Supporting Information

An approach for the generation of γ-propenylidene-γ-butenolides and application to the total synthesis of rubrolides

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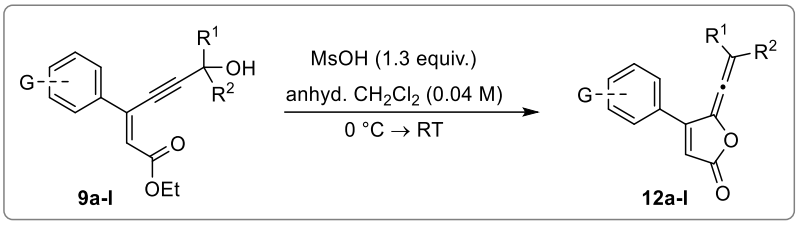
1. General information

All the solvents were distilled prior to use. Dry solvents were prepared according to the standard procedures. Commercially available chemicals were purchased from Sigma-Aldrich and Alfa Aesar and were used as received without further purification. Reactions requiring inert atmosphere were carried out under argon atmosphere. Infrared (IR) spectra were recorded on a JASCO 4100 FT-IR spectrometer. ^{1}H NMR spectra were measured on Bruker AVANCE 400 MHz spectrometers. Chemical shifts were reported in ppm relative to solvent signals. ^{13}C NMR spectra were recorded on Bruker 100 MHz spectrometers with complete proton decoupling. Chemical shifts were reported in ppm from the residual solvent as an internal standard [$CDCl_3$ δ = 7.26 ppm for ^{1}H, δ = 77.16 for ^{13}C or calibrated to tetramethylsilane (δ = 0.00; DMSO-d_6 δ = 2.50 ppm for ^{1}H, δ = 39.52 for ^{13}C). Peak multiplicities are designated by the following abbreviations: s, singlet; br s, broad singlet; d, doublet; t, triplet; q, quartet; m, multiplet; *J*, coupling constant in Hz. The coupling constant *J* (Hz) has been rounded to one decimal place for all compounds. Where a coupling pattern can be assigned as a combination of multiplicities, the above abbreviations have been combined to describe the observed patterns (i.e., dt - doublet of triplets). The high-resolution mass spectra (HRMS) were performed on Micromass QTOF micro mass spectrometer equipped with a Harvard apparatus syringe pump. For thin layer chromatography (TLC) analysis throughout this work, E-merck precoated TLC plates (silica gel 60 F254 grade, 0.25 mm) were used. Acme (India) silica gel (100-200 mesh) was used for column chromatography.

2. General procedure 1: Procedure for acid promoted allene formation

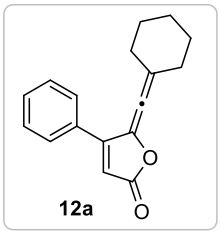


To a well stirred solution of the (*Z*)-enynoate-propargylic alcohol (1 equiv.) in anhydrous dichloromethane (0.04 M), methanesulfonic acid (MsOH) (1.3 equiv.) was added drop wise at 0 °C under nitrogen. The mixture was stirred at same temperature until the TLC showed complete consumption of the starting material. After completion, the reaction was quenched by addition of saturated $NaHCO_3$ solution. The aqueous layer was extracted with CH_2Cl_2 (3 times). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in-vacuo* at 0 to 5 °C. Quick purification of crude product via a silica gel column chromatography (Hexane:EtOAc) provided the desired allene derivatives **12a-l**.

[**N.B.** The allenes were found to be very sensitive to heat. Thus the column fractions were also concentrated under reduced pressure at 0 to 5 °C and submitted for NMR analysis immediately after evaporation and then stored at -20 °C].

5-(cyclohexylidenemethylene)-4-phenylfuran-2(5*H*)-one (12a)

According to the **General Procedure 1**, propargylic alcohol **9a** (60 mg, 0.2 mmol, 1.0 equiv.), methanesulfonic acid (MsOH) (0.017 mL, 0.26 mmol, 1.3 equiv.) were used in 5 mL anhydrous CH_2Cl_2, affording the desired allene **12a** as a white crystalline solid (46 mg, 0.18 mmol, 90%) by using Hexane/EtOAc (9:1) as eluent.



^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.58 – 7.53 (m, 2H), 7.47 – 7.40 (m, 3H), 6.25 (s, 1H), 2.39 – 2.33 (m, 4H), 1.84 – 1.70 (m, 3H) and 1.62 – 1.60 (m, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ_C 187.1, 169.0, 156.6, 130.9, 130.6, 128.8, 128.3, 128.1, 121.3, 113.0, 32.3, 26.9 and 25.7 ppm.

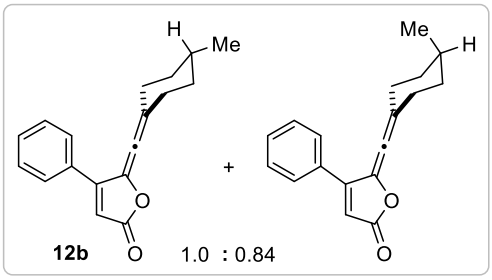
IR (ATR): 3452, 1758, 1200, 1079, 936, 768, 692, 466 and 420 cm^{-1}.

HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{17}H_{16}NaO_2$ 275.1048; found 275.1061.

TLC: R_f = 0.4 (9:1, Hex/EtOAc).

MP: 86 – 88 °C (recrystallized from CH_2Cl_2/ Hexane: 1:1).

5-((4-methylcyclohexylidene)methylene)-4-phenylfuran-2(5*H*)-one (12b)



(Inseparable mixture of diastereomers with *d.r.* = 1.0:0.84).

According to the **General Procedure 1**, propargylic alcohol **9b** (62 mg, 0.2 mmol, 1.0 equiv.), methanesulfonic acid (MsOH) (0.017 mL, 0.26 mmol, 1.3 equiv.) were used in 5 mL anhydrous CH_2Cl_2, affording the desired allene **12b** as on yellow liquid (46 mg, 0.18 mmol, 86%) by using Hexane/EtOAc (9:1) as eluent.

^{1}H NMR (400 MHz, $CDCl_3$): **Major isomer:** δ_H 7.63 – 7.56 (1H, m), 7.56 – 7.49 (1H, m), 7.49 – 7.35 (3H, m), 6.25 (1H, s), 2.61 – 2.46 (2H, m), 2.29 (td, *J* = 13.4, 4.0 Hz, 2H), 1.96 – 1.78 (3H, m), 1.35 – 1.27 (1H, m), 1.14 – 1.02 (1H, m) and 0.94 (d, *J* = 6.5 Hz, 3H) ppm.

Minor isomer: δ_H 7.63 – 7.56 (1H, m), 7.56 – 7.49 (1H, m), 7.49 – 7.35 (3H, m), 6.25 (1H, s), 2.61 – 2.46 (2H, m), 2.20 (td, *J* = 13.3, 4.1 Hz, 2H), 1.96 – 1.78 (3H, m), 1.35 – 1.27 (1H, m), 1.14 – 1.02 (1H, m) and 0.97 (d, *J* = 6.5 Hz, 3H) ppm.

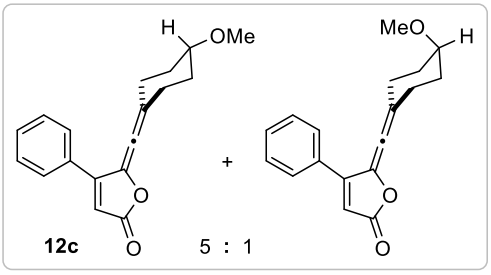
^{13}C NMR (100 MHz, $CDCl_3$): δ_C 187.0, 168.9, 156.5, 130.9, 130.8, 130.4, 130.4, 128.8, 128.6, 128.1, 127.9, 125.3, 125.1, 121.0, 120.8, 112.9, 112.7, 35.0, 34.8, 31.9, 31.7, 31.6, 31.5, 21.9 and 21.7 ppm.

IR (ATR): 2961, 2936, 1808, 1366, 1288, 1219, 1179, 963, 953, 818, 774, 767, 758 and 736 cm^{-1}.

HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{18}H_{18}NaO_2$ 289.1204; found 289.1212.

TLC: R_f = 0.45 (9:1, Hex/EtOAc).

5-((4-methoxycyclohexylidene)methylene)-4-phenylfuran-2(5*H*)-one (12c)



(Inseparable mixture of diastereomers with *d.r.* = 5:1).

According to the **General Procedure 1**, propargylic alcohol **9c** (66 mg, 0.2 mmol, 1.0 equiv.), methanesulfonic acid (MsOH) (0.017 mL, 0.26 mmol, 1.3 equiv.) were used in 5 mL anhydrous CH_2Cl_2, affording the desired allene **12c** as a colourless oil (46 mg, 0.16 mmol, 81%) by using Hexane/EtOAc (4:1) as eluent.

^{1}H NMR (400 MHz, $CDCl_3$): **Major isomer:** δ_H 7.57 – 7.51 (2H, m), 7.50 – 7.39 (3H, m), 6.26 (1H, s), 3.49 – 3.40 (1H, m), 3.37 (3H, s), 2.67 – 2.57 (m, 2H), 2.31 – 2.23 (2H, m), 1.91 – 1.77 (3H, m) and 1.74 – 1.70 (1H, m) ppm.

Minor isomer: δ_H 7.57 – 7.51 (2H, m), 7.50 – 7.39 (3H, m), 6.26 (1H, s), 3.49 – 3.40 (1H, m), 3.37 (3H, s), 2.57 – 2.52 (m, 2H), 2.37 – 2.31 (2H, m), 1.91 – 1.77 (3H, m) and 1.74 – 1.70 (1H, m) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): **Major isomer:** δ_C 187.1, 168.8, 156.55, 130.9, 130.5, 128.8, 128.03, 125.4, 120.1, 113.1, 75.4, 56.0, 30.6 and 28.0 ppm.

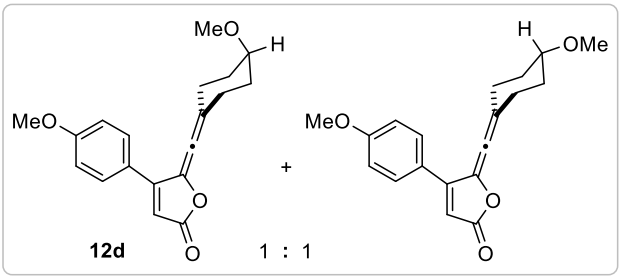
Minor isomer: δ_C 187.1, 168.8, 156.48, 131.0, 130.3, 128.9, 128.00, 125.4, 119.8, 113.0, 75.9, 56.1, 30.8 and 28.4 ppm.

IR (ATR): 2944, 1759, 1451, 1277, 1263, 1203, 1100, 1077, 940, 912, 766 and 749 cm^{-1}.

HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{18}H_{19}O_3$ 283.1329; found 283.1341.

TLC: R_f = 0.25 (9:1, Hex/EtOAc).

5-((4-methoxycyclohexylidene)methylene)-4-(4-methoxyphenyl)furan-2(5*H*)-one (12d)



(Inseparable mixture of diastereomers with *d.r.* = 1:1)

According to the **General Procedure 1**, propargylic alcohol **9d** (72 mg, 0.2 mmol, 1.0 equiv.), methanesulfonic acid (MsOH) (0.017 mL, 0.26 mmol, 1.3 equiv.) were used in 5 mL anhydrous CH_2Cl_2, affording the desired allene **12d** as a colourless oil (54 mg, 0.17 mmol, 86%) by using Hexane/EtOAc (2:1) as eluent.

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.53 (d, *J* = 8.1, 4H), 6.93 (d, *J* = 8.0, 4H), 6.17 (s, 2H), 3.86 (s, 6H), 3.50 – 3.42 (m, 2H), 3.38 (s, 3H), 3.37 (s, 3H), 2.69 – 2.52 (m, 4H), 2.37 – 2.24 (m, 4H), 1.89 – 1.82 (m, 4H) and 1.82 – 1.70 (m, 4H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ_C 187.1, 169.2, 169.1, 161.9, 161.8, 155.9, 155.8, 129.5, 125.6, 125.4, 122.9, 122.8, 119.8, 119.5, 114.3, 114.2, 111.3, 111.1, 75.9, 75.5, 56.1, 56.0, 55.5, 30.8, 30.6, 28.3 and 28.1 ppm.

IR (ATR): 2952, 1761, 1449, 1279, 1242, 1119, 1105, 1060, 952, 920, 771 and 755 cm^{-1}.

HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{19}H_{21}O_4$ 313.1434; found 313.1430.

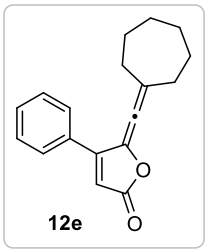
TLC: R_f = 0.25 (9:1, Hex/EtOAc).

5-(cycloheptylidenemethylene)-4-phenylfuran-2(5*H*)-one (12e)

According to the **General Procedure 1**, propargylic alcohol **9e** (62 mg, 0.2 mmol, 1.0 equiv.), methanesulfonic acid (MsOH) (0.017 mL, 0.26 mmol, 1.3 equiv.) were used in 5 mL dry CH_2Cl_2, affording the desired allene **12e** as a pale yellow oil (46 mg, 0.17 mmol, 87%) by using Hexane/EtOAc (9:1) as eluent.

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.62 – 7.50 (2H, m), 7.49 – 7.37 (3H, m), 6.25 (1H, s), 2.59 – 2.43 (4H, m), 1.80 – 1.71 (2H, m) and 1.67 – 1.54 (6H, m) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ_C 190.2, 169.1, 156.6, 130.9, 130.5, 128.8, 128.0, 125.3, 124.0, 112.9, 33.4, 29.4 and 27.7 ppm.



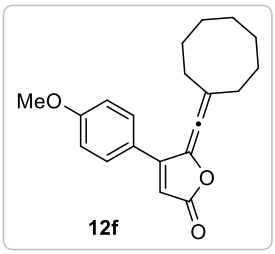
HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{18}H_{18}NaO_2$ 289.1199; found 289.1207.

TLC: R_f = 0.45 (9:1, Hex/EtOAc).

5-(cyclooctylidenemethylene)-4-(4-methoxyphenyl)furan-2(5*H*)-one (12f)

According to the **General Procedure 1**, propargylic alcohol **9f** (71 mg, 0.2 mmol, 1.0 equiv.), methanesulfonic acid (MsOH) (0.017 mL, 0.26 mmol, 1.3 equiv.) were used in 5 mL anhydrous CH_2Cl_2, affording the desired allene **12f** as colourless gummy liquid (47 mg, 0.15 mmol, 75%) by using Hexane/EtOAc (4:1) as eluent.

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.52 (d, *J* = 8.0, 2H), 6.92 (d, *J* = 8.0, 2H), 6.17 (s, 1H), 3.85 (s, 3H), 2.53 – 2.44 (m, 2H), 2.42 – 2.34 (m, 2H), 1.83 – 1.70 (m, 4H) and 1.65 – 1.48 (m, 6H) ppm.



^{13}C NMR (100 MHz, $CDCl_3$): δ_C 190.3, 169.5, 161.8, 156.0, 129.5, 126.4, 124.8, 123.0, 114.3, 111.2, 55.5, 32.6, 26.9, 26.8 and 25.6 ppm.

IR (ATR): 3654, 2925, 2852, 1751, 1604, 1509, 1455, 1257, 1180, 1074, 1029, 953 and 920 cm^{-1}.

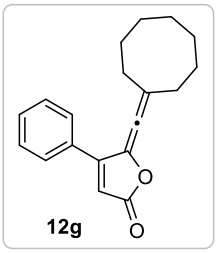
HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{20}H_{23}O_3$ 311.1642; found 311.1636.

TLC: R_f = 0.45 (4:1, Hex/EtOAc).

5-(cyclooctylidenemethylene)-4-phenylfuran-2(5*H*)-one (12g)

According to the **General Procedure 1**, propargylic alcohol **9g** (65 mg, 0.2 mmol, 1.0 equiv.), methanesulfonic acid (MsOH) (0.017 mL, 0.26 mmol, 1.3 equiv.) were used in 5 mL anhydrous CH_2Cl_2, affording the desired allene **12g** as colourless gummy liquid (40 mg, 0.14 mmol, 71%) by using Hexane/EtOAc (9:1) as eluent.

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.58 – 7.50 (2H, m), 7.48-7.38 (3H, m), 6.25 (1H, s), 2.52 – 2.43 (2H, m), 2.42 – 2.33 (2H, m), 1.78 – 1.69 (4H, m) and 1.64 – 1.46 (6H, m) ppm.

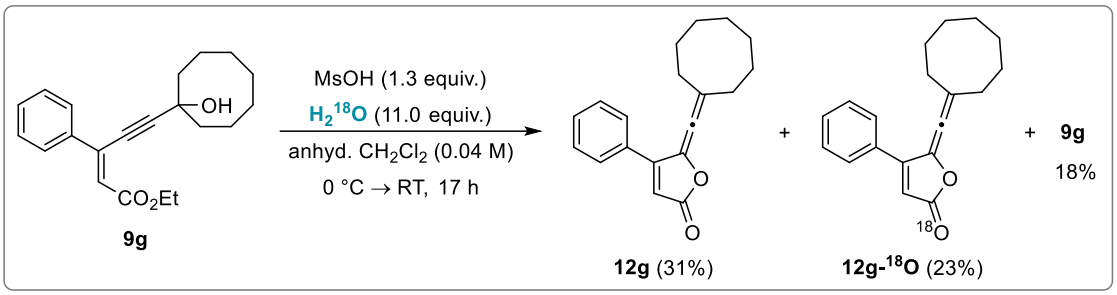


^{13}C NMR (100 MHz, $CDCl_3$): δ_C 190.3, 169.2, 156.6, 130.8, 130.6, 128.9, 128.0, 126.4, 125.1, 113.1, 32.6, 26.8 and 25.6 ppm.

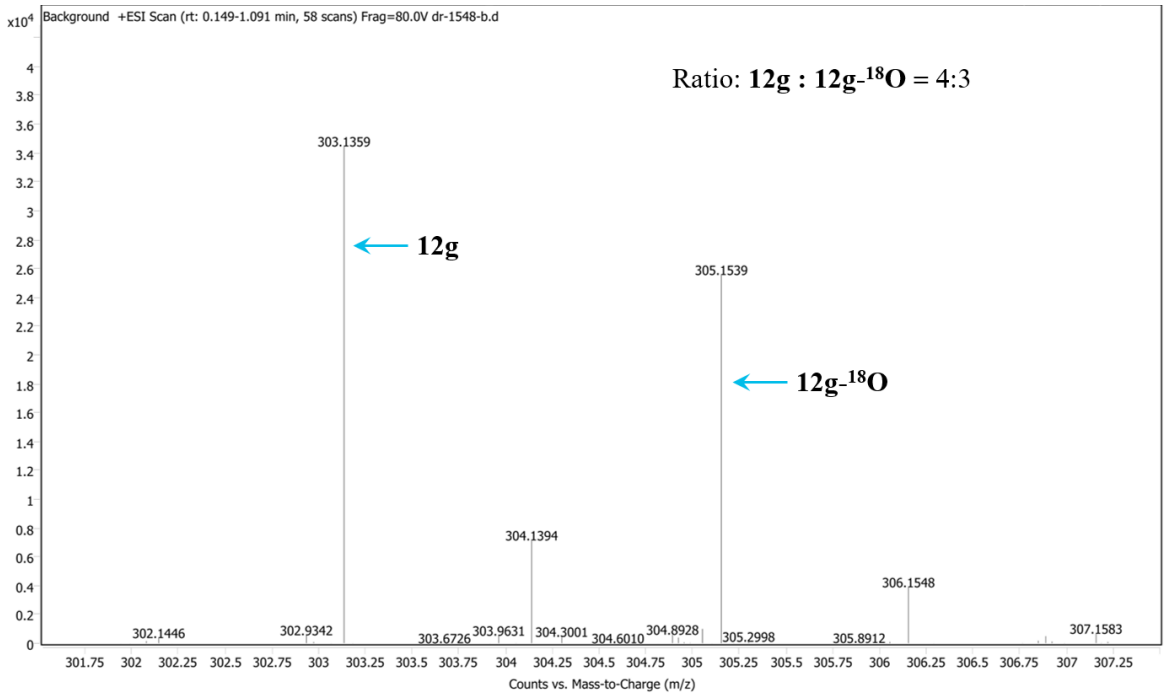
HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{19}H_{20}NaO_2$ 303.1361; found 303.1368.

TLC: R_f = 0.6 (9:1, Hex/EtOAc).

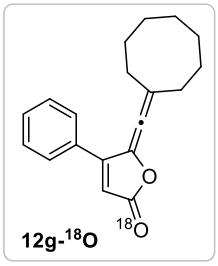
3. Procedure 2: Procedure for ^{18}O labelling experiment.



To a well stirred solution of the ethyl (*Z*)-5-(1-hydroxycyclooctyl)-3-phenylpent-2-en-4-ynoate **9g** (65 mg, 0.2 mmol, 1.0 equiv.) in 5 mL anhydrous dichloromethane and $H_2{}^{18}O$ (40 μL, 11.0 equiv.) methanesulfonic acid (MsOH) (1.3 equiv.) was added drop wise at 0 °C under nitrogen. The mixture was stirred at same temperature until the TLC showed complete consumption of the starting material. After completion, the reaction was quenched by addition of saturated $NaHCO_3$ solution. The aqueous layer was extracted with CH_2Cl_2 (3 times). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in-vacuo* at 0 to 5 °C. Quick purification of crude product via silica gel column chromatography (Hexane:EtOAc 9:1) provided an inseparable mixture of 5-(cyclooctylidenemethylene)-4-phenylfuran-2(5*H*)-one **12g** (17 mg, 0.06 mmol, 31%) and its ^{18}O analogue **12g-^{18}O** (13 mg, 0.05 mmol, 23%) in 4:3 ratio.[1] High resolution positive ion electrospray mass spectra (HRMS-ESI) for the final products were shown.



5-(cyclooctylidenemethylene)-4-phenylfuran-2(5*H*)-one-^{18}O (12g-^{18}O)



^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.59 – 7.50 (m, 2H), 7.49 – 7.37 (m, 3H), 6.25 (s, 1H), 2.52 – 2.43 (m, 2H), 2.42 – 2.34 (m, 2H), 1.77 – 1.68 (m, 5H) and 1.65 – 1.48 (m, 5H) ppm.

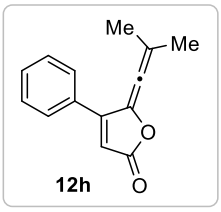
^{13}C NMR (100 MHz, $CDCl_3$): δ_C 190.3, 169.2, 156.7, 130.8, 130.6, 128.9, 128.0, 126.4, 125.1, 113.1, 32.6, 26.8 and 25.6 ppm.

HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{19}H_{21}Na^{18}O^{16}O$ 305.1398; found 305.1539.

TLC: R_f = 0.6 (9:1, Hex/EtOAc).

5-(2-methylprop-1-en-1-ylidene)-4-phenylfuran-2(5*H*)-one (12h)

According to the **General Procedure 1**, propargylic alcohol **9h** (52 mg, 0.2 mmol, 1.0 equiv.), methanesulfonic acid (MsOH) (0.017 mL, 0.26 mmol, 1.3 equiv.) were used in 5 mL anhydrous CH_2Cl_2, affording the desired allene **12h** as a colourless oil (34 mg, 0.16 mmol, 78%) by using Hexane/EtOAc (9:1) as eluent.



^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.59 – 7.50 (2H, m), 7.50 – 7.38 (3H, m), 6.26 (1H, s) and 1.98 (6H, s) ppm.

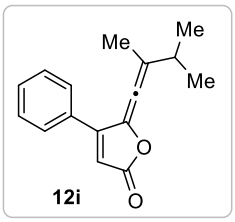
^{13}C NMR (100 MHz, $CDCl_3$): δ_C 190.3, 168.9, 156.5, 130.9, 130.5, 128.9, 127.9, 125.4, 115.2, 113.3 and 21.6 ppm.

HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{14}H_{12}NaO_2$ 235.0730; found 235.0732.

TLC: R_f = 0.4 (9:1, Hex/EtOAc).

5-(2,3-dimethylbut-1-en-1-ylidene)-4-phenylfuran-2(5*H*)-one (12i)

According to the **General Procedure 1**, propargylic alcohol **9i** (57 mg, 0.2 mmol, 1.0 equiv.), methanesulfonic acid (MsOH) (0.017 mL, 0.26 mmol, 1.3 equiv.) were used in 5 mL anhydrous CH_2Cl_2, affording the desired allene **12i** as a colourless oil (44 mg, 0.18 mmol, 91%) by using Hexane/EtOAc (9:1) as eluent.



^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.60 – 7.51 (2H, m), 7.49 – 7.39 (3H, m), 6.27 (1H, s), 2.47 – 2.34 (1H, m), 1.99 (3H, s) 1.10 (3H, d, *J* = 8.0 Hz) and 1.05 (3H, d, *J* = 8.0 Hz) ppm.

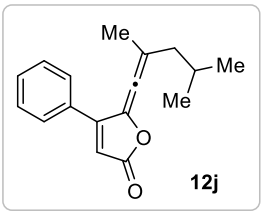
^{13}C NMR (100 MHz, $CDCl_3$): δ_C 189.2, 169.0, 156.4, 130.8, 130.4, 128.8, 127.9, 127.6, 125.2, 113.0, 34.2, 21.1, 20.8 and 18.2 ppm.

HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{16}H_{16}NaO_2$ 263.1043; found 263.1047.

TLC: R_f = 0.45 (9:1, Hex/EtOAc).

5-(2,4-dimethylpent-1-en-1-ylidene)-4-phenylfuran-2(5*H*)-one (12j)

According to the **General Procedure 1**, propargylic alcohol **9j** (60 mg, 0.2 mmol, 1.0 equiv.), methanesulfonic acid (MsOH) (0.017 mL, 0.26 mmol, 1.3 equiv.) were used in 5 mL anhydrous CH_2Cl_2, affording the desired allene **12j** as a colourless oil (46 mg, 0.18 mmol, 89%) by using Hexane/EtOAc (9:1) as eluent.



^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.56 – 7.50 (2H, m), 7.48 – 7.38 (3H, m), 6.25 (1H, s), 2.10 (2H, d, *J* = 7.1 Hz), 1.97 (3H, s), 1.84 – 1.75 (1H, m) and 0.86 (6H, d, *J* = 5.9 Hz) ppm.

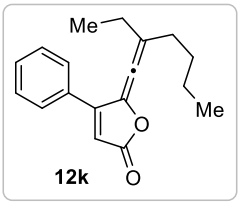
^{13}C NMR (100 MHz, $CDCl_3$): δ_C 190.6, 169.0, 156.5, 130.9, 130.5, 128.9, 128.0, 126.4, 118.4, 113.1, 44.7, 26.6, 22.5, 22.5 and 20.3 ppm.

HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{17}H_{19}O_2$ 255.1385; found 255.1404.

TLC: R_f = 0.5 (9:1, Hex/EtOAc).

5-(2-ethylhex-1-en-1-ylidene)-4-phenylfuran-2(5*H*)-one (12k)

According to the **General Procedure 1**, propargylic alcohol **9k** (63 mg, 0.2 mmol, 1.0 equiv.), methanesulfonic acid (MsOH) (0.017 mL, 0.26 mmol, 1.3 equiv.) were used in 5 mL anhydrous CH_2Cl_2, affording the desired allene **12k** as a colourless oil (47 mg, 0.18 mmol, 88%) by using Hexane/EtOAc (6:1) as eluent.



^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.58 – 7.53 (2H, m), 7.50 – 7.37 (3H, m), 6.27 (1H, s), 2.32 – 2.17 (m, 4H), 1.44 (dq, *J* = 14.7, 7.5, 2H), 1.29 (dt, *J* = 20.9, 7.1, 3H), 1.07 (t, *J* = 7.5, 3H) and 0.84 (t, *J* = 7.3, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ_C 189.5, 169.1, 156.3, 130.8, 130.5, 129.9, 128.8, 127.9, 126.2, 113.0, 33.8, 29.5, 27.4, 22.3, 13.9 and 12.0 ppm.

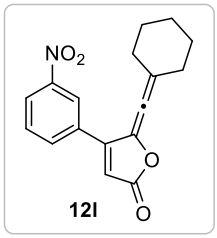
IR (ATR): 2961, 2936, 1808, 1366, 1288, 1219, 1179, 963, 953, 818, 774, 767, 758 and 736 cm^{-1}.

HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{18}H_{20}NaO_2$ 291.1356; found 291.1368.

TLC: R_f = 0.25 (9:1, Hex/EtOAc).

5-(cyclohexylidenemethylene)-4-(3-nitrophenyl)furan-2(5*H*)-one (12l)

According to the **General Procedure 1**, propargylic alcohol **9l** (69 mg, 0.2 mmol, 1.0 equiv.), methanesulfonic acid (MsOH) (0.017 mL, 0.26 mmol, 1.3 equiv.) were used in 5 mL anhydrous CH_2Cl_2, affording the desired allene **12l** as an orange crystalline solid (27 mg, 0.09 mmol, 46%) by using Hexane/EtOAc (4:1) as eluent.



^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.48 (s, 1H), 8.34 (d, *J* = 8.2 Hz, 1H), 7.91 (d, *J* = 7.7 Hz, 1H), 7.66 (t, *J* = 7.9 Hz, 1H), 6.40 (s, 1H), 2.45 – 2.38 (m, 4H) and 1.86 – 1.65 (m, 6H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ_C 186.6, 168.2, 153.4, 133.9, 132.0, 130.1, 125.31 123.0, 122.8, 114.7, 32.3, 26.8 and 25.5 ppm.

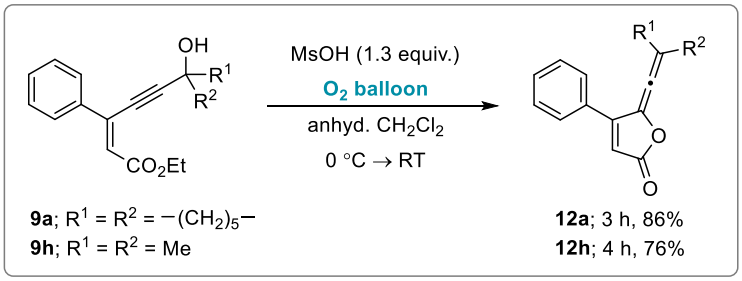
IR (ATR): 3056, 2939, 1757, 1533, 1448, 1352, 1270, 1202, 1075, 987, 923, 755, 740 and 700 cm^{-1}.

HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{17}H_{16}NO_4$ 298.1074; found 298.1070.

TLC: R_f = 0.2 (6:1, Hex/EtOAc).

MP: 90 – 92 °C (recrystallized from CH_2Cl_2/ Hexane: 1:1).

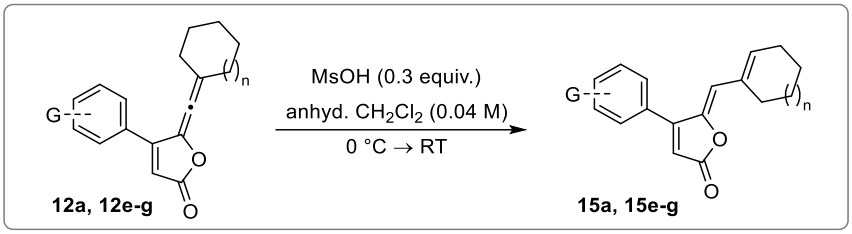
4. Procedure 3: Acid promoted allene formation in presence of oxygen.



To a well stirred solution of the (*Z*)-enynoate-propargylic alcohol **9a** and **9h** (1 equiv.) in anhydrous dichloromethane (0.04 M), methanesulfonic acid (MsOH) (1.3 equiv.) was added drop wise in a 15 mL tube with an O_2 balloon at 0 °C. The mixture was stirred at same temperature under oxygen atmosphere until the TLC showed complete consumption of the starting material. After completion, the reaction was quenched by addition of saturated $NaHCO_3$ solution. The aqueous layer was extracted with CH_2Cl_2 (3 times). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in-vacuo* at 0 to 5 °C. Quick purification of crude product via a silica gel column chromatography

(Hexane:EtOAc) provided the desired allene derivatives **12a** (86%) and **12h** (76%) respectively.

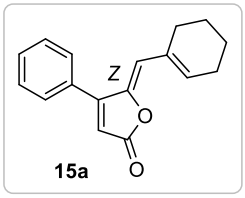
5. General procedure 4: Procedure for acid catalysed isomerization of allenes.



To a solution of the freshly prepared allene (1equiv.) in anhydrous CH_2Cl_2, methanesulfonic acid (MsOH) (0.3 equiv.) was added drop wise at 0 °C under nitrogen. The reaction mixture was warmed to room temperature and stirred until the TLC showed complete consumption of the allene. The reaction was quenched by addition of saturated $NaHCO_3$ solution. The aqueous layer was extracted with CH_2Cl_2 (3 times). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in-vacuo*. Purification of crude product via a silica gel column chromatography (Hexanes/EtOAc) provided desired triene derivatives.

(*Z*)-5-(cyclohex-1-en-1-ylmethylene)-4-phenylfuran-2(5*H*)-one (15a)

According to the **General Procedure 4**, freshly prepared allene **12a** (25 mg, 0.1 mmol, 1.0 equiv.), methanesulfonic acid (MsOH) (0.002 mL, 0.03 mmol, 0.3 equiv.) were used in 3 mL anhydrous CH_2Cl_2, affording the desired triene **15a** as a colourless oil (23 mg, 0.093 mmol, 93%) by using Hexane/EtOAc (9:1) as eluent.



^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.54 – 7.40 (5H, m), 6.22 – 6.12 (1H, m), 6.10 (1H, s), 5.79 (1H, s), 2.66 – 2.57 (2H, m), 2.26 – 2.16 (2H, m), 1.74 – 1.66 (2H, m) and 0.92 – 0.82 (2H, m) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ_C 169.4, 158.8, 145.7, 138.5, 134.8, 131.0, 130.3, 129.1, 128.6, 118.4, 113.8, 27.4, 27.0, 22.6 and 21.7 ppm.

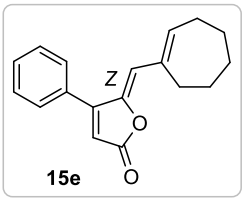
IR (ATR): 2949, 2361, 1761, 1686, 1519, 1405, 1201, 1141, 1053, 959, 845 and 759 cm^{-1}.

HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{17}H_{17}O_2$ 253.1223; found 253.1230.

TLC: R_f = 0.5 (9:1, Hex/EtOAc).

(*Z*)-5-(cyclohept-1-en-1-ylmethylene)-4-phenylfuran-2(5*H*)-one (15e)

According to the **General Procedure 4**, freshly prepared allene **12e** (27 mg, 0.1 mmol, 1.0 equiv.), methanesulfonic acid (MsOH) (0.002 mL, 0.03 mmol, 0.3 equiv.) were used in 3 mL anhydrous CH_2Cl_2, affording the desired diene **15e** as a colourless oil (24 mg, 0.09 mmol, 90%) by using Hexane/EtOAc (9:1) as eluent.



^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.52 – 7.38 (m, 5H), 6.39 (t, *J* = 6.9 Hz, 1H), 6.09 (s, 1H), 5.78 (s, 1H), 2.78 – 2.71 (m, 2H), 2.33 – 2.35 (m, 2H), 1.84 – 1.74 (m, 2H) and 1.62 – 1.48 (m, 4H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ_C 169.3, 159.0, 145.3, 144.0, 141.2, 130.9, 130.2, 129.0, 128.6, 119.2, 113.5, 32.3, 30.4, 29.5, 26.4 and 26.3 ppm.

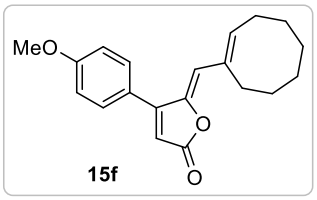
IR (ATR): 3155, 3005, 2361, 1785, 1683, 1523, 1402, 1201, 1148, 1046, 850 and 721 cm^{-1}.

HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{18}H_{19}O_2$ 267.1380; found 267.1382.

TLC: R_f = 0.5 (9:1, Hex/EtOAc).

(*Z*)-5-(((*E*)-cyclooct-1-en-1-yl)methylene)-4-(4-methoxyphenyl)furan-2(5*H*)-one (15f)

According to the **General Procedure 4**, freshly prepared allene **12f** (31 mg, 0.1 mmol, 1.0 equiv.), methanesulfonic acid (MsOH) (0.002 mL, 0.027 mmol, 0.3 equiv.) were used in 3 mL anhydrous CH_2Cl_2, affording the desired triene **15f** as a yellow oil (30 mg, 0.096 mmol, 96%) by using Hexane/EtOAc (9:1) as eluent.



^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.39 (d, *J* = 7.7 Hz, 2H), 7.00 (d, *J* = 7.8 Hz, 2H), 6.18 (t, *J* = 8.2 Hz, 1H), 6.03 (s, 1H), 5.81 (s, 1H), 3.87 (s, 3H), 2.75 – 2.65 (m, 2H), 2.33 – 2.23 (m, 2H), 1.76 – 1.68 (m, 2H), and 1.56 – 1.41 (m, 6H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ_C 169.6, 161.4, 158.6, 145.4, 142.0, 137.6, 130.1, 123.3, 118.1, 114.5, 112.6, 55.6, 30.0, 29.0, 28.0, 27.1, 26.3 and 25.9 ppm.

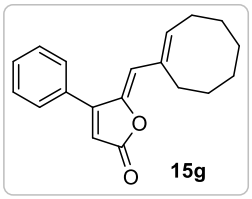
IR (ATR): 3492, 2923, 2850, 1757, 1605, 1506, 1454, 1341, 1298, 1254, 1179, 1086, 1028, 957, 914 and 828 cm^{-1}.

HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{20}H_{23}O_3$ 311.1642; found 311.1641.

TLC: R_f = 0.7 (4:1, Hex/EtOAc).

(*Z*)-5-(((*E*)-cyclooct-1-en-1-yl)methylene)-4-phenylfuran-2(5*H*)-one (15g)

According to the **General Procedure 4**, freshly prepared allene **12g** (28 mg, 0.1 mmol, 1.0 equiv.), methanesulfonic acid (MsOH) (0.002 mL, 0.03 mmol, 0.3 equiv.) were used in 3 mL anhydrous CH_2Cl_2, affording the desired diene **15g** as a yellow oil (26 mg, 0.094 mmol, 94%) by using Hexane/EtOAc (9:1) as eluent.



^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.54 – 7.46 (3H, m), 7.46 – 7.41 (2H, m), 6.18 (1H, t, *J* = 8.4 Hz), 6.10 (1H, s), 5.80 (1H, s), 2.76 – 2.65 (2H, m), 2.31 – 2.24 (2H, m), 1.76 – 1.70 (2H, m) and 1.56 – 1.43 (6H, m) ppm.

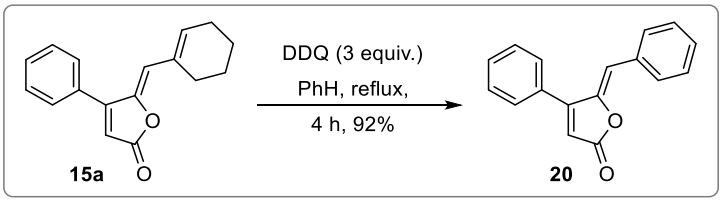
^{13}C NMR (100 MHz, $CDCl_3$): δ_C 169.4, 158.9, 145.3, 142.4, 137.6, 131.0, 130.2, 129.1, 128.7, 118.0, 113.7, 30.0, 29.0, 28.0, 27.1, 26.2 and 25.9 ppm.

IR (ATR): 3680, 3152, 3010, 2361, 1792, 1680, 1520, 1400, 1201, 1150, 1042, 836 and 717 cm^{-1}.

HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{19}H_{21}O_2$ 281.1536; found 281.1530.

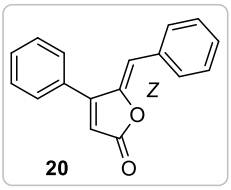
TLC: R_f = 0.6 (9:1, Hex/EtOAc).

6. Procedure 5: Procedure for oxidative aromatization of triene 15a.



To a well stirred solution of triene **15a** (18 mg, 0.07 mmol, 1 equiv.) in benzene was added DDQ (49 mg, 0.21 mmol, 3 equiv.) at room temperature under nitrogen. Reaction mixture was then refluxed in a preheated oil bath for 4 h after which TLC showed complete consumption of the starting material. Solvent was evaporated *in-vacuo*. Purification of crude product via a silica gel column chromatography (9:1 Hexanes/EtOAc) provided the desired aromatized product **20** (16 mg, 0.06 mmol, 92% yield) as an orange solid.

(*Z*)-5-benzylidene-4-phenylfuran-2(5*H*)-one (20)



^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.85 – 7.76 (m, 2H), 7.58 – 7.47 (m, 5H), 7.43 – 7.36 (m, 2H), 7.36 – 7.30 (m, 1H), 6.21 (s, 1H) and 6.18 (s, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ_C 169.0, 158.9, 148.1, 133.1, 130.9, 130.6, 129.4, 129.2, 128.9, 128.6, 114.7 and 114.0 ppm.

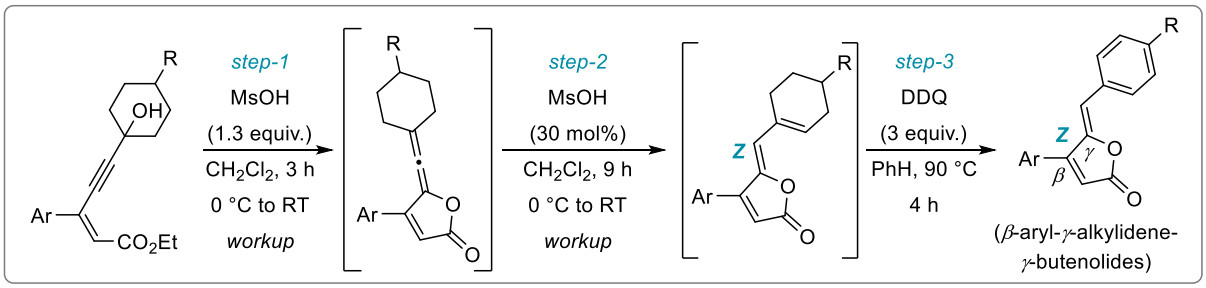
IR (ATR): 1757, 1642, 1495, 1449, 1358, 1221, 1181 and 1132 cm^{-1}.

HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{17}H_{13}O_2$ 249.0916; found 249.0915.

TLC: R_f = 0.55 (4:1, Hex/EtOAc).

M.P.: 120 – 122 ^{o}C (recrystallized from CH_2Cl_2/ Hexane: 1:2).

7 General procedure 5: Procedure for synthesis of *β*-aryl-*γ*-alkylidene-*γ*–butenolides derivatives from corresponding propargylic alcohols without isolation of intermediates.



Step 1

To a well stirred solution of the (*Z*)-enynoate-propargylic alcohol (1 equiv.) in anhydrous dichloromethane, methanesulfonic acid (MsOH) (1.3 equiv.) was added drop wise at 0 °C under nitrogen. The mixture was stirred at same temperature for 2.5 – 3 h. After completion, the reaction was quenched by addition of saturated $NaHCO_3$ solution. The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure at 0 to 5 °C. The crude material was directly used for the next step.

Step 2

To a solution of the freshly prepared allene (1equiv.) in anhydrous CH_2Cl_2, methanesulfonic acid (MsOH) (0.3 equiv.) was added drop wise at 0 °C under nitrogen. The reaction mixture was warmed to room temperature and stirred for 9 h. The reaction was quenched by addition of saturated $NaHCO_3$ solution. The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The

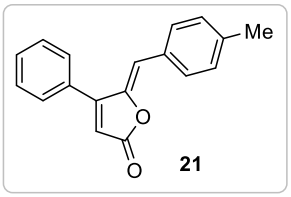
combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo to give the crude triene which was directly used for the next step.

Step 3

To a well stirred solution of freshly prepared triene (1 equiv.) in benzene was added DDQ (3 equiv.) at room temperature under nitrogen. Reaction mixture was then refluxed in a preheated oil bath for 4 h. Upon completion solvent was evaporated *in-vacuo*. Purification of crude product via a silica gel column chromatography (Hexanes/EtOAc) provided the desired triene.

(*Z*)-5-(4-methylbenzylidene)-4-phenylfuran-2(5*H*)-one (21)

According to the **General Procedure 5**, propargylic alcohol **9b** (30 mg, 0.096 mmol, 1 equiv.) and methanesulfonic acid (0.008 mL, 0.125 mmol, 1.3 equiv.) were used in **Step 1** to afford the corresponding allene. The crude allene was used directly with methanesulfonic acid (0.002 mL, 0.029 mmol, 0.3 equiv.) in **Step 2** to yield the triene **12b**. In **Step 3**, crude triene **12b** and DDQ (65 mg, 0.29 mmol, 3 equiv.) were used in 4 mL benzene, affording the desired aromatized product **21** as an orange gummy liquid (17 mg, 0.065 mmol, 68%) by using Hexane/EtOAc (14:1) as eluent.



^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.71 (d, *J* = 8.0 Hz, 2H), 7.58 – 7.45 (m, 5H), 7.20 (d, *J* = 8.0 Hz, 2H), 6.19 (s, 1H), 6.17 (s, 1H) and 2.38 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ_C 169.2, 158.9, 147.5, 139.9, 131.0, 130.7, 130.5, 130.4, 129.7, 129.2, 128.7, 114.3, 114.2 and 21.6 ppm.

IR (ATR): 2924, 1759, 1350, 1223, 1184, 1084, 957, 918, 868, 825, 771 and 698 cm^{-1}.

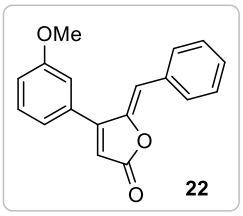
HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{18}H_{15}O_2$ 263.1067; found 263.1067.

TLC: R_f = 0.75 (4:1, Hex/EtOAc).

(*Z*)-5-benzylidene-4-(3-methoxyphenyl)furan-2(5*H*)-one (22)

According to the **General Procedure 5**, propargylic alcohol **9l** (30 mg, 0.09 mmol, 1 equiv.) and methanesulfonic acid (0.008 mL, 0.12 mmol, 1.3 equiv.) were used in **Step 1** to afford the corresponding allene. The crude allene was used directly with methanesulfonic acid (0.002 mL, 0.03 mmol, 0.3 equiv.) in **Step 2** to yield the corresponding triene. In **Step 3**, crude triene and DDQ (61 mg, 0.27 mmol, 3 equiv.) were used in 4 mL benzene, affording the desired

aromatized product **22** as a yellow gummy liquid (18 mg, 0.063 mmol, 70%) by using Hexane/EtOAc (14:1) as eluent.



^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.80 (d, *J* = 8.0 Hz, 2H), 7.47 – 7.31 (m, 4H), 7.11 – 7.04 (m, 2H), 7.02 (s, 1H), 6.21 (s, 1H), 6.20 (s, 1H) and 3.87 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ_C 168.9, 160.0, 158.8, 148.0, 133.1, 131.8, 131.0, 130.3, 129.4, 128.9, 120.9, 115.9, 114.7, 114.4, 114.0 and 55.6 ppm.

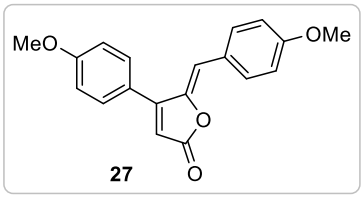
IR (ATR): 2930, 1763, 1577, 1485, 1454, 1346, 1265, 1211, 1180, 1041, 930, 841, 787 and 694 cm^{-1}.

HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{18}H_{15}O_3$ 279.1016; found 279.1019.

TLC: R_f = 0.7 (4:1, Hex/EtOAc).

(*Z*)-5-(4-methoxybenzylidene)-4-(4-methoxyphenyl)furan-2(5*H*)-one (27)

According to the **General Procedure 5**, propargylic alcohol **9d** (30 mg, 0.084 mmol, 1 equiv.) and methanesulfonic acid (0.007 mL, 0.11 mmol, 1.3 equiv.) were used in **Step 1** to afford the allene **12d**. The crude allene was used directly with methanesulfonic acid (0.002 mL, 0.025 mmol, 0.3 equiv.) in **Step 2** to yield the corresponding triene. In **Step 3**, crude triene and DDQ (57 mg, 0.25 mmol, 3 equiv.) were used in 4 mL benzene, affording the desired aromatized product **27** as a yellow solid (18 mg, 0.058 mmol, 69%) by using Hexane/EtOAc (14:1) as eluent.



^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.77 (d, *J* = 8.2 Hz, 2H), 7.46 (d, *J* = 8.0 Hz, 2H), 7.03 (d, *J* = 8.0 Hz, 2H), 6.92 (d, *J* = 8.2 Hz, 2H), 6.16 (s, 1H), 6.09 (s, 1H), 3.89 (s, 3H) and 3.84 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ_C 169.5, 161.5, 160.6, 158.5, 146.8, 132.7, 130.1, 126.1, 123.1, 114.7, 114.5, 113.8, 112.4, 55.6 and 55.5 ppm.

IR (ATR): 2930, 2852, 1751, 1613, 1515, 1428, 1179, 1090, 1036, 891 and 836 cm^{-1}.

HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{19}H_{17}O_4$ 309.1121; found 309.1119.

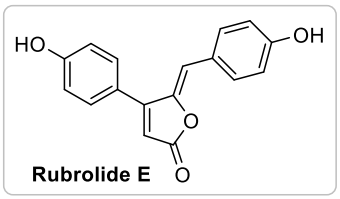
TLC: R_f = 0.7 (2:1, Hex/EtOAc).

MP: 134 – 137 °C.

8. Procedure 7: Procedure for deprotection of methyl ether with boron tribromide

To a stirred solution of **26** (18 mg, 0.058 mmol, 1 equiv.) in anhyd CH_2Cl_2 (4 mL) at –78 °C, was added a 1 M solution of BBr_3 in CH_2Cl_2 (0.18 mL, 0.18 mmol, 3 equiv.) drop wise. The mixture was then allowed to warm up to room temperature and stirred for further 24 h. The reaction was quenched with H_2O (5 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with H_2O, brine and dried (Na_2SO_4) and concentrated *in vacuo*. Purification of crude product via a silica gel column chromatography (3:2 Hexanes/EtOAc) provided the desired Rubrolide E (16 mg, 0.056 mmol, 96% yield) as a yellow solid.

(*Z*)-5-(4-hydroxybenzylidene)-4-(4-hydroxyphenyl)furan-2(5*H*)-one – Rubrolide E[2]



^{1}H NMR (400 MHz, DMSO-*d6*): δ_H 10.08 (br s, 1H), 10.01 (br s, 1H), 7.69 (d, *J* = 8.0 Hz, 2H), 7.49 (d, *J* = 7.8 Hz, 2H), 6.93 (d, *J* = 7.8 Hz, 2H), 6.84 (d, *J* = 8.0 Hz, 2H), 6.37 (s, 1H) and 6.32 (s, 1H) ppm.

^{13}C NMR (100 MHz, DMSO-*d6*): δ_C 168.7, 159.7, 158.7, 158.1, 145.3, 132.6, 130.4, 124.2, 120.7, 115.93, 115.91, 113.4 and 110.9 ppm.

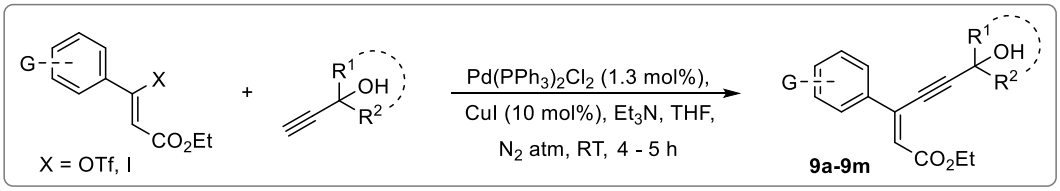
IR (ATR): 3274, 1765, 1727, 1677, 1606, 1520, 1206, 1049 and 746 cm^{-1}.

HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{17}H_{13}O_4$ 281.0808; found 281.0804.

TLC: R_f = 0.5 (1:1, Hex/EtOAc).

MP: 282 – 283 °C.

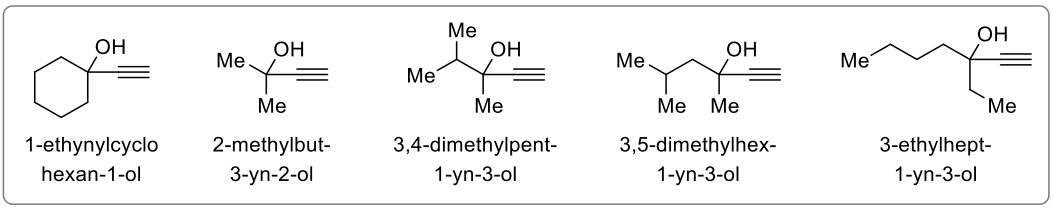
9. General procedure 8: Procedure for Sonogashira reaction



To a solution of the corresponding (Z)-enol triflate/iodide (1 equiv.) and the terminal alkyne (1 equiv.) in THF were added $PdCl_2(PPh_3)_2$ (1.3 mol%) and CuI (10 mol%) followed by addition of triethylamine (0.5 mL/ mmol). The resulting mixture was stirred at room temperature until the TLC showed complete consumption of the (*Z*)-enol triflate/iodide. After completion, the reaction was quenched by addition of saturated NH_4Cl solution. The aqueous layer was

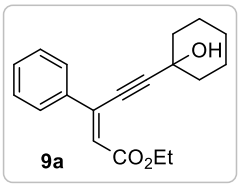
extracted with EtOAc (3 times). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in-vacuo*. Purification of crude product via a silica gel column chromatography (Hexanes/EA) provided the desired propargyl alcohols **9a-9m**.

List of commercially available propargylic alcohols used in Sonogashira reaction



ethyl (*Z*)-5-(1-hydroxycyclohexyl)-3-phenylpent-2-en-4-ynoate (9a)

According to the **General Procedure 8**, (*Z*)-enol triflate[3] (324 mg, 1 mmol, 1 equiv.), 1-ethynylcyclohexan-1-ol (124 mg, 1 mmol, 1 equiv.), CuI (19 mg, 0.1 mmol, 10 mol%), $Pd(PPh_3)_2Cl_2$ (9 mg, 0.013 mmol, 1.3 mol %) and 0.5 mL of triethylamine were used in 15 mL THF, affording the desired propargylic alcohol **9a** as pale yellow oil (280 mg, 0.94 mmol, 94%) by using Hexane/EtOAc (4:1) as eluent.



^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.73 – 7.66 (m, 2H), 7.41 – 7.35 (3H, m), 6.53 (s, 1H), 4.24 (q, *J* = 7.1 Hz, 2H), 3.37 (br s, 1H), 2.12 – 2.04 (m, 2H), 1.77-1.52 (m, 8H) and 1.30 (t, *J* = 7.1 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ_C 165.5, 137.2, 136.4, 130.0, 128.7, 127.2, 122.9, 107.0, 81.5, 69.3, 60.6, 39.8, 25.4, 23.4 and 14.4 ppm.

IR (ATR): 3431, 2930, 2856, 2370, 2211, 1698, 1450, 1377, 1266, 1168, 1074, 1022, 961, 861 and 770 cm^{-1}.

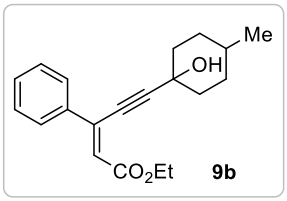
HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{19}H_{22}NaO_3$ 321.1461; found 321.1474.

TLC: R_f = 0.15 (9:1, Hex/EtOAc).

ethyl (*Z*)-5-(1-hydroxy-4-methylcyclohexyl)-3-phenylpent-2-en-4-ynoate (9b)

According to the **General Procedure 8**, (*Z*)-enol triflate[3] (324 mg, 1 mmol, 1 equiv.), 1-ethynyl-4-methylcyclohexan-1-ol[4] (138 mg, 1 mmol, 1 equiv.), CuI (19 mg, 0.1 mmol, 10 mol%), $Pd(PPh_3)_2Cl_2$ (9 mg, 0.013 mmol, 1.3 mol %) and 0.5 mL of triethylamine were used in 15 mL THF, affording the desired propargylic alcohol **9b** as a pale yellow oil (275 mg, 0.88 mmol, 88%) by using Hexane/EtOAc (4:1) as eluent.

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.75-7.65 (m, 2H), 7.44-7.33 (m, 3H), 6.53 (s, 1H), 4.23 (q, *J* = 7.1 Hz, 2H), 3.36 (br s, 1H), 2.20-2.09 (m, 2H), 1.75-1.62 (m, 4H), 1.47-1.35 (m, 3H), 1.29 (t, *J* = 7.1 Hz, 3H) and 0.94 (d, *J* = 4.9 Hz, 3H) ppm.



^{13}C NMR (100 MHz, $CDCl_3$): δ_C 165.4, 137.2, 136.4, 130.0, 128.7, 127.3, 122.9, 106.5, 82.1, 70.1, 60.5, 39.9, 32.5, 31.9, 21.9 and 14.4 ppm.

IR (ATR): 3437, 2935, 1716, 1600, 1454, 1369, 1269, 1173, 1045, 764 and 694 cm^{-1}.

HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{20}H_{25}O_3$ 313.1798; found 313.1803.

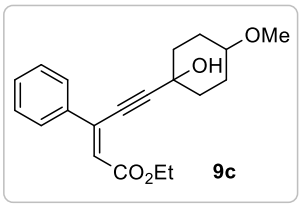
TLC: R_f = 0.15 (9:1, Hex/EtOAc).

ethyl (*Z*)-5-(1-hydroxy-4-methoxycyclohexyl)-3-phenylpent-2-en-4-ynoate (9c)

According to the **General Procedure 8**, (*Z*)-enol triflate[3] (324 mg, 1 mmol, 1 equiv.), 1-ethynyl-4-methoxycyclohexan-1-ol **26** (154 mg, 1 mmol, 1 equiv.), CuI (19 mg, 0.1 mmol, 10 mol%), $Pd(PPh_3)_2Cl_2$ (9 mg, 0.013 mmol, 1.3 mol %) and 0.5 mL of triethylamine were used in 15 mL THF, affording the desired propargylic alcohol **9c** as a pale yellow oil (289 mg, 0.88 mmol, 88%) by using Hexane/EtOAc (4:1) as eluent.

(Inseparable mixture of diastereomers with *d.r.*~2:1)

^{1}H NMR (400 MHz, $CDCl_3$): **Major isomer:** δ_H 7.75 – 7.63 (m, 2H), 7.44-7.32 (m, 3H), 6.53 (1H, s), 4.23 (q, *J* = 7.1 Hz, 2H,), 3.40 – 3.35 (m, 1H), 3.32 (s, 3H), 2.24 – 2.15 (m, 1H), 2.11 – 1.96 (m, 2H), 1.95 – 1.81 (m, 4H), 1.80 – 1.68 (m, 1H) and 1.34 – 1.27 (m, 3H) ppm.



Minor isomer: δ_H 7.75 – 7.63 (m, 2H), 7.44-7.32 (m, 3H), 6.53 (s, 1H), 4.23 (q, *J* = 7.1 Hz, 2H), 3.36 (s, 3H), 3.30 – 3.24 (m, 1H), 2.36 – 2.24 (m, 1H), 2.11 – 1.96 (m, 2H), 1.95 – 1.81 (m, 4H), 1.80 – 1.68 (m, 1H) and 1.34 – 1.27 (m, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): **Major isomer:** δ_C 165.4, 137.05, 136.36, 130.06, 128.72, 127.2, 106.6, 81.0, 75.3, 68.3, 60.5, 56.6, 35.3, 27.01 and 14.4 ppm.

Minor isomer: δ_C 165.48, 136.96, 136.46, 130.09, 128.75, 122.9, 106.3, 81.6, 77.3, 68.6, 60.6, 55.9, 36.5, 27.8 and 14.4 ppm.

IR (ATR): 3433, 2940, 1710, 1599, 1449, 1370, 1267, 1174, 1092, 1028, 970 and 770 cm^{-1}.

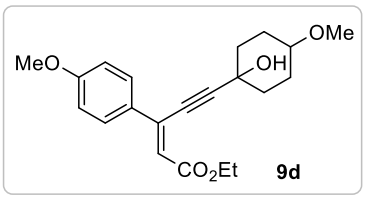
HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{20}H_{25}O_4$ 329.1747; found 329.1691.

TLC: R_f = 0.15 (9:1, Hex/EtOAc).

ethyl (*Z*)-5-(1-hydroxy-4-methoxycyclohexyl)-3-(4-methoxyphenyl)pent-2-en-4-ynoate (9d)

(Inseparable mixture of diastereomers with *d.r.*~1:0.8)

According to the **General Procedure 8**, (*Z*)-vinyliodide **23** (302 mg, 1 mmol, 1 equiv.), 1-ethynyl-4-methoxycyclohexan-1-ol **26** (154 mg, 1 mmol, 1 equiv.), CuI (19 mg, 0.1 mmol, 10 mol%), $Pd(PPh_3)_2Cl_2$ (9 mg, 0.013 mmol, 1.3 mol %) and 0.5 mL of triethylamine were used in 15 mL THF, affording the desired propargylic alcohol **9d** as a pale yellow oil (337 mg, 0.94 mmol, 94%) by using Hexane/EtOAc (4:1) as eluent.



^{1}H NMR (400 MHz, $CDCl_3$): **Major isomer:** δ_H 7.66 (d, *J* = 8.0 Hz, 2H), 6.90 (d, *J* = 8.0 Hz, 2H), 6.47 (1H, s), 4.24 (q, *J* = 8.0 Hz, 2H,), 3.84 (s, 3H), 3.31 (s, 3H), 3.32 – 3.26 (m, 1H), 2.25 – 2.12 (m, 1H), 2.10 – 1.97 (m, 2H), 1.95 – 1.85 (m, 3H), 1.80 – 1.68 (m, 3H) and 1.31 (t, *J* = 8.0 Hz, 3H) ppm.

Minor isomer: δ_H 7.66 (d, *J* = 8.0 Hz, 2H), 6.90 (d, *J* = 8.0 Hz, 2H), 6.47 (1H, s), 4.24 (q, *J* = 8.0 Hz, 2H,), 3.84 (s, 3H), 3.42 – 3.36 (m, 1H), 3.33 (s, 3H), 2.25 – 2.12 (m, 1H), 2.10 – 1.97 (m, 2H), 1.95 – 1.85 (m, 3H), 1.80 – 1.68 (m, 3H) and 1.31 (t, *J* = 8.0 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ_C 165.7, 165.6, 161.4, 161.3, 135.8, 135.7, 129.3, 129.2, 128.7, 121.0, 114.2, 114.1, 105.9, 105.8, 82.0, 81.3, 75.3, 68.9, 68.5, 60.4, 60.4, 56.0, 55.7, 55.5, 36.6, 35.4, 29.8, 27.9, 27.1 and 14.5 ppm.

IR (ATR): 3436, 3056, 2936, 2862, 1711, 1601, 1511, 1454, 1262, 1171, 1092 and 739 cm^{-1}.

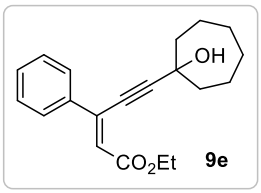
HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{21}H_{27}O_5$ 359.1853; found 359.1850.

TLC: R_f = 0.15 (9:1, Hex/EtOAc).

ethyl (*Z*)-5-(1-hydroxycycloheptyl)-3-phenylpent-2-en-4-ynoate (9e)

According to the **General Procedure 8**, (*Z*)-enol triflate[3] (324 mg, 1 mmol, 1 equiv.), 1-ethynylcycloheptan-1-ol[5] (138 mg, 1 mmol, 1 equiv.), CuI (19 mg, 0.1 mmol, 10 mol%), $Pd(PPh_3)_2Cl_2$ (9 mg, 0.013 mmol, 1.3 mol %) and 0.5 mL of triethylamine were used in 15 mL THF, affording the desired propargylic alcohol **9e** as a pale yellow oil (287 mg, 0.92 mmol, 92%) by using Hexane/EtOAc (4:1) as eluent.

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.75 – 7.63 (m, 2H), 7.43 – 7.31 (m, 3H), 6.52 (s, 1H), 4.24 (q, *J* = 8.0 Hz, 2H), 3.41 (br s, 1H), 2.23 – 2.15 (m, 2H), 2.03 – 1.94 (m, 2H), 1.77 – 1.57 (m, 8H) and 1.30 (t, *J* = 8.0 Hz, 3H) ppm.



^{13}C NMR (100 MHz, $CDCl_3$): δ_C 165.5, 137.2, 136.5, 130.0, 128.7, 127.2, 122.7, 108.1, 80.7, 72.3, 60.5, 42.8, 28.3, 22.2 and 14.4 ppm.

IR (ATR): 3432, 2934, 2856, 2370, 2211, 1699, 1450, 1377, 1266, 1168, 1074, 1022, 961, 861 and 775 cm^{-1}.

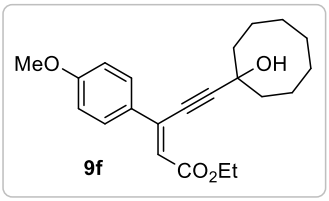
HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{20}H_{24}NaO_3$ 335.1618; found 335.1639.

TLC: R_f = 0.15 (9:1, Hex/EtOAc).

ethyl (*Z*)-5-(1-hydroxycyclooctyl)-3-(4-methoxyphenyl)pent-2-en-4-ynoate (9f)

According to the **General Procedure 8**, (*Z*)-vinyliodide **23** (302 mg, 1 mmol, 1 equiv.), 1-ethynylcyclooctan-1-ol[6] (152 mg, 1 mmol, 1 equiv.), CuI (19 mg, 0.1 mmol, 10 mol%), $Pd(PPh_3)_2Cl_2$ (9 mg, 0.013 mmol, 1.3 mol %) and 0.5 mL of triethylamine were used in 15 mL THF, affording the desired propargylic alcohol **9f** as a pale yellow oil (314 mg, 0.88 mmol, 88%) by using Hexane/EtOAc (4:1) as eluent.

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.44 (d, *J* = 8.0 Hz, 2H), 6.86 (d, *J* = 8.0 Hz, 2H), 6.46 (s, 1H), 4.10 (q, *J* = 8.0 Hz, 2H), 3.82 (s, 3H), 2.05 – 1.89 (m, 5H), 1.74 – 1.61 (m, 6H), 1.57 – 1.43 (m, 4H) and 1.18 (t, *J* = 8.0 Hz, 3H) ppm.



^{13}C NMR (100 MHz, $CDCl_3$): δ_C 165.7, 160.4, 137.5, 130.5, 128.5, 123.3, 113.3, 99.3, 84.6, 71.9, 60.4, 55.4, 38.2, 28.0, 24.6, 22.2 and 14.2 ppm.

IR (ATR): 3436, 2926, 2857, 1712, 1598, 1511, 1457, 1364, 1259, 1171, 1032, 839 and 740 cm^{-1}.

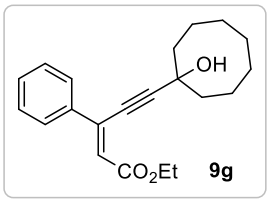
HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{22}H_{29}O_4$ 357.2060; found 357.2063.

TLC: R_f = 0.2 (9:1, Hex/EtOAc).

ethyl (*Z*)-5-(1-hydroxycyclooctyl)-3-phenylpent-2-en-4-ynoate (9g)

According to the **General Procedure 8**, (*Z*)-enol triflate[3] (324 mg, 1 mmol, 1 equiv.), 1-ethynylcyclooctan-1-ol[6] (152 mg, 1 mmol, 1 equiv.), CuI (19 mg, 0.1 mmol, 10 mol%), $Pd(PPh_3)_2Cl_2$ (9 mg, 0.013 mmol, 1.3 mol %) and 0.5 mL of triethylamine were used in 15 mL

THF, affording the desired propargylic alcohol **9g** as a pale yellow oil (277 mg, 0.85 mmol, 85%) by using Hexane/EtOAc (4:1) as eluent.



^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.75 – 7.64 (m, 2H), 7.44 – 7.31 (m, 3H), 6.54 (s, 1H), 4.26 (q, *J* = 8.0 Hz, 2H), 2.57 (br s, 1H), 2.15 – 2.03 (m, 4H), 1.79 – 1.59 (m, 9H), 1.58 – 1.48 (m, 3H) and 1.33 (3H, t, *J* = 8.0 Hz) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ_C 165.4, 137.2, 136.5, 129.9, 128.6, 127.2, 122.6, 108.0, 80.4, 71.8, 60.5, 37.8, 28.0, 24.6, 22.1 and 14.4 ppm.

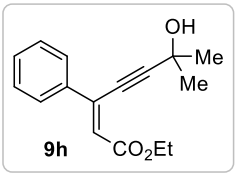
IR (ATR): 3436, 2925, 2860, 2361, 2211, 1696, 1450, 1380, 1269, 1180, 1074, 1022, 961, 844 and 775 cm^{-1}.

HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{21}H_{27}O_3$ 327.1955; found 327.1945.

TLC: R_f = 0.2 (9:1, Hex/EtOAc).

ethyl (*Z*)-6-hydroxy-6-methyl-3-phenylhept-2-en-4-ynoate (9h)

According to the **General Procedure 8**, (*Z*)-enol triflate[3] (324 mg, 1 mmol, 1 equiv.), 2-methylbut-3-yn-2-ol (84 mg, 1 mmol, 1 equiv.), CuI (19 mg, 0.1 mmol, 10 mol%), $Pd(PPh_3)_2Cl_2$ (9 mg, 0.013 mmol, 1.3 mol %) and 0.5 mL of triethylamine were used in 15 mL THF, affording the desired propargylic alcohol **9h** as a yellow oil (219 mg, 0.85 mmol, 85%) by using Hexane/EtOAc (4:1) as eluent.



^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.72 – 7.62 (m, 2H), 7.41 – 7.29 (m, 3H), 6.50 (s, 1H), 4.39 (br s, 1H), 4.22 (q, *J* = 8.0 Hz, 2H), 1.67 (s, 6H) and 1.28 (t, *J* = 8.0 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ_C 165.5, 136.9, 136.5, 129.9, 128.6, 127.1, 122.4, 107.8, 79.2, 65.4, 60.5, 31.0 and 14.3 ppm.

IR (ATR): 3415, 2984, 1699, 1532, 1409, 1199, 1022, 954, 833 and 593 cm^{-1}.

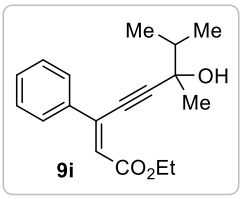
HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{16}H_{18}NaO_3$ 281.1148; found 281.1174.

TLC: R_f = 0.15 (9:1, Hex/EtOAc).

ethyl (*Z*)-6-hydroxy-6,7-dimethyl-3-phenyloct-2-en-4-ynoate (9i)

According to the **General Procedure 8**, (*Z*)-enol triflate[3] (324 mg, 1 mmol, 1 equiv.), 3,4-dimethylpent-1-yn-3-ol (112 mg, 1 mmol, 1 equiv.), CuI (19 mg, 0.1 mmol, 10 mol%),

$Pd(PPh_3)_2Cl_2$ (9 mg, 0.013 mmol, 1.3 mol %) and 0.5 mL of triethylamine were used in 15 mL THF, affording the desired propargylic alcohol **9i** as a yellow oil (254 mg, 0.89 mmol, 89%) by using Hexane/EtOAc (5:1) as eluent.



^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.75 – 7.63 (m, 2H), 7.43 – 7.31 (3H, m), 6.53 (s, 1H), 4.24 (q, *J* = 8.0 Hz, 2H), 3.19 (br s, 1H), 2.0 – 1.90 (m, 1H), 1.58 (s, 3H), 1.31 (t, *J* = 7.1 Hz, 3H), 1.13 (d, *J* = 8.0 Hz, 3H) and 1.09 (d, *J* = 8.0 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ_C 165.4, 137.1, 136.3, 130.0, 128.7, 127.2, 123.0, 106.3, 81.5, 72.4, 60.5, 39.1, 26.9, 18.0, 17.8 and 14.4 ppm.

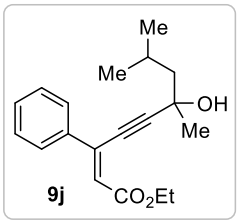
IR (ATR): 3412, 2978, 1762, 1701, 1606, 1400, 1218, 1170, 1022, 830 and 596 cm^{-1}.

HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{18}H_{22}NaO_3$ 309.1461; found 309.1470.

TLC: R_f = 0.2 (9:1, Hex/EtOAc).

ethyl (*Z*)-6-hydroxy-6,8-dimethyl-3-phenylnon-2-en-4-ynoate (9j)

According to the **General Procedure 8**, (*Z*)-enol triflate[3] (324 mg, 1 mmol, 1 equiv.), 3,5-dimethylhex-1-yn-3-ol (126 mg, 1 mmol, 1 equiv.), CuI (19 mg, 0.1 mmol, 10 mol%), $Pd(PPh_3)_2Cl_2$ (9 mg, 0.013 mmol, 1.3 mol %) and 0.5 mL of triethylamine were used in 15 mL THF, affording the desired propargylic alcohol **9j** as a pale yellow oil (270 mg, 0.9 mmol, 90%) by using Hexane/EtOAc (5:1) as eluent.



^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.71 – 7.65 (m, 2H), 7.38 – 7.32 (m, 3H), 6.50 (s, 1H), 4.22 (q, *J* = 8.0 Hz, 2H), 4.09 (br s, 1H), 2.10 – 2.00 (m, 1H), 1.81 – 1.69 (m, 2H), 1.65 (s, 3H), 1.28 (t, *J* = 8.0 Hz, 3H) and 1.03 (t, *J* = 8.0 Hz, 6H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ_C 165.4, 136.9, 136.5, 129.9, 128.5, 127.1, 122.4, 107.7, 80.6, 68.4, 60.4, 51.6, 30.4, 25.1, 24.3, 24.2 and 14.3 ppm.

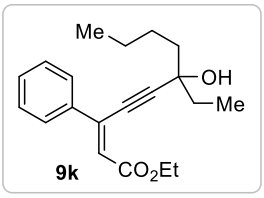
IR (ATR): 3425, 2978, 1700, 1529, 1401, 1205, 1015, 951, 833 and 599 cm^{-1}.

HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{19}H_{24}NaO_3$ 323.1618; found 323.1628.

TLC: R_f = 0.3 (9:1, Hex/EtOAc).

ethyl (*Z*)-6-ethyl-6-hydroxy-3-phenyldec-2-en-4-ynoate (9k)

According to the **General Procedure 8**, (*Z*)-enol triflate[3] (324 mg, 1 mmol, 1 equiv.), 3-ethylhept-1-yn-3-ol (140 mg, 1 mmol, 1 equiv.), CuI (19 mg, 0.1 mmol, 10 mol%), $Pd(PPh_3)_2Cl_2$ (9 mg, 0.013 mmol, 1.3 mol %) and 0.5 mL of triethylamine were used in 15 mL THF, affording the desired propargylic alcohol **9k** as a pale yellow oil (267 mg, 0.85 mmol, 85%) by using Hexane/EtOAc (5:1) as eluent.



^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.74 – 7.64 (m, 2H), 7.43 – 7.34 (m, 3H), 6.53 (s, 1H), 4.24 (q, *J* = 8.0 Hz, 2H), 3.09 (br s, 1H), 1.87 – 1.72 (m, 4H), 1.63 – 1.53 (m, 2H), 1.39 (dt, *J* = 14.6, 7.3 Hz, 2H), 1.31 (t, *J* = 7.1 Hz, 3H), 1.12 (t, *J* = 7.4 Hz, 3H) and 0.93 (t, *J* = 7.3 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ_C 165.4, 137.1, 136.3, 130.0, 128.7, 127.2, 122.9, 106.2, 81.8, 72.4, 60.5, 41.1, 34.7, 26.6, 23.1, 14.4, 14.2 and 8.8 ppm.

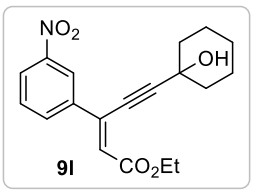
IR (ATR): 2960, 2938, 1706, 1599, 1372, 1266, 1177, 766, 751 and 692 cm^{-1}.

HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{20}H_{27}O_3$ 315.1955; found 315.1951.

TLC: R_f = 0.3 (9:1, Hex/EtOAc).

ethyl (Z)-5-(1-hydroxycyclohexyl)-3-(3-nitrophenyl)pent-2-en-4-ynoate (9l)

According to the **General Procedure 8**, (*Z*)-vinyliodide **28** (347 mg, 1 mmol, 1 equiv.), 1-ethynylcyclohexan-1-ol (124 mg, 1 mmol, 1 equiv.), CuI (19 mg, 0.1 mmol, 0.1 equiv.), $Pd(PPh_3)_2Cl_2$ (9 mg, 0.013 mmol, 1.3 mol %) and 0.5 mL of triethylamine were used in 15 mL THF, affording the desired propargylic alcohol **9l** as a brown crystalline solid (305 mg, 0.89 mmol, 89%) by using Hexane/EtOAc (4:1) as eluent.



^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.58 (s, 1H), 8.25 (d, *J* = 8.1 Hz, 1H), 8.03 (d, *J* = 7.8 Hz, 1H), 7.59 (t, *J* = 8.0 Hz, 1H), 6.63 (s, 1H), 4.28 (q, *J* = 7.0 Hz, 2H), 3.39 (br s, 1H), 2.13 – 2.06 (m, 2H), 1.78 – 1.51 (m, 8H) and 1.34 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ_C 164.8, 148.6, 138.8, 133.8, 132.8, 129.8, 124.7, 124.5, 122.2, 108.2, 80.5, 69.4, 61.0, 39.7, 25.3, 23.4 and 14.4 ppm.

IR (ATR): 3055, 2987, 2939, 2305, 1717, 1534, 1444, 1422, 1350, 1265, 1184, 1167, 896, 739 and 706 cm^{-1}.

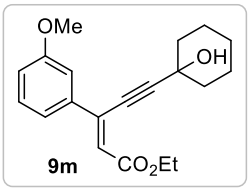
HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{19}H_{22}NO_5$ 344.1492; found 344.1460.

TLC: R_f = 0.25 (4:1, Hex/EtOAc).

MP: 75 – 77 °C (recrystallized from CH_2Cl_2/ Hexane: 1:1).

ethyl (*Z*)-5-(1-hydroxycyclohexyl)-3-(3-methoxyphenyl)pent-2-en-4-ynoate (9m)

According to the **General Procedure 8**, (*Z*)-enol triflate[7] (354 mg, 1 mmol, 1 equiv.), 1-ethynylcyclohexan-1-ol (124 mg, 1 mmol, 1 equiv.), CuI (19 mg, 0.1 mmol, 0.1 equiv.), $Pd(PPh_3)_2Cl_2$ (14 mg, 0.02 mmol, 0.02 equiv.) and 0.5 mL of triethylamine were used in 15 mL THF, affording the desired propargylic alcohol **9m** as a pale yellow oil (285 mg, 0.87 mmol, 87%) by using Hexane/EtOAc (9:1) as eluent.



^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.31 – 7.22 (m, 3H), 6.97 – 6.89 (m, 1H), 6.51 (1H, s), 4.23 (q, *J* = 8.0 Hz, 2H), 3.81 (s, 3H), 3.87 – 3.64 (br s, 1H), 2.13 – 2.04 (m, 2H), 1.79 – 1.54 (m, 7H) and 1.30 (t, *J* = 8.0 Hz, 3H) ppm.

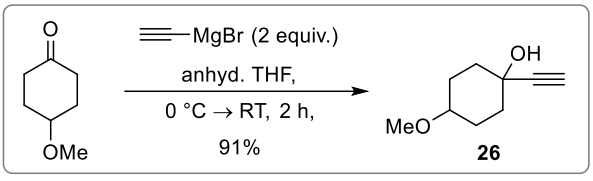
^{13}C NMR (100 MHz, $CDCl_3$): δ_C 165.4, 159.7, 138.6, 136.3, 129.6, 122.8, 119.5, 115.9, 112.7, 107.0, 81.3, 69.2, 60.5, 55.3, 39.7, 25.3, 23.4 and 14.4 ppm.

IR (ATR): 3440, 2939, 1712, 1593, 1454, 1281, 1219, 1169, 1041, 968, 864 and 787 cm^{-1}.

HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{20}H_{25}O_4$ 329.1747; found 329.1738.

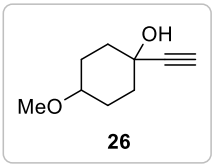
TLC: R_f = 0.3 (9:1, Hex/EtOAc).

10. Procedure 9: Procedure for preparation of propargyl alcohol (26):



To the stirred solution of 4-methylcyclohexan-1-one[8] (256 mg, 2 mmol, 1.0 equiv.) in anhydrous THF was added ethynyl magnesium bromide (2 mL, 2.0 equiv., 0.5 M in THF) drop wise at 0 °C under nitrogen. The mixture was stirred at same temperature for 2 h. The reaction mixture was quenched with saturated NH_4Cl solution. The aqueous layer was extracted with EtOAc (3 times). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in-vacuo*. Purification of crude product via silica gel column chromatography (Hexanes/EA) provided a diastereomeric mixture (*anti*:*syn* = 3:1) of the desired propargyl alcohol **26** as a colourless oil (280 mg, 1.8 mmol, 91%).

1-ethynyl-4-methoxycyclohexan-1-ol (26)



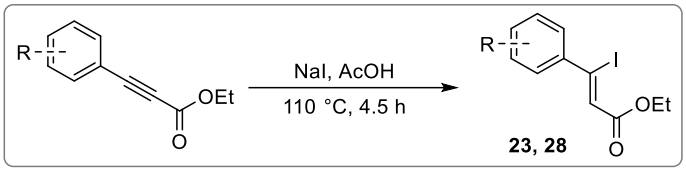
^{1}H NMR (400 MHz, $CDCl_3$): δ_H 3.48 – 3.13 (m, 4H), 2.86 – 2.36 (m, 2H), 2.22 – 1.69 (m, 7H) and 1.69 – 1.54 (m, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ_C 87.6, 87.2, 75.2, 72.7, 71.7, 68.0, 67.5, 55.9, 55.6, 36.7, 35.4, 27.7 and 26.9 ppm.

HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_9H_{14}NaO_2$ 177.0886; found 177.0879.

TLC: R_f = 0.35 (2:1, Hex/EtOAc).

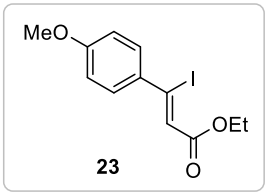
11. General procedure 10: for preparation of vinyl iodide:



A mixture of propiolate ester derivative and sodium iodide in acetic acid was heated in a preheated oil bath at 110 °C for 4.5 h. The mixture was cooled and partitioned between ethyl acetate and water. The layers were separated, and the aqueous layer was extracted with ethyl acetate. The combined extracts were washed with saturated aqueous sodium hydrogen carbonate, sodium thiosulfate, and brine, dried over Na_2SO_4, and filtered. Purification of crude product via silica gel column chromatography (Hexanes/EA) provided the desired vinyl iodide.

ethyl (*Z*)-3-iodo-3-(4-methoxyphenyl)acrylate (23)

According to the **General Procedure 10**, ethyl 3-(4-methoxyphenyl)propiolate[9] (510 mg, 2.5 mmol, 1.0 equiv.) and sodium iodide (1.12 g, 7.5 mmol, 3.0 equiv.) were used in 1.9 mL (13 equiv.) acetic acid, affording the desired vinyl iodide **23** as a colourless oil (797 mg, 2.4 mmol, 96%) by using Hexane/EtOAc (9:1) as eluent.



^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.30 (d, *J* = 8.3 Hz, 2H), 6.81 (d, *J* = 8.4 Hz, 2H), 6.57 (s, 1H), 4.02 (q, *J* = 7.0 Hz, 2H), 3.81 (s, 3H) and 1.12 (t, *J* = 7.1 Hz, 3H) ppm.

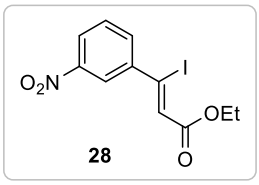
^{13}C NMR (100 MHz, $CDCl_3$): δ_C 163.8, 160.3, 131.6, 129.8, 125.0, 113.2, 111.5, 80.3, 60.6, 55.4 and 14.0 ppm.

HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{12}H_{14}IO_3$ 332.9982; found 332.9982.

TLC: R_f = 0.45 (19:1, Hex/EtOAc).

ethyl (Z)-3-iodo-3-(3-nitrophenyl)acrylate (28)

According to the **General Procedure 10**, ethyl 3-(3-nitrophenyl)propiolate[10] (548 mg, 2.5 mmol, 1.0 equiv.) and sodium iodide (1.2 g, 8.0 mmol, 3.2 equiv.) were used in 1.8 mL (12.8 equiv.) acetic acid, affording the desired vinyl iodide **28** as a yellow crystalline solid (824 mg, 2.4 mmol, 95%) by using Hexane/EtOAc (9:1) as eluent.



28

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.38 (s, 1H), 8.22 (d, *J* = 8.1 Hz, 1H), 7.86 (d, *J* = 7.8 Hz, 1H), 7.58 (t, *J* = 8.0 Hz, 1H), 6.73 (s, 1H), 4.32 (q, *J* = 7.1 Hz, 2H) and 1.36 (t, *J* = 7.1 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ_C 164.2, 148.1, 145.0, 134.6, 129.7, 129.3, 124.5, 123.5, 111.6, 61.3 and 14.3 ppm.

IR (ATR): 3055, 2986, 1723, 1607, 1533, 1356, 1310, 1302, 1266, 1180, 1029, 897, 806, 738, 705 cm^{-1}.

HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{11}H_{11}INO_4$ 347.9727; found 347.9707.

TLC: R_f = 0.75 (4:1, Hex/EtOAc).

MP: 69 – 71 °C (recrystallized from hot hexanes).

11. References

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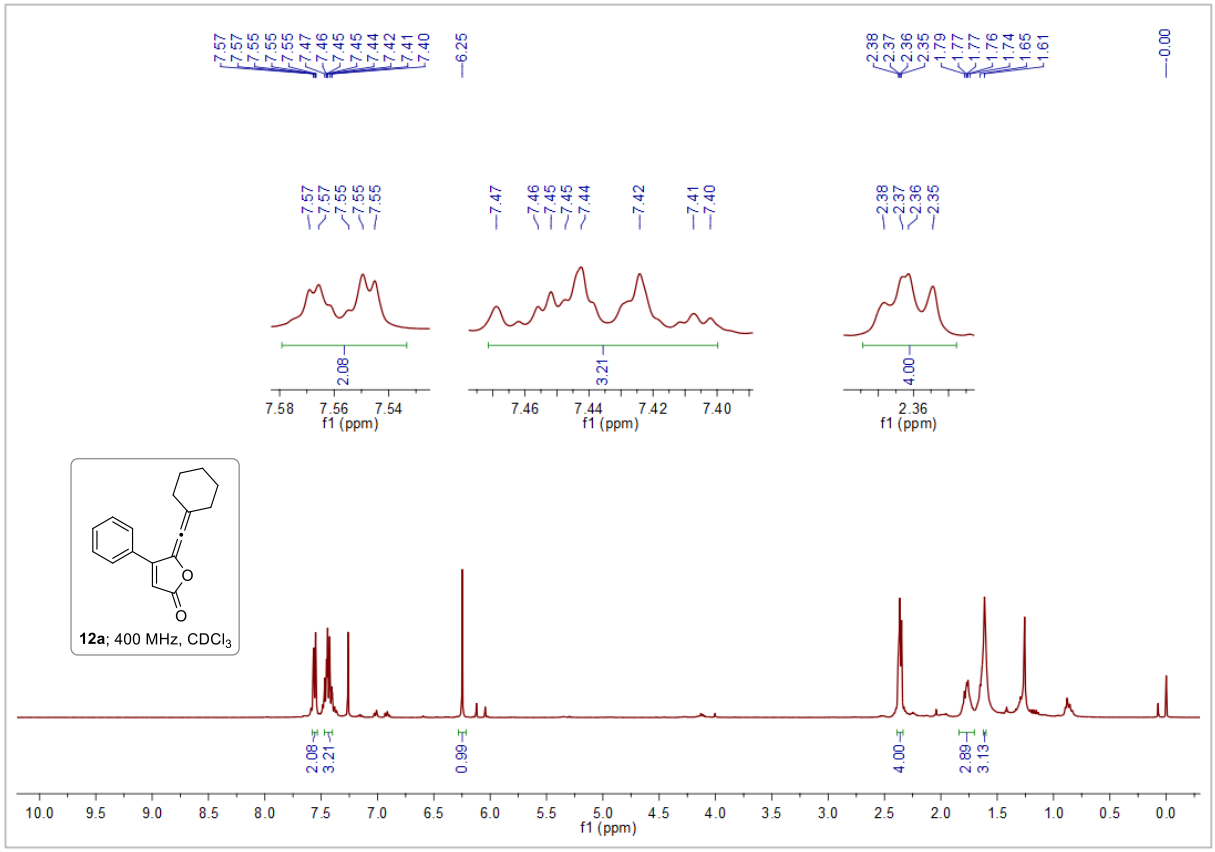
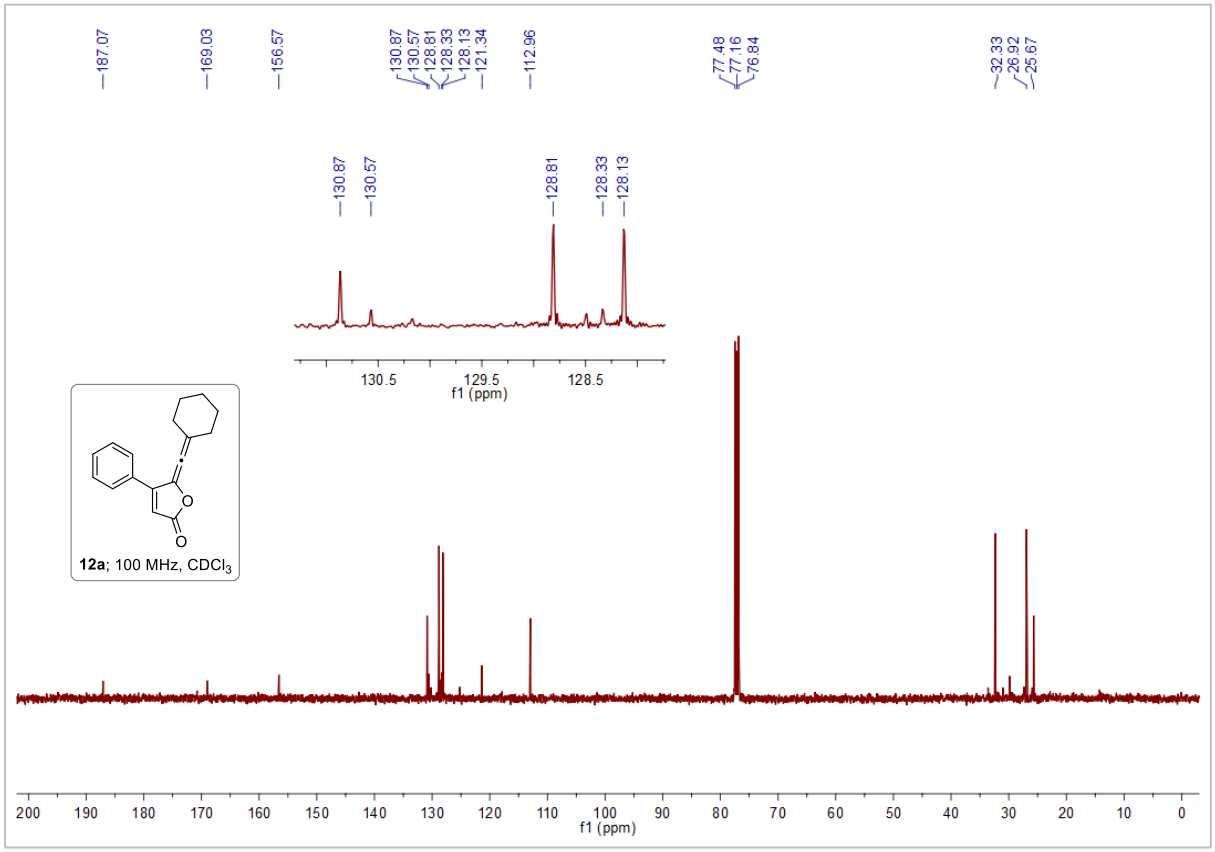
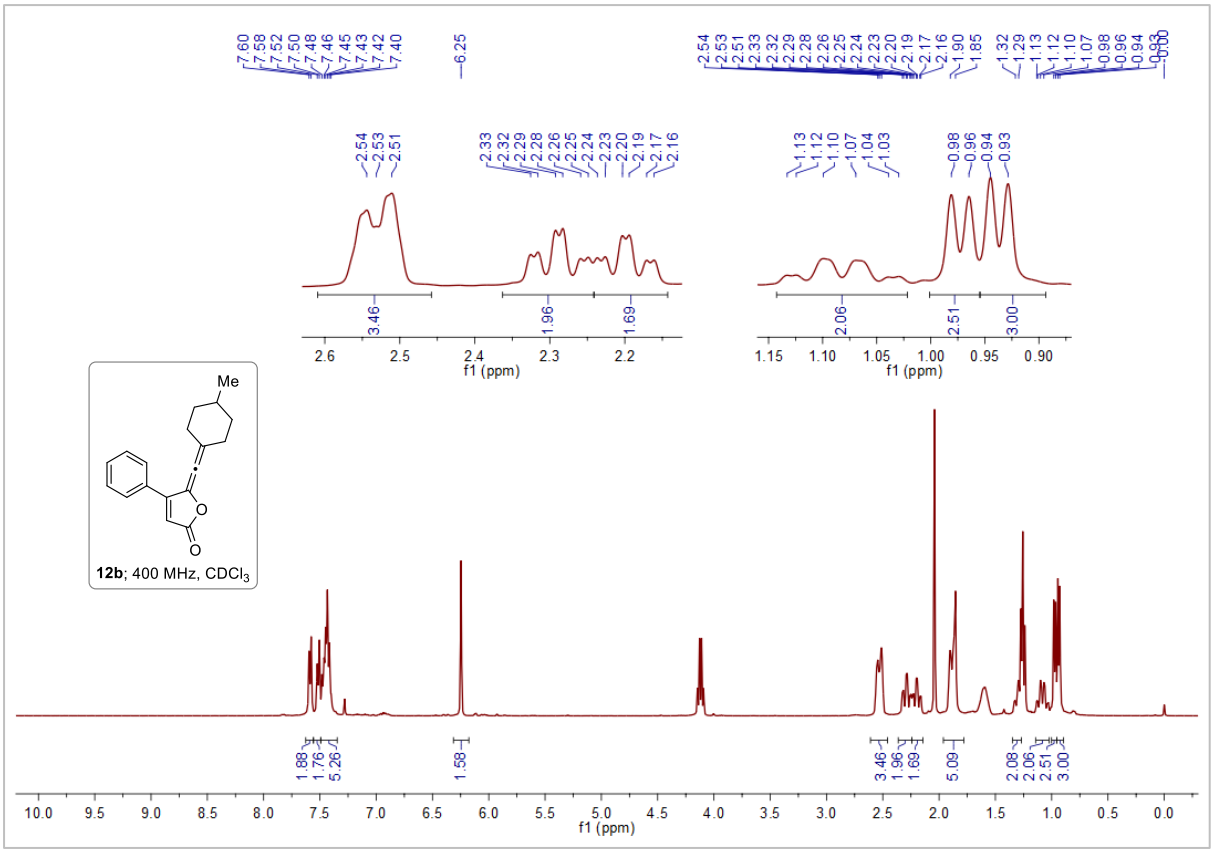
12. Copy of ^{1}H and ^{13}C NMR spectra of all new compounds

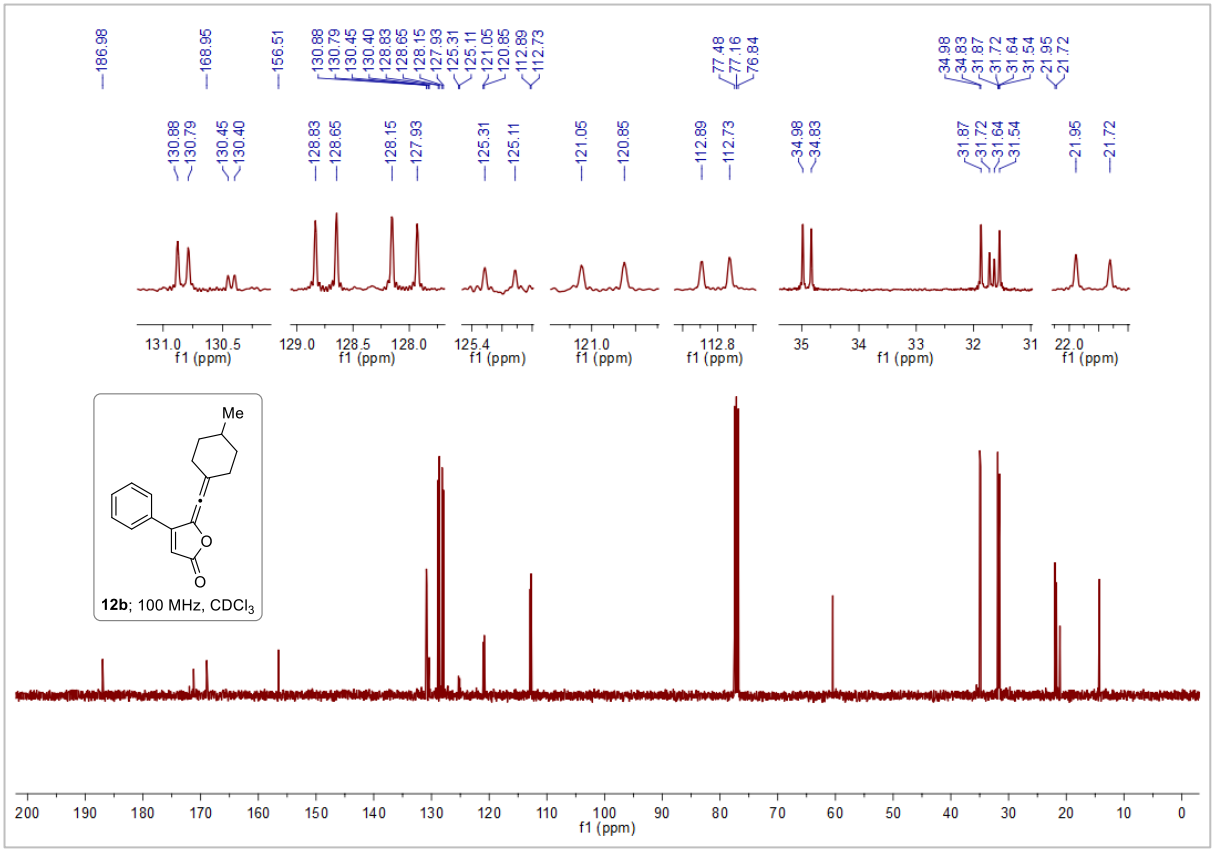
^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) of **12a**.



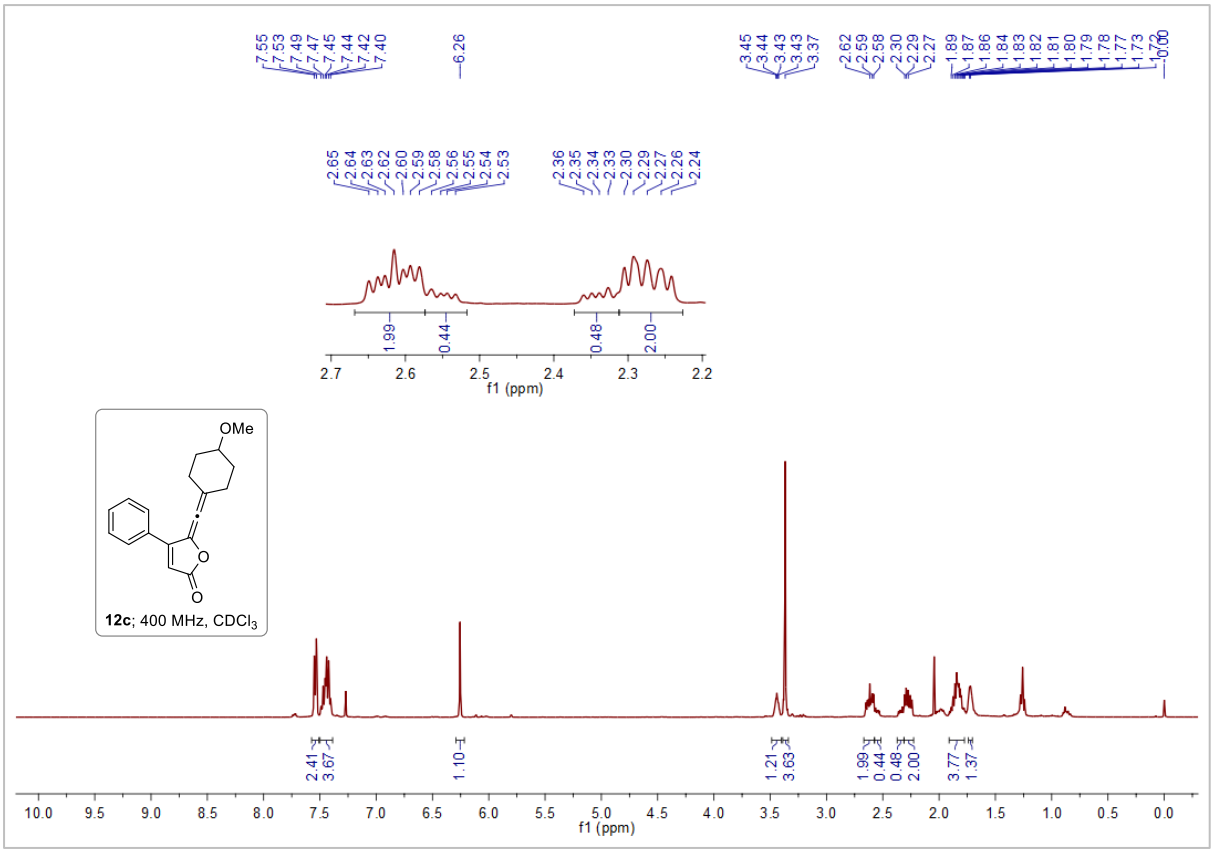


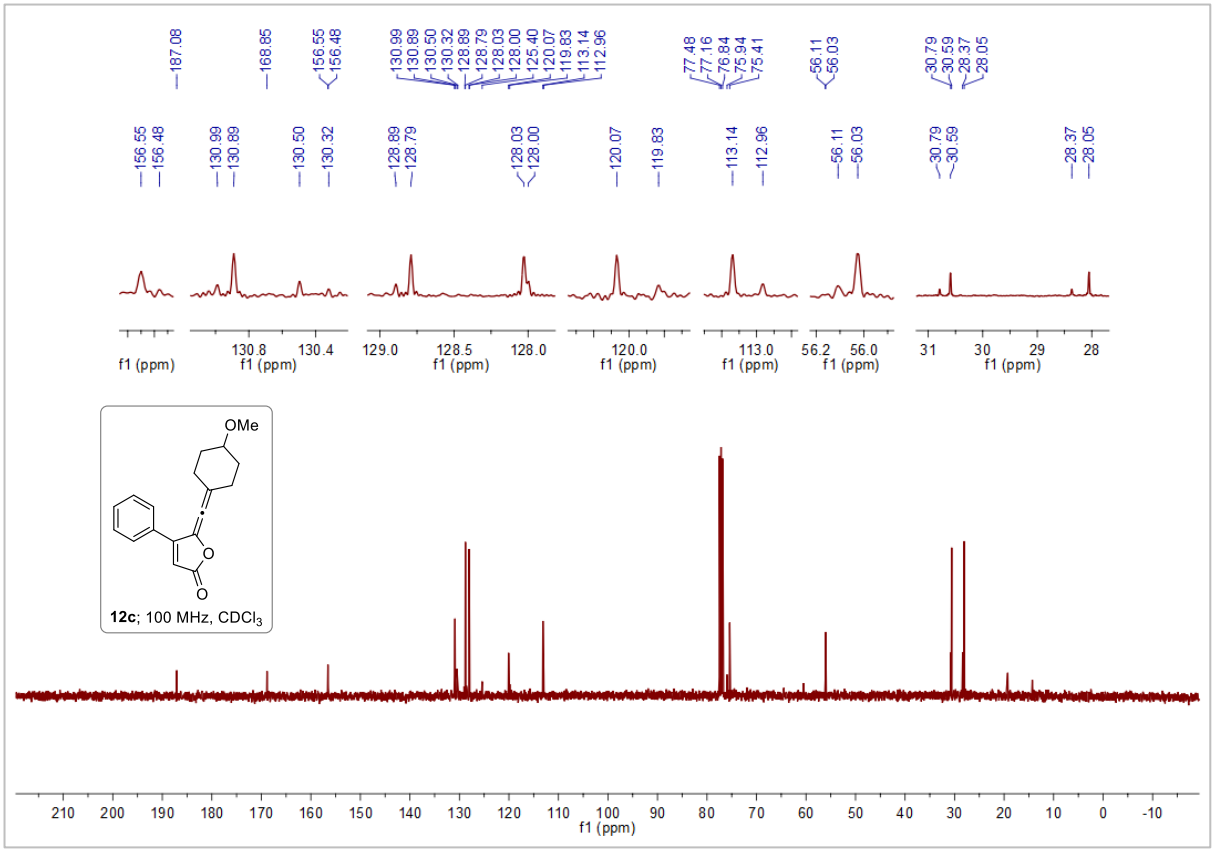
^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) of **12b**.



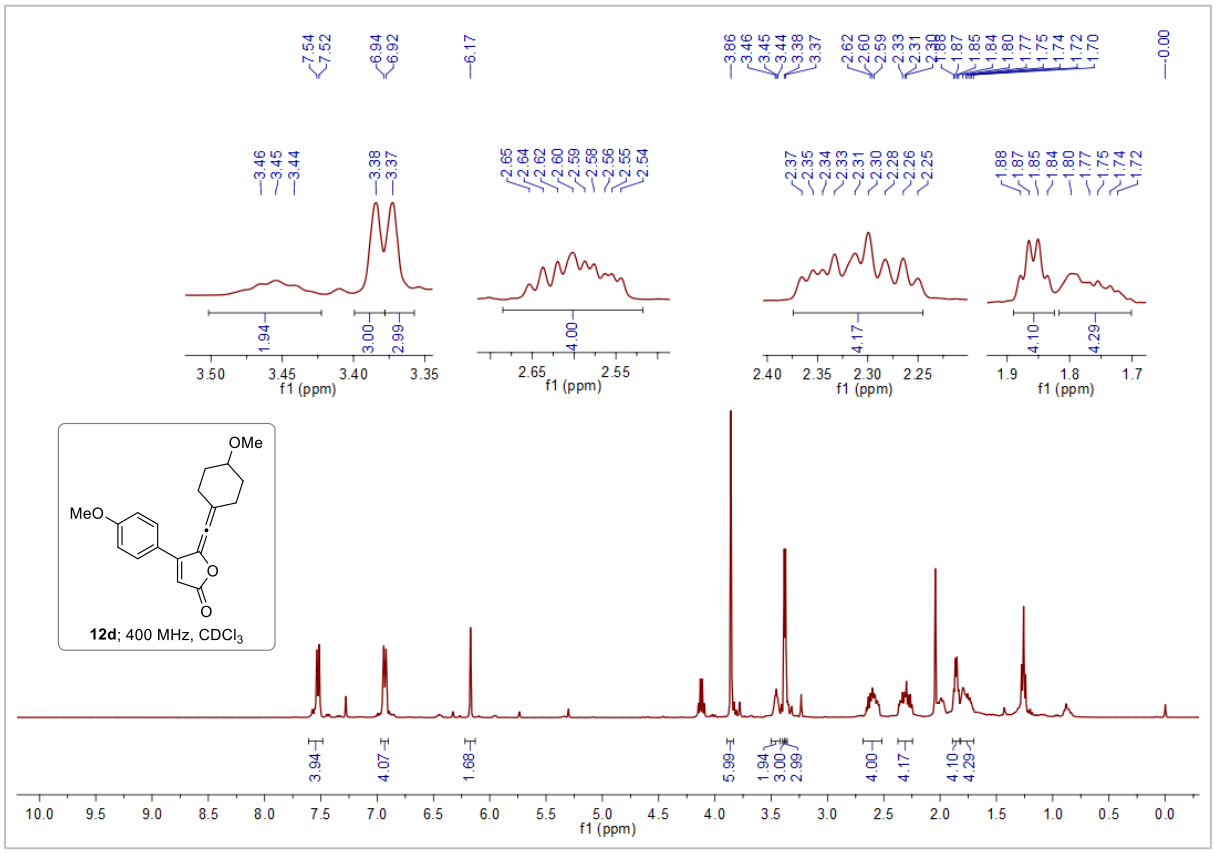


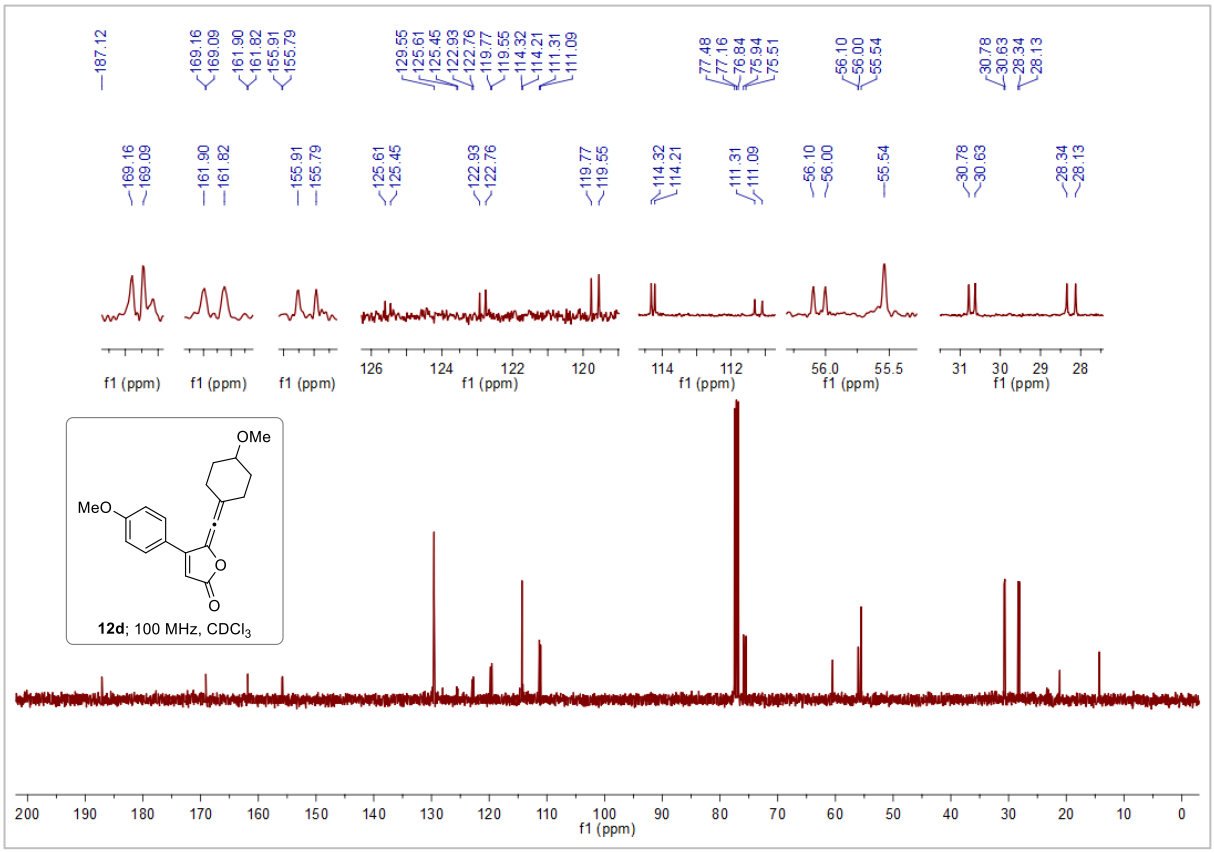
^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) of **12c**.



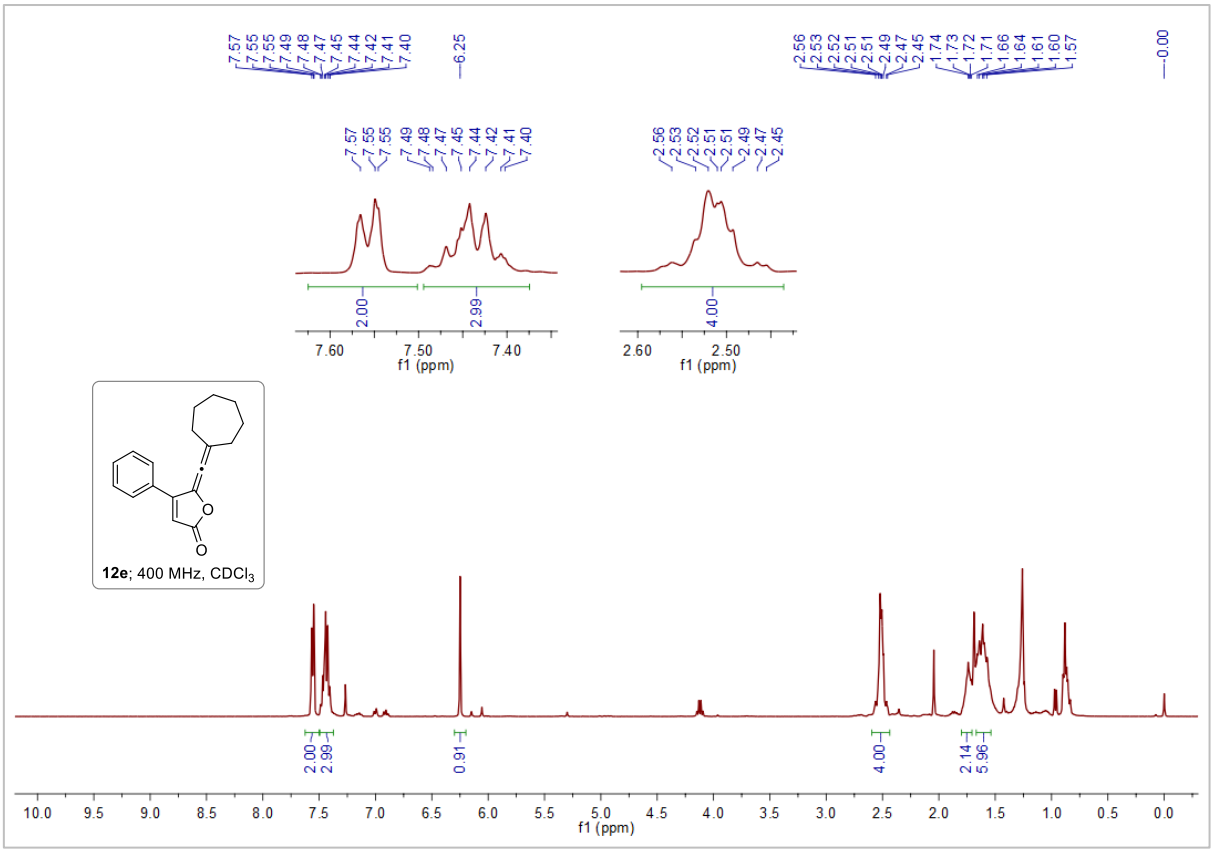


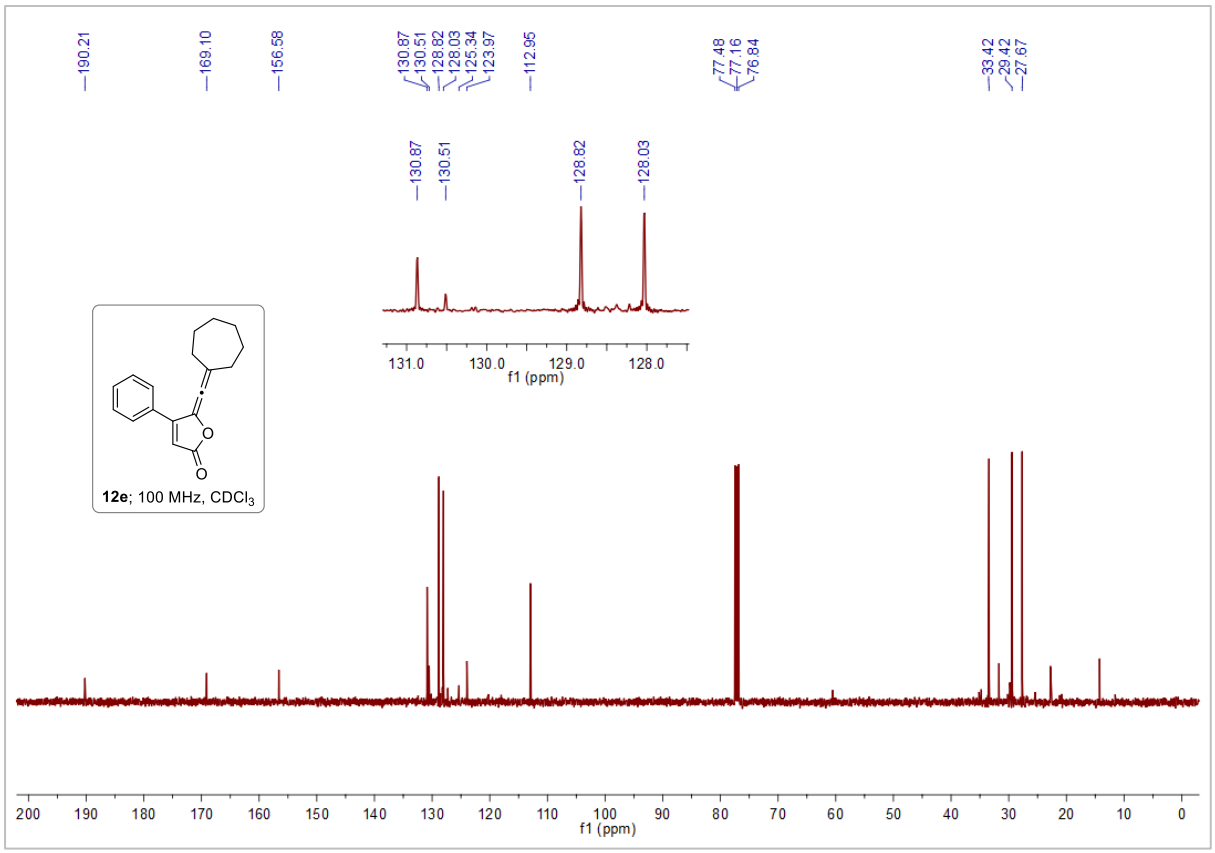
^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) of **12d**.



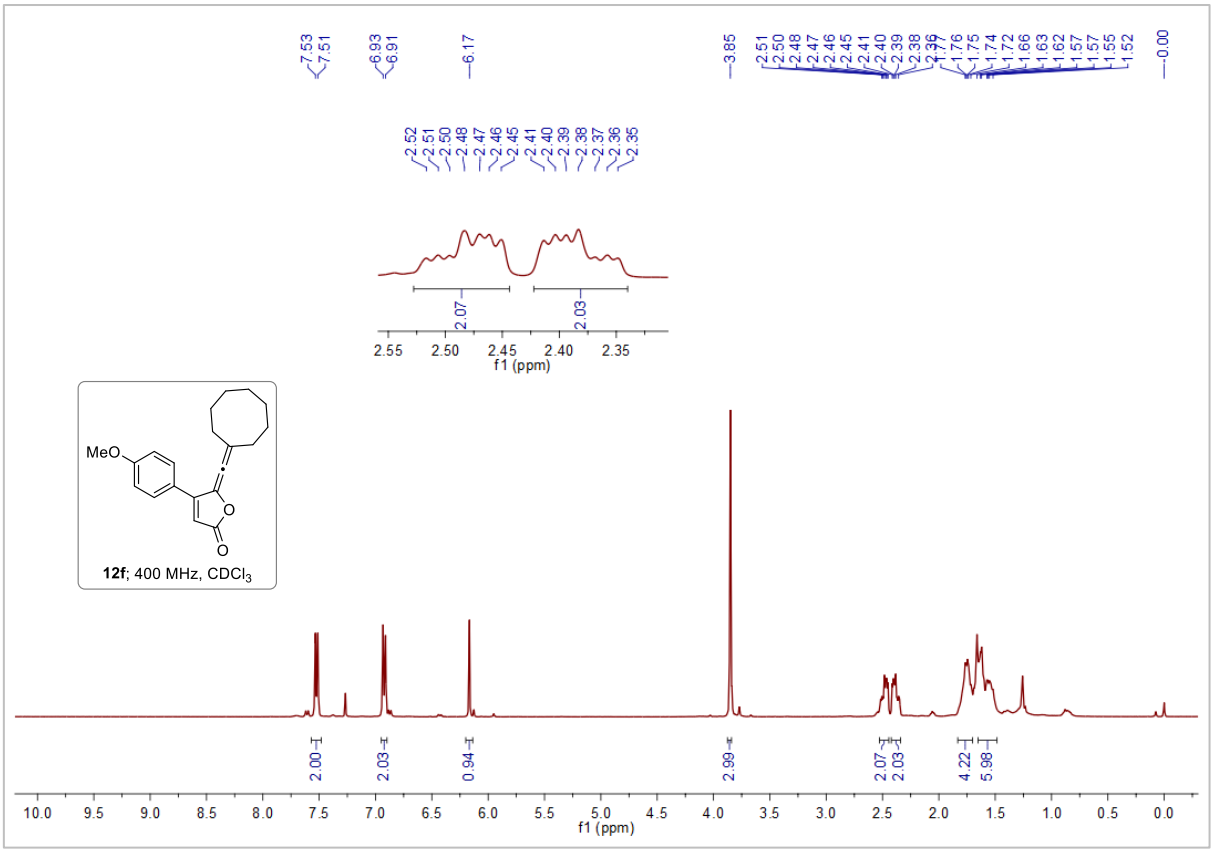


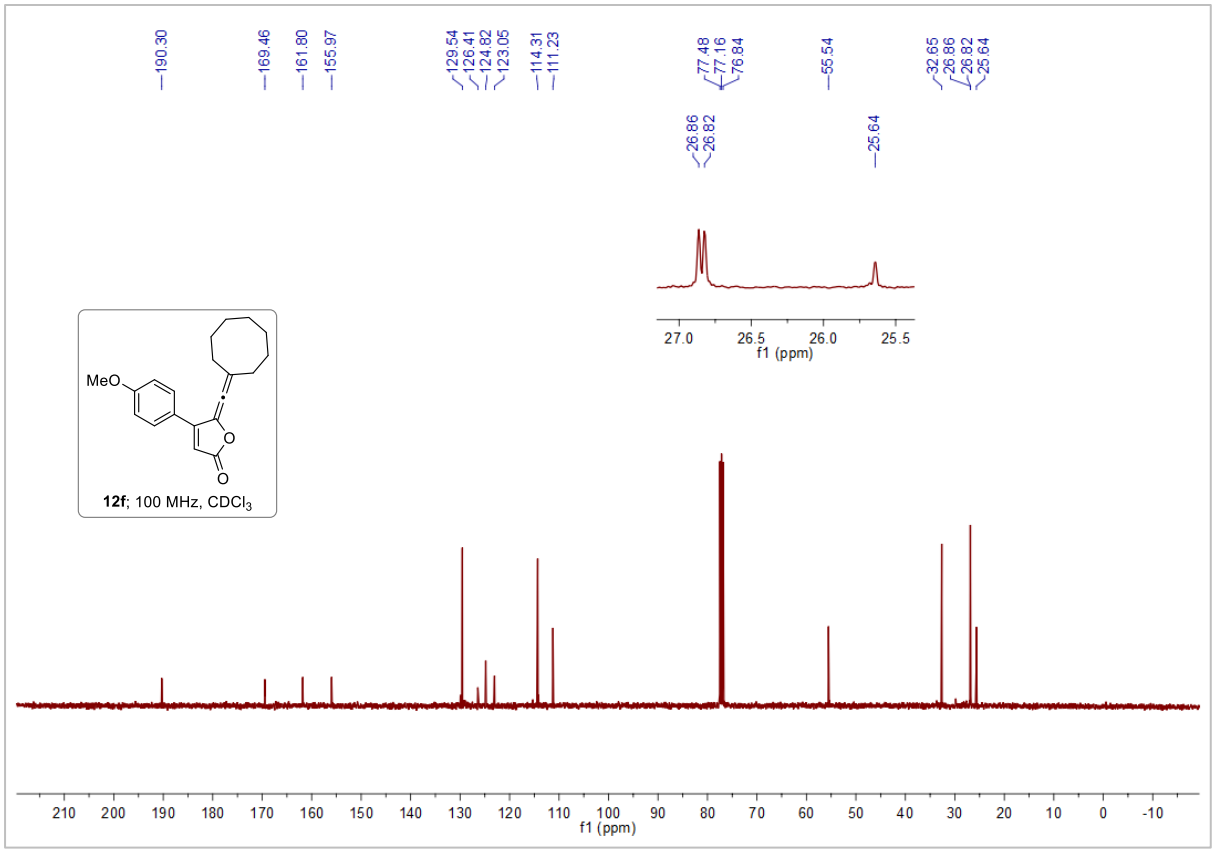
^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) of **12e**.



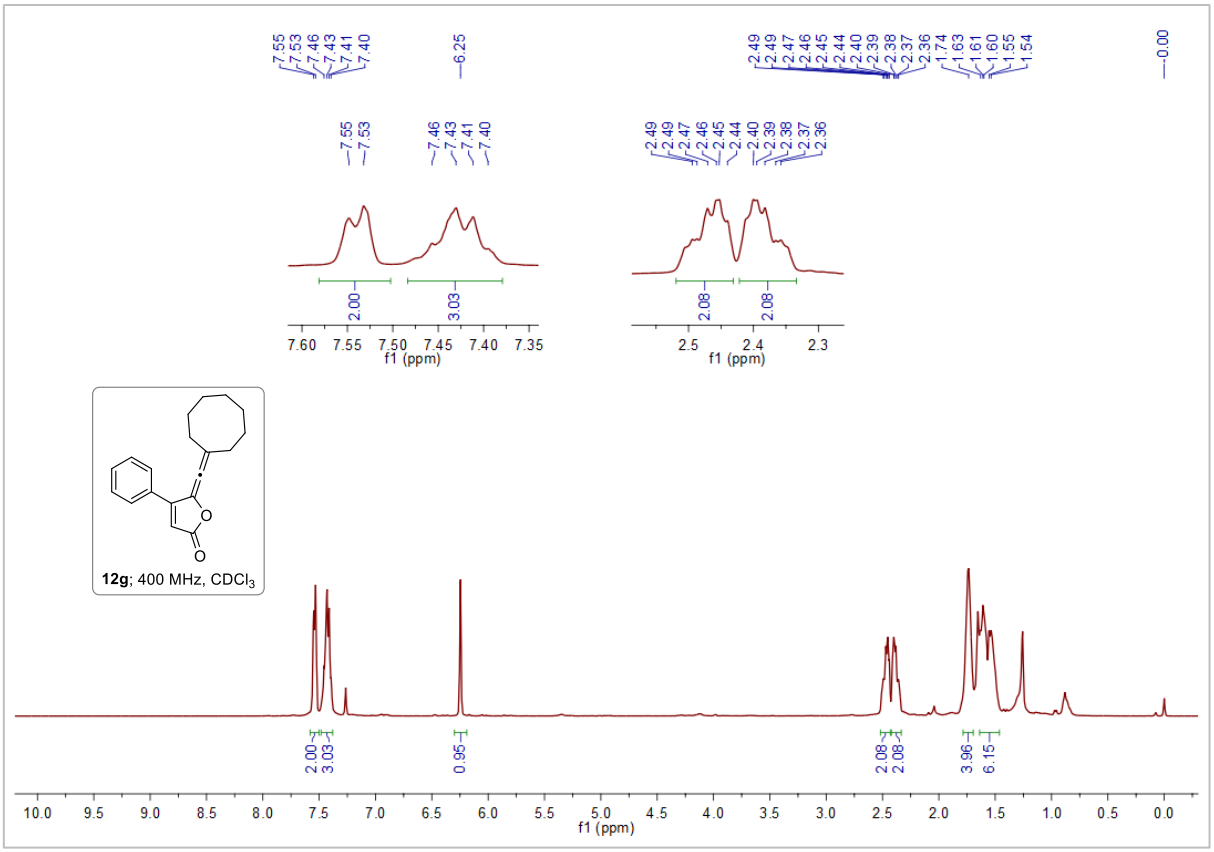


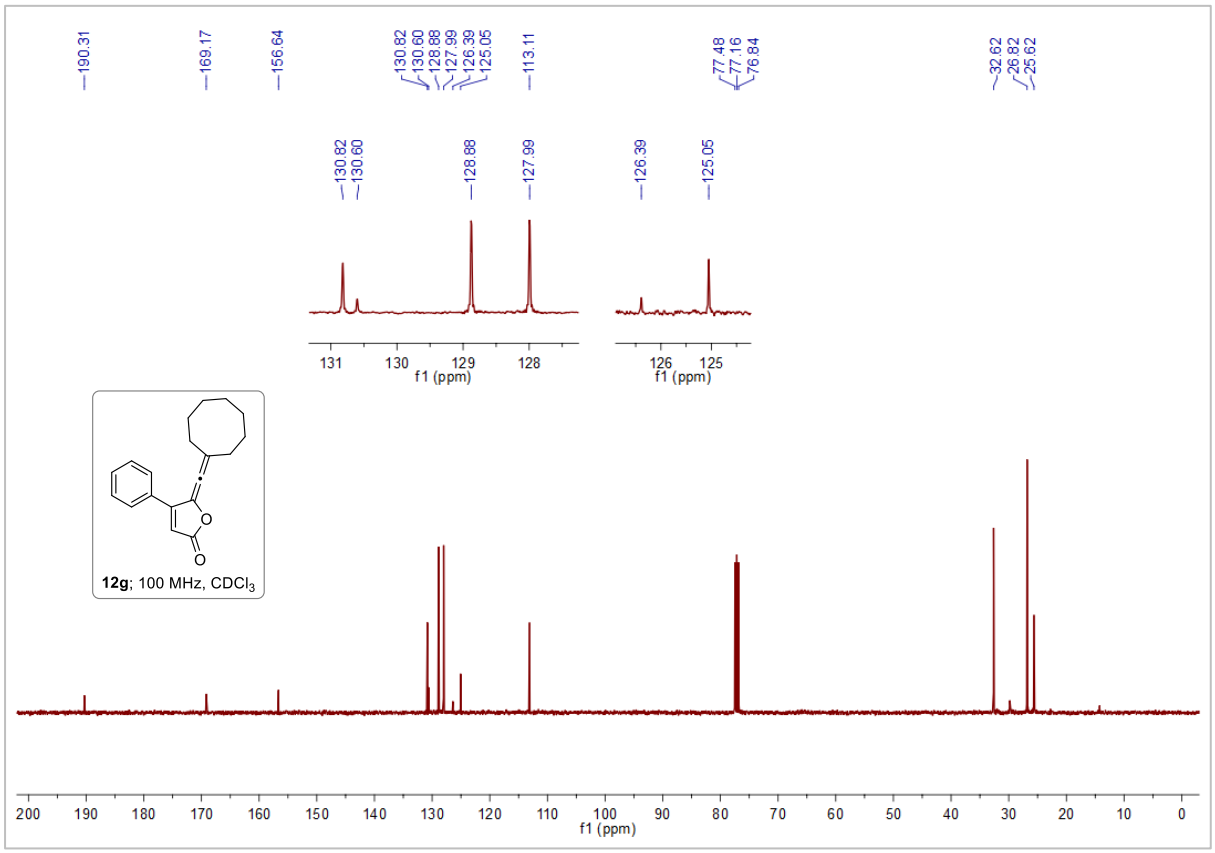
^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) of **12f**.



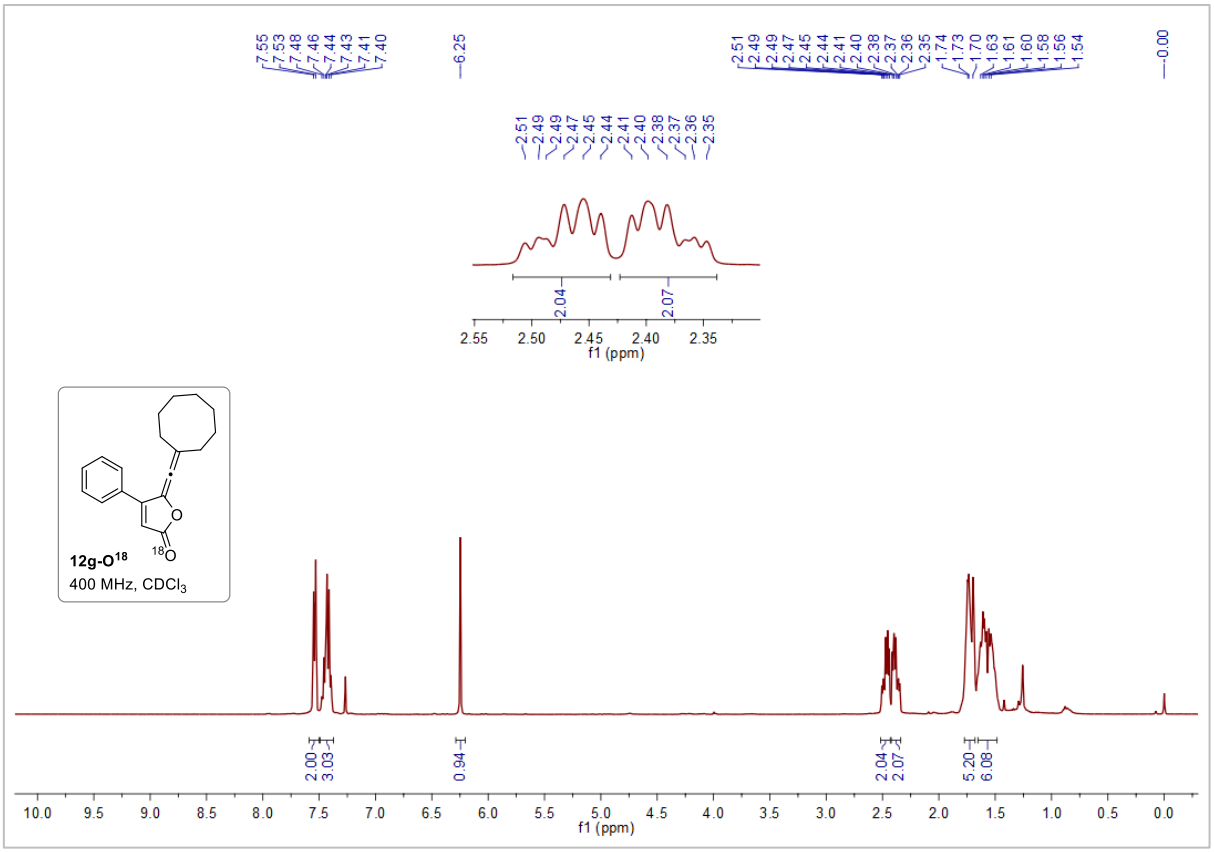


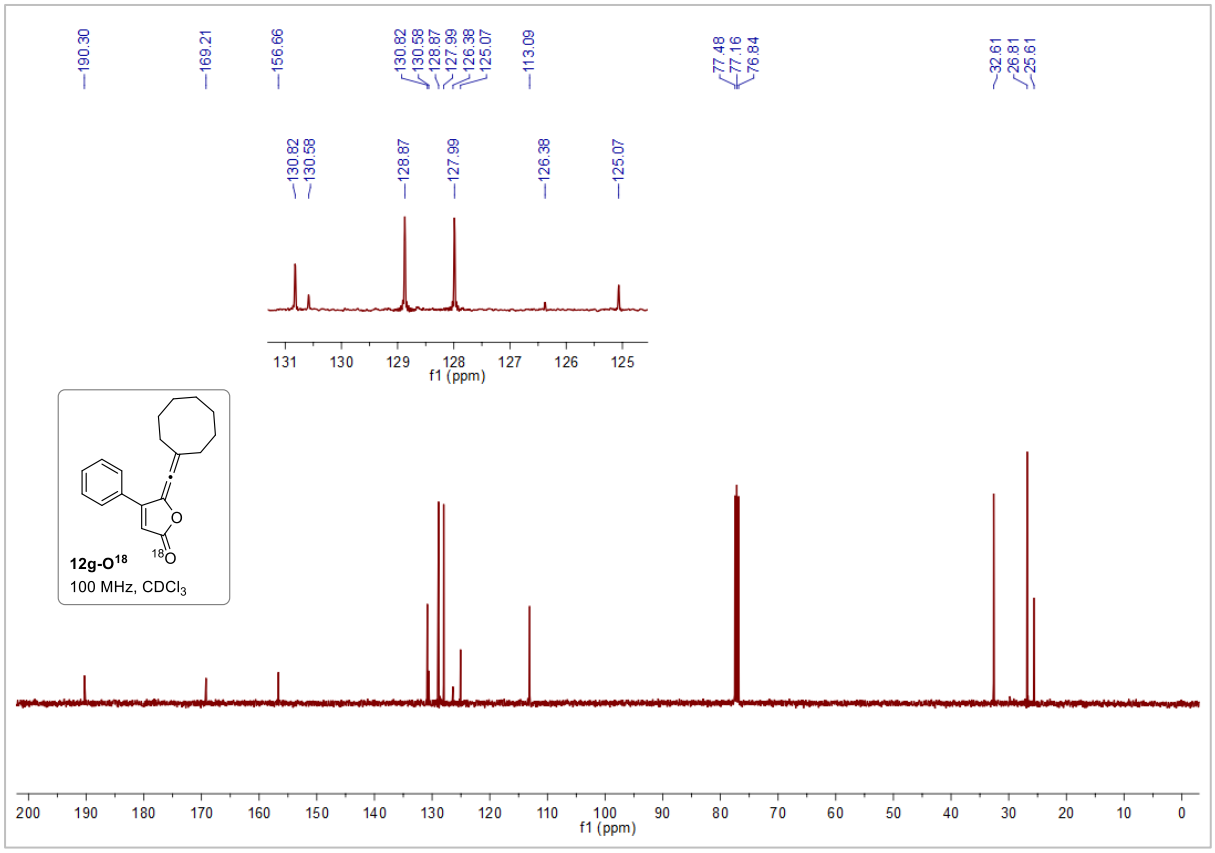
^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) of **12g**.



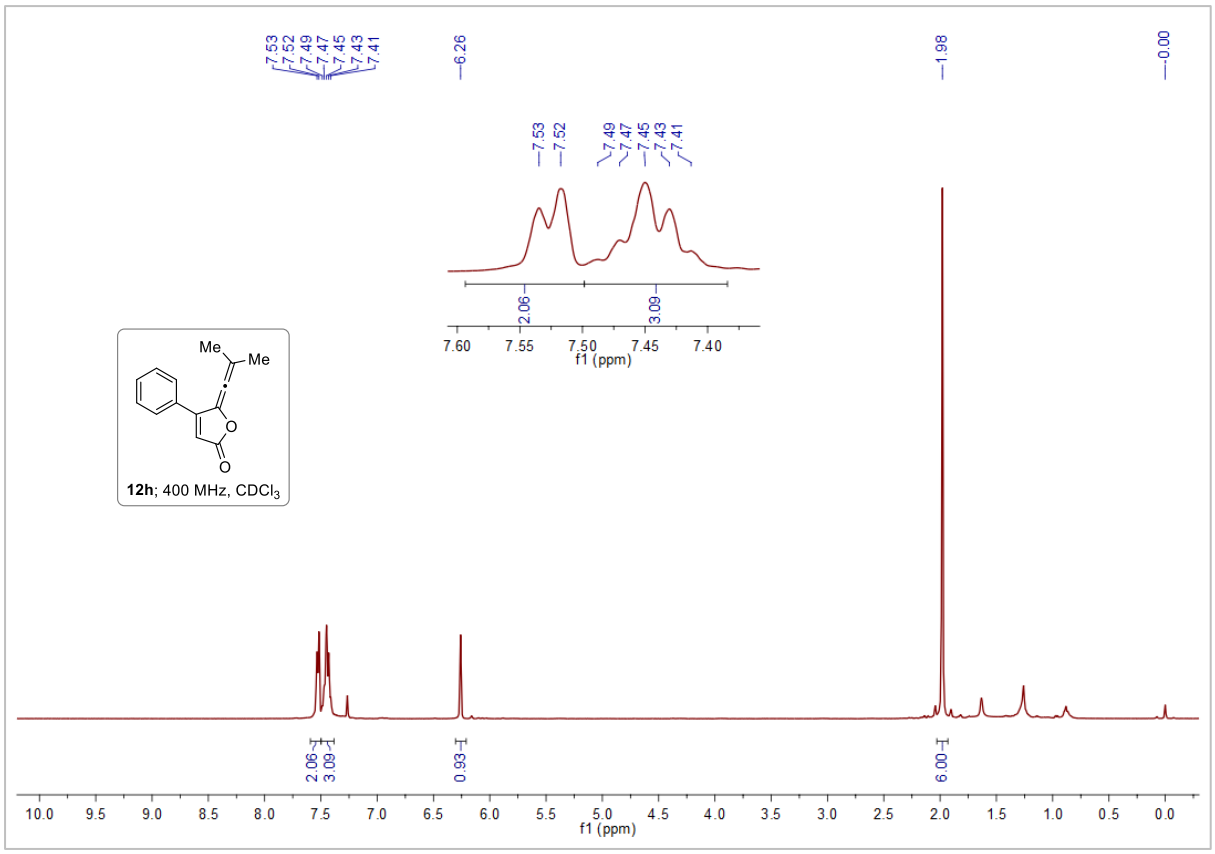


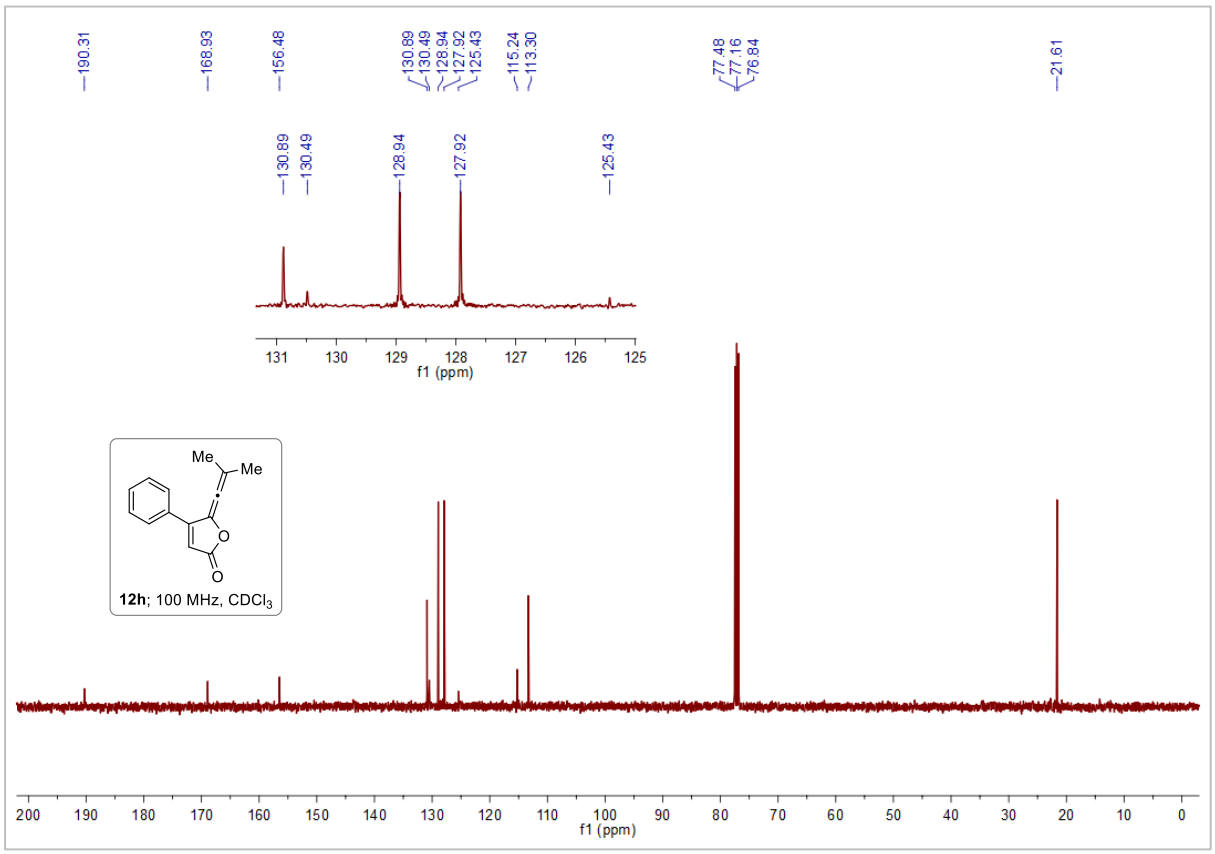
^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) of **12g-O^{18}**.



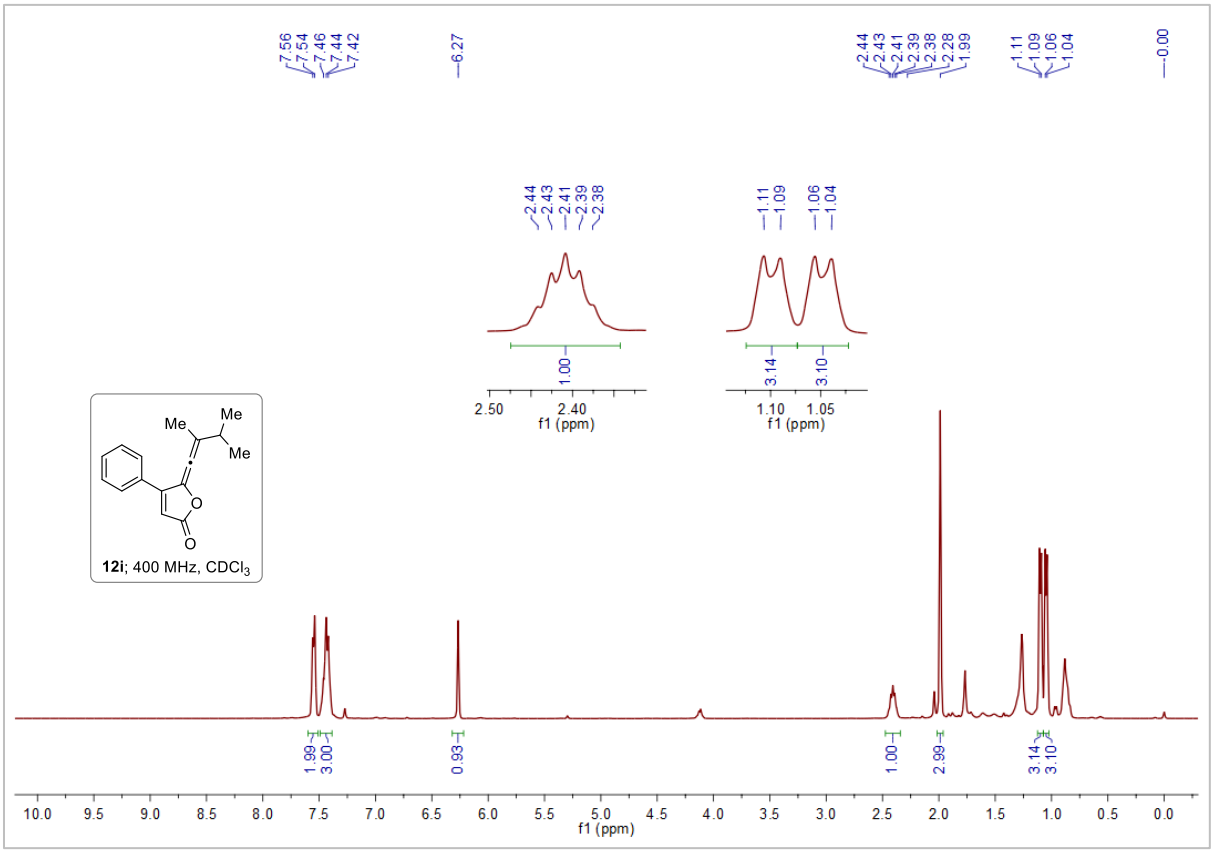


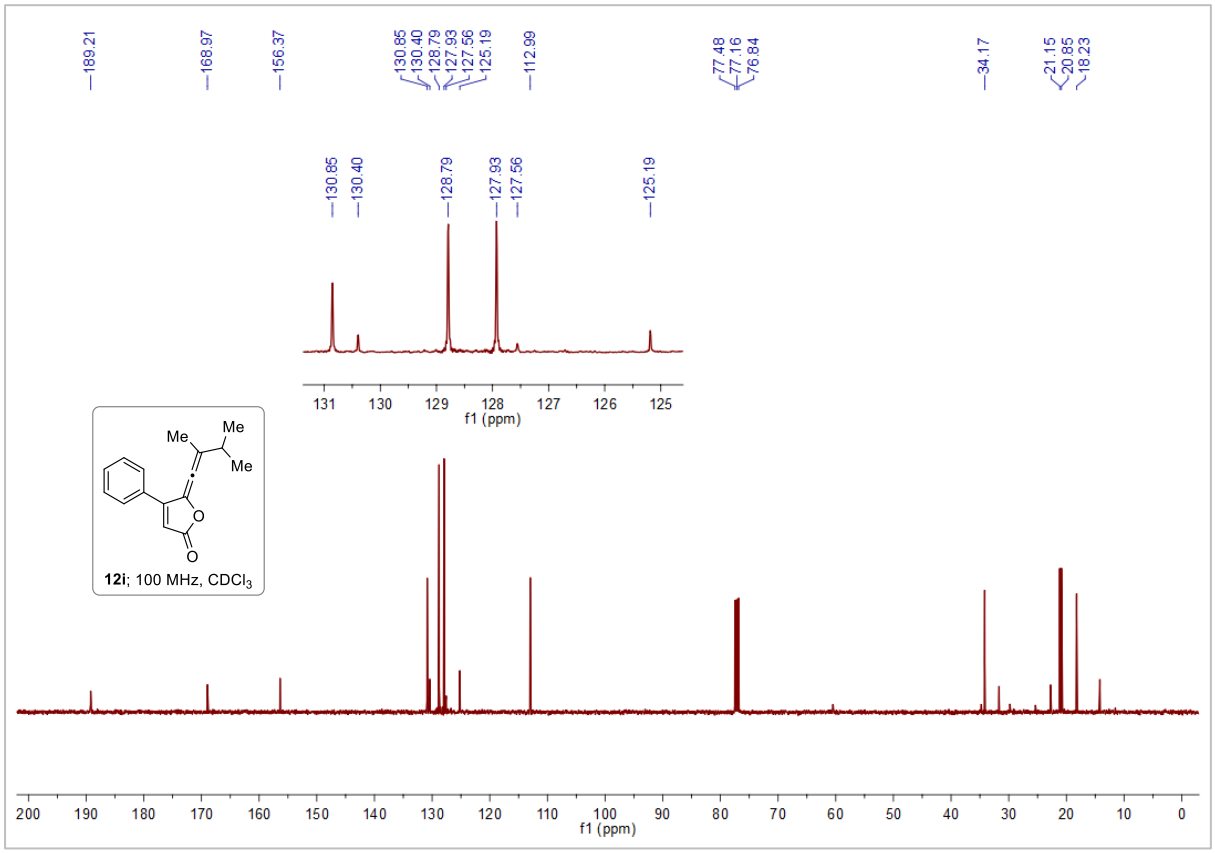
^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) of **12h**.



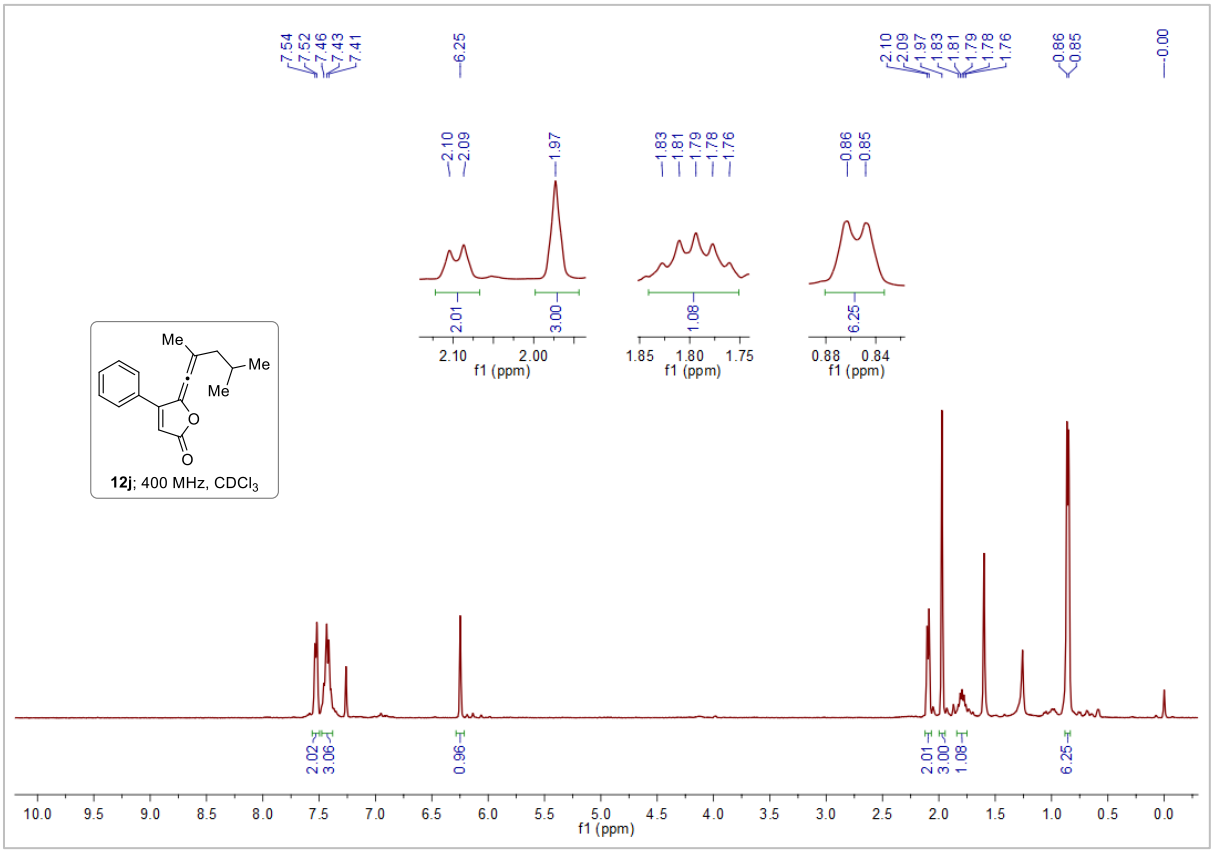


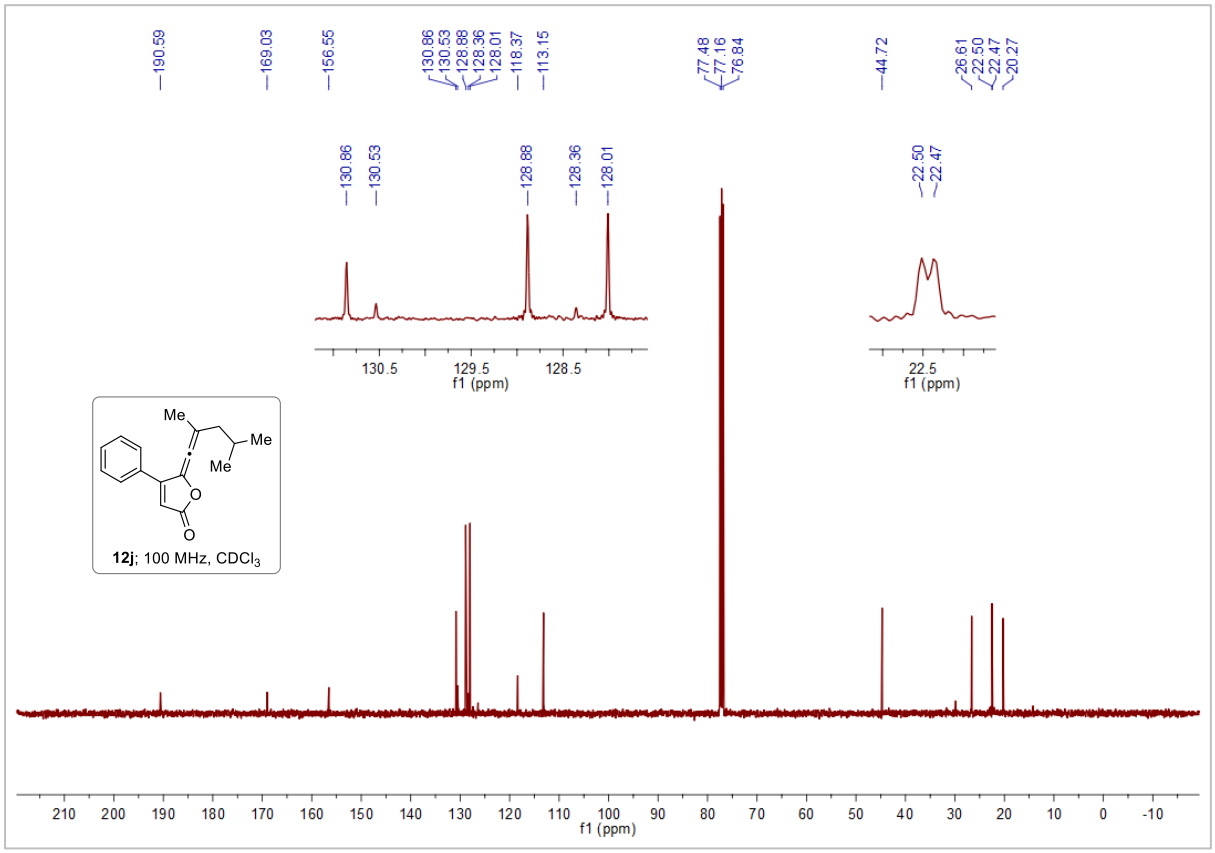
^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) of **12i**.



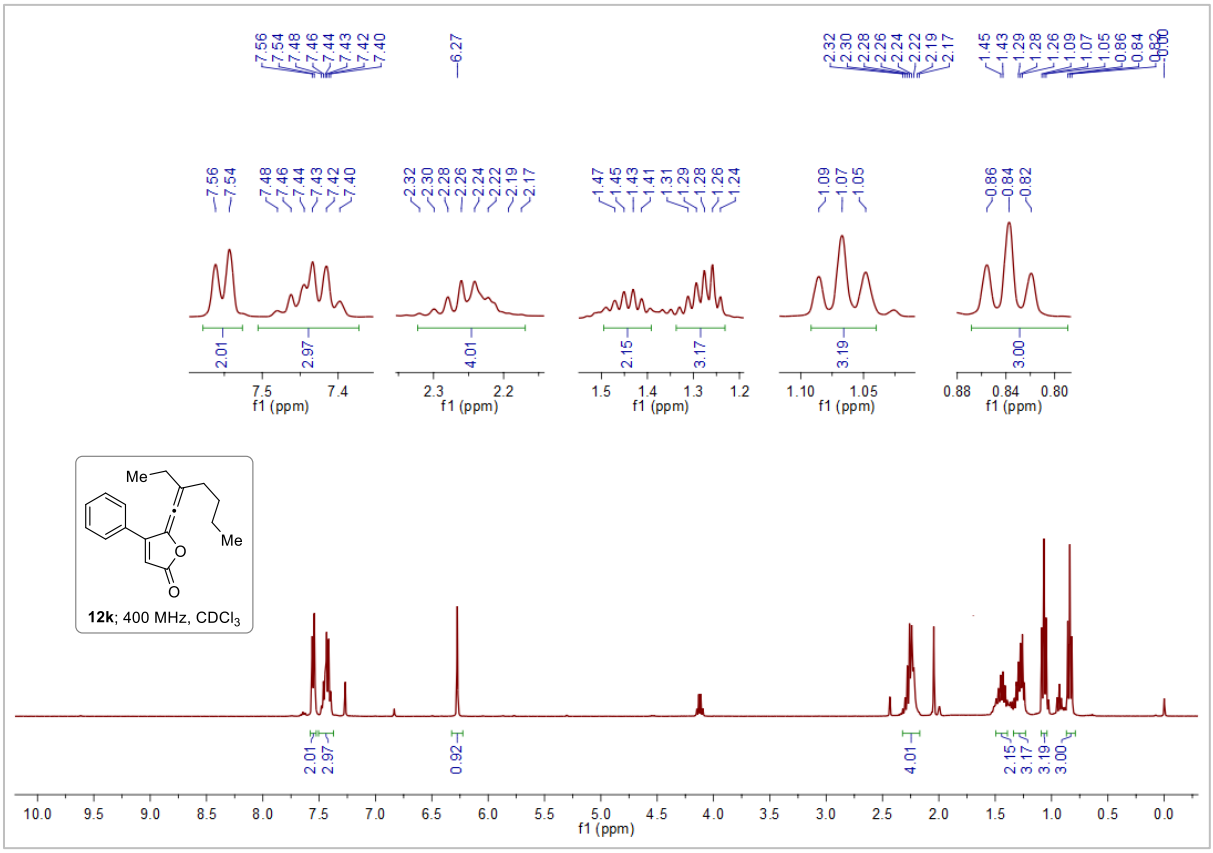


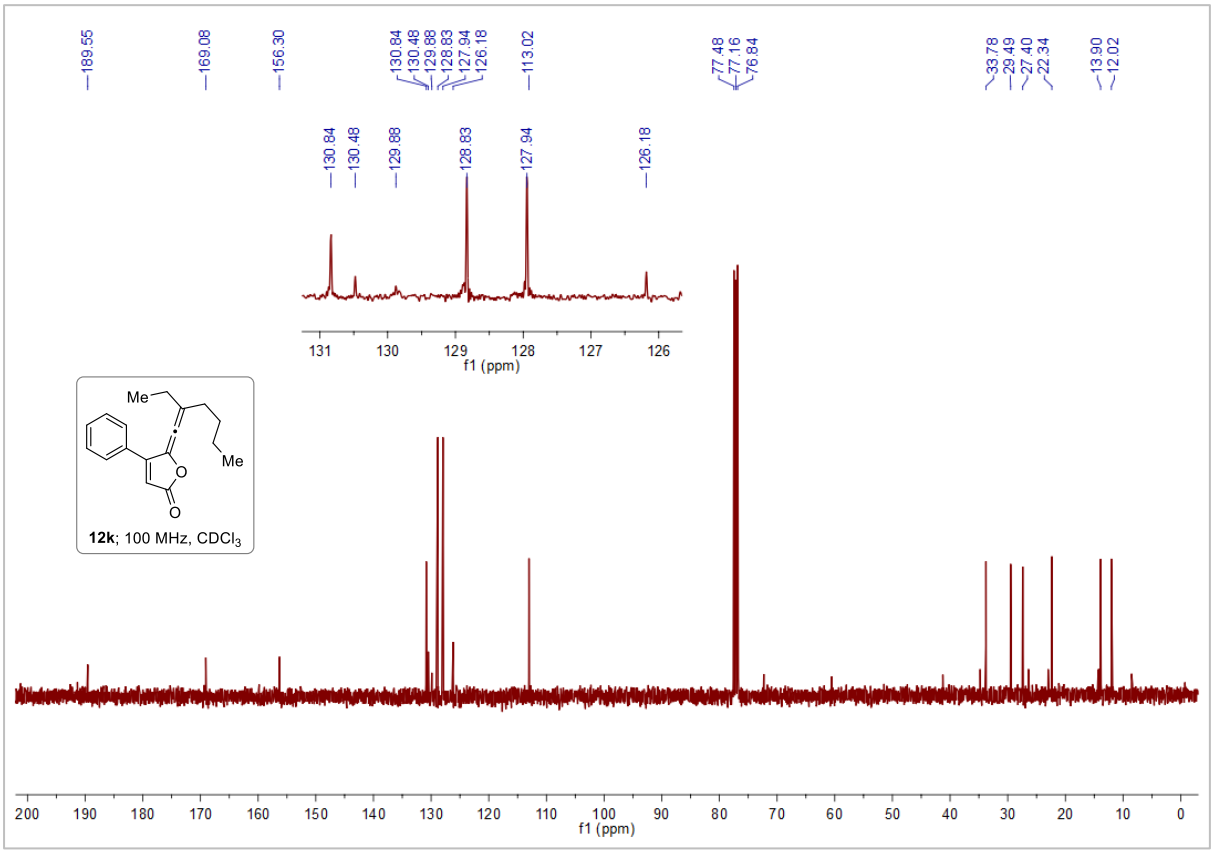
^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) of **12j**.



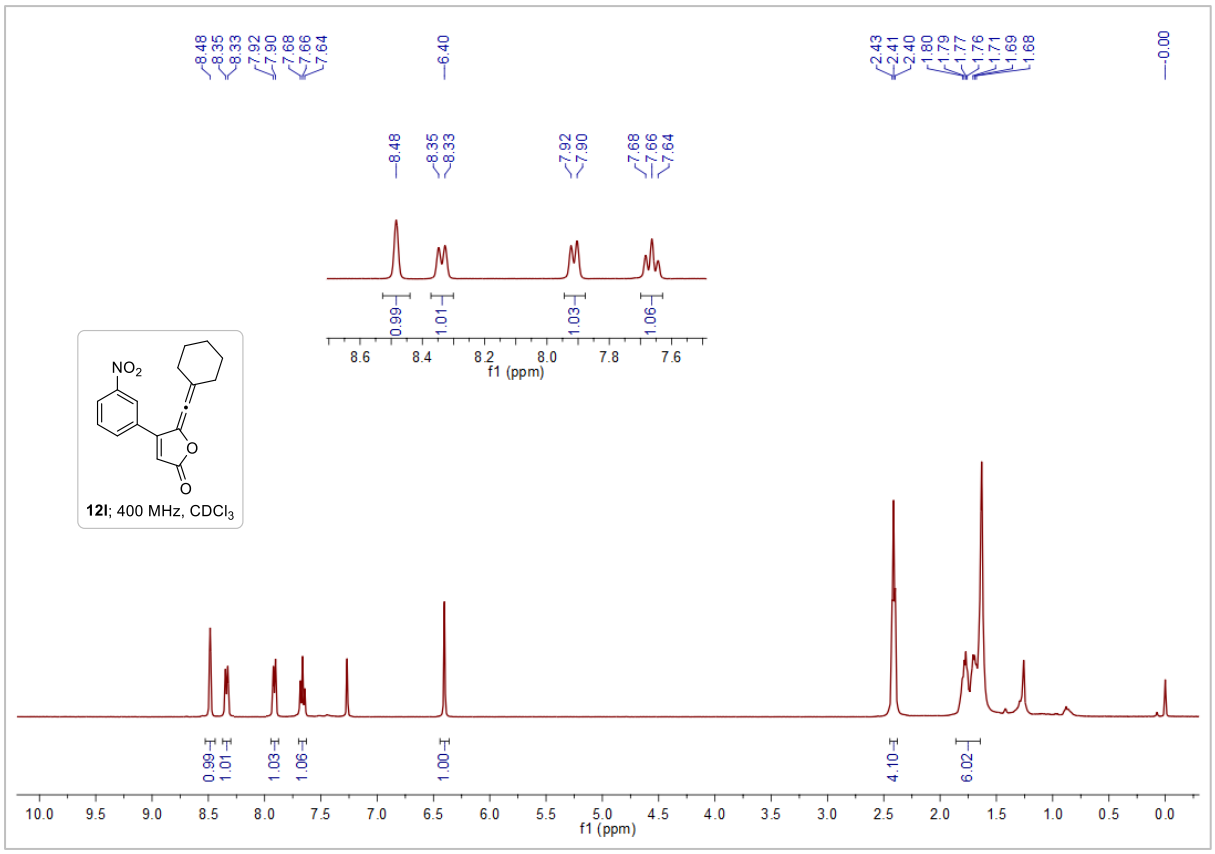


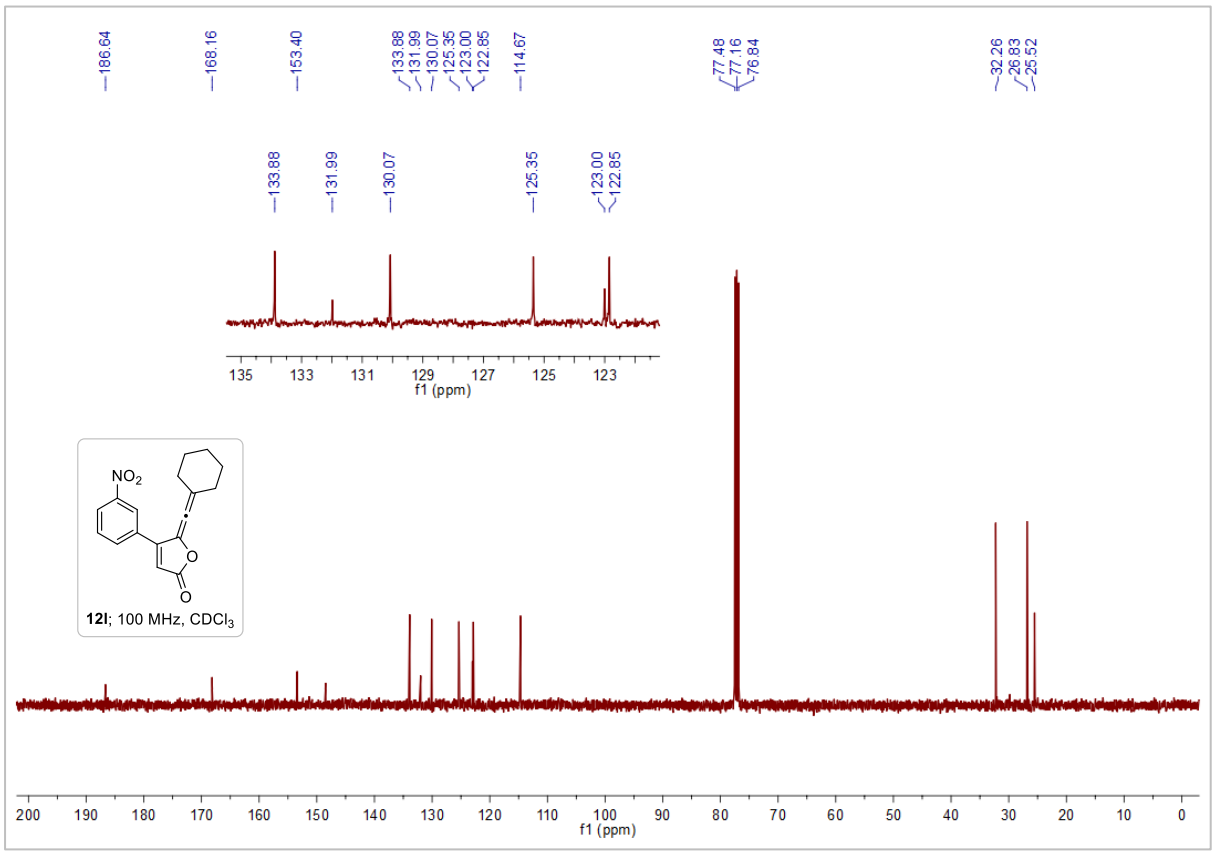
^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) of **12k**.



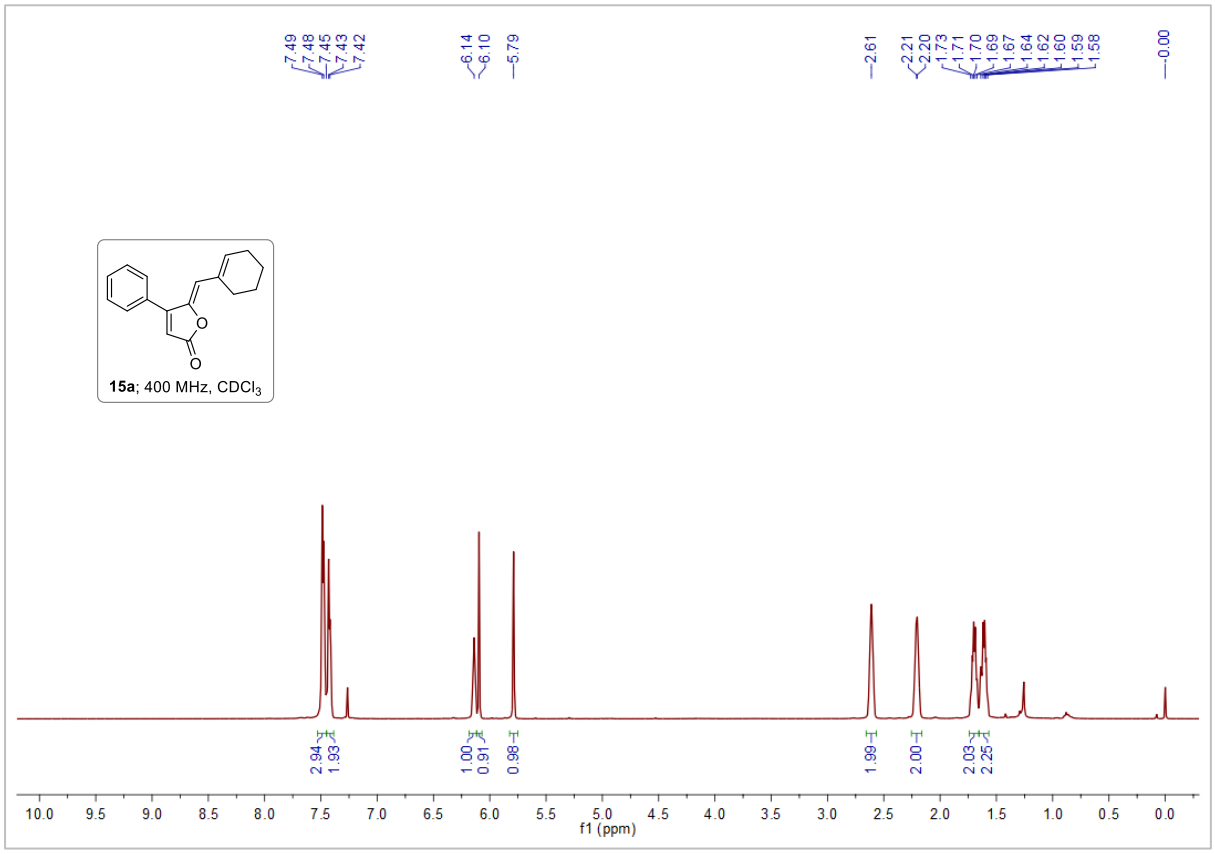


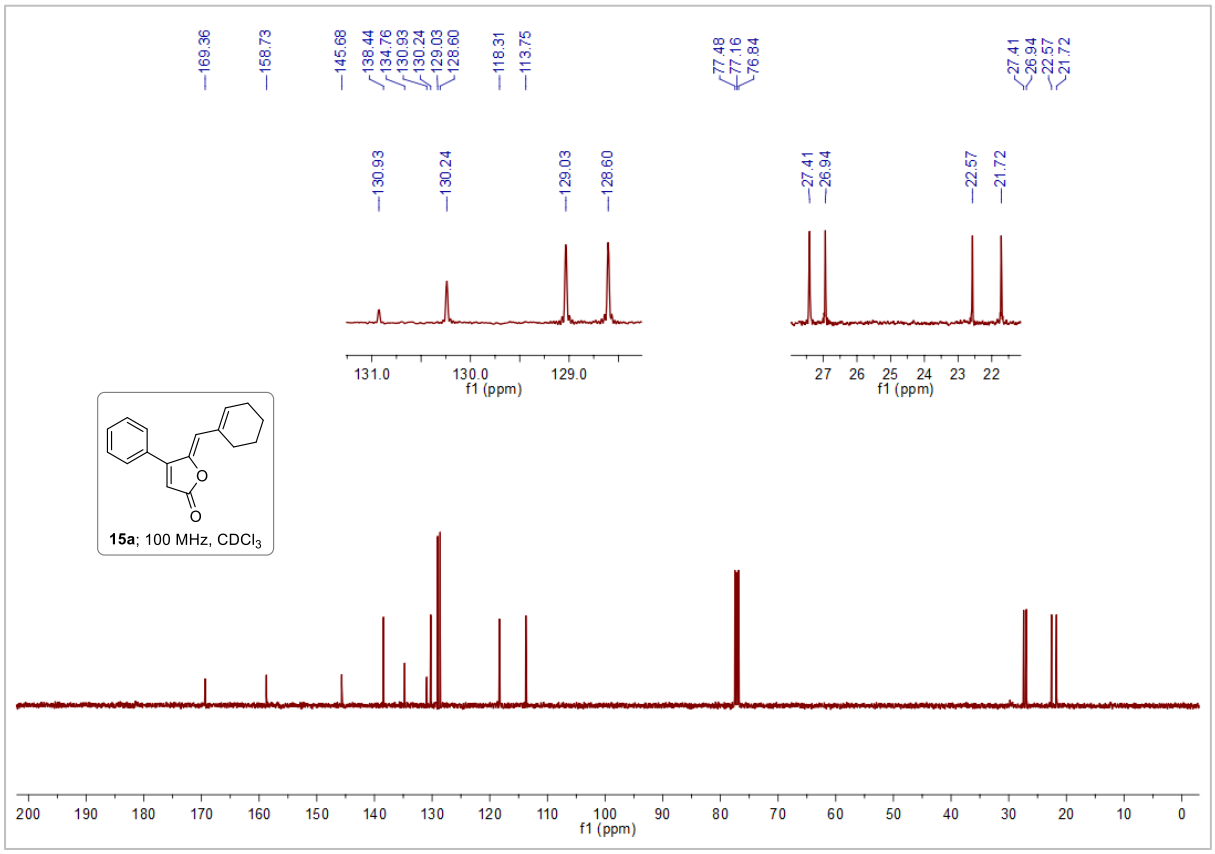
^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) of **xx**.



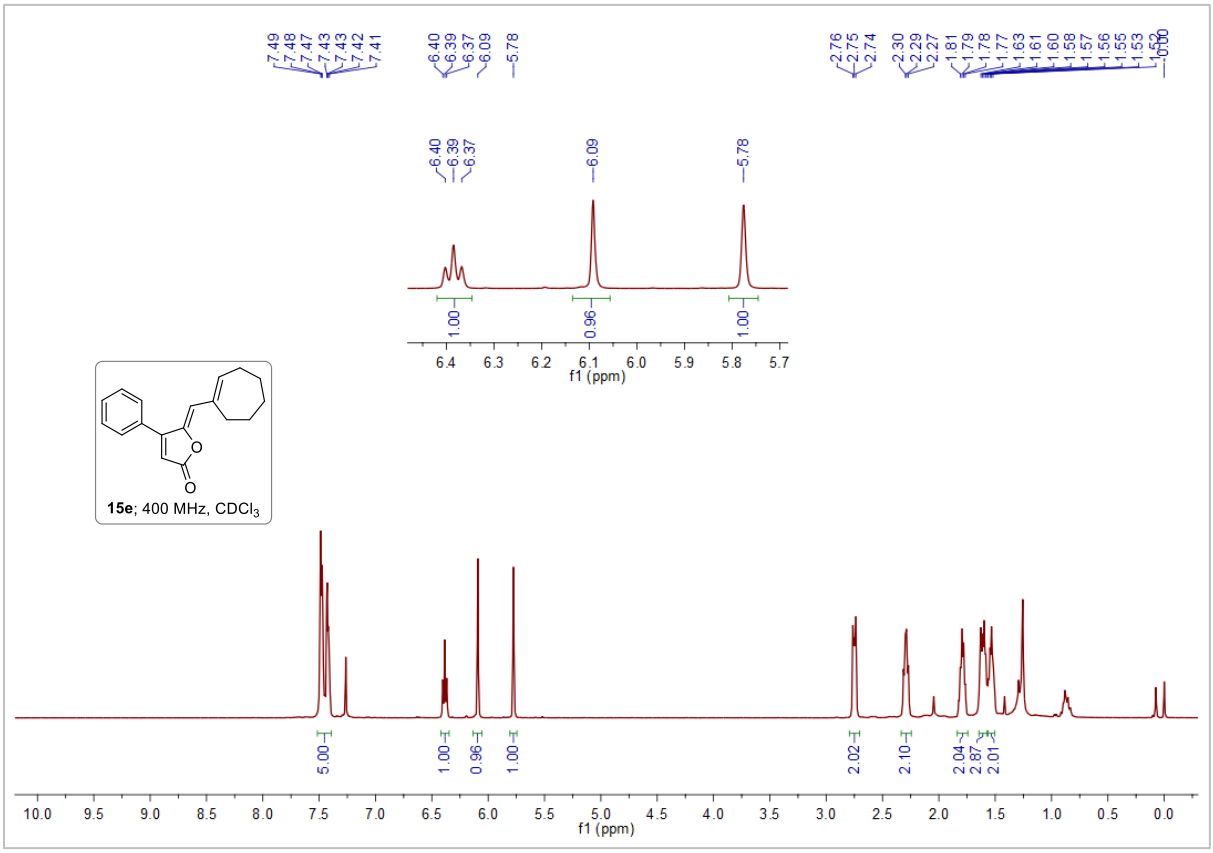


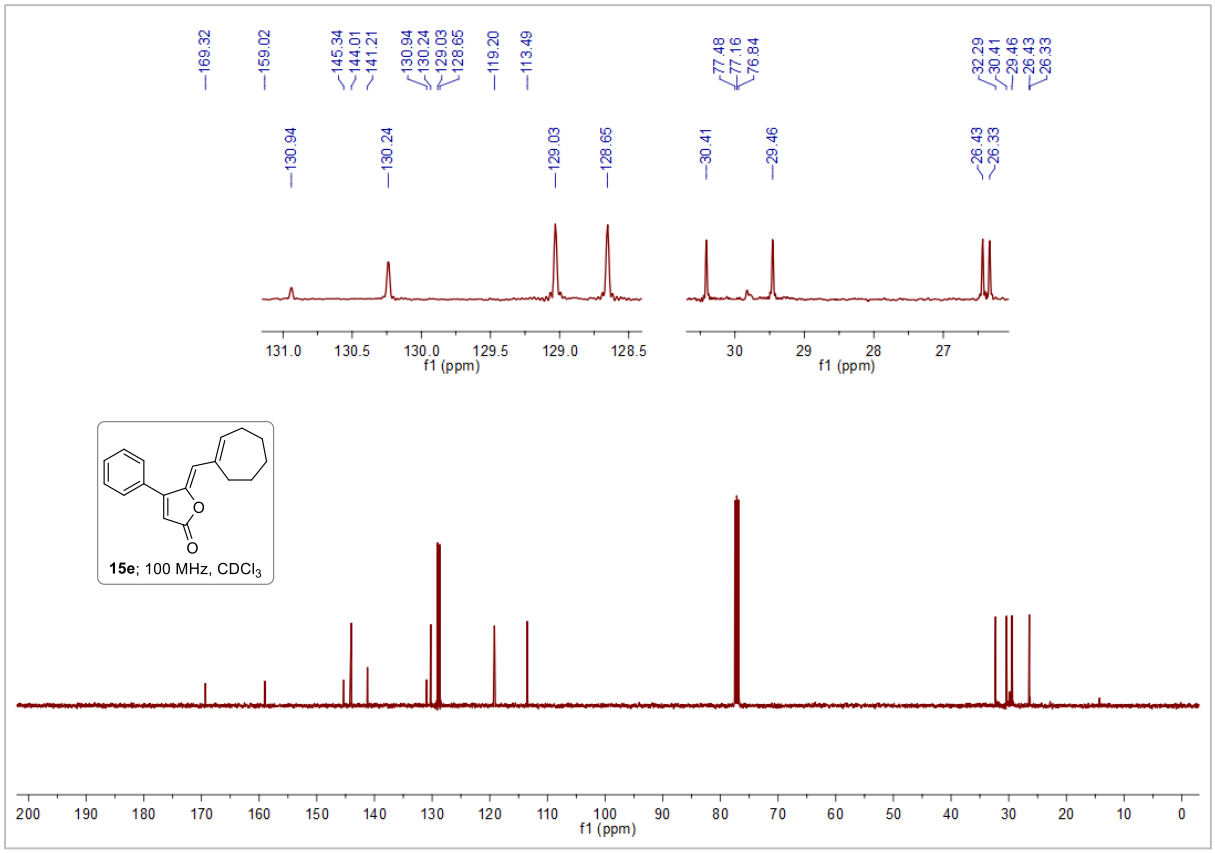
^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) of **15a**.



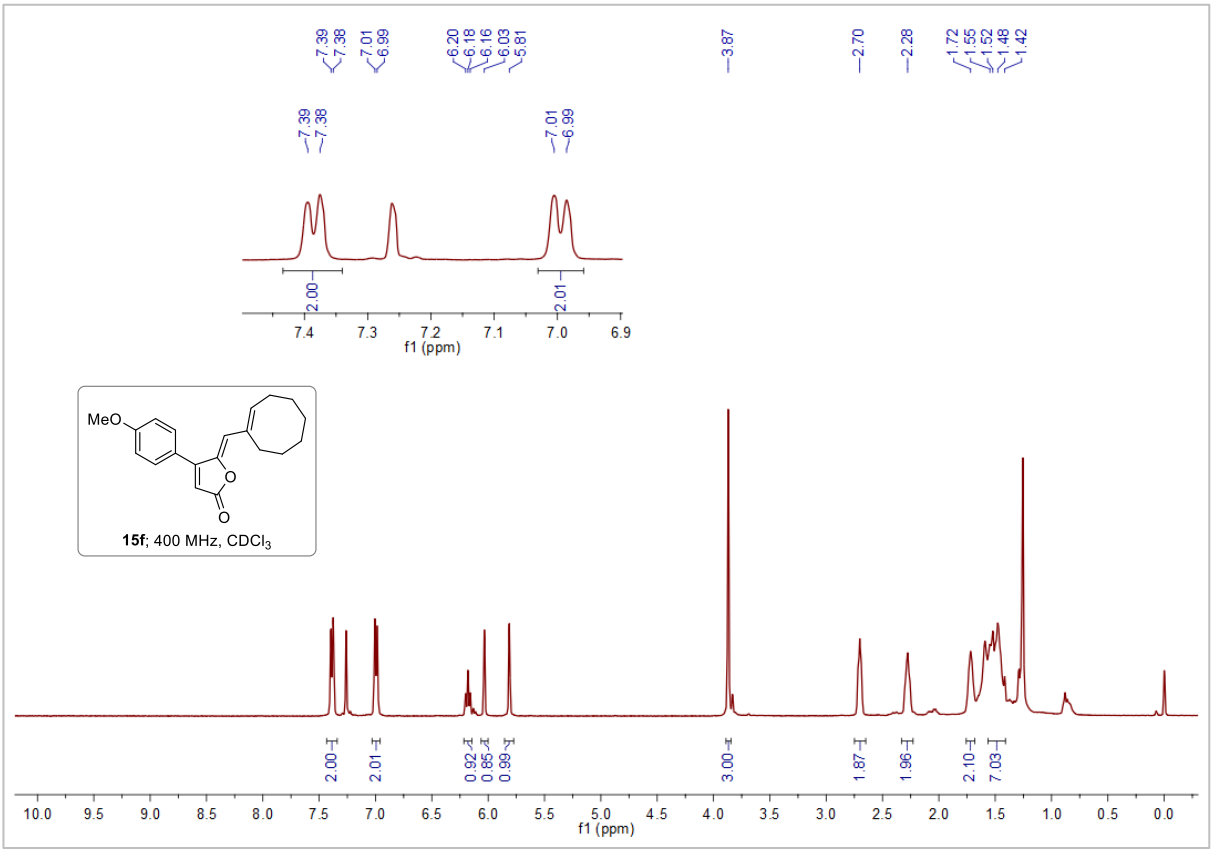


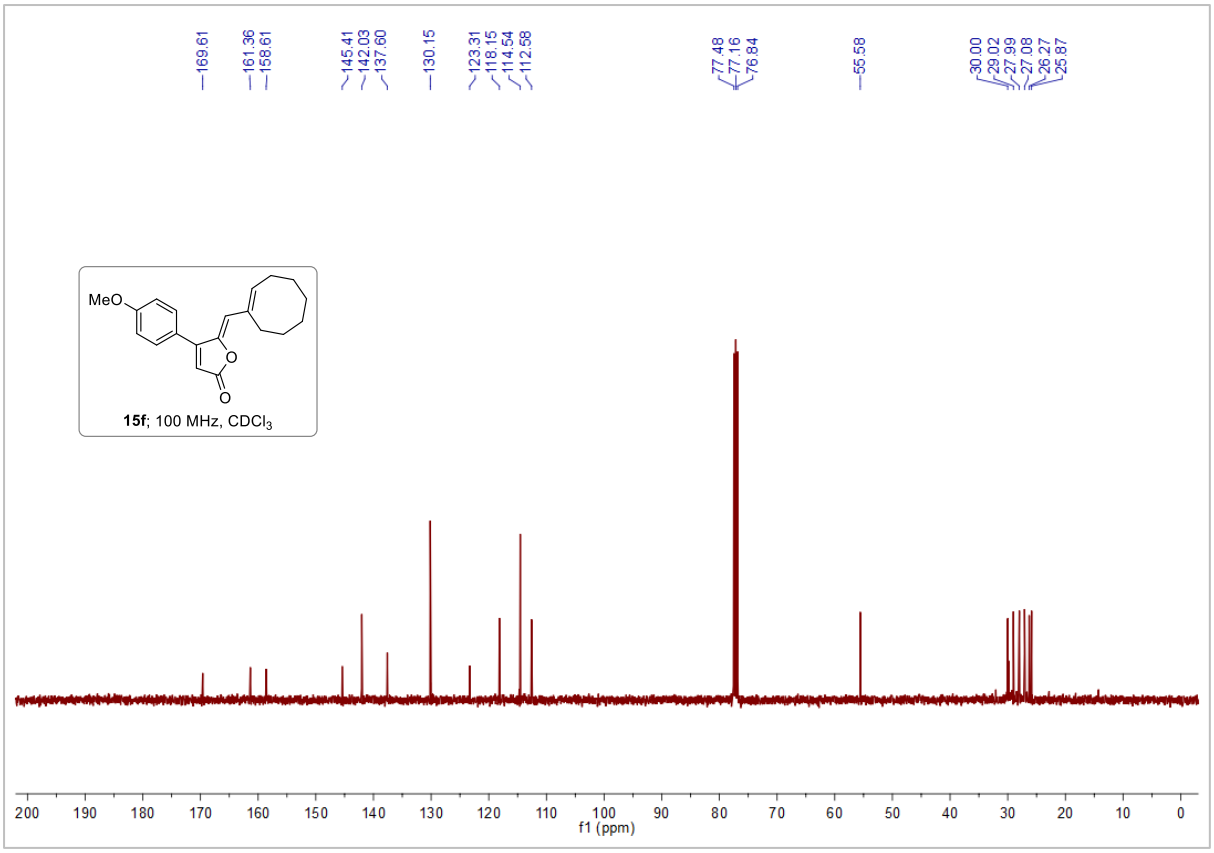
^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) of **15e**.



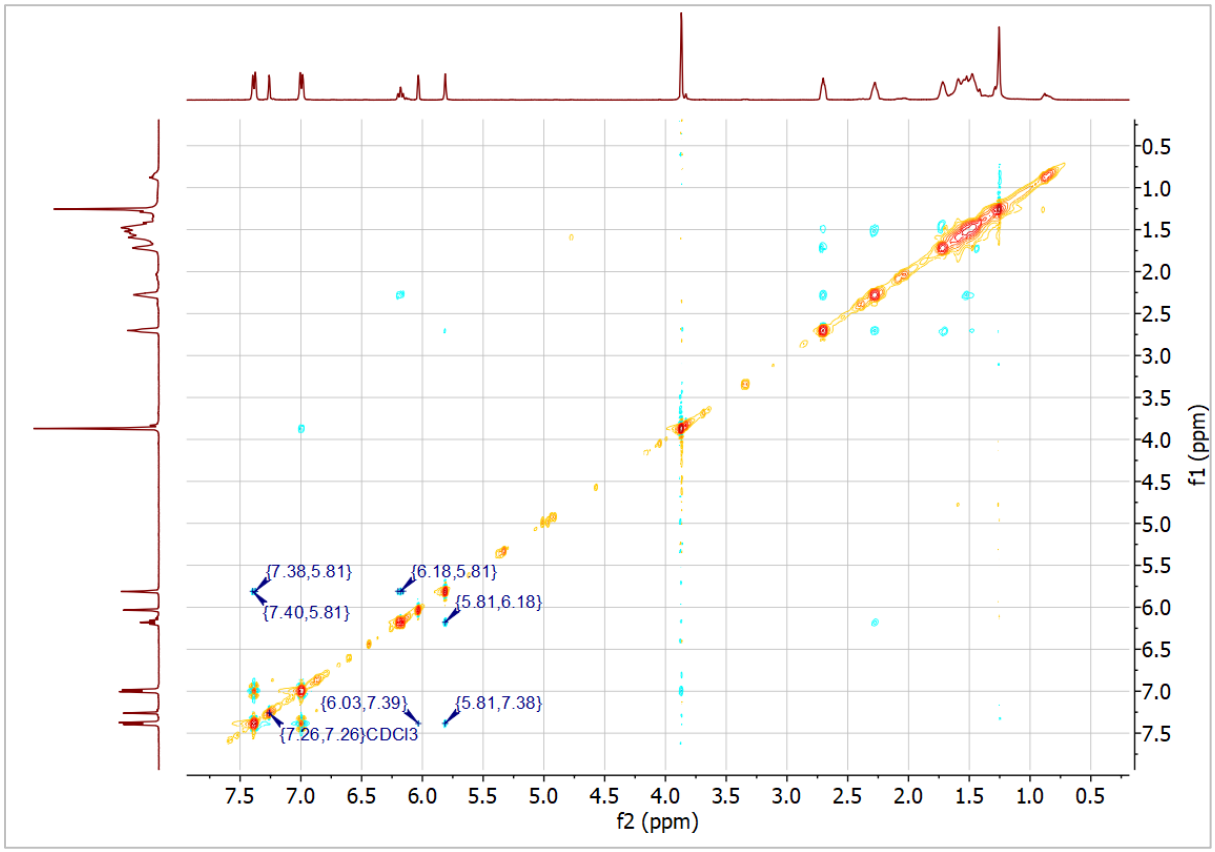


^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) of **15f**.

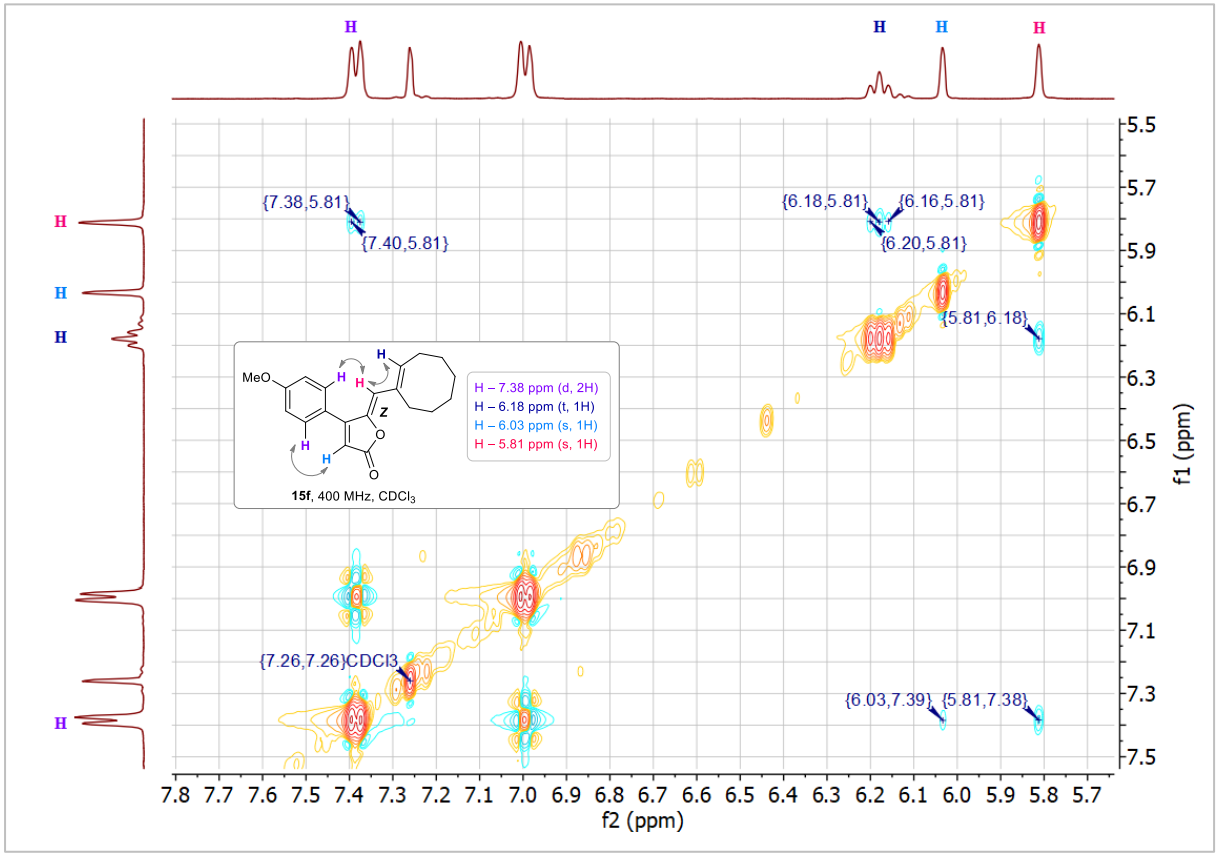




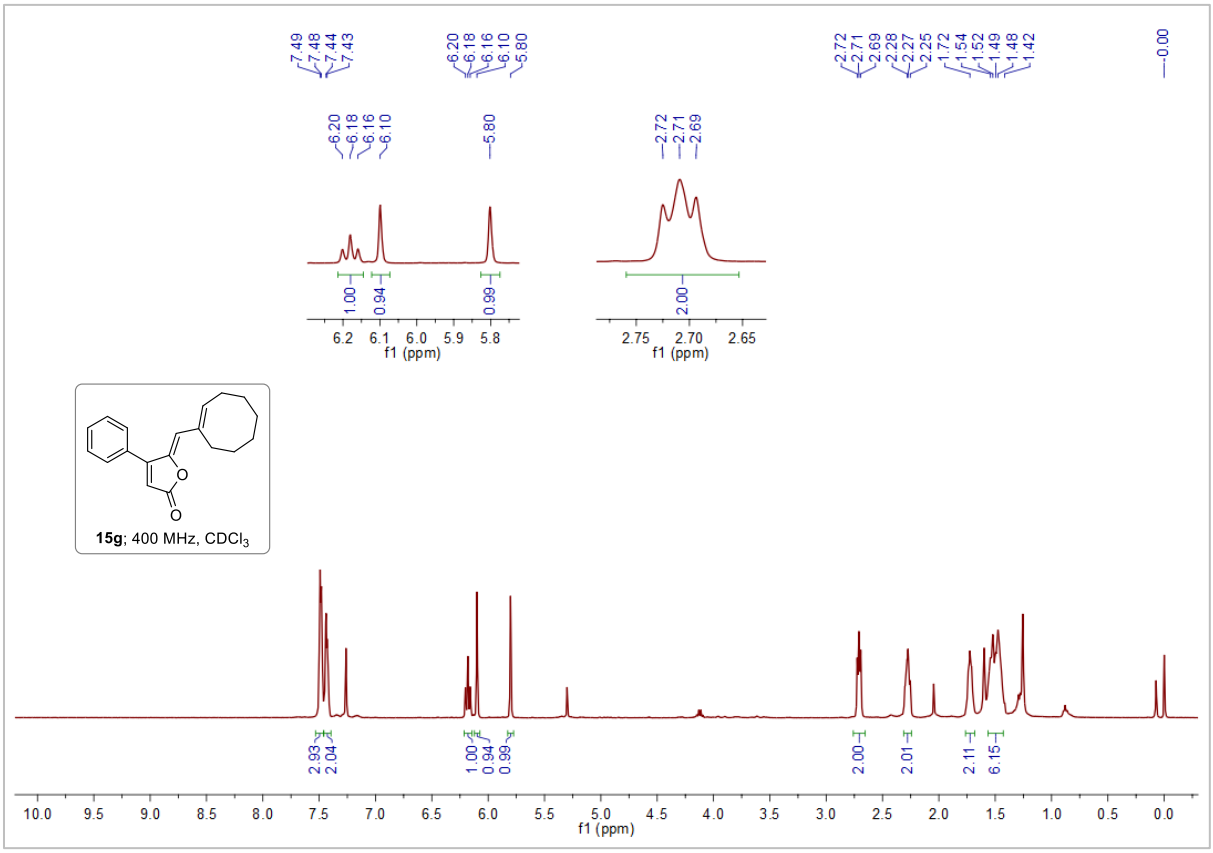
NOESY NMR analysis of **15f** (400 MHz, $CDCl_3$)

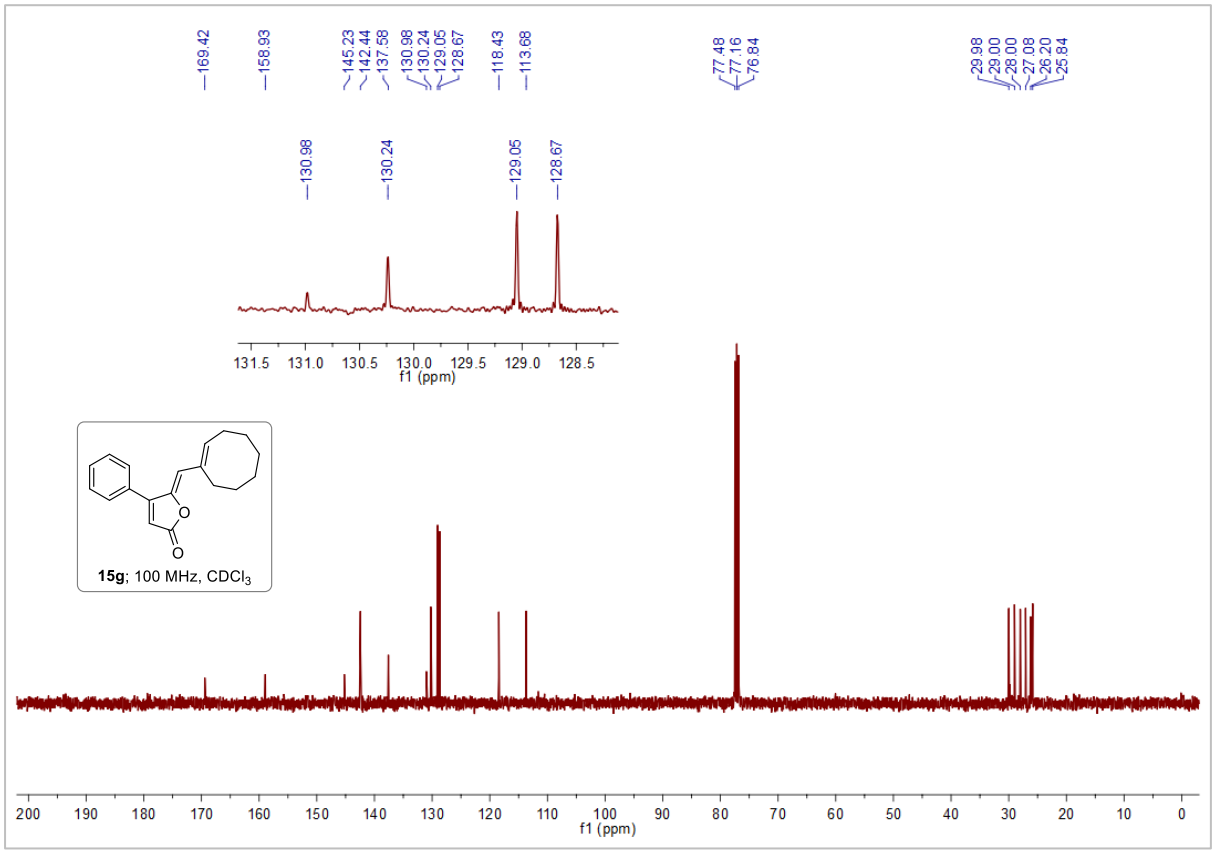


NOESY NMR of **15f** (400 MHz, $CDCl_3$) (zoomed)

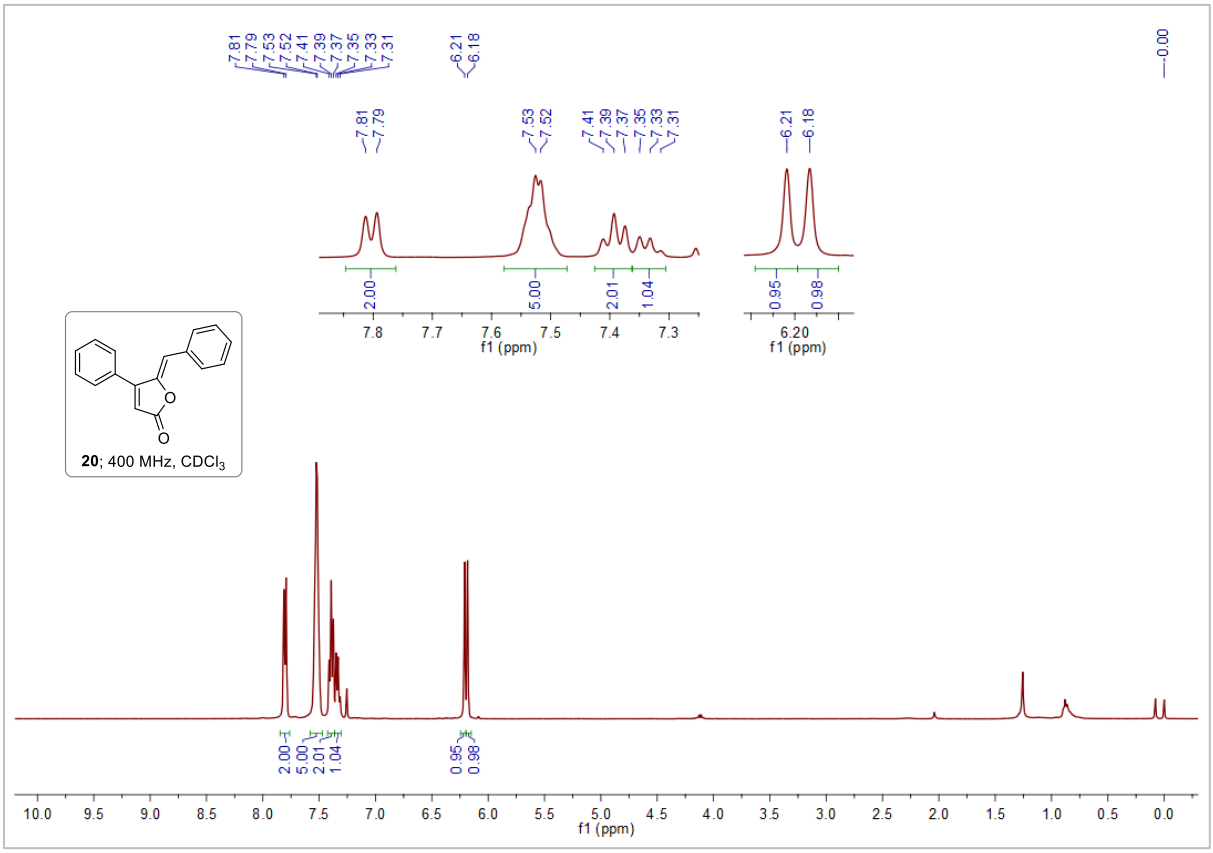


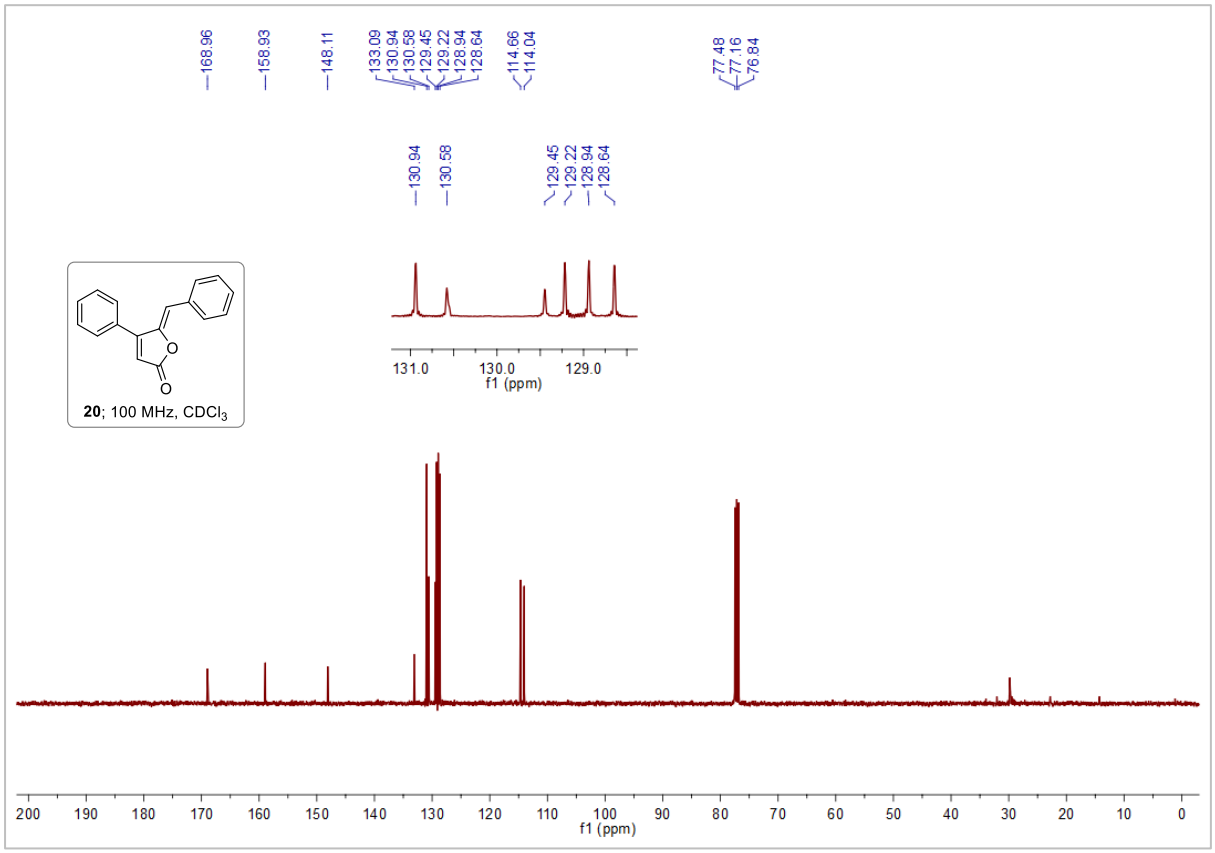
^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) of **15g**.



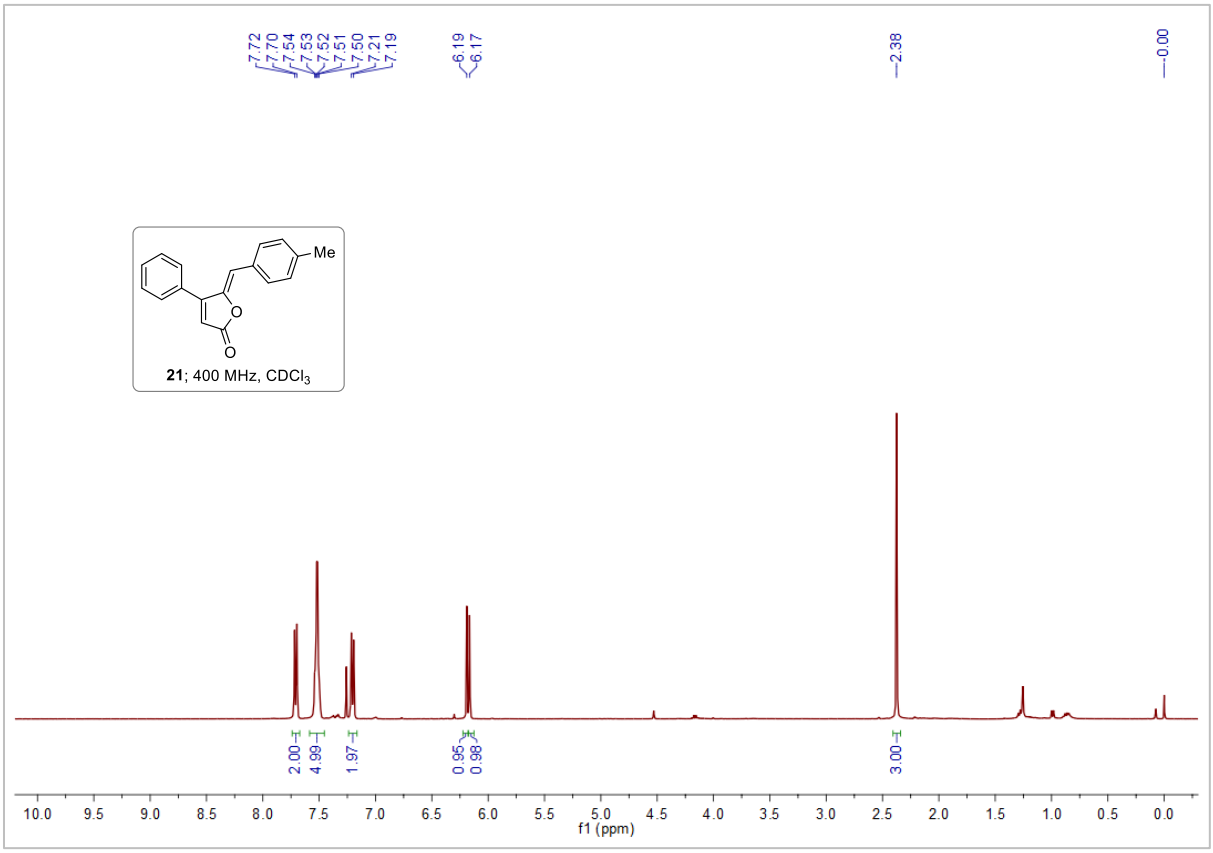


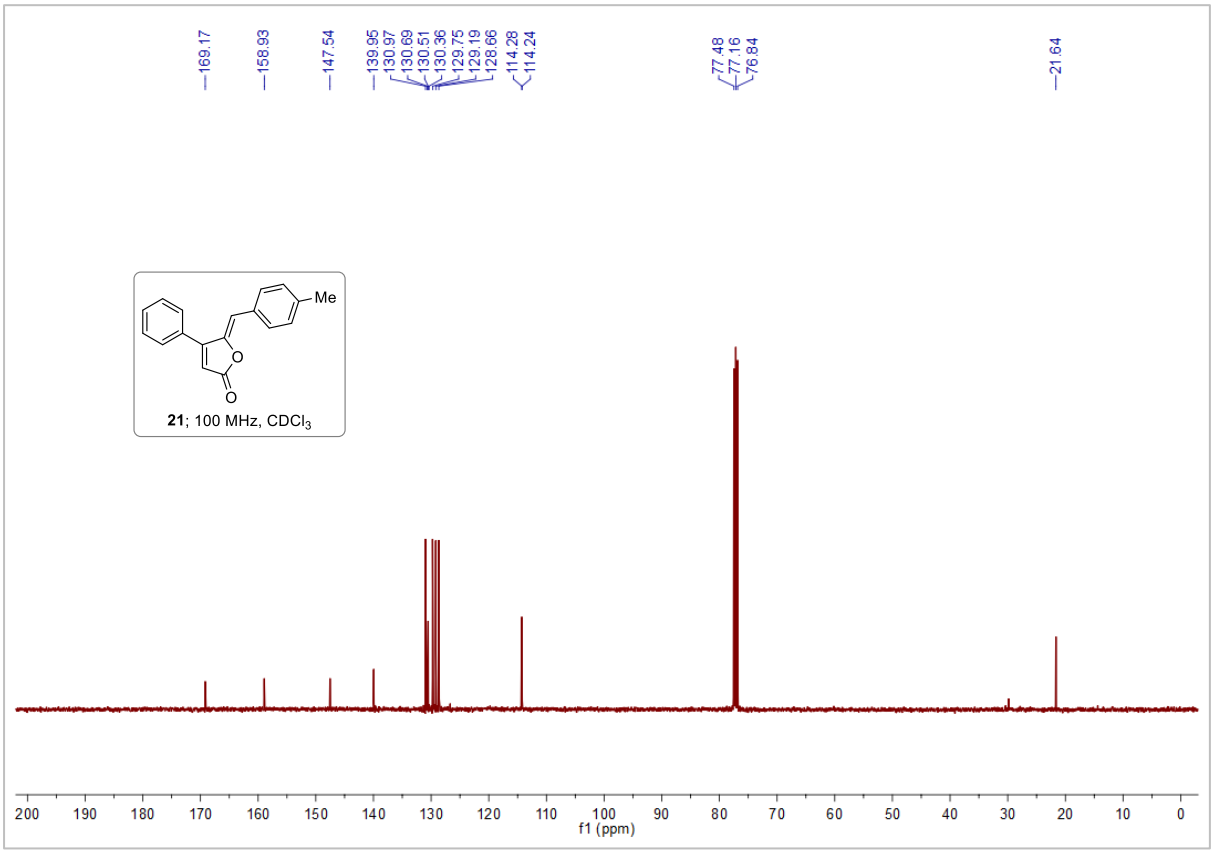
^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) of **20**.



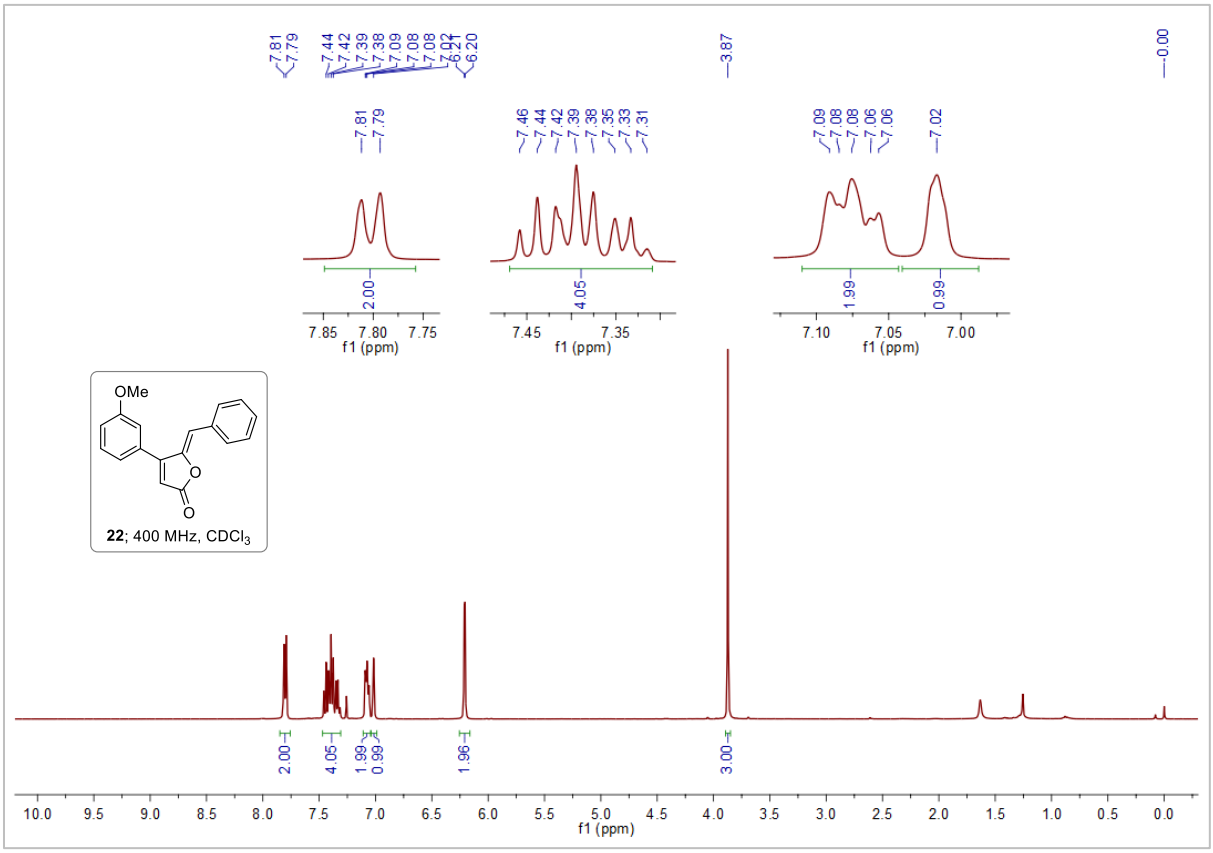


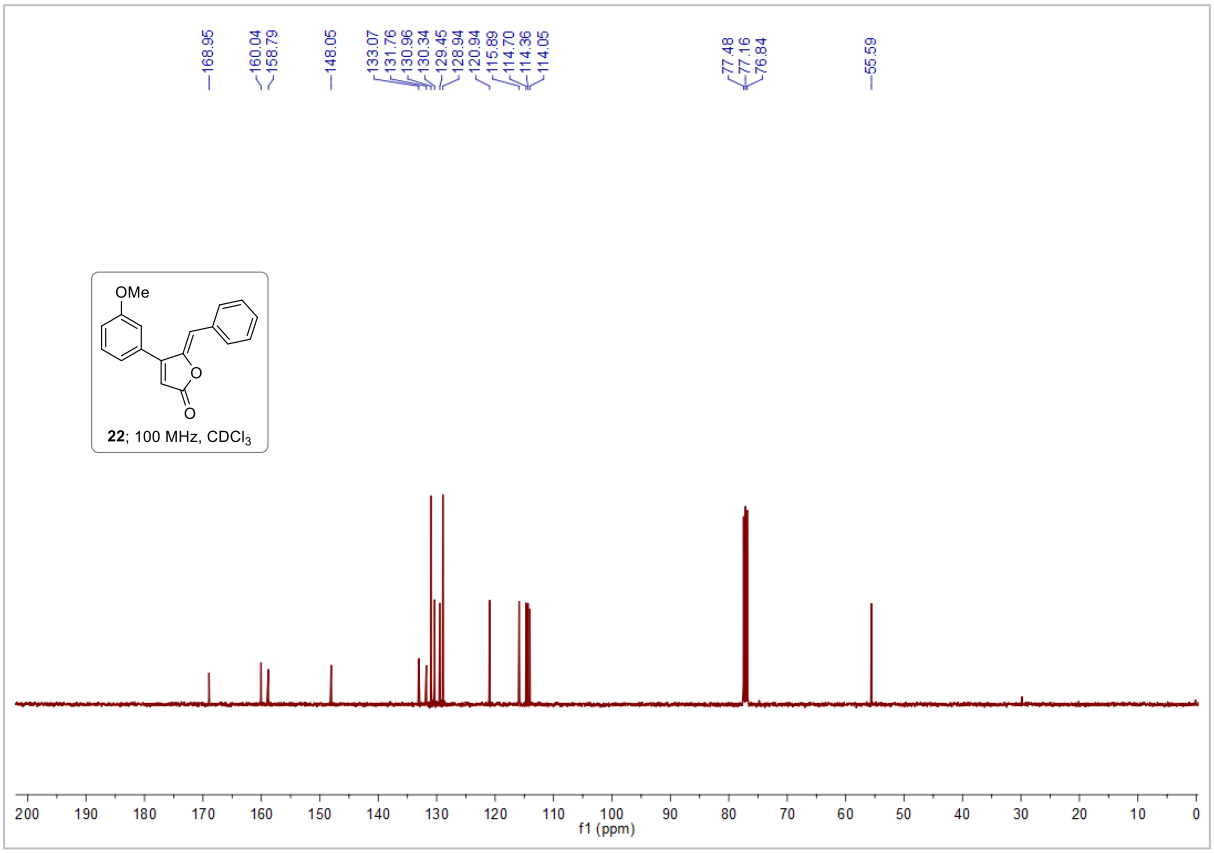
^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) of **21**.



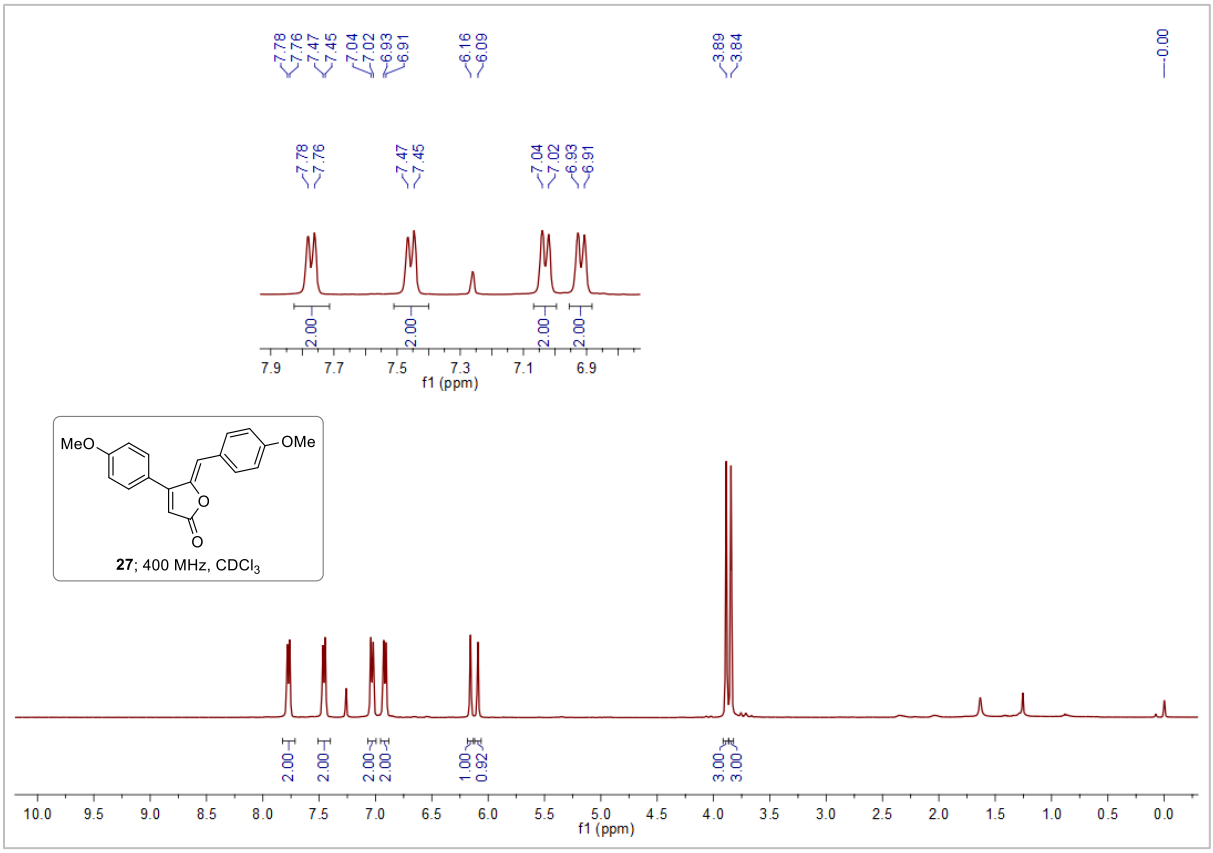


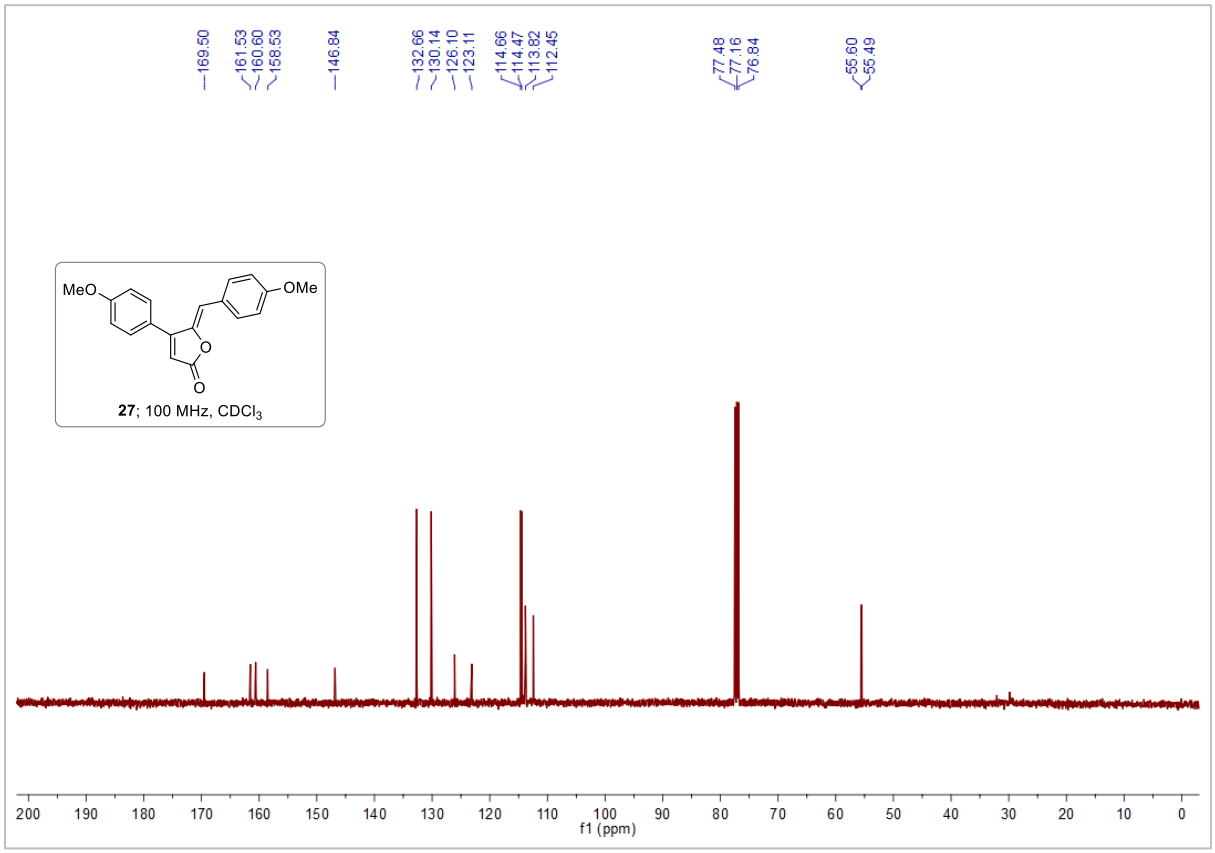
^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) of **22**.



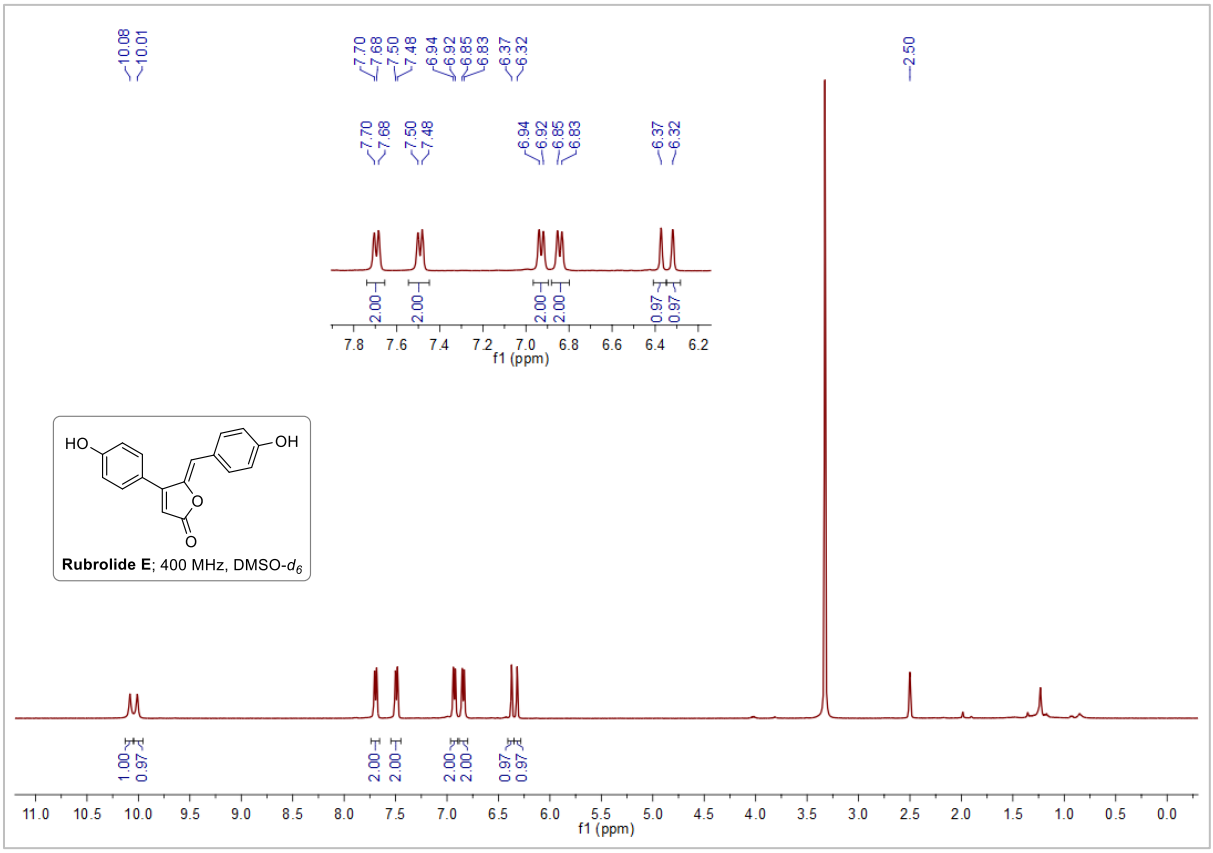


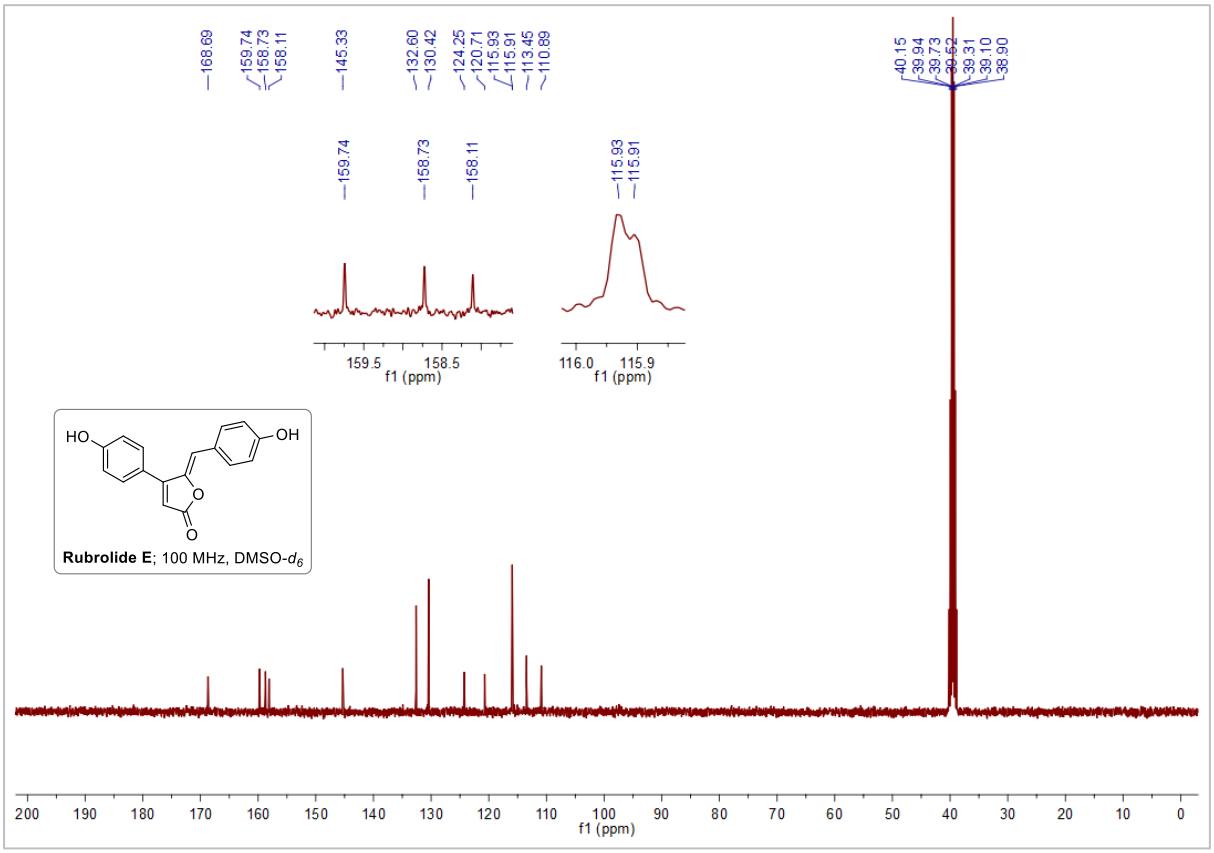
^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) of **27**.



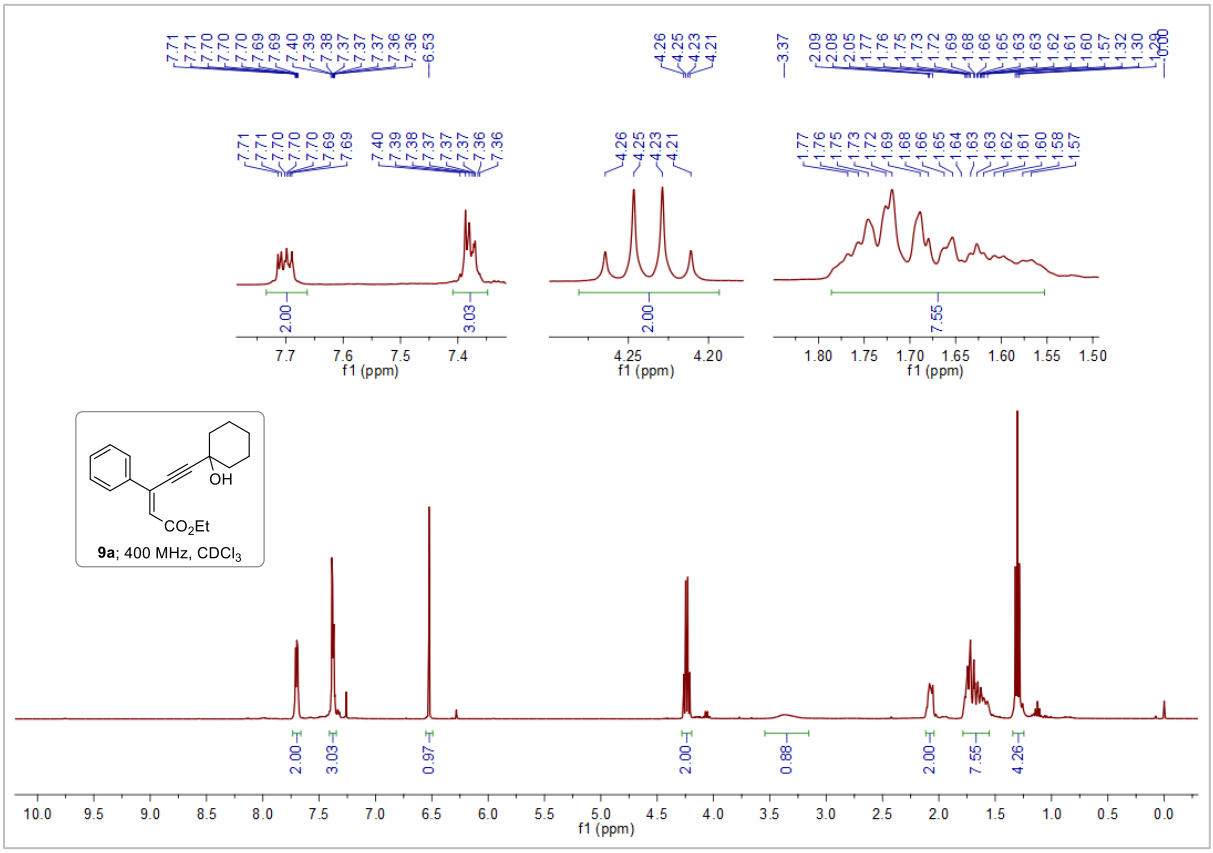


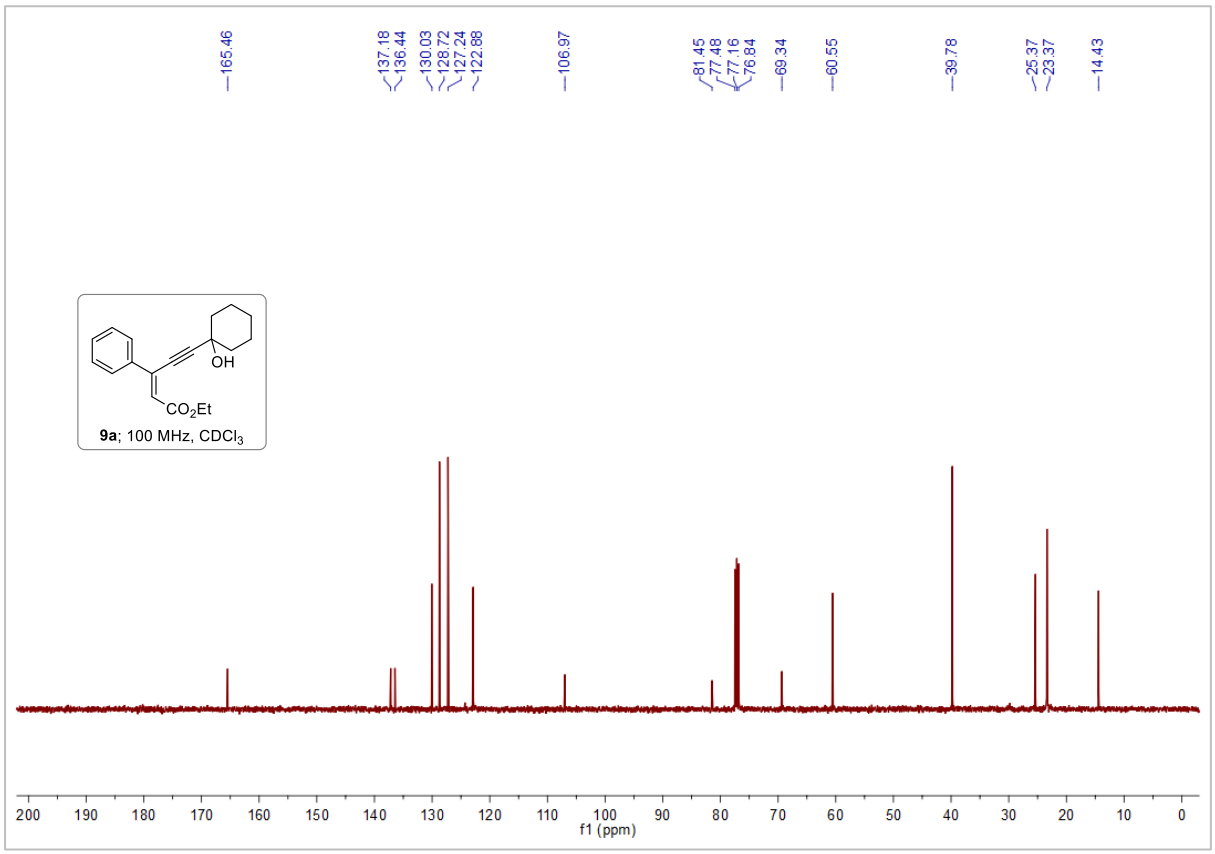
^{1}H NMR (400 MHz, DMSO-d_6) and ^{13}C NMR (100 MHz, DMSO-d_6) of Rubrolide E.



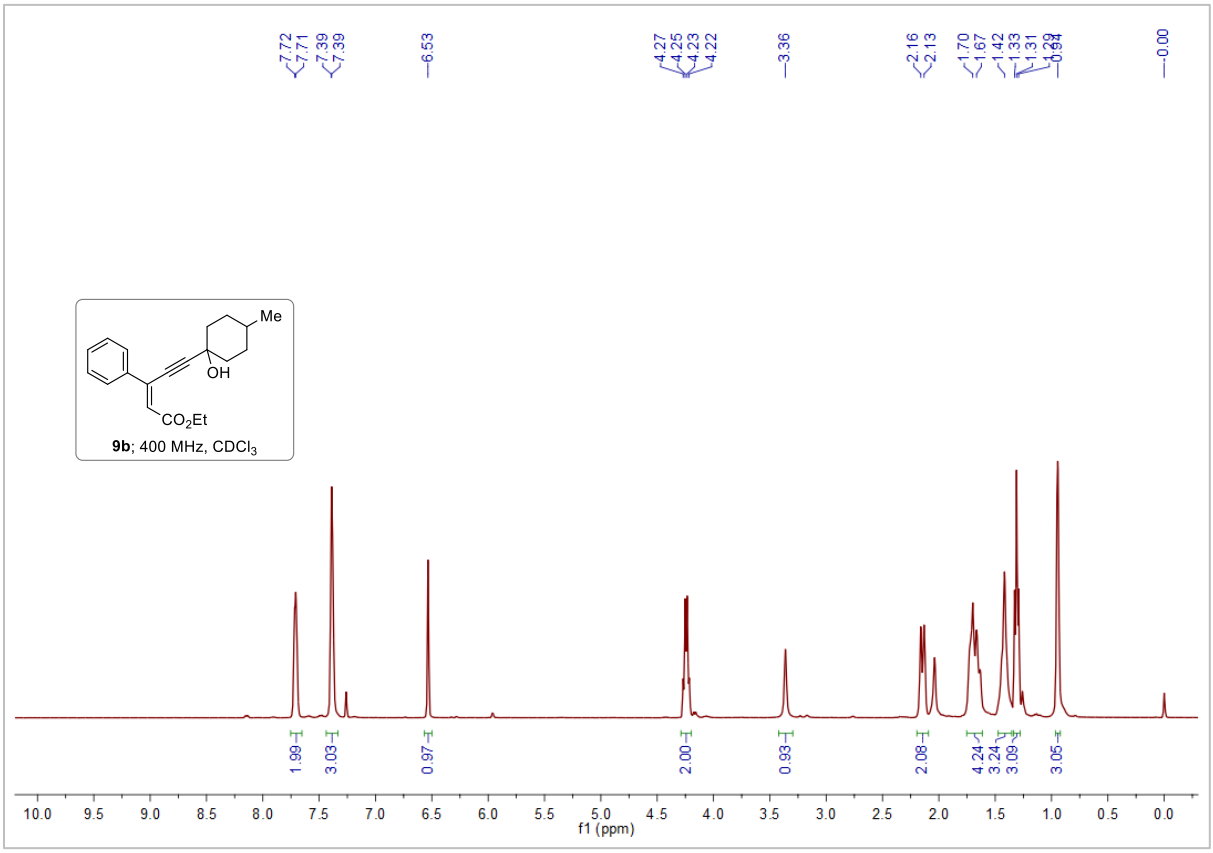


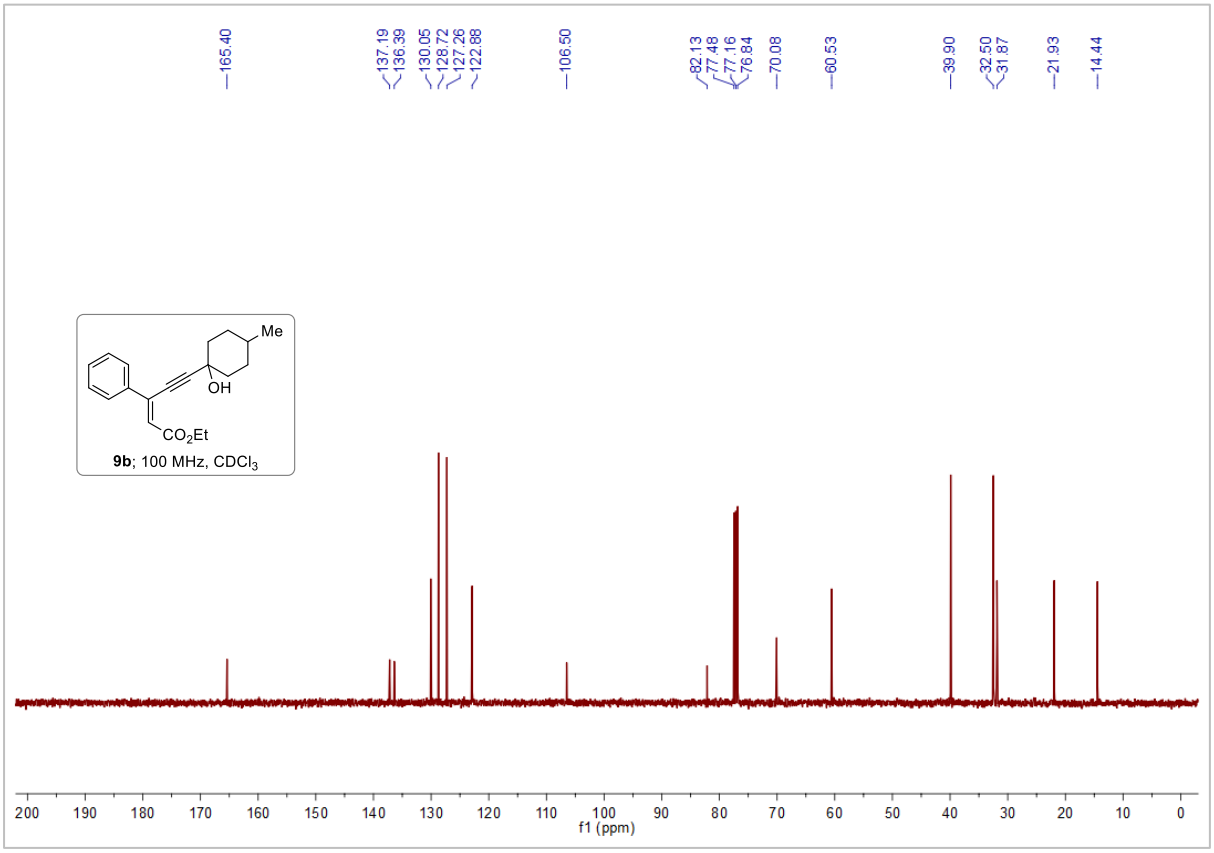
^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) of **9a**.



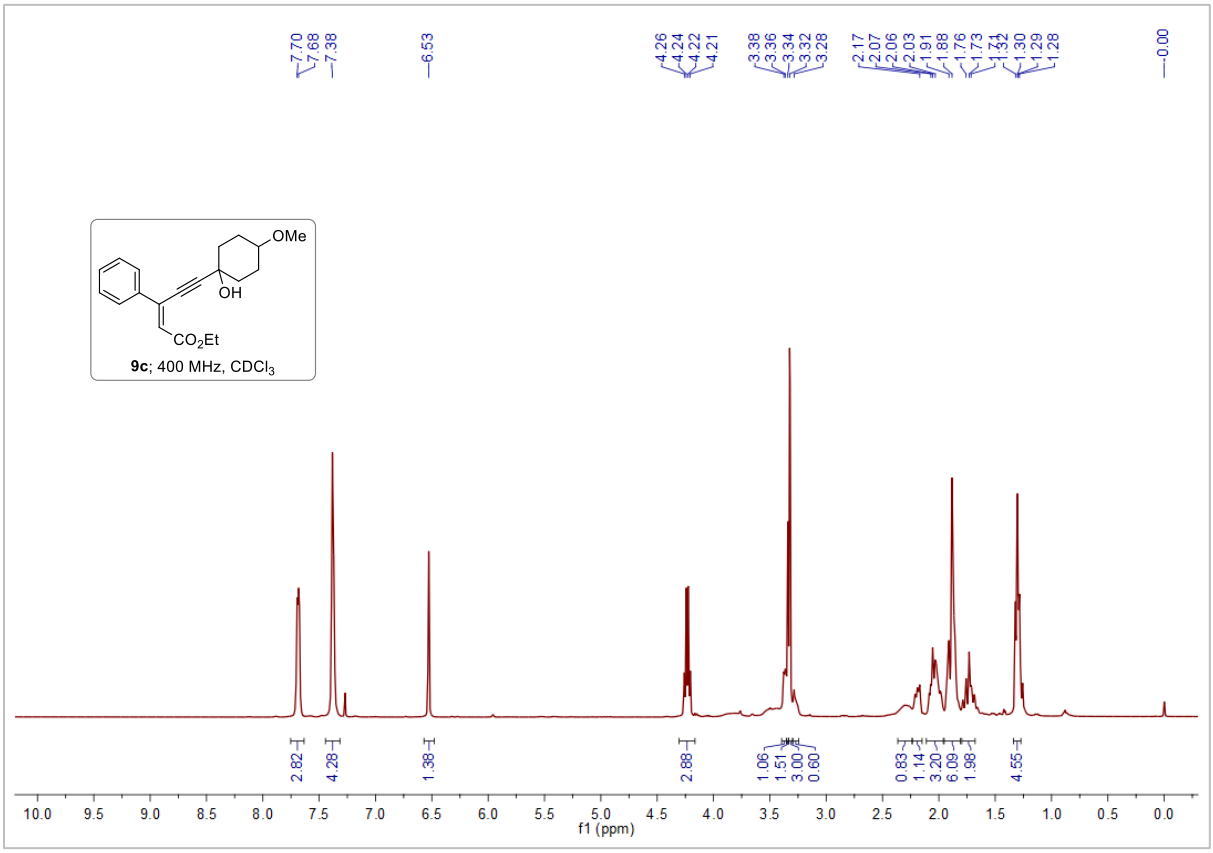


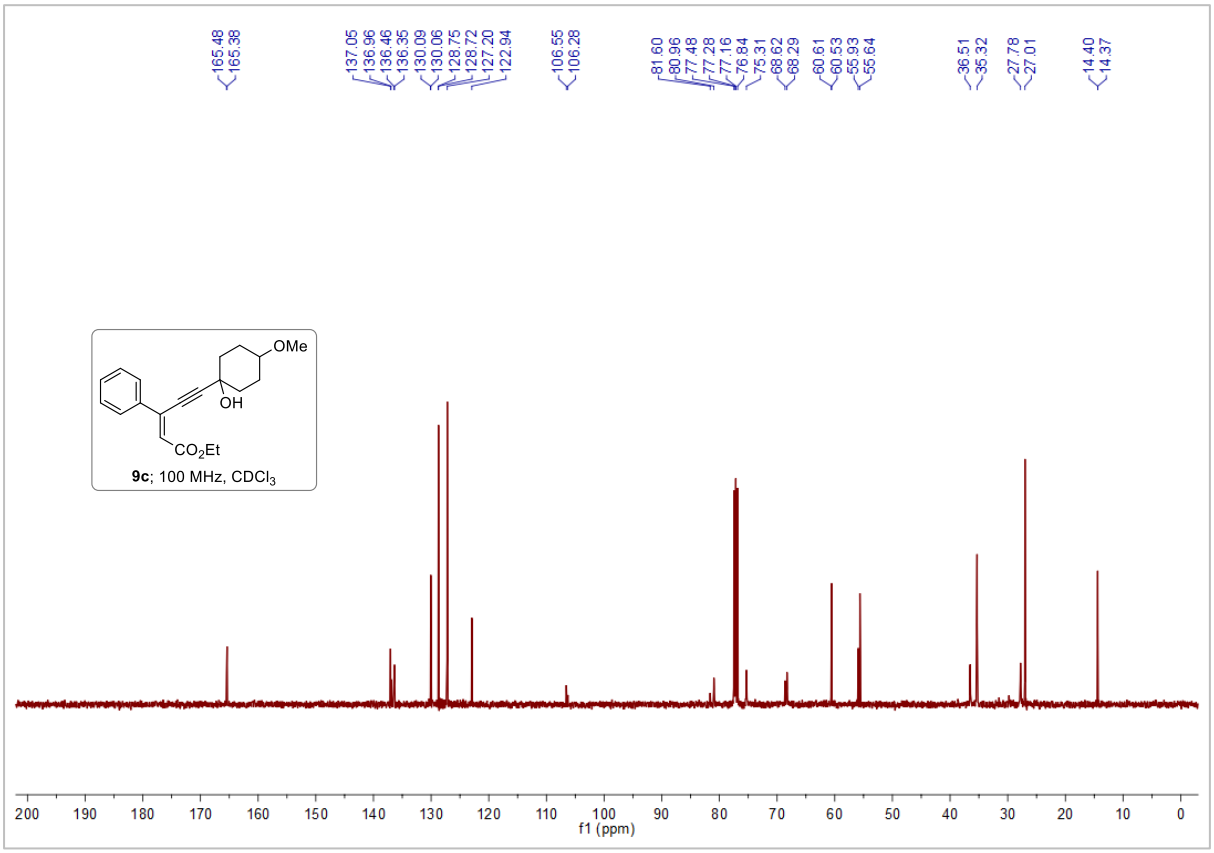
^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) of **9b**.



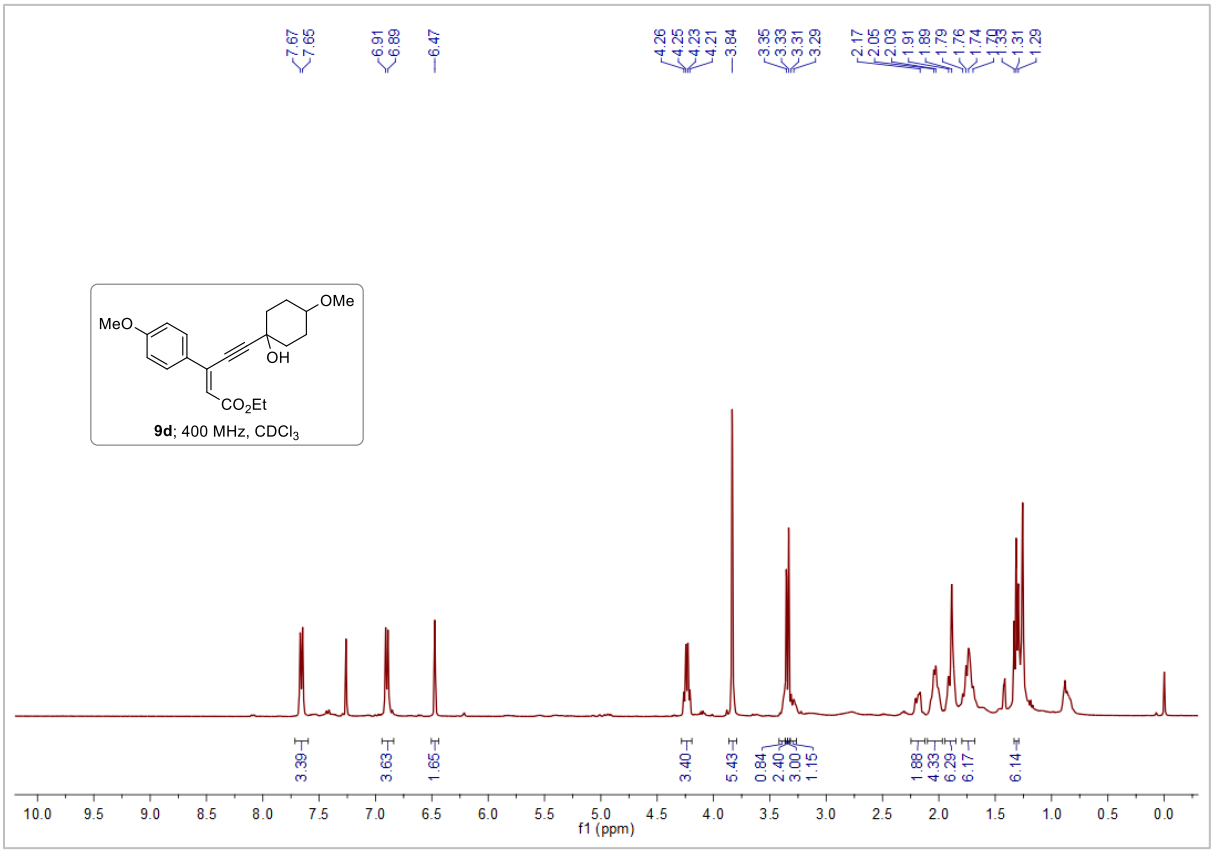


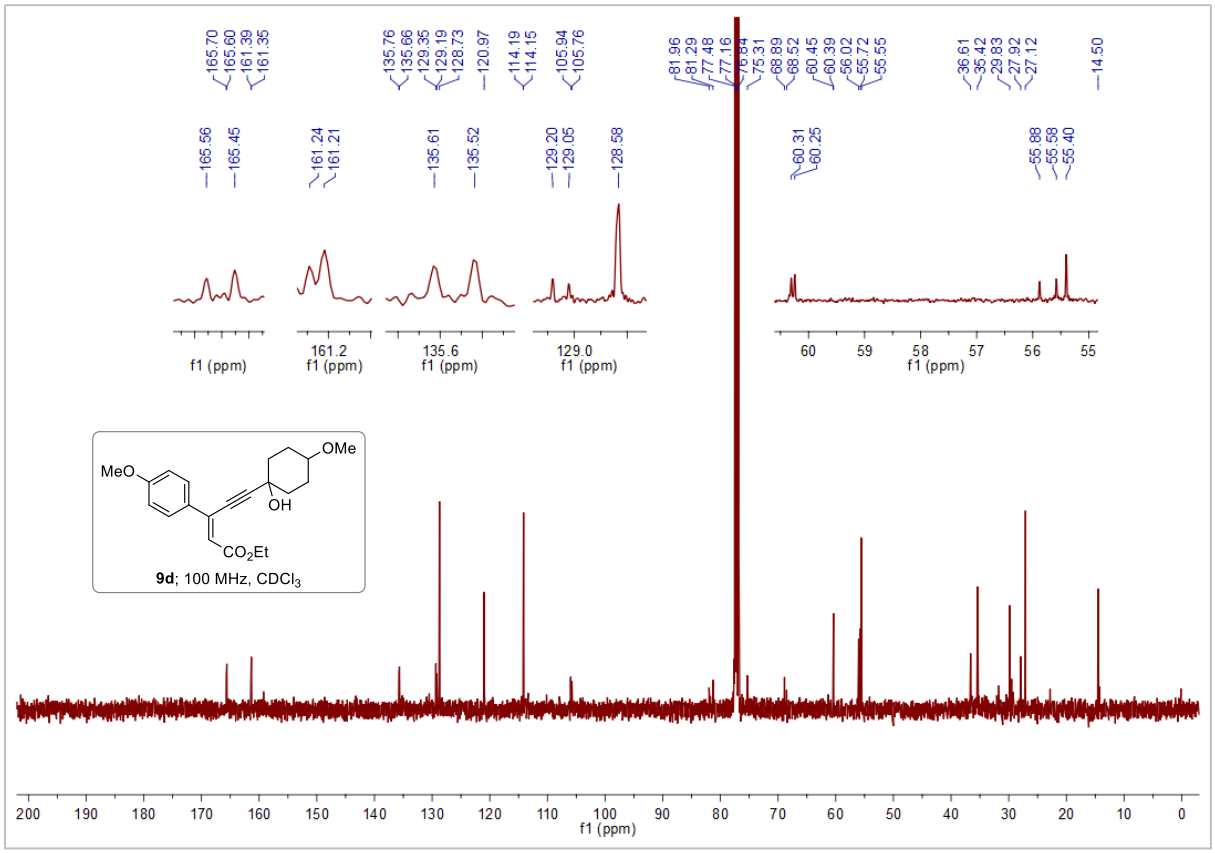
^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) of **9c**.



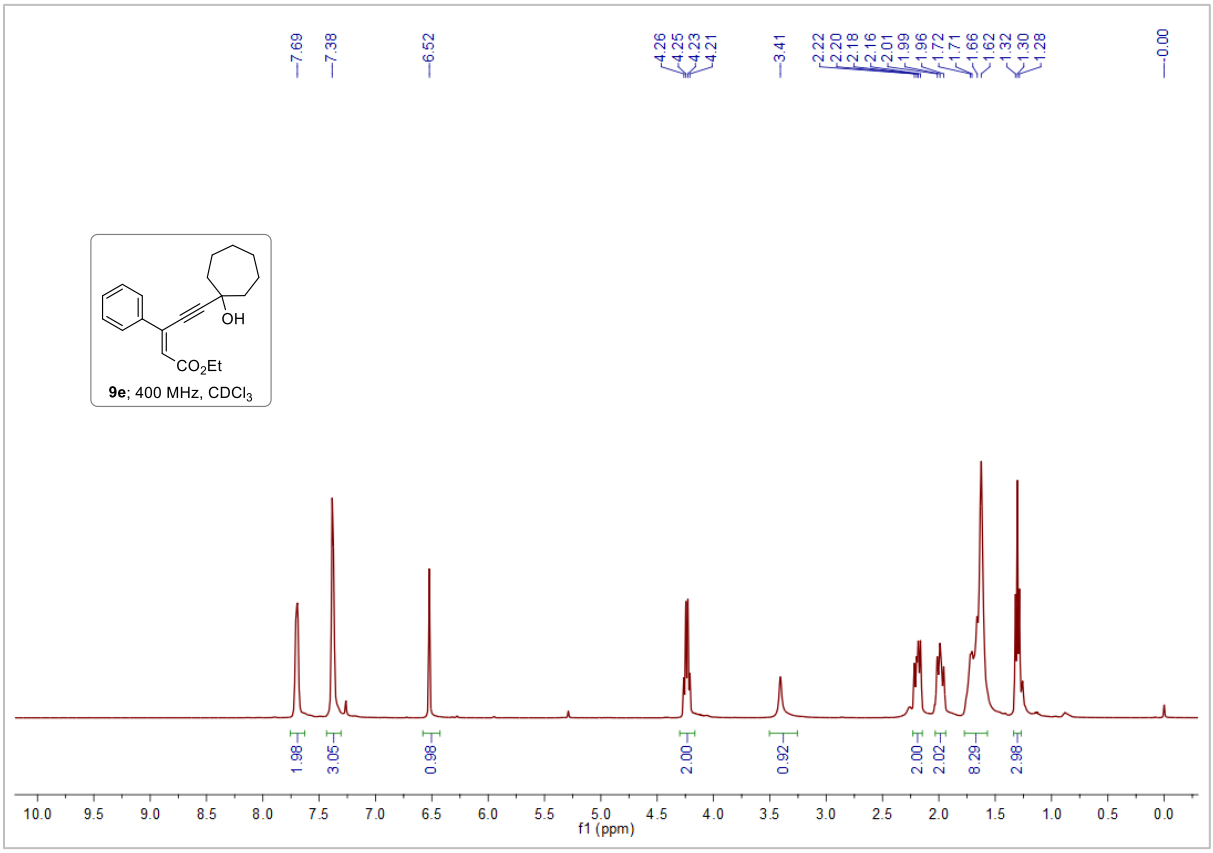


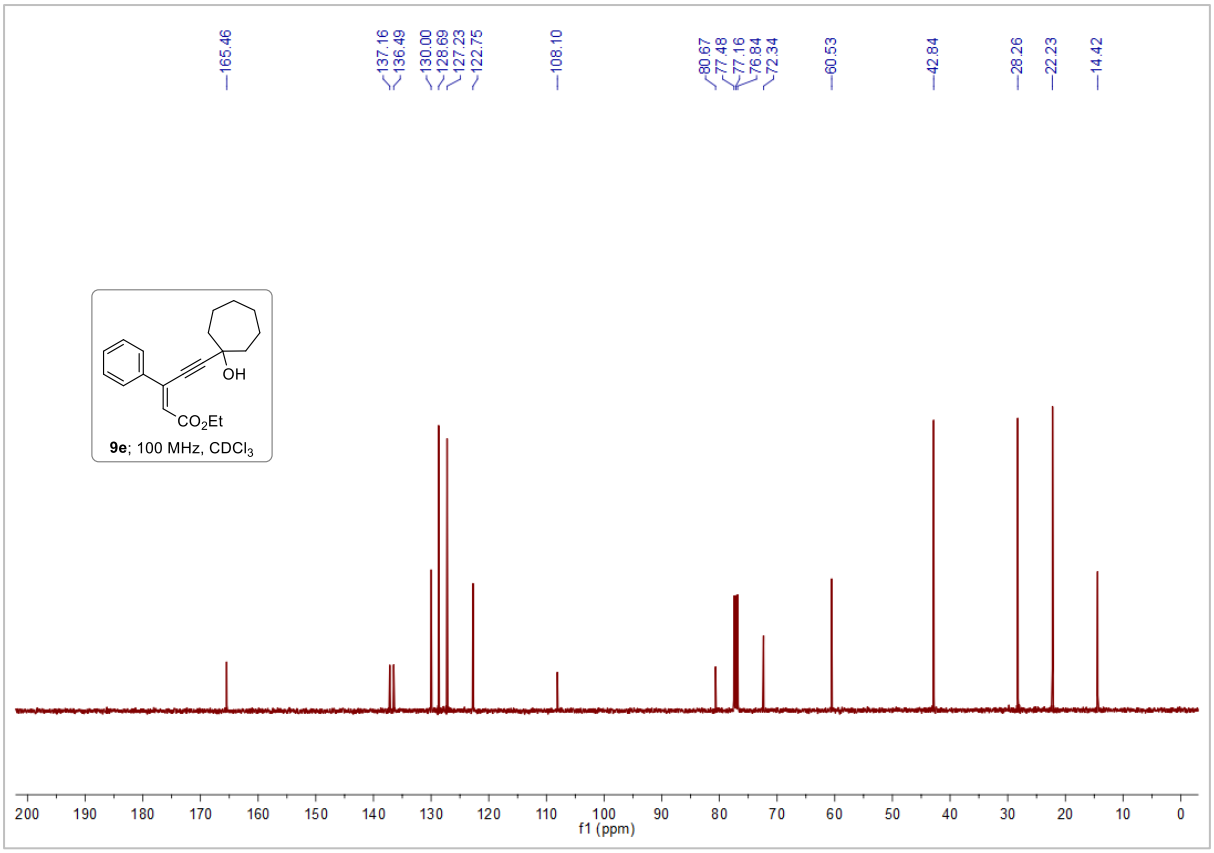
^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) of **9d**.



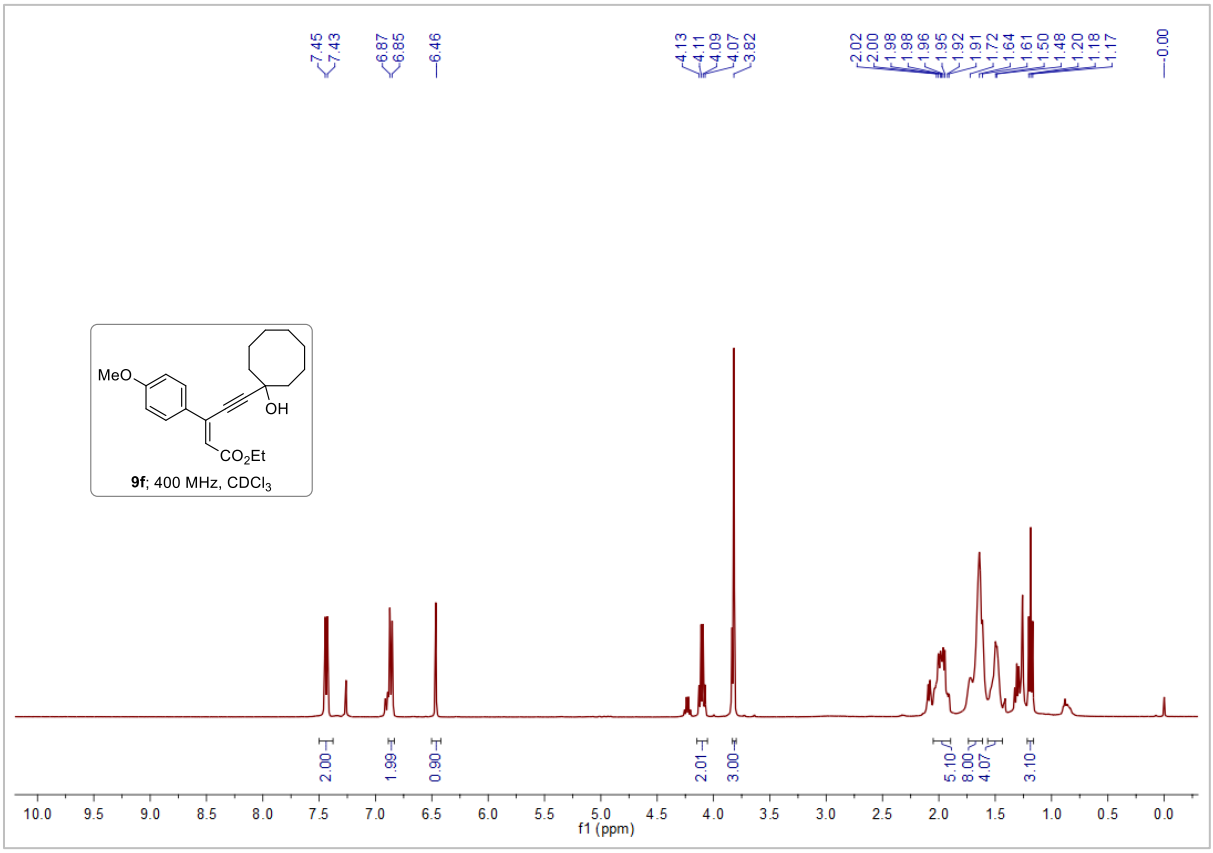


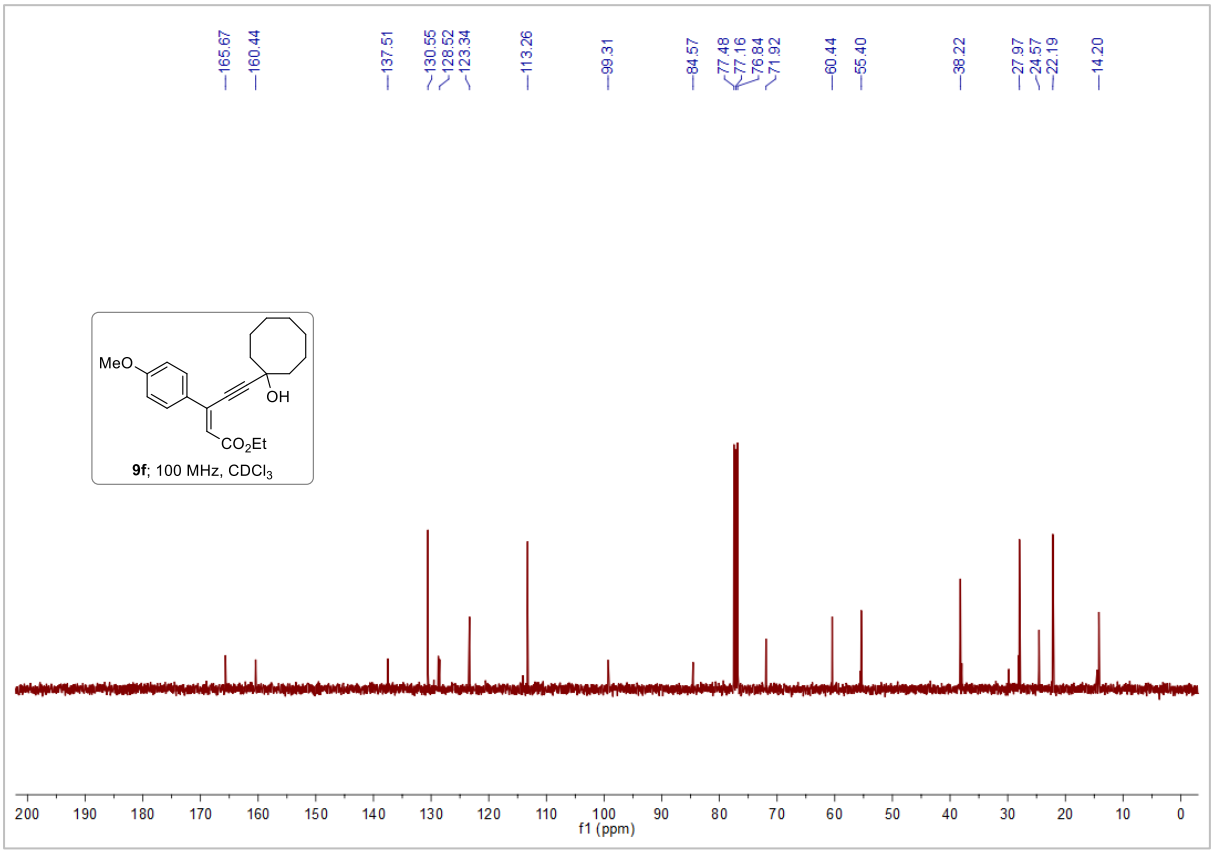
^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) of **9e**.



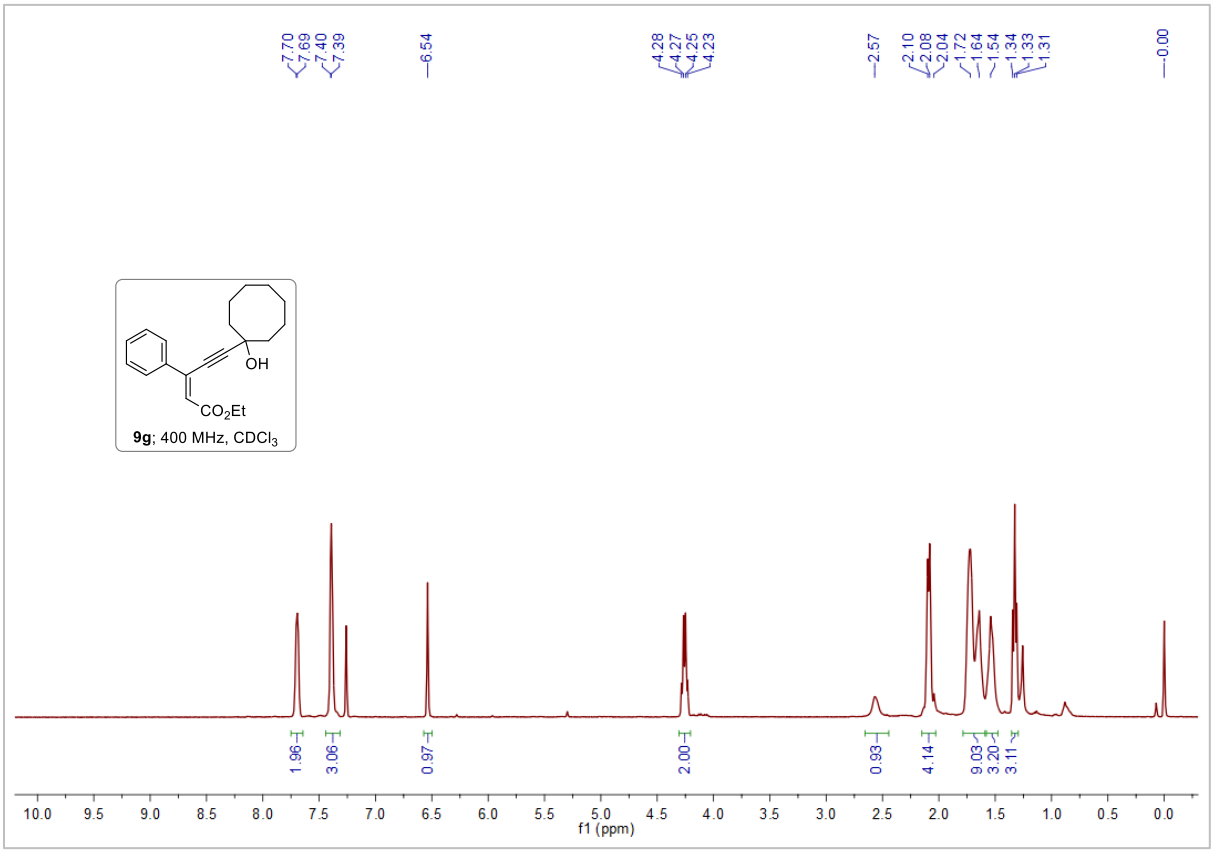


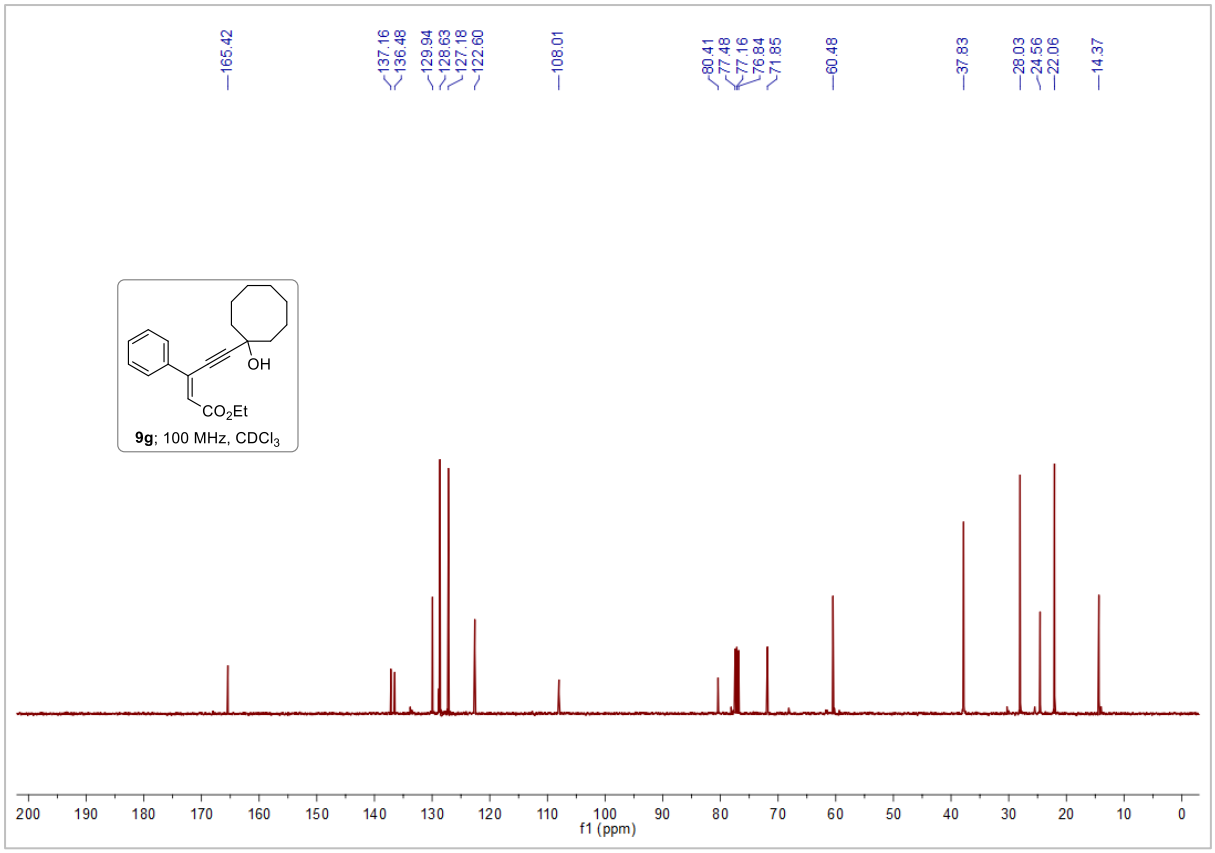
^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) of **9f**.



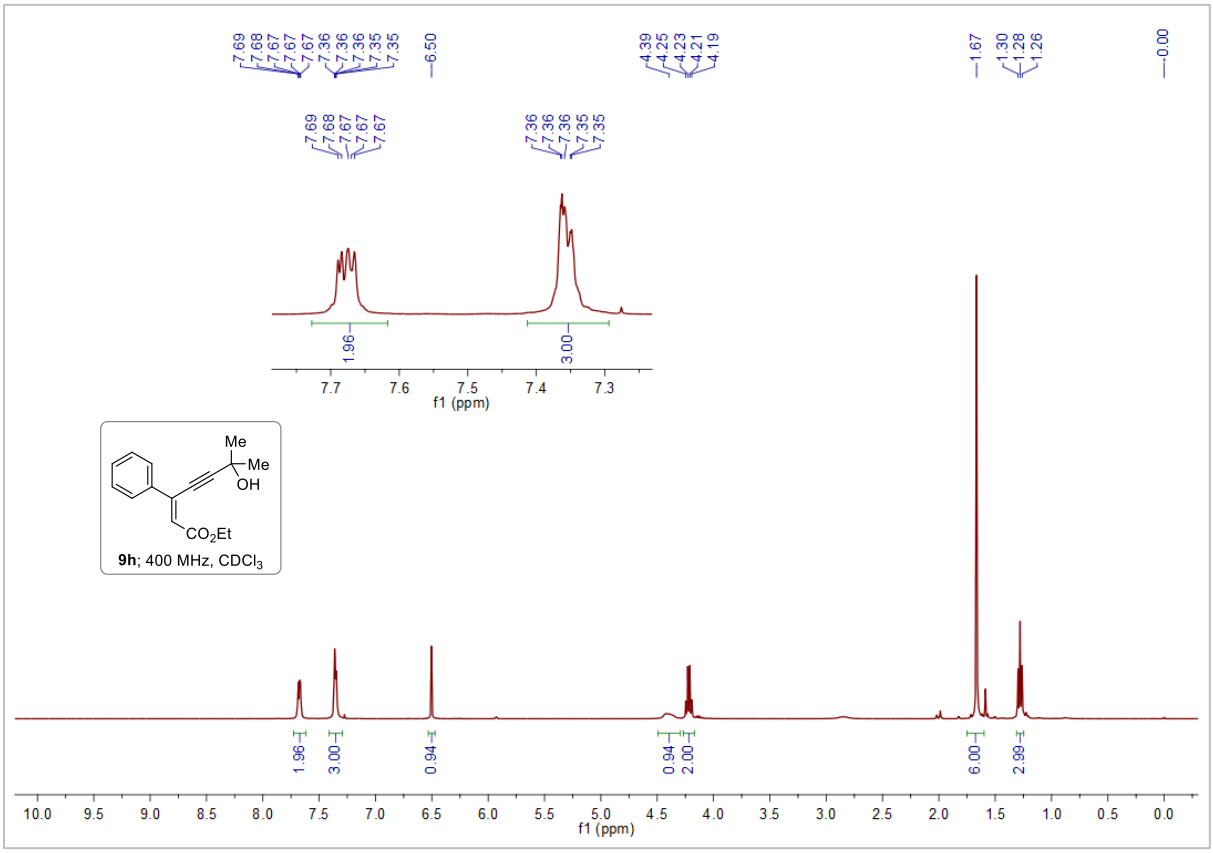


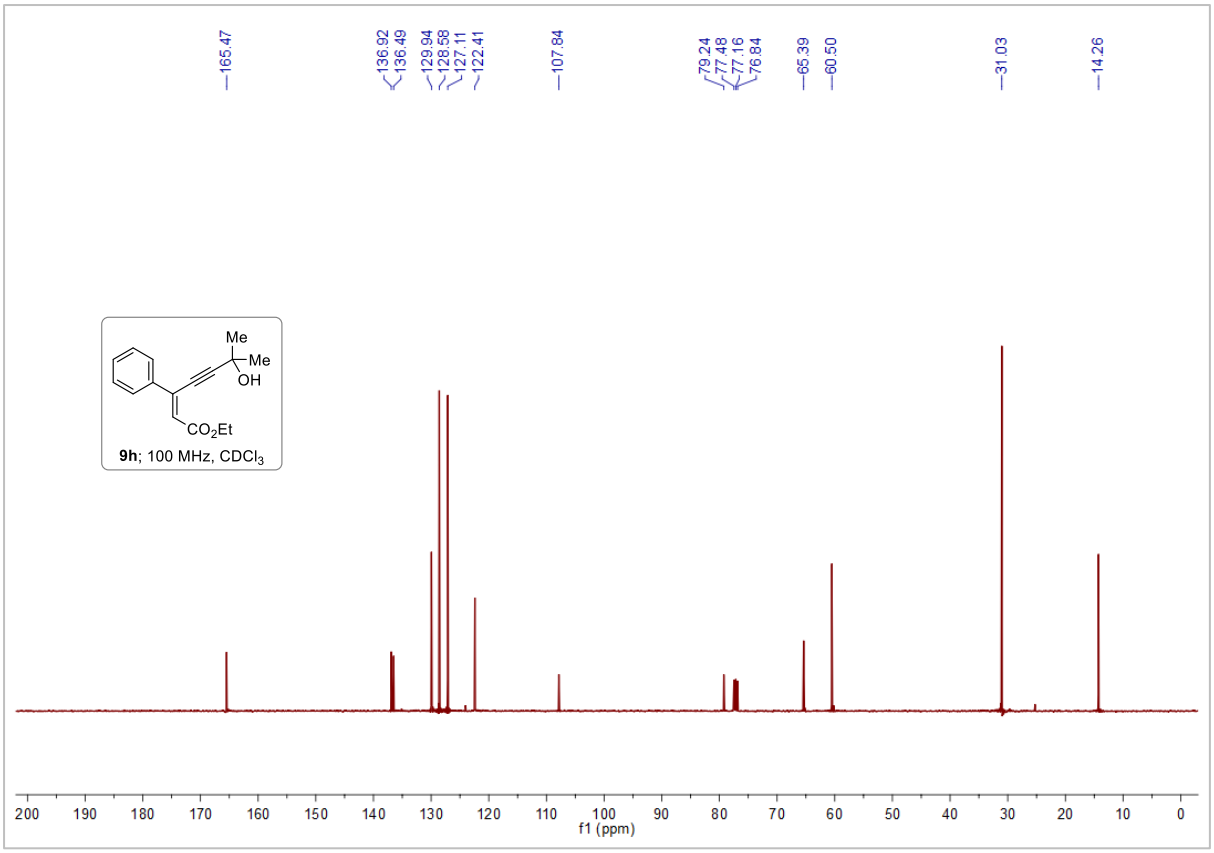
^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) of **9g**.



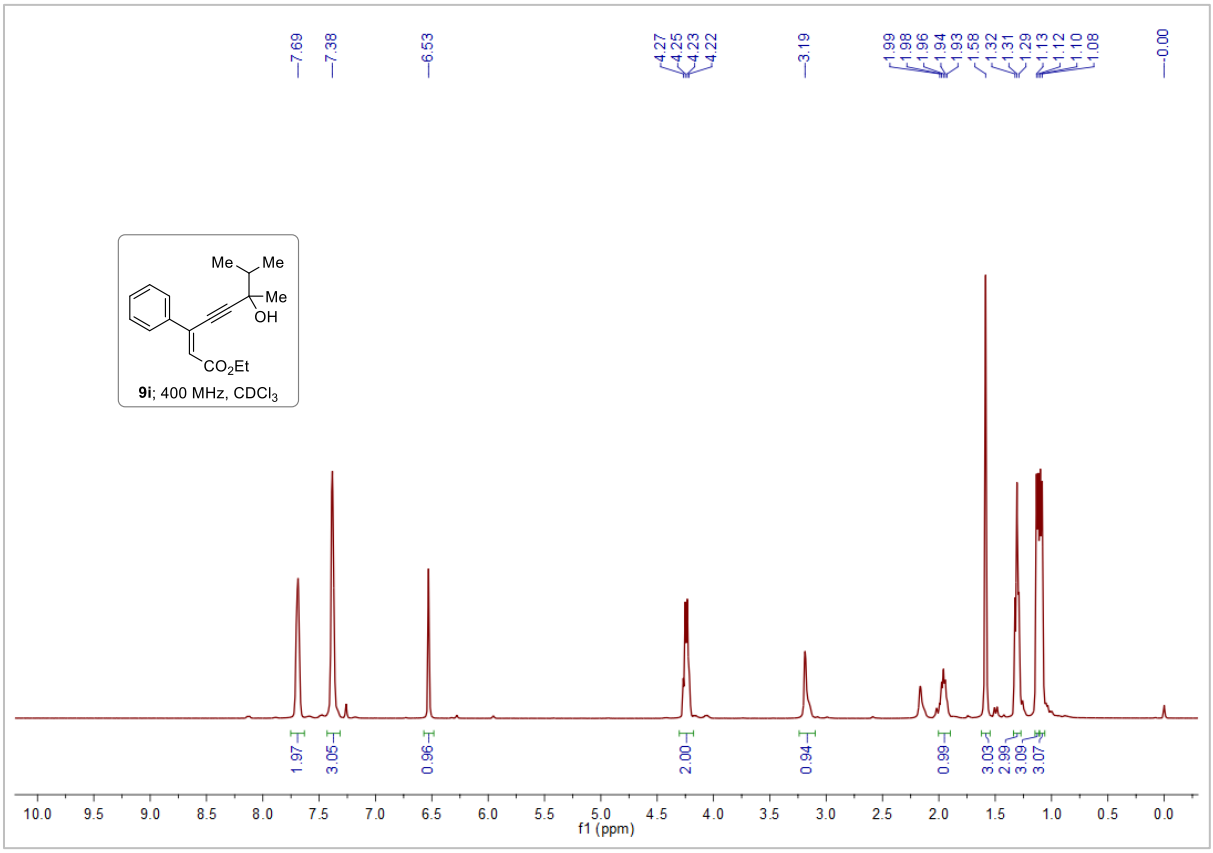


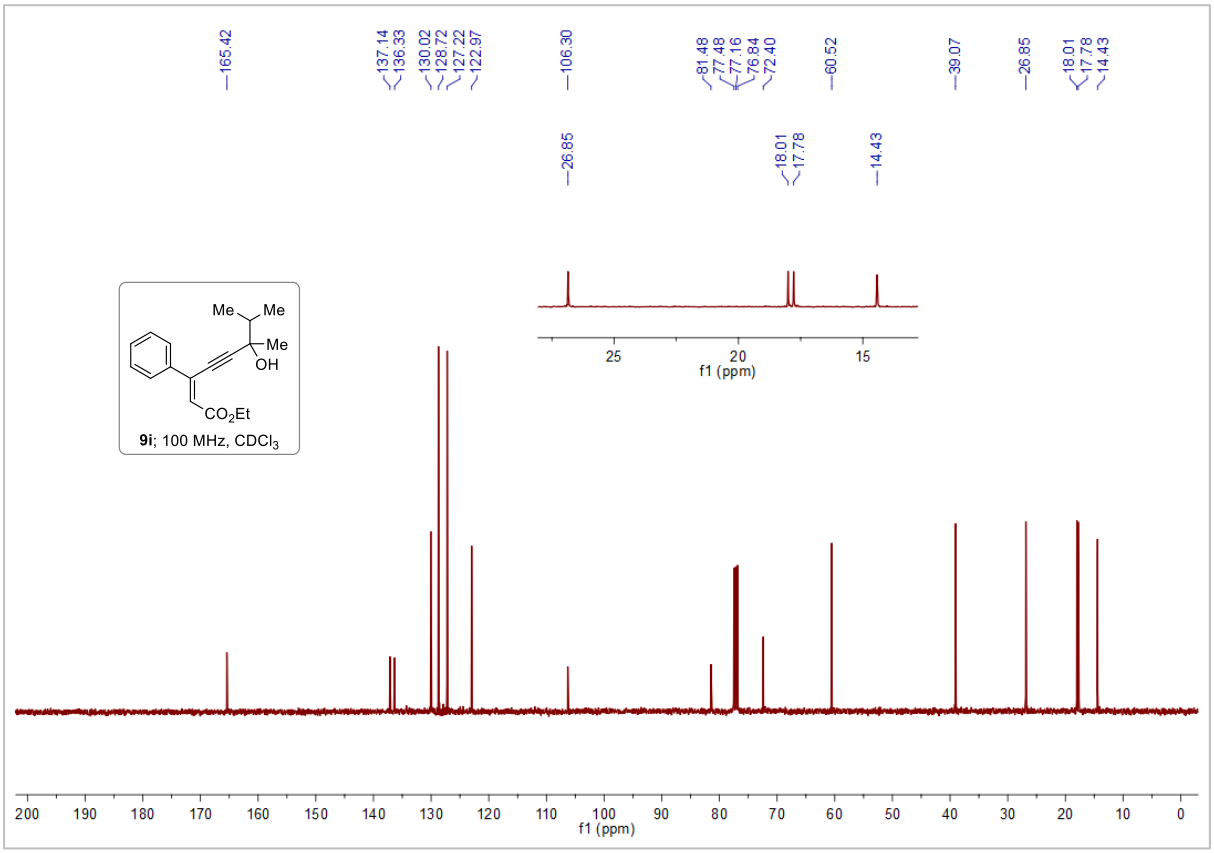
^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) of **9h**.



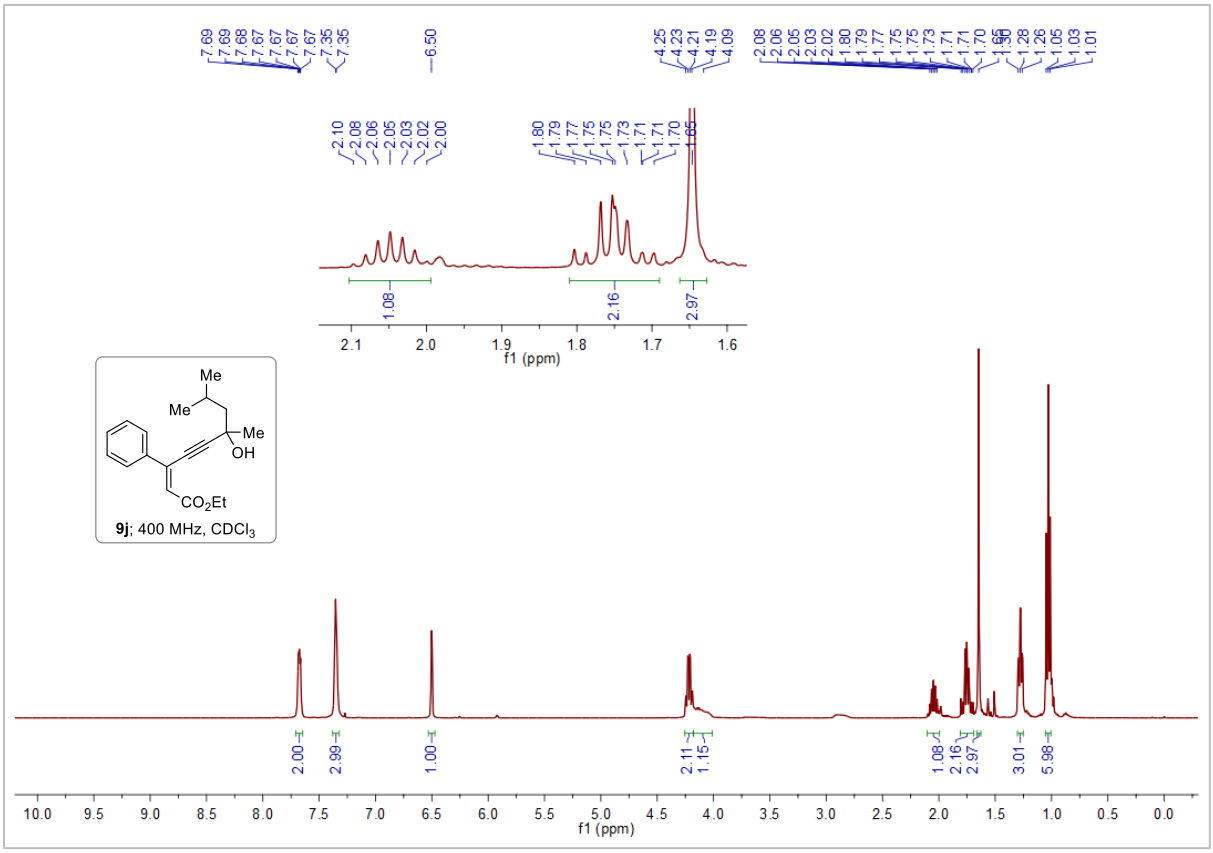


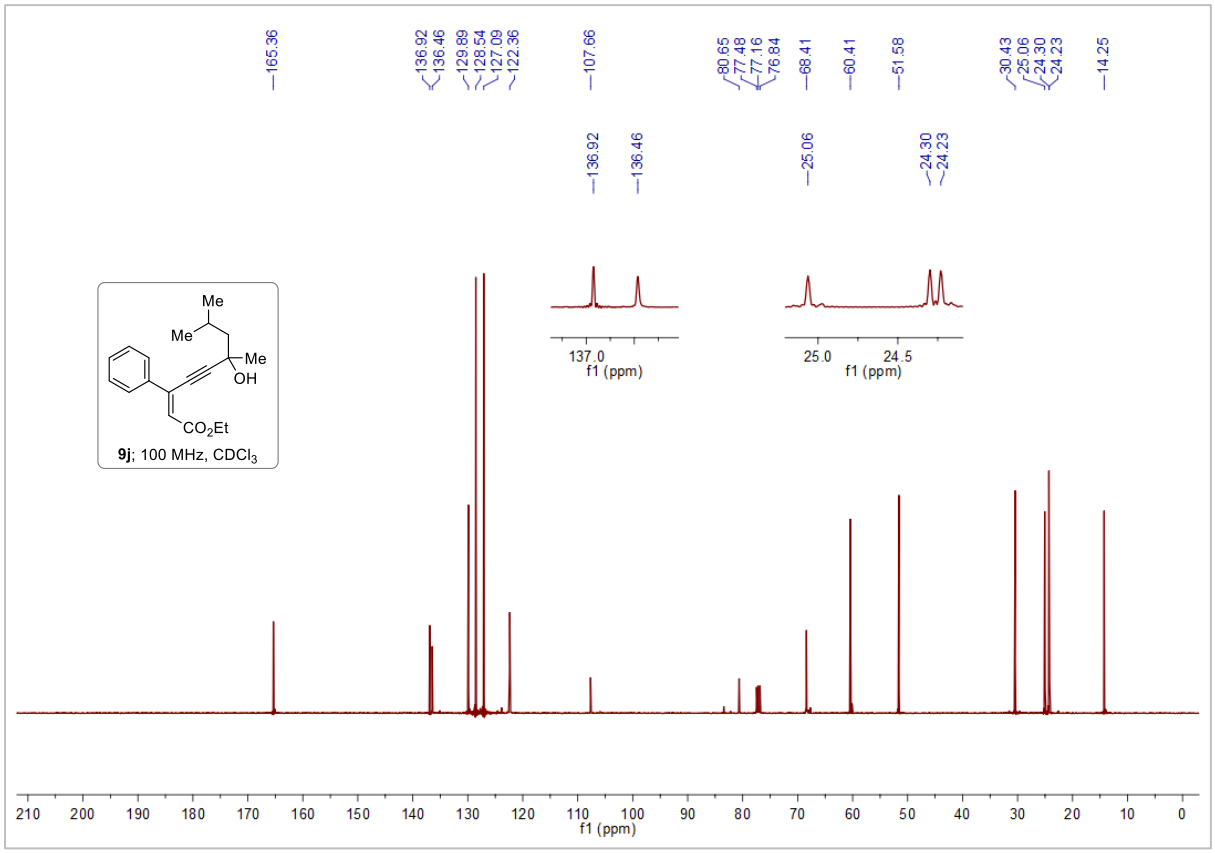
^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) of **9i**.



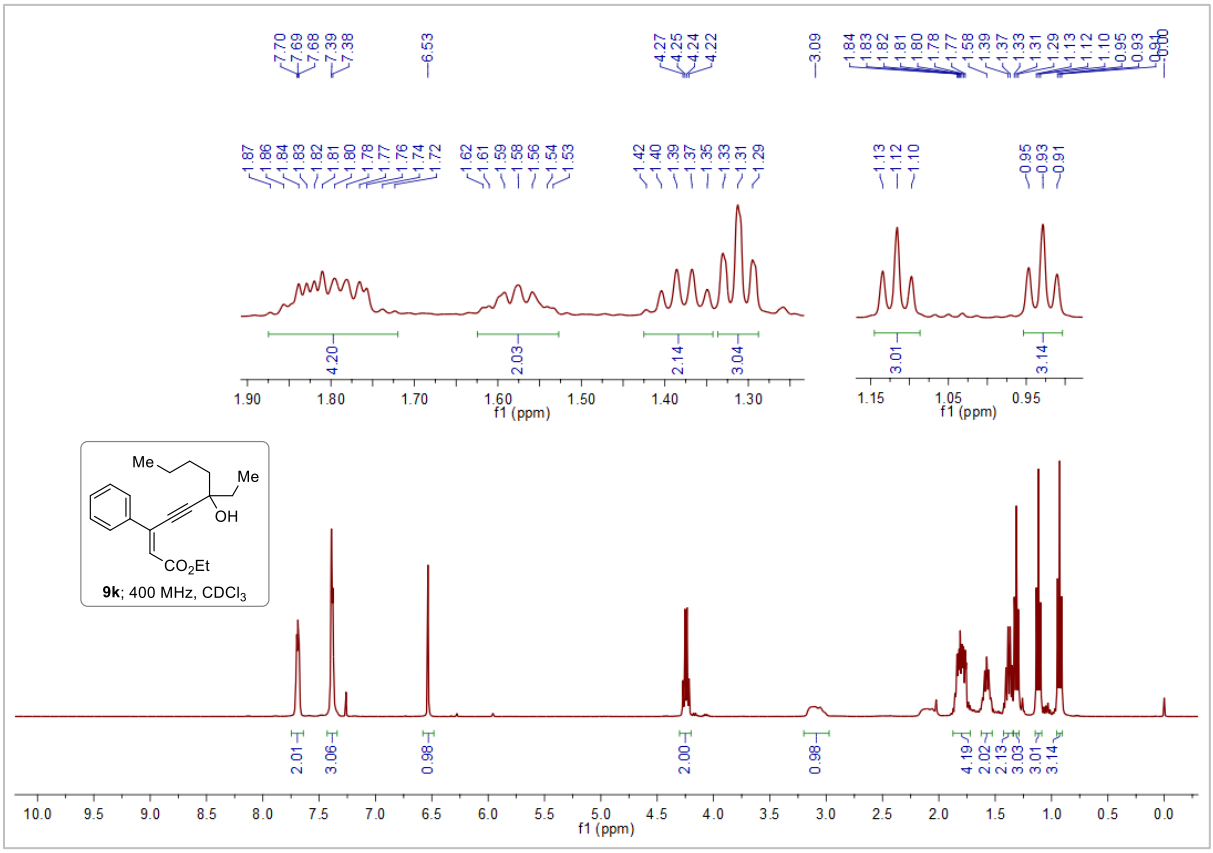


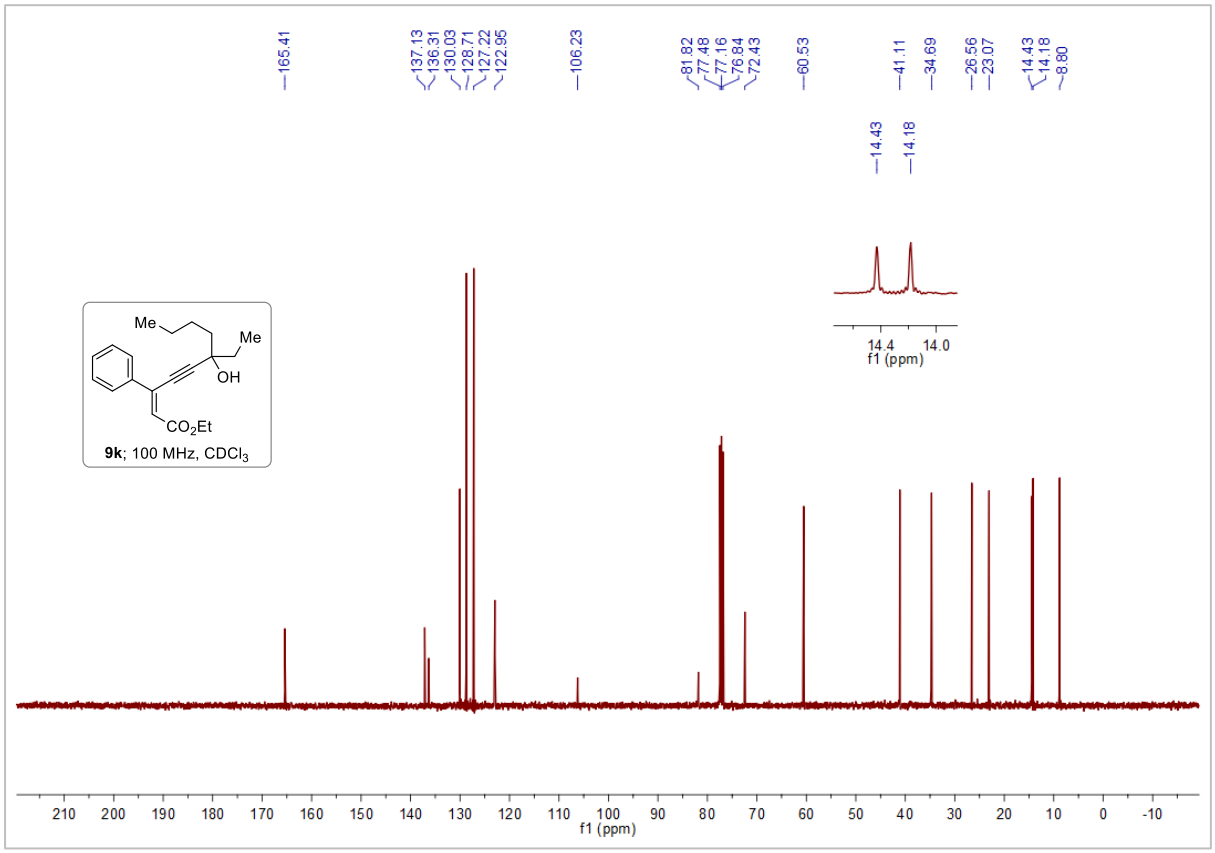
^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) of **9j**.



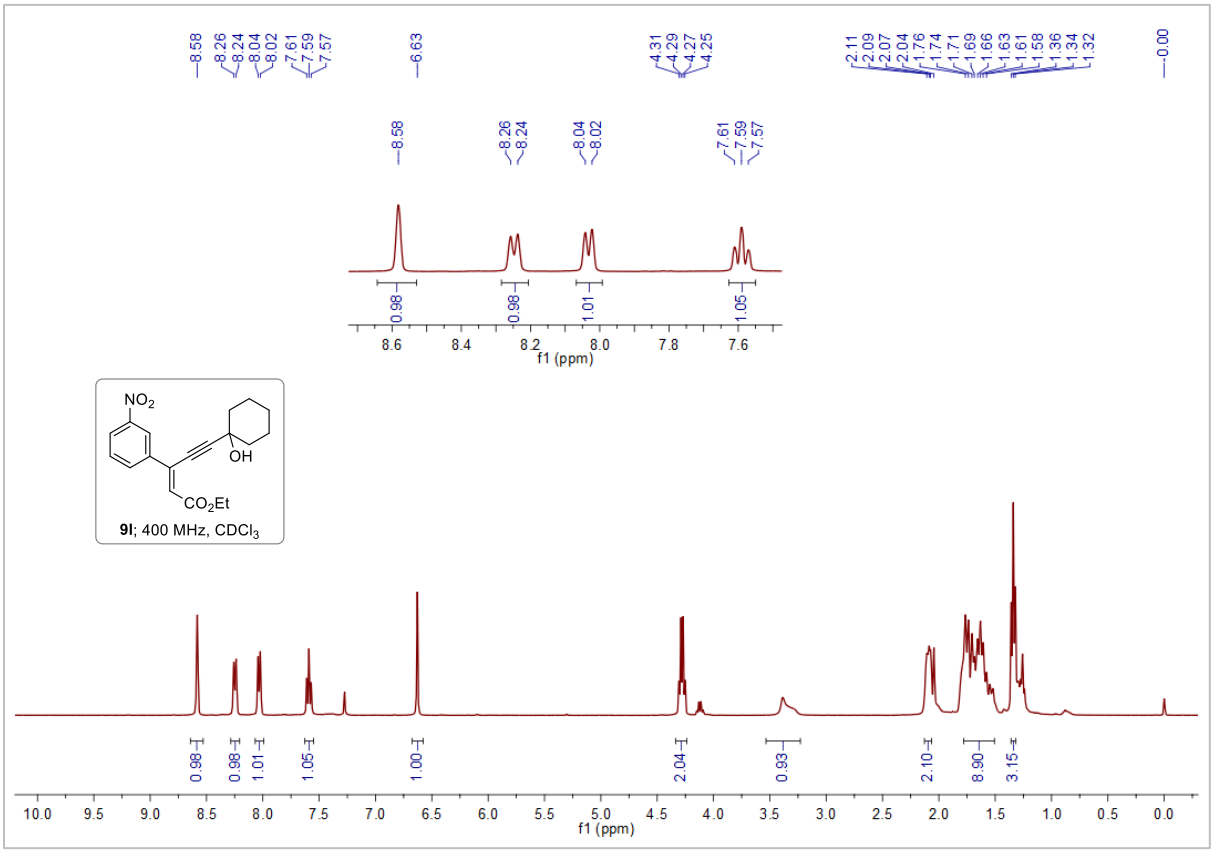


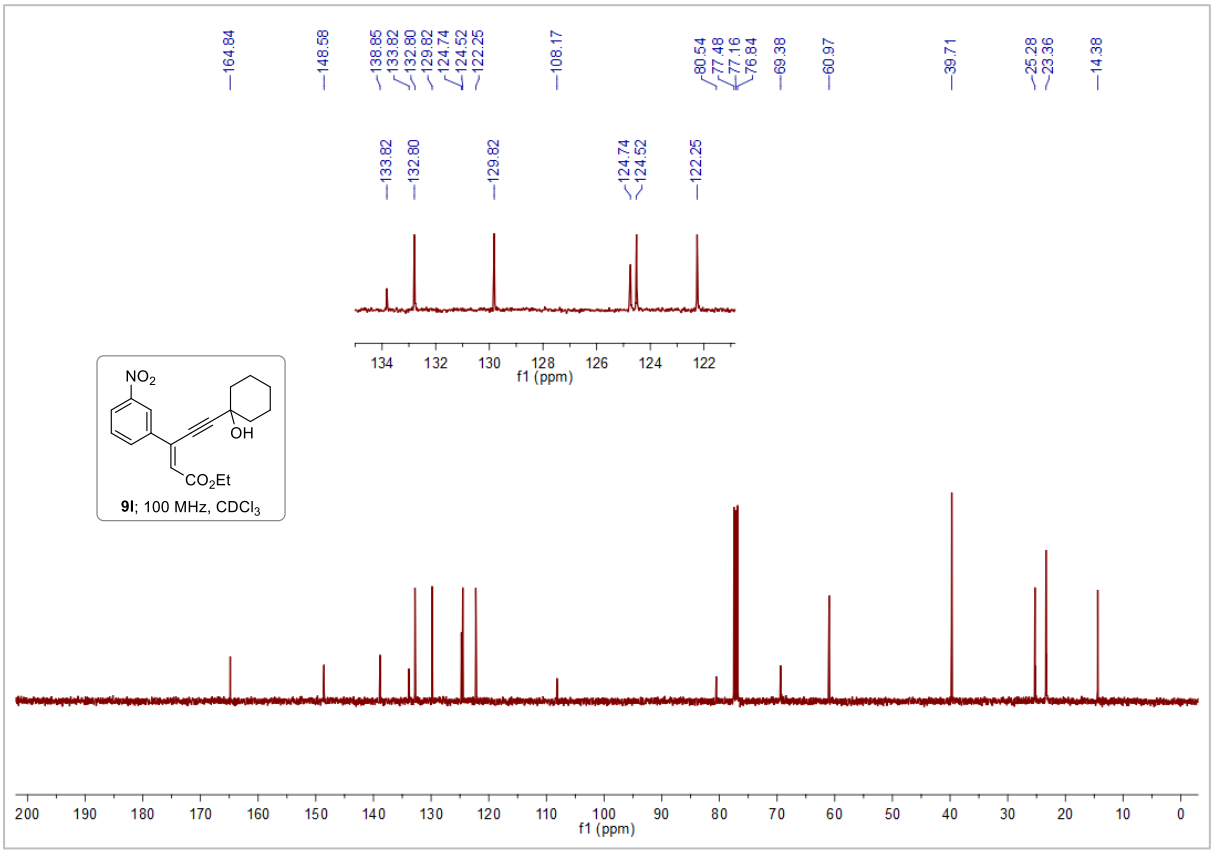
^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) of **9k**.



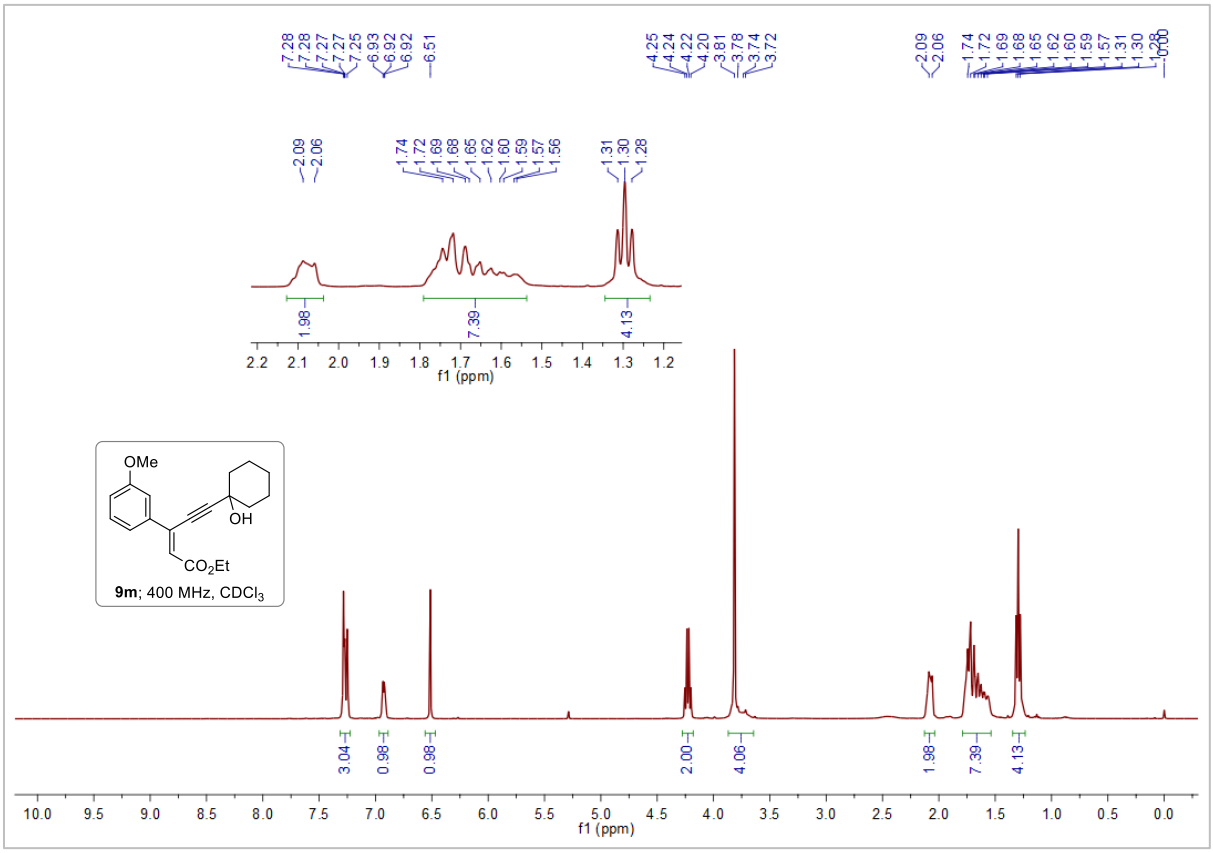


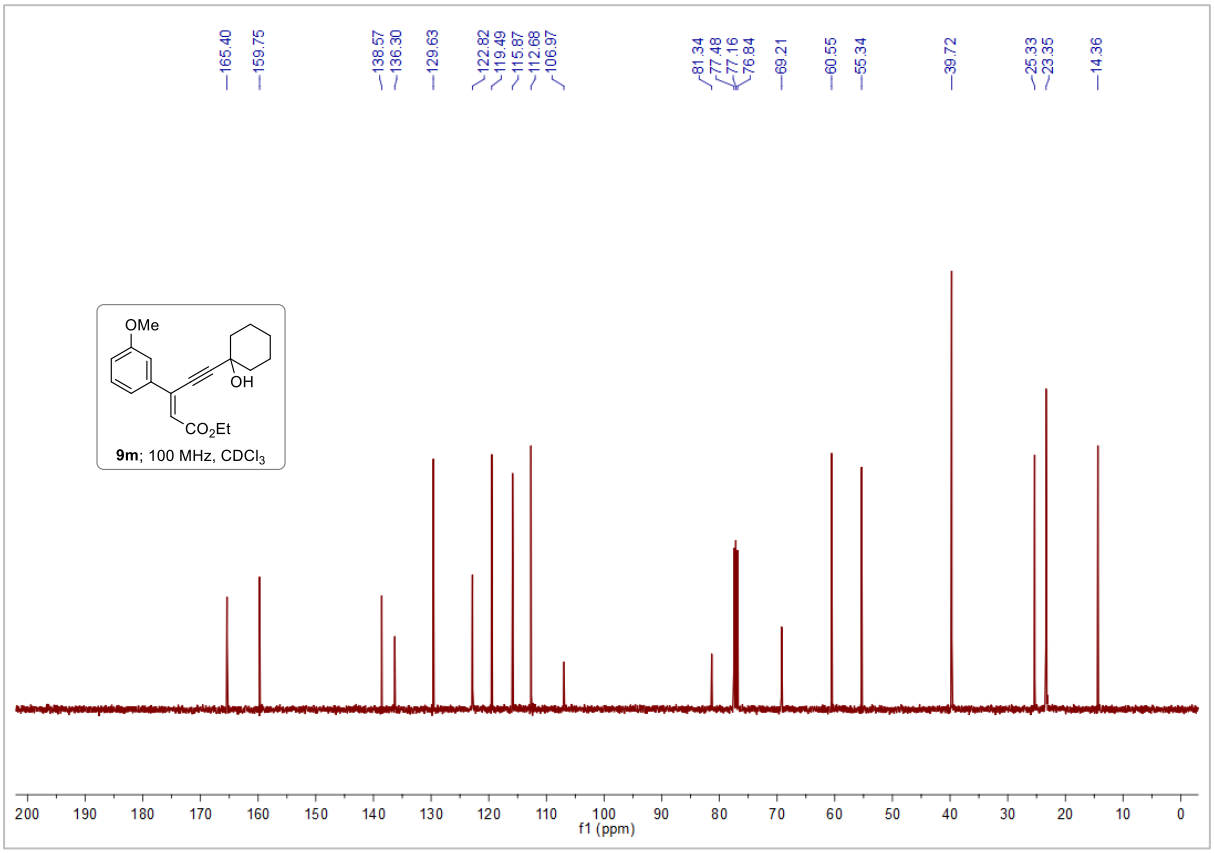
^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) of **9l**.



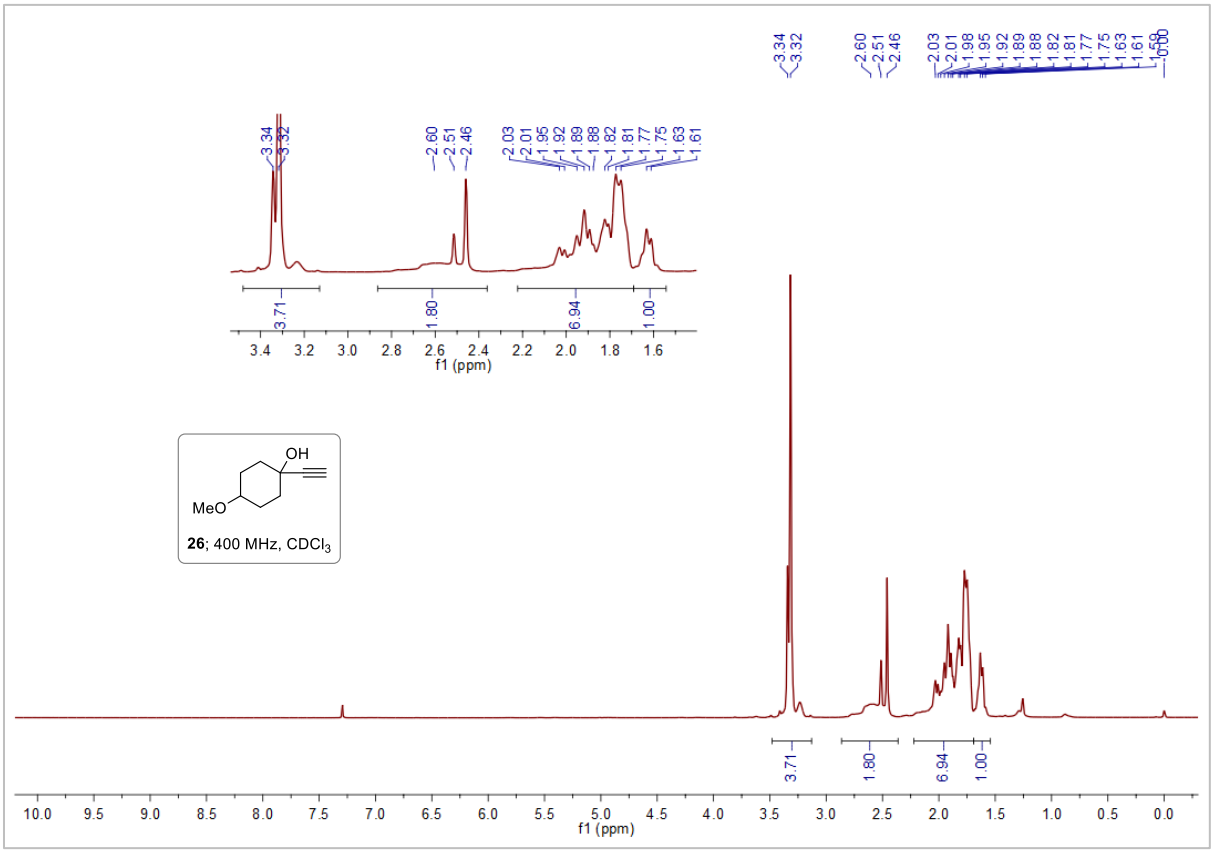


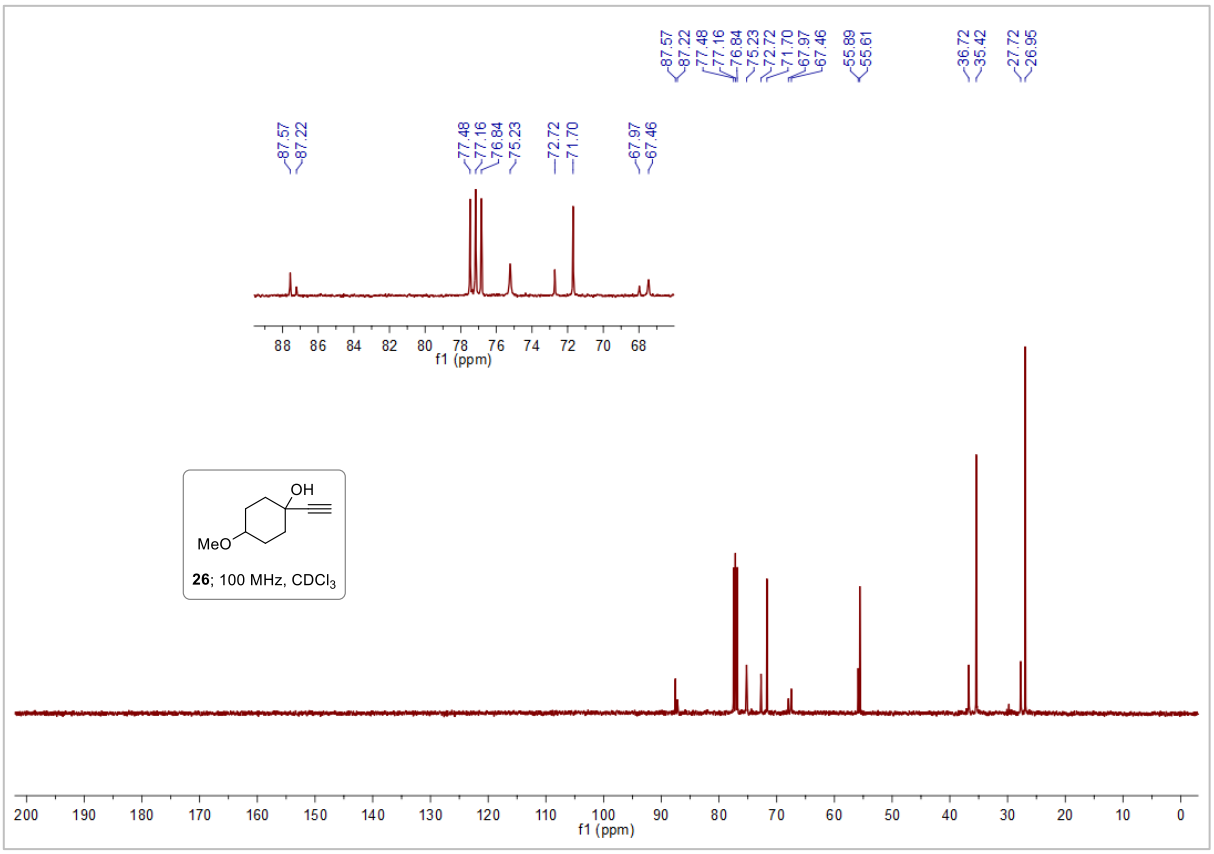
^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) of **9m**.



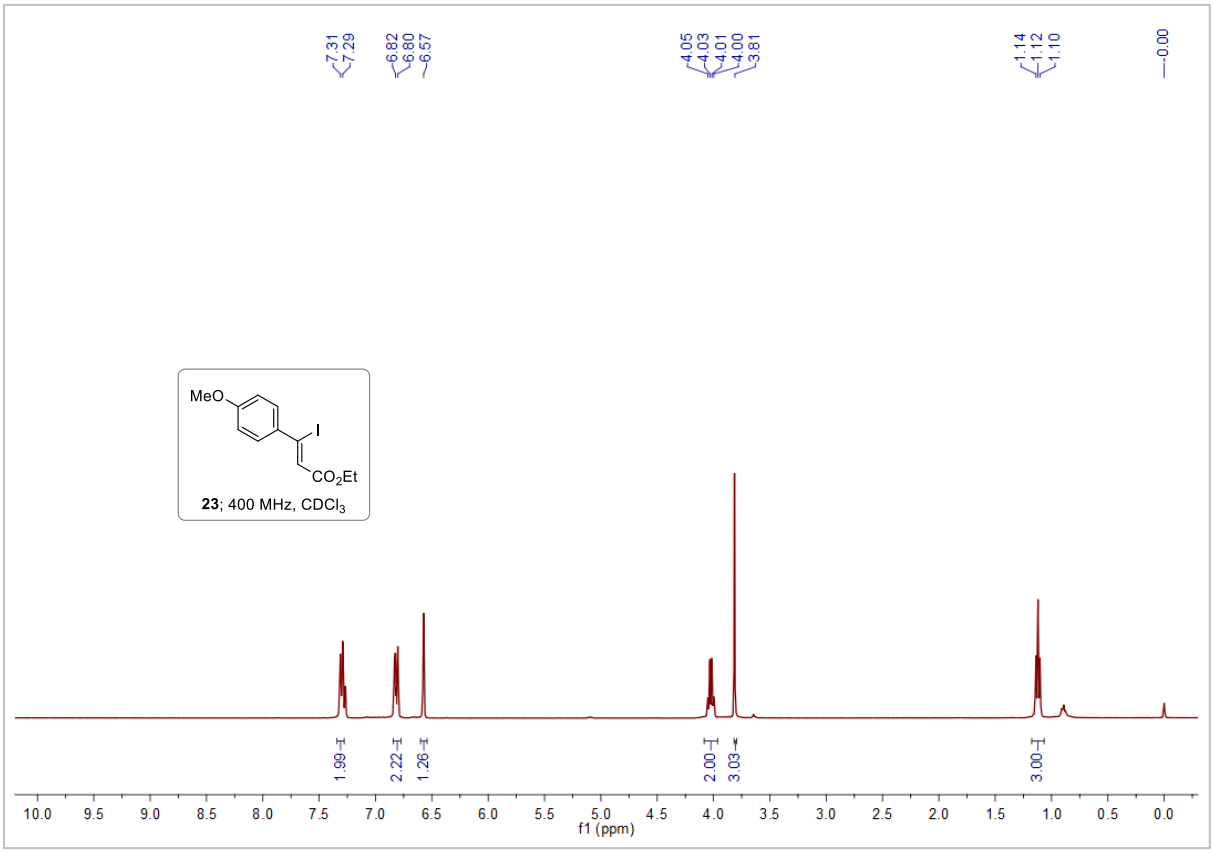


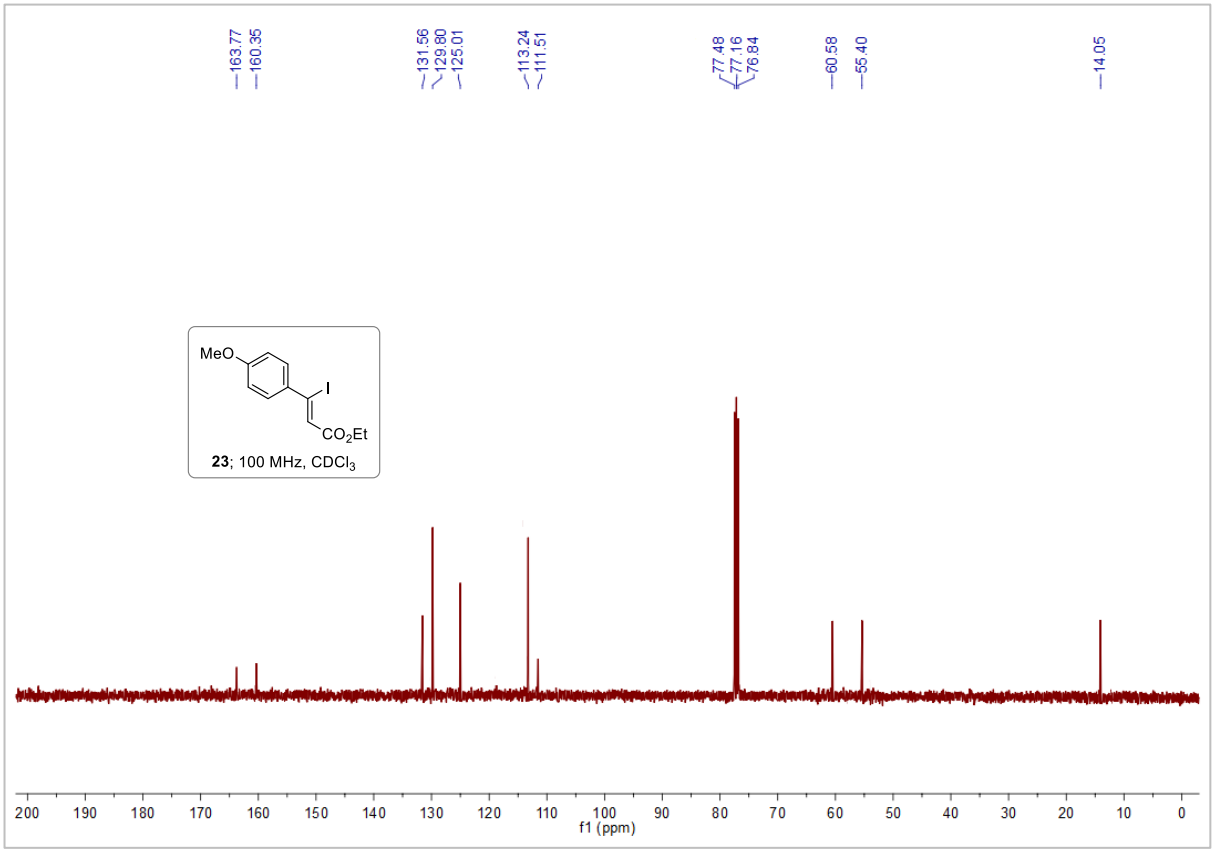
^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) of **26**.





^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) of **23**.





^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) of **28**.