Supporting Information

Effective Synthesis and Biological Evaluation of Functionalized 2,3-dihydrofuro[3,2-c]coumarins via Imidazole Catalyzed Green Multicomponent Approach

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General Information

All reactions were performed in standard glassware with no special precautions taken for the exclusionon moisture or air unless otherwise mentioned. All reagents were of reagent grade quality, purchased commercially from Sigma-Aldrich, Avara, and used without further purification. Products were purified by column chromatography on 200-400 mesh size silica gel using ethyl acetate (EtOAc) and hexane. TLC analyses were performed using 0.25 mm Merck silica gel plates 60 F254, and checked by UV light and stained with anisaldehyde stain. NMR spectra were recorded on Bruker High Performance Digital FT-NMR (Model: AVANCE III HD, AscendTM WB, 500 MHz Equipment control: Topspin 3.2 Features Standard operating procedure) and Bruker ALPHA (Eco-ATR) spectrometer by using $CDCl_3$ as a solvent and TMS is the internal reference. The HRMS data were collected using a 6545 LC/Q-TOF HRMS.

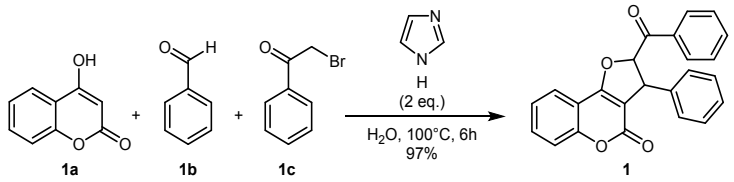
The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet,q = quartet, dd = doublet of doublet, ddd = doublet of a doublet of a doublet, dt = doublet of a triplet, m = multiplet, br = broad

General procedure for the synthesis of Functionalized 2,3-dihydrofuro[3,2-*c*]coumarins:

A mixture of 4-hydroxy coumarin **1a** (0.308 mmol) and aldehyde **1b** (0.308 mmol) in 5 mL water was stirred at 100°C for 10 min. Subsequently, 2-bromoacetophenone **1c** (0.308 mmol) and imidazole (0.616 mmol) were added and the mixture stirred at 100 °C for 6-8 h. After completion of the reaction (TLC), the reaction mixture was cooled to room temperature, and the product was extracted with EtOAc (2x10 mL). The organic layer was dried over anhydrous Na_2SO_4 and the solvent removed on a rotavapor under reduced pressure and purified by silica gel chromatography using ethyl acetate/hexane mixture to obtained desired product.

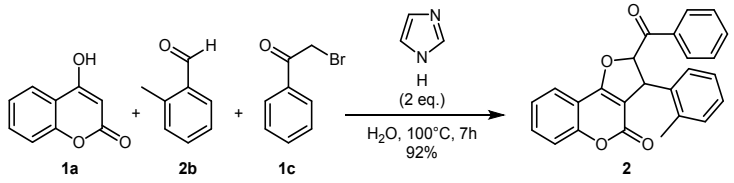
Synthesis of Compound 1-25

Synthesis of compound 1



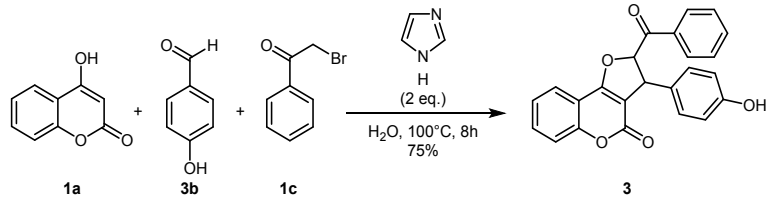
Following general procedure, compound **1** was obtained as a white solid (110 mg, 0.299 mmol, 97%); R*f* = 0.5 (EtOAc-hexane 1:1.5); **IR**: ν_{max}/cm^{-1}: 1220, 1652, 1718; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.90 (dd, *J* = 8.3, 1.0 Hz, 2H), 7.85 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.68 – 7.58 (m, 2H), 7.50 (t, *J* = 7.8 Hz, 2H), 7.41 – 7.29 (m, 7H), 6.18 (d, *J* = 4.9 Hz, 1H), 4.80 (d, *J* = 4.9 Hz, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 192.12, 166.41, 159.33, 155.41, 139.57, 134.48, 133.15, 132.96, 129.32, 129.12, 129.06, 128.21, 127.58, 124.20, 123.24, 117.07, 112.19, 105.37, 92.66, 49.37.

Synthesis of compound 2



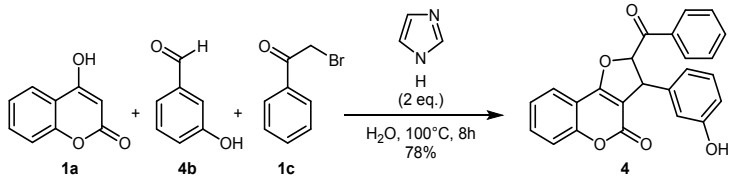
Following general procedure, compound **2** was obtained as a white powder (108 mg, 0.283 mmol, 92%); R*f* = 0.4 (EtOAc-hexane 1:2.3); **IR**: ν_{max}/cm^{-1}: 1024, 1220, 1558, 1652, 1699; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.92 (d, *J* = 7.4 Hz, 2H), 7.85 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.64 (ddd, *J* = 15.8, 11.8, 4.5 Hz, 2H), 7.51 (t, *J* = 7.8 Hz, 2H), 7.44 – 7.32 (m, 2H), 7.30 – 7.20 (m, 4H), 6.22 (d, *J* = 4.9 Hz, 1H), 5.14 (d, *J* = 4.9 Hz, 1H), 2.34 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 192.14, 165.95, 159.21, 155.32, 138.35, 136.37, 134.45, 133.33, 132.80, 130.86, 129.07, 128.99, 127.91, 127.19, 126.88, 124.12, 123.14, 117.05, 112.25, 106.43, 93.00, 44.85, 19.72.

Synthesis of compound 3



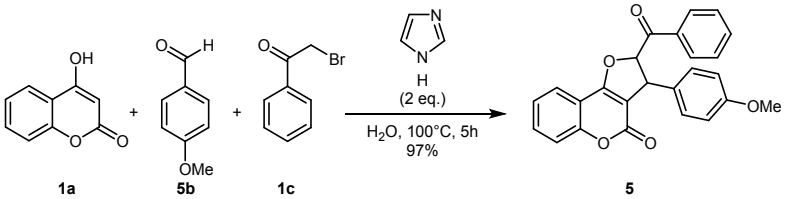
Following general procedure compound **3** was obtained as a white solid (89 mg, 0.231 mmol, 75%); R*f* = 0.3 (EtOAc-hexane 1:1); **IR**: ν_{max}/cm^{-1}: 1022, 1218, 1558, 1710; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.94 – 7.87 (m, 3H), 7.66 (ddd, *J* = 15.9, 11.1, 4.5 Hz, 2H), 7.55 – 7.51 (m, 2H), 7.44 (d, *J* = 8.4 Hz, 1H), 7.39 (dd, *J* = 11.0, 4.2 Hz, 1H), 7.14 (t, *J* = 5.8 Hz, 2H), 6.77 (t, *J* = 7.3 Hz, 2H), 6.17 (t, *J* = 6.2 Hz, 1H), 5.47 (s, 1H), 4.72 (d, *J* = 5.0 Hz, 1H); **^{13}C NMR** (126 MHz, DMSO-d_6) δ 193.68, 166.16, 158.72, 157.45, 155.14, 149.63, 142.34, 134.83, 133.84, 133.54, 130.30, 129.46, 129.14, 125.11, 123.47, 117.24, 116.11, 105.44, 92.70, 48.66; **HRMS:** m/z calcd for C_{24} H_{16} N O_5 [(M+H)+[-H_2O]$^+$: 367.0965; found: 367.0954, cal. [M+] $^+$ 384.0992; found: 384.1047, cal. [M+H+]$^+$ 385.1071; found: 385.1067**,** cal. [M+H+]$^+$ 387.1132; found: 387.1169,cal. (M+NH4)+ 402.1336; found: 402.1328, cal. (M+K)+ 423.0629; found: 423.0643.

Synthesis of compound 4



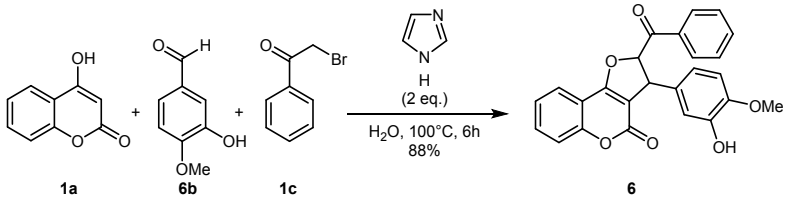
Following general procedure, compound **4** was obtained as a white amorphous solid (92 mg, 0.240 mmol, 78%); R*f* = 0.3 (EtOAc-hexane 1:1.5); **IR**: ν_{max}/cm^{-1}: 931, 1216, 1558, 1699; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.98 – 7.92 (m, 2H), 7.87 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.66 (ddd, *J* = 16.2, 11.3, 4.5 Hz, 2H), 7.53 (t, *J* = 7.8 Hz, 2H), 7.43 (d, *J* = 8.3 Hz, 1H), 7.38 (t, *J* = 7.6 Hz, 1H), 7.24 (t, *J* = 7.9 Hz, 1H), 6.86 (d, *J* = 7.8 Hz, 1H), 6.81 – 6.73 (m, 2H), 6.19 (d, *J* = 4.9 Hz, 1H), 5.33 (s, 1H), 4.76 (d, *J* = 4.8 Hz, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 192.21, 166.99, 159.95, 156.68, 155.48, 141.13, 134.63, 133.22, 133.19, 130.61, 129.27, 129.22, 124.46, 123.42, 119.51, 117.23, 115.45, 114.84, 112.28, 105.23, 92.69, 49.25; **HRMS:** m/z calcd for $C_{24}H_{16}O_5$ [M]$^+$: 384.0992; found: 384.0964, cal. [M+H] $^+$ 385.1071; found: 385.1067, cal. [M+K]$^+$ 423.0629; found: 423.0623**,** cal. [M+K]$^+$ 424.0663; found: 424.0658.

Synthesis of compound 5



Following general procedure, compound **5** was obtained as a pale yellow solid(119 mg, 0.299 mmol, 97%); R*f* = 0.6 (EtOAc-hexane 1:4); **IR**: ν_{max}/cm^{-1}: 1218, 1697; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.90 (dd, J = 8.3, 1.1 Hz, 2H), 7.86 (dd, J = 7.8, 1.5 Hz, 1H), 7.70 – 7.58 (m, 2H), 7.50 (t, J = 7.8 Hz, 2H), 7.42 – 7.31 (m, 2H), 7.25 – 7.20 (m, 2H), 6.91 (d, J = 8.7 Hz, 2H), 6.15 (d, J = 4.9 Hz, 1H), 4.72 (d, J = 4.9 Hz, 1H), 3.81 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 192.34, 166.34, 159.56, 159.48, 155.53, 134.55, 133.30, 132.99, 131.73, 129.20, 129.16, 128.79, 124.27, 123.34, 117.19, 114.81, 112.37, 105.63, 92.91, 55.48, 49.02.

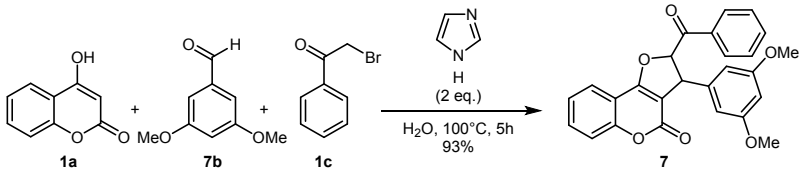
Synthesis of compound 6



1a 6b 1c 6

Following general procedure, compound **6** was obtained as a white solid (112 mg, 0.271 mmol, 88%); R*f* = 0.4; (EtOAc-hexane 1:2.3**)**; **IR**: ν_{max}/cm^{-1}: 1030, 1218, 1697; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.95 – 7.89 (m, 2H), 7.85 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.67 – 7.59 (m, 2H), 7.51 (t, *J* = 7.8 Hz, 2H), 7.41 – 7.33 (m, 2H), 6.82 (ddd, *J* = 10.2, 6.9, 2.0 Hz, 3H), 6.14 (d, *J* = 4.8 Hz, 1H), 5.67 (s, 1H), 4.67 (d, *J* = 4.8 Hz, 1H), 3.89 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 192.31, 166.42, 159.51, 155.52, 146.61, 146.48, 134.54, 133.26, 133.00, 132.89, 129.22, 129.16, 124.28, 123.34, 119.78, 117.17, 113.25, 112.36, 111.07, 105.52, 92.81, 56.14, 49.19; **HRMS:** m/z calcd for $C_{25}H_{18}O_6$ M+[-H_2O] : 396.0992; found: 396.0964, cal. [M+] $^+$ 414.1098; found: 414.1045, cal. $[M+H]^+$ 415.1176; found: 415.1204**,** cal. $[M+Na]^+$ 437.0996; found: 437.1058, cal. $[M+Na]^+$ 438.1029; found: 438.1053.

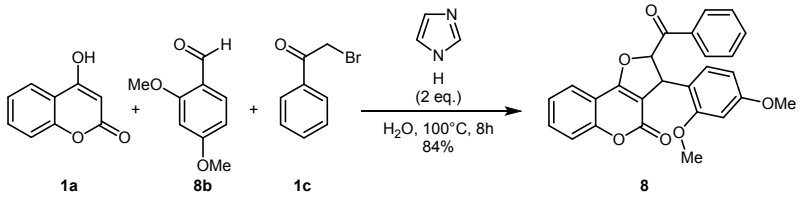
Synthesis of compound 7



1a 7b 1c 7

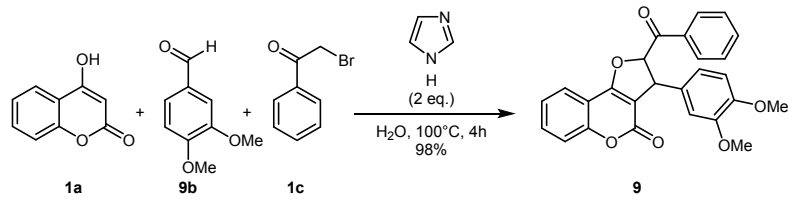
Following general procedure compound **7** was obtained as a white solid (123 mg, 0.286 mmol, 93%); R*f* = 0.4 (EtOAc-hexane 1:2.3); **IR**: ν_{max}/cm^{-1}: 1050, 1218, 1430, 1716; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.96 – 7.91 (m, 2H), 7.83 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.63 (ddd, *J* = 15.8, 11.8, 4.5 Hz, 2H), 7.51 (t, *J* = 7.8 Hz, 2H), 7.40 (d, *J* = 8.4 Hz, 1H), 7.35 (t, *J* = 7.6 Hz, 1H), 6.42 (s, 3H), 6.16 (d, *J* = 4.9 Hz, 1H), 4.72 (d, *J* = 4.9 Hz, 1H), 3.76 (s, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 192.23, 166.64, 161.54, 159.44, 155.54, 142.05, 134.60, 133.30, 133.09, 129.33, 129.14, 124.29, 123.35, 117.21, 112.29, 105.88, 105.10, 99.85, 92.58, 55.54, 49.56; **HRMS:** m/z calcd for $C_{26}H_{20}O_6$ $[M+H]^+$ [-H_2O]: 411.1276; found: 411.1227, $(M+NH_4)$+[-H_2O]: 428.1471; found

Synthesis of compound 8



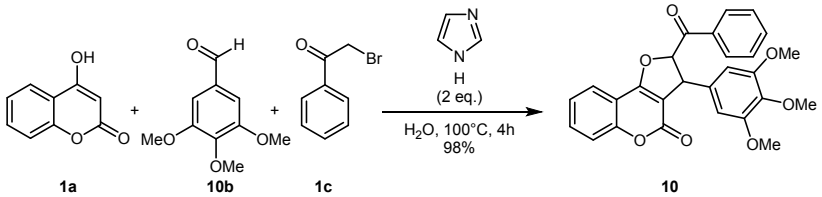
Following general procedure, compound **8** was obtained as a light yellow solid with (111 mg, 0.258 mmol, 84%); R*f* = 0.4 (EtOAc-hexane 1:4); **IR**: ν_{max}/cm^{-1}: 1054, 1454, 1710; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.92 (d, *J* = 7.4 Hz, 2H), 7.80 (dd, *J* = 7.8, 1.1 Hz, 1H), 7.61 (ddd, *J* = 17.2, 11.7, 4.4 Hz, 2H), 7.49 (t, *J* = 7.8 Hz, 2H), 7.41 (d, *J* = 8.4 Hz, 1H), 7.32 (t, *J* = 7.6 Hz, 1H), 7.07 (d, *J* = 8.3 Hz, 1H), 6.49 – 6.43 (m, 2H), 6.08 (d, *J* = 5.5 Hz, 1H), 5.08 (d, *J* = 5.4 Hz, 1H), 3.80 (s, 3H), 3.54 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 193.10, 166.94, 160.85, 159.77, 158.05, 155.47, 134.19, 134.09, 132.74, 129.58, 129.22, 128.90, 124.12, 123.17, 119.77, 117.11, 112.53, 104.76, 104.07, 99.14, 91.20, 55.56, 55.28, 44.21; **HRMS:** m/z calcd for $C_{26}H_{20}O_6$ $[(M+NH_4)+[-H_2O]^+$ 428.1492; found: 428.1504, cal. $[(M+Na)+[-H_2O]^+$ 433.1046; found: 433.1019.

Synthesis of compound 9



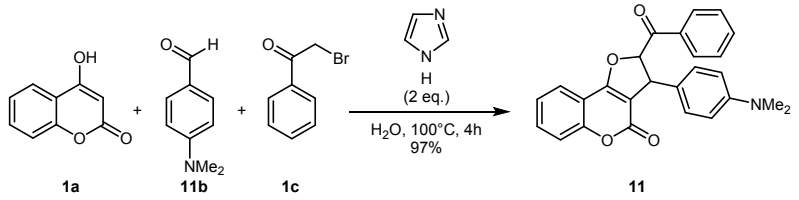
Following general procedure, compound **9** was obtained as a light yellow solid with (129 mg, 0.302 mmol, 98%); R*f* = 0.3 (EtOAc-hexane 1:1.5); **IR**: ν_{max}/cm^{-1}: 933, 1031, 1216, 1652, 1718; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.93 – 7.89 (m, 2H), 7.86 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.64 (ddd, *J* = 15.8, 11.8, 4.5 Hz, 2H), 7.50 (t, *J* = 7.8 Hz, 2H), 7.41 (d, *J* = 8.3 Hz, 1H), 7.38 – 7.33 (m, 1H), 6.90 – 6.83 (m, 2H), 6.77 (d, *J* = 1.8 Hz, 1H), 6.16 (d, *J* = 5.2 Hz, 1H), 4.73 (d, *J* = 5.2 Hz, 1H), 3.88 (s, 3H), 3.83 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 192.38, 166.43, 159.50, 155.53, 149.57, 149.03, 134.60, 133.32, 133.06, 132.07, 129.29, 129.13, 124.30, 123.37, 119.73, 117.22, 112.33, 111.86, 110.86, 105.26, 92.82, 56.10, 56.10, 49.40; **HRMS:** m/z calcd for $C_{27}H_{22}O_7$ $[M]^+$: 458.1397; found: 458.1360, cal. $[M+NH_4]^+$ 476.1642; found: 476.1704, cal. $[M+K]^+$ 497.1020; found: 497.0997

Synthesis of compound 10



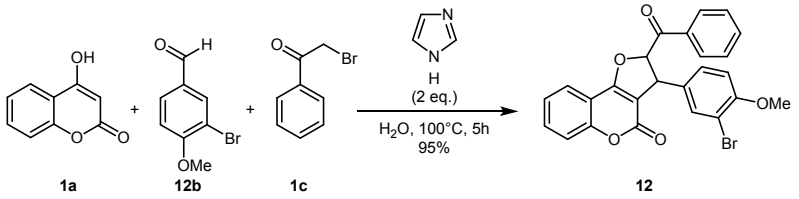
Following general procedure, compound **10** was obtained as a white solid (138 mg, 0.302 mmol, 98%); R*f* = 0.3 (EtOAc-Hexane 1:1.5); **IR**: ν_{max}/cm^{-1}: 1054, 1220, 1652, 1710; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.93 (d, *J* = 7.5 Hz, 2H), 7.86 (d, *J* = 7.8 Hz, 1H), 7.65 (dt, *J* = 16.2, 7.3 Hz, 2H), 7.52 (t, *J* = 7.8 Hz, 2H), 7.42 (d, *J* = 8.4 Hz, 1H), 7.37 (t, *J* = 7.6 Hz, 1H), 6.45 (s, 2H), 6.14 (d, *J* = 5.4 Hz, 1H), 4.75 (d, *J* = 5.3 Hz, 1H), 3.84 (s, 3H), 3.80 (s, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 192.30, 166.67, 159.50, 155.57, 153.97, 137.91, 135.17, 134.67, 133.38, 133.18, 129.41, 129.12, 124.35, 123.42, 117.27, 112.26, 104.81, 104.61, 92.69, 60.97, 56.33, 49.83; **HRMS:** m/z calcd for $C_{27}H_{22}BrO_7$ $[M]^+$ 458.1360; found: 458.1339, cal. $[M+H]^+$ 459.1438; found: 459.1438, cal. $[M+NH_4]^+$ 476.1704; found: 476.1713**,** Cal. $[M+NH_4]^+$ 477.1737; found: 477.1742, cal. $[M+Na]^+$ 481.1258; found: 481.1257, cal. $[M+Na]^+$ 483.1319; found: 483.1318, cal. $[M+K]^+$ 497.0997; found: 497.0995, cal. $[M+K]^+$ 498.1031; found: 498.1029.

Synthesis of compound 11



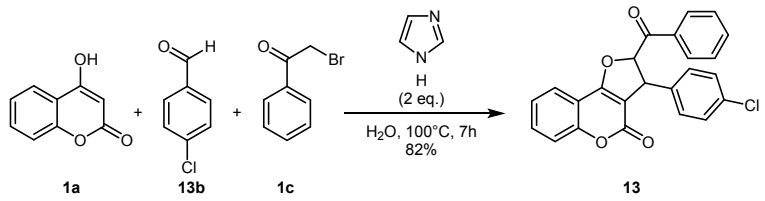
Following general procedure, compound **11** was obtained as a yellow solid (123 mg, 0.298 mmol, 97%); R*f* = 0.3 (EtOAc-hexane 1:3); **IR**: ν_{max}/cm^{-1}: 945, 1159, 1218, 1540, 1716; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.90 (d, *J* = 7.3 Hz, 2H), 7.87 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.65 (t, *J* = 7.5 Hz, 1H), 7.60 (dd, *J* = 11.5, 4.3 Hz, 1H), 7.50 (t, *J* = 7.8 Hz, 2H), 7.37 (dd, *J* = 17.2, 8.1 Hz, 2H), 7.16 (d, *J* = 8.7 Hz, 2H), 6.72 (d, *J* = 8.7 Hz, 2H), 6.16 (d, *J* = 4.8 Hz, 1H), 4.64 (d, *J* = 4.8 Hz, 1H), 2.95 (s, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 191.00, 165.09, 162.66, 153.54, 135.34, 134.70, 133.95, 132.86, 130.13, 129.32, 129.31, 129.24, 128.68, 128.07, 125.41, 124.27, 123.48, 116.94, 115.51, 91.53, 70.55.

Synthesis of compound 12



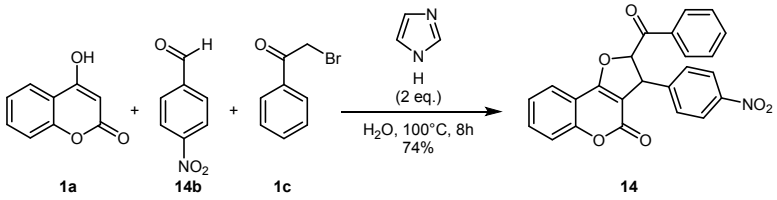
Following general procedure, compound **12** was obtained as a white solid (140 mg, 0.293 mmol, 95%); R*f* = 0.4 (EtOAc-hexane 1:2.3); **IR**: ν_{max}/cm^{-1}: 945, 1159, 1218, 1716 **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.93 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.68 – 7.63 (m, 1H), 7.61 – 7.54 (m, 3H), 7.45 – 7.37 (m, 4H), 6.94 (d, *J* = 2.2 Hz, 1H), 6.77 (dd, *J* = 8.5, 2.2 Hz, 1H), 6.60 (d, *J* = 10.4 Hz, 1H), 6.55 (d, *J* = 8.5 Hz, 1H), 5.01 (d, *J* = 10.4 Hz, 1H), 3.74 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 192.57, 167.19, 159.26, 155.51, 155.48, 135.38, 134.16, 133.79, 133.35, 128.98, 128.66, 127.82, 124.45, 123.68, 117.27, 112.16, 111.62, 111.55, 105.07, 90.14, 56.28, 49.17, 37.24; **HRMS:** m/z calcd for $C_{25}H_{17}BrO_5$ (M+H)+: 477.0332; found: 477.0329, cal. $[M+H]^+$ 479.0315; found: 479.0309, cal. $[M+H]^+$ 480.0347; found: 480.0343**,** cal. $[M+H]^+$ 481.0375; found: 481.0384, cal. $[M+H]^+$ 482.0402; found: 482.0415, cal. $[M+NH_4]^+$ 496.0581; found: 496.0613, cal. $[M+Na]^+$ 500.0185; found: 00.0183, cal. $[M+Na]^+$ 501.0135; found: 501.0128, cal. $[M+K]^+$ 516.9874; found: 516.9867, cal. $[M+K]^+$ 518.9885; found: 518.9889.

Synthesis of compound 13



Following general procedure, compound **13** was obtained as a pale pink solid (102 mg, 0.253 mmol, 82%); R*f* = 0.4 (EtOAc-hexane 1:3); **IR**: ν_{max}/cm^{-1}: 771, 933, 1093, 1218, 1716; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.93 – 7.88 (m, 2H), 7.84 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.70 – 7.60 (m, 2H), 7.52 (t, *J* = 7.9 Hz, 2H), 7.41 (d, *J* = 8.1 Hz, 1H), 7.38 – 7.33 (m, 3H), 7.26 – 7.23 (m, 2H), 6.12 (d, *J* = 5.1 Hz, 1H), 4.81 (d, *J* = 5.1 Hz, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 191.97, 166.61, 159.35, 155.57, 138.17, 134.71, 134.25, 133.25, 129.63, 129.25, 129.24, 129.23, 129.10, 124.39, 123.37, 117.27, 112.19, 105.09, 92.55, 48.80.

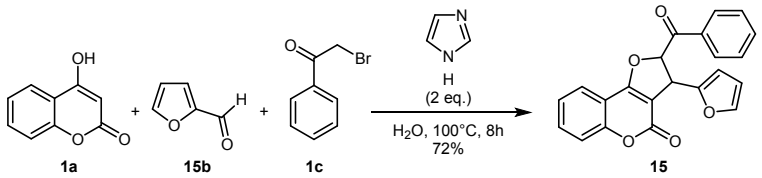
Synthesis of compound 14



Following general procedure, compound **14** was obtained as a dark yellow solid (99 mg, 0.240 mmol, 74%); R*f* = 0.3 (EtOAc-hexane 1:4); **IR**: ν_{max}/cm^{-1}: 773, 980, 1093, 1218, 1750; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.27 – 8.21 (m, 2H), 7.94 (dd, *J* = 8.3, 1.1 Hz, 2H), 7.82 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.71 – 7.62 (m, 2H), 7.56 – 7.48 (m, 4H), 7.43 – 7.34 (m, 2H), 6.13 (d, *J* = 5.4 Hz, 1H), 5.07 (d, *J* = 5.4 Hz, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 191.52, 166.79, 159.20, 155.61, 147.85, 146.77, 134.88, 133.56, 133.32, 129.31, 129.30, 128.85, 124.64, 124.53, 123.38, 117.34, 111.96, 104.46, 92.09,

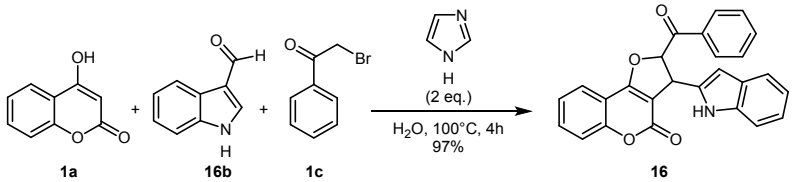
48.52; **HRMS:** m/z calcd for $C_{24}H_{15}NO_6$ cal.$[M+H]^+$: 414.0972, found: 414.0970.

Synthesis of compound 15



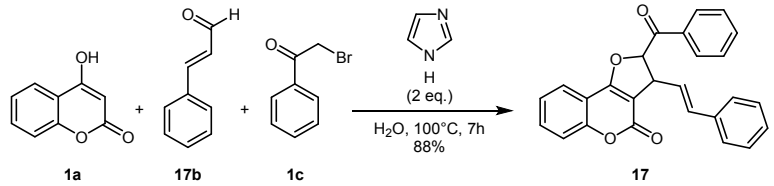
Following general procedure, compound **15** was obtained as a light yellow solid (74 mg, 0.222 mmol, 72%); R*f* = 0.3 (EtOAc-hexane 1:4;); **IR**: ν_{max}/cm^{-1}: 1054, 1220, 1454, 1695; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.02 (dd, *J* = 8.5, 1.3 Hz, 2H), 7.81 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.70 – 7.66 (m, 1H), 7.64 – 7.59 (m, 1H), 7.57 – 7.53 (m, 2H), 7.43 – 7.39 (m, 2H), 7.36 – 7.32 (m, 1H), 6.39 (dd, *J* = 3.3, 1.9 Hz, 1H), 6.35 – 6.33 (m, 2H), 5.01 (d, *J* = 4.8 Hz, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 191.85, 167.03, 159.39, 155.53, 150.95, 142.96, 134.66, 133.23, 129.31, 129.21, 124.32, 123.37, 117.21, 112.29, 111.12, 108.44, 102.45, 95.19, 89.26, 42.84; **HRMS:** m/z calcd for $C_{22}H_{14}N\,O_5$ [(M+H)+[-H2O]$^+$: 341.0808; found: 341.0798, cal. $[M]^+$ 358.0836; found: 358.0889, cal. [(M+NH4)+[-H2O]$^+$ 358.1074; found: 358.1113**,** cal. $[M+H]^+$ 359.0914; found 359.0914, Cal. $[M+H]^+$ 361.097; found: 361.0975, Cal. $[M+H]^+$ 362.1002; found: 362.1016, Cal. $[M+NH4]^+$ 376.1179; found: 376.1195, Cal. $[M+K+[-H_2O]^+$ 434.0870; found: 434.0849, Cal. . $[M+Na]^+$ 381.0733; found: 381.0728, Cal. $[M+Na]^+$ 383.0794; found: 383.0800, Cal. $[M+K]^+$ 397.0473; found: 397.0449.

Synthesis of compound 16



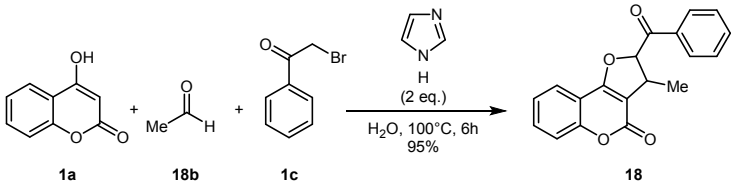
Following general procedure, compound **16** was obtained as a yellow solid (122 mg, 0.299 mmol,97%); R*f* = 0.3 (EtOAc-hexane 1:3); **IR**: ν_{max}/cm^{-1}: 931, 1033, 1218, 1558, 1699; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.84 (s, 1H), 7.97 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.88 (dd, *J* = 8.4, 1.2 Hz, 2H), 7.67 – 7.58 (m, 2H), 7.45 – 7.36 (m, 6H), 7.16 – 7.10 (m, 1H), 7.03 – 6.97 (m, 1H), 6.85 (s, 1H), 6.39 (d, *J* = 5.0 Hz, 1H), 5.01 (d, *J* = 5.0 Hz, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 192.76, 166.53, 160.22, 155.41, 137.26, 134.45, 133.23, 133.05, 129.27, 129.05, 125.09, 124.44, 124.16, 123.50, 122.40, 119.95, 118.34, 117.16, 112.44, 112.36, 112.22, 104.39, 91.22, 42.52; **HRMS:** m/z calcd for $C_{26}H_{17}NO_4$ $[M+H]^+$: 408.1230; found: 408.1225, cal. $[M+H]^+$ 409.1263; found: 409.1258, cal. $[M+Na]^+$ 430.1050; found: 430.1041**,** cal. $[M+Na]^+$ 432.1112; found: 432.1108.

Synthesis of compound 17



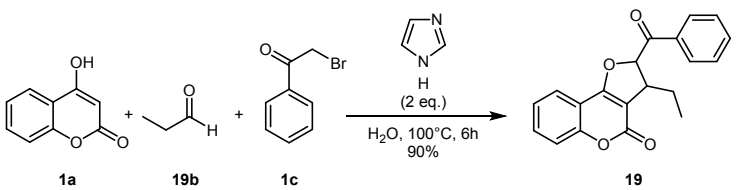
Following general procedure, compound **17** was obtained as a light yellow solid (107 mg, 0.271 mmol, 88%); R*f* = 0.3 (EtOAc-hexane 1:1); **IR**: ν_{max}/cm^{-1}: 931, 1031, 1218, 1718; 771, 931, 1031, 1218, 1718; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.06 – 7.99 (m, 2H), 7.86 – 7.78 (m, 1H), 7.68 (t, *J* = 7.5 Hz, 1H), 7.63 – 7.59 (m, 1H), 7.54 (t, *J* = 7.8 Hz, 2H), 7.41 (d, *J* = 7.9 Hz, 3H), 7.33 (td, *J* = 7.7, 6.0 Hz, 3H), 7.28 (d, *J* = 7.3 Hz, 1H), 6.68 (d, *J* = 15.7 Hz, 1H), 6.39 (dd, *J* = 15.7, 8.4 Hz, 1H), 6.12 (d, *J* = 4.8 Hz, 1H), 4.45 (dd, *J* = 8.3, 4.8 Hz, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 192.27, 166.66, 159.66, 155.48, 136.19, 134.61, 134.14, 133.34, 133.09, 129.24, 129.15, 128.78, 128.32, 126.84, 125.96, 124.29, 123.28, 117.18, 112.41, 103.87, 90.33, 47.44; **HRMS:** m/z calcd for $C_{26}H_{18}N\ O_4$ $[M+H]^+$: 395.1278; found: 395.1273, cal. $[M+H]^+$ 396.1312; found: 396.1308, cal. $[M+H]^+$ 397.1341; found: 397.1337**,** cal. $[M+Na]^+$ 417.1097; found: 417.1090, Cal. $[M+Na]^+$ 418.1131; found: 418.1125, Cal. $[M+Na]^+$ 419.1161; found: 419.1167, Cal. $[M+K]^+$ 433.0837; found: 433.0853, Cal. $[M+K]^+$ 434.0870; found: 434.0849.

Synthesis of compound 18



Following general procedure, compound **18** as a light yellow solid (90 mg, 0.293 mmol, 95%); R*f* = 0.5 (EtOAc-hexane 1:9); **IR**: ν_{max}/cm^{-1}: 734, 1218, 1583, 1728; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.05 – 7.95 (m, 2H), 7.75 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.67 (t, *J* = 7.5 Hz, 1H), 7.62 – 7.51 (m, 3H), 7.39 (d, *J* = 8.3 Hz, 1H), 7.34 – 7.29 (m, 1H), 5.83 (d, *J* = 5.4 Hz, 1H), 3.86 – 3.73 (m, 1H), 1.61 (d, *J* = 6.8 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 191.00, 165.09, 162.67, 153.54, 134.70, 133.95, 132.86, 129.31, 128.07, 125.41, 124.27, 123.48, 116.94, 115.51, 91.52, 70.55, 14.27.

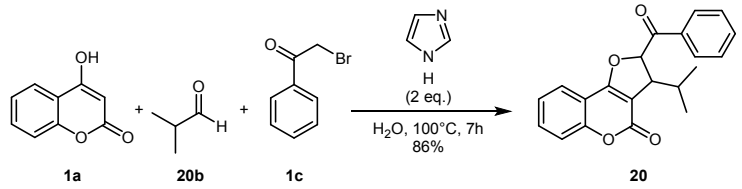
Synthesis of compound 19



Following general procedure, compound **19** as a light yellow solid (88.88mg, 0.2774mmol, 90%); R*f* = 0.5 (EtOAc-hexane 1:2.3); **IR**: ν_{max}/cm^{-1}: 1218, 1558, 1652, 1699, 2832; **^{1}H NMR**

(500 MHz, $CDCl_3$) δ 8.00 (dd, J = 8.2, 1.0 Hz, 2H), 7.71 (dd, J = 7.8, 1.5 Hz, 1H), 7.65 (dd, J = 10.7, 4.2 Hz, 1H), 7.55 (ddd, J = 15.6, 11.4, 4.6 Hz, 3H), 7.37 (d, J = 8.4 Hz, 1H), 7.30 – 7.26 (m, 1H), 5.92 (d, J = 5.0 Hz, 1H), 3.82 (dt, J = 6.9, 4.6 Hz, 1H), 2.12 – 1.88 (m, 2H), 1.01 (t, J = 7.5 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 193.49, 166.23, 160.11, 155.20, 134.28, 133.90, 132.70, 129.09, 129.01, 124.13, 122.96, 116.98, 112.28, 104.50, 89.34, 44.71, 25.02, 10.31.

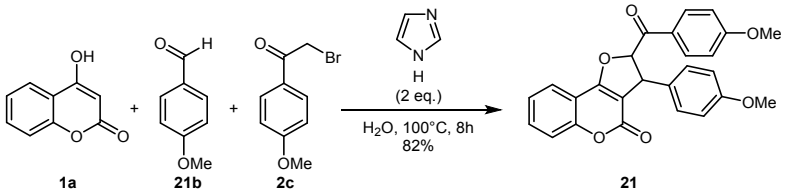
Synthesis of compound 20



1a 20b 1c 20

Following general procedure, compound **20** was obtained as a White solid (89 mg, 0.265 mmol,86%); R*f* = 0.3 (EtOAc-hexane 1:3); **IR**: ν_{max}/cm^{-1}: 931, 1033, 1218, 1541, 1699, 2843; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.05 – 8.00 (m, 2H), 7.66 (dd, *J* = 15.8, 7.7 Hz, 2H), 7.56 (dt, *J* = 15.4, 4.5 Hz, 3H), 7.38 (d, *J* = 8.4 Hz, 1H), 7.28 (t, *J* = 7.6 Hz, 1H), 5.94 (d, *J* = 4.6 Hz, 1H), 3.88 (d, *J* = 3.8 Hz, 1H), 2.50 (ddd, *J* = 10.2, 6.9, 3.4 Hz, 1H), 0.99 (t, *J* = 6.7 Hz, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 193.91, 166.30, 160.27, 155.25, 134.22, 134.15, 132.73, 129.23, 129.06, 124.13, 122.96, 117.04, 112.24, 104.08, 86.74, 49.23, 20.09, 18.18; **HRMS:** m/z calcd for $C_{21}H_{18}O_4$ $[M]^+$: 334.1200; found: 334.118, cal. $[M+H]^+$ 335.1278; found: 335.1311, cal. $[M+H]^+$ 336.1312; found: 336.1283**,** cal. $[M+NH_4]^+$ 352.1543; found: 352.1499.

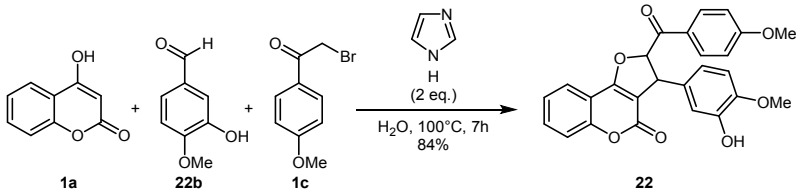
Synthesis of compound 21



1a 21b 2c 21

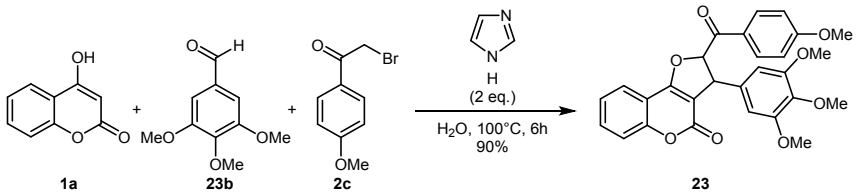
Following general procedure, compound **21**was obtained as a light-yellow solid (108 mg, 0.252 mmol, 82%); R*f* = 0.3 (EtOAc-hexane 1:1); **IR**: ν_{max}/cm^{-1}: 1218, 1558, 1652, 2826; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.86 (ddd, *J* = 11.0, 7.4, 1.7 Hz, 3H), 7.60 (ddd, *J* = 8.7, 7.5, 1.6 Hz, 1H), 7.39 (d, *J* = 8.2 Hz, 1H), 7.35 – 7.33 (m, 1H), 7.23 (d, *J* = 8.7 Hz, 2H), 6.96 (d, *J* = 8.9 Hz, 2H), 6.91 (d, *J* = 8.7 Hz, 2H), 6.10 (d, *J* = 5.0 Hz, 1H), 4.72 (d, *J* = 5.0 Hz, 1H), 3.90 (s, 3H), 3.81 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 190.85, 166.41, 164.64, 159.54, 155.54, 132.93, 132.65, 131.90, 131.57, 128.83, 126.22, 124.23, 123.35, 117.17, 114.79, 114.41, 112.44, 105.67, 92.76, 55.76, 55.48, 49.21.

Synthesis of compound 22



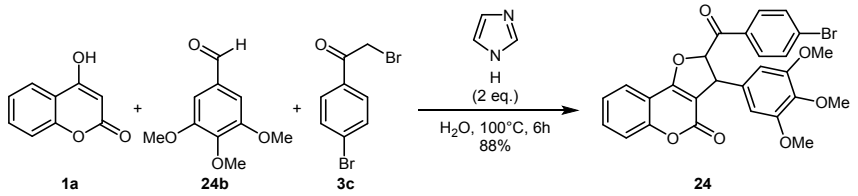
Following general procedure, compound **22** was obtained as a light yellow solid (115 mg, 0.258 mmol, 84%); R*f* = 0.3 (EtOAc-hexane 1:1); **IR**: ν_{max}/cm^{-1}: 931, 1033, 1215, 1670; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.91 – 7.86 (m, 2H), 7.84 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.63 – 7.57 (m, 1H), 7.39 (d, *J* = 8.4 Hz, 1H), 7.36 – 7.32 (m, 1H), 6.96 (d, *J* = 8.9 Hz, 2H), 6.82 (ddd, *J* = 17.3, 8.2, 2.0 Hz, 3H), 6.10 (d, *J* = 4.9 Hz, 1H), 5.70 (s, 1H), 4.67 (d, *J* = 4.9 Hz, 1H), 3.89 (d, *J* = 4.3 Hz, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 190.81, 166.47, 164.61, 159.57, 155.49, 146.56, 146.44, 133.03, 132.93, 131.56, 126.15, 124.23, 123.34, 119.76, 117.13, 114.39, 113.31, 112.39, 111.06, 105.55, 92.64, 56.12, 55.75, 49.36.

Synthesis of compound 23



Following general procedure, compound **23** was obtained as a light yellow solid (135 mg, 0.277 mmol, 90%); R*f* = 0.3 (EtOAc-hexane 1:1); **IR**: ν_{max}/cm^{-1}: 952, 1218, 1558, 1652; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.94 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.65 (ddd, *J* = 8.7, 7.4, 1.6 Hz, 1H), 7.62 – 7.58 (m, 2H), 7.44 (d, *J* = 8.4 Hz, 1H), 7.42 – 7.37 (m, 1H), 6.86 – 6.82 (m, 2H), 6.57 (d, *J* = 10.7 Hz, 1H), 6.06 (s, 2H), 5.02 (d, *J* = 10.7 Hz, 1H), 3.84 (s, 3H), 3.68 (s, 3H), 3.58 (s, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 191.03, 167.35, 164.07, 159.47, 155.47, 152.92, 133.25, 130.81, 130.33, 128.66, 124.39, 123.76, 117.25, 113.93, 112.27, 106.15, 104.96, 90.05, 60.75, 56.03, 55.72, 50.82, 32.08.

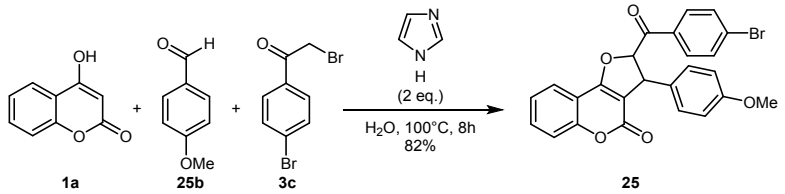
Synthesis of compound 24



Following general procedure, compound **24** was obtained as a light yellow solid (145 mg, 0.271mmol, 88%); R*f* = 0.3 (EtOAc-hexane 1:1); **IR**: ν_{max}/cm^{-1}: 1130, 1220, 1652, 1718; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.82 – 7.79 (m, 2H), 7.68 – 7.65 (m, 2H), 7.56 – 7.51 (m, 1H), 7.42

(d, *J* = 8.1 Hz, 1H), 7.38 – 7.33 (m, 2H), 6.46 (s, 2H), 6.06 (d, *J* = 5.5 Hz, 1H), 4.80 (d, *J* = 5.5 Hz, 1H), 3.84 (s, 3H), 3.81 (d, *J* = 4.3 Hz, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 191.44, 166.36, 159.39, 155.55, 154.02, 135.00, 133.25, 132.65, 132.50, 132.21, 130.83, 130.16, 128.59, 124.39, 123.32, 117.30, 112.17, 104.60, 92.62, 60.97, 56.37, 49.54.

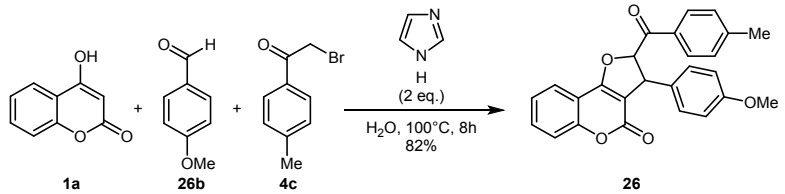
Synthesis of compound 25



1a **25b** **3c** **25**

Following general procedure, **25** compound was obtained as a light yellow solid (120 mg, 0.252 mmol, 82%); R*f* = 0.3 (EtOAc-hexane 1:1); **IR**: ν_{max}/cm^{-1}: 1218, 1652, 1718, 2931; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.82 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.80 – 7.74 (m, 2H), 7.67 – 7.59 (m, 3H), 7.39 (d, *J* = 8.2 Hz, 1H), 7.38 – 7.32 (m, 1H), 7.22 (d, *J* = 8.7 Hz, 2H), 6.91 (d, *J* = 8.7 Hz, 2H), 6.08 (d, *J* = 5.1 Hz, 1H), 4.74 (d, *J* = 5.1 Hz, 1H), 3.81 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 191.46, 166.12, 159.62, 159.37, 155.50, 133.06, 132.53, 132.06, 131.49, 130.62, 130.03, 128.78, 124.30, 123.26, 117.21, 114.86, 112.26, 105.55, 92.79, 55.48, 48.85.

Synthesis of compound 26



1a **26b** **4c** **26**

Following general procedure, **26** compound was obtained as a light yellow solid (121 mg, 0.252 mmol, 95%); R*f* = 0.4 (EtOAc-hexane 2:8); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.85 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.79 (d, *J* = 8.2 Hz, 2H), 7.63 – 7.57 (m, 1H), 7.39 (d, *J* = 8.3 Hz, 1H), 7.34 (dd, *J* = 11.7, 4.2 Hz, 1H), 7.29 (d, *J* = 8.1 Hz, 2H), 7.25 – 7.19 (m, 2H), 6.90 (d, *J* = 8.7 Hz, 2H), 6.12 (d, *J* = 5.0 Hz, 1H), 4.71 (d, *J* = 4.9 Hz, 1H), 3.81 (s, 3H), 2.44 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 191.92, 166.38, 159.48, 155.47, 145.68, 132.92, 132.89, 131.79, 130.70, 129.83, 129.27, 128.77, 124.22, 123.32, 117.12, 114.74, 112.36, 105.59, 92.82, 55.43, 49.07, 21.94; **HRMS-ESI**: m/z calcd for $C_{26}H_{20}O_5$ [M^+]: 412.1305; found: 412.1258.

Materials and Methods:

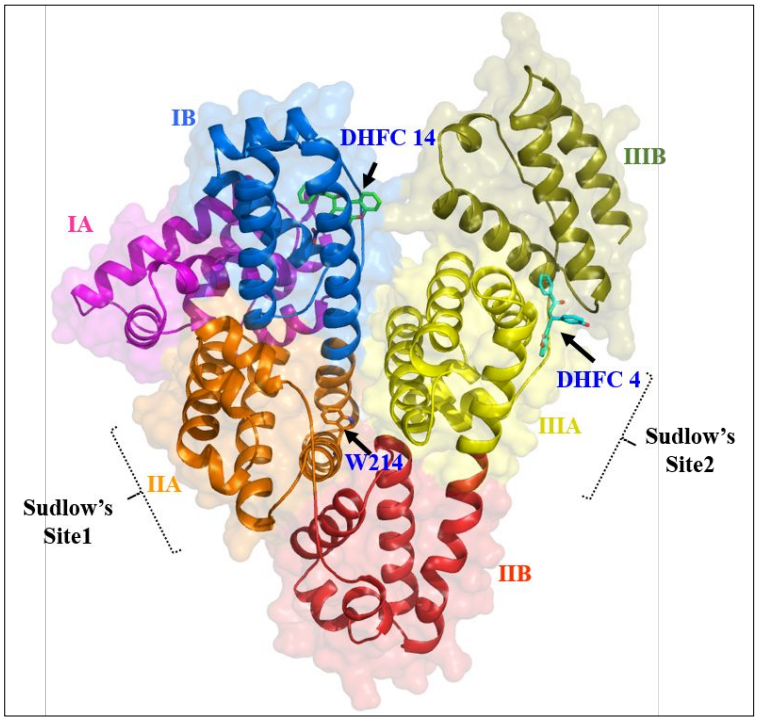
Molecular Docking Study:

The 2D structure of Ligands was drawn with the online tool ChemDraw which is a drawing tool from PerkinElmer Informatics. Further three-dimensional structures were obtained from the Open Babble[1] software. The three-dimensional structure of the protein target (PDB Id: 1AO6)[2] was downloaded from RCSB PDB[3]. The target file was prepared for docking by removing the water molecules and adding the Kollman charges and polar hydrogens as well as

the grid box of 1 Å spacing and 84x80x88 Å was selected for the docking study. Molecular docking was performed with AutoDock Tools 1.5.6.[4] The different ligands' binding affinity with protein target was evaluated on the basis of binding affinity score and best-selected ligands were further taken for *in silico* study like simulation. Pymol and Ligplot were used to prepare figures and to plot 2D amino acid interaction profiles obtained from molecular docking analysis.

Molecular Dynamics (MD) Simulation study:

All atomistic Molecular dynamics simulation studies of the protein and ligand complexes were performed with the NAMD 2.14 software[5]. VMD (Visual Molecular Dynamics)[6] was also used for simulation setup and structure file generation like psf files etc. The docked protein-ligand complexes generated by AutoDock Tools 1.5.6[4] were used to prepare the simulation files. The Ligand Reader and Modeller tool[7] of the web-based Charmm-Gui software[8] [7] have been used to generate force field and topology files for the ligands. The cubic solvation box of 5Å was created and the Langevin dynamics were used to generate an isothermal-isobaric ensemble (NPT) environment for simulation. Minimization of the system was done for 1000 steps while the steps for dcd, xst, and restart frequency were kept to 5000 steps and for output energy, to 50 steps. The production run was performed for 30ns with 2fs time-step per cycle. Only protein was also simulated for 30ns keeping the environment and other parameters similar to the protein-ligand complex. The Root Mean square deviation (RMSD) in trajectories generated during the simulation was also calculated and analysed by the VMD interface using the tcl script files as well as the inbuilt tools. Origin was used to plot graphs to analyse the Cα RMSD trajectories obtained through MD simulations.



Supplementary Figure S1: Multiple independent ligand binding sites of HSA. The colour coded three-dimensional structural map represents the relative locations of different subdomains of HSA which can serve as the independent binding sites for multiple indigenous and exogenous ligands. The arrows indicate the HSA docking sites of two DHFC ligands as well

as the position of the intrinsic fluorophore tryptophan 214 (W214).

Supplementary Table S1: *In silico* molecular docking based binding energy estimation of synthesized *trans*-2,3-dihydrofuro[3,2-c] coumarin (DHFC) derivatives with HSA.

Sr. No	DHFC Derivatives	Binding Energy (kcal/mol)
1	1	-9.5
2	2	-9.3
3	3	-9.1
4	4	**-9.2**
5	5	-9.5
6	6	-9.7
7	7	-8.6
8	8	-9
9	9	-8.2
10	10	-8.5
11	11	-9.1
12	12	-9
13	13	-9.4
14	14	**-10.3**
15	15	-8.8
16	16	-10.3
17	17	-9.5
18	18	-9
19	19	-8.7
20	20	-8.2
21	21	-7.7
22	22	-9.4
23	23	-9
24	24	-8
25	25	-9.3

Fluorescence Studies:

The interaction studies of these **2,3-dihydrofuro [3,2-c]coumarin [DHFC] derivatives** with Human Serum Albumin (HSA) have been performed on a Spectrofluorometer (JASCO FP-8300) using a quartz cuvette of 1cm path length. The Stock solution of HSA (concentration 150 μM) was prepared in 1X PBS (pH 7.4). The concentration of HSA in the final reaction mixtures was kept constant at 0.5 μM. The tested ligands were initially dissolved in 100% DMSO then the final concentrations were reached by diluting with 1X PBS, while the final percentage of DMSO was kept 1% in each ligand concentrations. Varying concentrations (1 μM, 2 μM, 3 μM, 5 μM, 10 μM, 25 μM & 50 μM) of both the compounds **(14 & 4)** have been used in the final reaction mixture for the titration. The final reaction mixture contains protein, varying concentrations of ligands, and the reaction volume was made up to 3 mL by adding 1X PBS. The DMSO percentage was kept to 1% in all the final reaction mixtures. The excitation and emission bandwidth were fixed at 10 nm and the scan speed was set at 200 nm min^{-1}. The fluorescence emission spectra, $\lambda_{Em.}$ were recorded from 300 nm to 700 nm keeping excitation

wavelength, $\lambda_{Ex.}$ at 280nm. The results of the fluorescence titrations were plotted and analysed by using Origin software package.

References:

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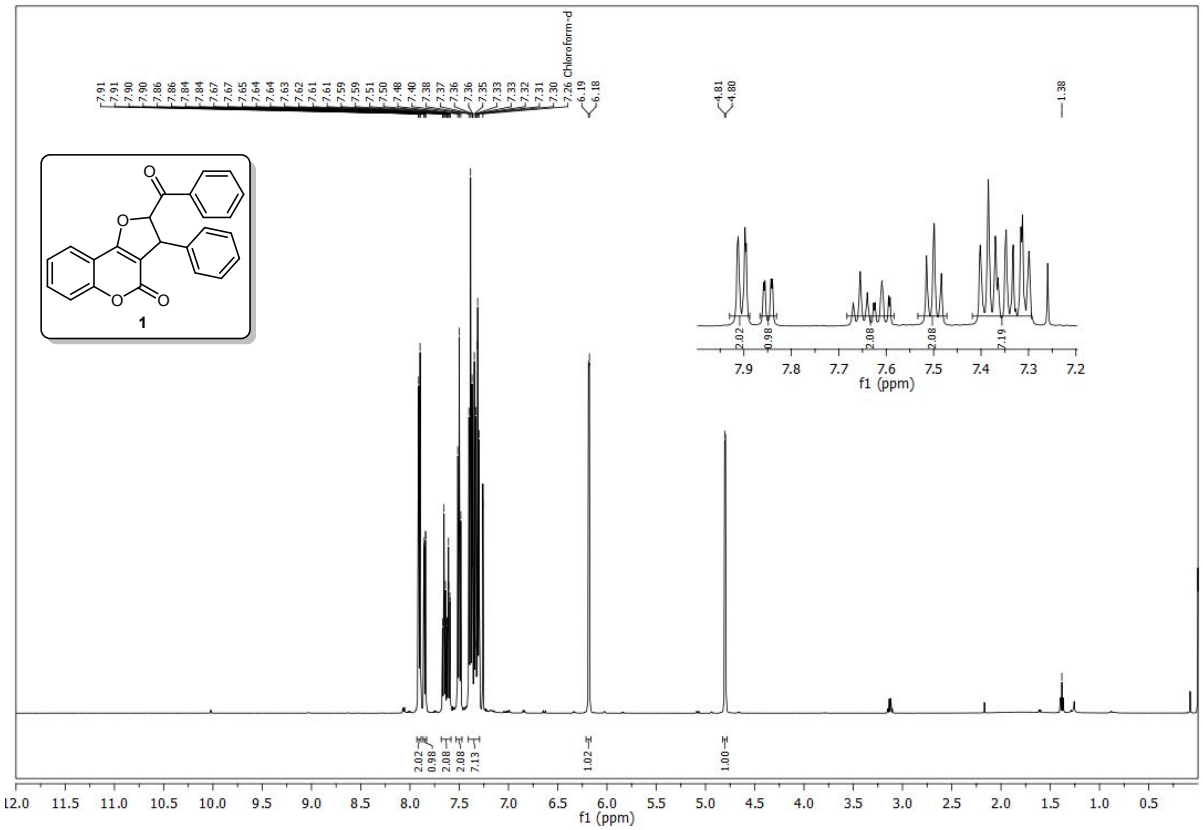
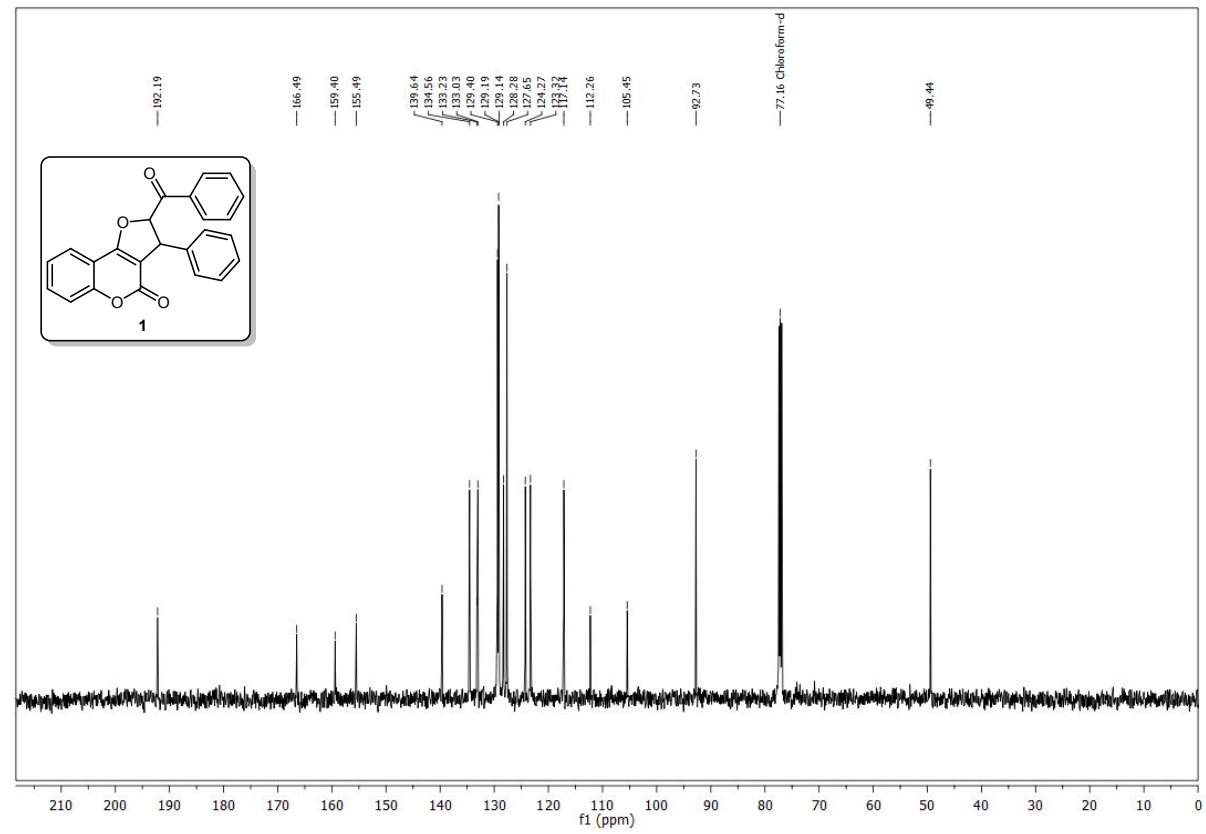
(7) Kim, S.; Lee, J.; Jo, S.; Brooks, C. L.; Lee, H. S.; Im, W. *J. Comput. Chem*. **2017**, *38*, 1879.
(8) Jo, S.; Kim, T.; Iyer, V. G.; Im, W. *J. Comput. Chem*. **2008**, *29*, 1859.

^{1}H NMR (500 MHz, $CDCl_3$) of **1**



^{13}C NMR (126 MHz, $CDCl_3$) of **1**



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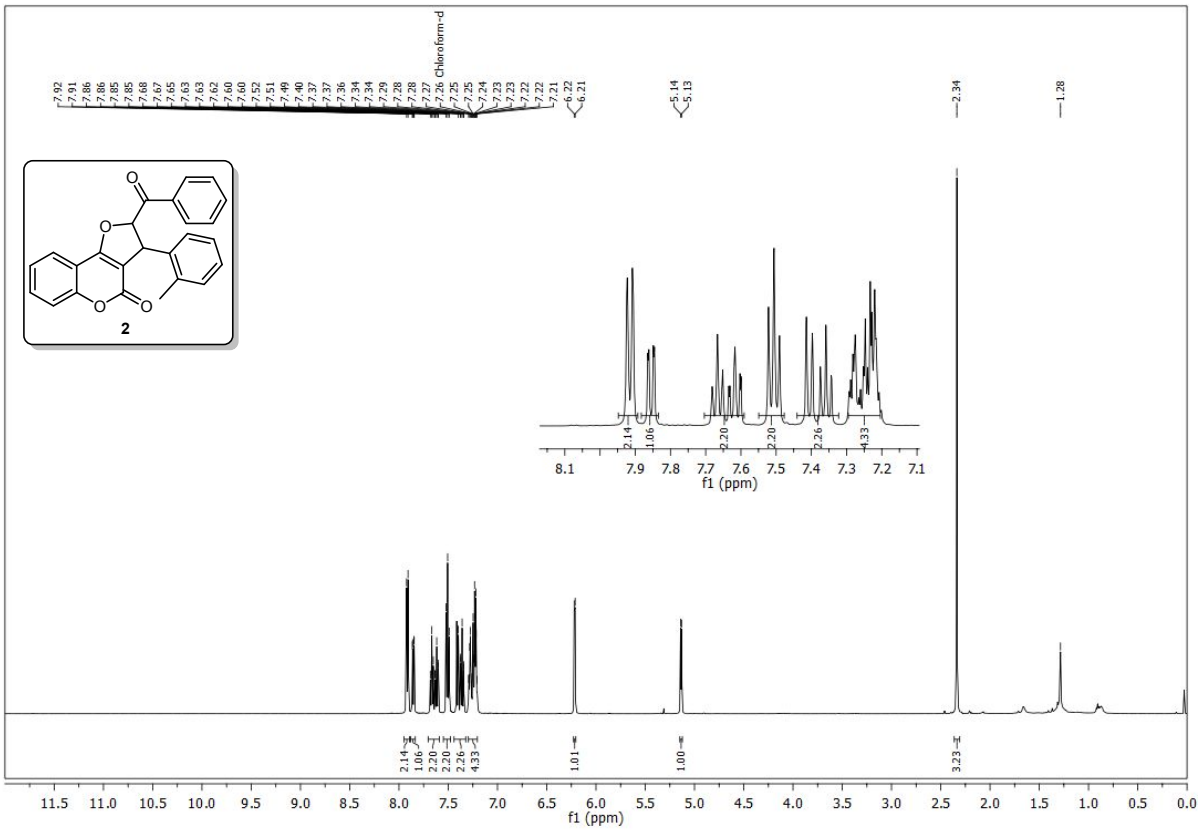

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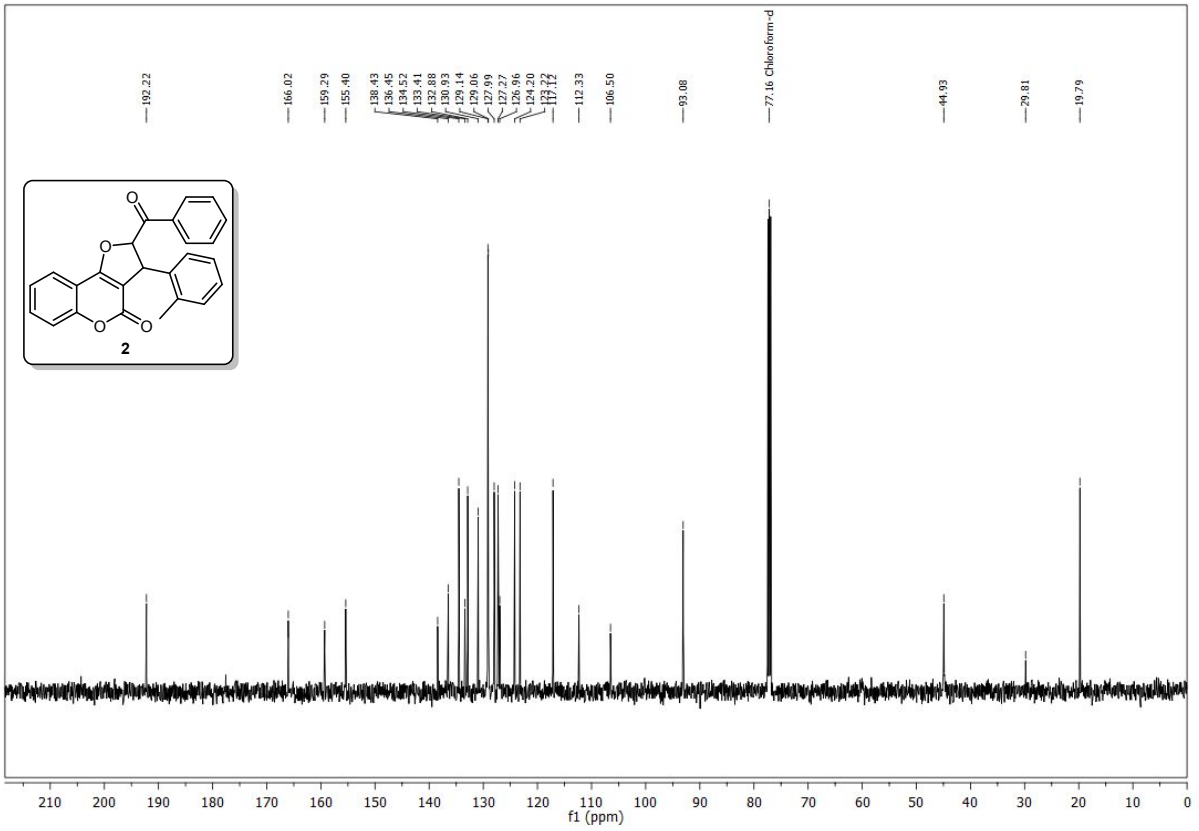

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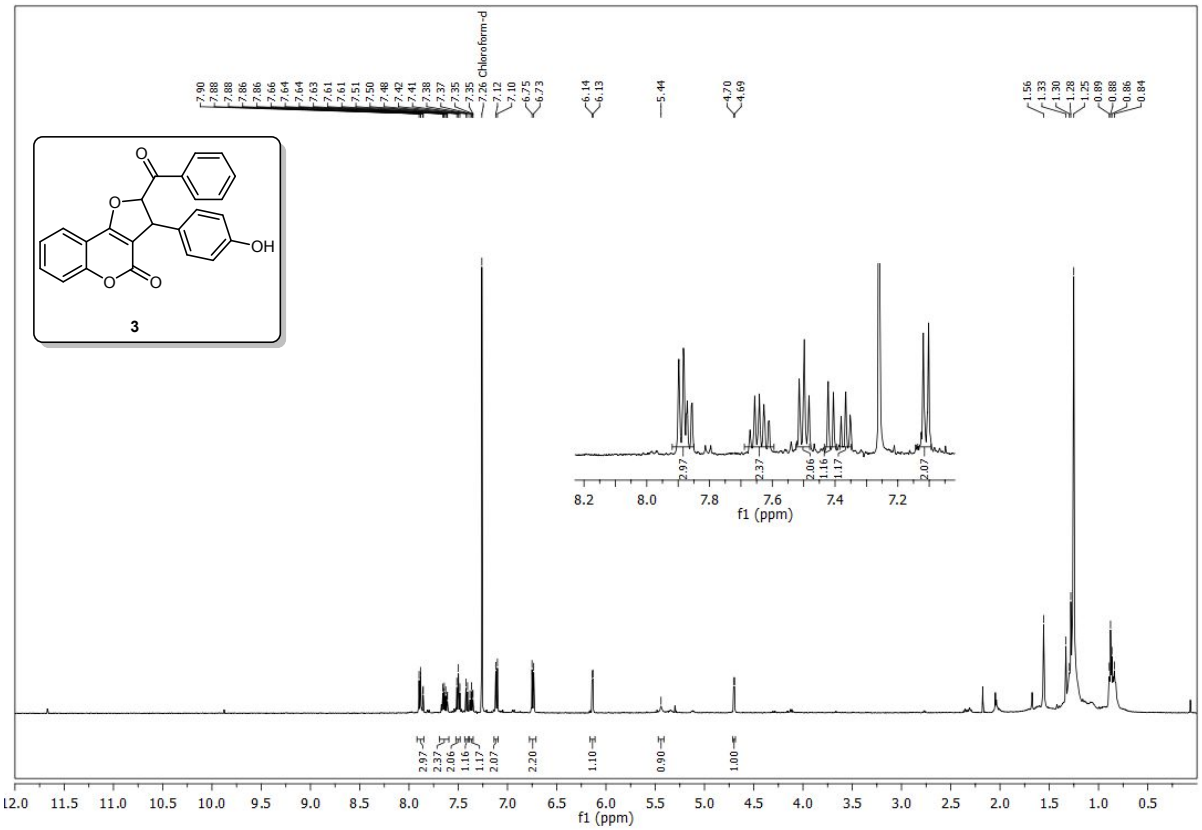
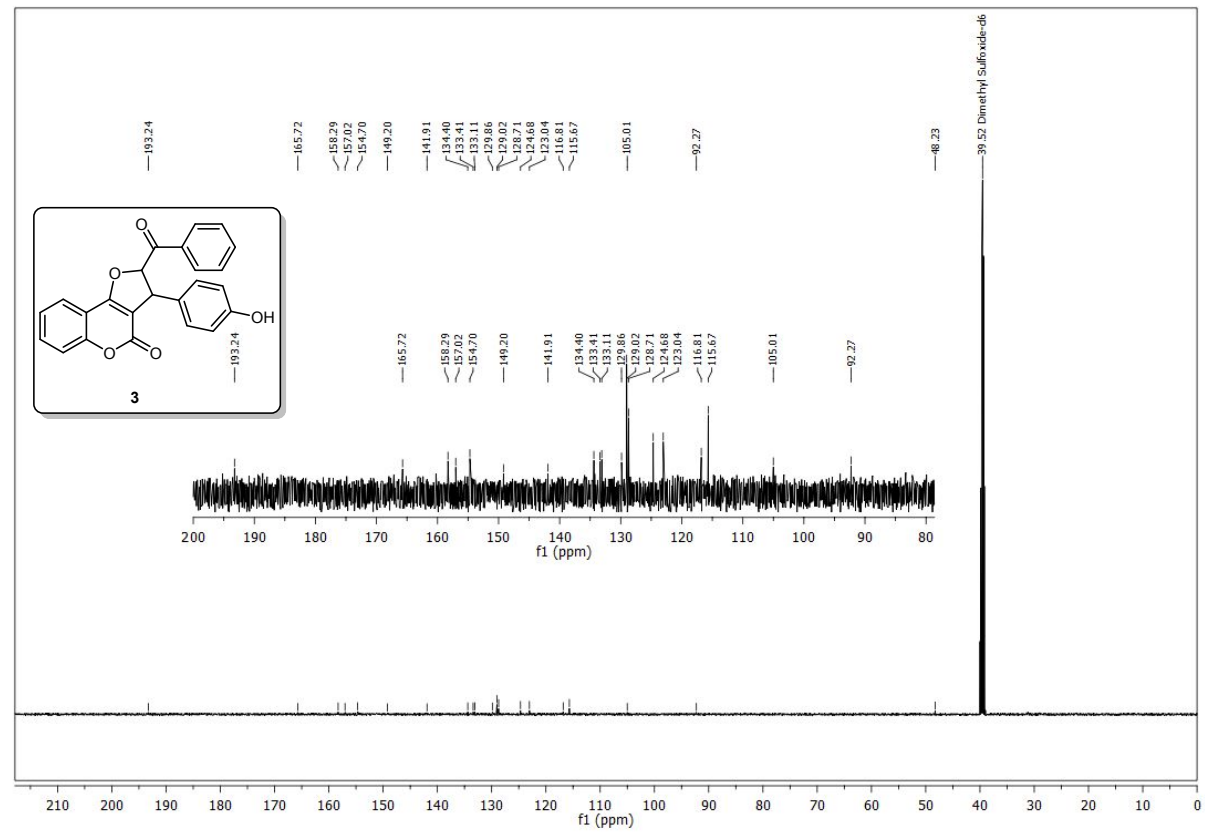


^{13}C NMR (126 MHz, $CDCl_3$) of **3**



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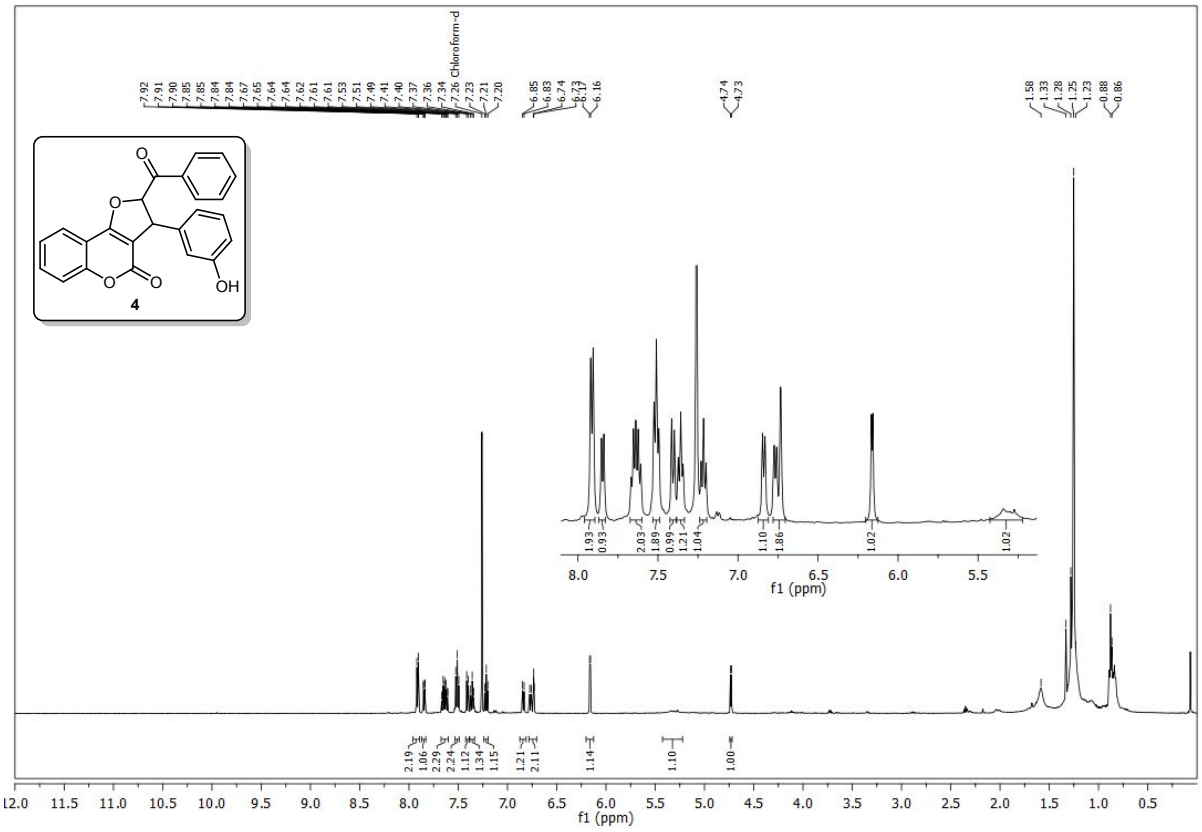
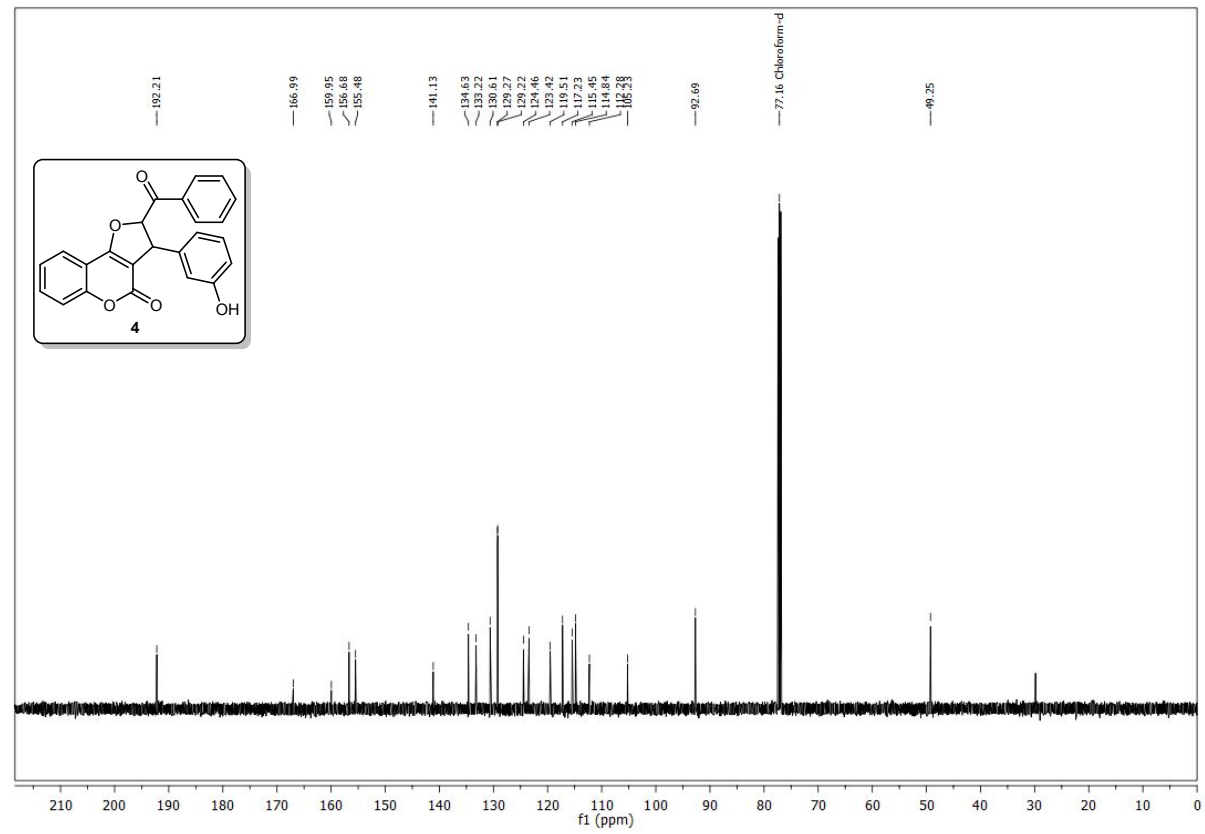
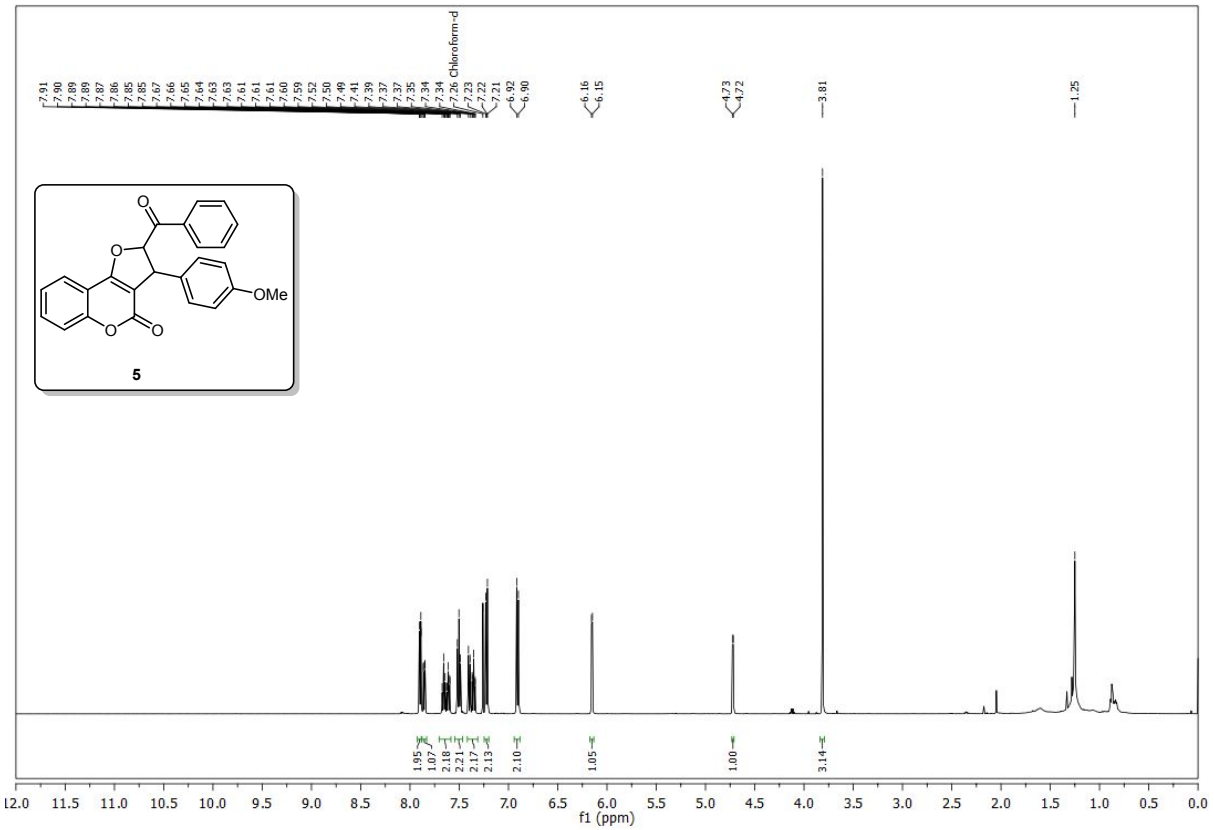


^{13}C NMR (126 MHz, $CDCl_3$) of **4**



^{1}H NMR (500 MHz, $CDCl_3$) of **5**



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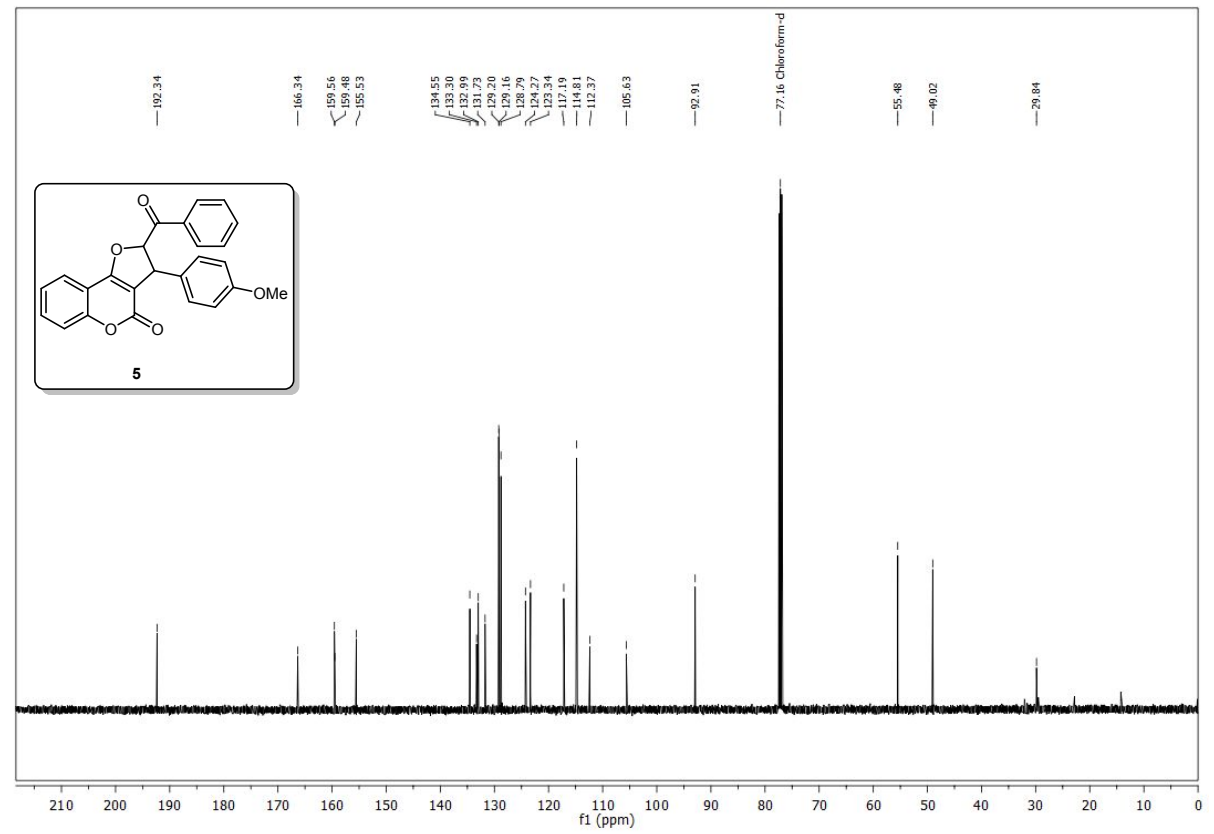

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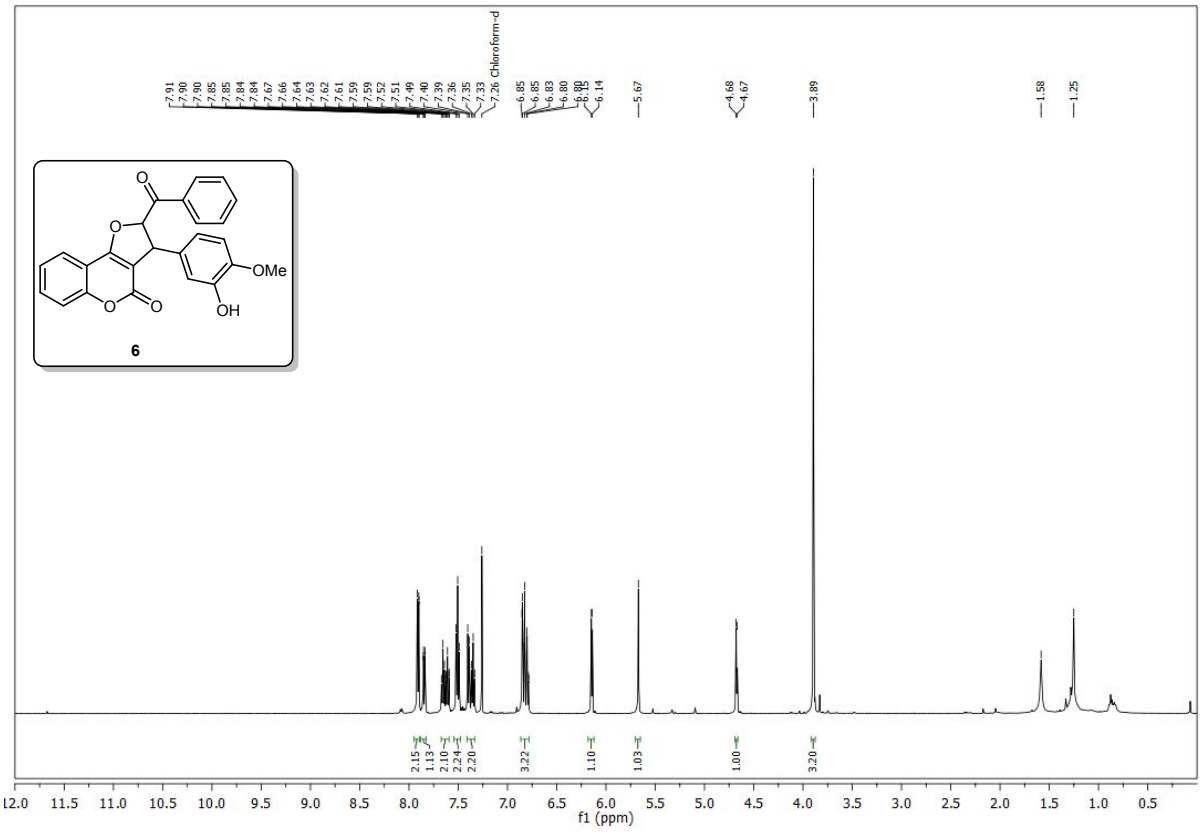

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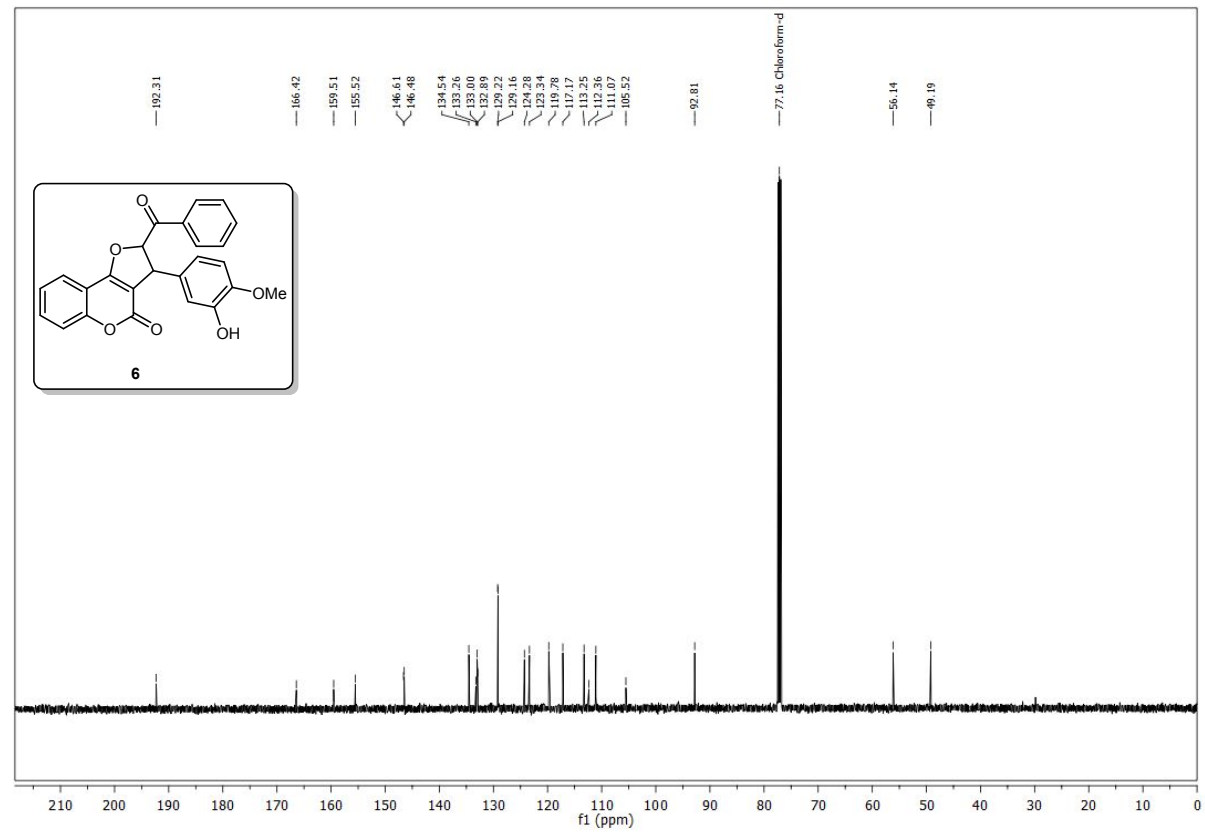

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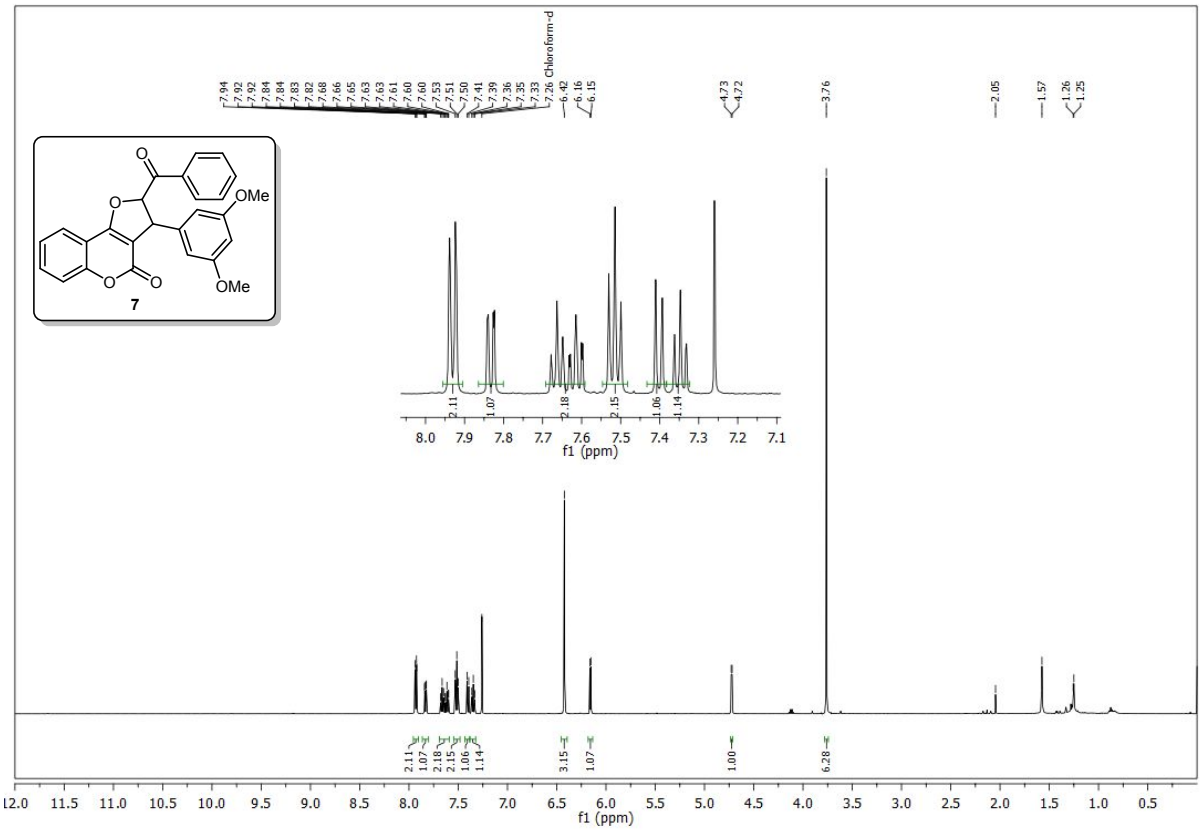

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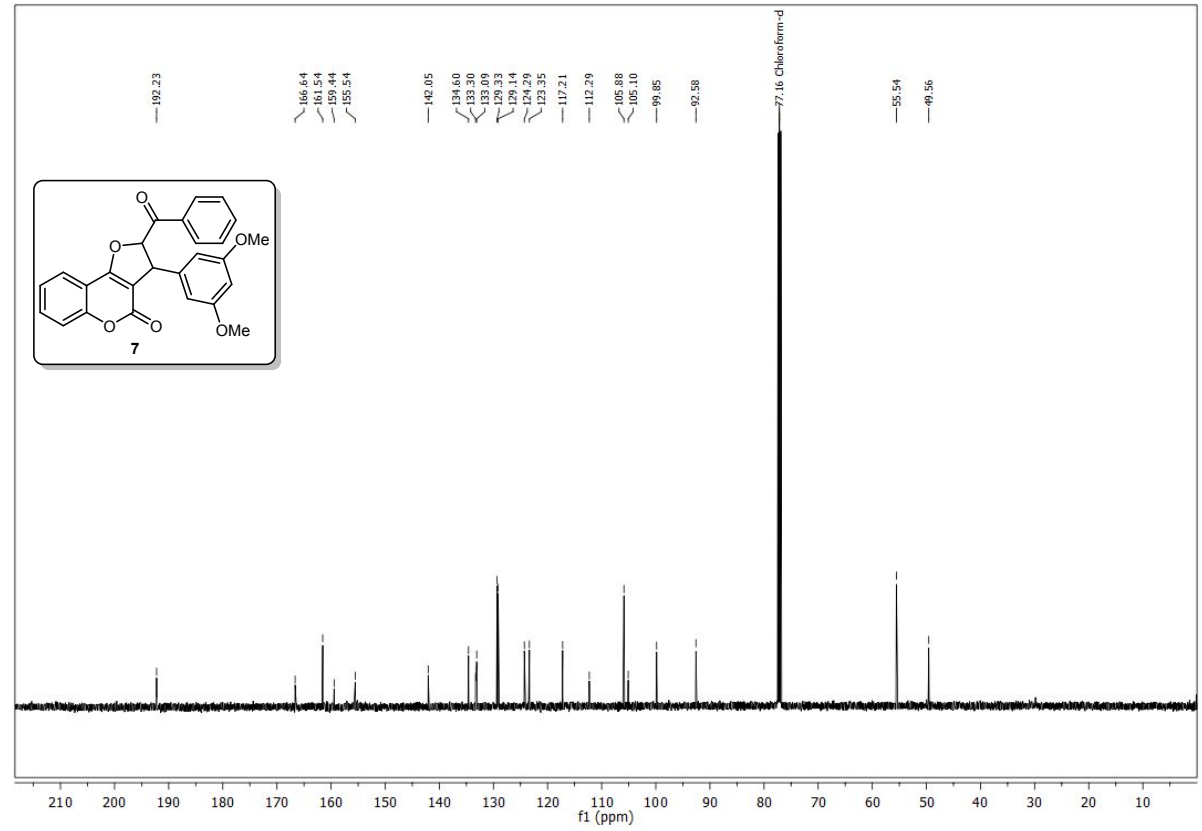
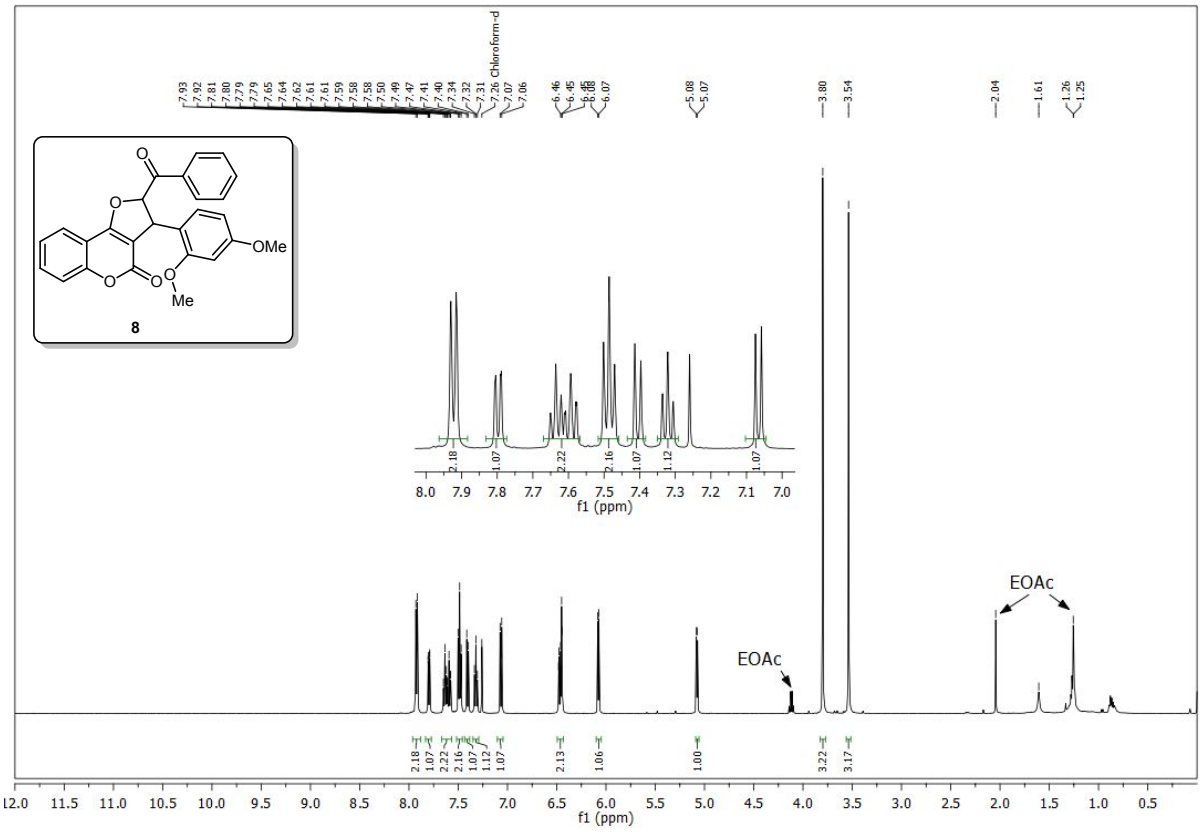
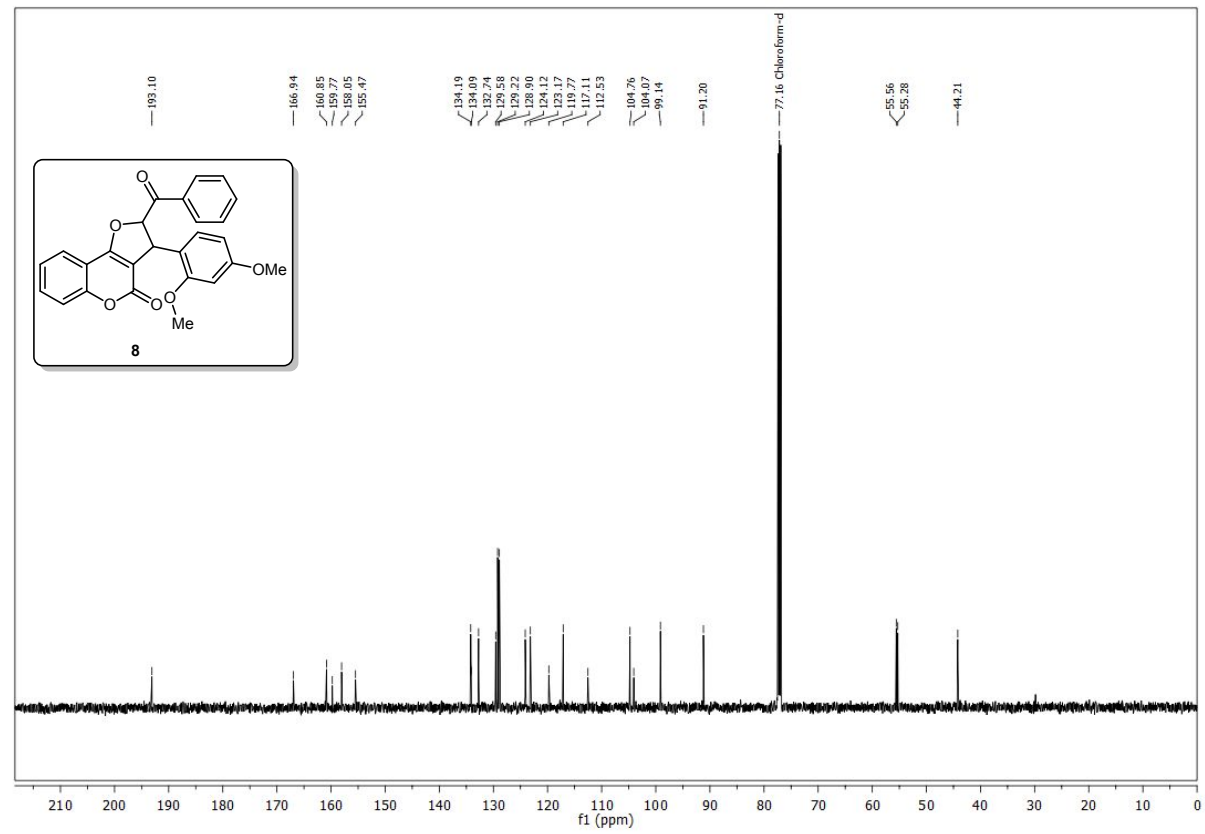


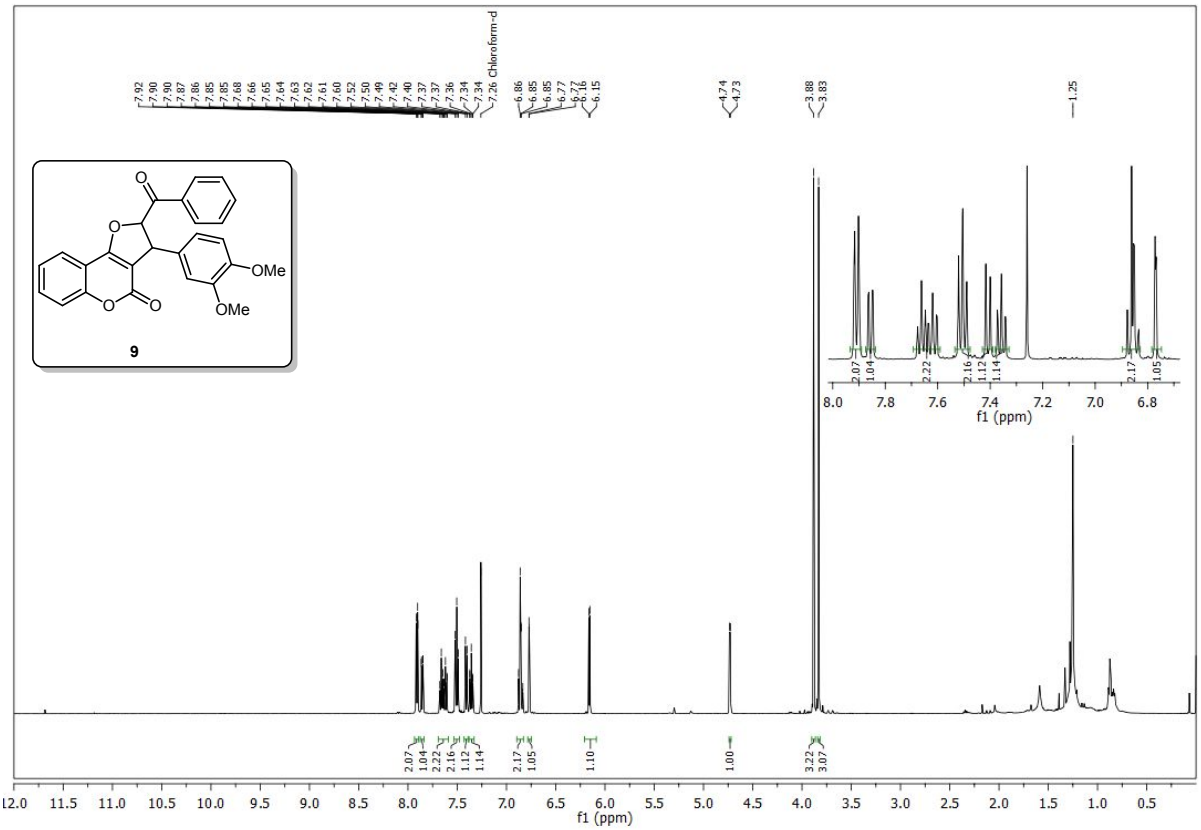
^{1}H NMR (500 MHz, $CDCl_3$) of **8**



^{13}C NMR (126 MHz, $CDCl_3$) of **8**



^{1}H NMR (500 MHz, $CDCl_3$) of **9**



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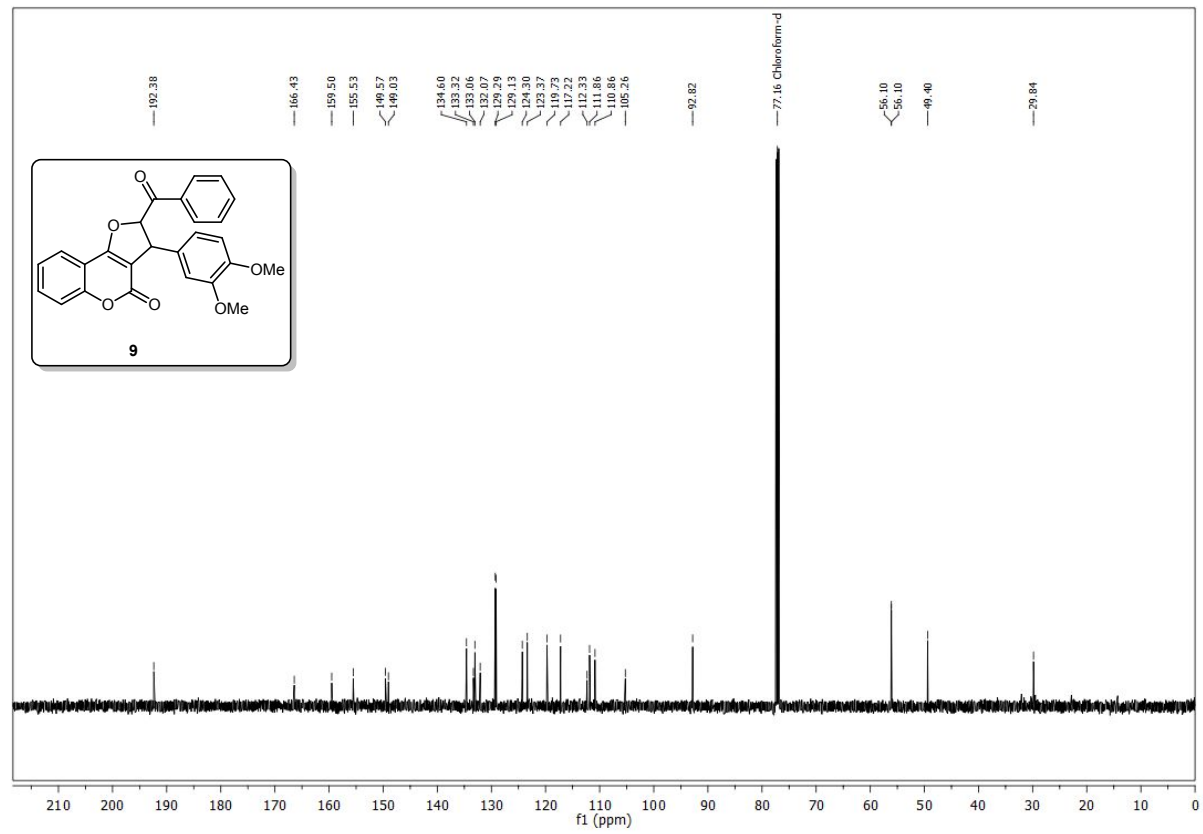

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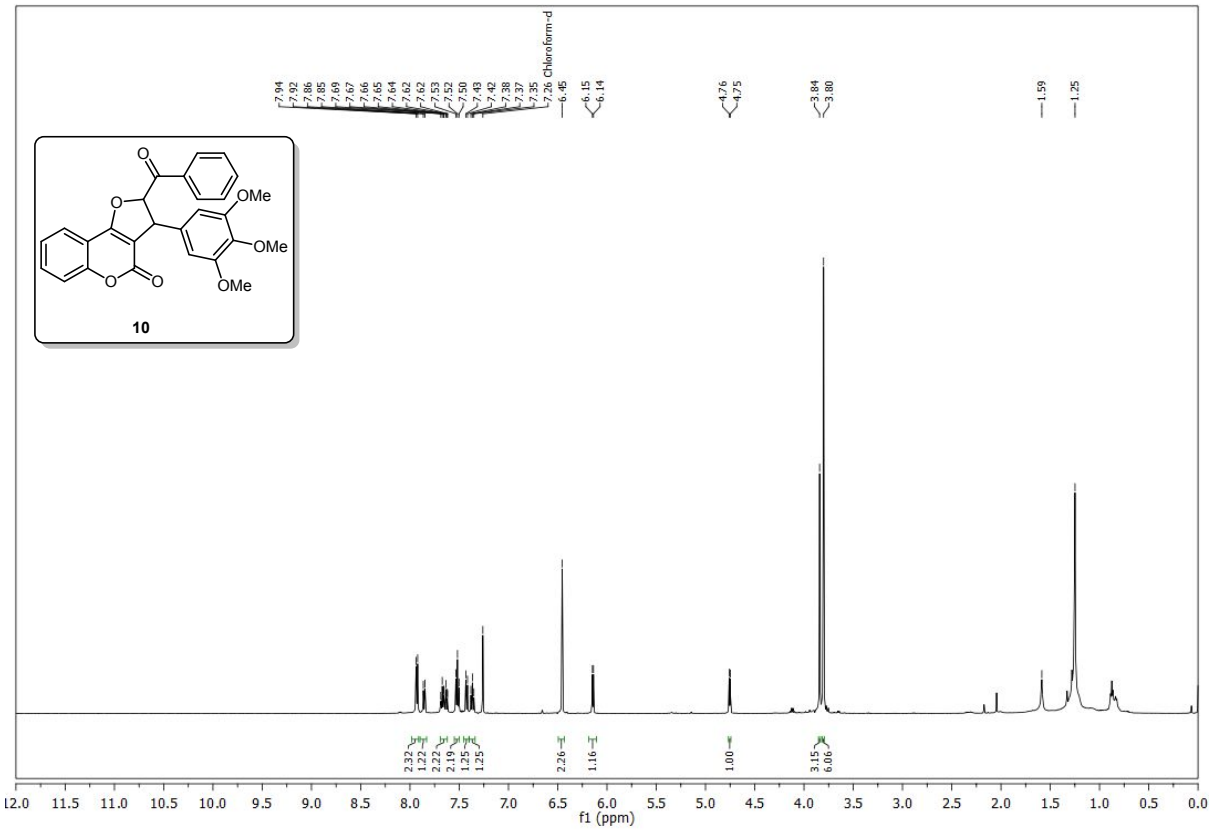

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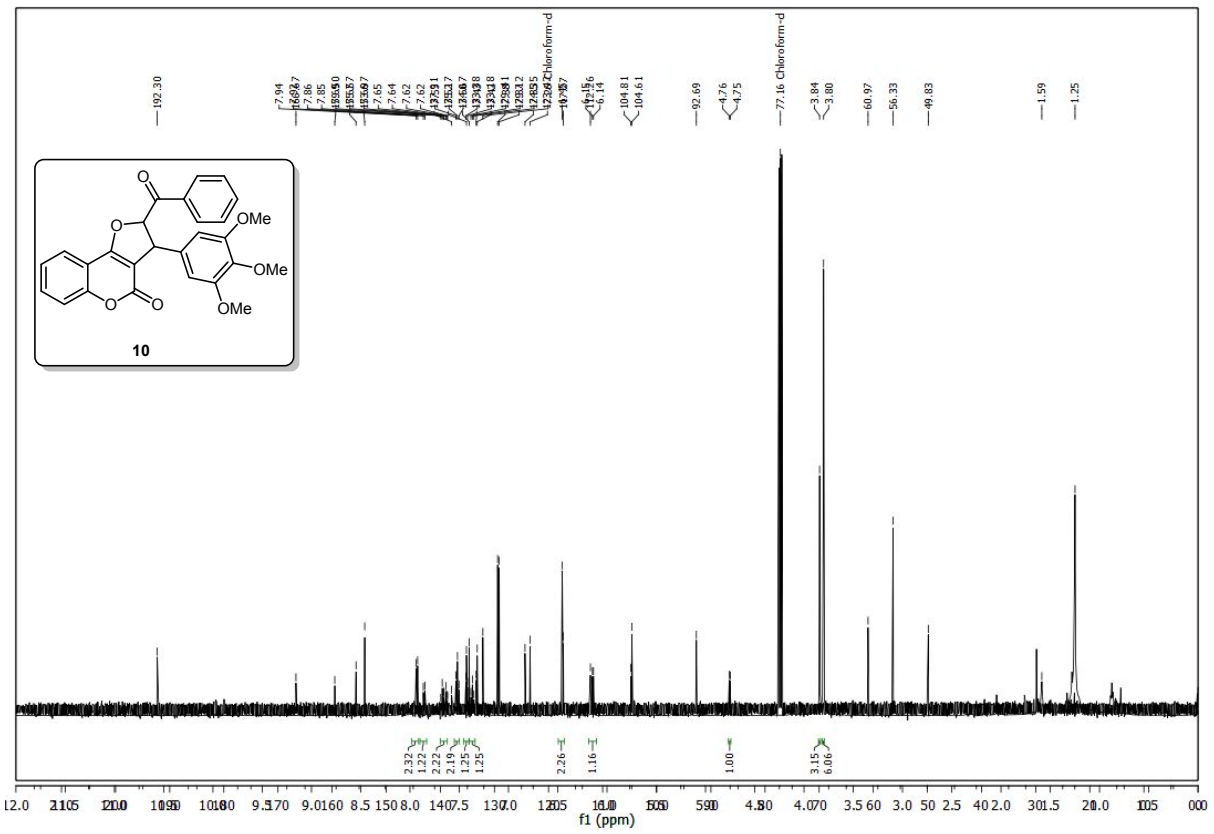
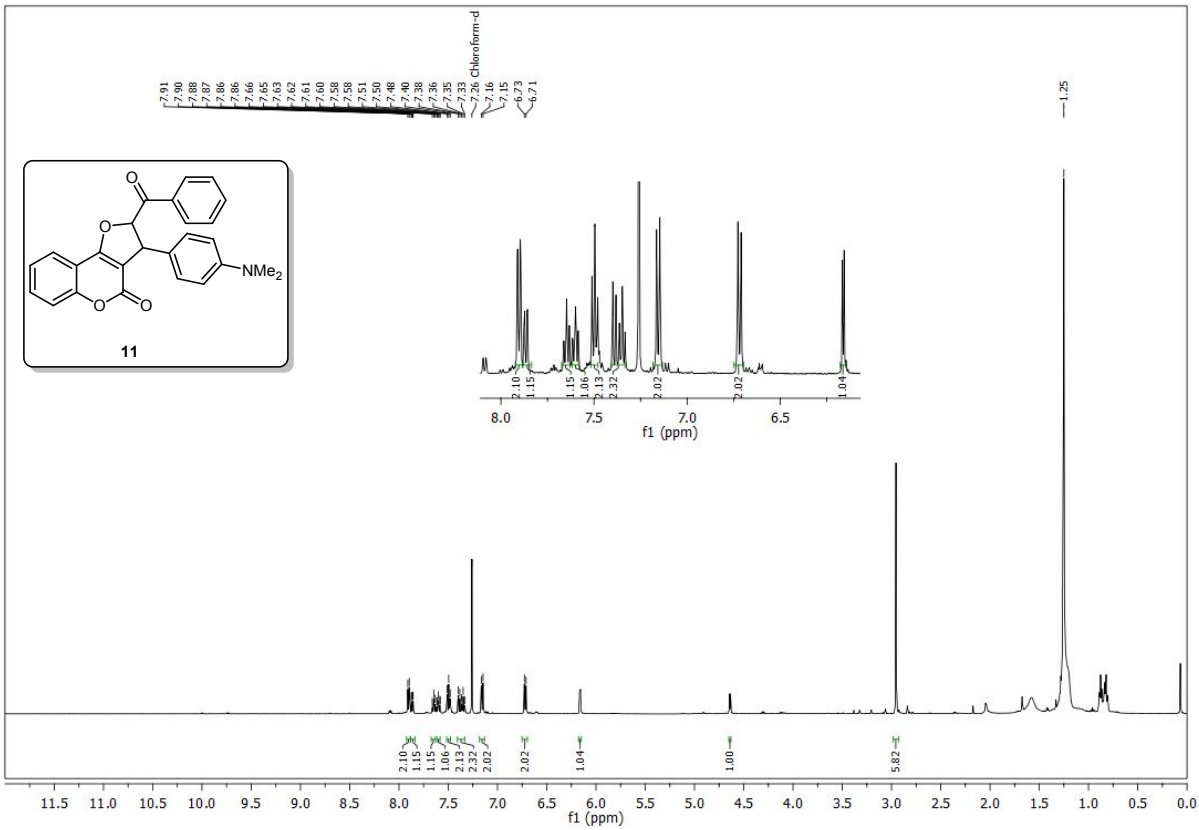


^{1}H NMR (500 MHz, $CDCl_3$) of **11**



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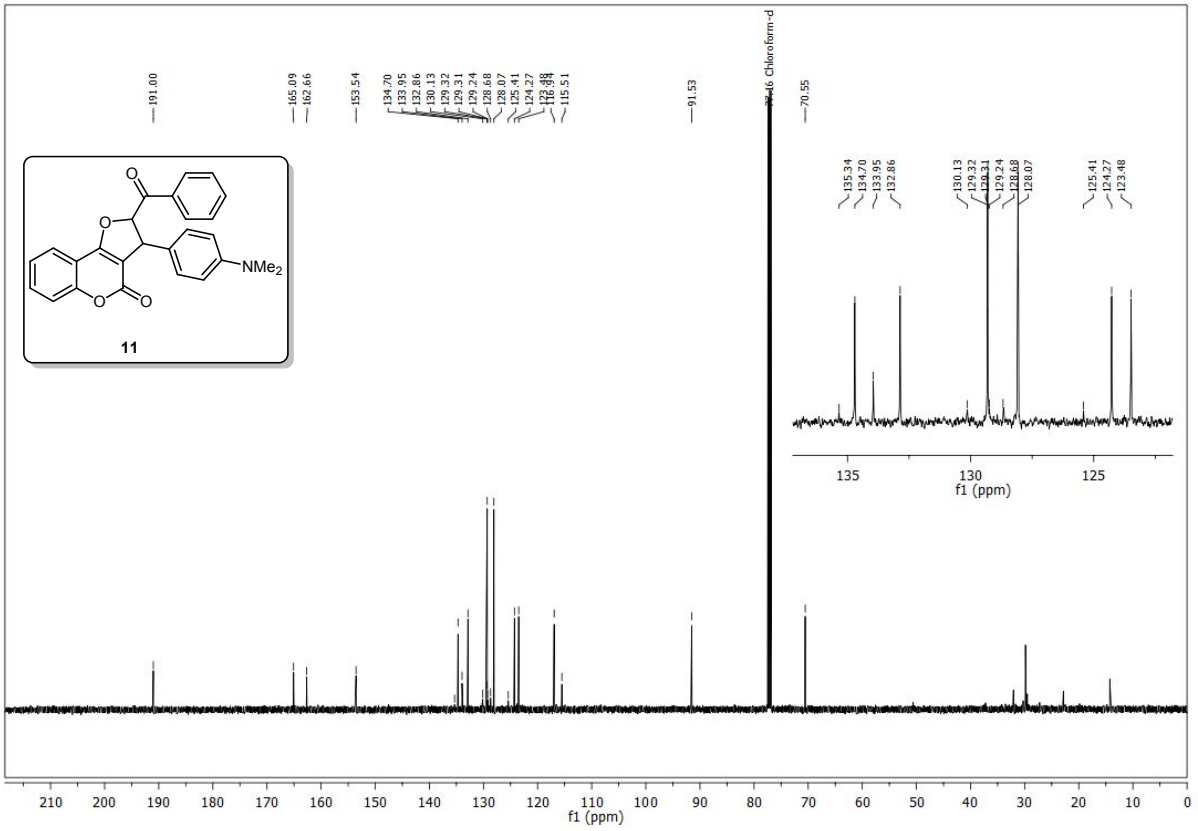

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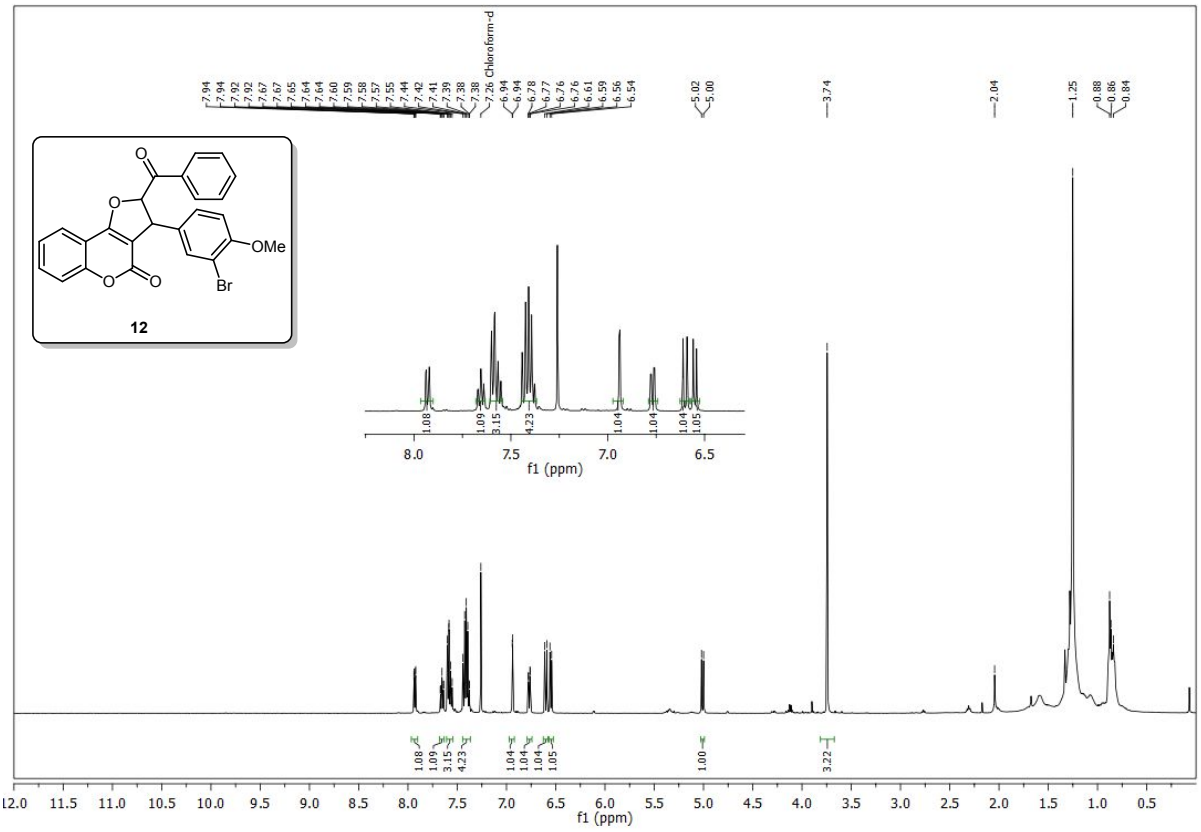

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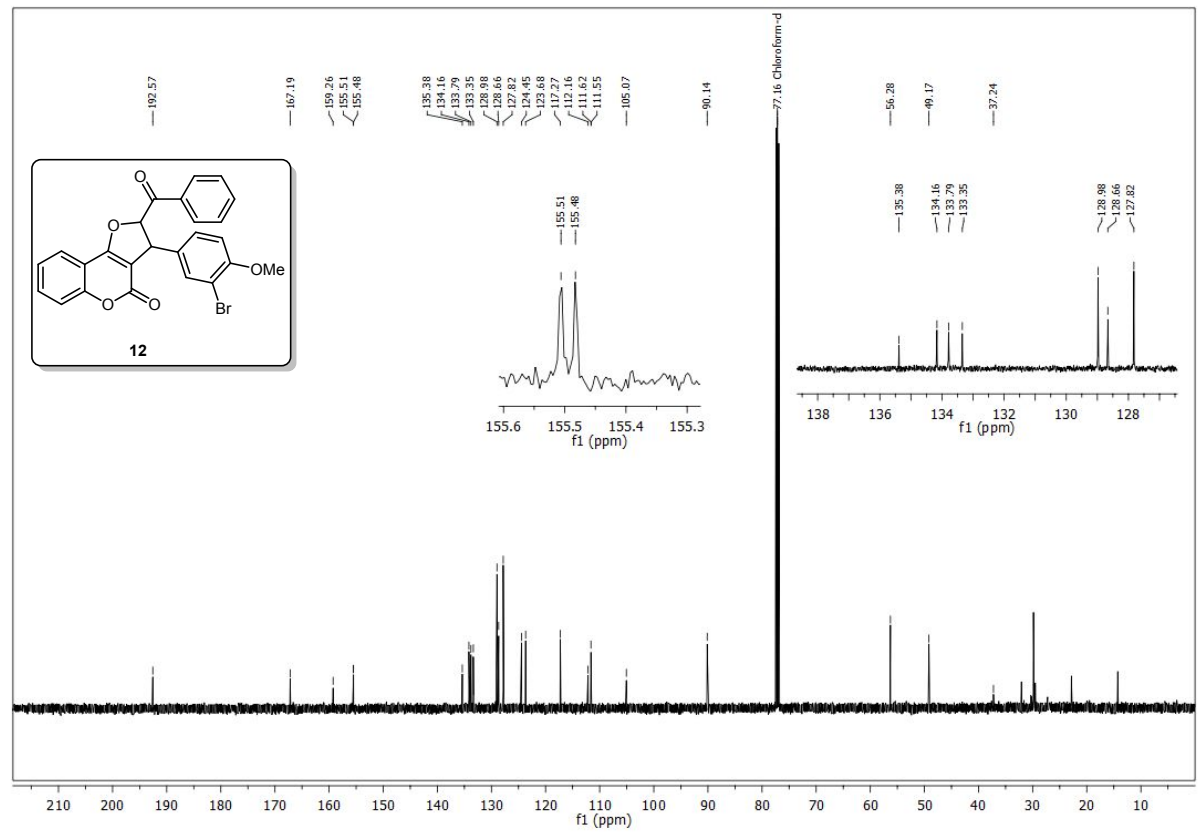

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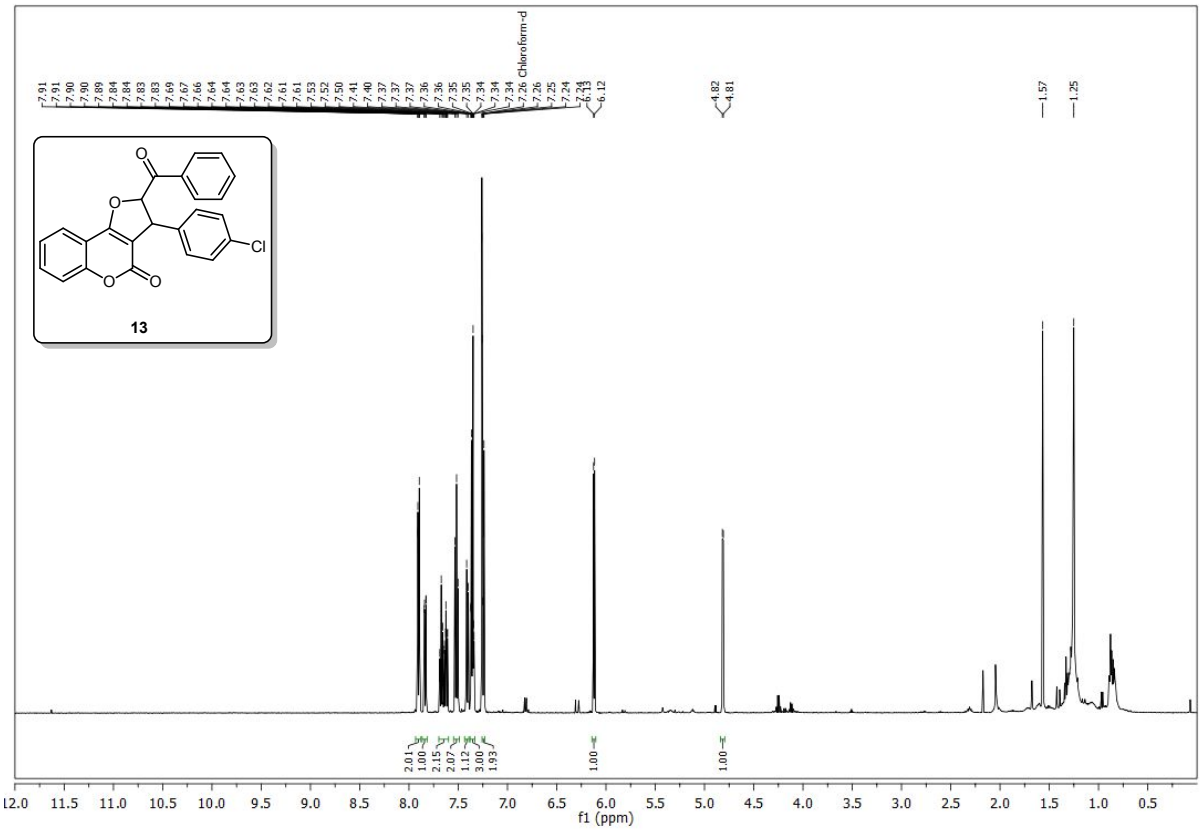

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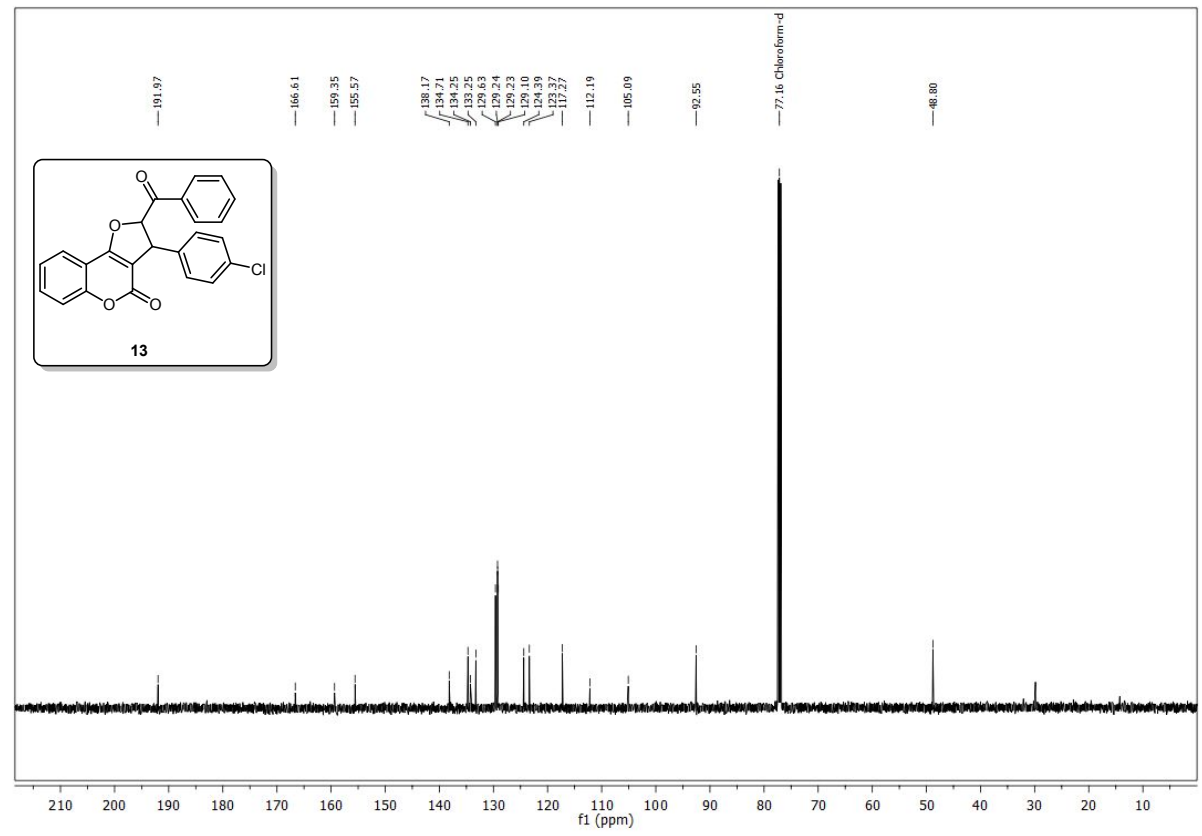

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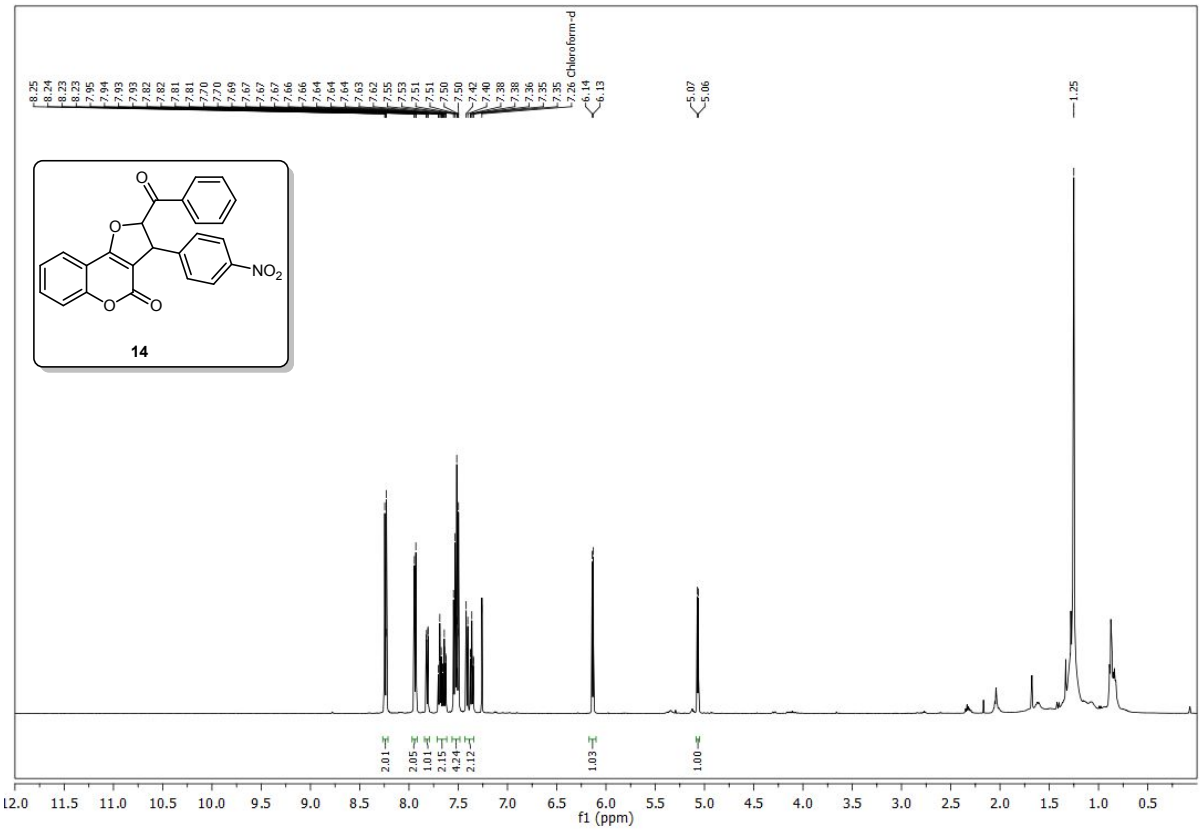

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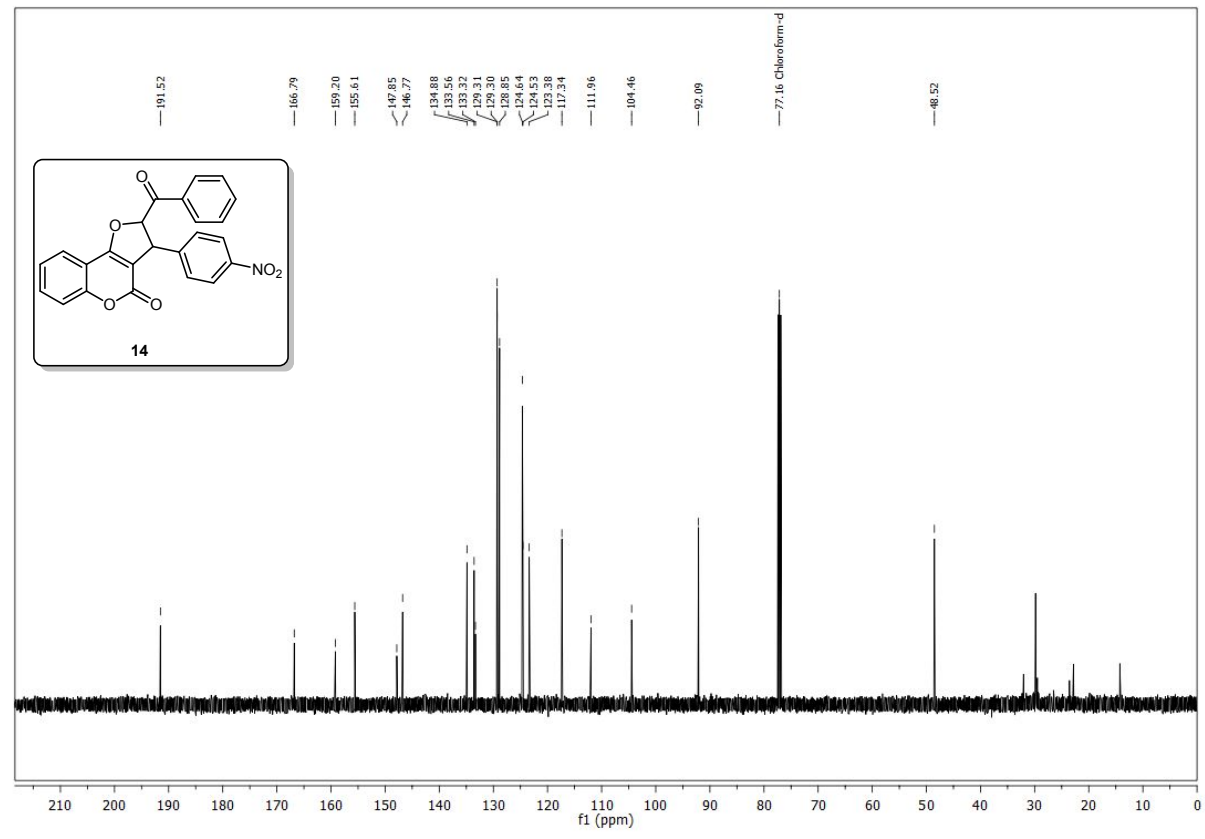

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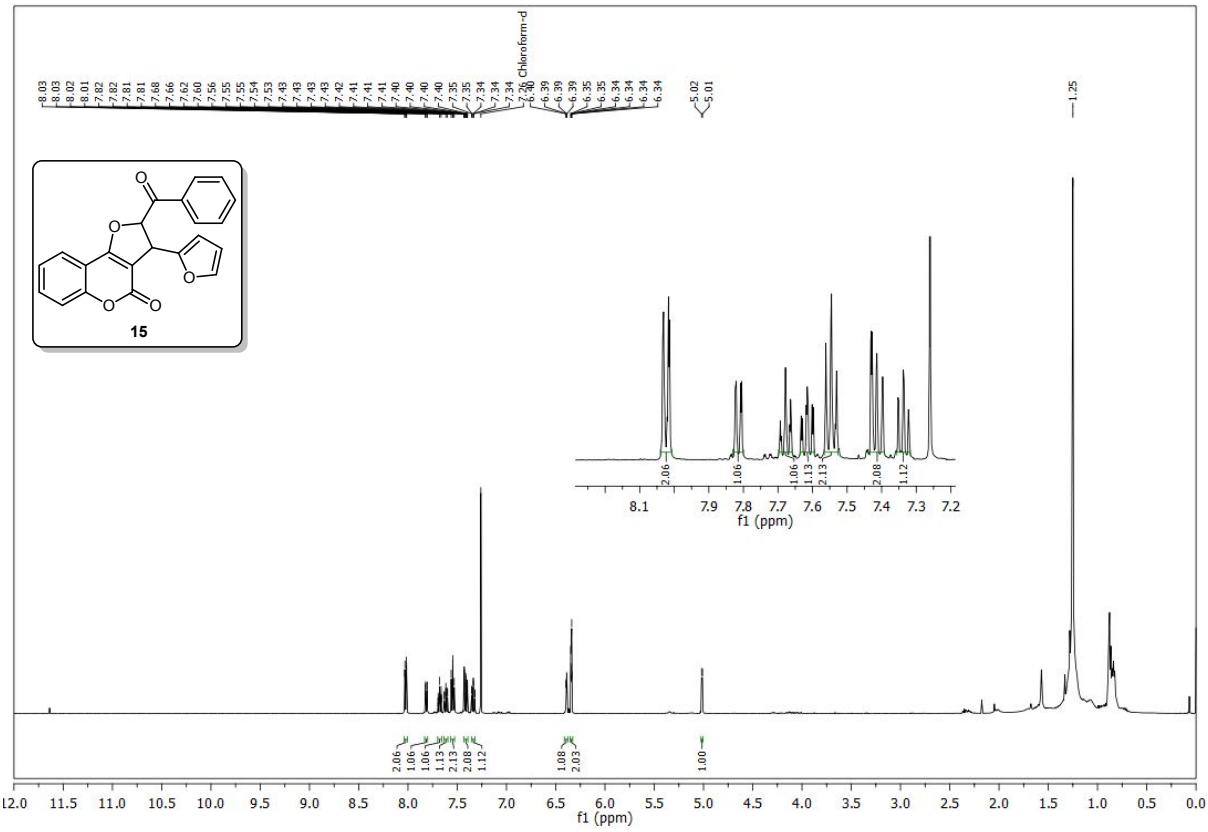

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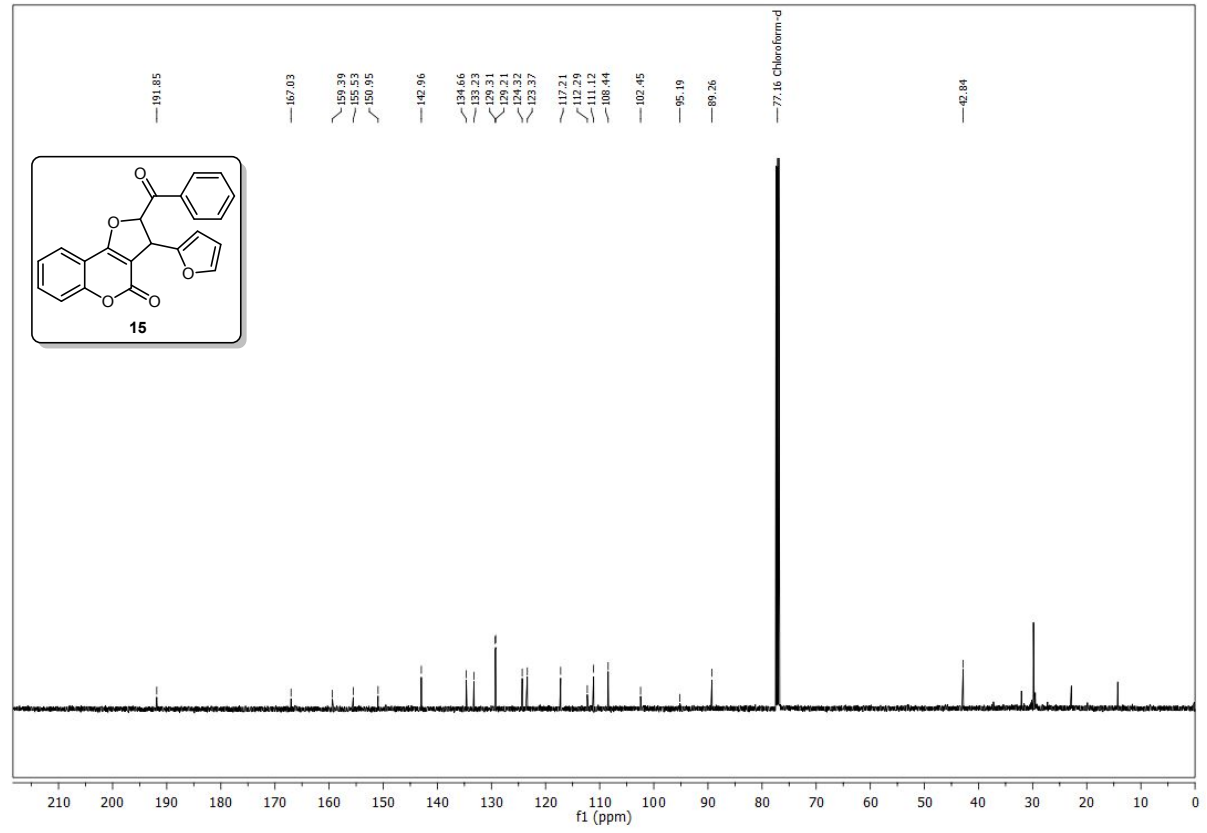

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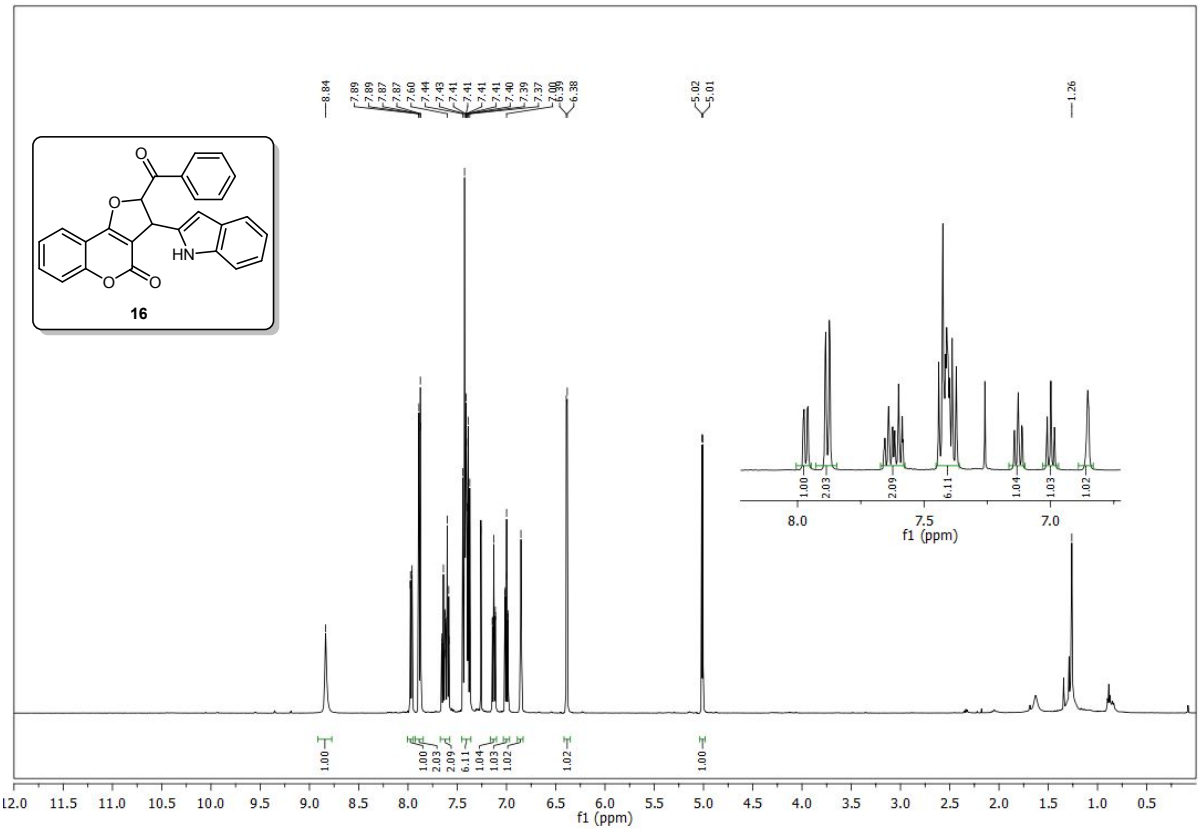

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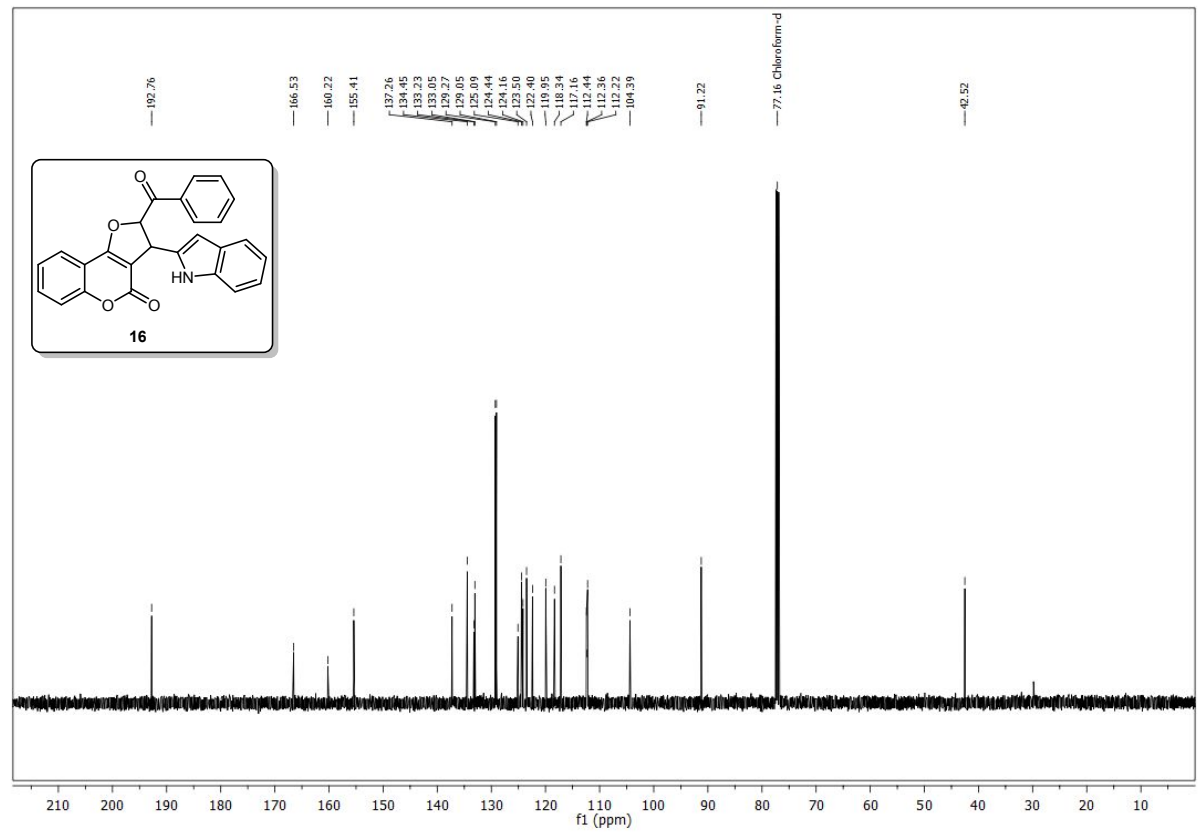

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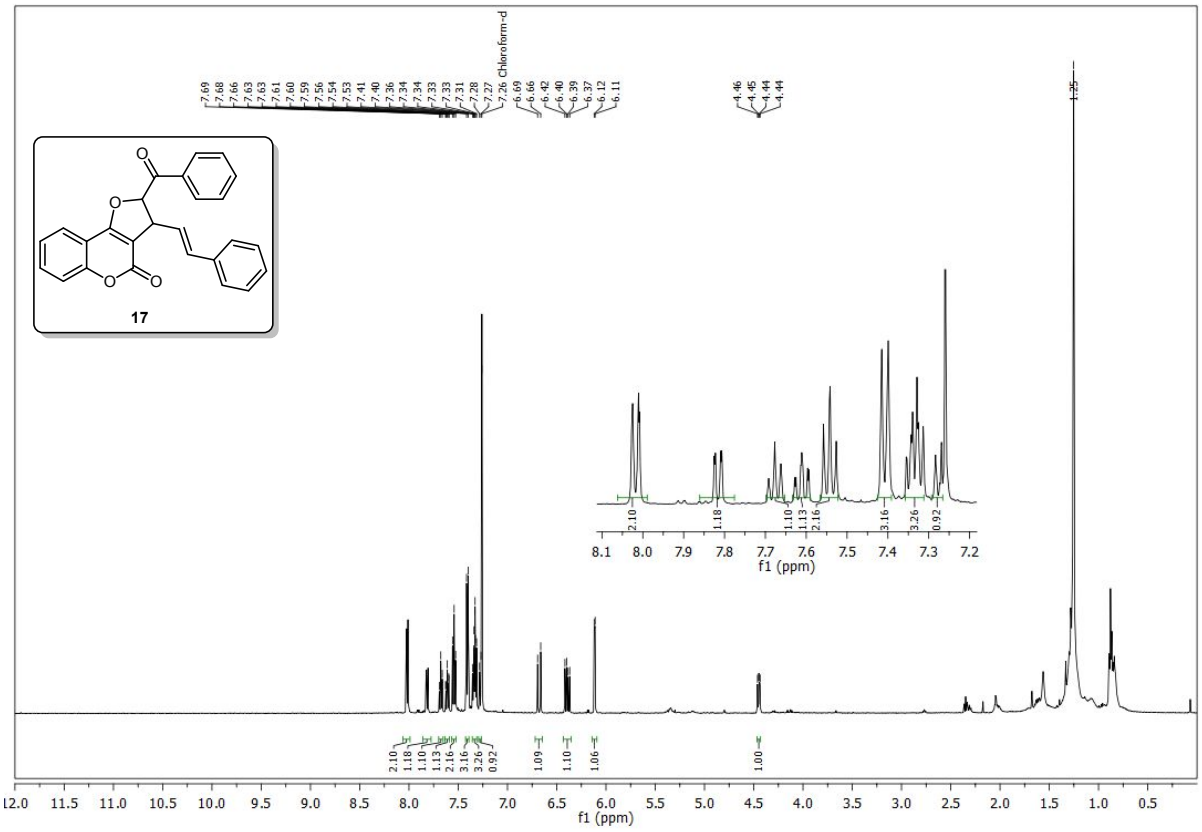

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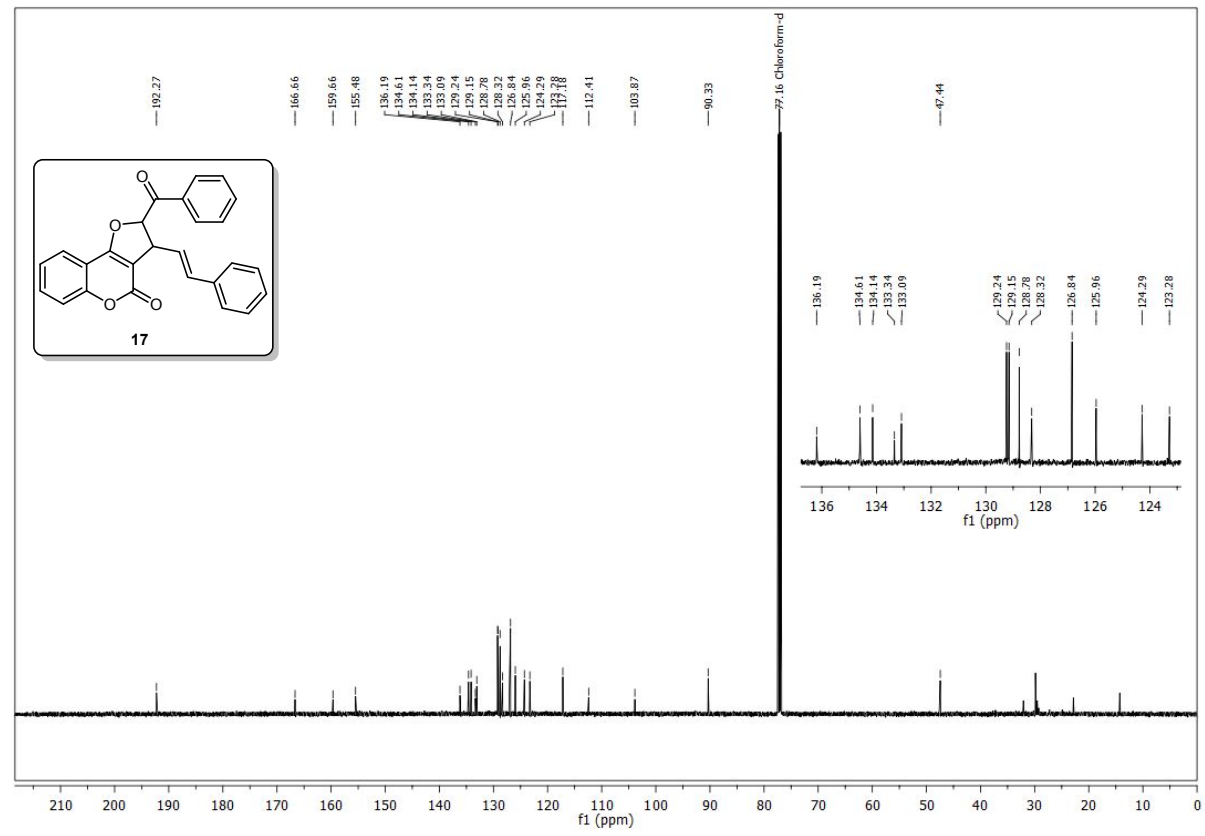

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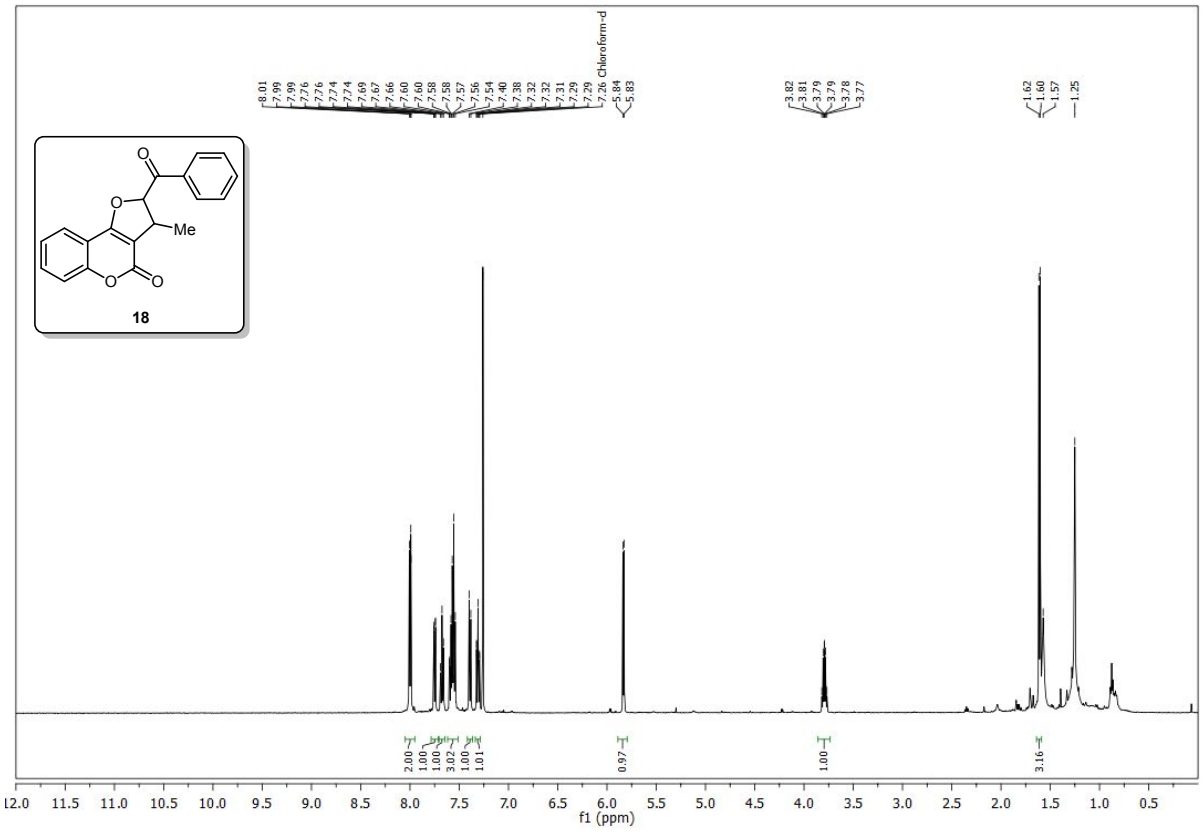

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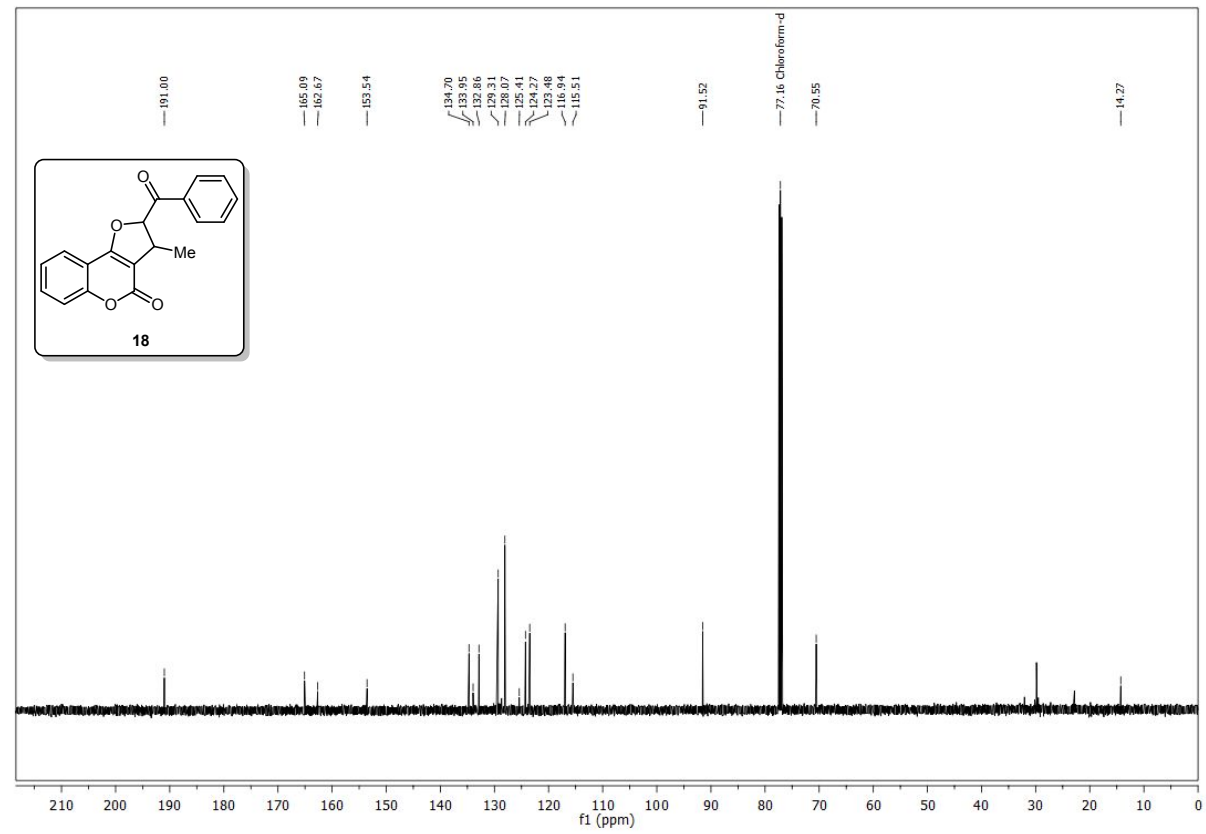

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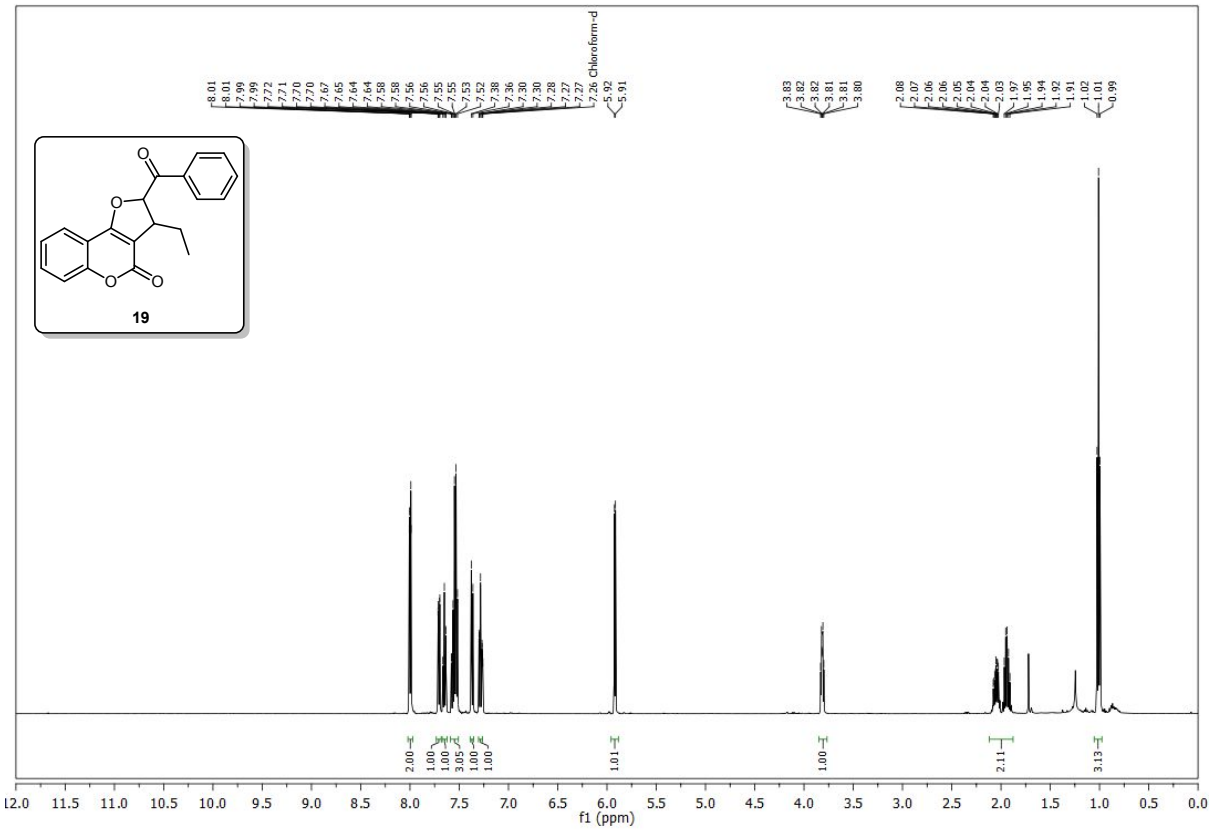

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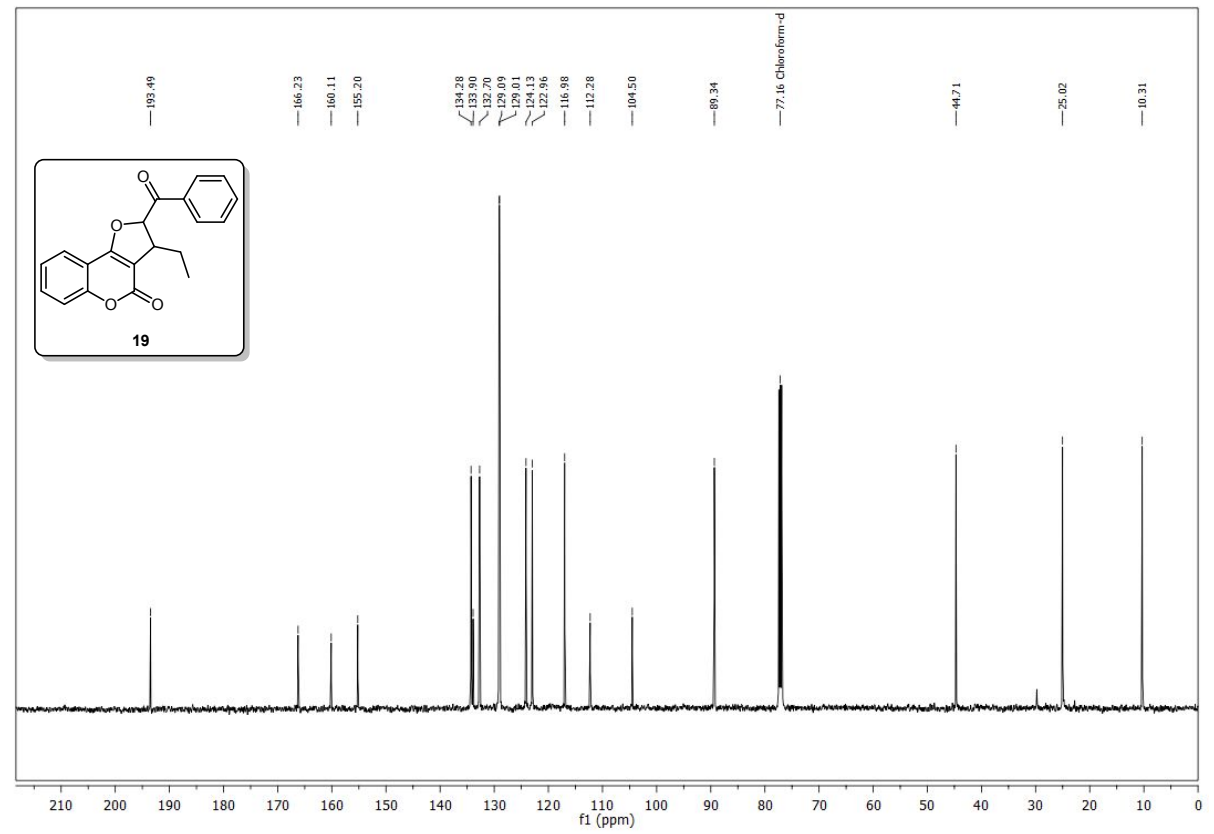

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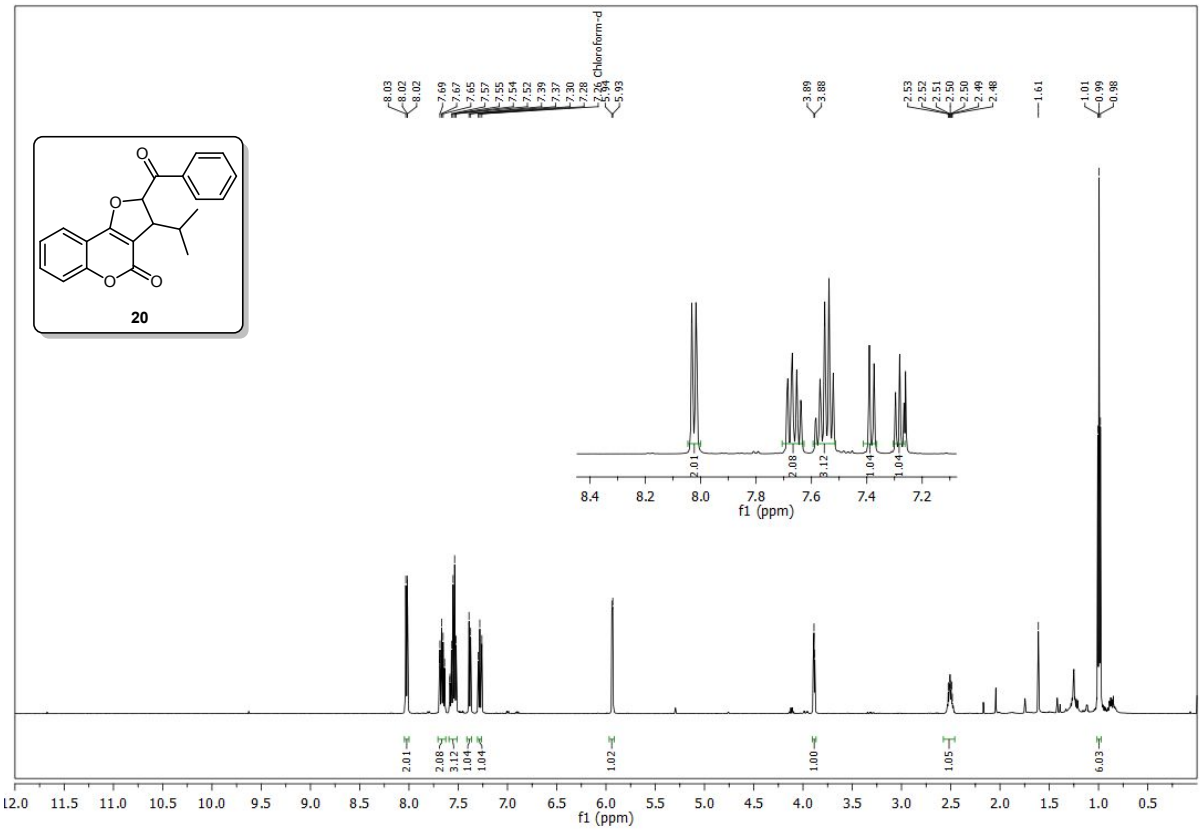

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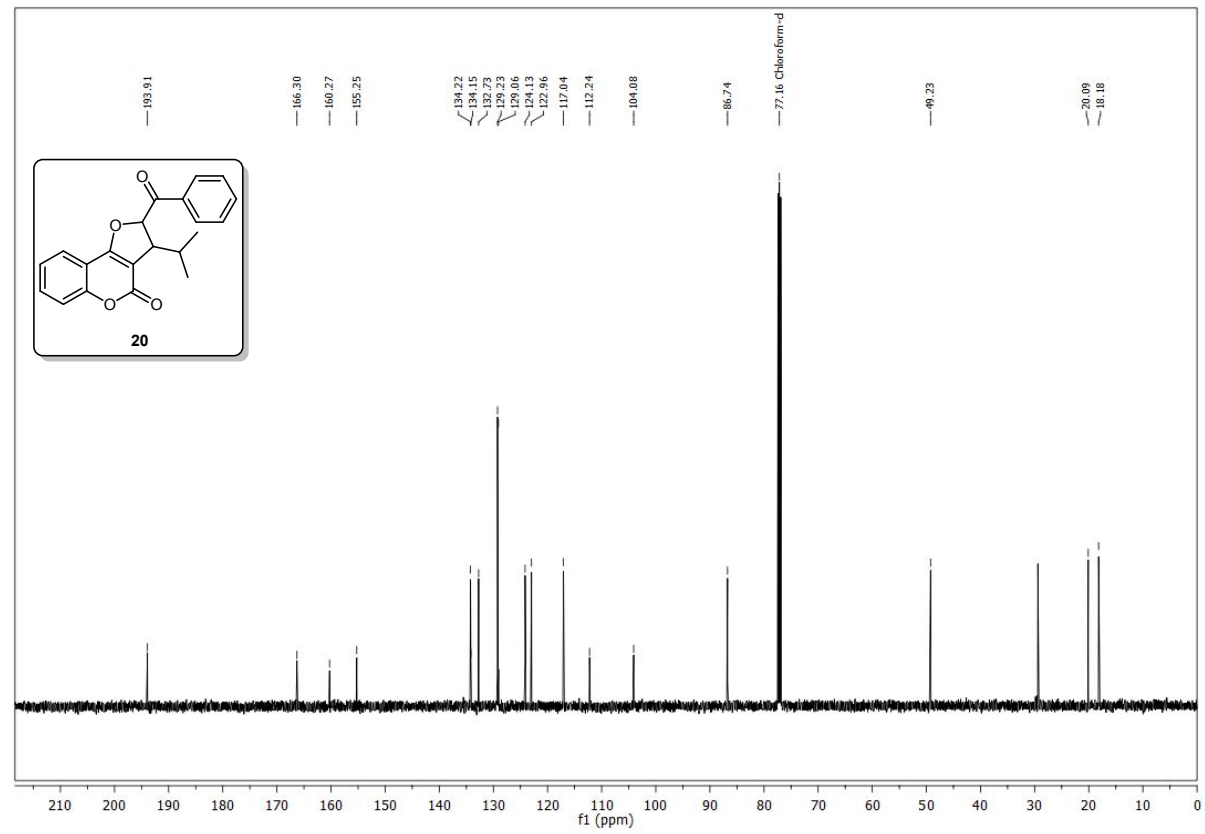

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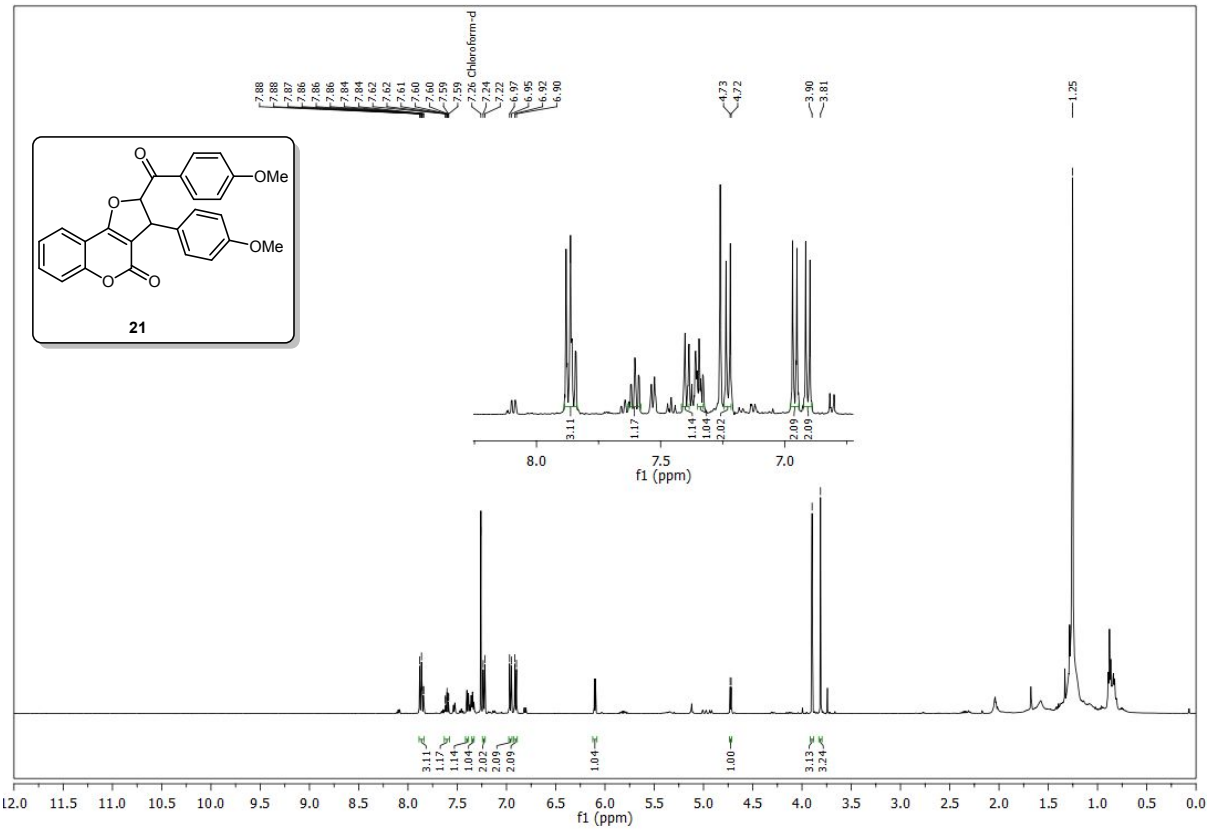
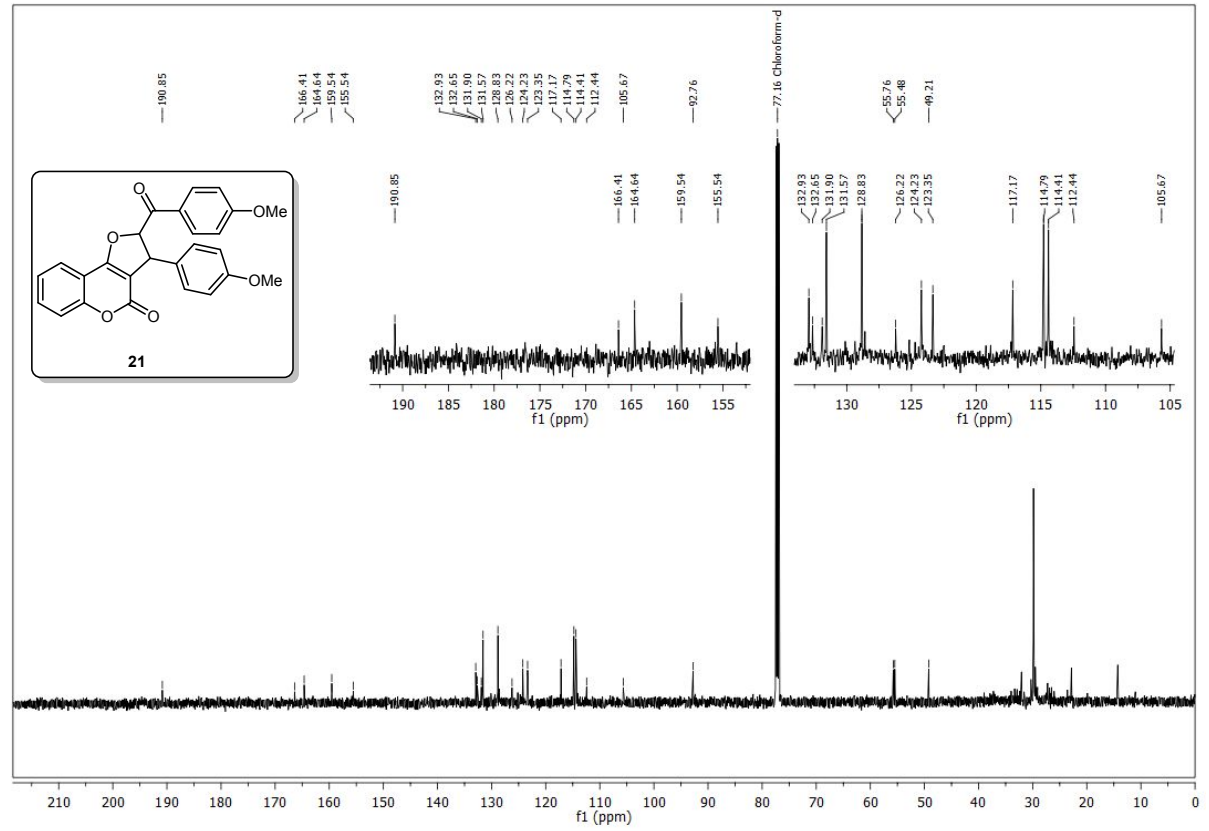
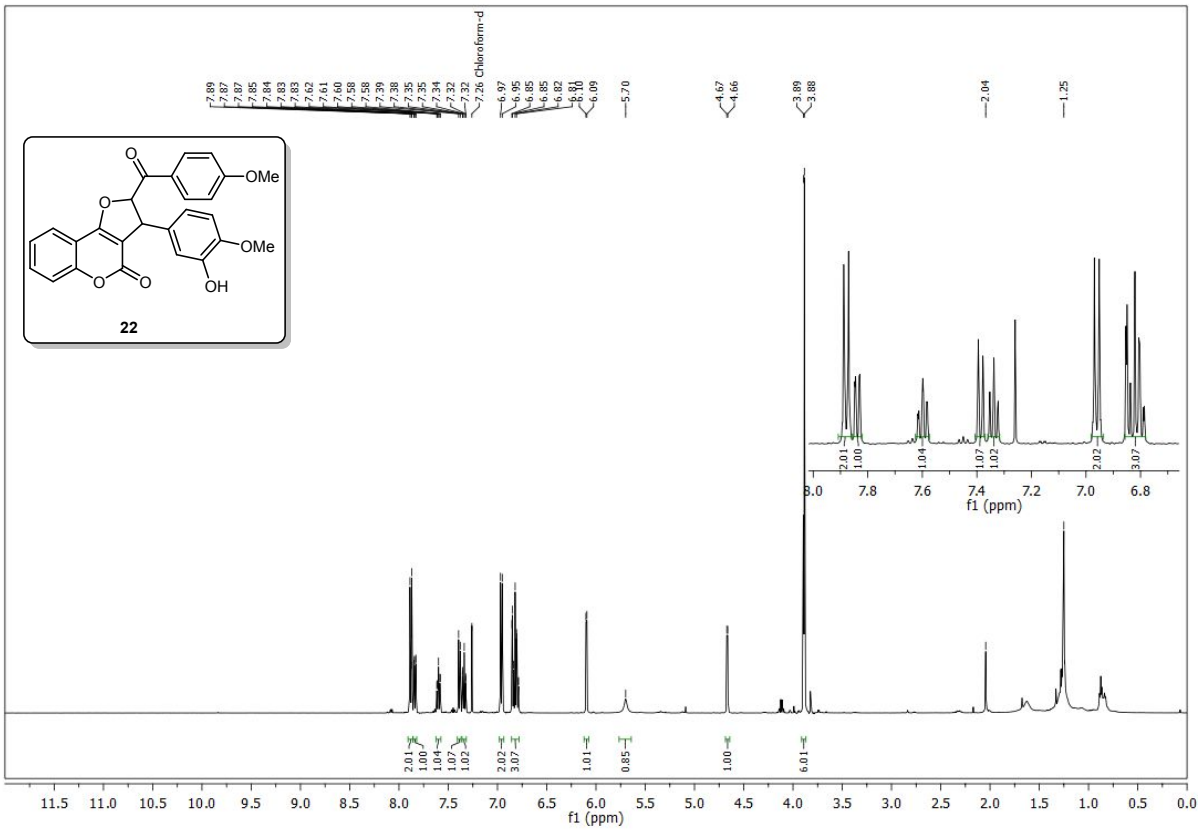


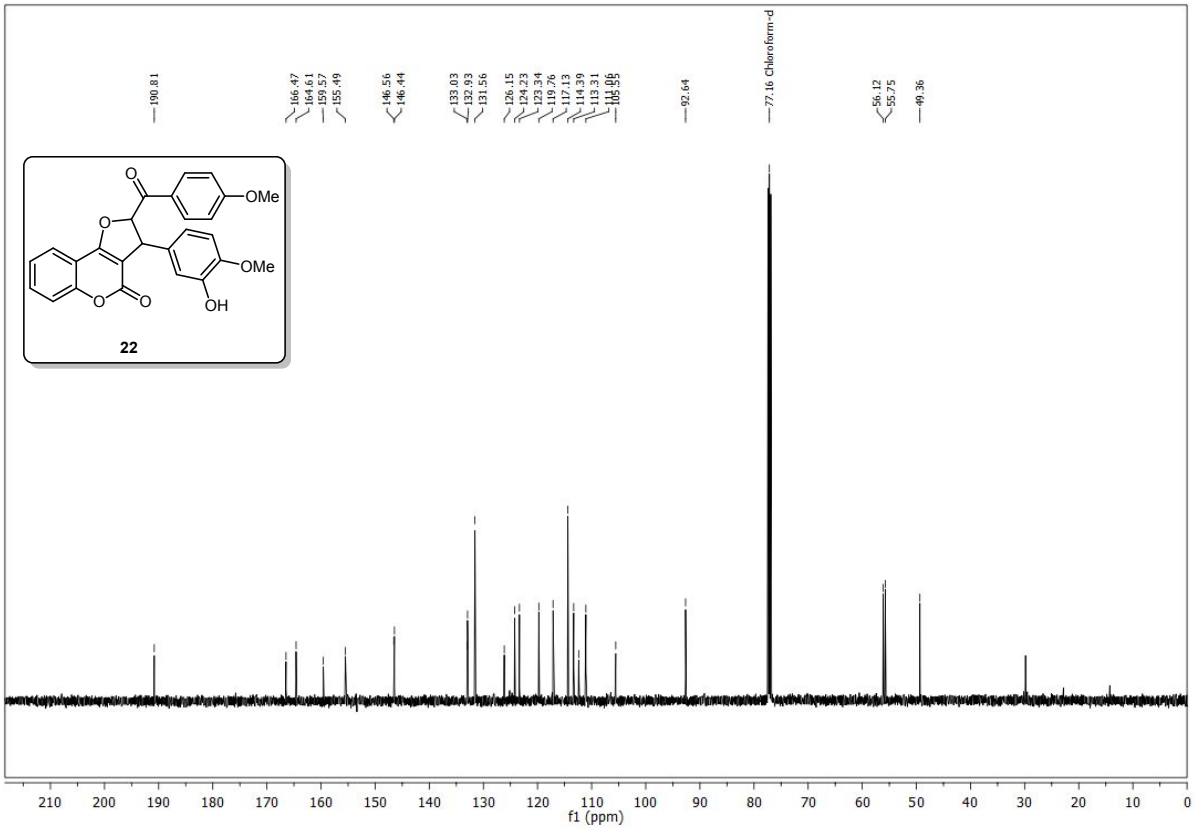
^{13}C NMR (126 MHz, $CDCl_3$) of **21**



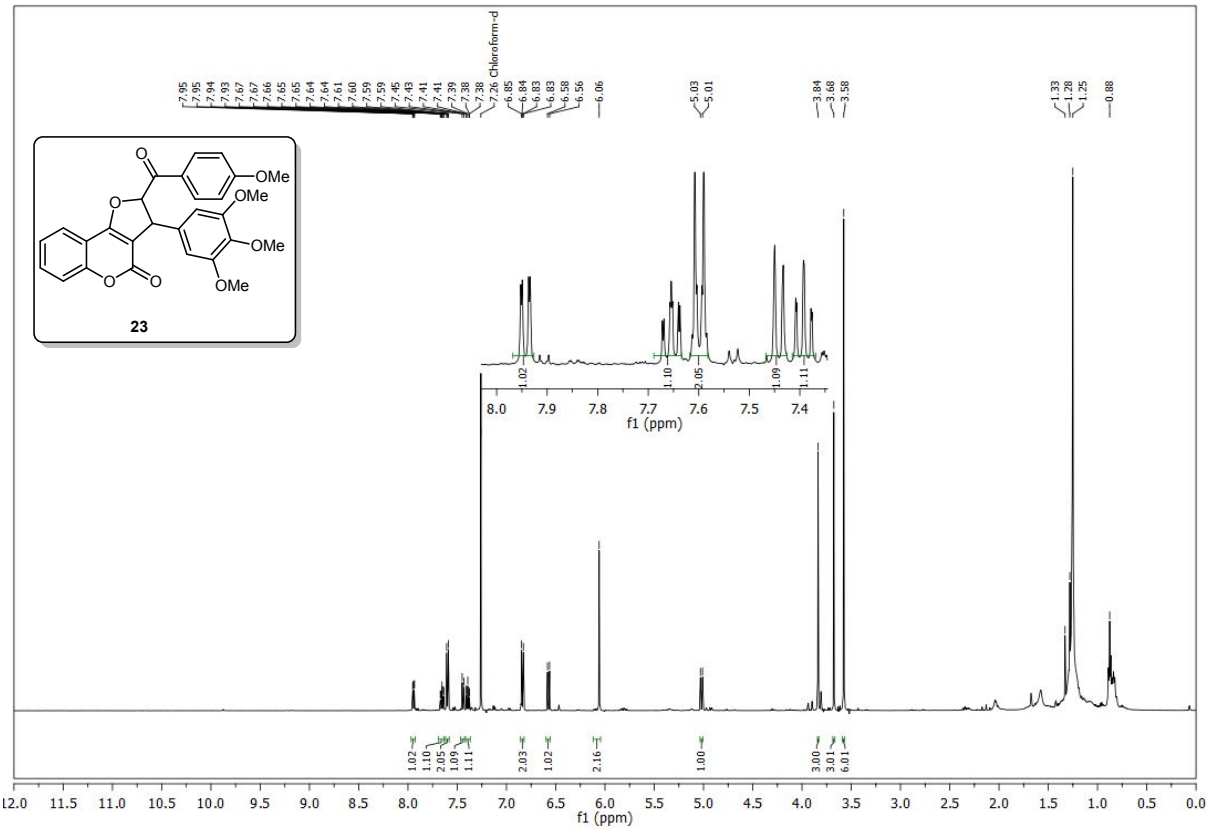
^{1}H NMR (500 MHz, $CDCl_3$) of **22**



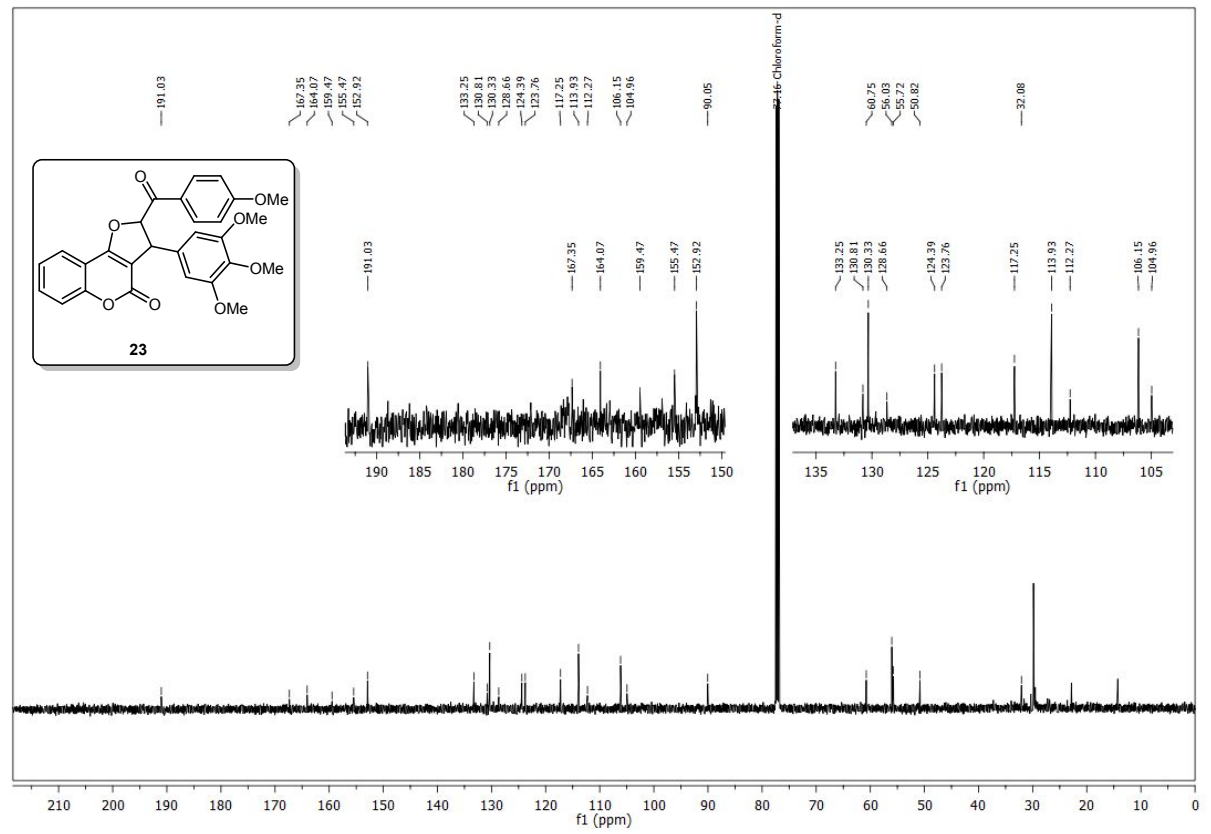
^{13}C NMR (126 MHz, $CDCl_3$) of **22**



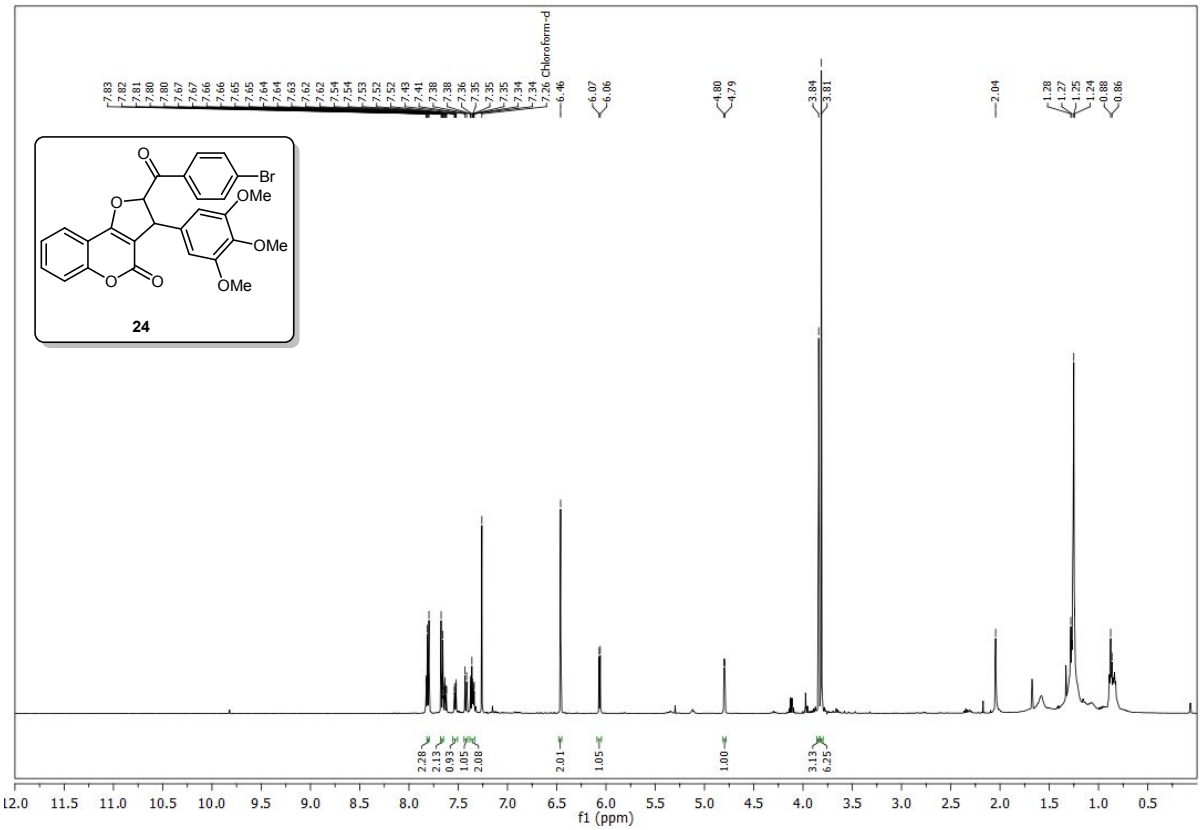
^{1}H NMR (500 MHz, $CDCl_3$) of **23**



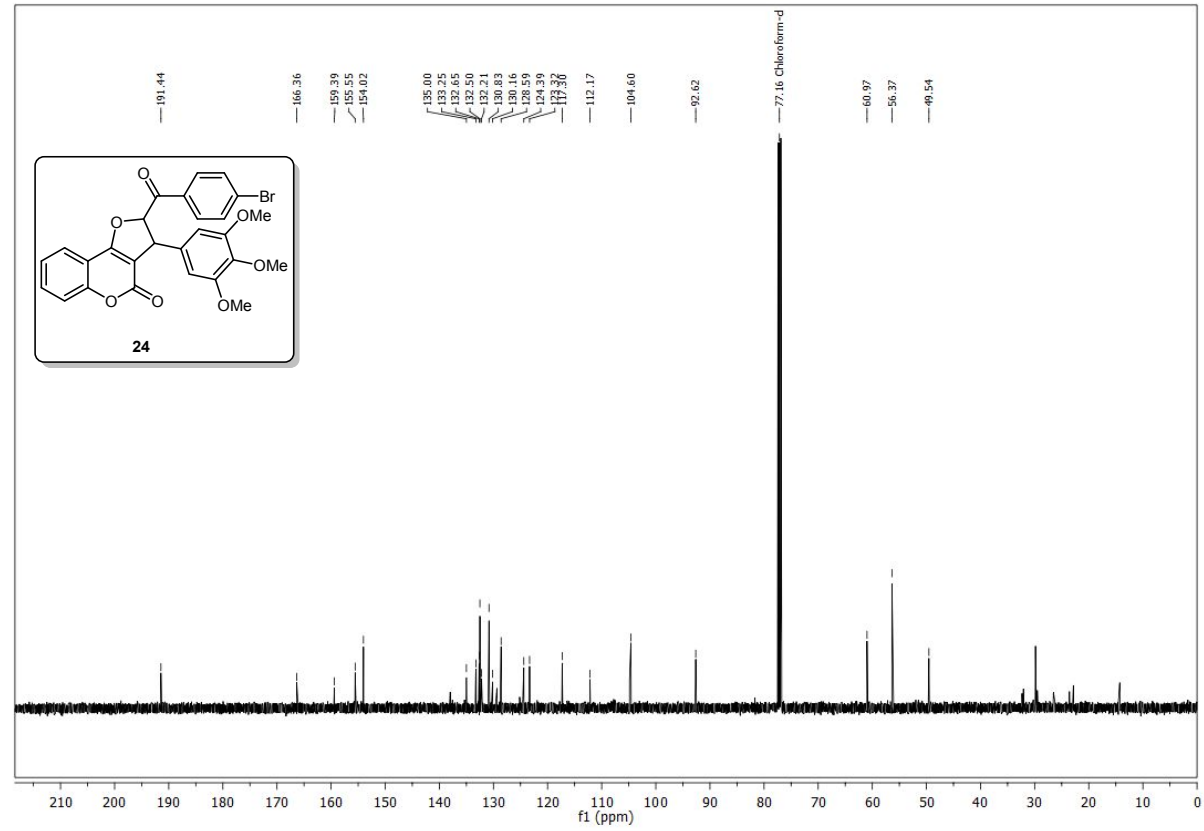
^{13}C NMR (126 MHz, $CDCl_3$) of **23**



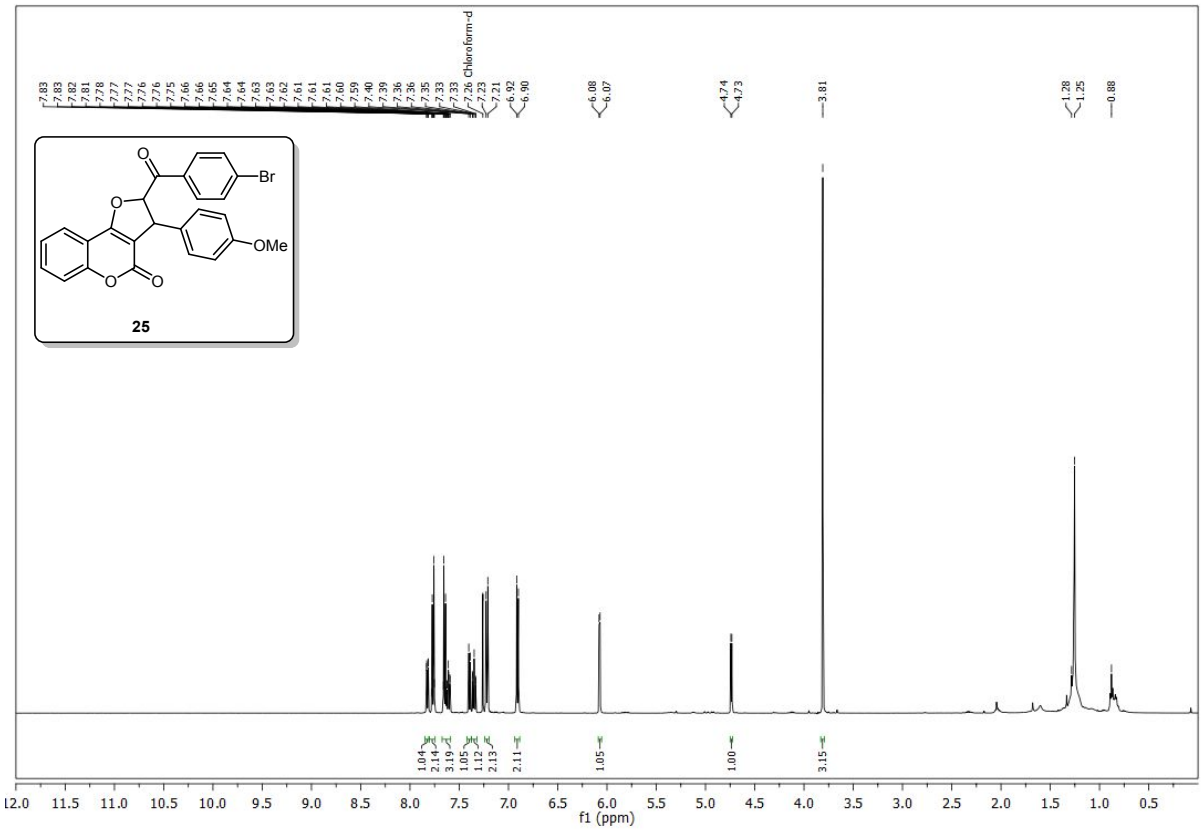
^{1}H NMR (500 MHz, $CDCl_3$) of **24**



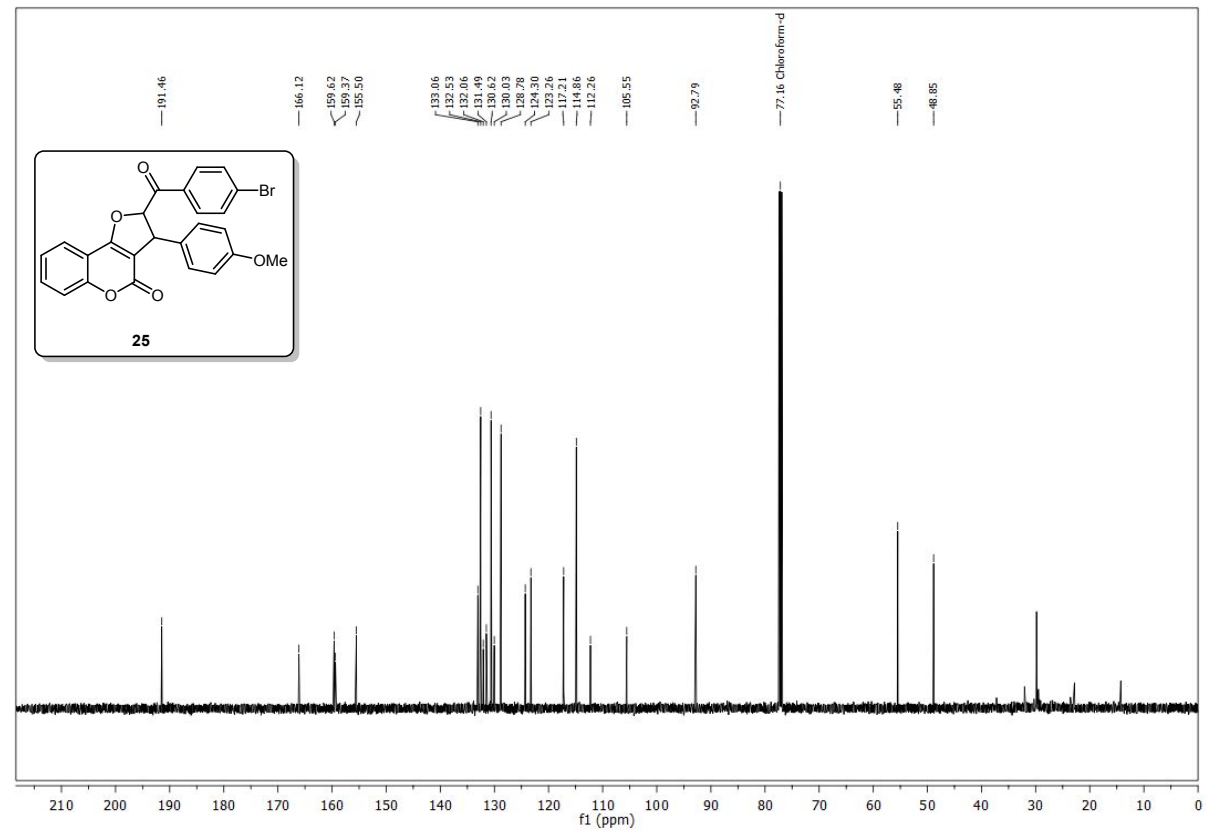
^{13}C NMR (126 MHz, $CDCl_3$) of **24**



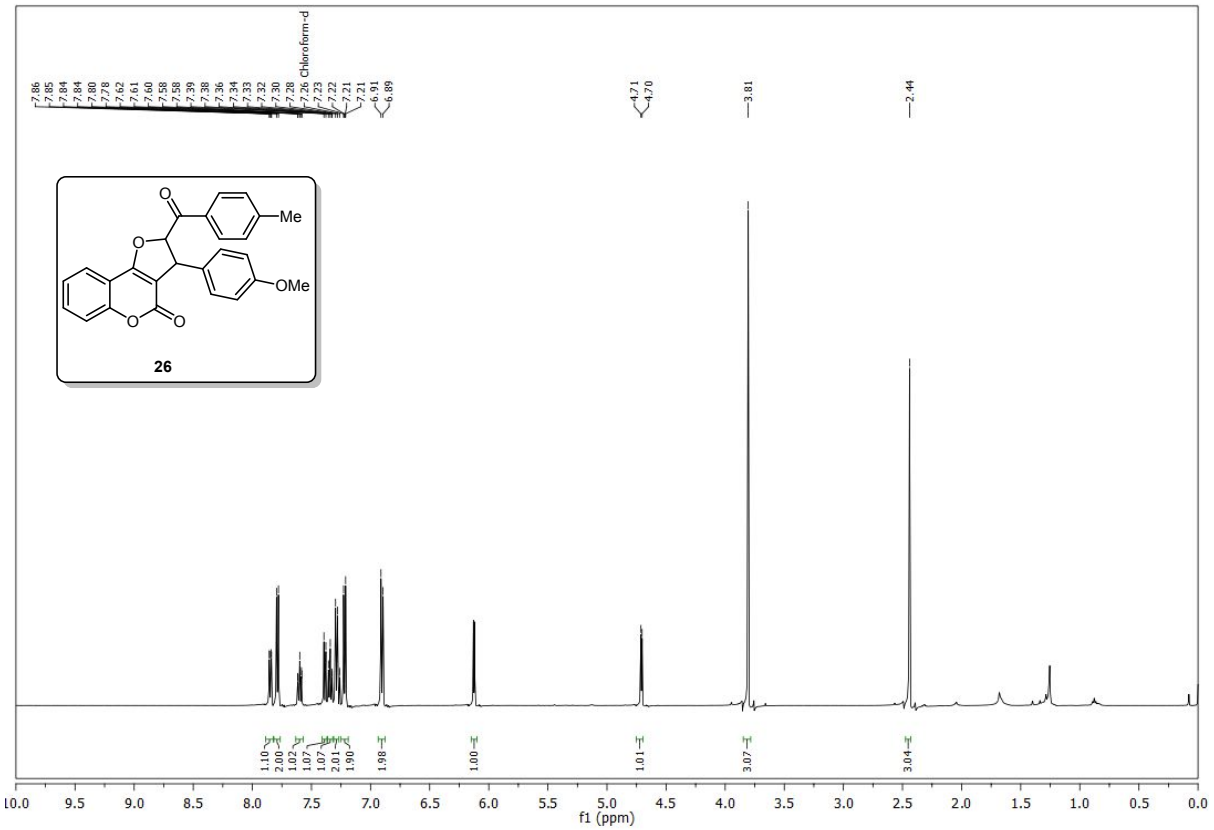
^{1}H NMR (500 MHz, $CDCl_3$) of **25**



^{13}C NMR (126 MHz, $CDCl_3$) of **25**



^{1}H NMR (500 MHz, $CDCl_3$) of **26**



^{13}C NMR (126 MHz, $CDCl_3$) of **26**