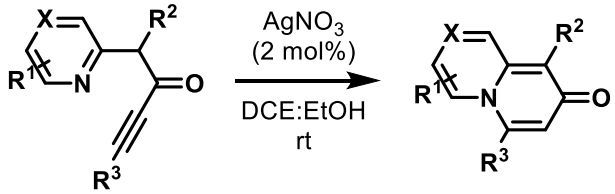
General experimental procedures

General procedure A: pyridine-ynone formation



Based on a modified literature procedure.[1] To a solution of DIPA (2.1 mmol) in THF (15 mL) at 0 °C under argon was added *n*-BuLi (0.85 mL, 2.1 mmol, 2.5 M in hexanes) dropwise. The mixture was stirred at 0 °C for 15 min and then cooled to −78 °C before the 2-alkylpyridine (1.0 mmol) was added dropwise. After stirring at −78 °C for 30 min the methyl propiolate ester (1.05 mmol, neat or in THF) was added and the mixture was stirred at −78 °C for a further 30 min. The reaction was then quenched at −78 °C with water (15 mL) and extracted with EtOAc (3 × 30 mL). The combined organics were dried ($MgSO_4$), concentrated *in vacuo* and purified by column chromatography to afford the pyridine-ynone product.

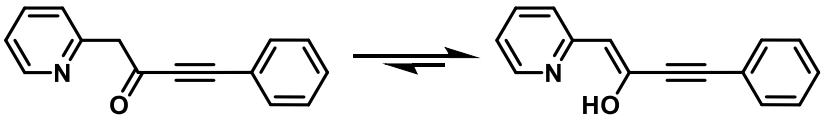
General procedure B: pyridine-ynone cyclisations



To a solution of pyridine-ynone (1 equiv.) in DCE (5 mL/mmol) and EtOH (5 mL/mmol) at RT was added $AgNO_3$ (2 mol%). The reaction mixture was stirred at rt until completion was observed by TLC then concentrated *in vacuo*. The crude product was dissolved in CH_2Cl_2 and purified by column chromatography (typically 5 → 10% MeOH in EtOAc) to afford the desired quinolizinone compound.

Experimental procedures and characterisation data

4-Phenyl-1-(pyridin-2-yl)but-3-yn-2-one (5a)



Synthesised using general procedure A with DIPA (0.60 mL, 4.26 mmol), *n*-BuLi (1.70 mL, 4.26 mmol, 2.5 M in hexanes), 2-methylpyridine (0.20 mL, 2.03 mmol), methyl phenylpropiolate (0.31 mL, 2.13 mmol) and THF (30 mL). Purification by column chromatography (10% EtOAc in hexane) afforded the *title compound* **5a** (316 mg, 70%, 85:15 *enol*:*keto*) as a yellow solid, mp 71–73 °C.

ATR-FTIR ν_{max} (cm^{-1}) 1741, 1694, 1491, 1388, 1366, 1160;

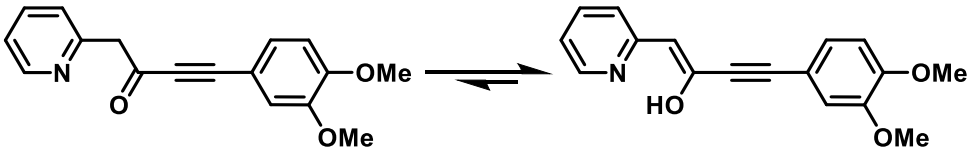
^{1}H NMR δ_H (400 MHz, $CDCl_3$) 4.19 (2H, s, *keto*), 5.90 (1H, s, *enol*), 6.97–7.06 (2H, m, *enol*), 7.24 (1H, dd, *J* = 7.5, 5.0 Hz, *keto*), 7.31–7.40 (6H, m, *enol* + *keto*), 7.41–7.50 (3H, m, *keto*), 7.51–7.59 (2H, m, *enol*), 7.64 (1H, ddd, *J* = 8.0, 8.0, 2.0 Hz, *enol*), 7.71 (1H, ddd, *J* = 8.0, 8.0, 2.0 Hz, *keto*), 8.28 (1H, br d, *J* = 5.0 Hz, *enol*), 8.64 (1H, br d, *J* = 4.5 Hz, *keto*), 15.02 (1H, br s, *enol*);

^{13}C NMR of enol tautomer δ_C (100 MHz, $CDCl_3$) 86.4 (C), 89.6 (C), 103.7 (CH), 119.1 (CH), 121.4 (CH), 122.0 (C), 128.3 (2CH), 128.9 (CH), 131.9 (2CH), 137.4 (CH), 144.0 (CH), 149.5 (C), 157.6 (C);

Characteristic **^{13}C NMR of keto tautomer** δ_C (100 MHz, $CDCl_3$) 54.3 (CH_2);

HRMS (ESI^+): Found: 222.0915; $C_{15}H_{12}NO$ (MH^+) Requires 222.0913 (−0.7 ppm error).

4-(3,4-Dimethoxyphenyl)-1-(pyridin-2-yl)but-3-yn-2-one (5b)



Synthesised using general procedure A with DIPA (2.94 mL, 21.0 mmol), *n*-BuLi (8.4 mL, 21.0 mmol, 2.5 M in hexanes), 2-methylpyridine (0.99 mL, 10.0 mmol) in THF (100 mL) and a solution of ester **XX**[2] (2.31 g, 10.5 mmol) in THF (50 mL). Purification by column chromatography (40% EtOAc in hexane) afforded the *title compound* **5b** (2.11 g, 75%, 77:23 *enol*:*keto*) as a yellow solid, mp 78–80 °C.

ATR-FTIR ν_{max} (cm^{-1}) 2200, 1595, 113, 1252, 1023, 808;

^{1}H NMR δ_H (400 MHz, $CDCl_3$) 3.87 (3H, s, *keto*), 3.89 (3H, s, *enol*), 3.91 (6H, s, *enol* + *keto*), 4.17 (2H, s, *keto*), 5.87 (1H, s, *enol*), 6.80–6.87 (2H, m, *enol* + *keto*), 6.95 (1H, br s, *keto*), 6.97–7.04 (2H,

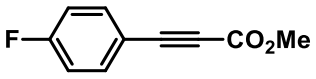
m, *enol*), 7.06 (1H, br s, *enol*), 7.12 (1H, dd, *J* = 8.5, 1.5 Hz, *keto*), 7.16 (1H, dd, *J* = 8.5, 1.5 Hz, *enol*) 7.24 (1H, d, *J* = 7.0, 5.5 Hz, *keto*), 7.33 (1H, d, *J* = 8.0 Hz, *keto*), 7.62 (1H, dd, *J* = 8.0, 7.5 Hz, *enol*), 7.71 (1H, dd, *J* = 7.5, 7.5 Hz, *keto*), 8.24–8.30 (1H, m, *enol*), 8.61–8.65 (1H, m, *keto*), 15.03 (1H, br s, *enol*);

^{13}C NMR of enol tautomer δ_C (100 MHz, $CDCl_3$) 55.86 (CH_3), 55.89 (CH_3), 85.2 (C), 90.0 (C), 103.2 (CH), 110.9 (CH), 114.0 (C), 114.5 (CH), 118.9 (CH), 121.3 (CH), 125.5 (CH), 137.4 (CH), 143.9 (CH), 148.6 (C) 149.8 (C), 150.0 (C), 157.7 (C);

Characteristic **^{13}C NMR of keto tautomer** δ_C (100 MHz, $CDCl_3$) 54.2 (CH_2);

HRMS (ESI^+): Found: 304.0944; $C_{17}H_{15}NNaO_3$ (MNa^+) Requires 304.0944 (−0.1 ppm error), Found: 282.1128; $C_{17}H_{16}NO_3$ (MH^+) Requires 282.1125 (−1.2 ppm error).

Methyl 3-(4-fluorophenyl)propiolate (S1)



To a solution of 1-ethynyl-4-fluorobenzene (533 mg, 4.44 mmol) in THF (44 mL) at −78 °C was added *n*-BuLi (1.95 mL, 4.88 mmol, 2.5 M in hexanes) dropwise. The mixture was stirred at −78 °C for 30 min before methyl chloroformate (0.38 mL, 4.88 mmol) was added dropwise. The mixture was stirred at −78 °C for a further 2 h before being quenched by the careful addition of sat. $NH_4Cl_{(aq)}$ (10 mL) and diluted with Et_2O (20 mL). The organics were separated and the aqueous extracted with Et_2O (3 × 30 mL). The organics were combined, washed with brine, dried ($MgSO_4$), concentrated *in vacuo* and purified by column chromatography (0 → 5% Et_2O in hexane) to afford the *title compound* **S1** (494 mg, 62%) as a white solid, mp 57–59 °C.

ATR-FTIR ν_{max} (cm^{-1}) 2224, 1708, 1304, 1203, 833;

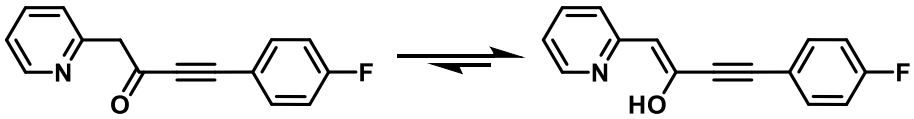
^{1}H NMR δ_H (400 MHz, $CDCl_3$) 3.85 (3H, s), 7.08 (2H, dd, *J* = 8.5, 8.0 Hz), 7.59 (2H, dd, *J* = 8.5, 5.5 Hz);

^{13}C NMR δ_C (100 MHz, $CDCl_3$) 52.8 (CH_3), 80.2 (C), 85.4 (C), 115.6 (C, d, *J* = 4.0 Hz), 116.1 (2CH, d, *J* = 22.0 Hz), 135.3 (2CH, d, *J* = 8.5 Hz), 154.4 (C), 163.9 (C, d, *J* = 254.0 Hz);

^{19}F NMR δ_F (376 MHz, $CDCl_3$) −106.1–−106.2 (1F, m).

Spectroscopic data matched those reported in the literature.[3]

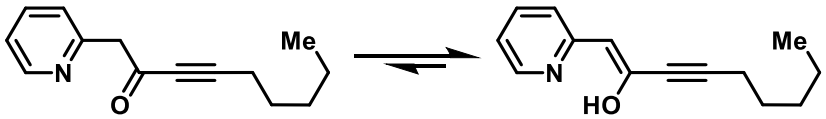
4-(4-Fluorophenyl)-1-(pyridin-2-yl)but-3-yn-2-one (5c)



Synthesised using general procedure A with DIPA (0.30 mL, 2.12 mmol), *n*-BuLi (0.85 mL, 2.12 mmol, 2.5 M in hexanes), 2-methylpyridine (0.1 mL, 1.01 mmol) in THF (10 mL) and a solution of methyl ester **S1** (189 mg, 1.06 mmol) in THF (5 mL). Purification by column chromatography (20% EtOAc in hexane) afforded the *title compound* **5c** (209 mg, 86%, 81:19 *enol*:*keto*) as a yellow solid, mp 74–76 °C.

ATR-FTIR ν_{max} (cm^{-1}) 1620, 1597, 1507, 1374, 1224, 834, 801;
^{1}H NMR δ_H (400 MHz, $CDCl_3$) 4.17 (2H, s, *keto*), 5.87 (1H, s, *enol*), 6.96–7.12 (6H, m, *enol* + *keto*), 7.24 (1H, dd, *J* = 7.5, 5.0 Hz, *keto*), 7.32 (1H, d, *J* = 8.0 Hz, *keto*), 7.44–7.50 (2H, m, *keto*), 7.50–7.57 (2H, m, *enol*), 7.63 (1H, ddd, *J* = 8.0, 8.0, 1.5 Hz, *enol*), 7.71 (1H, ddd, *J* = 8.0, 8.0, 1.5 Hz, *keto*), 8.27 (1H, d, *J* = 5.0 Hz, *enol*), 8.62 (1H, d, *J* = 4.5 Hz, *keto*), 15.04 (1H, br s, *enol*);
^{13}C NMR of enol tautomer δ_C (100 MHz, $CDCl_3$) 86.1 (C), 88.5 (C), 103.6 (CH), 115.7 (2CH, d, *J* = 22.0 Hz), 118.1 (C, d, *J* = 4.0 Hz), 119.1 (CH), 121.4 (CH), 133.9 (2CH, d, *J* = 7.5 Hz), 137.5 (CH), 144.0 (CH), 149.5 (C), 157.5 (C), 162.9 (C, d, *J* = 250.0 Hz);
Characteristic **^{13}C NMR of keto tautomer** δ_C (100 MHz, $CDCl_3$) 54.3 (CH_2);
^{19}F NMR δ_F (376 MHz, $CDCl_3$) −105.7–−105.8 (1F, m, *keto*), −109.4–−109.5 (1F, m, *enol*);
HRMS (ESI^+): Found: 240.0810; $C_{15}H_{11}FNO$ (MH^+) Requires 240.0819 (4.0 ppm error).

1-(Pyridin-2-yl)non-3-yn-2-one (5d)



Synthesised using general procedure A with DIPA (0.30 mL, 2.12 mmol), *n*-BuLi (0.85 mL, 2.12 mmol, 2.5 M in hexanes), 2-methylpyridine (0.1 mL, 1.01 mmol) in THF (15 mL) and methyl 2-octynoate (0.18 mL, 1.06 mmol). Purification by column chromatography (20% EtOAc in hexane) afforded the *title compound* **5d** (154 mg, 71%, 67:37 *enol*:*keto*) as a yellow oil.

ATR-FTIR ν_{max} (cm^{-1}) 2930, 2228, 1618, 1594, 1550, 1470, 1361, 1151, 805, 739;
^{1}H NMR δ_H (400 MHz, $CDCl_3$) 0.89 (3H, t, *J* = 7.5 Hz, *keto*), 0.92 (3H, t, *J* = 7.5 Hz, *enol*), 1.24–1.68 (12H, m, *enol* + *keto*), 2.31 (2H, t, *J* = 7.0 Hz, *keto*), 2.39 (2H, t, *J* = 7.0 Hz, *enol*), 4.06 (2H, s, *keto*), 5.71 (1H, s, *enol*), 6.92–7.01 (2H, m, *enol*), 7.22 (1H, dd, *J* = 7.5, 5.5 Hz, *keto*), 7.24–7.28 (1H,

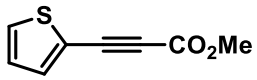
m, *keto*), 7.60 (1H, ddd, *J* = 8.0, 8.0, 1.5 Hz, *enol*), 7.68 (1H, ddd, *J* = 8.0, 8.0, 1.5 Hz, *keto*), 8.25 (1H, br d, *J* = 5.5 Hz, *enol*), 8.59 (1H, br d, *J* = 4.5 Hz, *keto*), 14.87 (1H, br s, *enol*);

^{13}C NMR of enol tautomer δ_C (100 MHz, $CDCl_3$) 13.9 (CH_3), 19.2 (CH_2), 22.2 (CH_2), 27.9 (CH_2), 31.0 (CH_2), 77.9 (C), 91.8 (C), 102.6 (CH), 118.7 (CH), 121.1 (CH), 137.2 (CH), 144.0 (CH), 149.7 (C), 157.8 (C);

Characteristic **^{13}C NMR of keto tautomer** δ_C (100 MHz, $CDCl_3$) 54.4 (CH_2);

HRMS (ESI^+): Found: 216.1385; $C_{14}H_{18}NO$ (MH^+) Requires 216.1383 (−1.0 ppm error).

Methyl 3-(thiophen-2-yl)propiolate (S2)



To a solution of 2-ethynylthiophene (0.5 mL, 4.99 mmol) in THF (50 mL) at −78 °C was added *n*-BuLi (2.20 mL, 5.49 mmol, 2.5 M in hexanes) dropwise. The mixture was stirred at −78 °C for 30 min before methyl chloroformate (0.42 mL, 5.49 mmol) was added dropwise. The mixture was stirred at −78 °C for a further 2 h before being quenched by the careful addition of sat. $NH_4Cl_{(aq)}$ (10 mL) and diluted with EtOAc (20 mL). The organics were separated and the aqueous extracted with EtOAc (3 × 30 mL). The organics were combined, washed with brine, dried ($MgSO_4$), concentrated *in vacuo* and purified by column chromatography (5 → 10% EtOAc in hexane) to afford the *title compound* **S2** (357 mg, 43%) as a yellow solid, mp 49–51 °C.

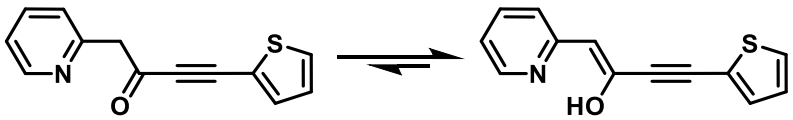
ATR-FTIR ν_{max} (cm^{-1}) 2207, 1709, 1269, 1221, 1160;

^{1}H NMR δ_H (400 MHz, $CDCl_3$) 3.85 (3H, s), 7.07 (1H, dd, *J* = 5.0, 3.5 Hz), 7.48 (1H, dd, *J* = 5.0 Hz), 7.50 (1H, dd, *J* = 3.5 Hz);

^{13}C NMR δ_C (100 MHz, $CDCl_3$) 52.8 (CH_3), 80.5 (C), 84.6 (C), 119.3 (C), 127.5 (CH), 131.2 (CH), 136.6 (CH), 154.3 (C).

Spectroscopic data matched those reported in the literature.[4]

1-(Pyridin-2-yl)-4-(thiophen-2-yl)but-3-yn-2-one (5e)



Synthesised using general procedure A with DIPA (0.30 mL, 2.12 mmol), *n*-BuLi (0.85 mL, 2.12 mmol, 2.5 M in hexanes), 2-methylpyridine (0.1 mL, 1.01 mmol) in THF (10 mL) and a solution of methyl ester **S2** (176 mg, 1.06 mmol) in THF (5 mL). Purification by column chromatography (20% EtOAc in hexane) afforded the *title compound* **5e** (96 mg, 42%, 85:15 *enol*:*keto*) as a yellow oil. (**Note:** this compound degrades overnight when stored at room temperature.)

ATR-FTIR ν_{max} (cm^{-1}) 2198, 1615, 1552, 1472, 705;

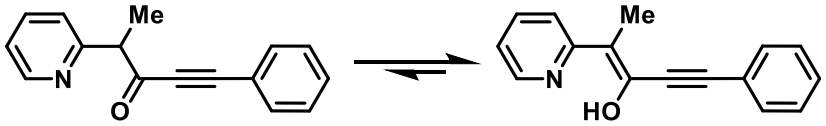
^{1}H NMR δ_H (400 MHz, $CDCl_3$) 4.17 (2H, s, *keto*), 5.87 (1H, s, *enol*), 6.98–7.08 (4H, m, *enol* + *keto*), 7.21–7.28 (2H, m, *keto*), 7.34 (2H, d, *J* = 4.5 Hz, *enol*), 7.41 (1H, d, *J* = 3.5 Hz, *keto*), 7.49 (1H, d, *J* = 5.5 Hz, *keto*), 7.63 (1H, ddd, *J* = 7.5, 7.5, 1.0 Hz, *enol*), 7.71 (1H, ddd, *J* = 7.5, 7.5, 1.0 Hz, *keto*), 8.26 (1H, br d, *J* = 5.0 Hz, *enol*), 8.62 (1H, br d, *J* = 4.5 Hz, *keto*), 15.07 (1H, br s, *enol*);

^{13}C NMR of enol tautomer δ_C (100 MHz, $CDCl_3$) 83.1 (C), 90.1 (C), 103.5 (CH), 119.0 (CH), 121.5 (CH), 122.0 (C), 127.2 (CH), 128.4 (CH), 133.3 (CH), 137.5 (CH), 143.8 (CH), 149.7 (C), 157.5 (C);

Characteristic **^{13}C NMR of keto tautomer** δ_C (100 MHz, $CDCl_3$) 54.0 (CH_2);

HRMS (ESI^+): Found: 228.0470; $C_{13}H_{10}NOS$ (MH^+) Requires 228.0478 (3.5 ppm error).

1-Phenyl-4-(pyridin-2-yl)pent-1-yn-3-one (5f)



Synthesised using general procedure A with DIPA (0.52 mL, 3.68 mmol), *n*-BuLi (1.47 mL, 3.68 mmol, 2.5 M in hexanes), 2-ethylpyridine (0.20 mL, 1.75 mmol), methyl phenylpropiolate (0.27 mL, 1.84 mmol) and THF (26 mL). Purification by column chromatography (20% EtOAc in hexane) afforded the *title compound* **5f** (138 mg, 33%, 97:3 *enol*:*keto*) as a yellow/green oil. (**Note**: this compound degrades overnight when stored at room temperature.)

ATR-FTIR ν_{max} (cm^{-1}) 1589, 1551, 1488, 1461, 755, 690;

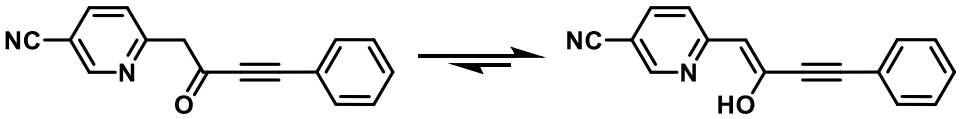
^{1}H NMR of enol tautomer δ_H (400 MHz, $CDCl_3$) 2.26 (3H, s), 7.11 (1H, d, *J* = 7.0, 5.5 Hz), 7.26 (1H, d, *J* = 8.0 Hz), 7.32–7.40 (3H, m), 7.54–7.61 (2H, m), 7.76 (1H, ddd, *J* = 8.0, 8.0, 1.0 Hz), 8.39 (1H, br d, *J* = 4.5 Hz, *enol*), 15.73 (1H, br s, *enol*);

^{13}C NMR of enol tautomer δ_C (100 MHz, $CDCl_3$) 15.4 (CH_3), 85.6 (C), 94.4 (C), 108.3 (C), 119.4 (CH), 119.7 (CH), 122.4 (C), 128.3 (2CH), 128.8 (CH), 131.7 (2CH), 137.6 (CH), 144.6 (CH), 145.1 (C), 159.2 (C);

Characteristic **^{13}C NMR of keto tautomer** δ_C (100 MHz, $CDCl_3$) 56.9 (CH);

HRMS (ESI^+): Found: 258.0887 $C_{16}H_{13}NNaO$ (MNa^+) Requires 258.0889 (0.7 ppm error), Found: 236.1078; $C_{16}H_{14}NO$ (MH^+) Requires 236.1070 (−3.5 ppm error).

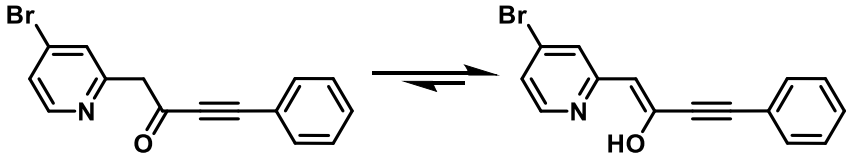
6-(2-Oxo-4-phenylbut-3-yn-1-yl)nicotinonitrile (5g)



Synthesised using general procedure A with DIPA (0.29 mL, 2.1 mmol), *n*-BuLi (0.84 mL, 2.1 mmol, 2.5 M in hexanes) in THF (10 mL), a solution of 5-Cyano-2-picoline (118 mg, 1.0 mmol) in THF (5 mL) and methyl phenylpropiolate (0.16 mL, 1.1 mmol). Purification by column chromatography (10% EtOAc in hexane) afforded the *title compound* **5g** (145 mg, 59%, 96:4 *enol*:*keto*) as a yellow solid, mp 126–128 °C.

ATR-FTIR ν_{max} (cm^{-1}) 2227, 2196, 1638, 1587, 1521, 1162, 837, 749, 688, 551;
^{1}H NMR of enol tautomer δ_H (400 MHz, $CDCl_3$) 5.97 (1H, s), 7.09 (1H, d, *J* = 9.0 Hz), 7.34–7.44 (3H, m), 7.53–7.60 (2H, m), 7.83 (1H, dd, *J* = 9.0, 2.0 Hz), 8.63 (1H, d, *J* = 2.0 Hz), 14.03 (1H, br s);
^{13}C NMR of enol tautomer δ_C (100 MHz, $CDCl_3$) 85.3 (C), 92.3 (C), 104.3 (CH), 104.5 (C), 116.7 (C), 121.18 (CH), 121.24 (C), 128.5 (2CH), 129.6 (CH), 132.1 (2CH), 139.4 (CH), 149.3 (CH), 151.0 (C), 160.6 (C);
Characteristic **^{13}C NMR of keto tautomer** δ_C (100 MHz, $CDCl_3$) 54.1 (CH_2);
HRMS (ESI^+): Found: 247.0869; $C_{16}H_{11}N_2O$ (MH^+) Requires 247.0866 (−1.2 ppm error).

1-(4-Bromopyridin-2-yl)-4-phenylbut-3-yn-2-one (5h)



Synthesised using general procedure A with DIPA (0.25 mL, 1.76 mmol), *n*-BuLi (0.70 mL, 1.76 mmol, 2.5 M in hexanes), 4-bromo-2-methylpyridine (0.10 mL, 0.84 mmol), methyl phenylpropiolate (0.14 mL, 0.92 mmol) and THF (13 mL). Purification by column chromatography (10% EtOAc in hexane) afforded the *title compound* **5h** (221 mg, 88%, 76:24 *enol*:*keto*) as a yellow solid, mp 93–95 °C.

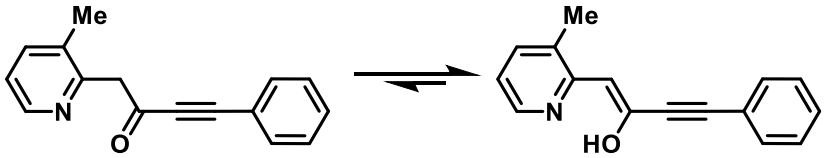
ATR-FTIR ν_{max} (cm^{-1}) 2202, 1616, 1573, 1531, 756, 690;
^{1}H NMR δ_H (400 MHz, $CDCl_3$) 4.17 (2H, s, *keto*), 5.84 (1H, s, *enol*), 7.19–7.24 (2H, m, *enol*), 7.33–7.48 (7H, m, *enol* + *keto*), 7.50–7.59 (5H, m, *enol* + *keto*), 8.16 (1H, d, *J* = 6.0 Hz, *enol*), 8.44 (1H, d, *J* = 5.5 Hz, *keto*), 14.46 (1H, br s, *enol*);

^{13}C NMR of enol tautomer δ_C (100 MHz, $CDCl_3$) 85.7 (C), 90.7 (C), 103.6 (CH), 121.7 (C), 122.8 (CH), 124.1 (CH), 128.4 (2CH), 129.2 (CH), 132.0 (2CH), 133.8 (C), 145.8 (CH), 149.1 (C), 158.8 (C);

Characteristic **^{13}C NMR of keto tautomer** δ_C (100 MHz, $CDCl_3$) 53.8 (CH_2);

HRMS (ESI^+): Found: 300.0006; $C_{15}H_{11}{}^{79}BrNO$ (MH^+) Requires 300.0019 (4.3 ppm error).

1-(3-Methylpyridin-2-yl)-4-phenylbut-3-yn-2-one (5i)



Synthesised using general procedure A with DIPA (0.26 mL, 1.85 mmol), *n*-BuLi (0.74 mL, 1.85 mmol, 2.5 M in hexanes), 2,3-lutidine (0.10 mL, 0.88 mmol), methyl phenylpropiolate (0.14 mL, 0.92 mmol) and THF (13 mL). Purification by column chromatography (30% EtOAc in hexane) afforded the *title compound* **5i** (165 mg, 80%, 92:8 *enol*:*keto*) as a yellow solid, mp 76–78 °C.

ATR-FTIR ν_{max} (cm^{-1}) 2202, 1589, 1562, 1435, 757, 690;

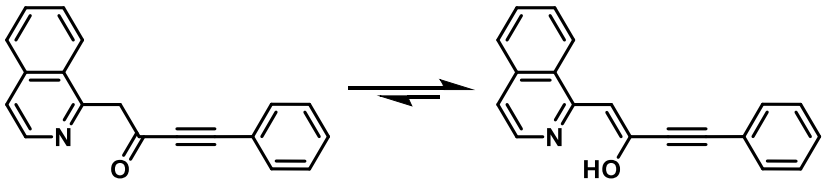
^{1}H NMR δ_H (400 MHz, $CDCl_3$) 2.28 (3H, s, *enol*), 2.34 (3H, s, *keto*), 4.22 (2H, s, *keto*), 5.88 (1H, s, *enol*), 6.87 (1H, dd, *J* = 7.5, 5.5 Hz, *enol*), 7.17 (1H, dd, *J* = 7.5, 5.0 Hz, *keto*), 7.32–7.40 (6H, m, *enol* + *keto*), 7.42–7.48 (3H, m, *enol* + *keto*), 7.52 (1H, d, *J* = 8.0 Hz, *keto*), 7.55–7.60 (2H, m, *enol*), 7.98 (1H, br d, *J* = 5.0 Hz, *enol*), 8.47 (1H, br d, *J* = 4.0 Hz, *keto*), 16.18 (1H, br s, *enol*);

^{13}C NMR of enol tautomer δ_C (100 MHz, $CDCl_3$) 18.3 (CH_3), 87.7 (C), 88.5 (C), 97.9 (CH), 117.4 (CH), 122.1 (C), 128.3 (2CH), 128.9 (CH), 129.0 (C), 132.0 (2CH), 138.1 (CH), 138.5 (CH), 154.6 (C), 155.9 (C);

Characteristic **^{13}C NMR of keto tautomer** δ_C (100 MHz, $CDCl_3$) 52.6 (CH_2);

HRMS (ESI^+): Found: 236.1062; $C_{16}H_{14}NO$ (MH^+) Requires 236.1070 (3.3 ppm error).

1-(Isoquinolin-1-yl)-4-phenylbut-3-yn-2-one (5j)



Synthesised using general procedure A with DIPA (0.22 mL, 1.58 mmol), *n*-BuLi (0.63 mL, 1.58 mmol, 2.5 M in hexanes), 1-methylisoquinoline (0.10 mL, 0.75 mmol), methyl phenylpropiolate (0.12 mL, 0.79 mmol) and THF (11 mL). Purification by column chromatography (40% EtOAc in

hexane) afforded the *title compound* **5j** (166 mg, 81%, >99:1 *enol*:*keto*) as a yellow solid, mp 123–125 °C.

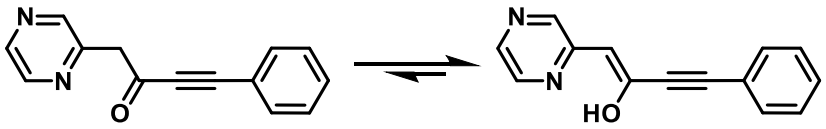
ATR-FTIR ν_{max} (cm^{-1}) 1588, 1550, 1493, 1250, 1207, 1143;

^{1}H NMR of enol tautomer δ_H (400 MHz, $CDCl_3$) 6.42 (1H, s), 6.90 (1H, d, *J* = 6.5 Hz), 7.33–7.45 (4H, m), 7.56 (1H, dd, *J* = 8.5, 7.5 Hz), 7.58–7.65 (3H, m), 7.70 (1H, dd, *J* = 7.5, 7.5 Hz), 8.14 (1H, d, *J* = 8.5 Hz), 15.67 (1H, br s);

^{13}C NMR of enol tautomer δ_C (100 MHz, $CDCl_3$) 86.6 (C), 90.2 (C), 92.6 (CH), 112.1 (CH), 121.8 (C), 123.8 (C), 124.7 (CH), 127.1 (CH), 127.7 (CH), 127.8 (CH), 128.3 (2CH), 129.2 (CH), 132.3 (CH), 132.4 (2CH), 135.6 (C), 154.0 (C), 168.8 (C)

HRMS (ESI^+): Found: 294.0890; $C_{19}H_{13}NNaO$ (MNa^+) Requires 294.0889 (−0.1 ppm error), Found: 272.1069; $C_{19}H_{14}NO$ (MH^+) Requires 272.1070 (0.4 ppm error).

4-Phenyl-1-(pyrazin-2-yl)but-3-yn-2-one (5k)



Synthesised using general procedure A with DIPA (0.30 mL, 2.12 mmol), *n*-BuLi (0.85 mL, 2.12 mmol, 2.5 M in hexanes), 2-methylpyrazine (0.09 mL, 1.01 mmol), methyl phenylpropiolate (0.16 mL, 1.06 mmol) and THF (15 mL) (**Note:** Reaction stirred at −78 °C for 1 h after the addition of the methyl ester). Purification by column chromatography (20 → 40% EtOAc in hexane) afforded the *title compound* **5k** (77 mg, 35%, 95:5 *enol*:*keto*) as a pale brown solid, mp 42–44 °C.

ATR-FTIR ν_{max} (cm^{-1}) 1618, 1506, 1117, 755;

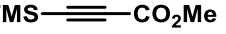
^{1}H NMR of enol tautomer δ_H (400 MHz, $CDCl_3$) 6.00 (1H, s), 7.34–7.44 (3H, m), 7.53–7.61 (2H, m), 8.30–8.38 (2H, m), 8.42 (1H, s), 13.26 (1H, br s);

^{13}C NMR of enol tautomer δ_C (100 MHz, $CDCl_3$) 85.1 (C), 91.5 (C), 102.3 (CH), 121.5 (C), 128.4 (2CH), 129.4 (CH), 132.0 (2CH), 140.0 (CH), 140.4 (CH), 143.8 (CH), 148.5 (C), 153.3 (C);

Characteristic **^{13}C NMR of keto tautomer** δ_C (100 MHz, $CDCl_3$) 51.5 (CH_2);

HRMS (ESI^+): Found: 245.0692; $C_{14}H_{10}N_2NaO$ (MNa^+) Requires 245.0685 (−2.6 ppm error).

Methyl 3-(trimethylsilyl)propiolate (S3)

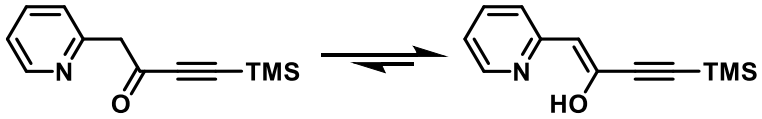


To a solution of ethynyltrimethylsilane (0.5 mL, 3.62 mmol) in THF (36 mL) at −78 °C was added *n*-BuLi (1.59 mL, 3.98 mmol, 2.5 M in hexanes) dropwise. The mixture was stirred at −78 °C for 30 min before methyl chloroformate (0.31 mL, 3.98 mmol) was added dropwise.

The mixture was stirred at −78 °C for a further 2 h before being quenched by the careful addition of sat. $NH_4Cl_{(aq)}$ (10 mL) and diluted with EtOAc (20 mL). The organics were separated and the aqueous extracted with EtOAc (3 × 30 mL). The organics were combined, washed with brine, dried ($MgSO_4$), concentrated *in vacuo* and purified by column chromatography (0 → 5% EtOAc in hexane) to afford the *title compound* **S3** (271 mg, 48%) as a colourless oil.

^{1}H NMR δ_H (400 MHz, $CDCl_3$) 0.25 (9H, s), 3.78 (3H, s);
^{13}C NMR δ_C (100 MHz, $CDCl_3$) −0.9 ($3CH_3$), 52.7 (CH_3), 94.3 (C), 99.9 (C), 192.2 (C).
Spectroscopic data matched those reported in the literature.[5]

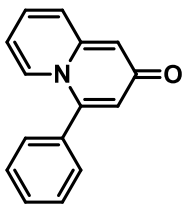
1-(Pyridin-2-yl)-4-(trimethylsilyl)but-3-yn-2-one (5l)



Synthesised using general procedure A with DIPA (0.49 mL, 3.47 mmol), *n*-BuLi (1.39 mL, 3.47 mmol, 2.5 M in hexanes), 2-methylpyridine (0.16 mL, 1.65 mmol) in THF (16.5 mL) and a solution of methyl ester **S3** (270 mg, 1.73 mmol) in THF (9 mL). Purification by column chromatography (15% EtOAc in hexane) afforded the *title compound* **5l** (240 mg, 67%, 91:9 *enol*:*keto*) as a yellow oil.

ATR-FTIR ν_{max} (cm^{-1}) 1617, 1595, 1552, 1472, 1249, 1149, 932, 843;
^{1}H NMR δ_H (400 MHz, $CDCl_3$) 0.18 (9H, s, *keto*), 0.25 (9H, s, *enol*), 4.07 (2H, s, *keto*), 5.82 (1H, s, *enol*), 6.98 (1H, d, *J* = 8.0 Hz, *enol*), 7.02 (1H, dd, *J* = 7.5, 5.0 Hz, *enol*), 7.22 (1H, dd, *J* = 7.5, 5.0 Hz, *keto*), 7.26 (1H, d, *J* = 8.0 Hz, *keto*), 7.62 (1H, ddd, *J* = 8.0, 7.5, 1.5 Hz, *enol*), 7.68 (1H, ddd, *J* = 8.0, 7.5, 1.5 Hz, *keto*), 8.28 (1H, br d, *J* = 5.0 Hz, *enol*), 8.59 (1H, br d, *J* = 5.0 Hz, *keto*), 14.78 (1H, br s, *enol*);
^{13}C NMR of enol tautomer δ_C (100 MHz, $CDCl_3$) −0.4 ($3CH_3$), 95.6 (C), 101.1 (C), 104.3 (CH), 119.3 (CH), 121.4 (CH), 137.4 (CH), 144.4 (CH), 148.3 (C), 157.6 (C);
Characteristic **^{13}C NMR of keto tautomer** δ_C (100 MHz, $CDCl_3$) 54.1 (CH_2);
HRMS (ESI^+): Found: 218.0988; $C_{12}H_{16}NOSi$ (MH^+) Requires 218.0996 (3.6 ppm error).

4-Phenyl-2*H*-quinolizin-2-one (6a)

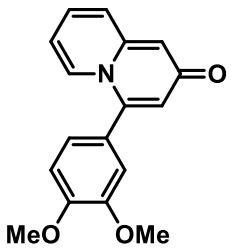


Synthesised using general procedure B with pyridine-ynone **5a** (66 mg, 0.3 mmol), $AgNO_3$ (1.0 mg, 6.0 μmol) in DCE (1.5 mL) and EtOH (1.5 mL) for 2 h. Purification by column chromatography (5 → 20% MeOH in EtOAc) afforded the

title compound **6a** (64 mg, 97%) as a pale brown solid, mp 174–176 °C.

ATR-FTIR ν_{max} (cm^{-1}) 3378, 1620, 1576, 1505, 749, 703;
^{1}H NMR δ_H (400 MHz, $CDCl_3$) 6.42 (1H, dd, *J* = 7.5, 6.5 Hz), 6.63 (1H, br s), 6.75 (1H, br s), 7.06 (1H, dd, *J* = 8.5, 6.5 Hz), 7.19 (1H, d, *J* = 8.5 Hz), 7.37–7.45 (2H, m), 7.50–7.59 (3H, m), 7.62 (1H, d, *J* = 7.5 Hz);
^{13}C NMR δ_C (100 MHz, $CDCl_3$) 111.6 (CH), 111.9 (CH), 124.5 (CH), 124.7 (CH), 128.4 (CH), 129.0 (2CH), 129.3 (CH), 129.5 (2CH), 130.1 (CH), 132.9 (C), 144.8 (C), 145.8 (C), 175.5 (C);
HRMS (ESI^+): Found: 244.0738; $C_{15}H_{11}NNaO$ (MNa^+) Requires 244.0733 (−2.1 ppm error), Found: 222.0923; $C_{15}H_{12}NO$ (MH^+) Requires 222.0913 (−4.5 ppm error).

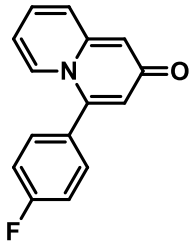
4-(3,4-Dimethoxyphenyl)-2*H*-quinolizin-2-one (6b)



Synthesised using general procedure B with pyridine-ynone **5b** (2.11 g, 7.50 mmol), $AgNO_3$ (25.5 mg, 0.15 mmol) in DCE (37.5 mL) and EtOH (37.5 mL) for 4 h. Purification by column chromatography (5 → 20% MeOH in EtOAc) afforded the *title compound* **6b** (2.09 g, 99%) as a pale brown solid, mp 211–213 °C.

ATR-FTIR ν_{max} (cm^{-1}) 3379, 1622, 1576, 1516, 1491, 1263, 1022, 756;
^{1}H NMR δ_H (400 MHz, $CDCl_3$) 3.88 (3H, s), 3.95 (3H, s), 6.44 (1H, ddd, *J* = 8.0, 6.5, 1.5 Hz), 6.62 (1H, d, *J* = 2.5 Hz), 6.77 (1H, d, *J* = 2.5 Hz), 6.89 (1H, d, *J* = 1.5 Hz), 6.96–7.03 (2H, m), 7.06 (1H, dd, *J* = 9.0, 6.5 Hz), 7.20 (1H, br d, *J* = 9.0 Hz), 7.72 (1H, d, *J* = 8.0 Hz);
^{13}C NMR δ_C (100 MHz, $CDCl_3$) 56.0 (CH_3), 56.1 (CH_3), 111.4 (CH), 111.6 (CH), 111.8 (CH), 111.9 (CH), 121.9 (CH), 124.4 (CH), 124.7 (CH), 125.2 (C), 128.4 (CH), 129.5 (CH), 144.8 (C), 145.7 (C), 149.6 (C), 150.3 (C), 175.4 (C);
HRMS (ESI^+): Found: 282.1121; $C_{17}H_{16}NO_3$ (MH^+) Requires 282.1125 (1.3 ppm error).

4-(4-Fluorophenyl)-2*H*-quinolizin-2-one (6c)



Synthesised using general procedure B with pyridine-ynone **5c** (72 mg, 0.3 mmol), $AgNO_3$ (1.0 mg, 6.0 μmol) in DCE (1.5 mL) and EtOH (1.5 mL) for 2 h. Purification by column chromatography (5 → 10% MeOH in EtOAc) afforded the *title compound* **6c** (72 mg, 100%) as a pale brown solid, mp 244–246 °C.

ATR-FTIR ν_{max} (cm^{-1}) 3380, 1623, 1577, 1515, 1486;

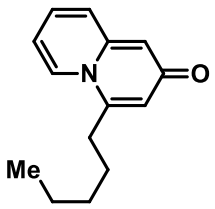
^{1}H NMR δ_H (400 MHz, $CDCl_3$) 6.42 (1H, dd, *J* = 7.0, 7.0 Hz), 6.60 (1H, d, *J* = 2.5 Hz), 6.71 (1H, d, *J* = 2.5 Hz), 7.05 (1H, dd, *J* = 9.0, 7.0 Hz), 7.18 (1H, d, *J* = 9.0 Hz), 7.21–7.29 (2H, m), 7.38–7.45 (2H, m), 7.57 (1H, br d, *J* = 7.0 Hz);

^{13}C NMR δ_C (100 MHz, $CDCl_3$) 111.8 (CH), 111.9 (CH), 116.8 (2CH, d, *J* = 22.0 Hz), 124.7 (CH), 124.9 (CH), 128.3 (CH), 129.0 (C, d, *J* = 4.0 Hz), 129.1 (CH), 131.2 (2CH, d, *J* = 8.5 Hz), 144.6 (C), 144.8 (C), 163.5 (C, d, *J* = 251.0 Hz), 175.5 (C);

^{19}F NMR δ_F (376 MHz, $CDCl_3$) −109.4–−109.5 (1F, m, *keto*);

HRMS (ESI^+): Found: 240.0825; $C_{15}H_{11}FNO$ (MH^+) Requires 240.0819 (−2.2 ppm error).

4-Pentyl-2*H*-quinolizin-2-one (6d)



Synthesised using general procedure B with pyridine-ynone **5d** (153 mg, 0.711 mmol), $AgNO_3$ (2.4 mg, 14.2 μmol) in DCE (3.6 mL) and EtOH (3.6 mL) for 3 h. Purification by column chromatography (5 → 10% MeOH in EtOAc) afforded the *title compound* **6d** (149 mg, 97%) as a pale brown solid, mp 69–71 °C.

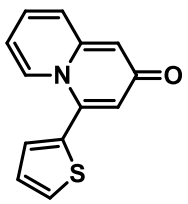
ATR-FTIR ν_{max} (cm^{-1}) 3369, 1622, 1574, 1489, 1177, 726;

^{1}H NMR δ_H (400 MHz, $CDCl_3$) 0.93 (3H, t, *J* = 7.0 Hz), 1.33–1.50 (4H, m), 1.74 (2H, tt, *J* = 8.0, 7.0 Hz), 2.84 (2H, t, *J* = 8.0 Hz), 6.58 (1H, d, *J* = 2.5 Hz), 6.64 (1H, dd, *J* = 7.5, 6.5 Hz), 6.77 (1H, d, *J* = 2.5 Hz), 7.09 (1H, dd, *J* = 9.0, 7.5 Hz), 7.20 (1H, d, *J* = 9.0 Hz), 7.57 (1H, br d, *J* = 7.5 Hz);

^{13}C NMR δ_C (100 MHz, $CDCl_3$) 13.8 (CH_3), 22.3 (CH_2), 26.2 (CH_2), 31.3 (CH_2), 32.4 (CH_2), 111.3 (CH), 112.4 (CH), 122.8 (CH), 125.2 (CH), 127.1 (CH), 127.9 (CH), 145.0 (C), 145.1 (C), 175.9 (C);

HRMS (ESI^+): Found: 216.1381; $C_{14}H_{18}NO$ (MH^+) Requires 216.1383 (1.1 ppm error).

4-(Thiophen-2-yl)-2*H*-quinolizin-2-one (6e)



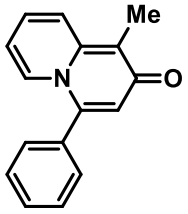
Synthesised using general procedure B with pyridine-ynone **5e** (80 mg, 0.352 mmol), $AgNO_3$ (1.2 mg, 7.0 μmol) in DCE (1.8 mL) and EtOH (1.8 mL) for 9 h. Purification by column chromatography (5 → 10% MeOH in EtOAc) afforded the *title compound* **6e** (47 mg, 59%) as a brown oil.

ATR-FTIR ν_{max} (cm^{-1}) 3379, 1618, 1577, 1485, 754;

^{1}H NMR δ_H (400 MHz, $CDCl_3$) 6.49 (1H, ddd, *J* = 7.0, 7.0, 1.5 Hz), 6.64 (1H, d, *J* = 2.5 Hz), 6.93 (1H, d, *J* = 2.5 Hz), 7.08 (1H, dd, *J* = 8.0, 7.0 Hz), 7.20 (1H, d, *J* = 8.0 Hz), 7.22 (1H, dd, *J* = 5.0, 3.5 Hz); 7.29 (1H, dd, *J* = 3.5, 1.0 Hz), 7.60 (1H, dd, *J* = 5.0, 1.0 Hz), 7.89 (1H, d, *J* = 7.0 Hz);

^{13}C NMR δ_C (100 MHz, $CDCl_3$) 112.0 (CH), 112.2 (CH), 124.6 (CH), 126.6 (CH), 127.9 (CH), 128.7 (CH), 129.1 (CH), 129.3 (CH), 130.1 (CH), 132.7 (C), 138.7 (C), 145.1 (C), 175.2 (C);
HRMS (ESI^+): Found: 228.0474; $C_{13}H_{10}NOS$ (MH^+) Requires 228.0478 (1.7 ppm error).

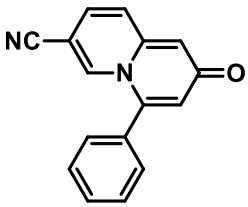
1-Methyl-4-phenyl-2*H*-quinolizin-2-one (6f)



Synthesised using general procedure B with pyridine-ynone **5f** (42 mg, 0.178 mmol), $AgNO_3$ (0.6 mg, 3.6 μmol) in DCE (0.9 mL) and EtOH (0.9 mL) for 18 h. Purification by column chromatography (5 → 10% MeOH in EtOAc) afforded the *title compound* **6f** (19 mg, 45%) as a brown oil.

ATR-FTIR ν_{max} (cm^{-1}) 3401, 1622, 1560, 1508, 761, 703;
^{1}H NMR δ_H (400 MHz, $CDCl_3$) 2.34 (3H, s), 6.41 (1H, ddd, *J* = 7.5, 7.0, 1.5 Hz), 6.80 (1H, s), 7.11 (1H, dd, *J* = 9.0, 7.0 Hz), 7.37–7.43 (2H, m), 7.47 (1H, d, *J* = 9.0 Hz), 7.51–7.57 (3H, m), 7.68 (1H, d, *J* = 7.5 Hz);
^{13}C NMR δ_C (100 MHz, $CDCl_3$) 10.3 (CH_3), 111.0 (CH), 118.1 (C), 122.0 (CH), 122.5 (CH), 127.7 (CH), 129.1 (CH), 129.4 (CH), 129.9 (CH), 130.0 (CH), 133.5 (C), 141.6 (C), 144.3 (C), 174.4 (C);
HRMS (ESI^+): Found: 236.1071; $C_{16}H_{14}NO$ (MH^+) Requires 236.1070 (−0.3 ppm error).

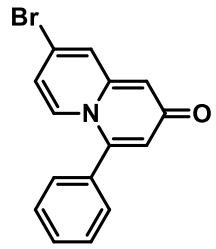
2-Oxo-4-phenyl-2*H*-quinolizine-7-carbonitrile (6g)



Synthesised using general procedure B with pyridine-ynone **5g** (74 mg, 0.3 mmol), $AgNO_3$ (1.0 mg, 6.0 μmol) in DCE (1.5 mL) and EtOH (1.5 mL) for 3 h. Purification by column chromatography (5 → 10% MeOH in EtOAc) afforded the *title compound* **6g** (61 mg, 82%) as a pale yellow solid, mp 243–245 °C.

ATR-FTIR ν_{max} (cm^{-1}) 2230, 1628, 1602, 1585, 1519, 1306;
^{1}H NMR δ_H (400 MHz, $CDCl_3$) 6.58 (1H, d, *J* = 2.5 Hz), 6.74 (1H, d, *J* = 2.5 Hz), 6.97 (1H, d, *J* = 9.5 Hz), 7.17 (1H, d, *J* = 9.5 Hz), 7.37–7.45 (2H, m), 7.56–7.67 (3H, m), 7.97 (1H, s);
^{13}C NMR δ_C (100 MHz, $CDCl_3$) 97.4 (C), 113.4 (CH), 115.6 (C), 125.4 (CH), 125.7 (CH), 125.9 (CH), 128.9 (2CH), 130.0 (2CH), 131.0 (CH), 131.4 (C), 136.6 (CH), 143.1 (C), 146.2 (C), 176.2 (C);
HRMS (ESI^+): Found: 269.0694 $C_{16}H_{10}N_2NaO$ (MNa^+) Requires 269.0685 (−3.1 ppm error), Found: 247.0872; $C_{16}H_{11}N_2O$ (MH^+) Requires 247.0866 (−2.6 ppm error).

8-Bromo-4-phenyl-2*H*-quinolizin-2-one (6h)



Synthesised using general procedure B with pyridine-ynone **5h** (90 mg, 0.3 mmol), $AgNO_3$ (1.0 mg, 6.0 μmol) in DCE (1.5 mL) and EtOH (1.5 mL) for 3 h. Purification by column chromatography (5 → 10% MeOH in EtOAc) afforded the *title compound* **6g** (90 mg, 82%) as a yellow solid, mp >300 °C.

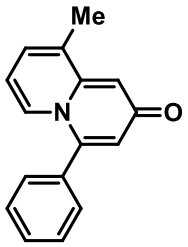
ATR-FTIR ν_{max} (cm^{-1}) 1625, 1578, 1505, 752;

^{1}H NMR δ_H (400 MHz, $CDCl_3$) 6.44 (1H, dd, *J* = 8.0, 2.0 Hz), 6.51 (1H, d, *J* = 2.5 Hz), 6.71 (1H, d, *J* = 2.5 Hz), 7.36 (1H, d, *J* = 2.0 Hz), 7.37–7.43 (2H, m), 7.46 (1H, d, *J* = 8.0 Hz), 7.52–7.61 (3H, m);

^{13}C NMR δ_C (100 MHz, $CDCl_3$) 111.1 (CH), 115.4 (CH), 123.2 (C), 124.7 (CH), 125.7 (CH), 129.0 (2CH), 129.6 (2CH), 130.1 (CH), 130.4 (CH), 132.6 (C), 144.7 (C), 145.8 (C), 175.7 (C);

HRMS (ESI^+): Found: 300.0022; $C_{15}H_{11}{}^{79}BrNO$ (MH^+) Requires 300.0019 (−1.2 ppm error).

9-Methyl-4-phenyl-2*H*-quinolizin-2-one (6i)



Synthesised using general procedure B with pyridine-ynone **5i** (71 mg, 0.3 mmol), $AgNO_3$ (1.0 mg, 6.0 μmol) in DCE (1.5 mL) and EtOH (1.5 mL) for 5 h. Purification by column chromatography (5 → 10% MeOH in EtOAc) afforded the *title compound* **6i** (52 mg, 73%) as a yellow oil.

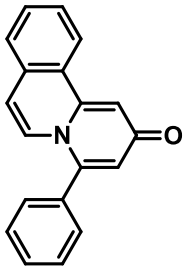
ATR-FTIR ν_{max} (cm^{-1}) 3391, 1625, 1586, 1524;

^{1}H NMR δ_H (400 MHz, $CDCl_3$) 2.37 (3H, s), 6.37 (1H, dd, *J* = 7.0, 7.0 Hz), 6.72–6.78 (2H, m), 6.96 (1H, d, *J* = 7.0 Hz), 7.37–7.45 (2H, m), 7.50–7.60 (4H, m);

^{13}C NMR δ_C (100 MHz, $CDCl_3$) 19.6 (CH_3), 109.0 (CH), 111.2 (CH), 124.1 (CH), 127.7 (CH), 128.0 (CH), 129.1 (2CH), 129.4 (2CH), 130.0 (CH), 130.9 (C), 133.6 (C), 145.2 (C), 146.4 (C), 175.8 (C);

HRMS (ESI^+): Found: 236.1065; $C_{16}H_{14}NO$ (MH^+) Requires 236.1070 (2.0 ppm error).

4-Phenyl-2*H*-pyrido[2,1-a]isoquinolin-2-one (6j)



Synthesised using general procedure B with ynone **5j** (81 mg, 0.3 mmol), $AgNO_3$ (1.0 mg, 6.0 μmol) in DCE (1.5 mL) and EtOH (1.5 mL) for 20 h. Purification by column chromatography (5 → 10% MeOH in EtOAc) afforded the *title compound* **6j** (58 mg, 70%) as a pale yellow solid, mp 139–141 °C.

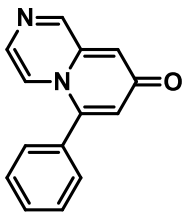
ATR-FTIR ν_{max} (cm^{-1}) 1626, 1601, 1572, 1582;

^{1}H NMR δ_H (400 MHz, $CDCl_3$) 6.64 (1H, d, *J* = 8.0 Hz), 6.72 (1H, d, *J* = 2.5 Hz), 7.40–7.69 (10H, m), 8.27 (1H, d, *J* = 7.5 Hz);

^{13}C NMR δ_C (100 MHz, $CDCl_3$) 109.9 (CH), 112.1 (CH), 122.5 (CH), 124.3 (CH), 125.3 (C), 125.7 (CH), 126.9 (CH), 128.9 (CH), 129.1 (2CH), 129.4 (2CH), 129.6 (C), 130.0 (CH), 131.1 (CH), 133.7 (C), 143.5 (C), 147.8 (C), 176.7 (C);

HRMS (ESI^+): Found: 272.1069; $C_{19}H_{14}NO$ (MH^+) Requires 272.1070 (0.2 ppm error).

6-Phenyl-8*H*-pyrido[1,2-a]pyrazin-8-one (6k)



Synthesised using general procedure B with pyridine-ynone **5k** (66 mg, 0.3 mmol), $AgNO_3$ (1.0 mg, 6.0 μmol) in DCE (1.5 mL) and EtOH (1.5 mL) for 5 h. Purification by column chromatography (5 → 20% MeOH in EtOAc) afforded the *title compound* **6k** (56 mg, 85%) as a yellow solid, mp 170–172 °C.

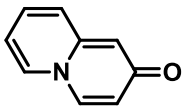
ATR-FTIR ν_{max} (cm^{-1}) 3400, 1619, 1600, 1567, 1505;

^{1}H NMR δ_H (400 MHz, $CDCl_3$) 6.81 (1H, d, *J* = 2.5 Hz), 6.84 (1H, d, *J* = 2.5 Hz), 7.32–7.45 (4H, m), 7.52–7.63 (3H, m), 8.65 (1H, s);

^{13}C NMR δ_C (100 MHz, $CDCl_3$) 114.1 (CH), 119.6 (CH), 126.3 (CH), 127.4 (CH), 129.0 (2CH), 129.6 (2CH), 130.7 (CH), 131.3 (C), 137.7 (C), 145.8 (C), 152.6 (CH), 176.5 (C);

HRMS (ESI^+): Found: 245.0678; $C_{14}H_{10}N_2NaO$ (MNa^+) Requires 245.0685 (2.9 ppm error), Found: 223.0865; $C_{14}H_{11}N_2O$ (MH^+) Requires 223.0866 (0.4 ppm error).

2*H*-Quinolizin-2-one (6l)



To a solution of TMS-ynone **5l** (98 mg, 0.451 mmol) in acetone (4.5 mL) was added $AgNO_3$ (15.3 mg, 90.2 μmol). The reaction mixture was stirred at rt for 19 h then concentrated *in vacuo*. The crude product was dissolved in CH_2Cl_2 and purified by column chromatography (5 → 20% MeOH in EtOAc) to afford the *title compound* **6l** (54 mg, 82%) as a brown solid, mp 38–40 °C.

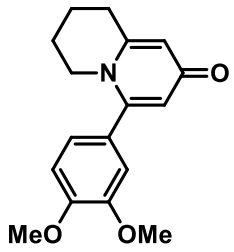
ATR-FTIR ν_{max} (cm^{-1}) 3301, 1649, 1571, 1513, 1486, 1427, 851;

^{1}H NMR δ_H (400 MHz, $CDCl_3$) 6.53 (1H, d, *J* = 2.5 Hz), 6.56 (1H, ddd, *J* = 7.0, 6.5, 1.0 Hz), 6.78 (1H, dd, *J* = 7.5, 2.5 Hz), 7.05 (1H, d, *J* = 9.0, 6.5 Hz), 7.11 (1H, br d, *J* = 9.0 Hz), 7.61 (1H, d, *J* = 7.0 Hz), 7.79 (1H, d, *J* = 7.5 Hz);

^{13}C NMR δ_C (100 MHz, $CDCl_3$) 111.2 (CH), 112.2 (CH), 123.0 (CH), 123.9 (CH), 128.5 (CH), 132.0 (CH), 135.1 (CH), 144.1 (C), 176.2 (C);

HRMS (ESI^+): Found: 146.0604; C_9H_8NO (MH^+) Requires 146.0600 (−2.7 ppm error).

6-(3,4-Dimethoxyphenyl)-3,4-dihydro-1*H*-quinolizin-8(2*H*)-one (8)



To a solution of pyridone **6b** (28 mg, 0.1 mmol) in MeOH (1 mL) was added Pd/C (14 mg). The mixture was evacuated *in vacuo* and backfilled with argon three times then evacuated *in vacuo* and backfilled with hydrogen three times. The mixture was stirred at rt for 16 h before being filtered through Celite®), eluting with EtOAc. The filtrate was then concentrated *in vacuo* to afford the *title compound* **8** (26 mg, 91%) as a pale yellow oil.

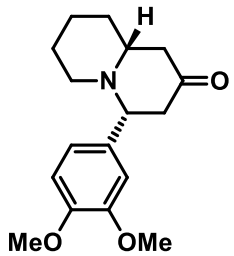
ATR-FTIR ν_{max} (cm^{-1}) 3359, 2935, 1623, 1509, 1262, 1248, 1024, 729;

^{1}H NMR δ_H (400 MHz, $CDCl_3$) 1.78–1.90 (4H, m), 2.78 (2H, t, *J* = 6.5 Hz), 3.68 (2H, t, *J* = 5.5 Hz), 3.87 (3H, s), 3.91 (3H, s), 6.29 (2H, s), 6.79 (1H, d, *J* = 1.5 Hz), 6.86 (1H, dd, *J* = 8.0, 2.5 Hz), 6.92 (1H, d, *J* = 8.0 Hz);

^{13}C NMR δ_C (100 MHz, $CDCl_3$) 18.3 (CH_2) , 22.4 (CH_2), 28.4 (CH_2), 47.0 (CH_2), 55.9 (CH_3), 56.0 (CH_3), 111.0 (CH), 111.6 (CH), 116.5 (CH), 119.1 (CH), 121.2 (CH), 126.9 (C), 149.0 (C), 149.8 (C), 150.7 (C), 151.9 (C), 178.4 (C);

HRMS (ESI^+): Found: 308.1265; $C_{17}H_{19}NNaO_3$ (MNa^+) Requires 308.1257 (−2.5 ppm error), Found: 286.1447; $C_{17}H_{20}NO_3$ (MH^+) Requires 286.1438 (−3.4 ppm error).

4-(3,4-Dimethoxyphenyl)hexahydro-1*H*-quinolizin-2(6*H*)-one (10)



To a solution of pyridone **6b** (1.05 g, 3.73 mmol) in AcOH (0.64 mL, 11.2 mmol) and EtOH (37 mL) was added PtO_2 (254 mg, 1.12 mmol). The mixture was evacuated *in vacuo* and backfilled with nitrogen three times then evacuated *in vacuo* and backfilled with hydrogen three times. The mixture was stirred at rt for 4 days before being filtered through Celite®, eluting with EtOAc. The filtrate was poured into sat. $NaCHO_{3(aq)}$ (30 mL) and diluted with EtOAc (50 mL). The organics were separated and the aqueous was extracted with EtOAc (4 × 50 mL). The organics were combined, dried ($MgSO_4$), and concentrated *in vacuo* to afford the crude hydrogenation product **9**, which was used in the next step without further purification.

To a solution of dry DMSO (1.33 mL, 18.7 mmol) in CH_2Cl_2 (65 mL) at −78 °C under argon was added oxalyl chloride (0.80 mL, 9.33 mmol). The mixture was stirred at −78 °C for 1 h, then a solution of the above crude product in CH_2Cl_2 (19 mL) was added. The mixture was stirred at −78 °C

for 1 h, then Et_3N (5.72 mL, 41.0 mmol) was added, the mixture was then allowed to warm to room temperature and stirred for a further 2 h. The reaction mixture was quenched by the careful addition of 2 M $NaOH_{(aq)}$ (30 mL) and diluted with CH_2Cl_2 (20 mL). The organics were separated and the aqueous extracted with CH_2Cl_2 (3 × 60 mL). The organics were combined, dried ($MgSO_4$), concentrated *in vacuo* and purified by column chromatography (0 → 2% MeOH in CH_2Cl_2) to afford the *title compound* **10** (730 mg, 68%) as a yellow oil.

ATR-FTIR ν_{max} (cm^{-1}) 2932, 1722, 1516, 1263, 1028;

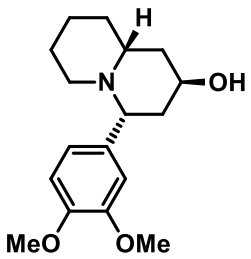
^{1}H NMR δ_H (400 MHz, $CDCl_3$) 1.19–1.35 (1H, m), 1.38–1.81 (6H, m), 2.22–2.37 (2H, m), 2.41 (1H, ddd, *J* = 13.5, 3.0, 3.0 Hz), 2.51 (1H, dd, *J* = 13.5, 13.0 Hz), 2.68 (1H, dd, *J* = 13.5, 12.5 Hz), 2.75–2.83 (1H m), 3.21 (1H, dd, *J* = 12.5, 3.0 Hz), 3.88 (3H, s), 3.91 (3H, s), 6.79–6.87 (2H, m), 6.91 (1H, br s);

^{13}C NMR δ_C (100 MHz, $CDCl_3$) 24.2 (CH_2), 25.8 (CH_2), 34.3 (CH_2), 48.7 (CH_2), 50.9 (CH_2), 52.8 (CH_2), 55.8 (CH_3), 56.0 (CH_3), 62.4 (CH), 70.0 (CH), 109.6 (CH), 110.9 (CH), 119.5 (CH), 135.1 (C), 148.3 (C), 149.3 (C), 208.0 (C);

HRMS (ESI^+): Found: 290.1752; $C_{17}H_{24}NO_3$ (MH^+) Requires 290.1751 (−0.6 ppm error).

Spectroscopic data matched those reported in the literature.[6]

(±)-Lasubine II (3)



To a solution of ketone **10** (724 mg, 2.50 mmol) in THF (25 mL) at −78 °C was added L-Selectride® (5.0 mL, 5.00 mmol, 1.0 M in THF) dropwise. The mixture was stirred at −78 °C for 3 h then warmed to 0 °C before being quenched by the careful addition of sat. $NaHCO_{3(aq)}$ (25 mL). The suspension was stirred at room temperature for 2 h and then diluted with EtOAc (40 mL). The organics were separated and the aqueous extracted with EtOAc (3 × 50 mL). The organics were combined, dried ($MgSO_4$), concentrated *in vacuo* and purified by column chromatography (10 → 20 → 30% MeOH in CH_2Cl_2) to afford the *title compound* **3** (527 mg, 72%) as an off-white foam, mp 41–43 °C.

ATR-FTIR ν_{max} (cm^{-1}) 2930, 1516, 1261, 1230, 1136, 1028;

^{1}H NMR δ_H (400 MHz, $CDCl_3$) 1.20–2.00 (12H, m), 2.33–2.47 (1H, m), 2.70 (1H, br d, *J* = 11.0 Hz), 3.32 (1H, br d, *J* = 10.5 Hz), 3.86 (3H, s), 3.89 (3H, s), 4.12–4.19 (1H, m), 6.79 (1H, d, *J* = 8.0 Hz), 6.82–7.00 (2H, m);

^{13}C NMR δ_C (100 MHz, $CDCl_3$) 24.8 (CH_2), 26.1 (CH_2), 33.6 (CH_2), 40.3 (CH_2), 42.7 (CH_2), 53.2 (CH_2), 55.8 (CH_3), 55.9 (CH_3), 56.4 (CH), 63.4 (CH), 65.0 (CH), 110.4 (CH), 110.8 (CH), 119.7 (CH), 137.1 (C), 147.7 (C), 148.9 (C);

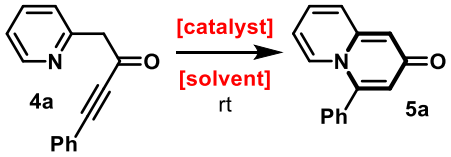
HRMS (ESI^+): Found: 292.1918; $C_{17}H_{26}NO_3$ (MH^+) Requires 292.1907 (−3.6 ppm error).

Spectroscopic data matched those reported in the literature.[6]

Table of optimisation results

To a solution of ynone **5a** (44 mg, 0.2 mmol) in the stated solvent (2 mL) was added the stated catalyst. The resulting solution was stirred at rt for the specified time before being quenched by the addition of sat. $NaHCO_{3(aq)}$ (2 mL) and diluted with CH_2Cl_2 (5 mL). The organics were separated and the aqueous extracted with CH_2Cl_2 (3 × 5 mL). The organics were combined, washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was then analysed by ^{1}H NMR spectroscopy to determine conversion.

Table 1. Catalyst Screening

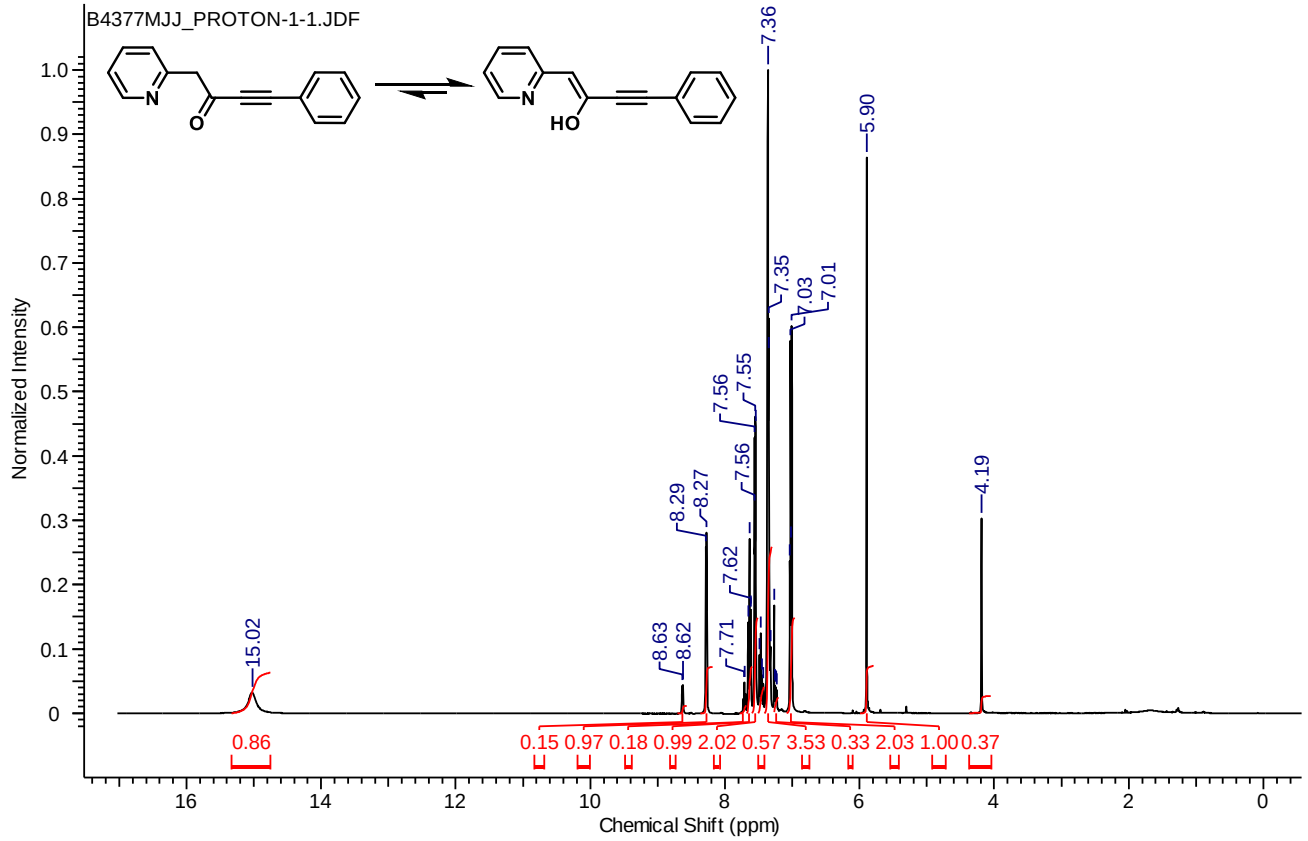


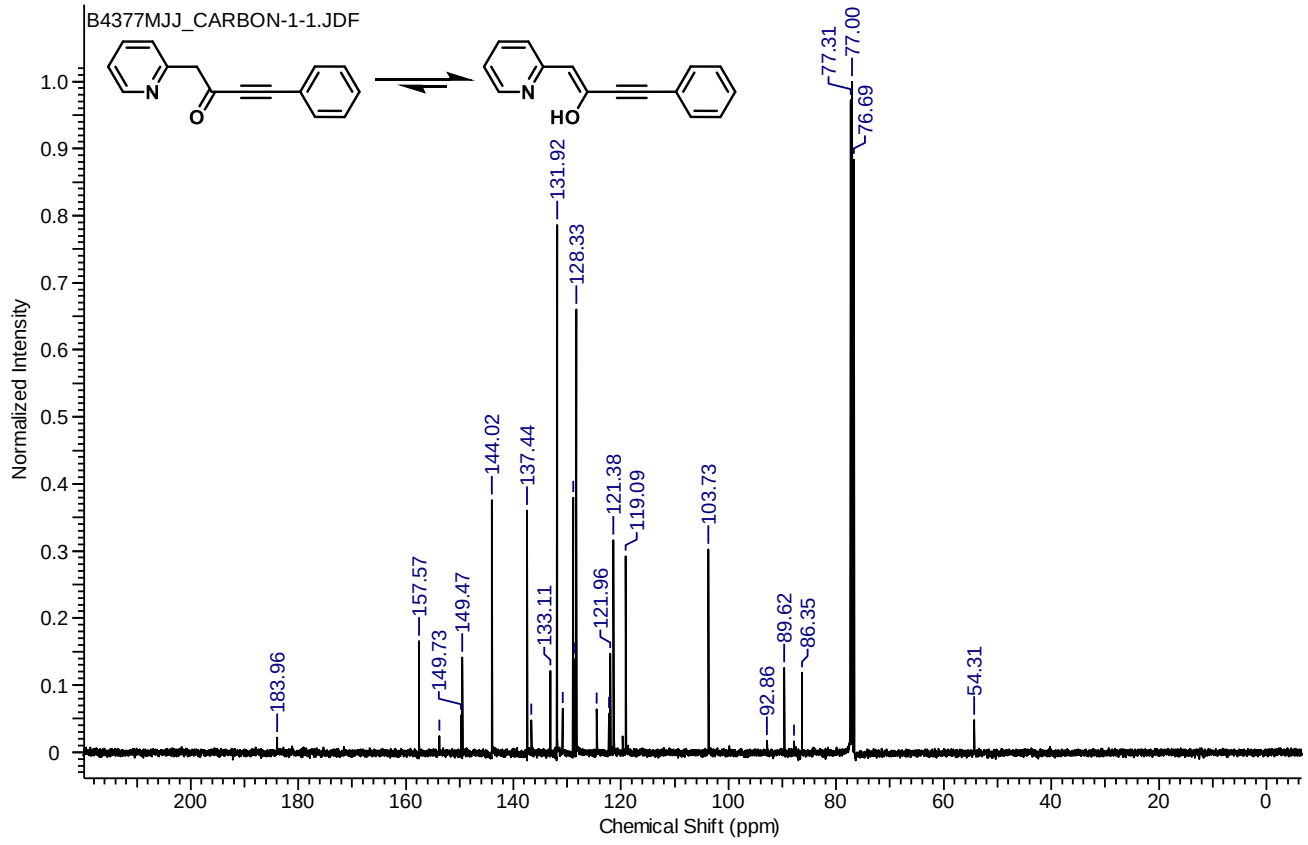
entry	catalyst[a]	solvent	time (h)	conv (%)[b]
1	$Cu(MeCN)_4PF_6$ (10 mol%)	CH_2Cl_2	16	0
2	$Cu(OTf)_2$ (10 mol%)	CH_2Cl_2	16	0
3	$Ph_3PAuNTf_2$ (10 mol%)	CH_2Cl_2	16	0
4	$Pd(OAc)_2$ (10 mol%)	CH_2Cl_2	16	0
5	AgOTf (10 mol%)	CH_2Cl_2	16	>95
6	$AgNO_3$ (2 mol%)	CH_2Cl_2	16	>95
7	AgOTf (2 mol%)	CH_2Cl_2	2	90
8	AgOAc (2 mol%)	CH_2Cl_2	2	65
9	$AgSbF_6$ (2 mol%)	CH_2Cl_2	2	25
10	$AgNTf_2$ (2 mol%)	CH_2Cl_2	2	>95
11	$AgNO_3$ (2 mol%)	CH_2Cl_2	2	>95
12	$AgNO_3$ (1 mol%)	CH_2Cl_2	0.5	50
13	$AgNO_3$ (1 mol%)	DCE	0.5	95
14	$AgNO_3$ (1 mol%)	EtOH	0.5	>95

[a] Reactions performed with 0.2 mmol of **5a** and catalyst in the stated solvent (0.1 M) at rt; [b] calculated by measuring the ratio of starting material to product using the ^{1}H NMR spectrum of the unpurified reaction mixture, rounded to the nearest 5%.

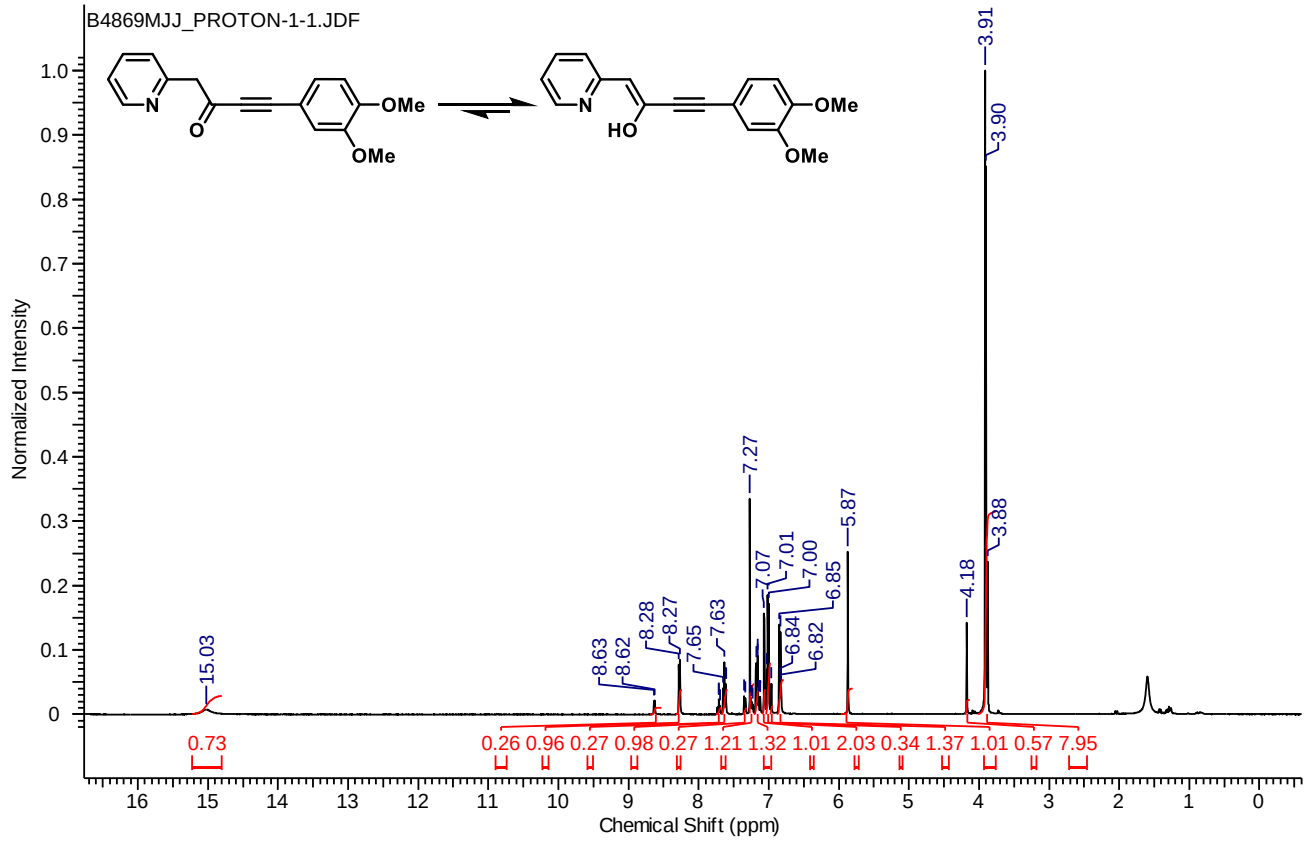
^{1}H and ^{13}C NMR spectra

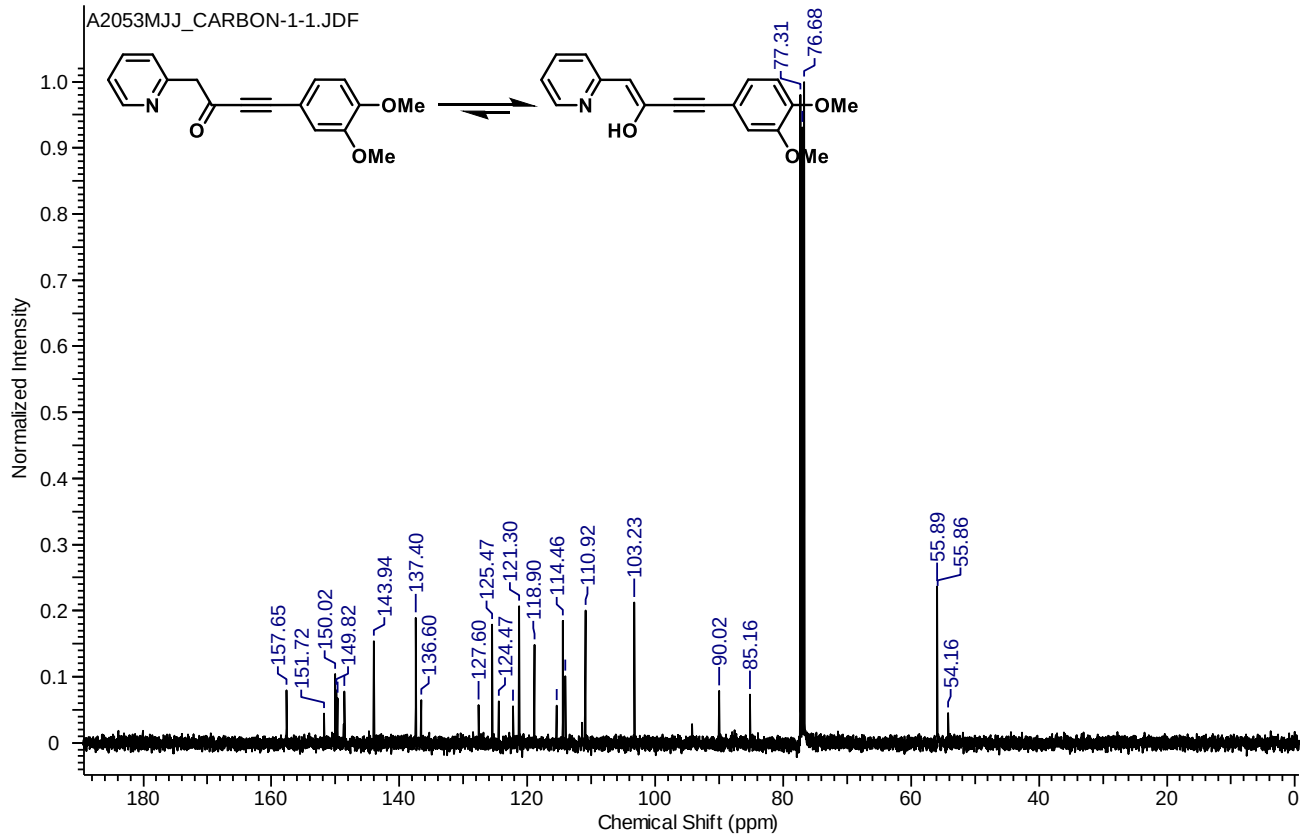
^{1}H & ^{13}C NMR spectra: **5a**



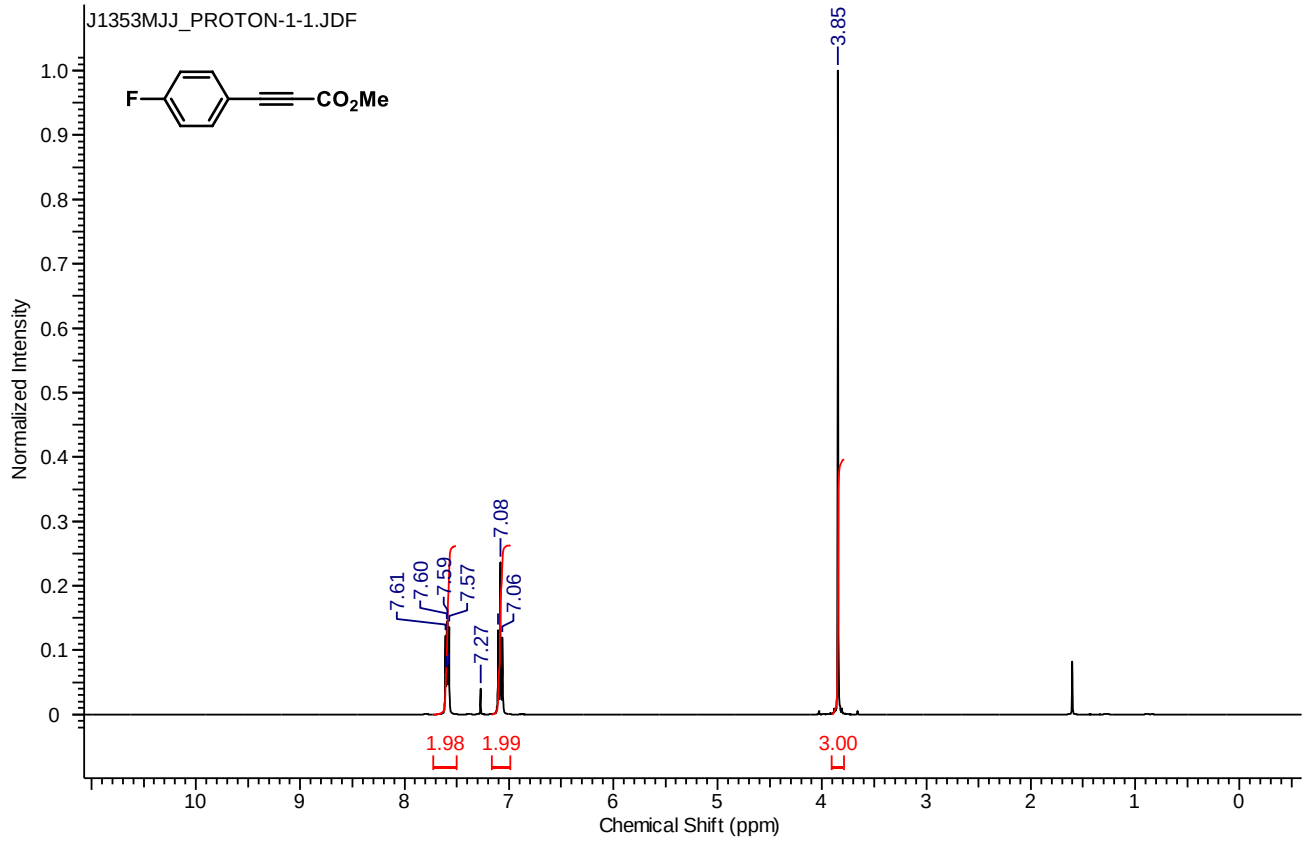


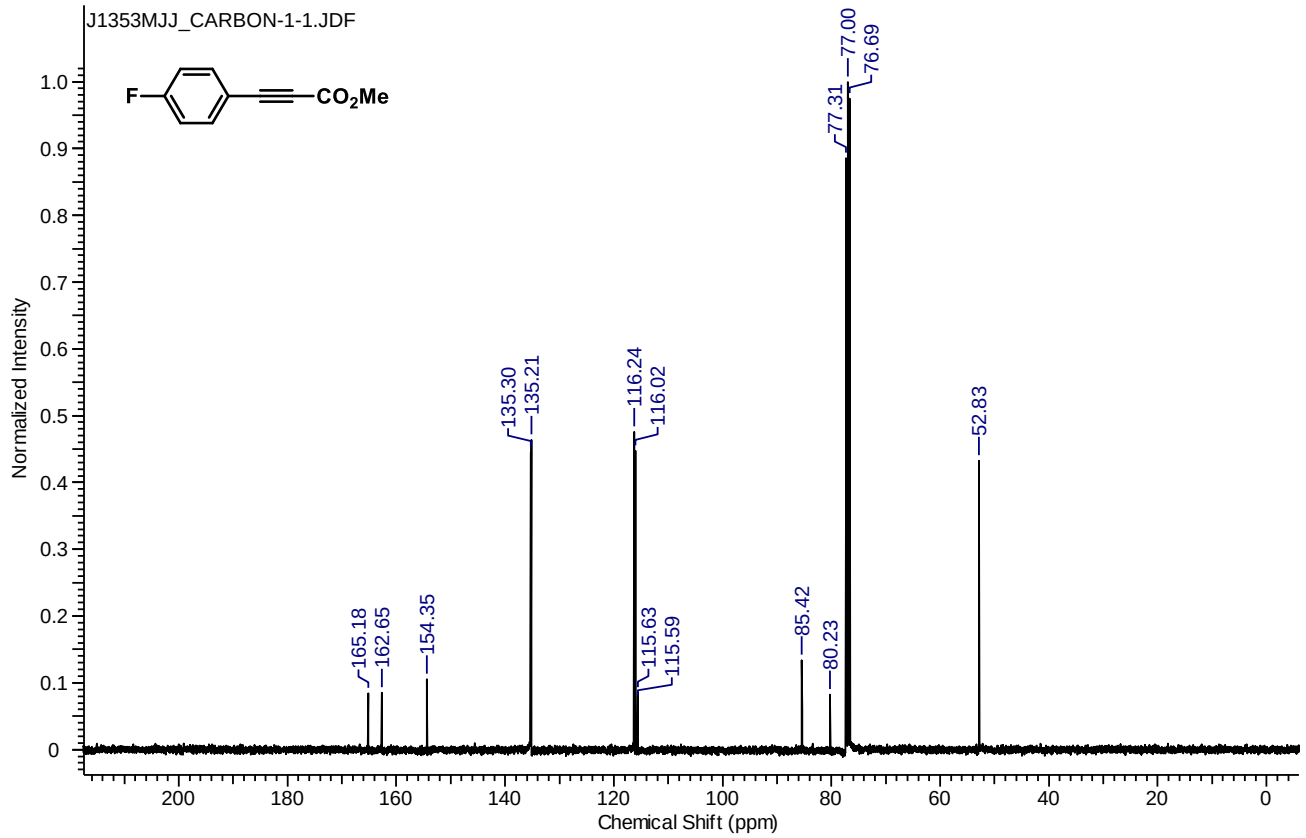
^{1}H & ^{13}C NMR spectra: **5b**

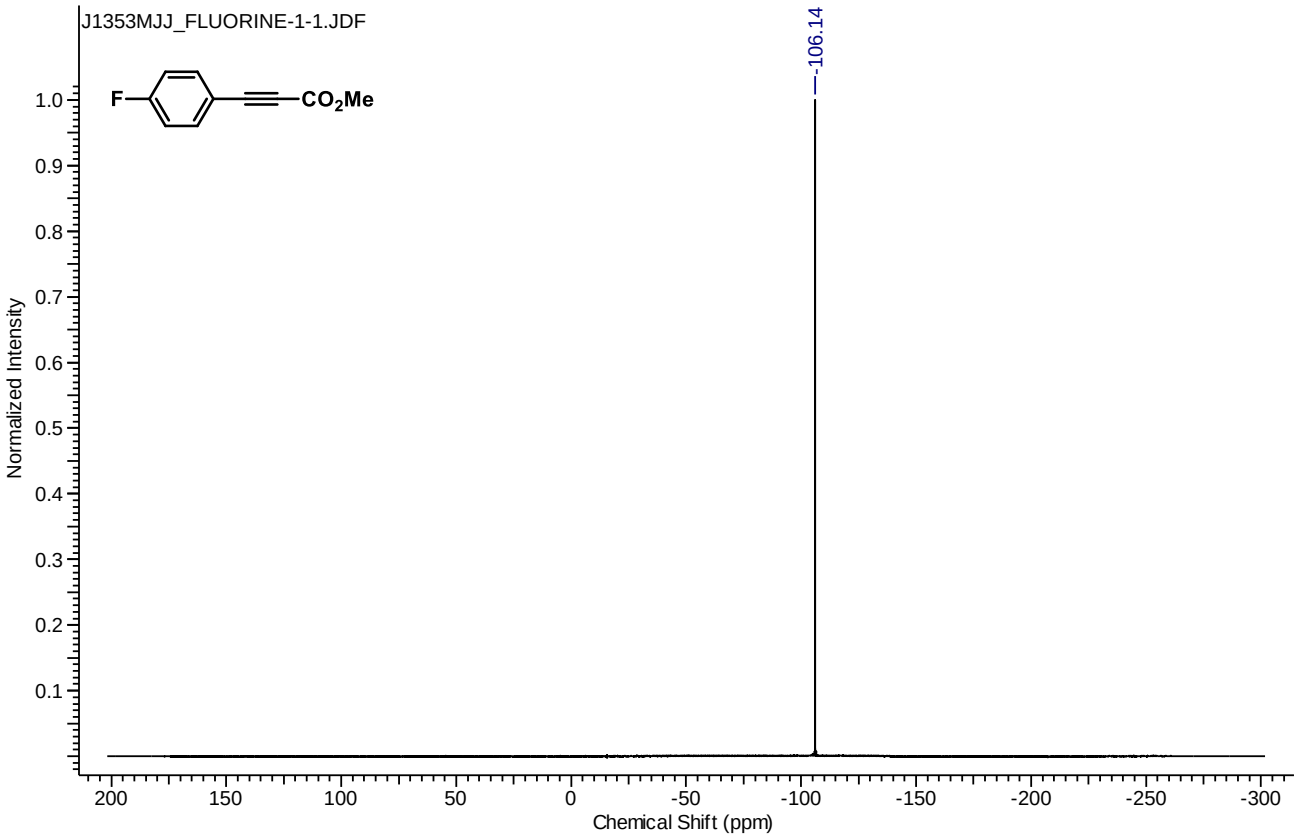




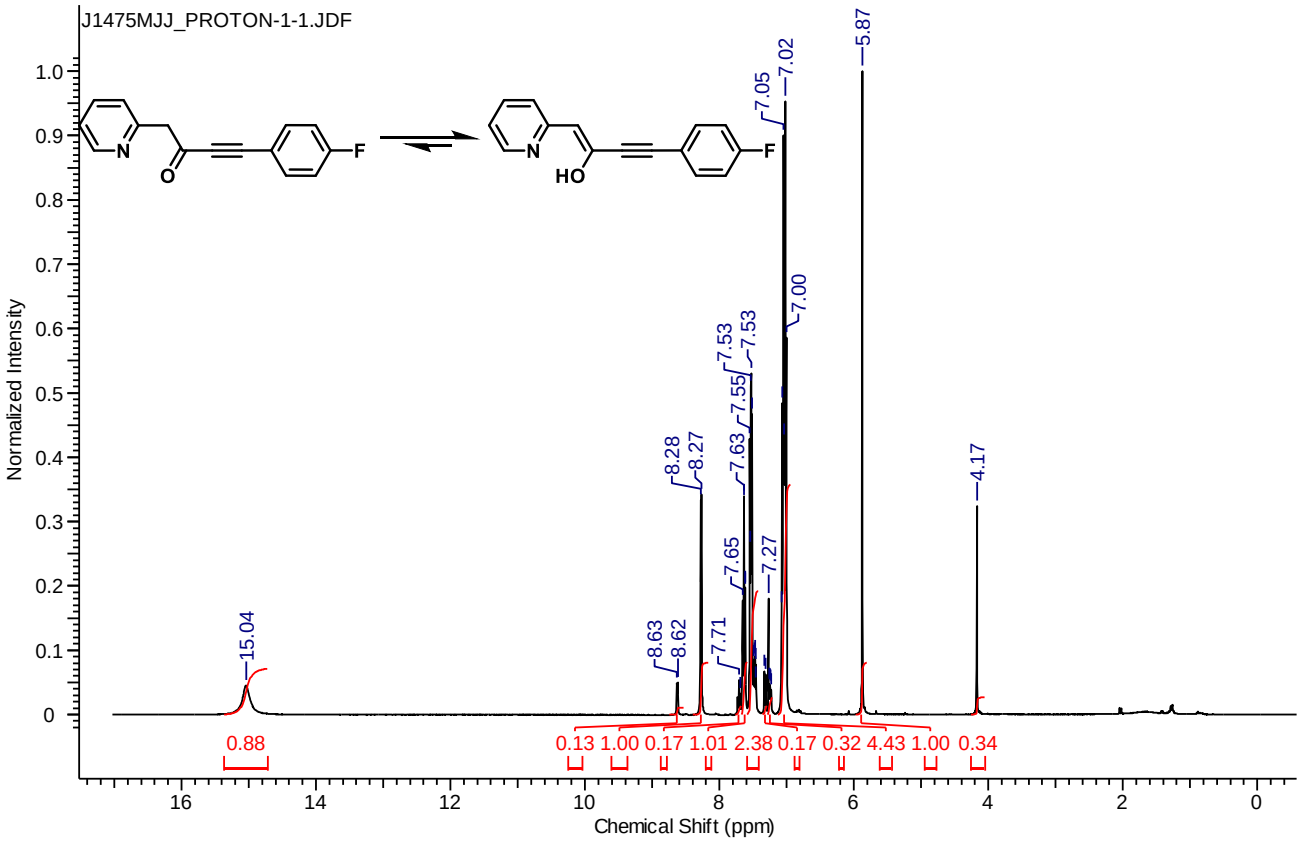
^{1}H, ^{13}C NMR & ^{19}F spectra: **S1**

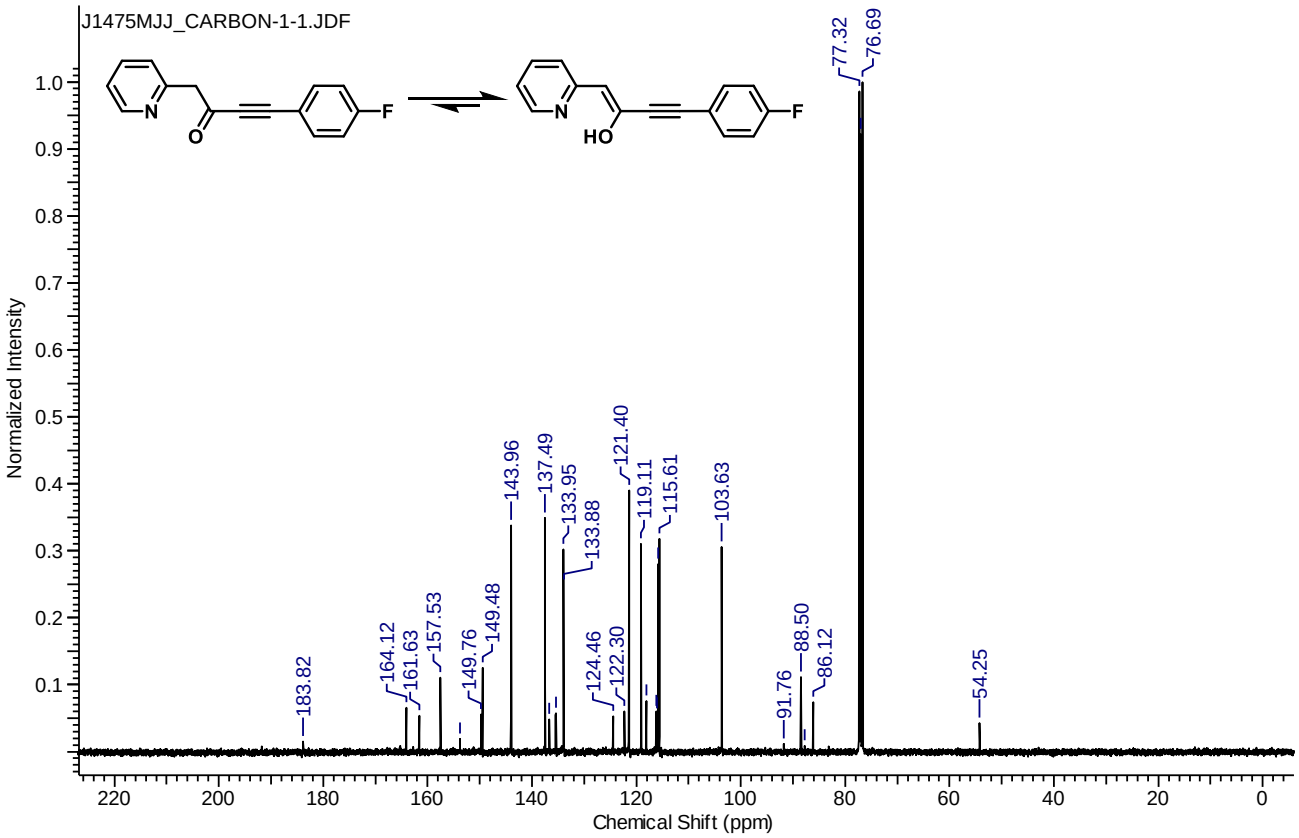


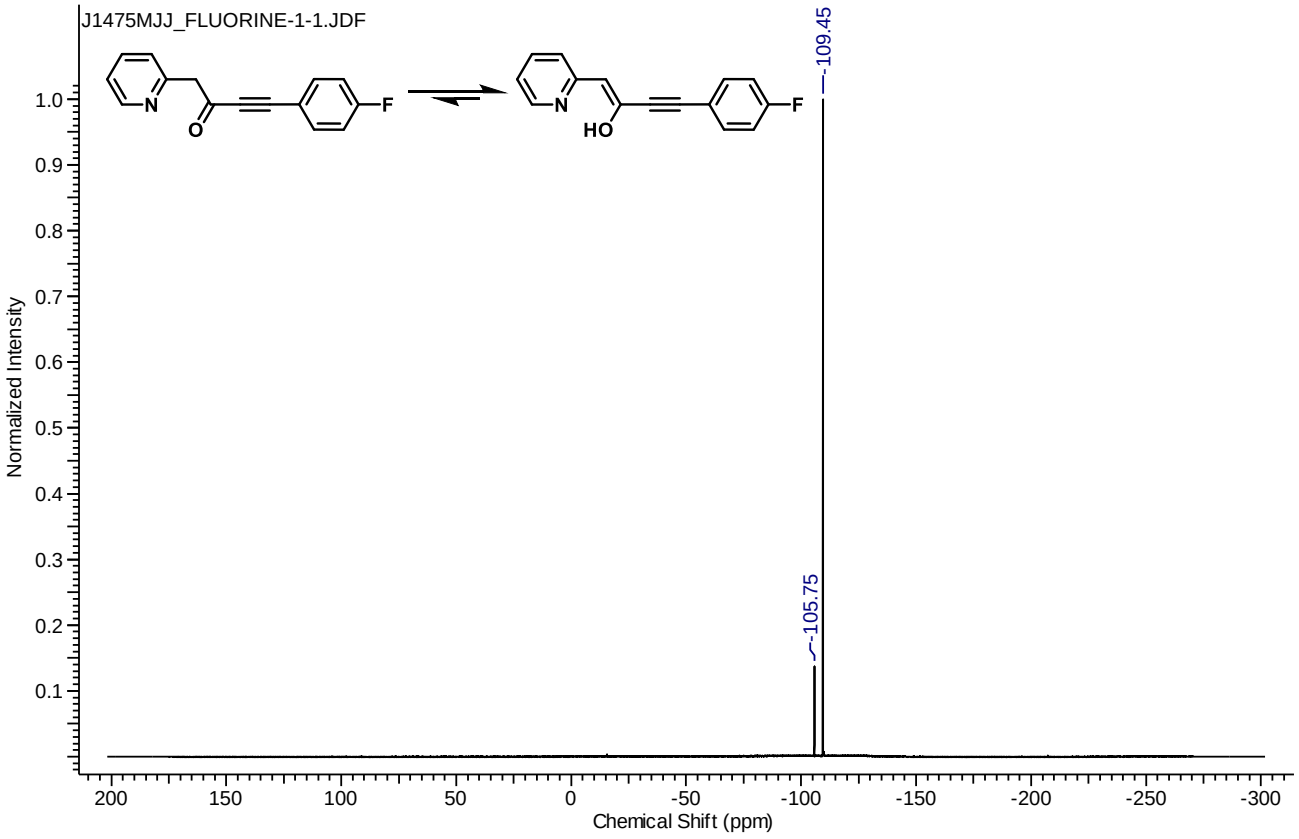




^{1}H, ^{13}C NMR & ^{19}F: **5c**




J1475MJJ_CARBON-1-1.JDF
Normalized Intensity
Chemical Shift (ppm)
183.82
164.12
161.63
157.53
149.76
149.48
143.96
137.49
133.95
133.88
124.46
122.30
121.40
119.11
115.61
103.63
91.76
88.50
86.12
77.32
76.69
54.25


J1475MJJ_FLUORINE-1-1.JDF
Normalized Intensity
Chemical Shift (ppm)
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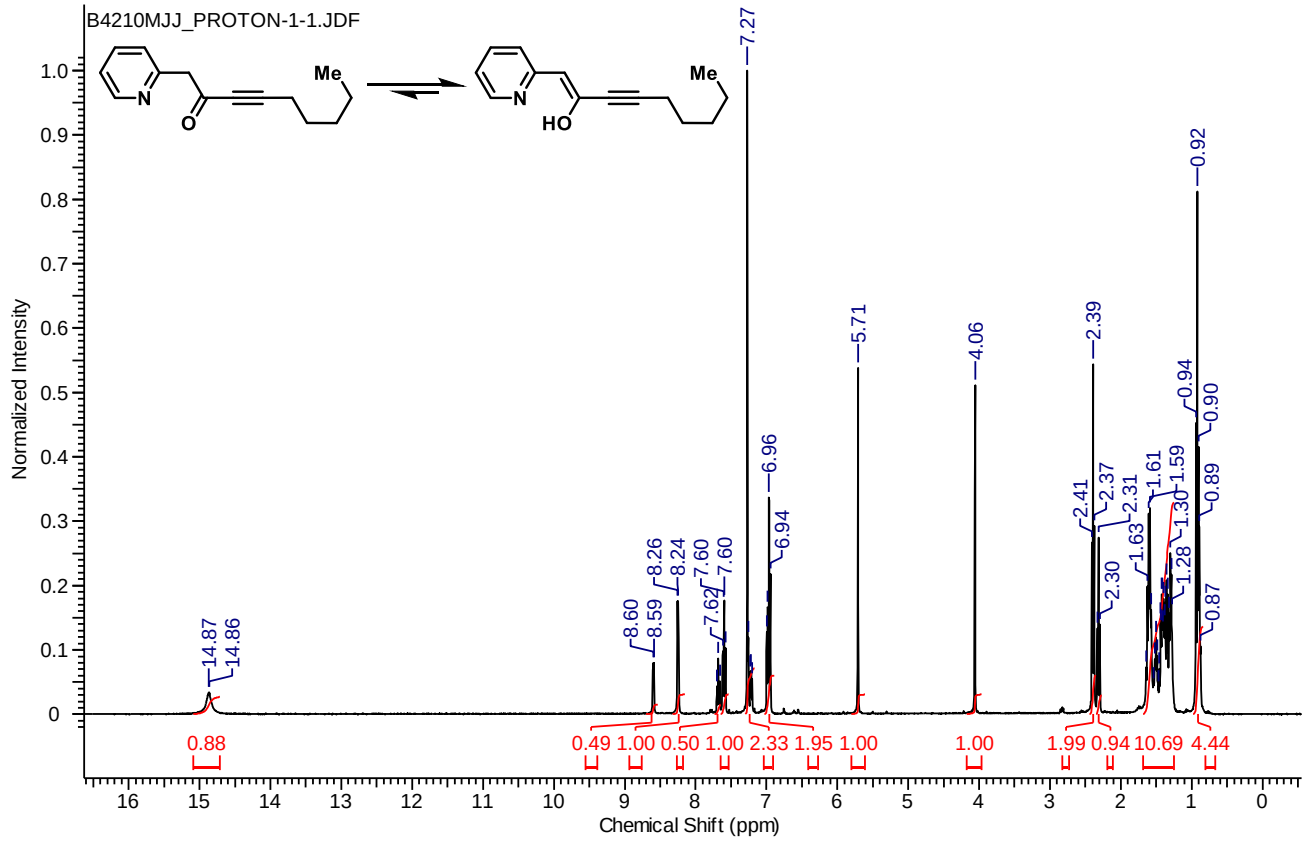
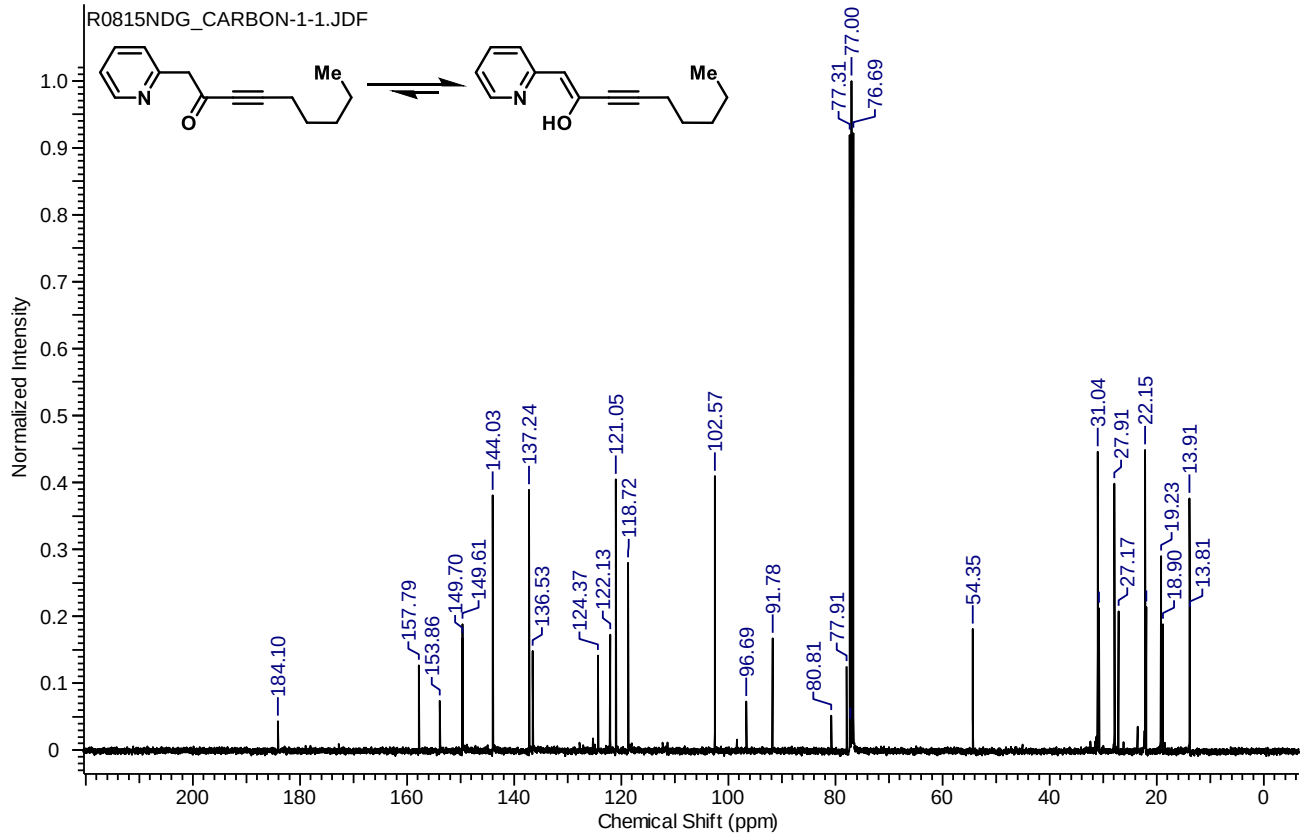
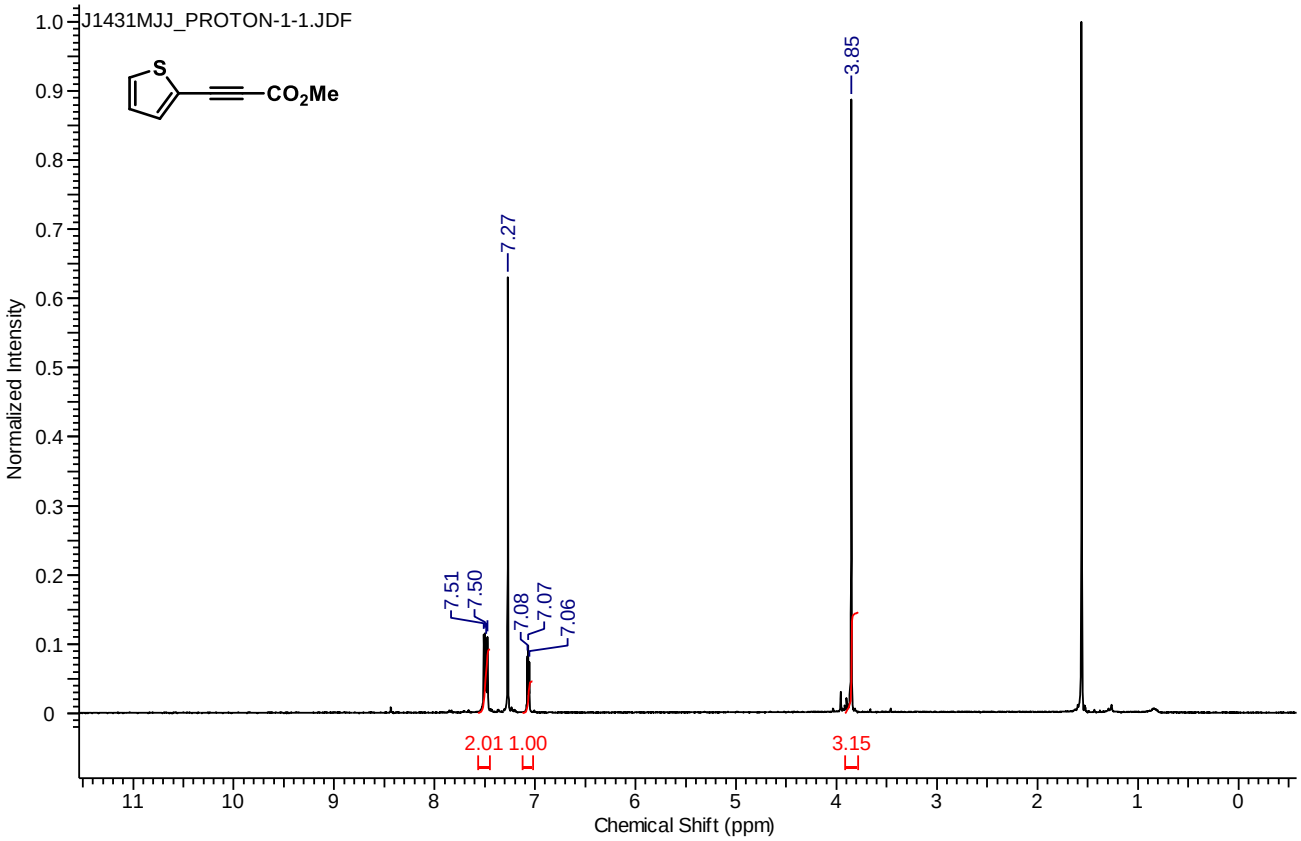
105.75

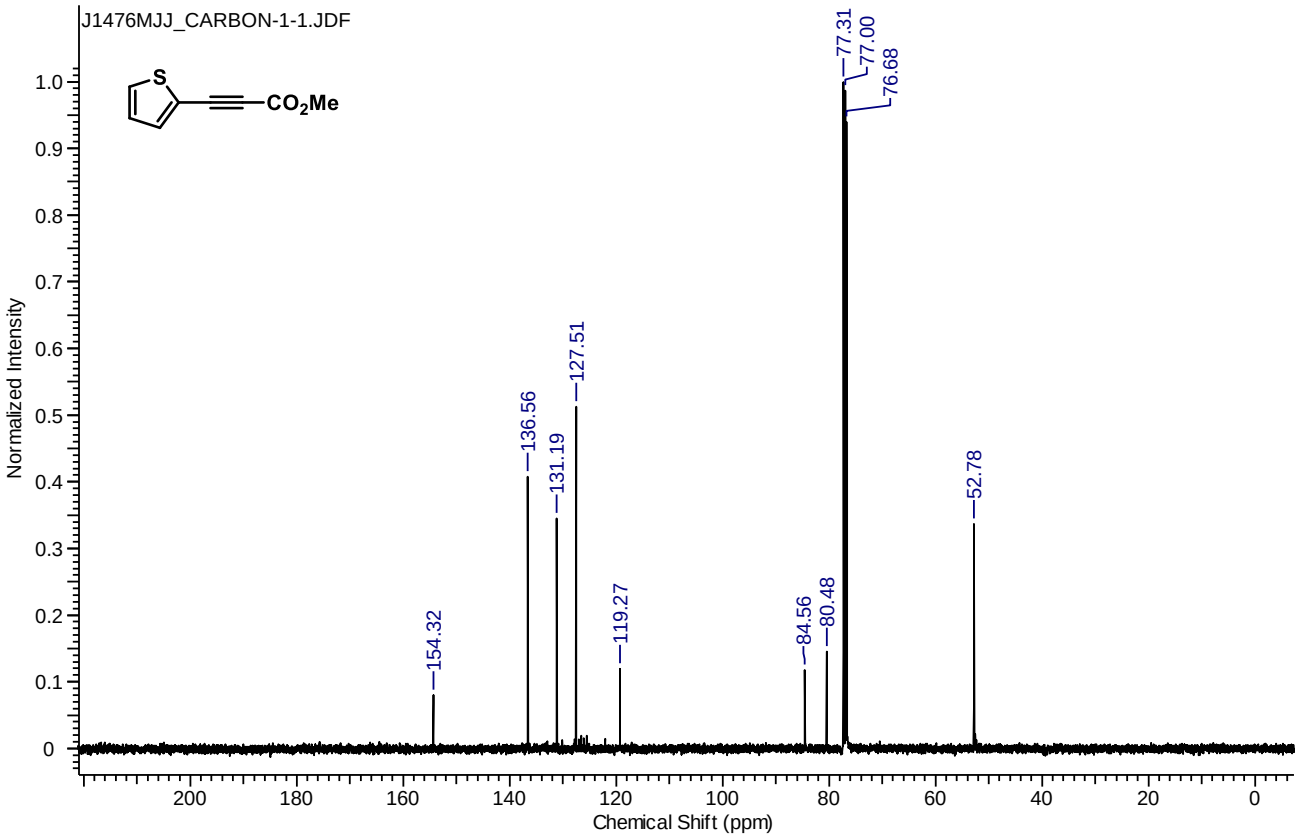
^{1}H & ^{13}C NMR spectra: **5d**



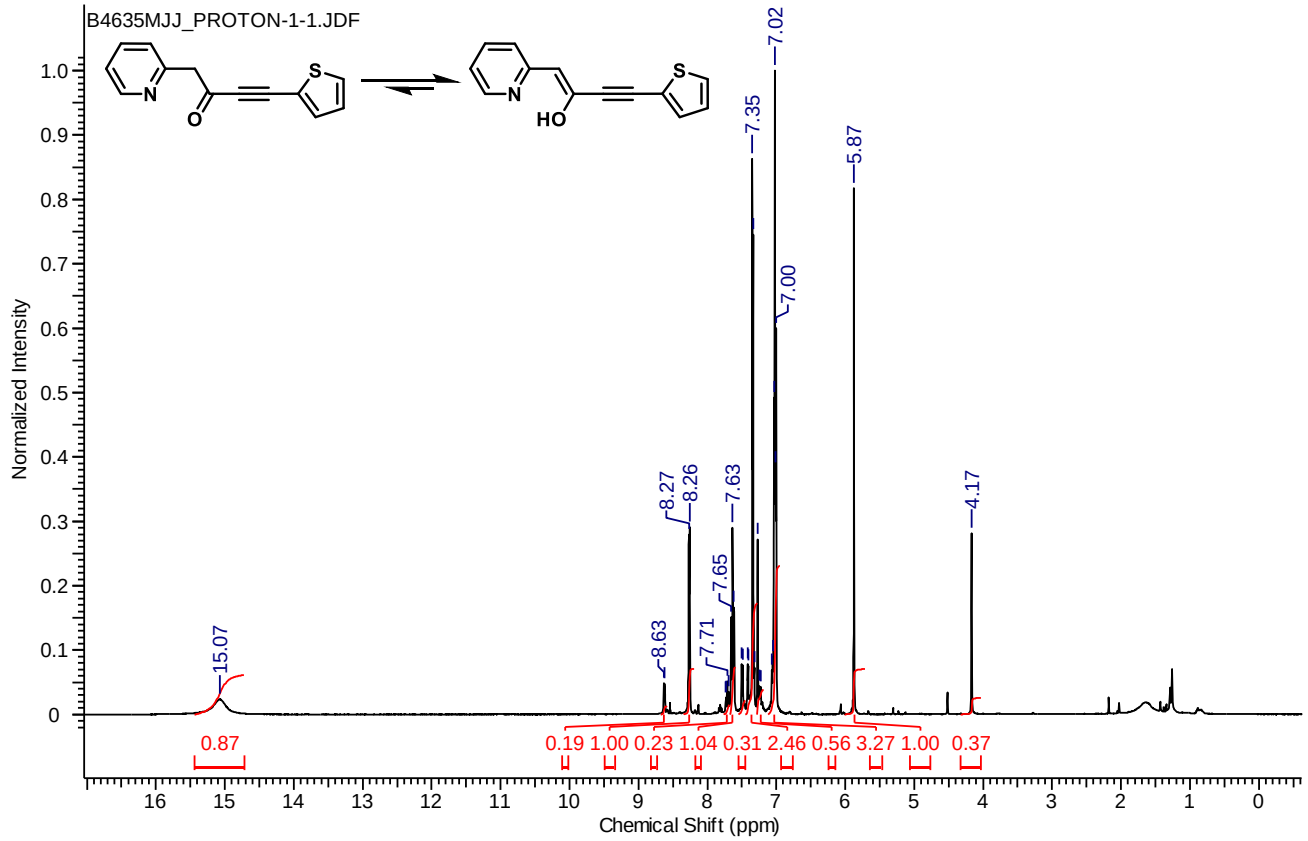


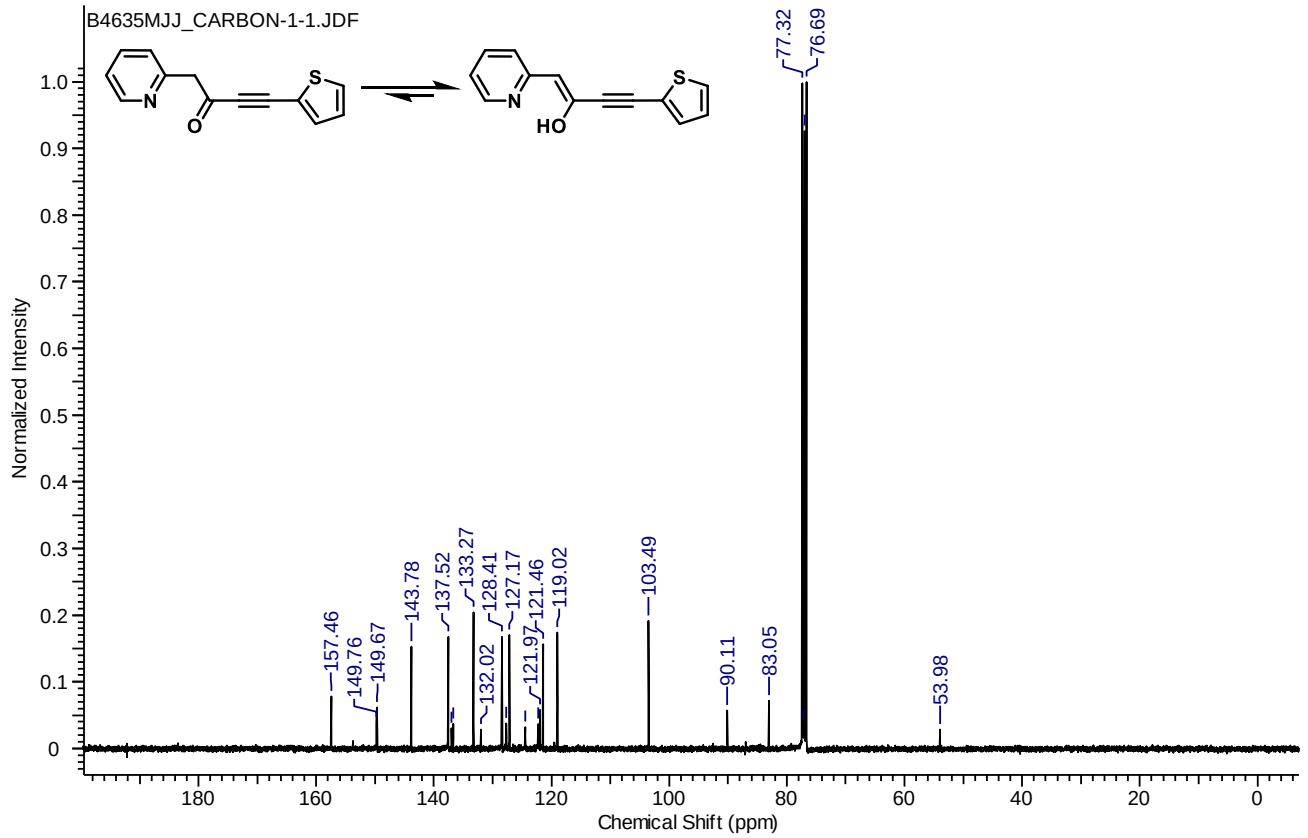
^{1}H & ^{13}C NMR spectra: **S2**



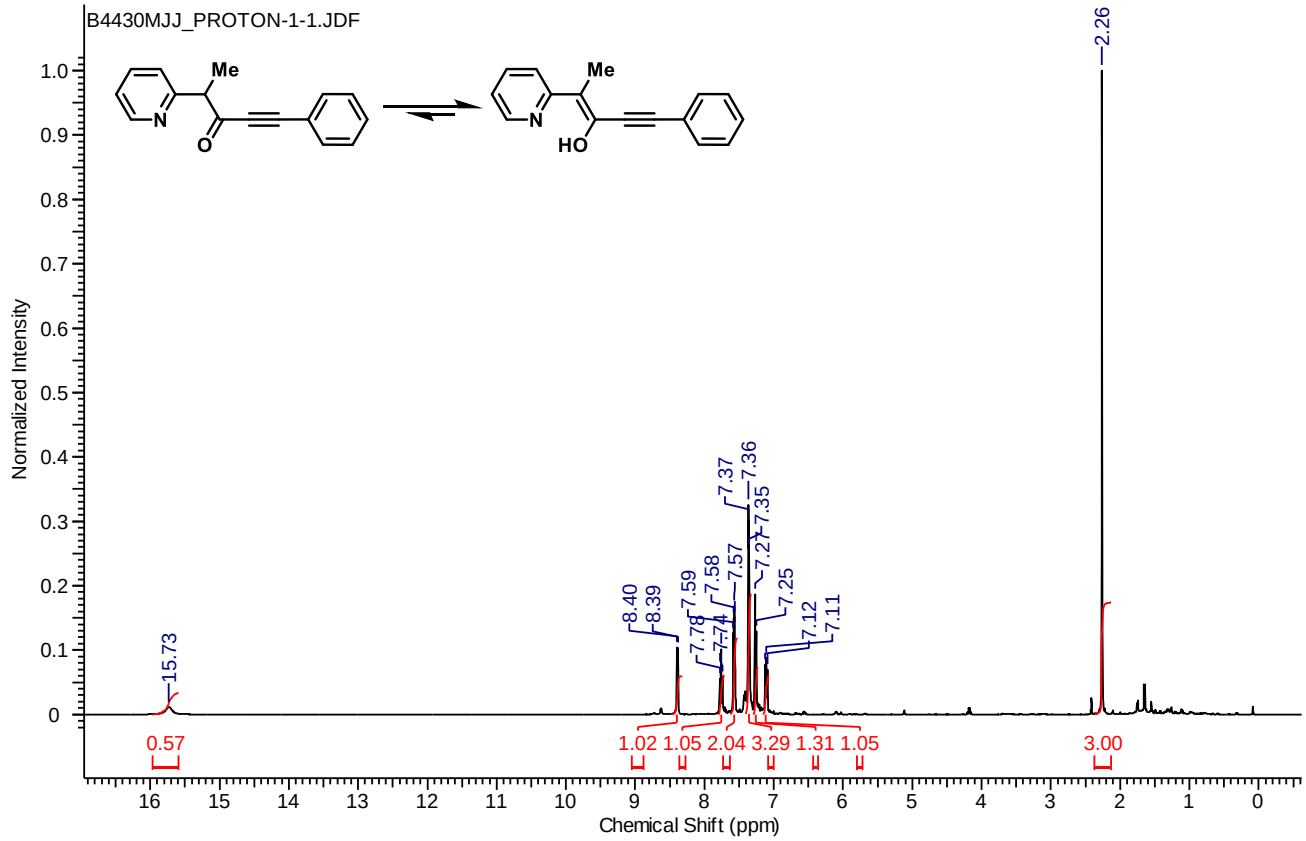


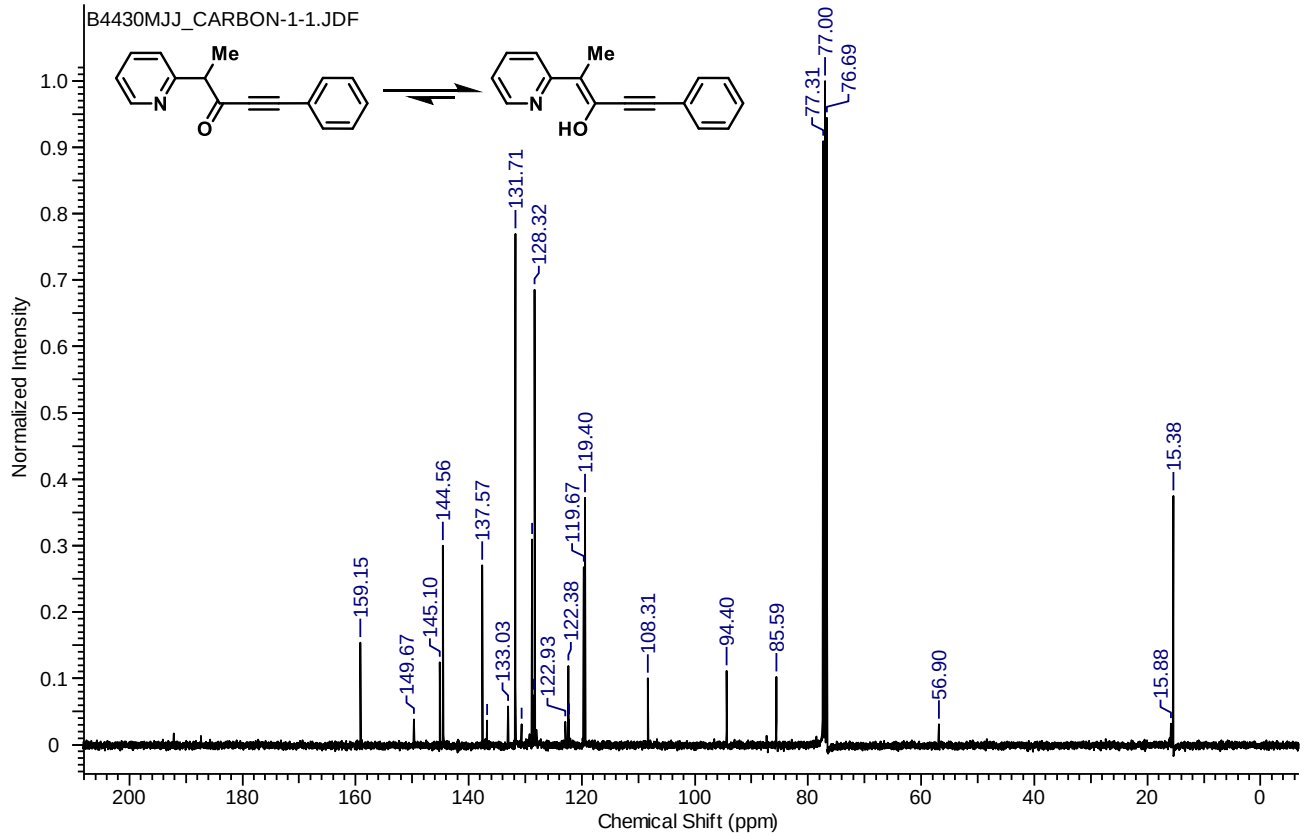
^{1}H & ^{13}C NMR spectra: **5e**



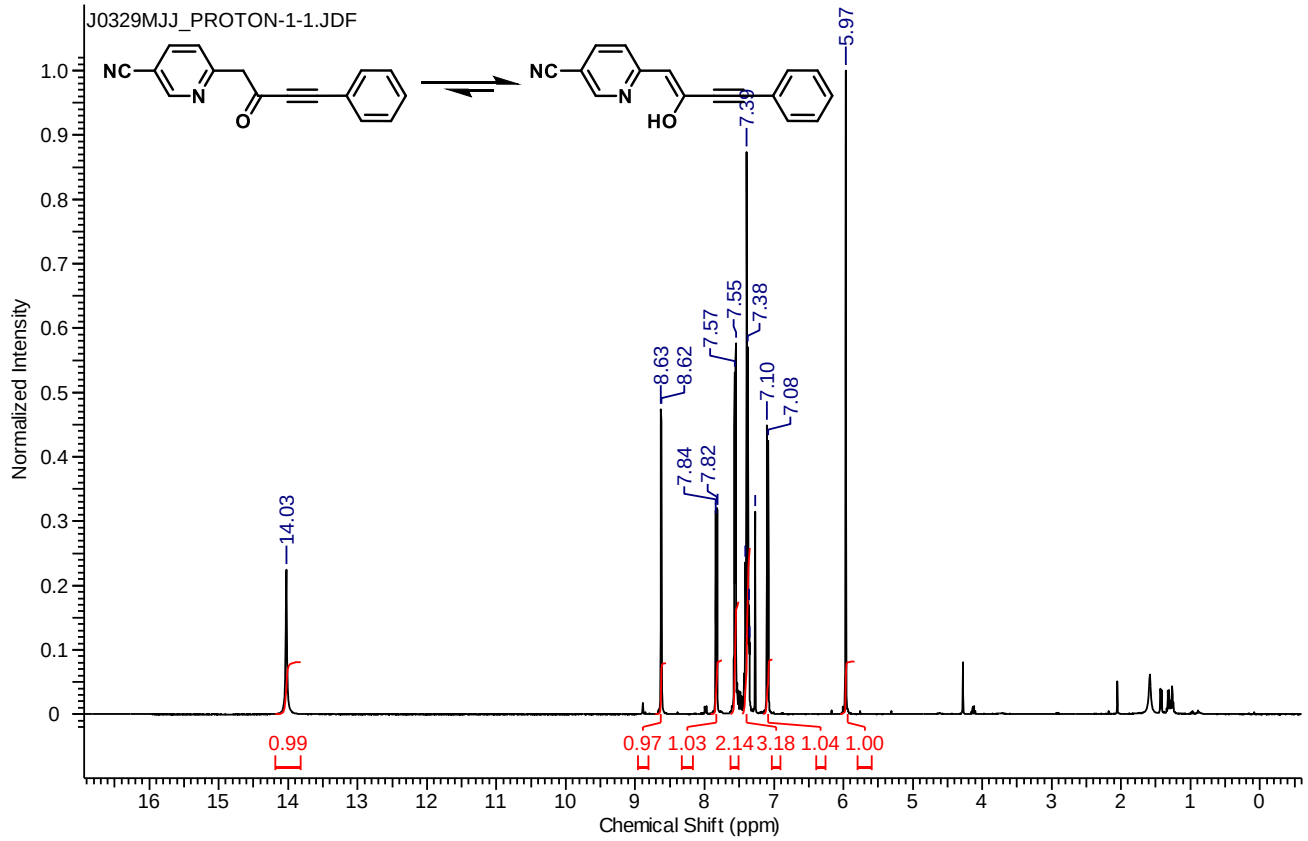


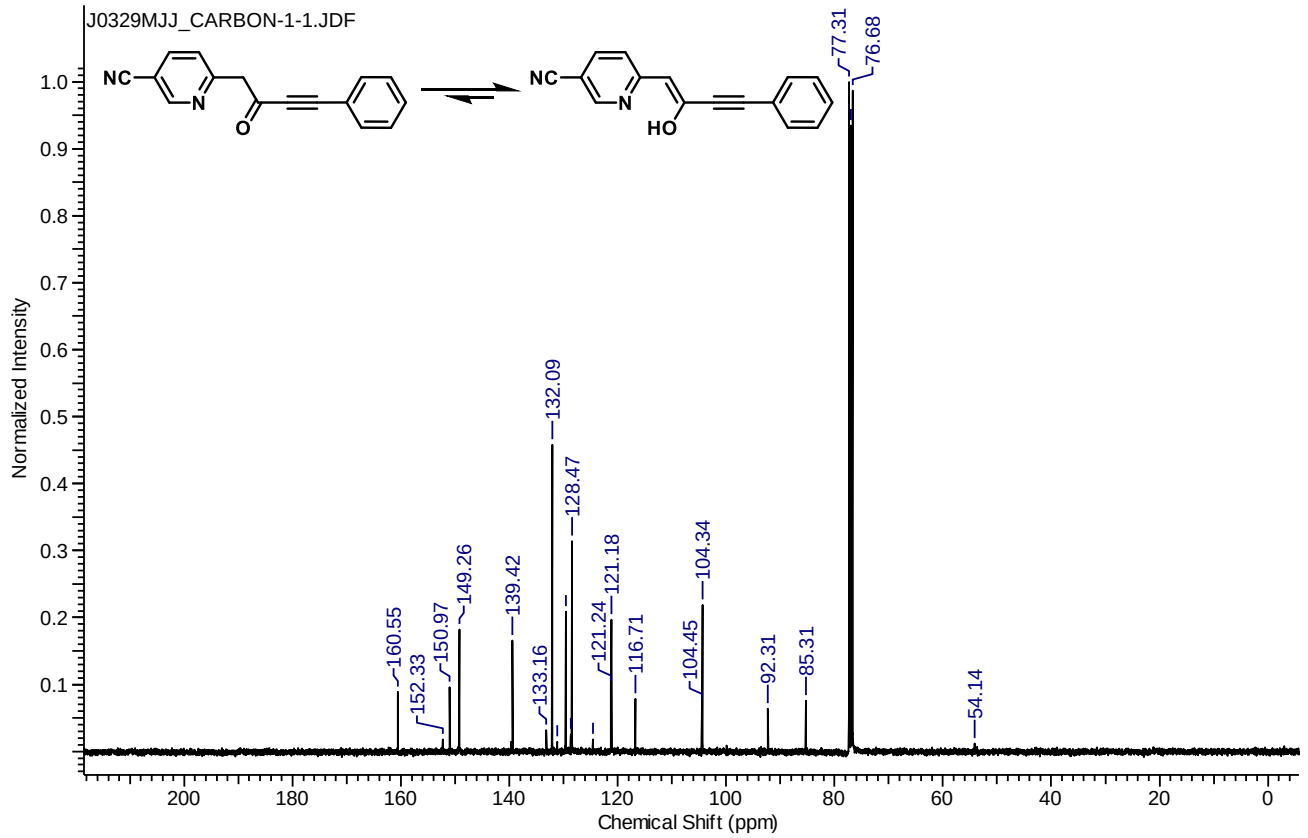
^{1}H & ^{13}C NMR spectra: **5f**



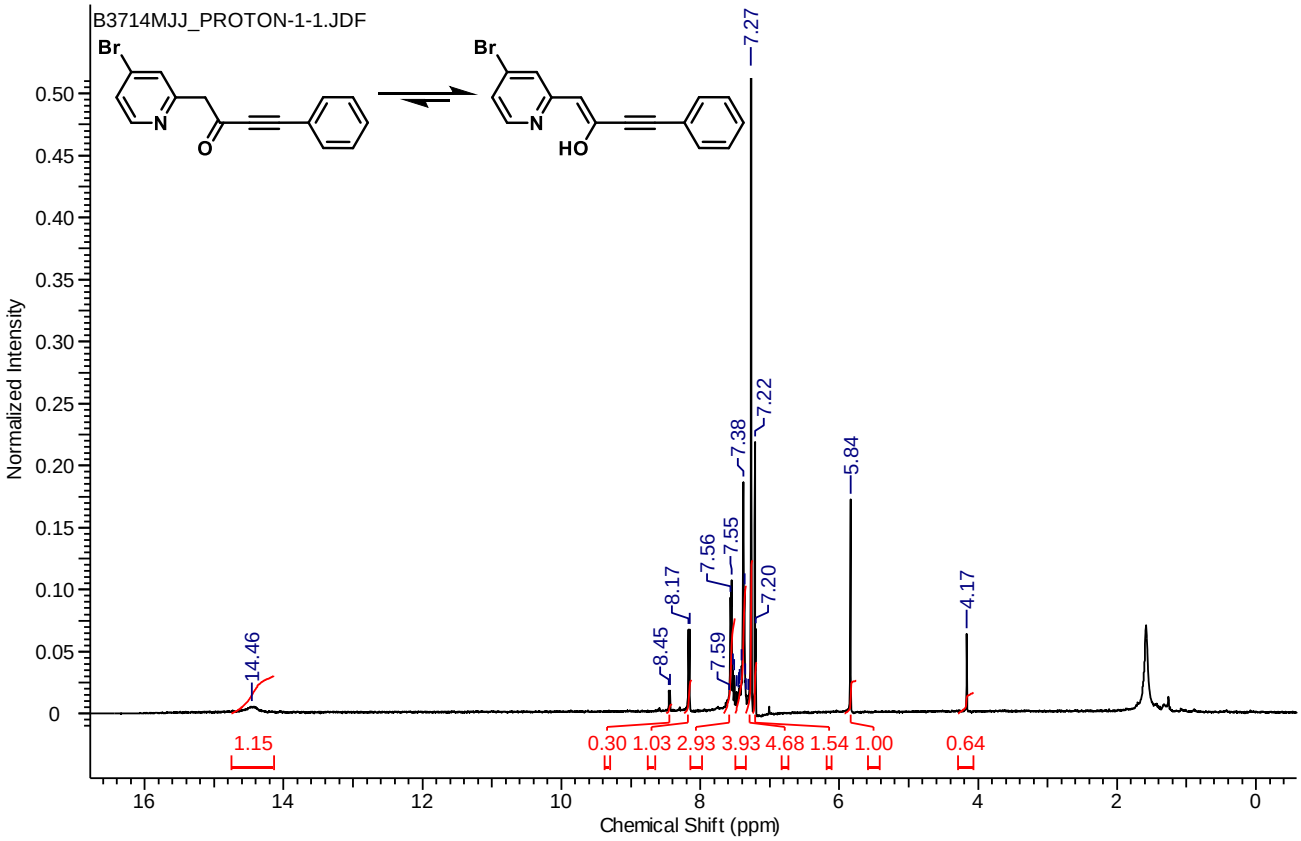


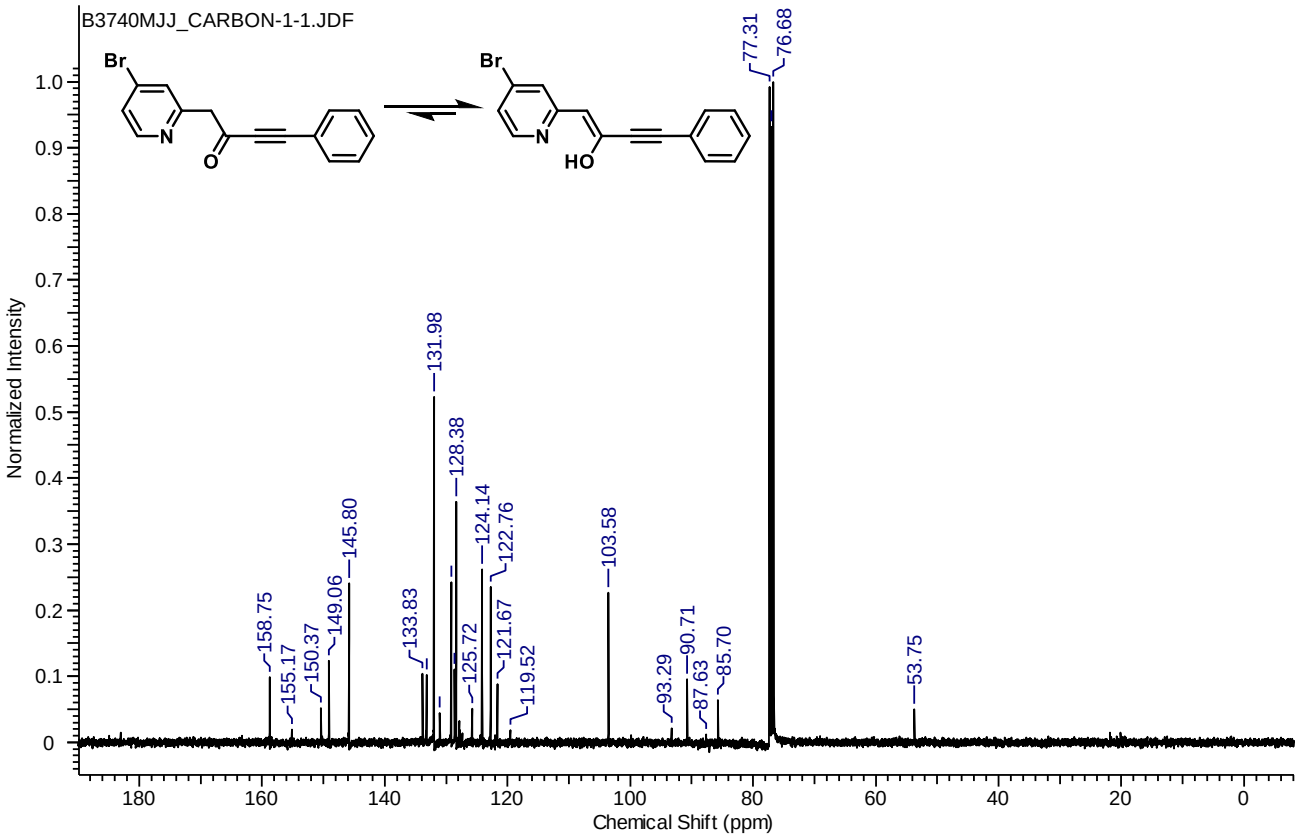
^{1}H & ^{13}C NMR spectra: **5g**



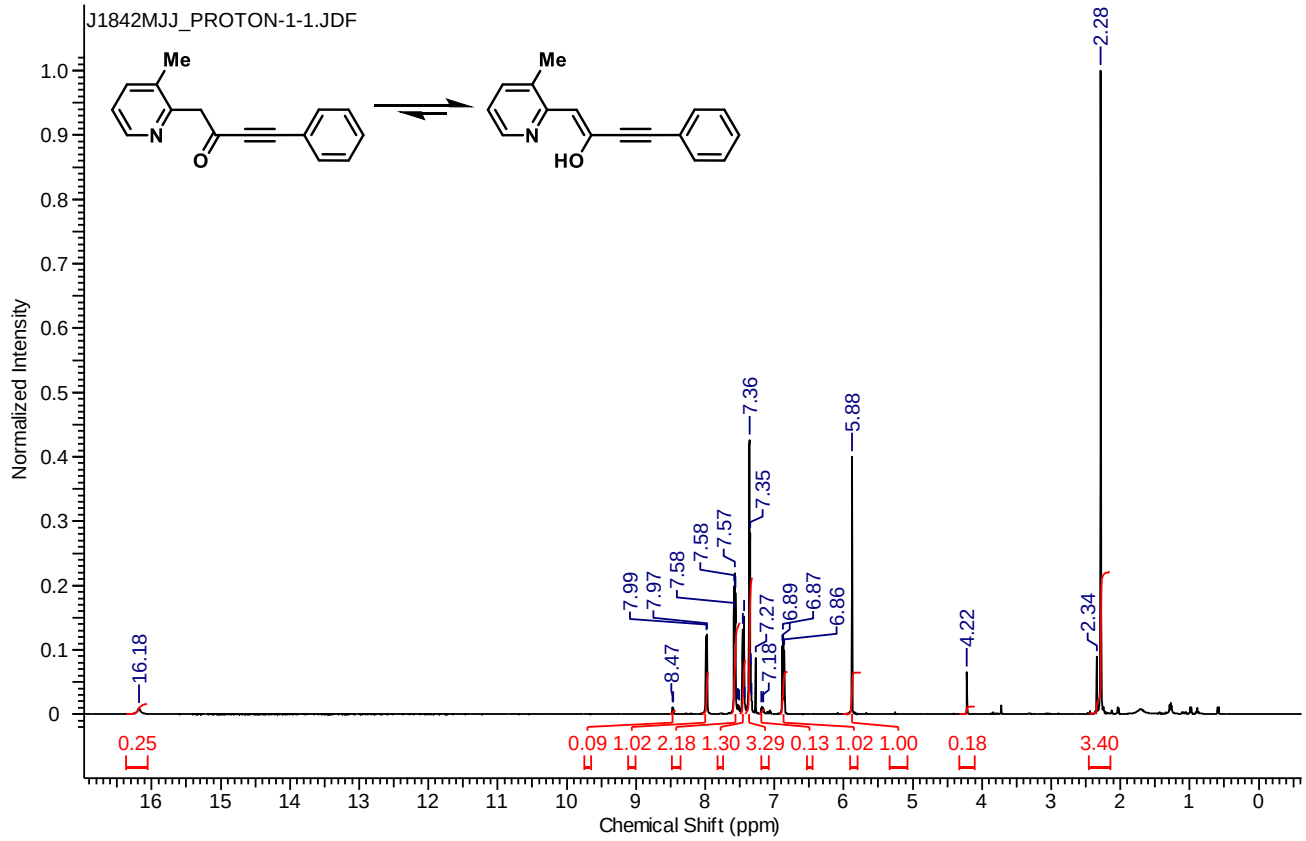


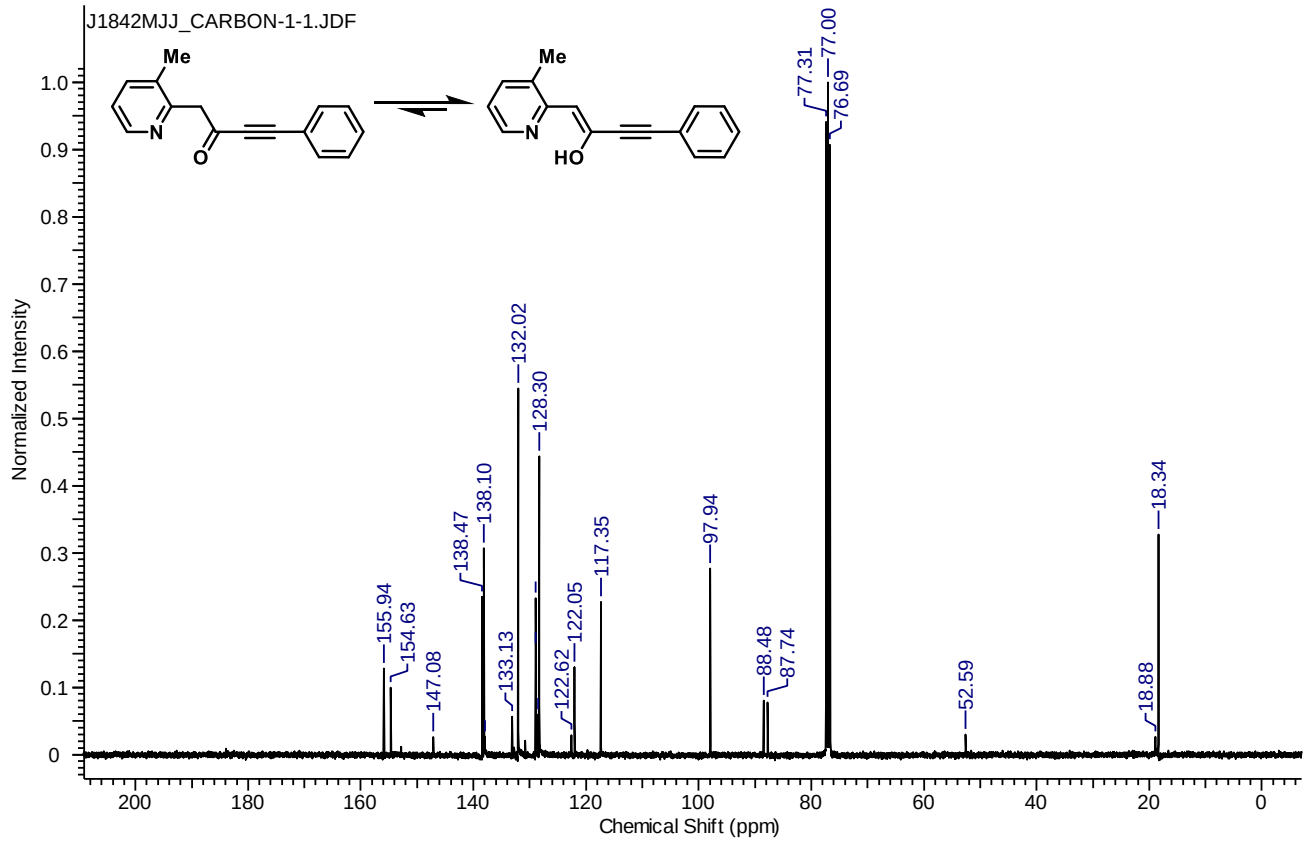
^{1}H & ^{13}C NMR spectra: **5h**



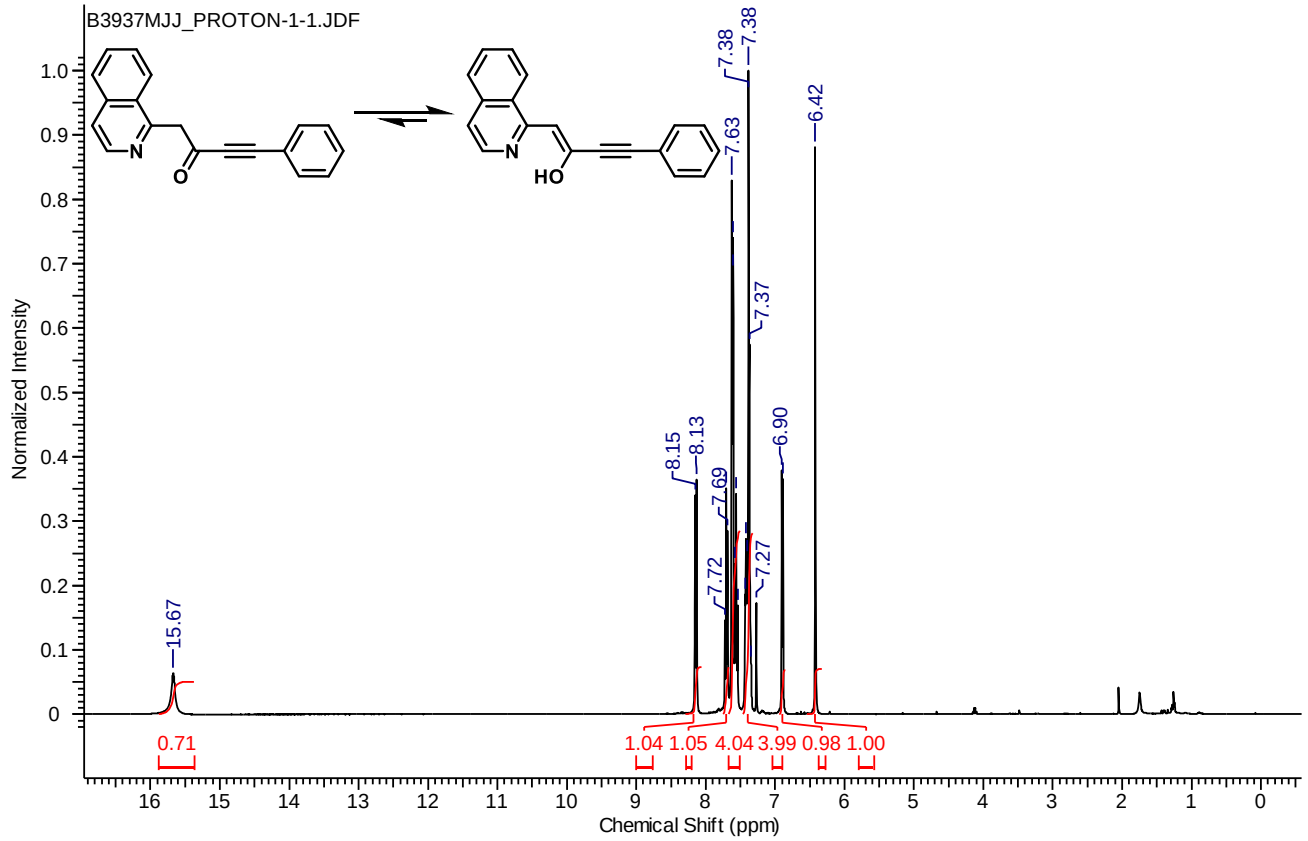


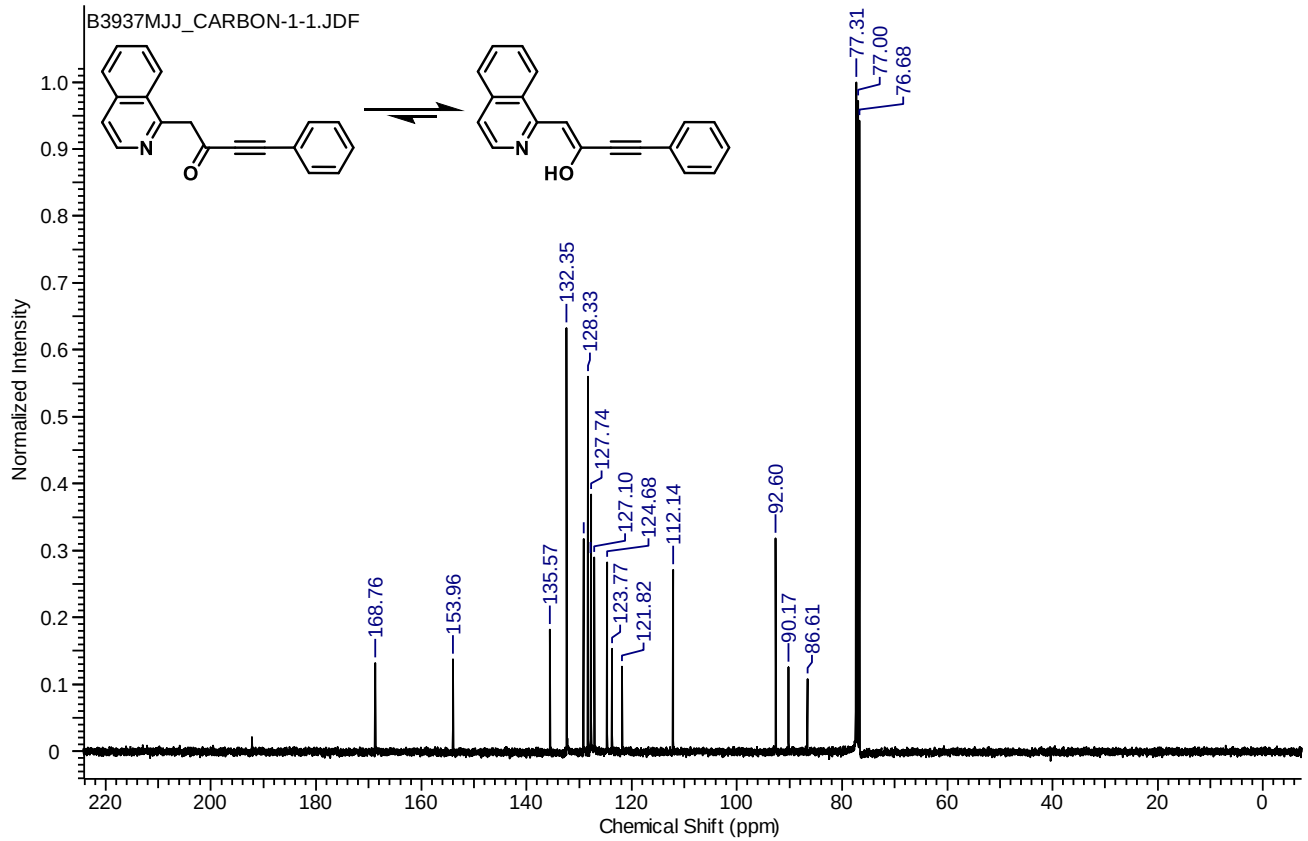
^{1}H & ^{13}C NMR spectra: **5i**



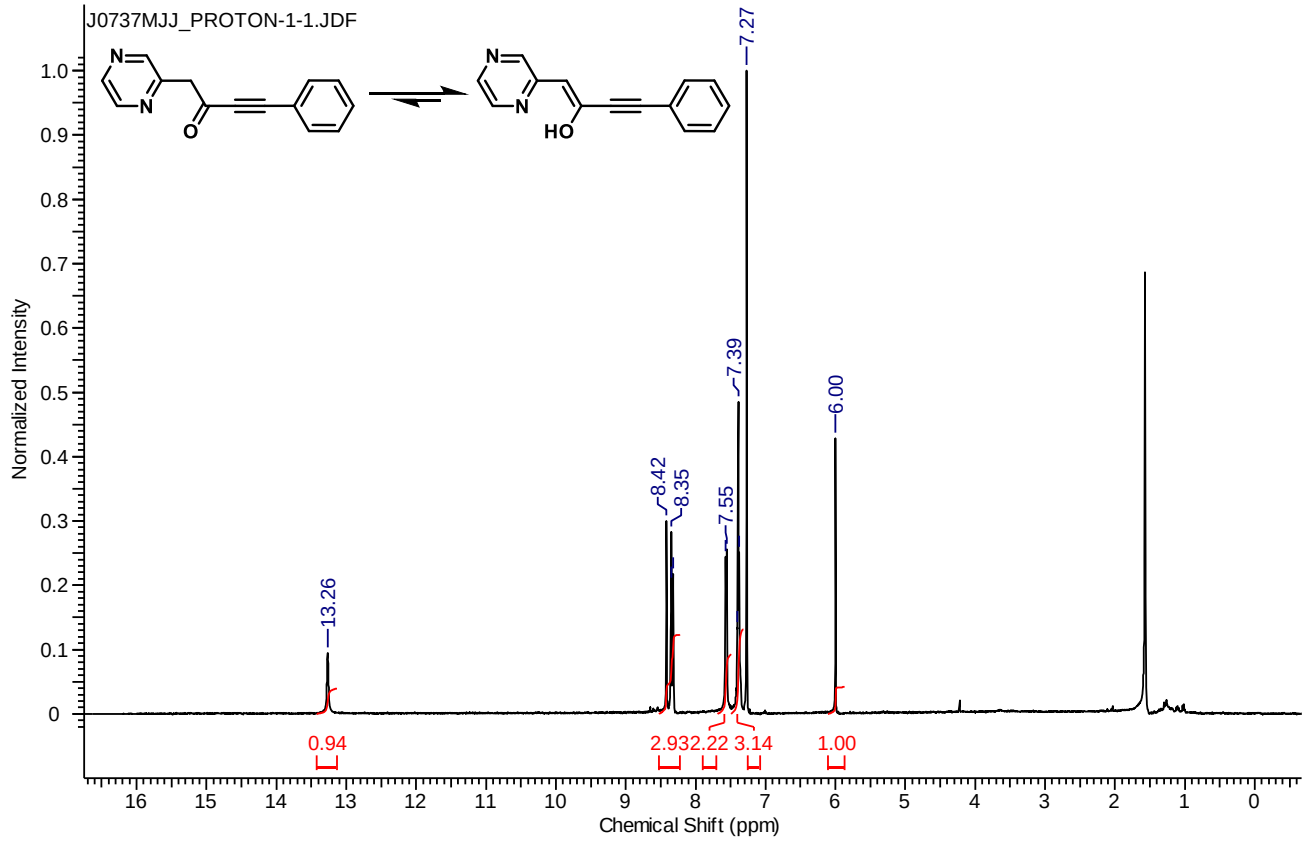


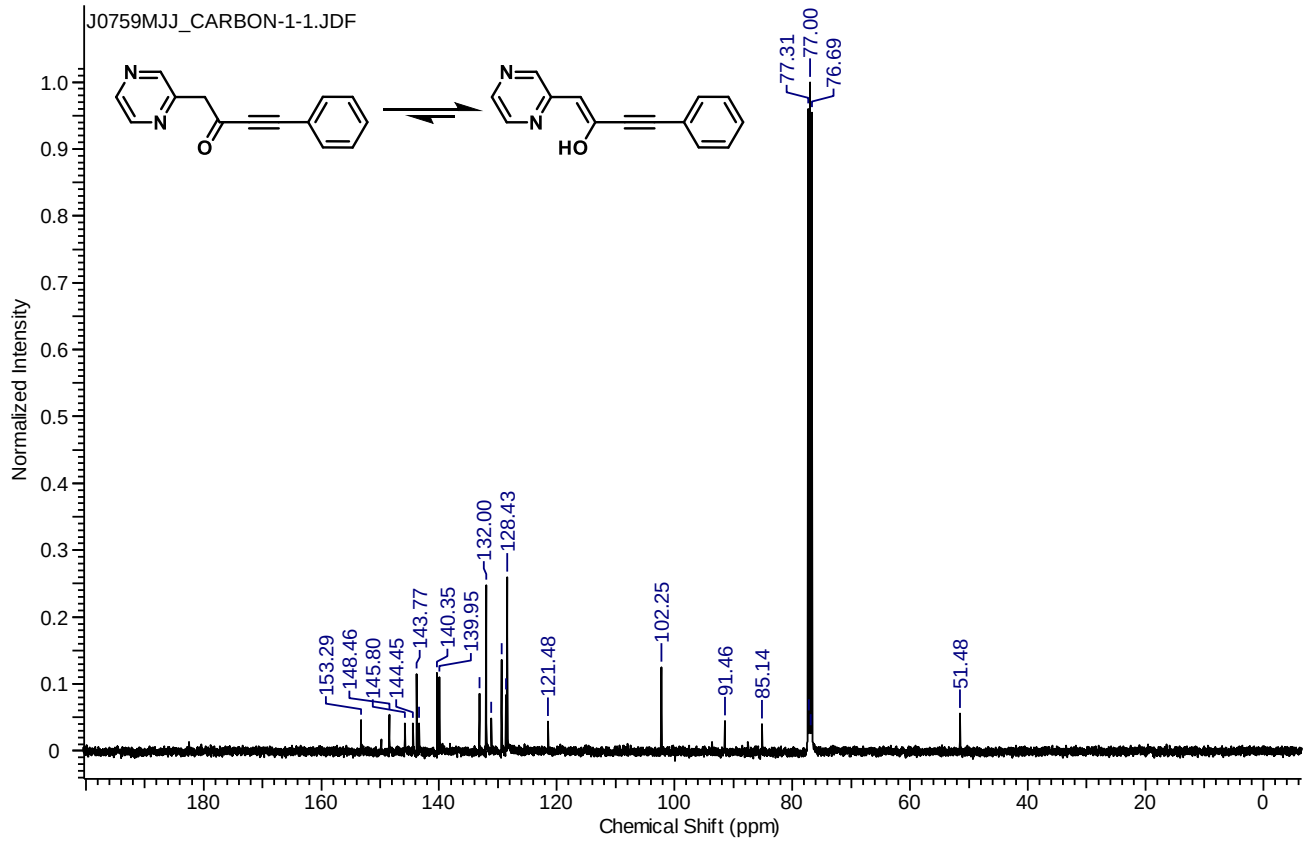
^{1}H & ^{13}C NMR spectra: **5j**



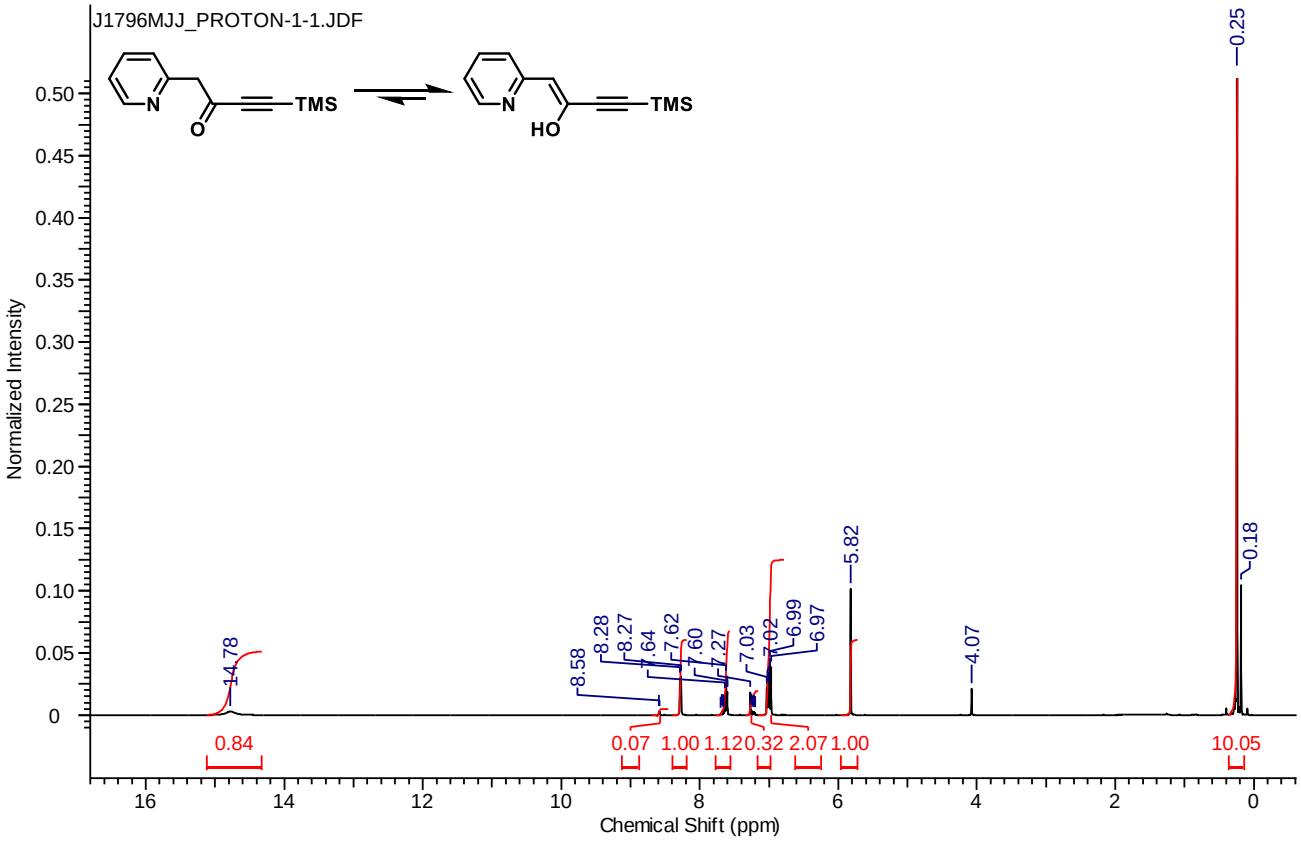


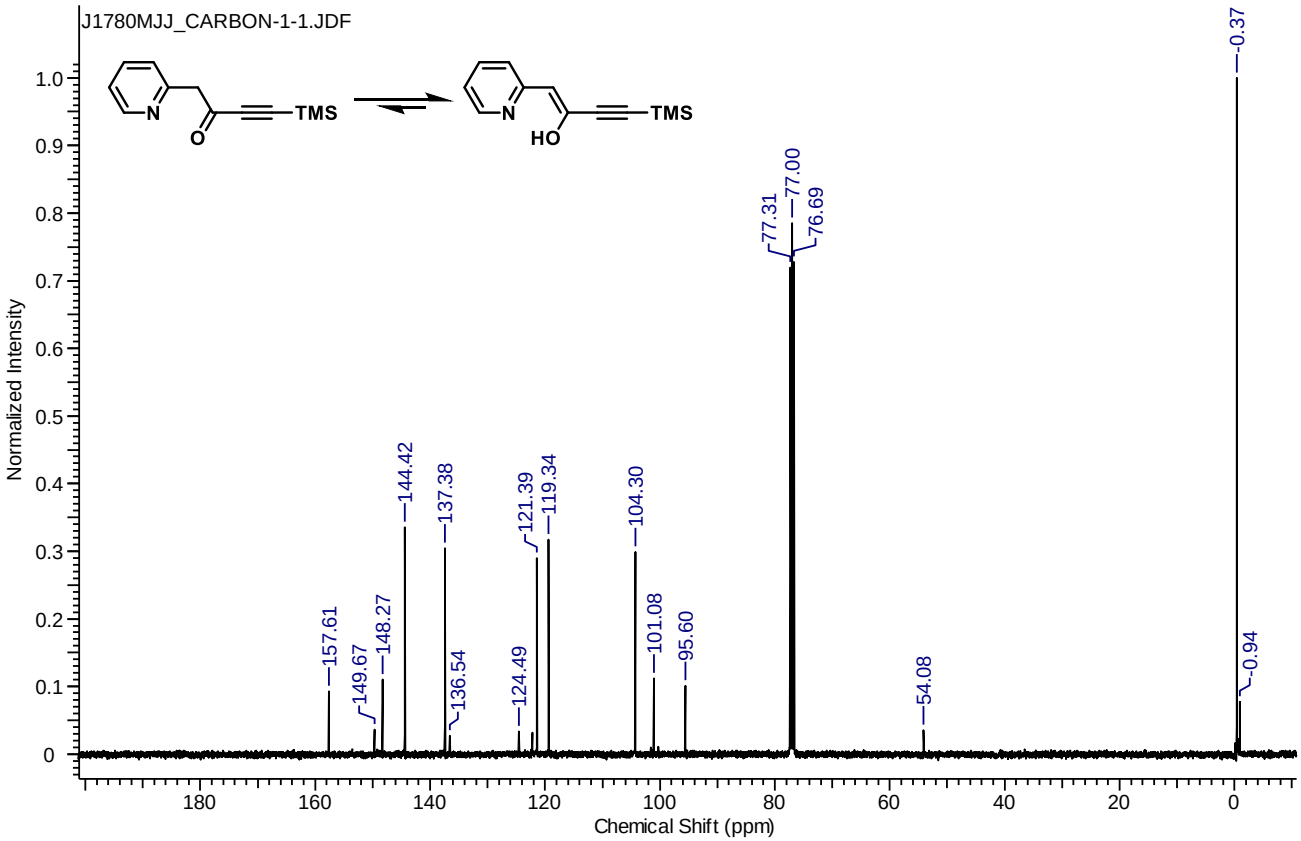
^{1}H & ^{13}C NMR spectra: **5k**



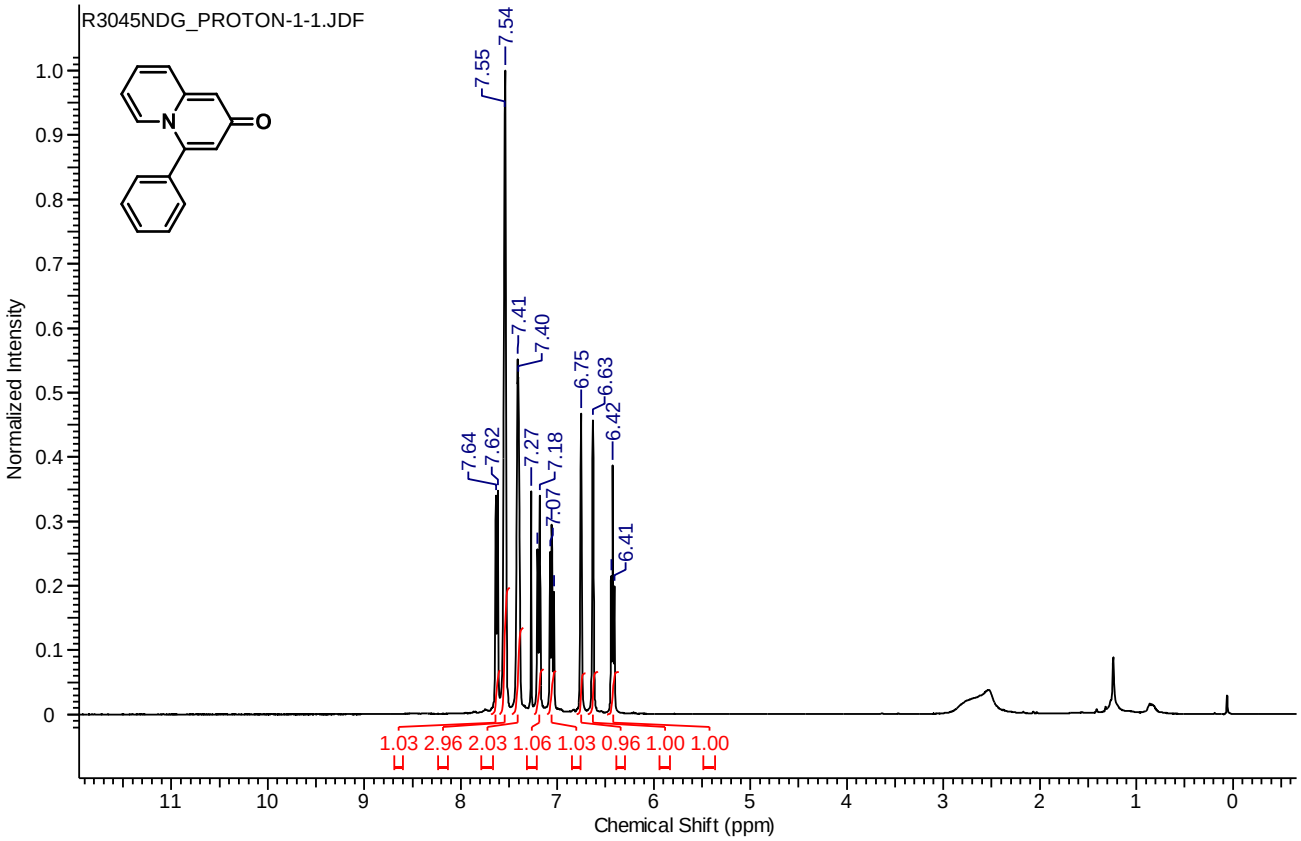


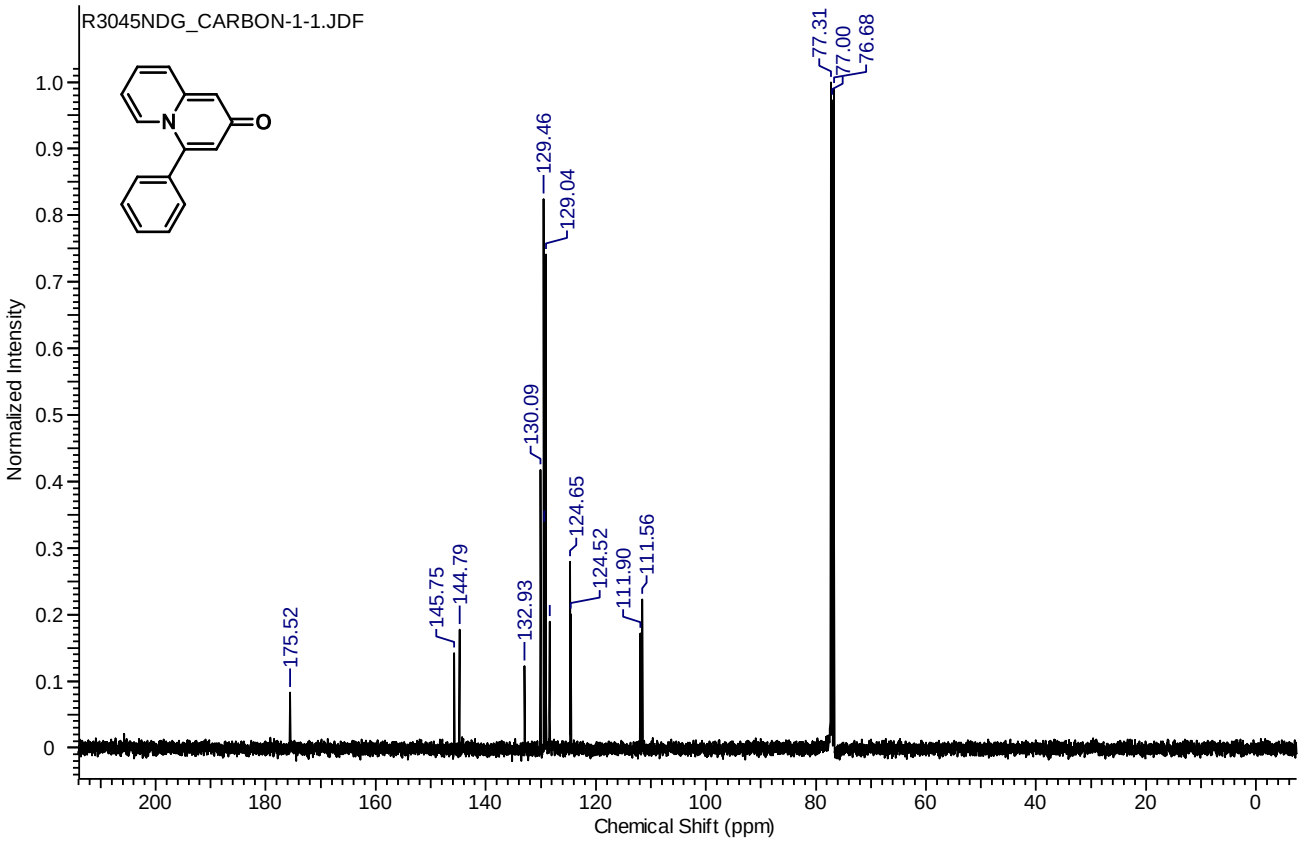
^{1}H & ^{13}C NMR spectra: **5l**



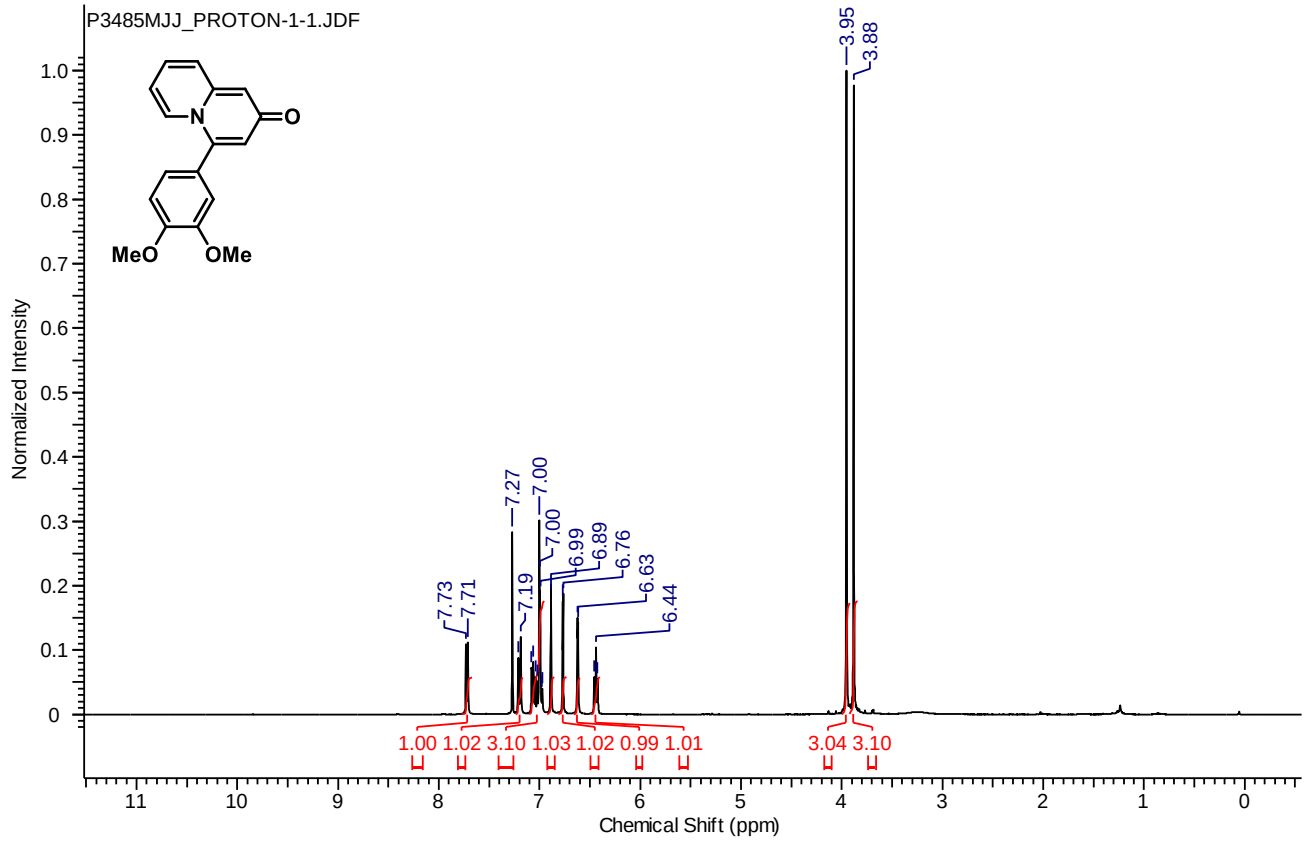


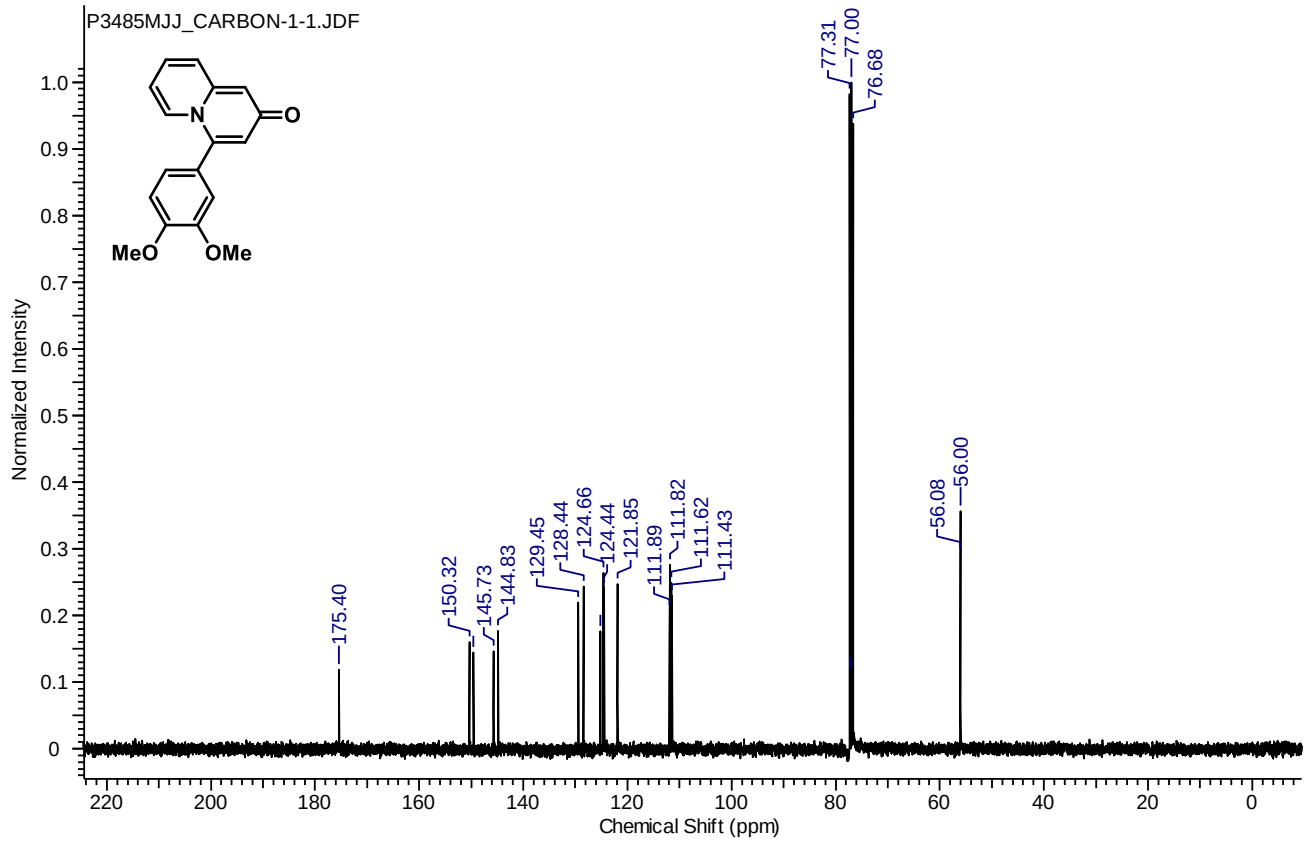
^{1}H & ^{13}C NMR spectra: **6a**



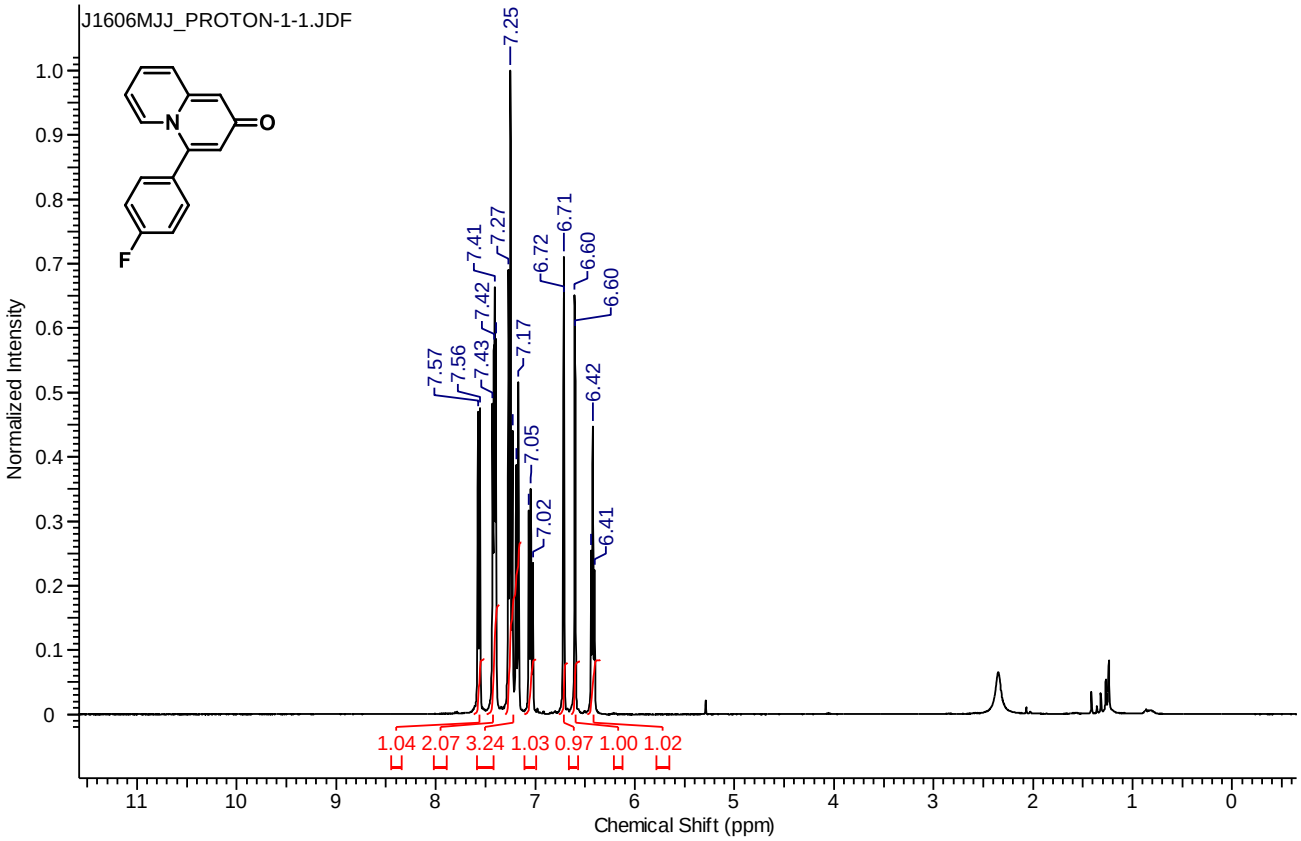


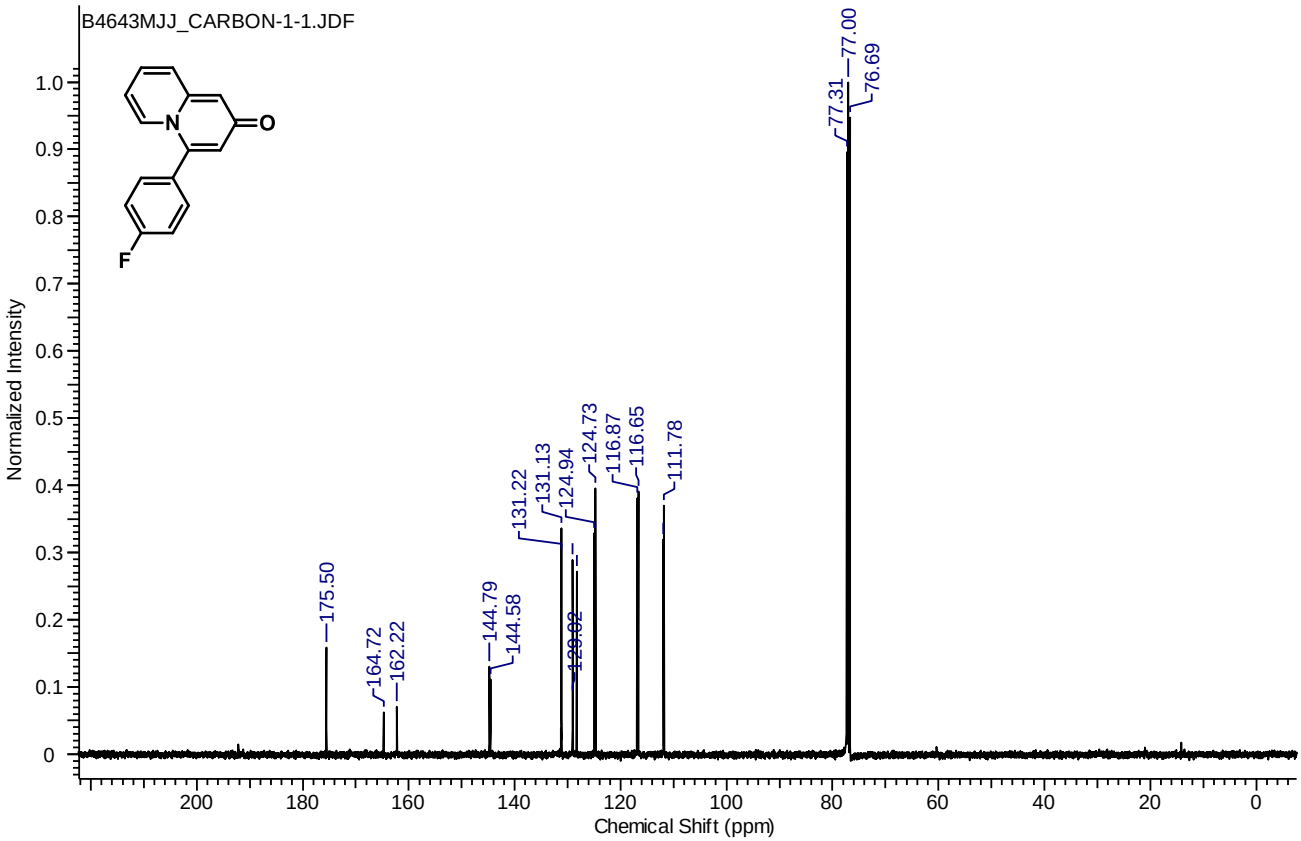
^{1}H & ^{13}C NMR spectra: **6b**

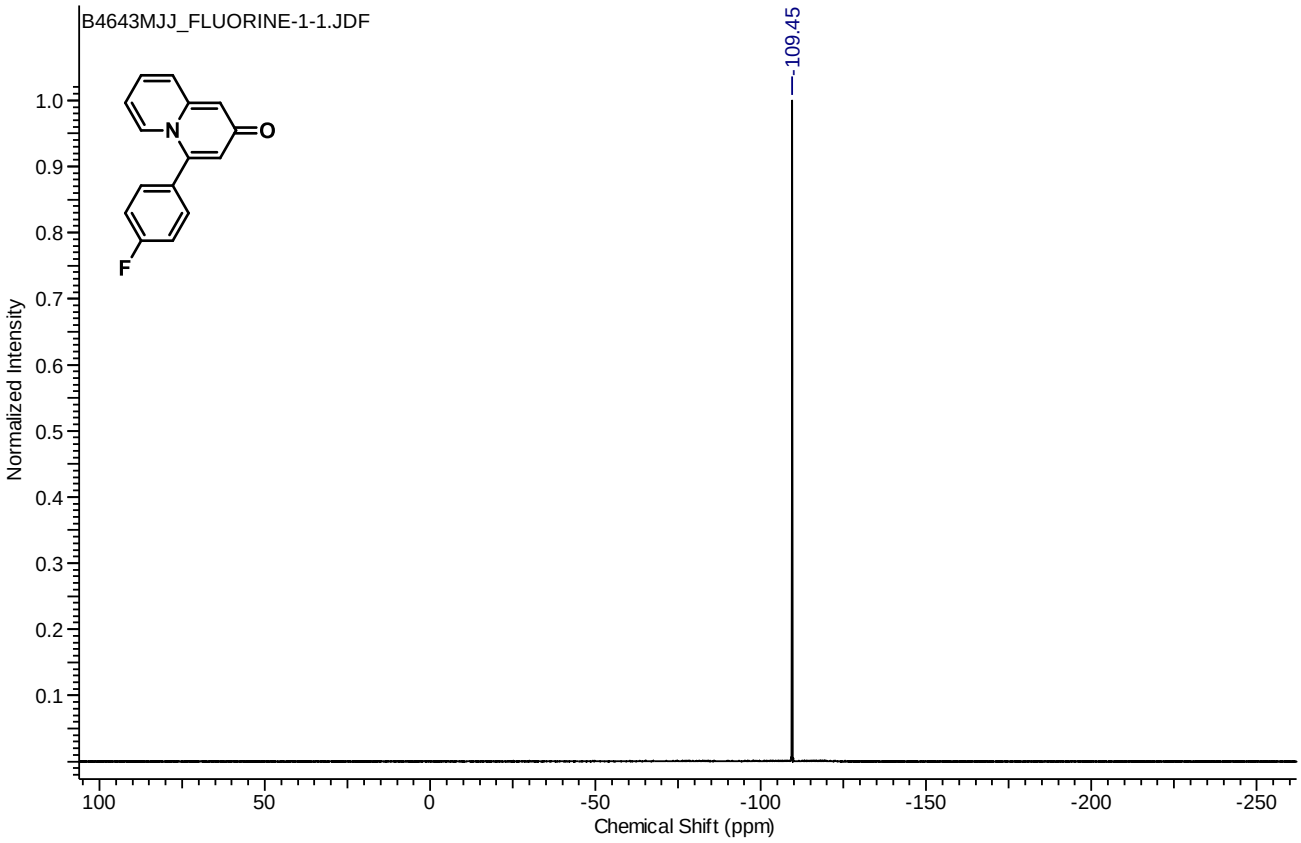




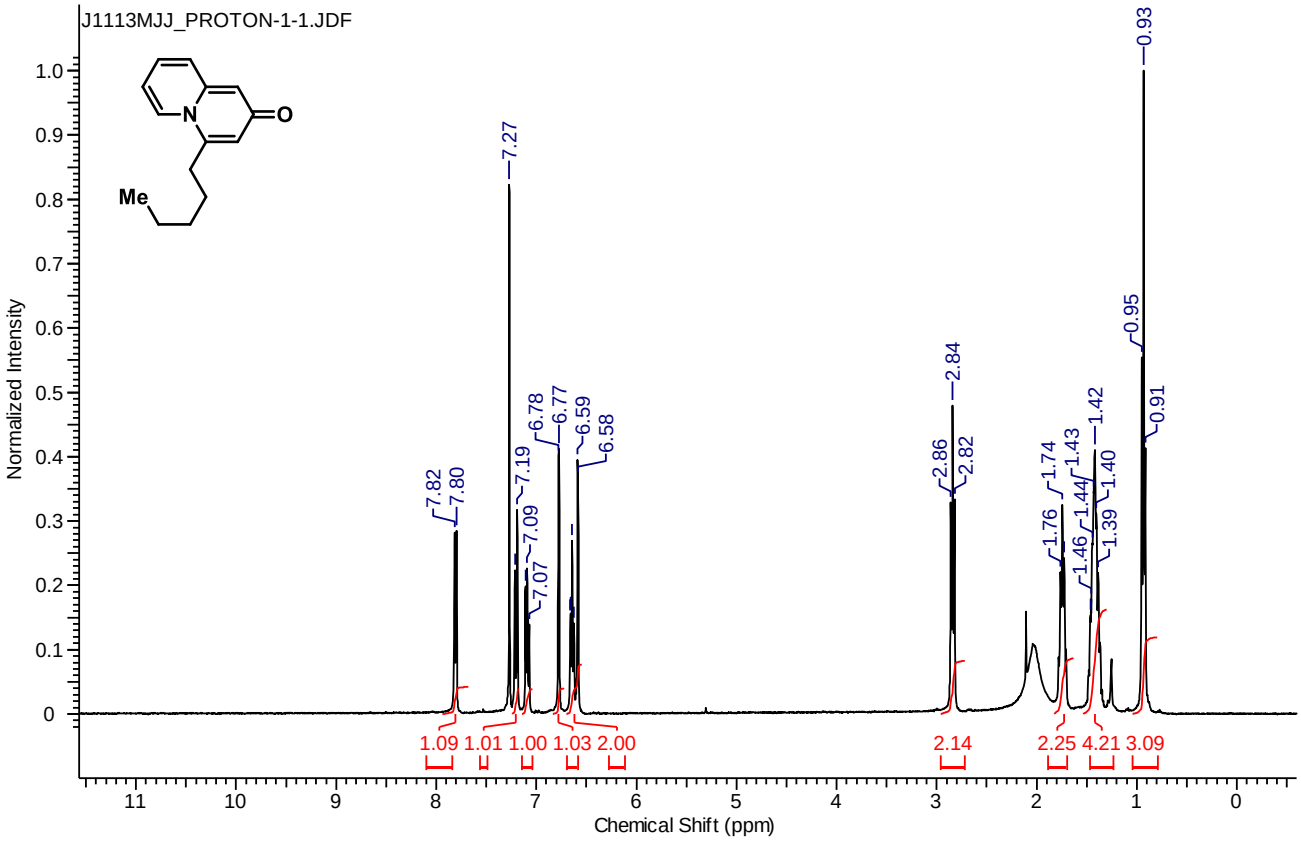
^{1}H, ^{13}C & ^{19}F NMR spectra: **6c**

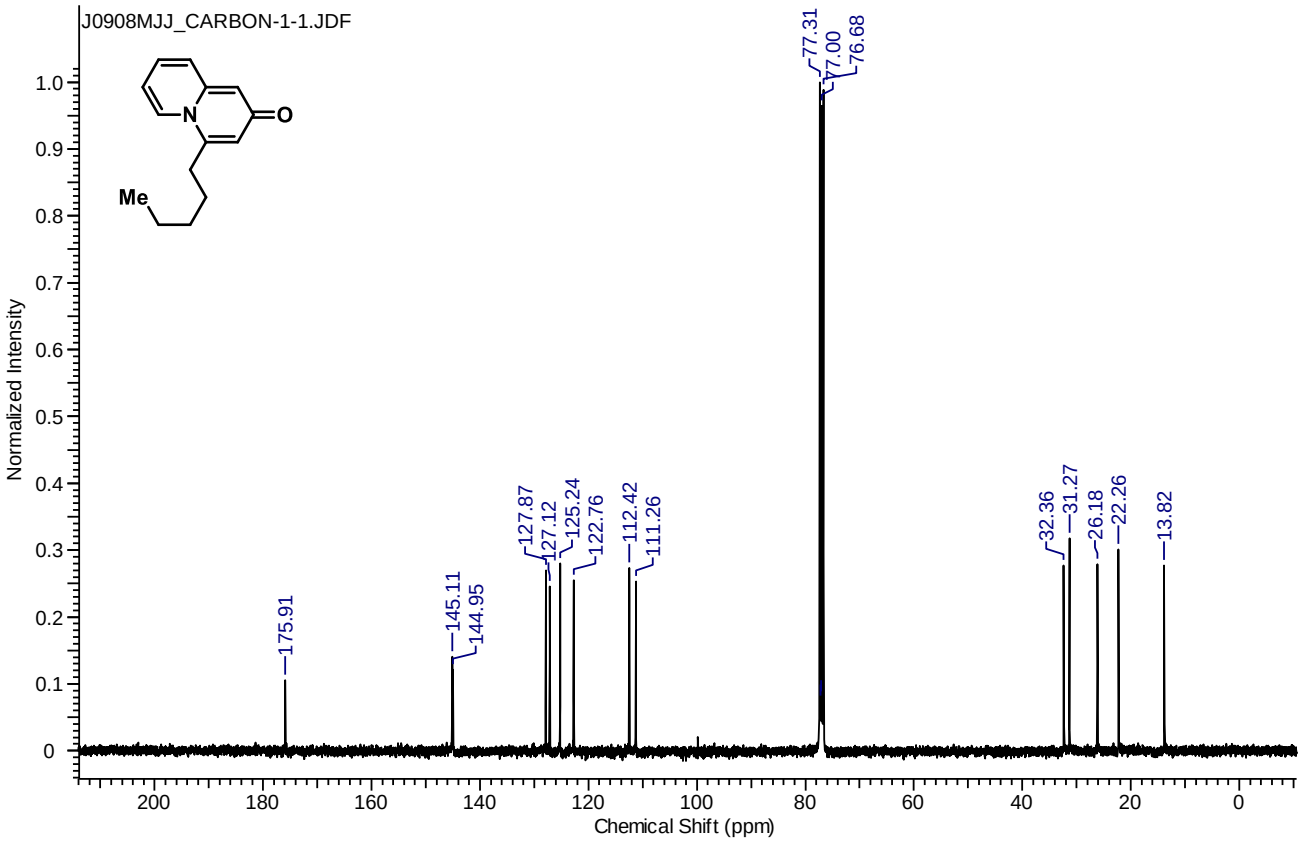




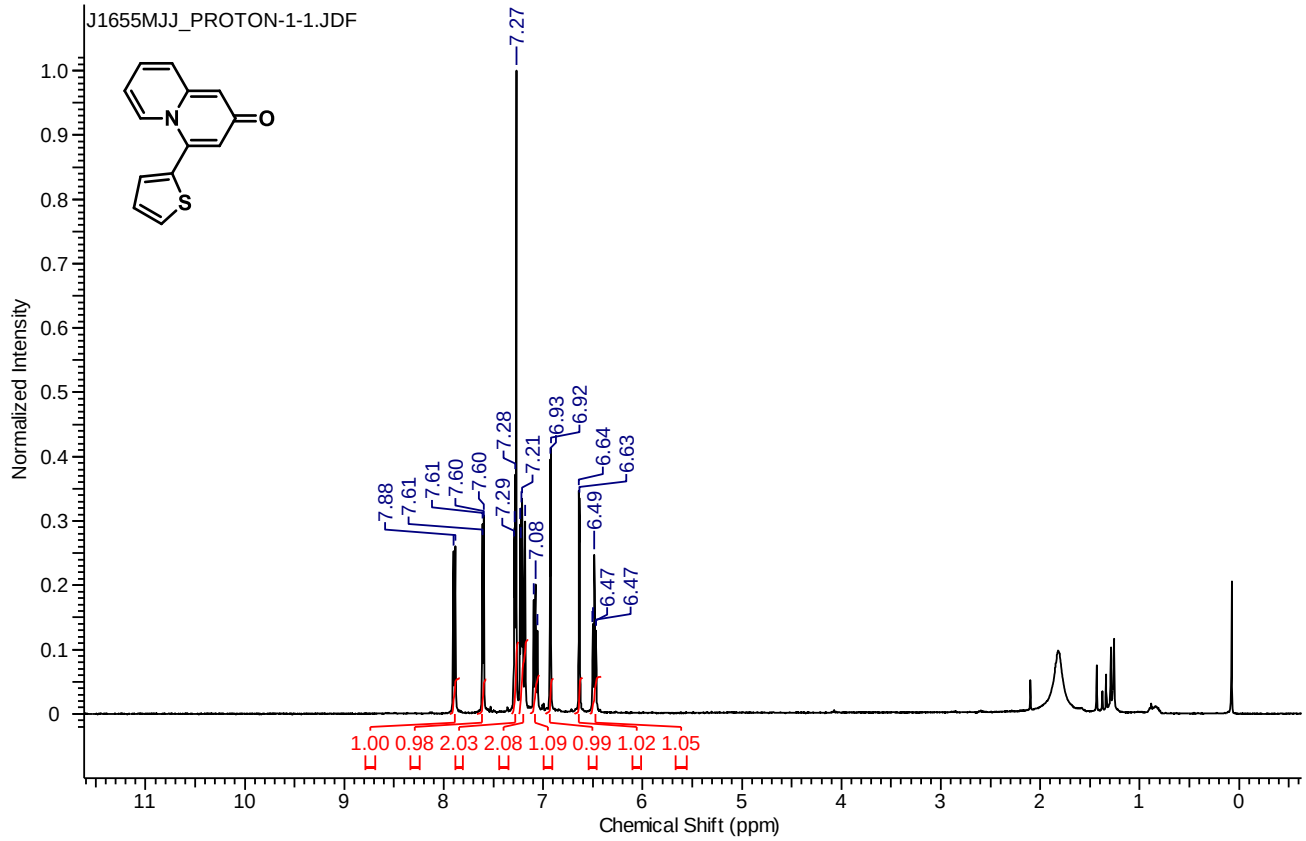

B4643MJJ_FLUORINE-1-1.JDF
-109.45
N
O
F
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
100
50
0
-50
-100
-150
-200
-250
Chemical Shift (ppm)

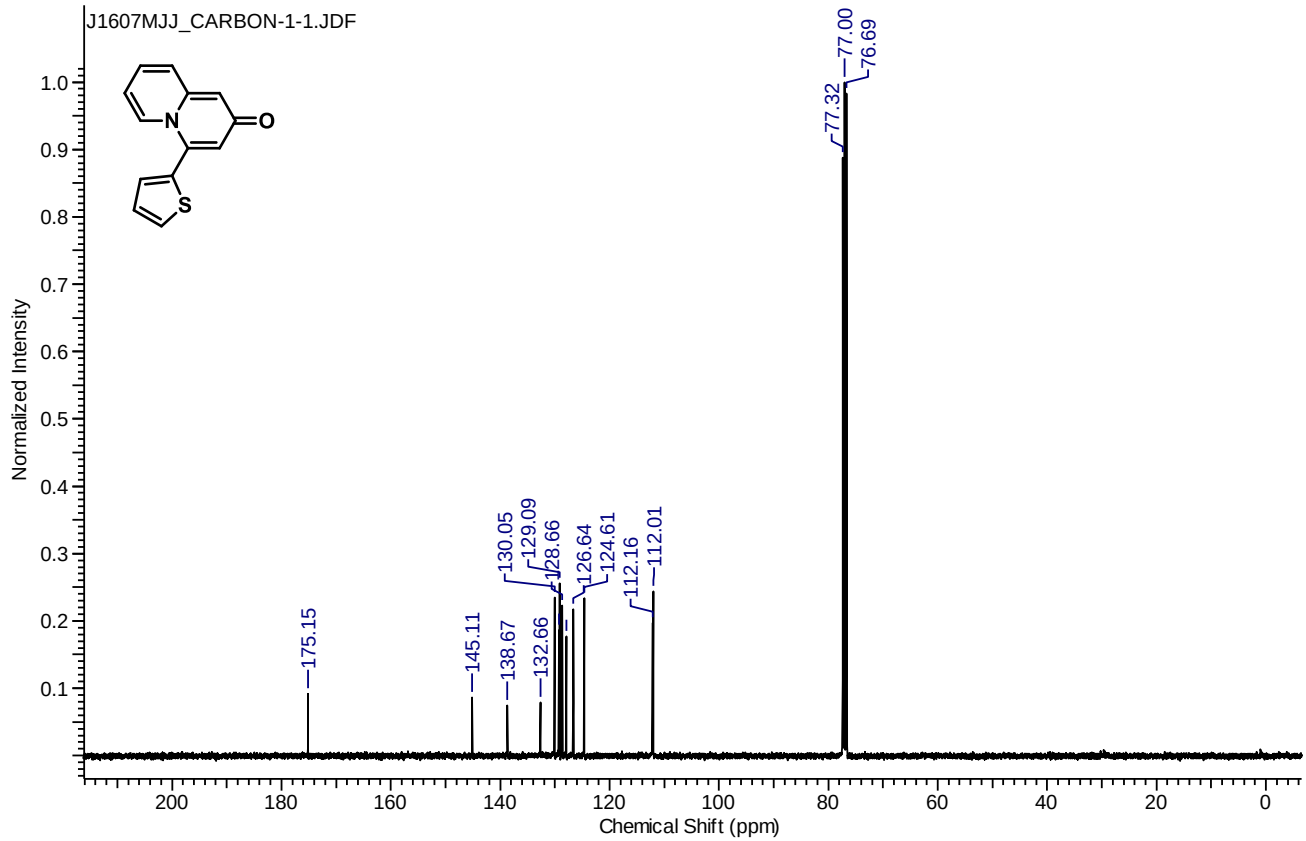
^{1}H & ^{13}C NMR spectra: **6d**



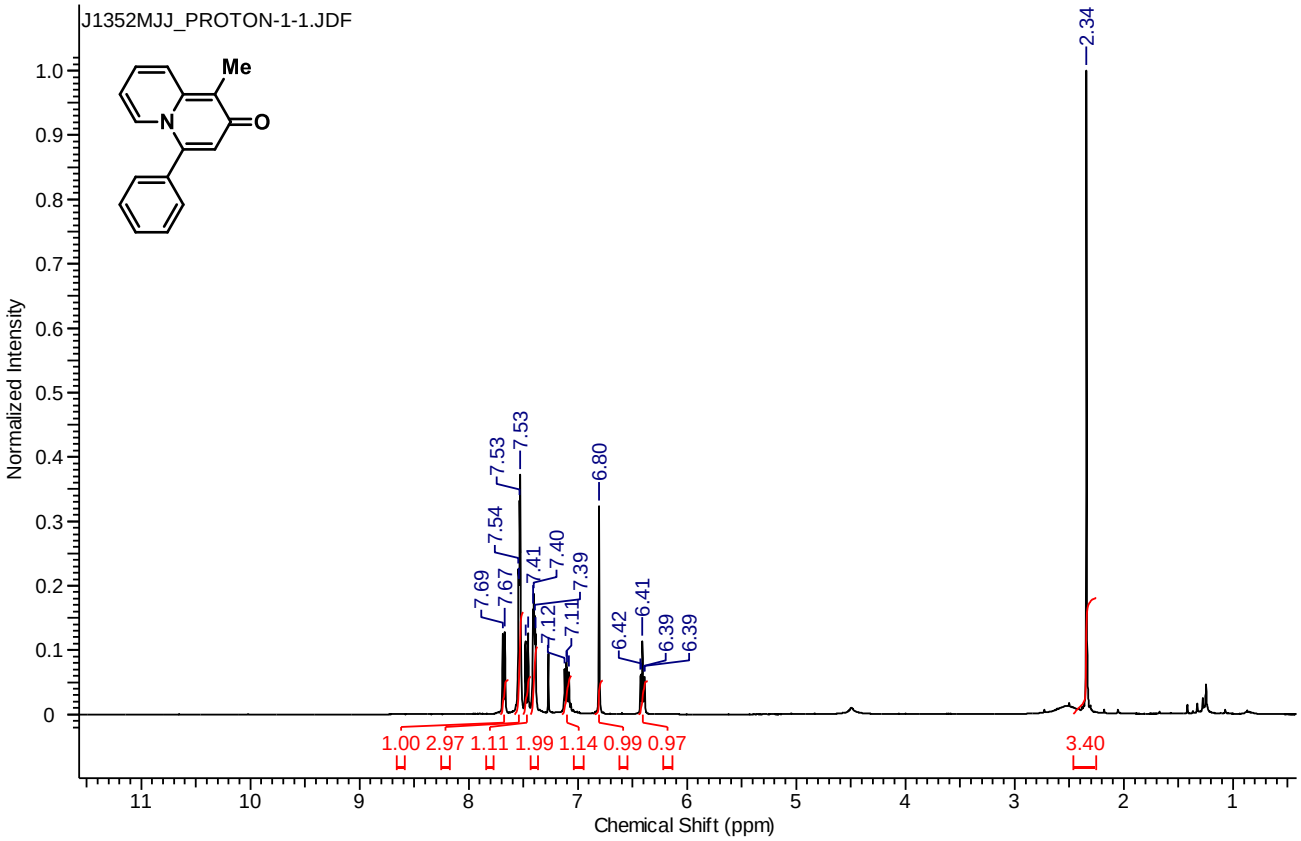


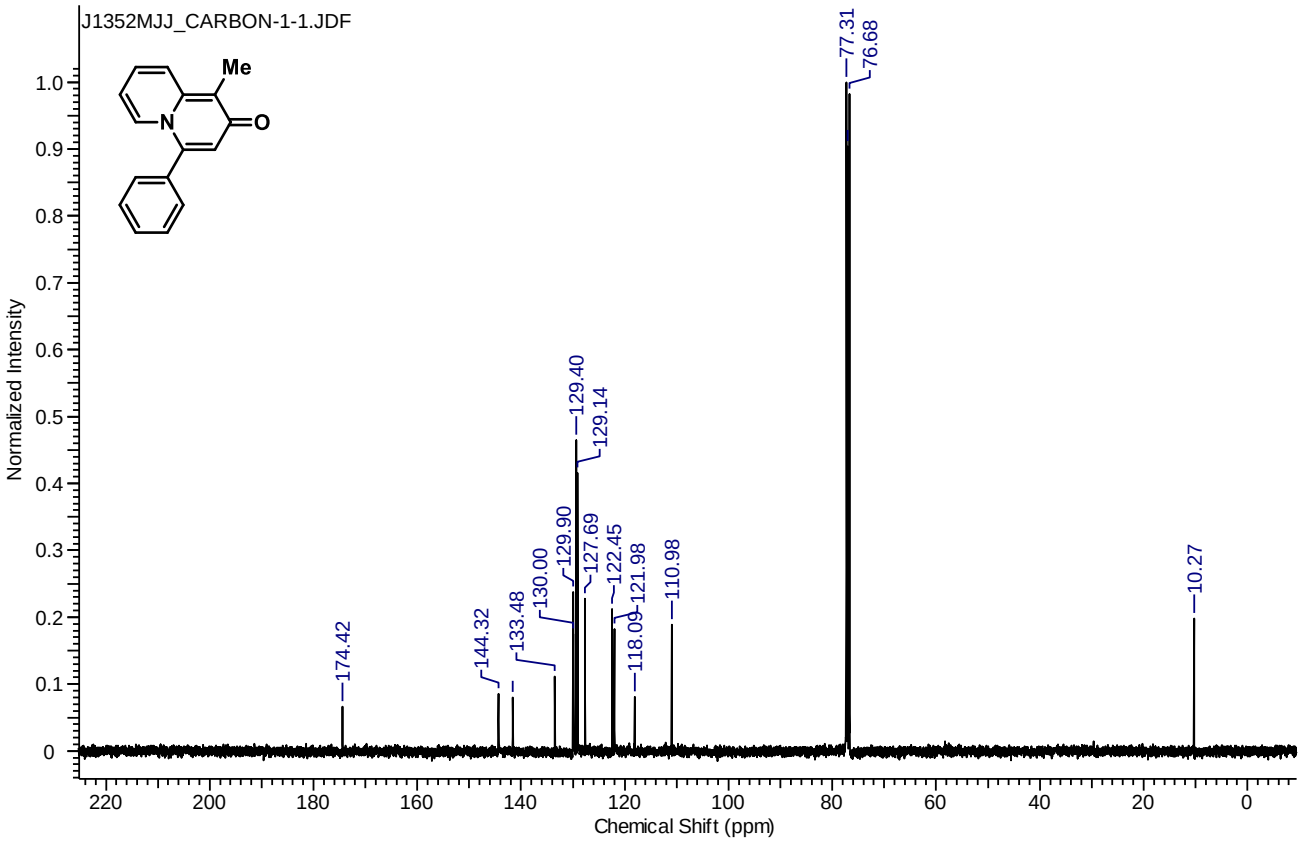
^{1}H & ^{13}C NMR spectra: **6e**



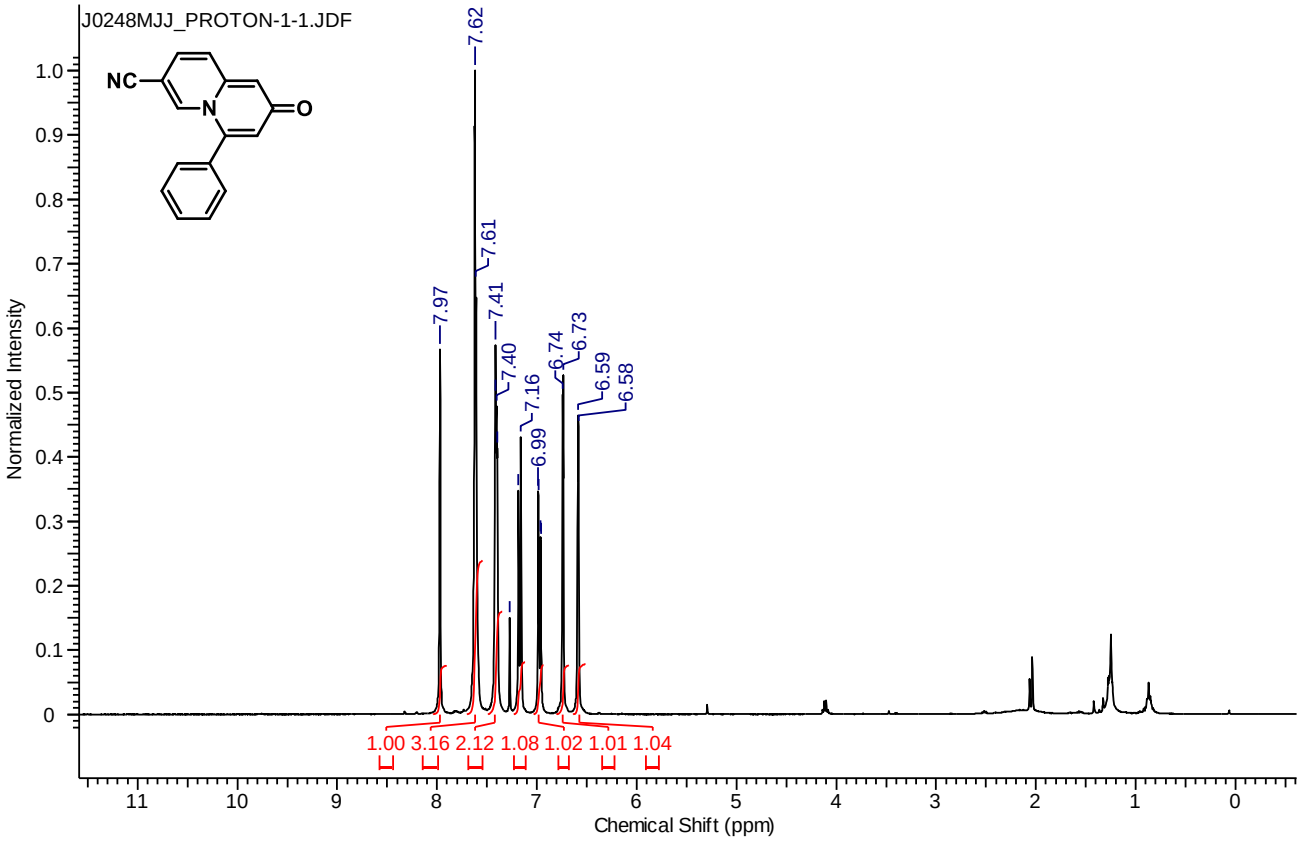


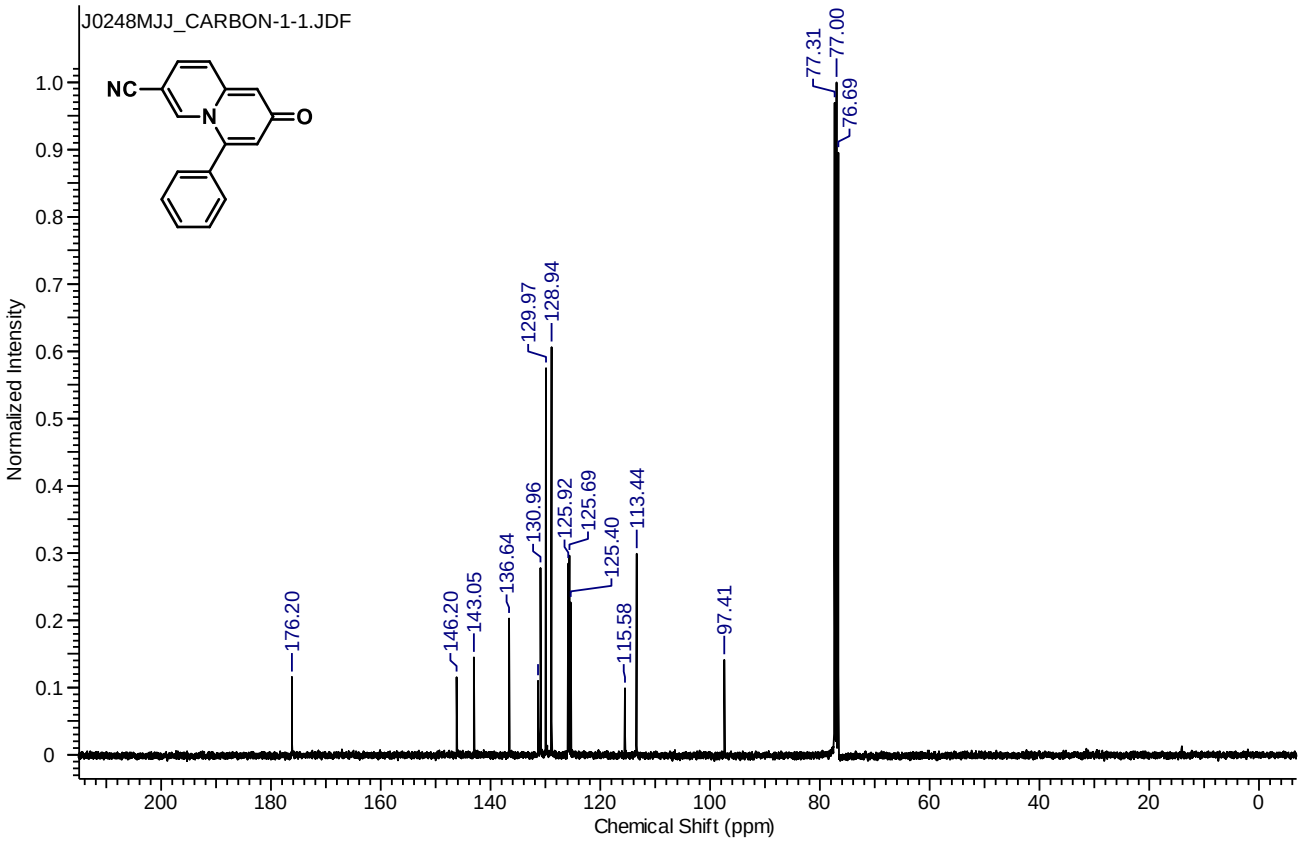
^{1}H & ^{13}C NMR spectra: **6f**



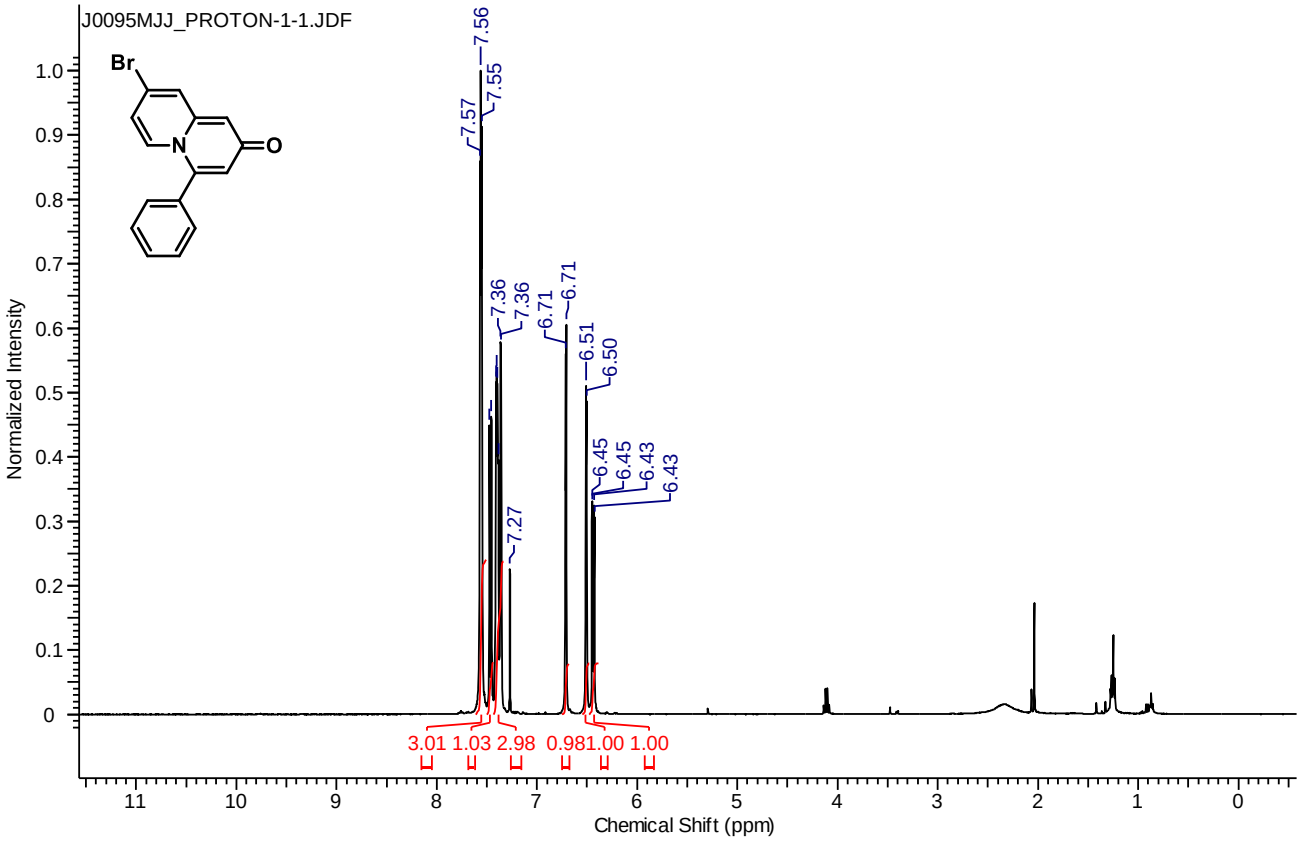


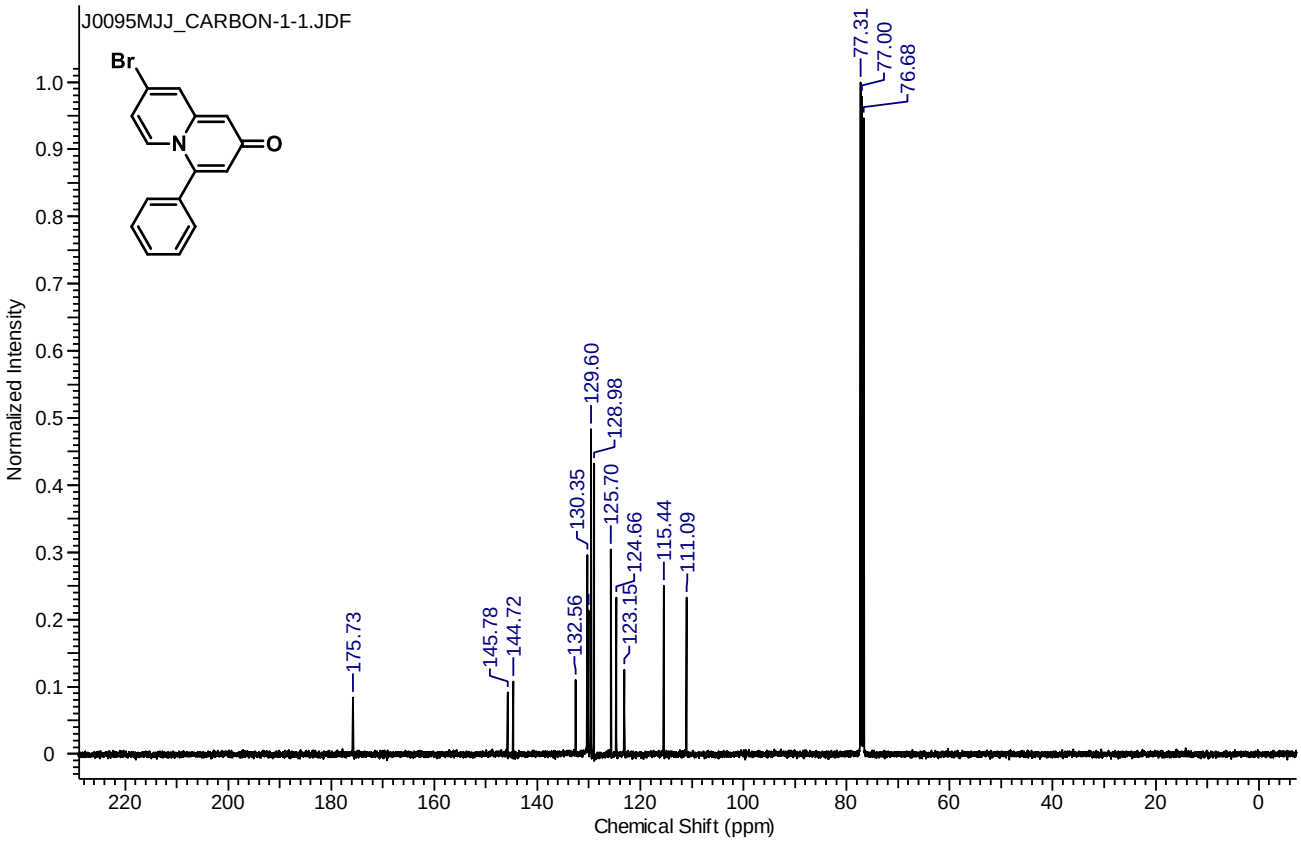
^{1}H & ^{13}C NMR spectra: **6g**



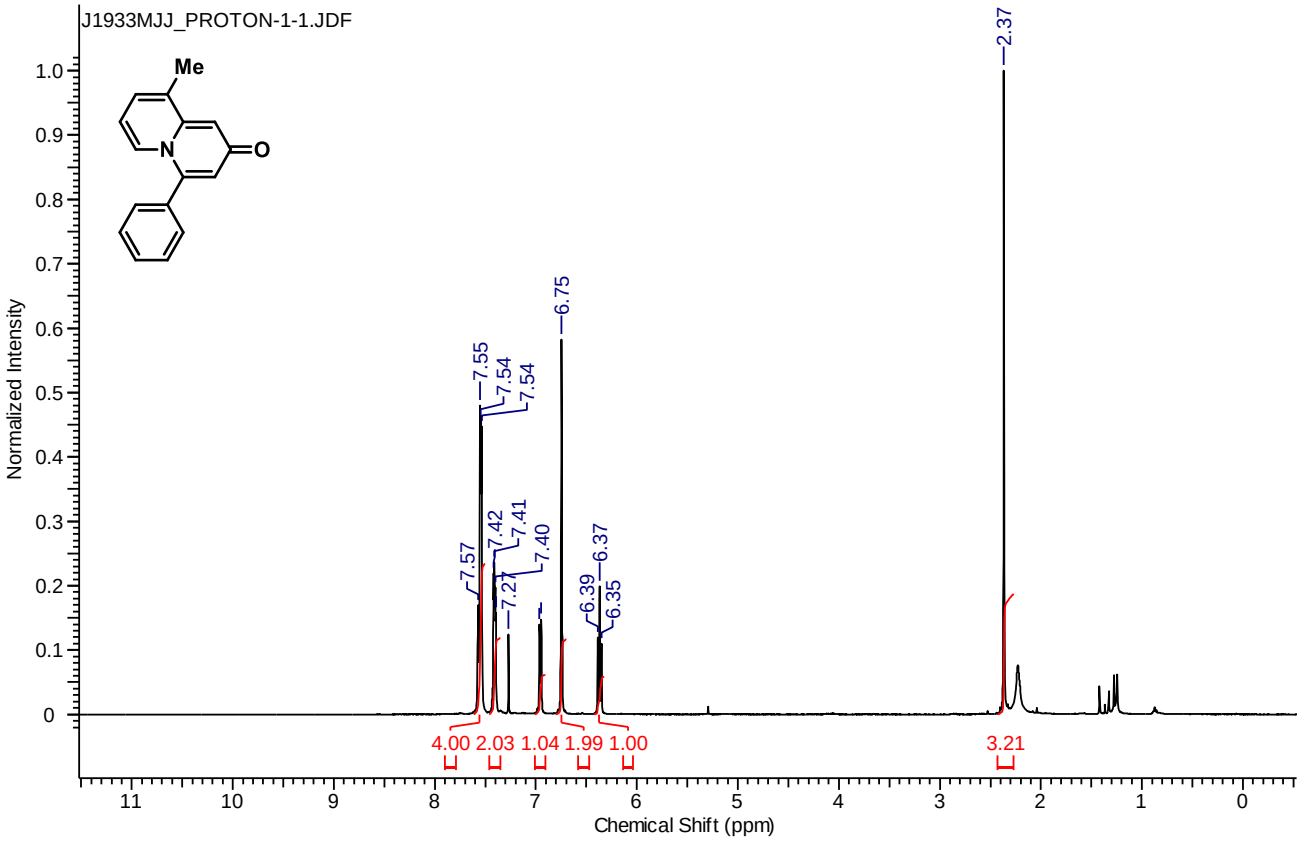


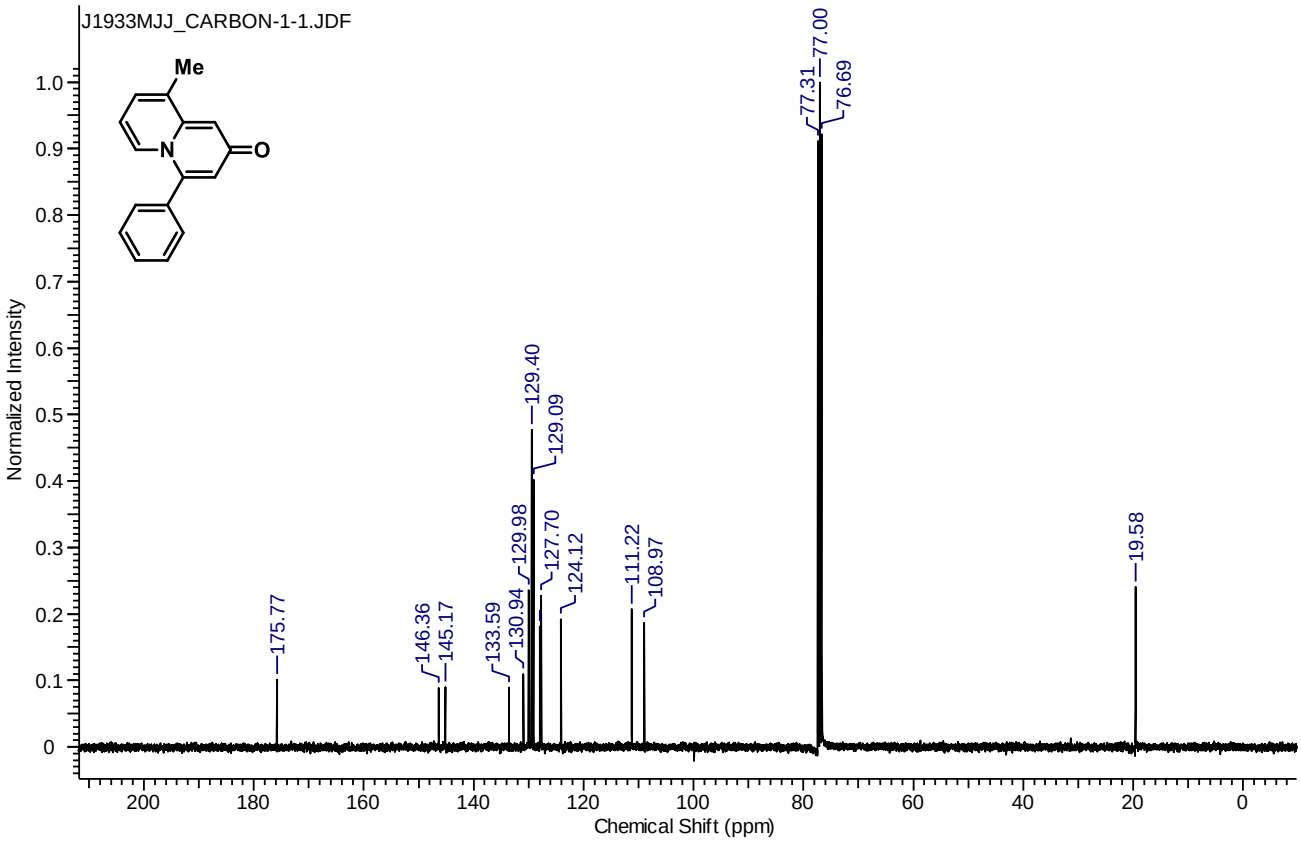
^{1}H & ^{13}C NMR spectra: **6h**



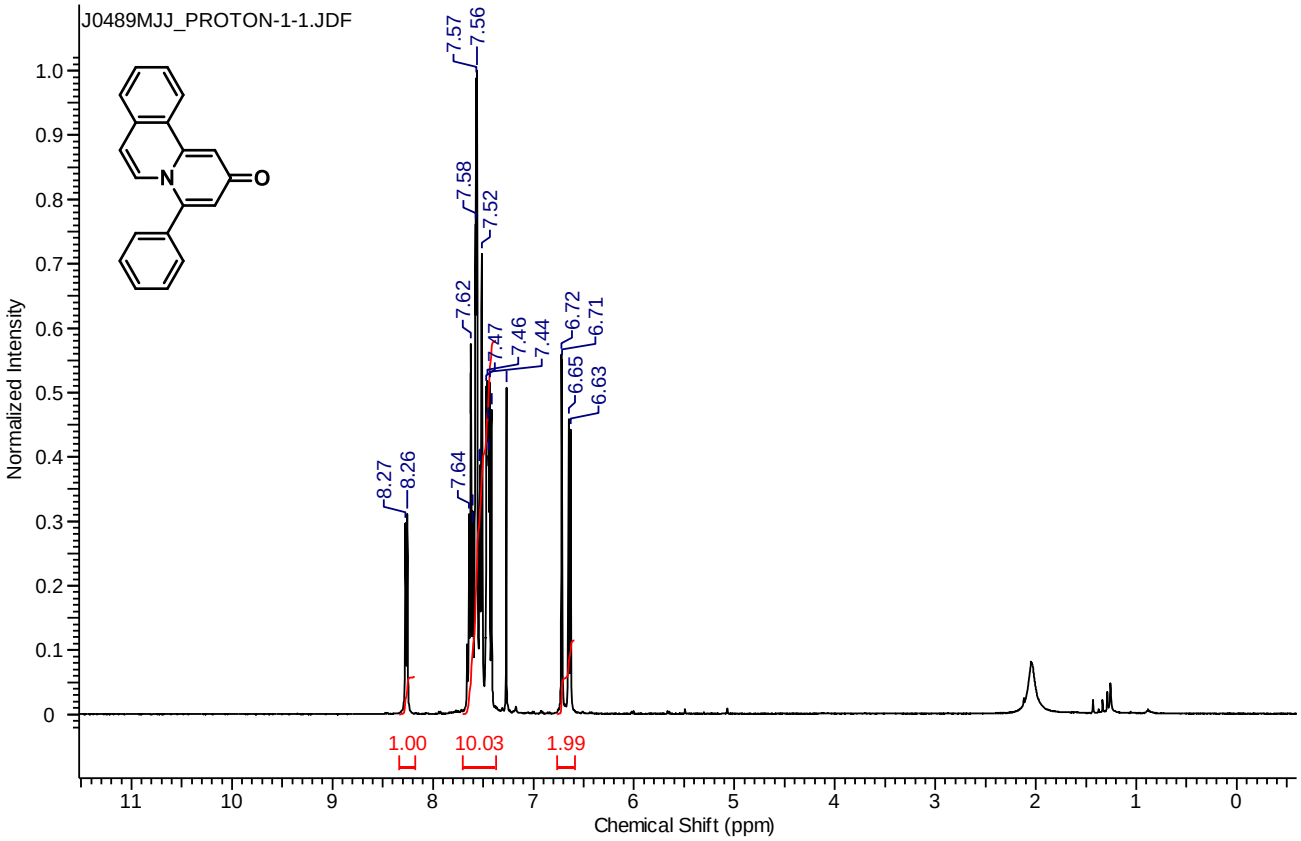


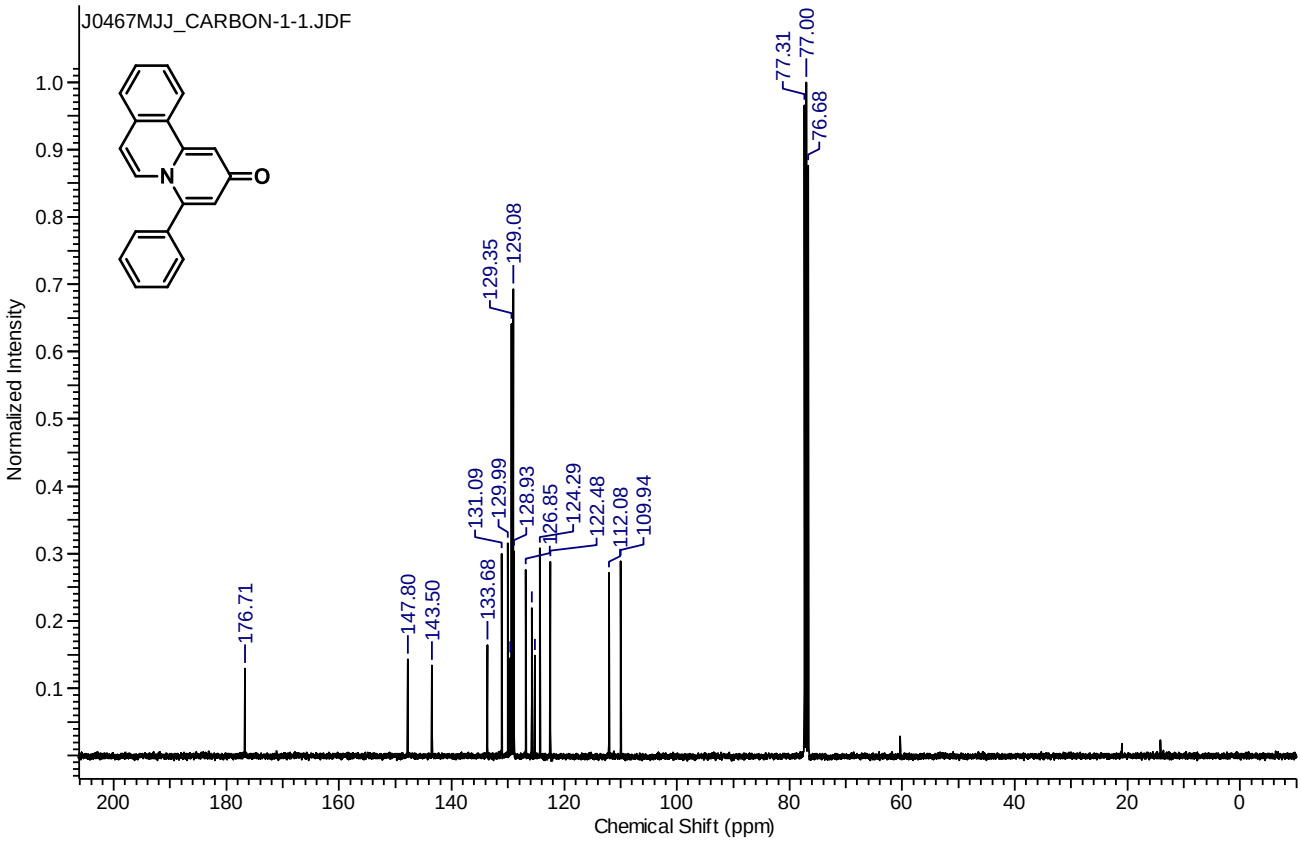
^{1}H & ^{13}C NMR spectra: **6i**



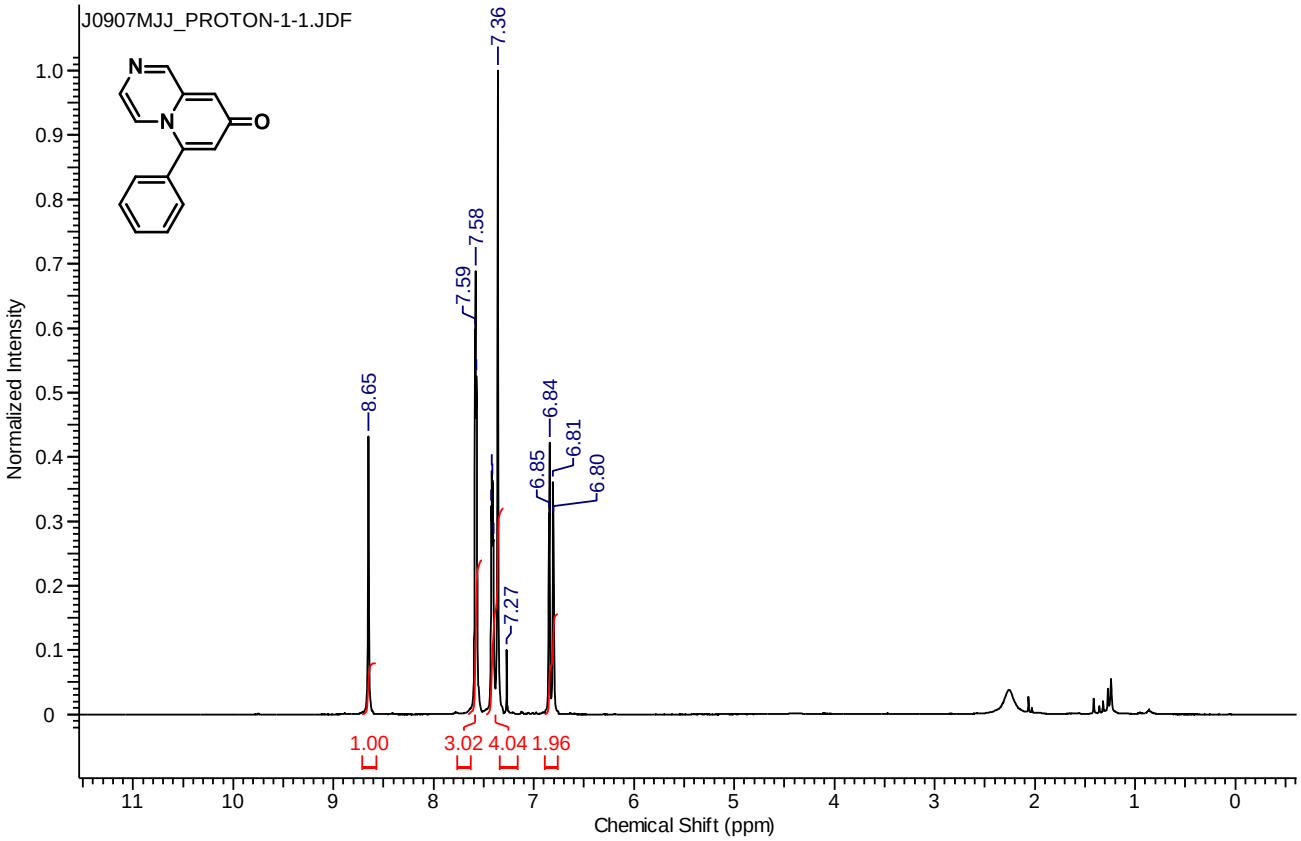


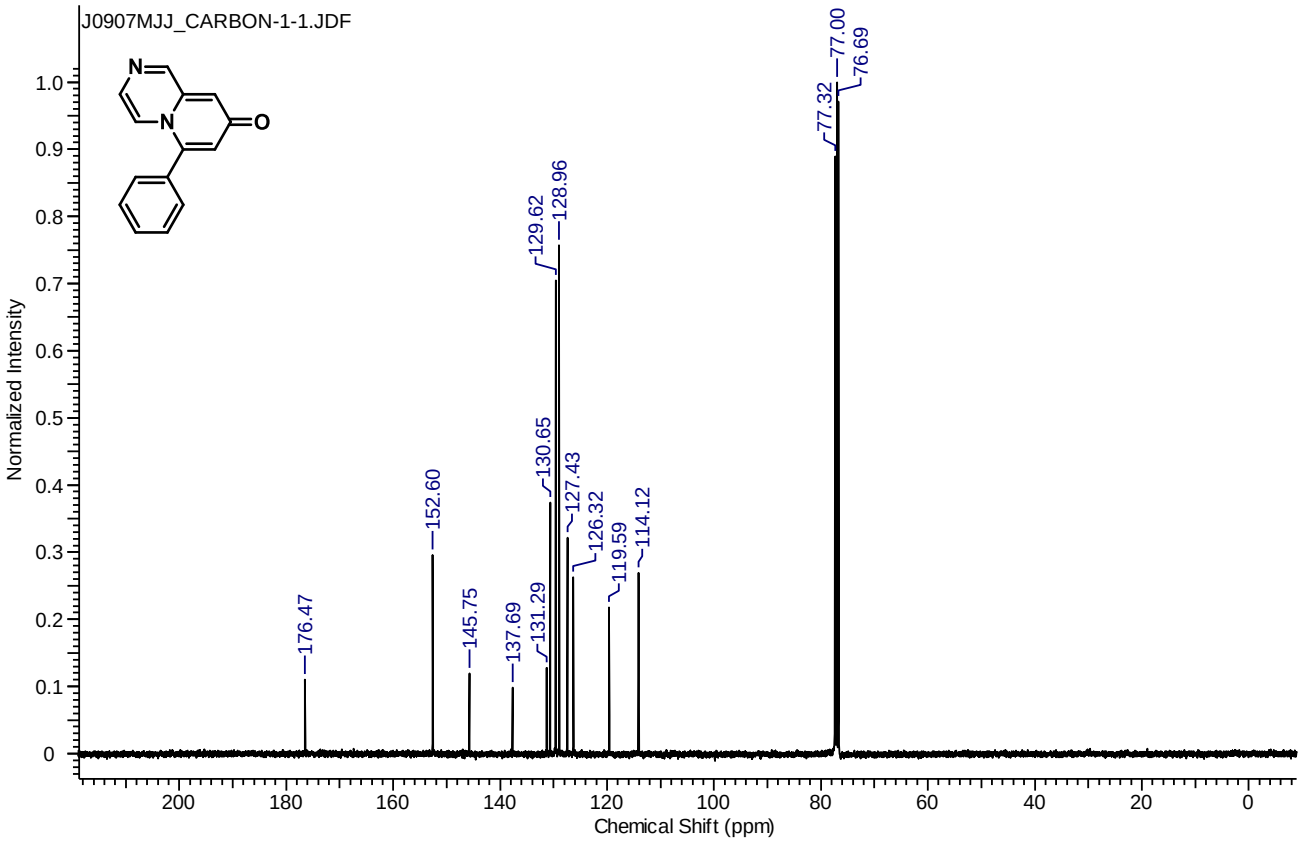
^{1}H & ^{13}C NMR spectra: **6j**



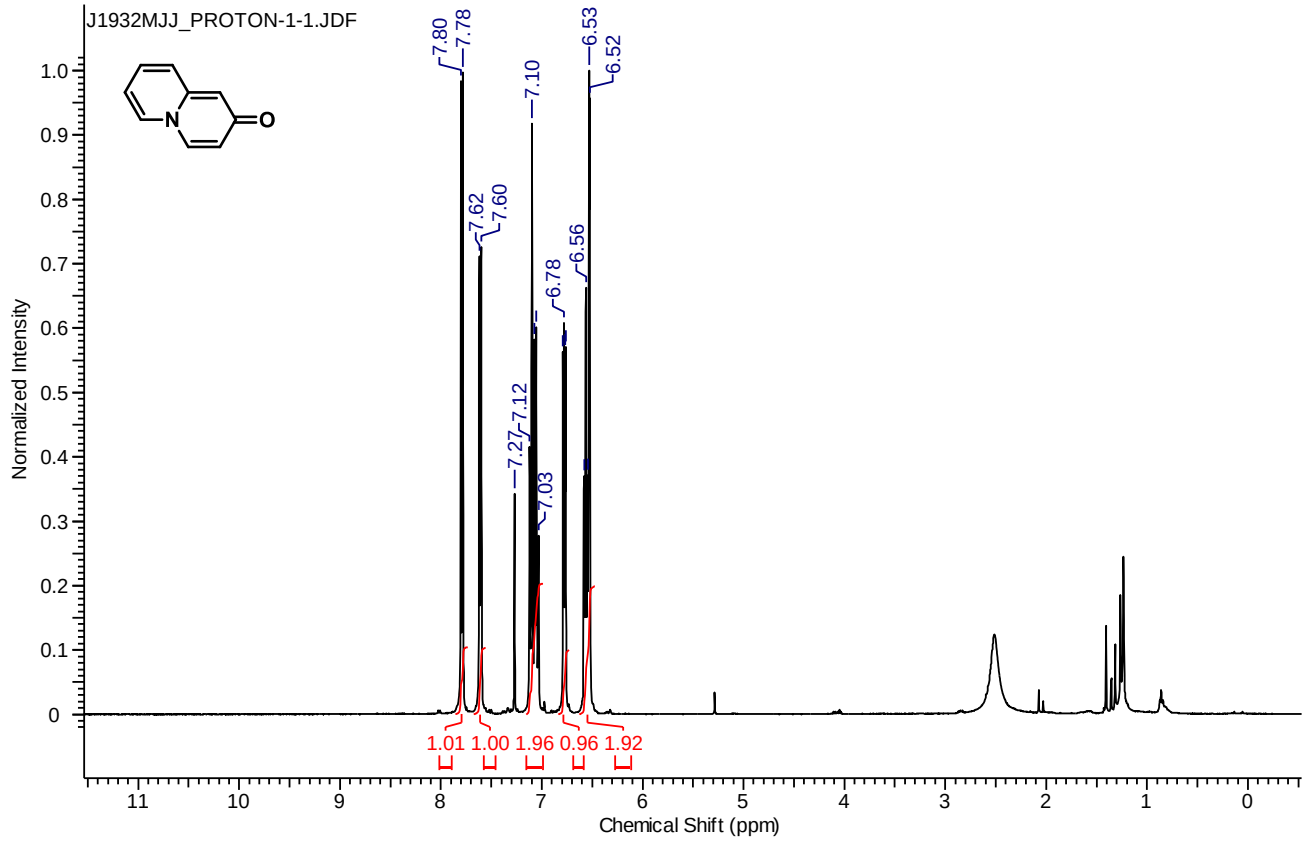


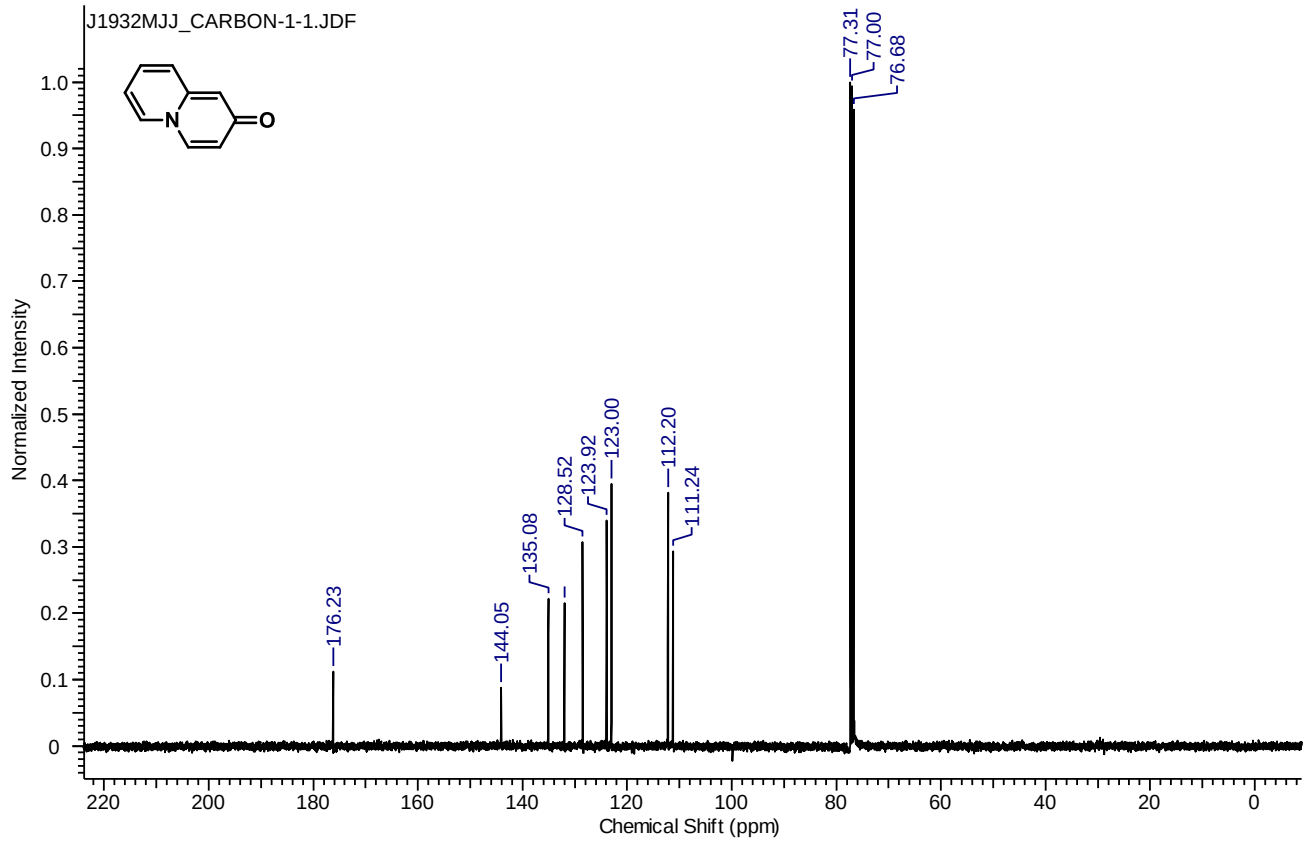
^{1}H & ^{13}C NMR spectra: **6k**



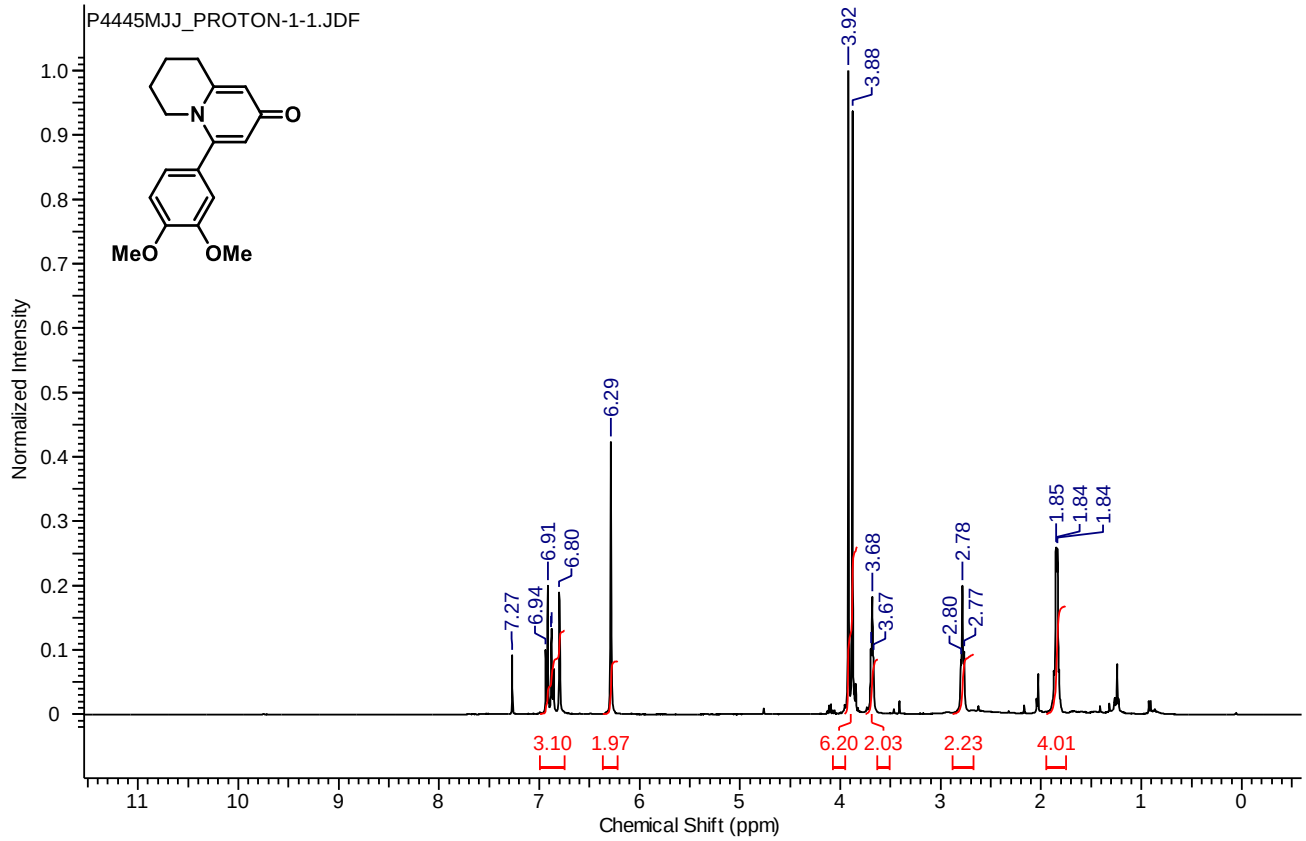


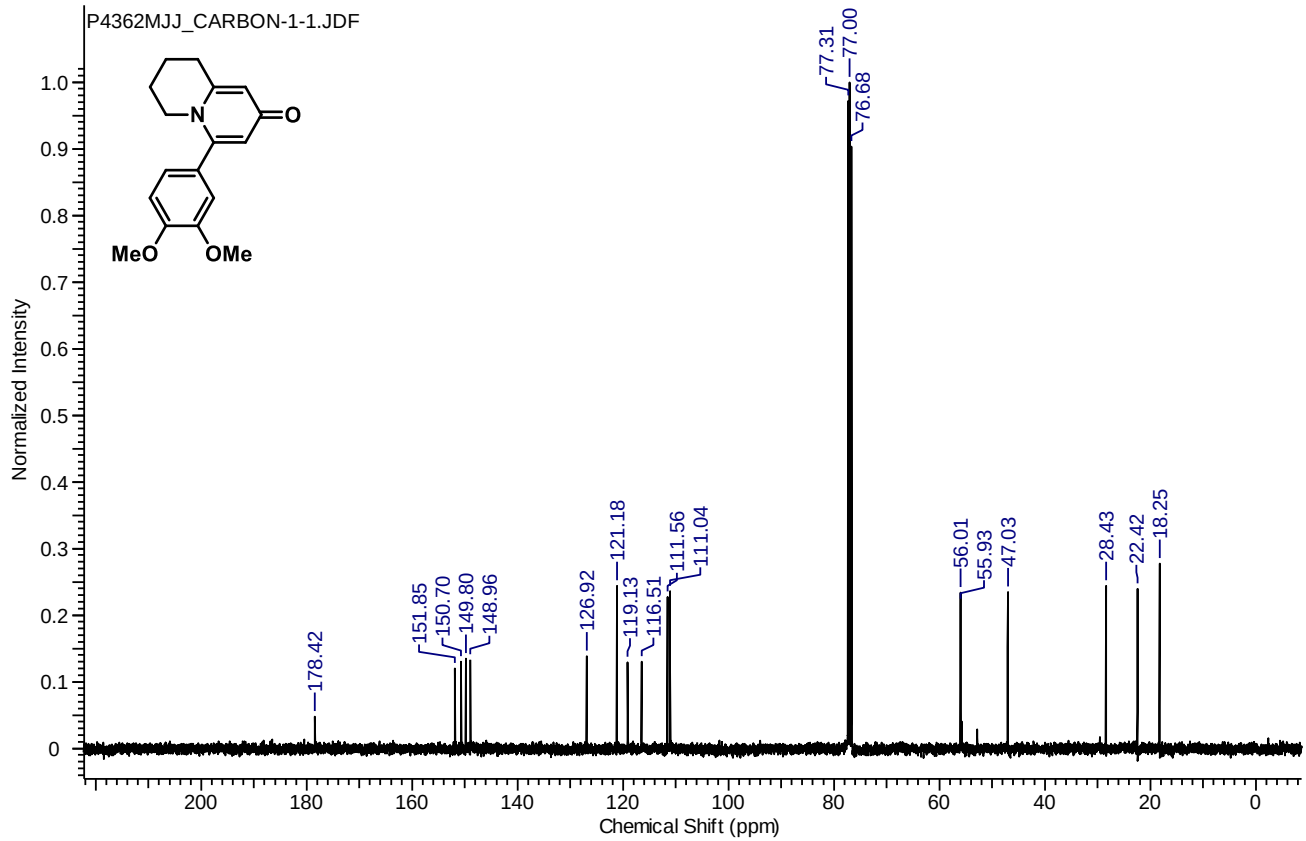
^{1}H & ^{13}C NMR spectra: **6l**



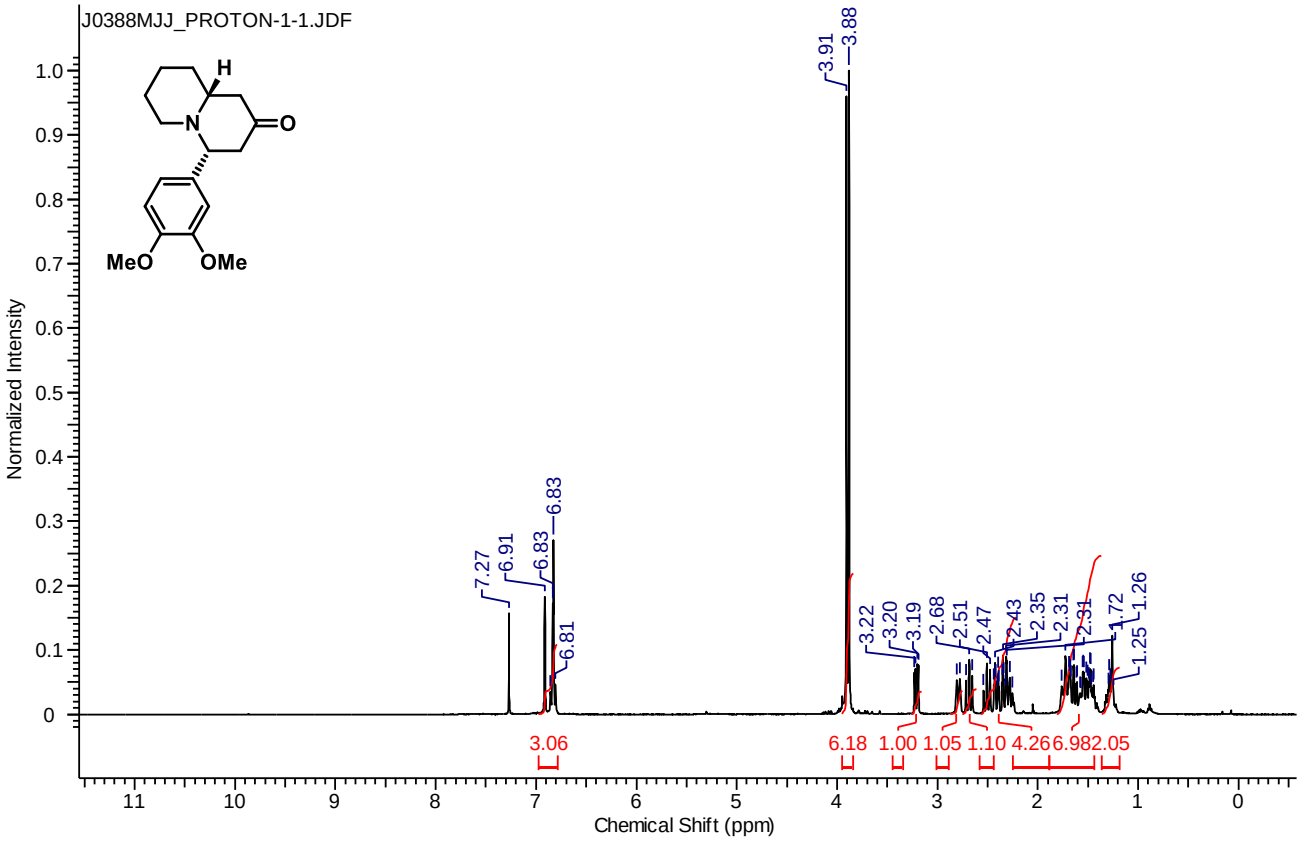


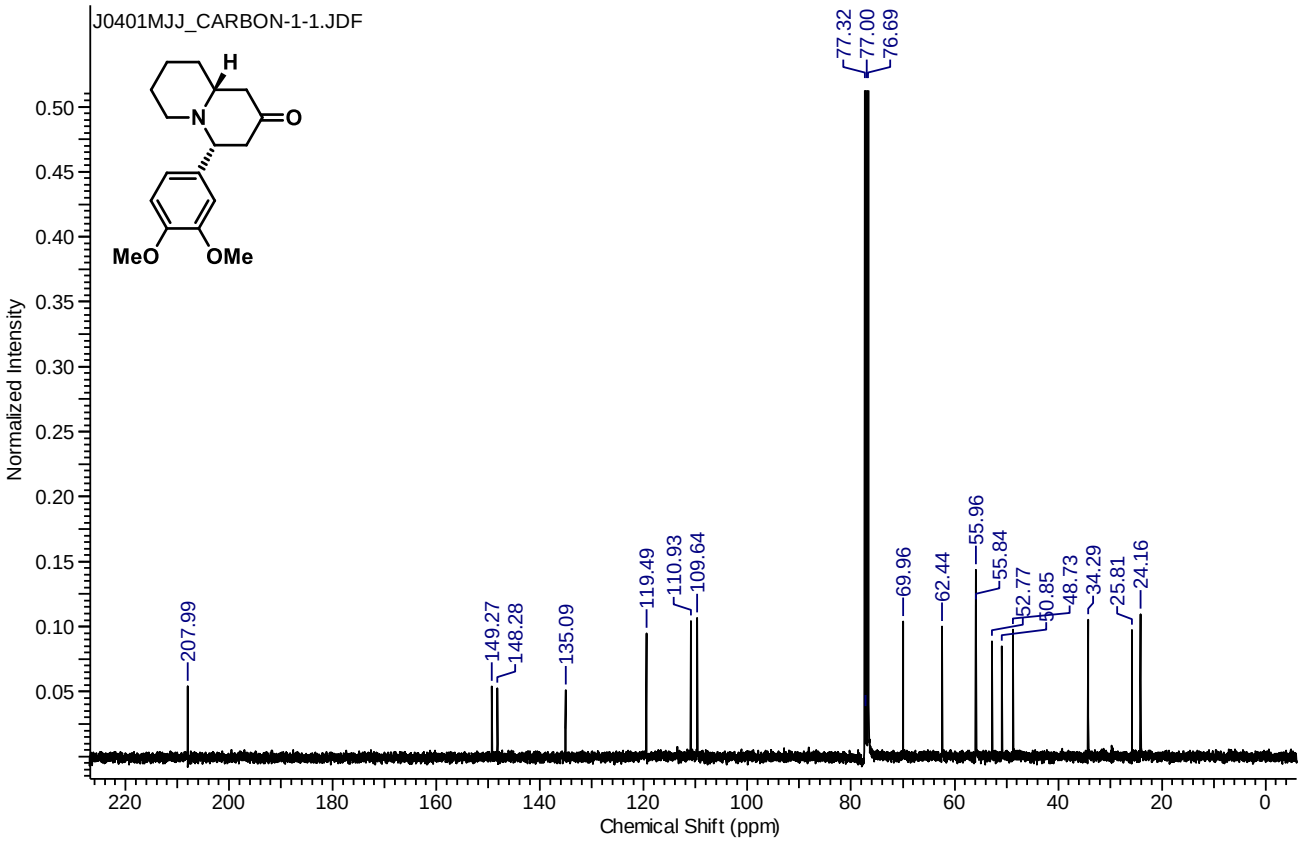
^{1}H & ^{13}C NMR spectra: **8**



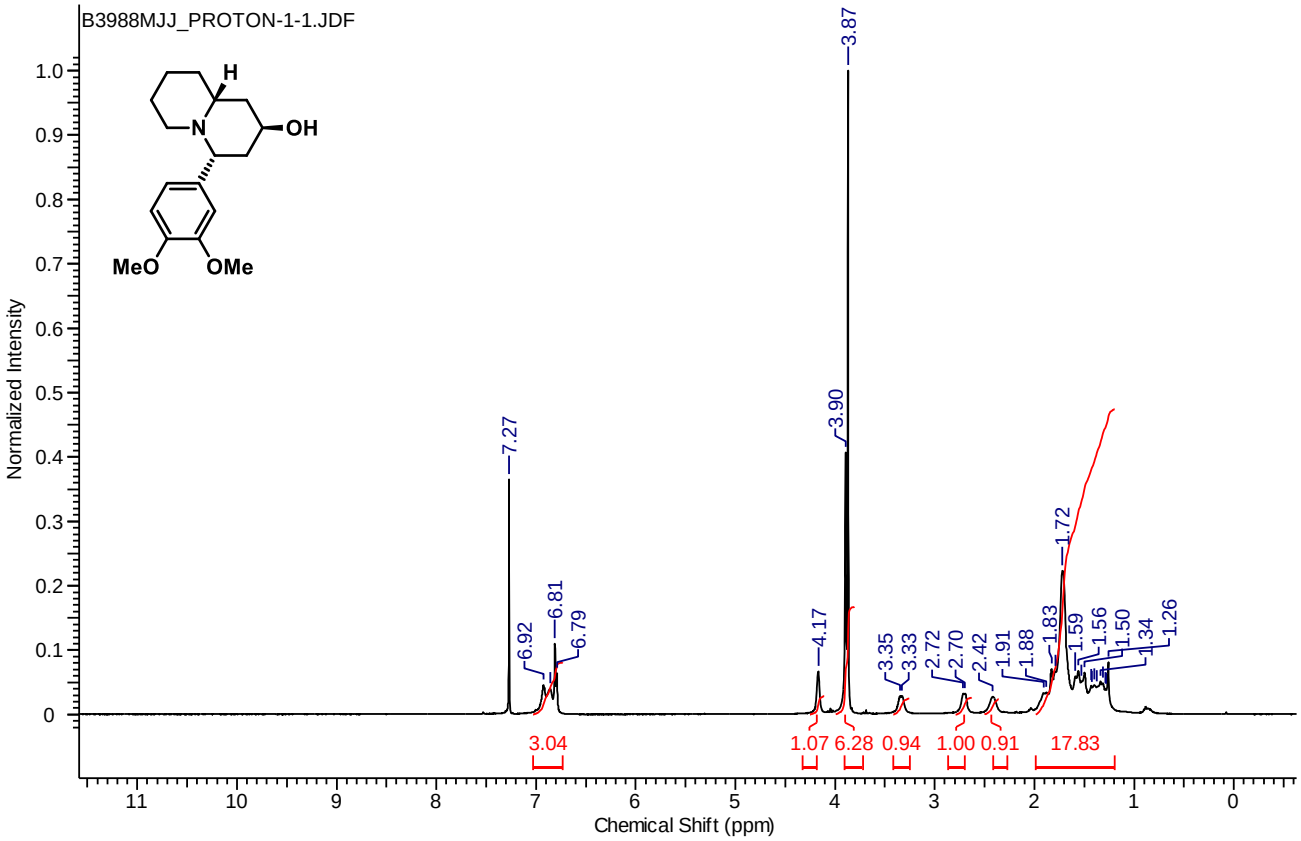


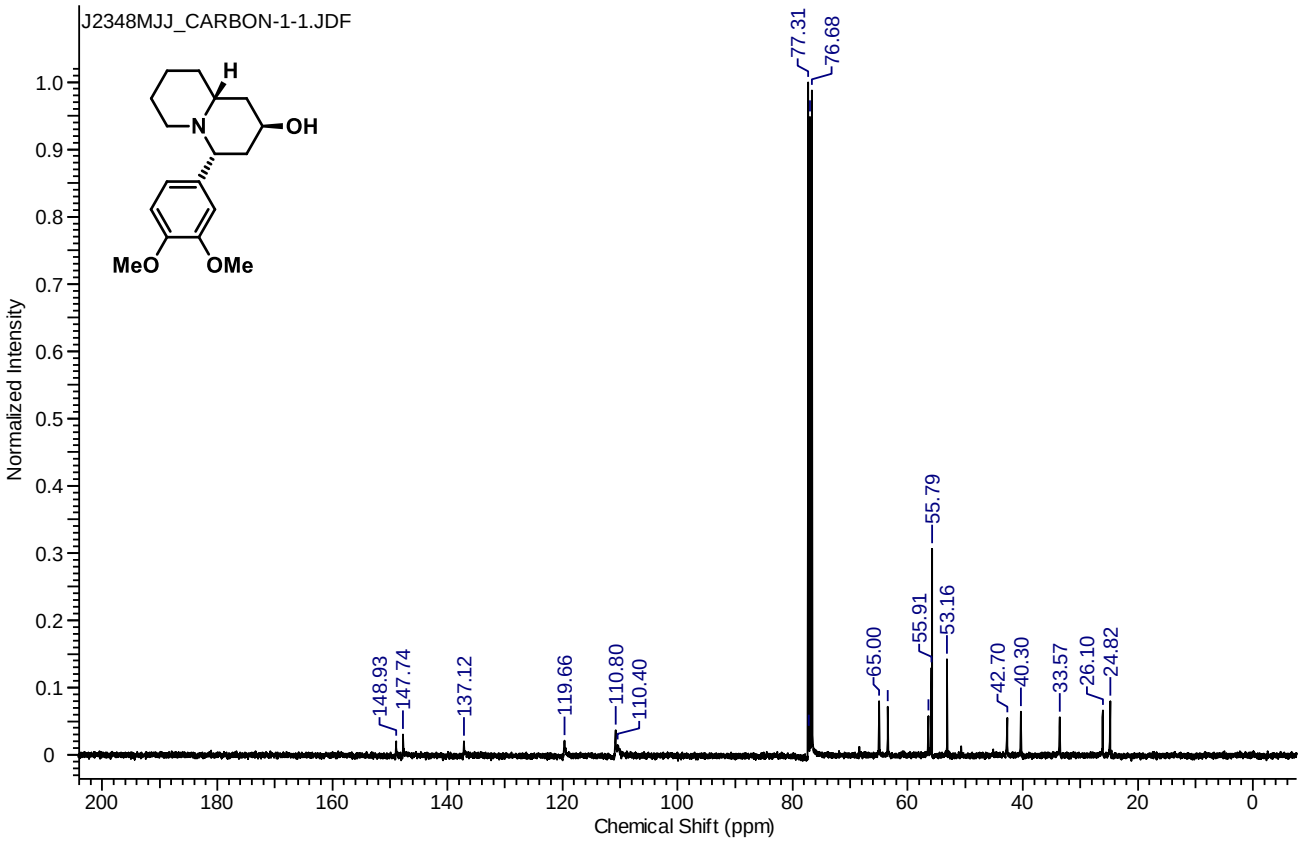
^{1}H & ^{13}C NMR spectra: **10**





^{1}H & ^{13}C NMR spectra: **(±)-lasubine II**, **3**





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