Synthesis of Isoquinolinone *via* Regioselective Palladium-Catalyzed C–H Activation/Annulation

Supporting Information

General Information

All chemicals were purchased as reagent grade and used without further purification. Solvents for purification (extraction and chromatography) were purchased as technical grade and distilled on the rotary evaporator prior to use. For column chromatography, SiO_2-60 (230-400 mesh) was used as stationary phase. Analytical thin layer chromatography (TLC) was performed on aluminium foil pre-coated with SiO_2-60 F_{254} (Merck) and visualized with a UV-lamp (254 nm) and $KMnO_4$ solution. Concentration in vacuo was performed at ~10 mbar and 40 °C. NMR spectra were measured by 400 MHz Bruker Avance III spectrometer. The resonance multiplicity is abbreviated as: s (singlet), d (doublet), t (triplet), q (quadruplet), m (multiplet) and b (broad). High resolution mass spectra (HRMS) analysis was performed on micro-TOF-Q II Bruker mass spectrometer with ESI as ionization source.

General procedure for the synthesis of N-methoxybenzamide from acid chloride

The synthesis followed a procedure reported by Booker-Milburn *et al*. [1]

Methoxylamine hydrochloride (840 mg, 10 mmol) and potassium carbonate (2.76 g, 20 mmol) were dissolved in a mixture of water (25 mL) and EtOAc (50 mL), and cooled to 0°C upon which acyl chloride (10 mmol) was added dropwise. The reaction was then allowed to warm to r.t. and stirred for between 5 h and overnight. The product was isolated by diluting the mixture with EtOAc/H_2O and separating the layers, the organic phase was then washed with brine and dried over MgSO4, filtered and concentrated to give the product which was then recrystallized (EtOAc/Hex) to give the target compound.

General procedure for the synthesis of N-methoxybenzamide from acid

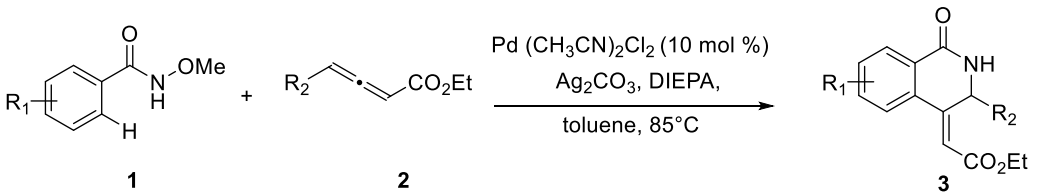
To a solution of substituted benzoic acid (10 mmol) in CH_2Cl_2 (30 mL) was added few drops of DMF, followed by slow addition of oxalyl chloride (1.7 mL, 20 mmol) at room temperature. The reaction was stirred overnight. The reaction mixture is evaporated under reduced pressure to give crude acyl chloride, which is used directly without further purification. Methoxylamine hydrochloride (840 mg, 10 mmol) and potassium carbonate (2.76 g, 20 mmol) were dissolved in a mixture of water (25 mL) and EtOAc (50 mL), and cooled to 0°C, acyl chloride (10 mmol) which is prepared abovementioned was added dropwise. The reaction was then allowed to warm to r.t. and stirred for between 5 h and overnight. The product was isolated by diluting the mixture with EtOAc/H2O and separating the layers, the organic phase was then washed with brine and dried over MgSO4, filtered and concentrated to give the product which was then recrystallized (EtOAc/Hex) to give the target compound.

General procedure for the synthesis of 2,3-allenoic acid esters

The synthesis followed a procedure reported by Kwon *et al*. [2]

Et_3N (63 mmol, 1.1 equiv) was added to a stirred solution of carbethoxymethylene) triphenylphosphorane (57.5 mmol, 1 equiv) in CH_2Cl_2 (200 mL). After stirring for 10 min, the required acyl chloride (57.5 mmol, 1 equiv) was added dropwise over 30 min at room temperature. After stirring overnight, the resulting mixture was poured unto a funnel packed with silica gel and was washed with CH_2Cl_2 several times. The combined filtrate was carefully concentrated and the resulting crude oil was purified by flash column chromatography (hexane/EtOAc, 20:1) to provide the 4-substituted 2,3-allenoic acid esters.

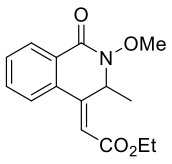
General procedure for Pd-catalyzed oxidative annulation with 2,3-allenoic acid esters



1 **2** **3**

An oven-dried round-bottom flask (25 mL) was charged with N-methoxybenzamide (0.50 mmol), 2, 3-allenoic acid esters (1.5 mmol, 3 equiv), silver(I) carbonate (0.275 g, 1 mmol, 2 equiv), N,N-diisopropylethylamine (DIPEA) (0.174 ml, 1 mmol, 2 equiv), (Bis(acetonitrile)dichloropalladium (II) (13.0 mg, 0.05 mmol) in 5 mL toluene. The mixture was heated at 85℃ for 4 hours under the atmosphere of argon, then allowed to cool down. The reaction mixture was diluted with EtOAc (10 mL) and filtered through a Celite pad, the filtrate was washed with water (10 mL). The aqueous layer was extracted with EtOAc (2×10 mL) and the combined organic layers were dried with anhydrous $MgSO_4$, then filtered and concentrated under reduced pressure. The crude product was purified by flash chromatograph, eluted with n-hexane/EtOAc to give the final product.

Ethyl (Z)-2-(2-methoxy-3-methyl-1-oxo-2,3-dihydroisoquinolin-4(1H)-ylidene)acetate, 3a

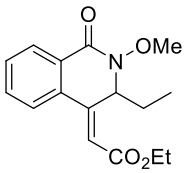


Prepared following the general procedure using N-methoxybenzamide (75.5 mg, 0.5 mmol) and

ethyl penta-2,3-dienoate (190.1 mg, 1.5mmol) to afford **3a** as colorless oil (117 mg, 85%).

IR (neat): 3356, 2978, 2918, 2848, 1708, 1676, 1632, 1596, 1373, 1296, 1179, 1021,735. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.30-8.27 (m, *J* = 4.8 Hz, 1H), 7.69-7.67 (m, 1H) 7.60-7.58 (m, 2H), 6.41 (s, 1H), 6.06-6.01 (q, *J* = 6.4 Hz, 1H), 4.34-4.37 (dq, *J* = 1.2Hz, 7.2Hz , 2H), 3.93 (s, 1H), 1.47-1.46 (d, *J* = 6.4 Hz, 3H), 1.41-1.37 (t, *J* = 7.2Hz, 3H). ^{13}C NMR (100MHz, $CDCl_3$, TMS): δ 165.3, 160.6, 150.9, 132.6, 132.6, 130.9, 128.5, 128.3, 124.4, 115.1, 62.4, 60.7, 55.6, 29.7, 19.1, 14.2. HRMS (ESI): calculated for $C_{15}H_{17}NNaO_4$ (M^+): 298.1055; found: 298.1065.

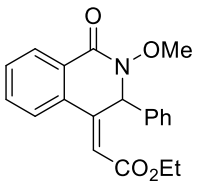
Ethyl (Z)-2-(3-ethyl-2-methoxy-1-oxo-2,3-dihydroisoquinolin-4(1H)-ylidene)acetate, 3b



Prepared following the general procedure using N-methoxybenzamide (75.5 mg, 0.5 mmol) and ethyl hexa-2,3-dienoate (211.1 mg, 1.5 mmol) to afford **3b** as yellow oil (111 mg, 77%).

IR (neat): 3357, 2968, 2919, 2849, 2359, 1710, 1676, 1372, 1296, 1251, 1178, 1008, 771, 692. ^{1}H NMR ($CDCl_3$, 400 MHz); δ 8.26-8.24 (d, *J* = 4.4 Hz, 1H), 7.65-7.56 (m, 3H), 6.42 (s, 1H), 6.06-6.03 (m, 1H), 4.33-4.27 (dq, *J* = 1.2 Hz, 7.2 Hz, 2H), 3.93 (s, 3H), 2.05-2.015 (m, 1H), 1.78-1.72 (m, 1H), 1.40-1.36 (t, *J* = 7.2Hz, 3H), 0.87-0.83 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100MHz, $CDCl_3$): δ 165.4, 160.5, 149.6, 133.7, 132.6, 130.8, 128.5, 128.4, 123.9, 116.5, 62.3, 60.6, 59.8, 29.7, 27.3, 14.2, 9.7. HRMS (ESI): calculated for $C_{16}H_{19}NNaO_4$ (M^+): 312.1212; found: 312.1200.

Ethyl (Z)-2-(2-methoxy-1-oxo-3-phenyl-2,3-dihydroisoquinolin-4(1H)-ylidene)acetate, 3c

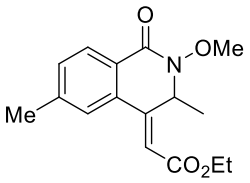


Prepared following the general procedure using N-methoxybenzamide (75.5 mg, 0.5 mmol) and ethyl 4-phenylbuta-2,3-dienoate (282.3 mg, 1.5 mmol) to afford **3c** as yellow oil (119.6 mg, 71%).

IR (neat): 3357, 2981, 2919, 2849, 1709, 1678, 1633, 1448, 1181, 1096, 992, 736, 699. ^{1}H NMR ($CDCl_3$, 400MHz); δ 8.32-8.30 (d, *J* = 6.8Hz, 1H), 7.56-7.55 (m, 3H), 7.34-7.32 (m, 3H), 7.25-7.24 (m, 3H), 6.40 (s, 1H), 4.38- 4.32 (q, *J* = 7.2Hz, 2H), 3.94 (s, 3H), 1.42-1.38 (t, 7.2Hz, 3H). ^{13}C NMR

(100MHz, $CDCl_3$): δ 165.5, 160.9, 149.1, 138.0, 133.6, 132.8, 130.9, 129.2, 128.7, 128.4, 128.1, 126.7, 126.5, 116.9, 62.7, 61.2, 60.8, 14.2. HRMS (ESI): calculated for $C_{20}H_{19}NNaO_4$ (M^+): 360.1212; found: 360.1209.

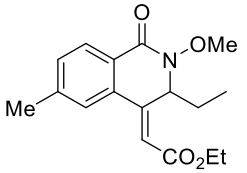
Ethyl (Z)-2-(2-methoxy-3,6-dimethyl-1-oxo-2,3-dihydroisoquinolin-4(1H)-ylidene)acetate, 3d



Prepared following the general procedure using N-methoxy-3-methylbenzamide (82.5 mg, 0.5 mmol) and ethyl penta-2,3-dienoate (190.1 mg, 1.5mmol) to afford **3d** as colorless oil (115.6 mg, 80%).

IR (neat): 2976, 2927, 1709, 1677, 1632, 1370, 1268, 1176, 1031, 901, 778, 692. ^{1}H NMR ($CDCl_3$, 400MHz); δ 8.17-8.14 (d, *J* = 8Hz, 1H), 7.47 (s, 1H), 7.40-7.38 (d, *J* = 8.0 Hz), 6.39 (s, 1H), 6.04-6.00 (q, *J* = 6.4 Hz, 1H), 4.31- 4.29 (q, *J* = 7.2 Hz, 2H), 3.92 (s, 3H), 2.47 (s, 3H), 1.45-1.44 (d, *J* = 6.4 Hz, 3H), 1.40-1.36 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100MHz, $CDCl_3$): δ 165.3, 160.8, 151.2, 143.2, 132.5, 131.9, 128.6, 125.8, 124.8, 114.7, 62.4, 60.61, 55.6, 21.7, 19.1, 14.2. HRMS (ESI): calculated for $C_{16}H_{19}NNaO_4$ (M^+): 312.1212; found: 312.1212.

Ethyl (Z)-2-(3-ethyl-2-methoxy-6-methyl-1-oxo-2,3-dihydroisoquinolin-4(1H)-ylidene)acetate, 3e

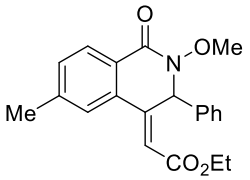


Prepared following the general procedure using N-methoxy-3-methylbenzamide (82.5 mg, 0.5 mmol) and ethyl hexa-2,3-dienoate (211.1 mg, 1.5 mmol) to afford **3e** as yellow oil (119.6 mg, 79%).

IR (neat): 3357, 2970, 2920, 2849, 1711, 1673, 1633, 1370, 1175, 1032, 879, 732, 696. 1H NMR (CDCl3, 400MHz); δ 8.14-8.12 (d, *J* = 7.6 Hz, 1H), 7.44 (s, 1H), 7.38- 7.36 (d, *J* = 8 Hz, 1H), 6.42 (s, 1H), 6.04-6.02 (t, *J* = 6.4 Hz, 1H), 4.31-4.27 (dq, *J* = 2.8 Hz, 7.2 Hz, 2H), 3.92 (s, 3H), 2.46 (s, 3H), 2.02-2.00 (m, 1H), 1,76-1.68 (m,1H), 1.40-1.38 (t, *J* = 7.2 Hz), 0.87-0.83 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100MHz, CDCl3, TMS): δ 165.5, 160.7, 149.9, 143.2, 133.6, 131.7, 128.4, 126.0, 124.4, 116.2, 62.3, 60.6, 59.8, 27.2, 21.7, 14.2, 9.7. HRMS (ESI): calculated for $C_{17}H_{21}NNaO_4$ (M+): 326.1368; found:

326.1364.

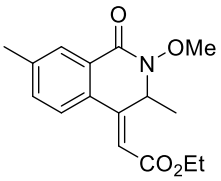
Ethyl (Z)-2-(2-methoxy-6-methyl-1-oxo-3-phenyl-2,3-dihydroisoquinolin-4(1H)-ylidene)acetate, 3f



Prepared following the general procedure using N-methoxy-3-methylbenzamide (82.5 mg, 0.5 mmol) and ethyl 4-phenylbuta-2,3-dienoate (282.3 mg, 1.5 mmol) to afford **3f** as yellow powder (114.6 mg, 65%).

IR (KBr): 3357, 2978, 2849, 1709, 1675, 1633, 1369, 1175, 1029, 757, 698. ^{1}H NMR ($CDCl_3$, 400MHz); δ 8.20-8.18 (d, *J* = 7.6 Hz, 1H), 7.39-7.31 (m, 5H), 7.27-7.24 (m, 3H), 6.39 (s, 1H), 4.38-4.32 (q, *J* = 7.2 Hz, 2H), 3.94 (s, 3H), 1.42-1.38 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (400MHz, $CDCl_3$): δ 165.6, 161.2, 149.4, 143.4, 138.1, 133.5 131.9, 128.6, 128.5, 128.0, 126.7, 125.9, 124.9, 116.5, 62.7, 61.2, 60.80, 21.6, 14.3. HRMS (ESI): calculated for $C_{21}H_{21}NNaO_4$ (M^+): 374.1368; found: 374.1362.

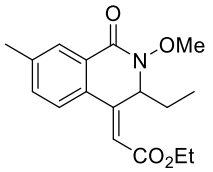
Ethyl (Z)-2-(2-methoxy-3,7-dimethyl-1-oxo-2,3-dihydroisoquinolin-4(1H)-ylidene)acetate, 3g



Prepared following the general procedure using N-methoxy-3-methylbenzamide (82.5 mg, 0.5 mmol) and ethyl penta-2,3-dienoate (190.1 mg, 1.5mmol) to afford **3g** as yellow oil (119.6 mg, 83 %).

IR (neat): 2980, 2924, 1709, 1678, 1632, 1370, 1265, 1174, 1025, 901, 775, 690. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.05 (d, *J* = 2.0 Hz, 1H), 7.54 (d, *J* = 8.1 Hz, 1H), 7.42 – 7.30 (m, 1H), 6.33 (d, *J* = 0.8 Hz, 1H), 6.05 – 5.81 (m, 1H), 4.25 (qd, *J* = 7.2, 1.3 Hz, 2H), 3.88 (s, 3H), 2.43 (s, 3H), 1.41 (d, *J* = 6.4 Hz, 3H), 1.34 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 165.38, 160.76, 151.05, 141.67, 133.51, 129.78, 128.79, 128.05, 124.39, 113.96, 77.35, 77.24, 77.03, 76.72, 62.38, 60.55, 55.66, 21.36, 19.24, 14.26. HRMS (ESI): calculated for $C_{16}H_{19}NNaO_4$ (M^+): 312.1212; found: 312.1216.

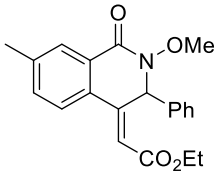
Ethyl (Z)-2-(3-ethyl-2-methoxy-7-methyl-1-oxo-2,3-dihydroisoquinolin-4(1H)-ylidene)acetate, 3h



Prepared following the general procedure using N-methoxy-3-methylbenzamide (82.5 mg, 0.5 mmol) and ethyl hexa-2,3-dienoate (211.1 mg, 1.5 mmol) to afford **3e** as yellow oil (121.0 mg, 80%).

IR (neat): 3363, 2965, 2923, 2847, 1708, 1671, 1636, 1369, 1169, 1031, 876, 727. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.09 – 7.95 (m, 1H), 7.51 (d, *J* = 7.9 Hz, 1H), 7.34 (dd, *J* = 8.1, 1.9 Hz, 1H), 6.35 (s, 1H), 5.99 (dd, *J* = 7.3, 5.0 Hz, 1H), 4.25 (qd, *J* = 7.1, 2.2 Hz, 2H), 3.88 (s, 3H), 2.43 (s, 3H), 2.10 – 1.89 (m, 1H), 1.80 – 1.68 (m, 1H), 1.34 (t, *J* = 7.1 Hz, 4H), 0.81 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.54, 160.67, 149.80, 141.45, 133.41, 130.91, 128.70, 128.30, 123.91, 115.36, 77.34, 77.23, 77.02, 76.71, 62.25, 60.53, 59.81, 27.40, 21.35, 14.26, 9.67. HRMS (ESI): calculated for $C_{17}H_{21}NNaO_4$ (M^+): 326.1368; found: 326.1371.

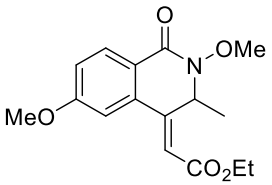
Ethyl (Z)-2-(2-methoxy-7-methyl-1-oxo-3-phenyl-2,3-dihydroisoquinolin-4(1H)-ylidene)acetate, 3i



Prepared following the general procedure using N-methoxy-3-methylbenzamide (82.5 mg, 0.5 mmol) and ethyl 4-phenylbuta-2,3-dienoate (282.3 mg, 1.5 mmol) to afford **3i** as white solid 115 mg, 66%).

IR (KBr): 3351, 2972, 2838, 1715, 1665, 1641, 1361, 1171, 1022, 743, 691. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.19 – 7.95 (m, 1H), 7.52 – 7.41 (m, 1H), 7.37 – 7.20 (m, 9H), 6.35 (s, 1H), 4.32 (d, *J* = 7.2 Hz, 2H), 3.92 (s, 3H), 2.46 (s, 3H), 1.38 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.62, 161.08, 149.21, 141.62, 133.64, 128.63, 126.69, 124.46, 124.06, 120.45, 115.82, 62.69, 61.29, 60.74, 21.40, 14.27. HRMS (ESI): calculated for $C_{21}H_{21}NNaO_4$ (M^+): 374.1368; found: 374.1361.

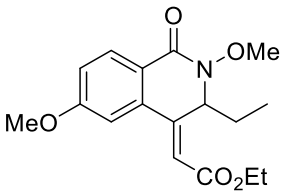
Ethyl (Z)-2-(2,6-dimethoxy-3-methyl-1-oxo-2,3-dihydroisoquinolin-4(1H)-ylidene)acetate, 3j



Prepared following the general procedure using N,4-dimethoxybenzamide (90.5 mg, 0.5 mmol) and ethyl penta-2,3-dienoate (190.1 mg, 1.5mmol) to afford **3j** as yellow oil (117.0 mg, 77 %).

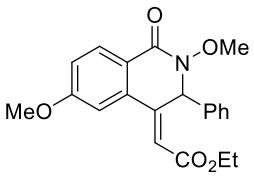
IR (neat): 3356, 2976, 2926, 2849, 1706, 1677, 1600, 1497, 1373, 1228, 1174, 1022, 829, 773. ^{1}H NMR ($CDCl_3$, 400MHz); δ 7.76-7.75 (d, *J* = 2.8 Hz, 1H), 7.62-7.60 (d, *J* = 8.8 Hz, 1H), 7.13-7.10 (dd, *J* = 2.8, 8.8 Hz), 6.28 (s, 1H), 6.03-5.98 (q, *J* = 6.4 Hz, 1H), 4.30-4.25 (q, *J* = 7.2 Hz, 2H), 3.94 (s, 3H), 3.92 (s, 3H), 1.47-1.45 (d, *J* = 6.4 Hz, 3H), 1.39-1.35 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100MHz, $CDCl_3$): δ 165.5, 162.00, 160.5, 150.9, 126.16, 120.5, 112.8, 111.1, 62.4, 60.5, 55.8, 19.4, 14.3. HRMS (ESI): calculated for $C_{16}H_{19}NNaO_5$ (M^+): 328.1161; found: 328.1155.

Ethyl (Z)-2-(3-ethyl-2,6-dimethoxy-1-oxo-2,3-dihydroisoquinolin-4(1H)-ylidene)acetate, 3k



Prepared following the general procedure using N,4-dimethoxybenzamide (90.5 mg, 0.5 mmol) and ethyl hexa-2,3-dienoate (211.1 mg, 1.5 mmol) to afford **3k** as yellow oil (129.0 mg, 81 %).
IR (neat): 3357, 2970, 2921, 2848, 1706, 1676, 1600, 1496, 1372, 1324, 1225, 1174, 1029, 881, 829, 786. ^{1}H NMR ($CDCl_3$, 400MHz,); δ 7.75-7.74 (d, *J* = 2.8Hz, 1H), 7.59-7.57 (d, *J* = 8.8Hz, 1H), 7.10-7.08 (dd, *J* = 2.8 Hz, 8.8 Hz, 1H), 6.31 (s, 1H), 6.05-6.02 (dq, *J* = 1.6 Hz, 7.2Hz, 2H), 4.30-4.25 (m, 2H), 3.93 (s, 3H), 3.92 (s, 1H), 2.01-1.97 (m, 1H), 1.81-1.75 (m, 1H), 1.39- 1.37 (t, *J* = 6Hz), 0.086 (t, *J* = 7.6Hz, 3H)^{13}C NMR (100MHz, $CDCl_3$): δ 165.6, 161.8, 160.4, 149.7, 130.3, 126.2, 125.6, 120.3, 114.1, 111.1, 62.2, 60.4, 59.9, 55.8, 27.6, 14.3, 9.6. HRMS (ESI): calculated for $C_{17}H_{21}NNaO_5$ (M^+): 342.1317; found: 342.1319.

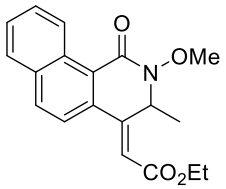
Ethyl (Z)-2-(2,6-dimethoxy-1-oxo-3-phenyl-2,3-dihydroisoquinolin-4(1H)-ylidene)acetate, 3l



Prepared following the general procedure using N,4-dimethoxybenzamide (90.5 mg, 0.5 mmol) and ethyl 4-phenylbuta-2,3-dienoate (282.3 mg, 1.5 mmol) to afford **3l** as yellow powder (112 mg, 61%).

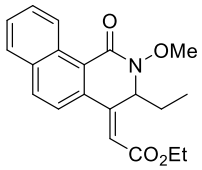
IR (KBr): 3442, 2917, 2848, 1705, 1674, 1601, 1175, 753, 693. ^{1}H NMR ($CDCl_3$, 400MHz); δ 7.8 (d, *J* = 2.8Hz, 1H), 7.5 (d, *J* = 8.8Hz, 1H), 7.33-7.29 (m, 3H), 7.26-7.24 (m, 3H), 7.09-7.06 (dd, *J* = 2.8 Hz, 8.8Hz, 1H), 6.30 (s, 1H), 4.35-4.30 (q, *J* = 7.2 Hz, 2H), 3.95 (s, 3H), 3.93 (s, 3H), 1.40-1.37 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100MHz, $CDCl_3$): δ 165.7, 162.0, 160.8, 149.0, 138.3, 129.0, 128.8, 128.6, 128.1, 126.8, 126.2, 120.4, 114.7, 111.3, 62.7, 61.5, 60.6, 55.8, 55.8, 14.3. HRMS (ESI): calculated for $C_{21}H_{21}NNaO_5$ (M^+): 390.1317; found: 390.1319.

ethyl (Z)-2-(2-methoxy-3-methyl-1-oxo-2,3-dihydrobenzo[h]isoquinolin-4(1H)-ylidene)acetate, 3m



Prepared following the general procedure using N-methoxy-1-naphthamide (100 mg, 0.5 mmol) and ethyl penta-2,3-dienoate (190.1 mg, 1.5mmol) to afford **3m** as white powder (99.0 mg, 61 %). IR (KBr): 3357, 2918, 2848, 1708, 1661, 1631, 1470, 1182,1031,984. ^{1}H NMR ($CDCl_3$, 400MHz); δ 9.78-9.76 (d, *J* = 6.6 Hz, 1H), 8.05-8.03 (d, *J* = 6.6 Hz, 1H), 7.89- 7.87 (d, *J* = 7.6 Hz, 1H), 7.70-7.61 (m, 3H), 6.46 (s, 1H), 6.10-6.06 (q, *J* = 6.4 Hz, 1H), 4.34-4.32 (dq, *J* = 1.2Hz, 7.2Hz, 2H), 4.01 (s, 3H), 1.51-1.49 (d, *J* = 6.4 Hz, 3H), 1.42-1.38 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100MHz, $CDCl_3$): δ 165.2, 161.5, 152.1, 135.1, 133.7, 132.9, 131.7, 128.7, 128.2, 128.1 127.5, 123.5, 121.4, 116.5, 62.6, 60.7, 55.2, 19.4, 14.3. HRMS (ESI): calculated for $C_{19}H_{19}NNaO_4$ (M^+): 348.1212; found: 348.1203.

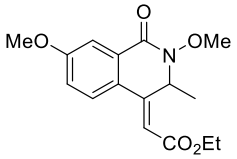
Ethyl (Z)-2-(3-ethyl-2-methoxy-1-oxo-2,3-dihydrobenzo[h]isoquinolin-4(1H)-ylidene)acetate, 3n



Prepared following the general procedure using N-methoxy-1-naphthamide (100 mg, 0.5 mmol) and ethyl hexa-2,3-dienoate (211.1 mg, 1.5 mmol) to afford **3n** as white powder (109.0 mg, 64 %).

IR (KBr): 3335, 2901, 2829, 1700, 1643, 1621, 1468, 1160, 1011, 972. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.68 (d, *J* = 8.8 Hz, 1H), 8.02 (d, *J* = 8.6 Hz, 1H), 7.97 – 7.83 (m, 2H), 7.69 (ddt, *J* = 8.7, 6.5, 2.3 Hz, 1H), 7.64 – 7.46 (m, 2H), 6.47 (s, 1H), 6.05 (t, *J* = 6.5 Hz, 1H), 4.31 (qd, *J* = 7.1, 2.1 Hz, 2H), 3.99 (s, 2H), 2.00 (ddd, *J* = 13.7, 7.6, 6.1 Hz, 1H), 1.74 (dp, *J* = 22.2, 7.3 Hz, 1H), 1.39 (d, *J* = 7.1 Hz, 2H), 0.90 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.36, 161.29, 151.02, 134.83, 133.76, 133.63, 132.14, 131.50, 128.62, 128.20, 128.01, 127.91, 127.44, 126.81, 123.87, 123.66, 121.17, 120.85, 117.59, 77.33, 77.22, 77.02, 76.70, 65.62, 62.26, 60.71, 59.33, 29.34, 27.53, 15.36, 14.26, 13.65, 10.02. HRMS (ESI): calculated for $C_{20}H_{21}NNaO_4$ (M^+): 362.1368; found: 362.1361.

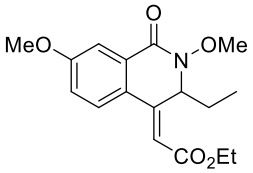
Ethyl (Z)-2-(2,7-dimethoxy-3-methyl-1-oxo-2,3-dihydroisoquinolin-4(1H)-ylidene)acetate, 3o



Prepared following the general procedure using N,3-dimethoxybenzamide (90.5 mg, 0.5 mmol) and ethyl penta-2,3-dienoate (190.1 mg, 1.5mmol) to afford **3o** as yellow oil (132.6 mg, 87 %).

IR (neat): 3341, 2968, 2914, 2852, 1700, 1661, 1570, 1481, 1358, 1202, 1161, 810, 758. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.73 (d, *J* = 2.7 Hz, 1H), 7.58 (d, *J* = 8.8 Hz, 1H), 7.08 (dd, *J* = 8.7, 2.7 Hz, 1H), 6.25 (s, 1H), 5.97 (q, *J* = 6.5 Hz, 1H), 4.24 (s, 2H), 3.90 (s, 3H), 3.89 (s, 3H), 1.43 (d, *J* = 6.5 Hz, 3H), 1.34 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.47, 161.97, 160.45, 150.89, 130.01, 126.15, 125.04, 120.47, 112.77, 111.10, 77.34, 77.22, 77.02, 76.70, 62.37, 60.44, 55.81, 19.42, 14.27. HRMS (ESI): calculated for $C_{16}H_{19}NNaO_5$ (M^+): 328.1161; found: 328.1166.

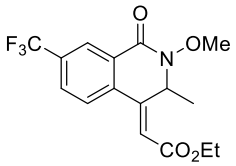
Ethyl (Z)-2-(3-ethyl-2,7-dimethoxy-1-oxo-2,3-dihydroisoquinolin-4(1H)-ylidene)acetate, 3p



Prepared following the general procedure using N,3-dimethoxybenzamide (90.5 mg, 0.5 mmol) and ethyl hexa-2,3-dienoate (211.1 mg, 1.5 mmol) to afford **3p** as yellow oil (130.0 mg, 82 %).

IR (neat): 3342, 2959, 2917, 2832, 1700, 1658, 1487, 1365, 1311, 1215, 1160, 877, 819, 767. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.74 (d, *J* = 2.7 Hz, 1H), 7.58 (d, *J* = 8.7 Hz, 1H), 7.09 (dd, *J* = 8.7, 2.7 Hz, 1H), 6.31 (s, 1H), 6.03 (dd, *J* = 7.1, 5.0 Hz, 1H), 4.27 (qd, *J* = 7.1, 1.8 Hz, 2H), 3.93 (s, 3H), 3.92 (s, 3H), 2.00 (dtt, *J* = 12.7, 7.5, 3.7 Hz, 1H), 1.79 (dp, *J* = 14.6, 7.5 Hz, 1H), 1.37 (t, *J* = 7.2 Hz, 3H), 0.84 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.62, 161.84, 160.38, 149.64, 130.26, 126.21, 125.63, 120.29, 114.13, 111.09, 77.33, 62.23, 60.43, 59.93, 55.79, 27.61, 14.27, 9.62. HRMS (ESI): calculated for $C_{17}H_{21}NNaO_5$ (M^+): 342.1317; found: 342.1315.

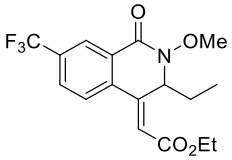
Ethyl (Z)-2-(2-methoxy-3-methyl-1-oxo-7-(trifluoromethyl)-2,3-dihydroisoquinolin-4(1H)-ylidene)acetate, 3q



Prepared following the general procedure using N-methoxy-3-(trifluoromethyl)benzamide (110.0 mg, 0.5 mmol) and ethyl penta-2,3-dienoate (190.1 mg, 1.5mmol) to afford **3** as yellow oil (97.0 mg, 57 %).

IR (neat): 3440, 3360, 2917, 2848, 1713, 1682, 1635, 1331, 1294, 1181, 1131, 1031, 840. ^{1}H NMR ($CDCl_3$, 400MHz); δ 8.56 (s, 1H), 7.85-7.78 (m, 2H), 6.46(s,1H), 6.09-6.03 (q, J = 6.4 Hz, 1H), 4.34-4.31 (dq, *J* = 1.5, 7.2 Hz, 2H), 3.95 (s, 3H), 1.48-1.47 (d, *J* = 6.8 Hz, 3H), 1.42-1.38 (t, *J* = 6.8 Hz). ^{13}C NMR (100MHz, $CDCl_3$): δ 164.8, 159.2, 149.1, 135.8, 133.1, 129.1, 125.8, 125.1, 122.0, 117.3, 62.6, 61.0, 29.7, 19.2, 14.2. HRMS (ESI): calculated for $C_{16}H_{16}F_3NNaO_4$ (M^+): 366.0929; found: 366.0933.

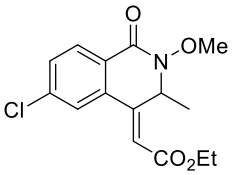
Ethyl (Z)-2-(3-ethyl-2-methoxy-1-oxo-7-(trifluoromethyl)-2,3-dihydroisoquinolin-4(1H)-ylidene)acetate, 3r



Prepared following the general procedure using N-methoxy-3-(trifluoromethyl)benzamide (110.0 mg, 0.5 mmol) and ethyl hexa-2,3-dienoate (211.1 mg, 1.5 mmol) to afford **3r** as yellow oil (109.0 mg, 61 %).

IR (neat): 3356, 2918, 2848, 1713, 1678, 1469, 1329, 1297, 1180, 1131, 1071, 783. ^{1}H NMR ($CDCl_3$, 400MHz); δ 8.53 (s, 1H), 7.83-7.74 (m, 2H), 6.48 (s, 1H), 6.08-6.05 (dd, *J* = 5.2, 7.6Hz, 1H), 4.33-4.30 (dq, *J* = 1.4, 7.2Hz, 2H), 3.93 (s, 3H), 2.10-1.97 (m, 1H), 1.76-1.69 (m, 1H), 1.41- 1.37 (t, *J* = 7.2 Hz, 3H), 0.87- 0.83 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (400MHz, $CDCl_3$): δ 164.9, 159.2, 147.9, 136.8, 132.6, 129.3 129.1, 129, 125.7, 124.7, 118.7, 62.4, 61.0, 60.0, 27.3, 14.2, 9.7. HRMS (ESI): calculated for $C_{17}H_{18}F_3NNaO_4$ (M^+): 380.1086; found: 380.1090.

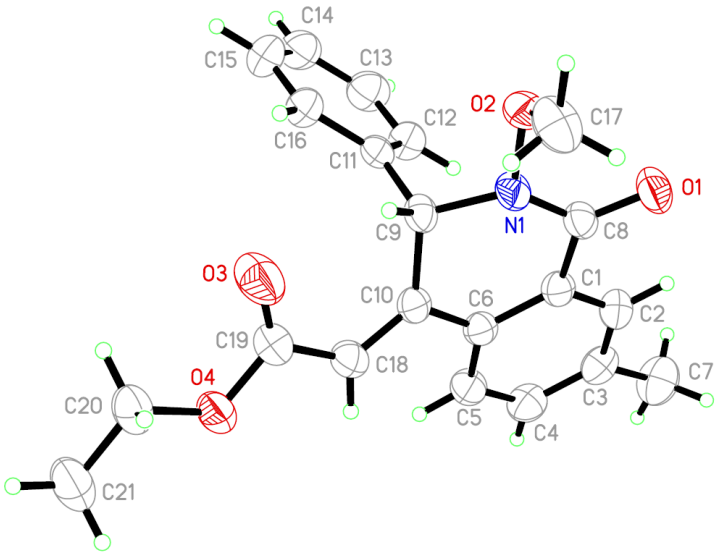
Ethyl (Z)-2-(6-chloro-2-methoxy-3-methyl-1-oxo-2,3-dihydroisoquinolin-4(1H)-ylidene)acetate, 3s



Prepared following the general procedure using 4-chloro-N-methoxybenzamide (92.0 mg, 0.5 mmol) and ethyl penta-2,3-dienoate (190.1 mg, 1.5mmol) to afford **3s** as yellow oil (82.0 mg, 53 %).

IR (neat): 3433, 3351, 2910, 2830, 1701, 1665, 1312, 1277, 1143, 1011, 812. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.18 (d, *J* = 8.4 Hz, 1H), 7.61 (d, *J* = 1.9 Hz, 1H), 7.51 (dd, *J* = 8.4, 2.0 Hz, 1H), 6.35 (s, 1H), 5.99 (q, *J* = 6.4 Hz, 1H), 4.27 (tt, *J* = 7.1, 3.6 Hz, 2H), 3.88 (s, 3H), 1.42 (d, *J* = 6.5 Hz, 3H), 1.35 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.93, 159.83, 149.42, 139.13, 134.17, 131.02, 130.16, 126.70, 124.38, 116.23, 62.51, 60.86, 55.55, 19.12, 14.21. HRMS (ESI): calculated for $C_{15}H_{16}ClNNaO_4$ (M^+): 332.0666; found: 332.0673.

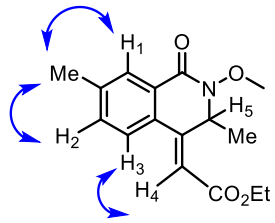
Crystal Data and Structure Refinement for 3i:



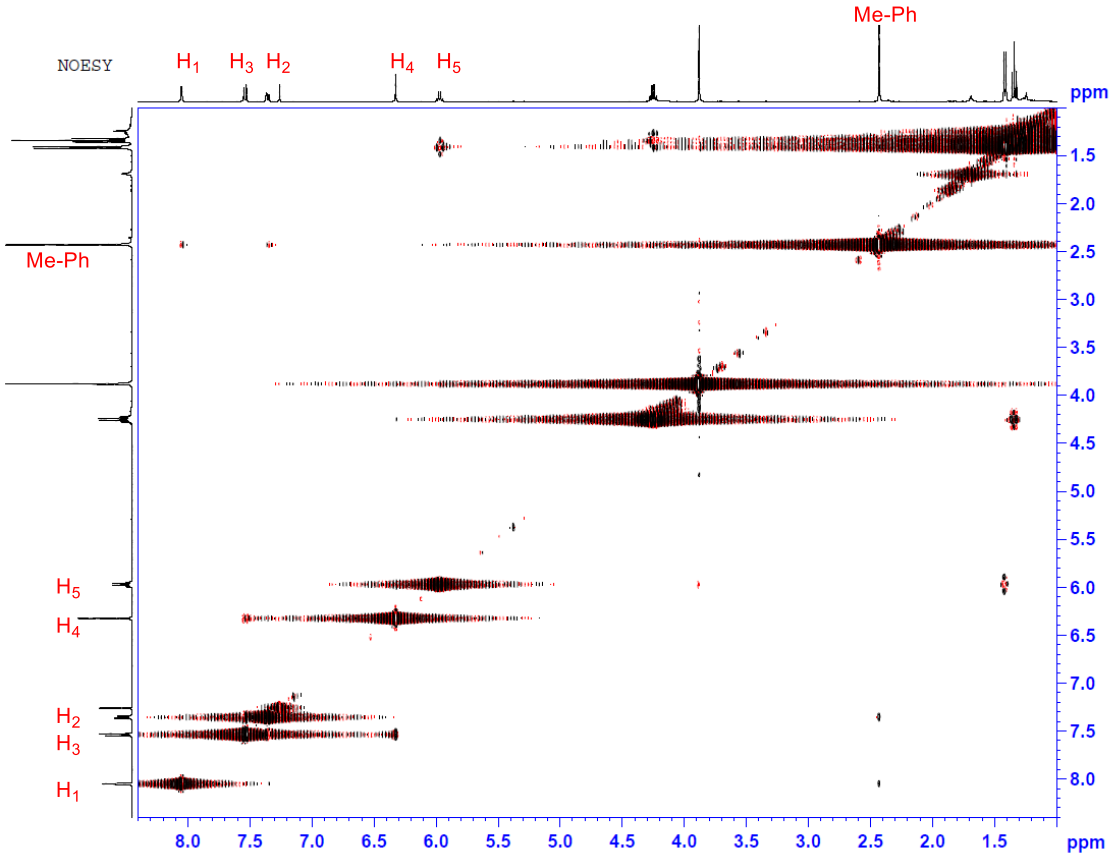
Identification code	yl03	
Empirical formula	C21 H21 N O4	
Formula weight	351.39	
Temperature	296(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 9.9002(6) Å	α= 81.346(2)°.
	b = 10.0585(6) Å	β= 85.430(2)°.
	c = 10.3273(6) Å	γ = 63.844(2)°.
Volume	912.48(10) $Å^3$	
Z	2	
Density (calculated)	1.279 Mg/m^3	
Absorption coefficient	0.089 mm^{-1}	
F(000)	372	
Crystal size	0.30 x 0.20 x 0.10 mm^3	
Theta range for data collection	3.017 to 25.995°.	
Index ranges	-12<=h<=12, -12<=k<=12, -11<=l<=12	
Reflections collected	11791	
Independent reflections	3388 [R(int) = 0.0696]	
Completeness to theta = 25.242°	96.1 %	

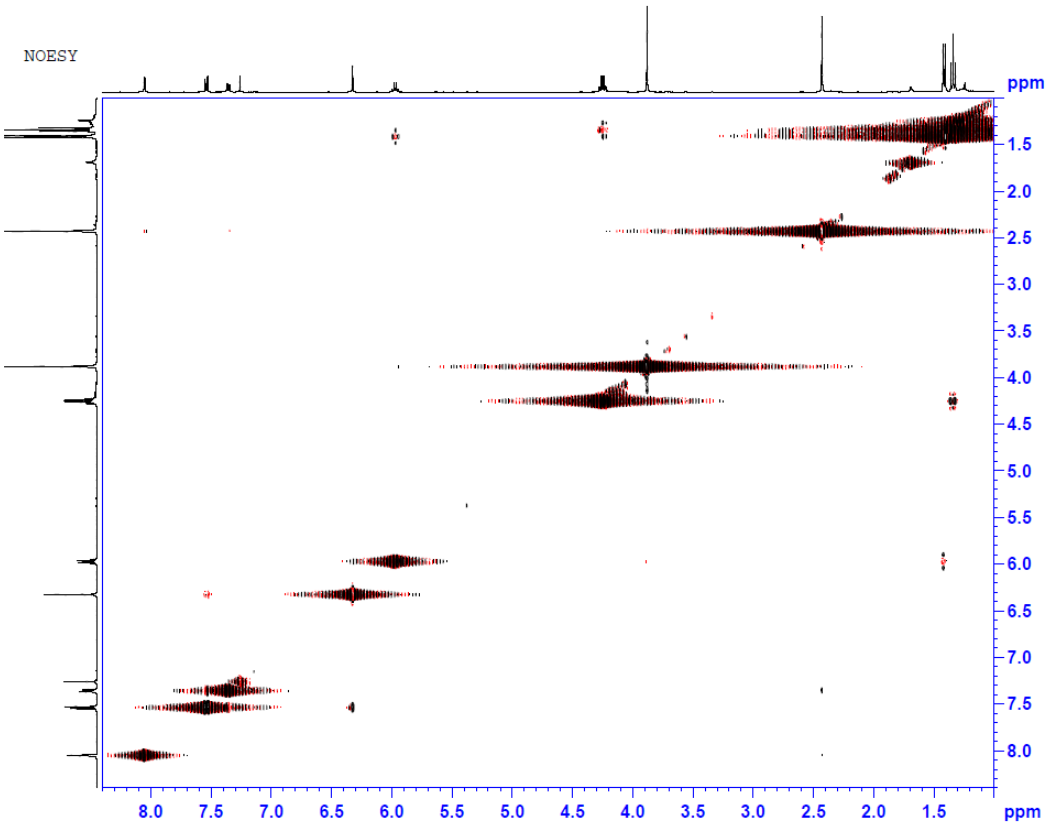
Absorption correction	Empirical (Bruker SADABS)
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3388 / 0 / 235
Goodness-of-fit on F^2	1.032
Final R indices [I>2sigma(I)]	R1 = 0.0557, wR2 = 0.1397
R indices (all data)	R1 = 0.0761, wR2 = 0.1552
Extinction coefficient	n/a
Largest diff. peak and hole	0.247 and -0.196 e.Å^{-3}

2D NMR Experiment (NOESY) (3g)



(**3g**)

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2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
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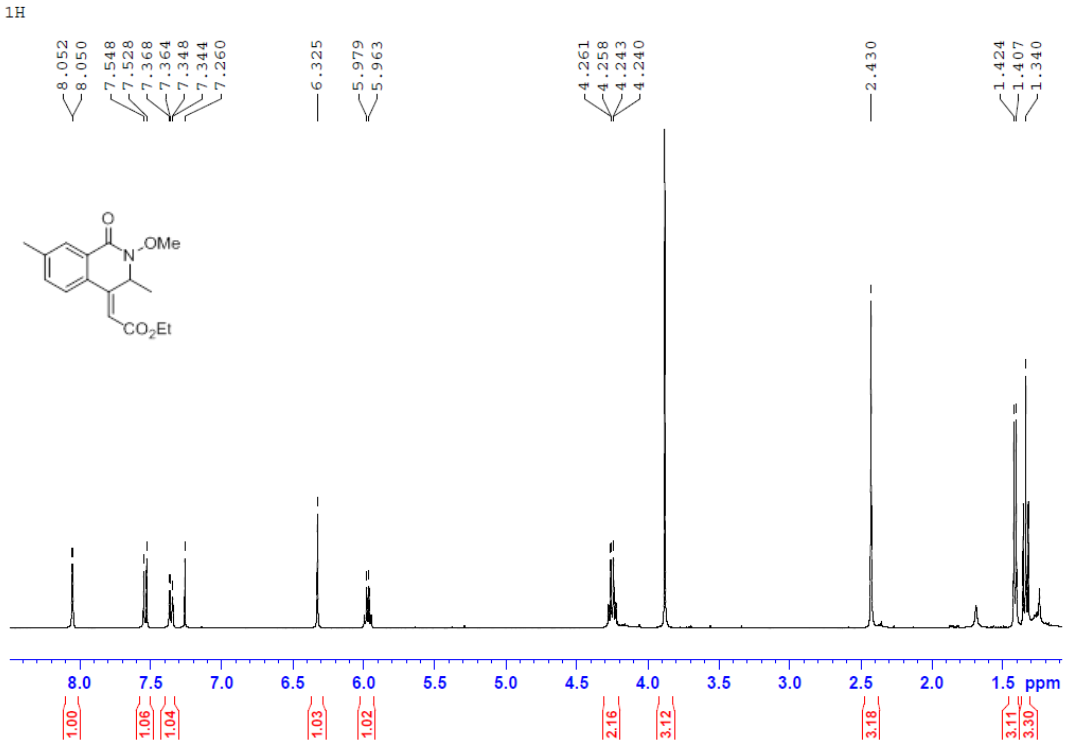
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 ppm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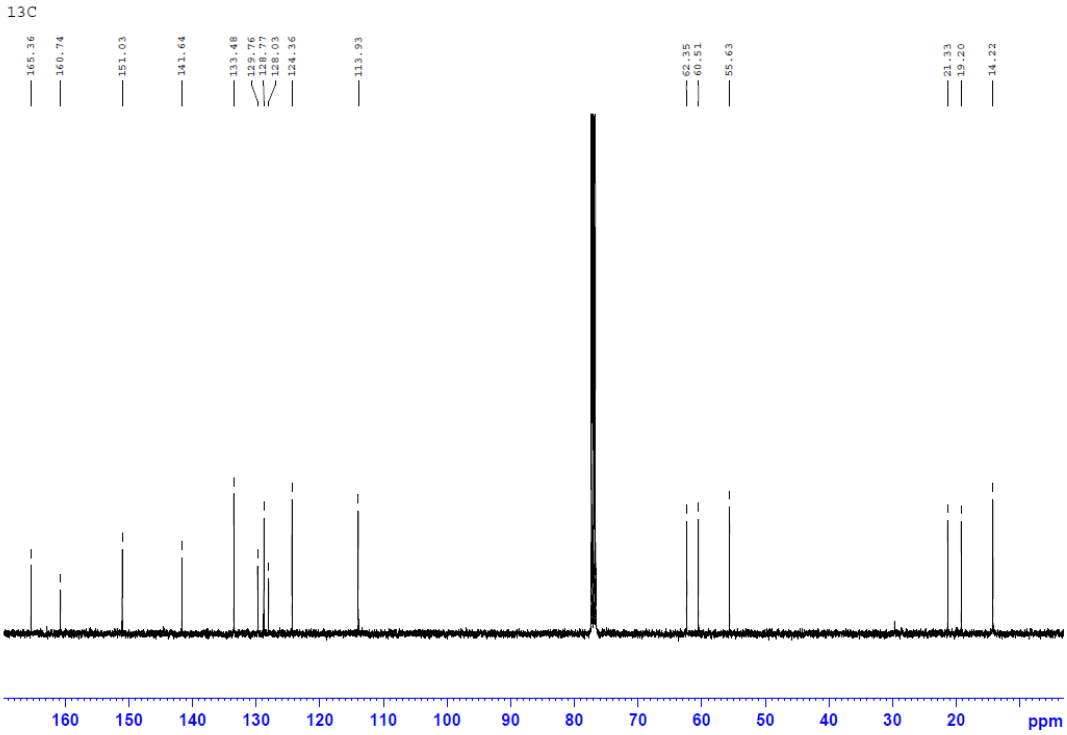
8.050
7.548
7.528
7.368
7.364
7.348
7.344
7.260
6.325
5.979
5.963
4.261
4.258
4.243
4.240
2.430
1.424
1.407
1.340
O
N
OMe
CO2Et
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 ppm
1.00
1.06
1.04
1.03
1.02
2.16
3.12
3.18
3.11
3.30


13C
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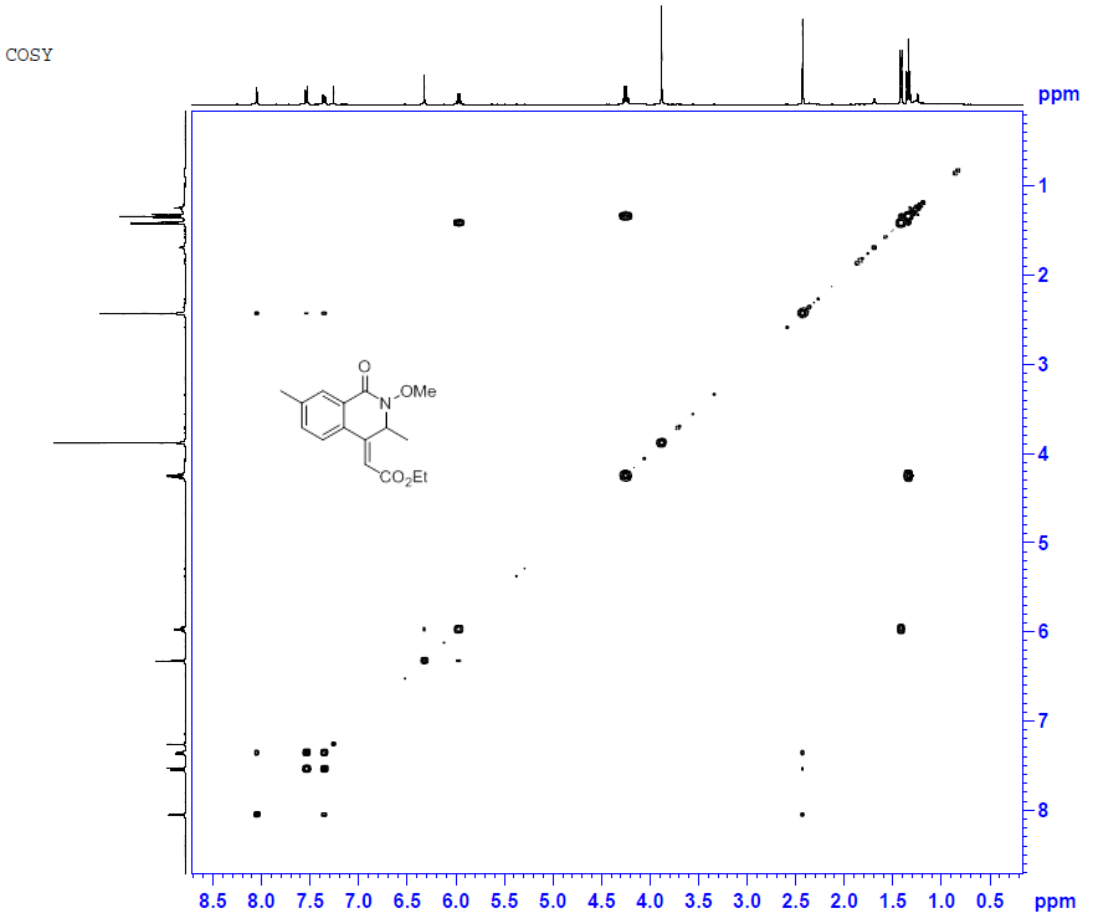
128.77
128.03
124.36
113.93
62.35
60.51
55.63
21.33
19.20
14.22
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm


COSY
ppm
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2
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4
5
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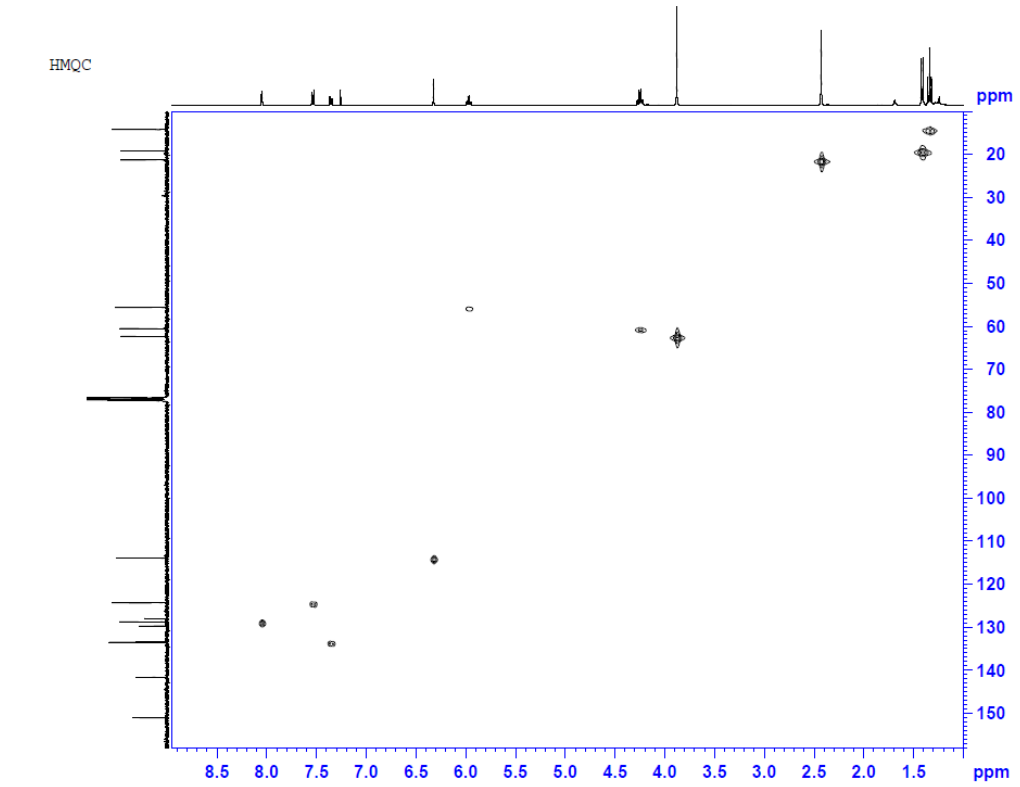
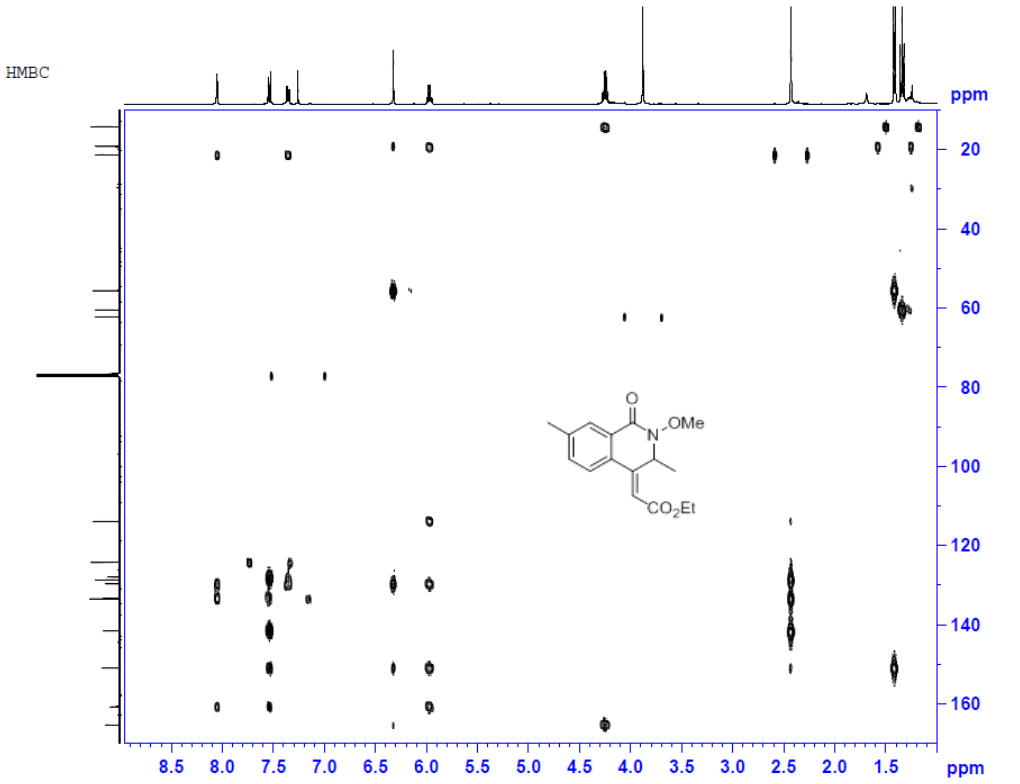
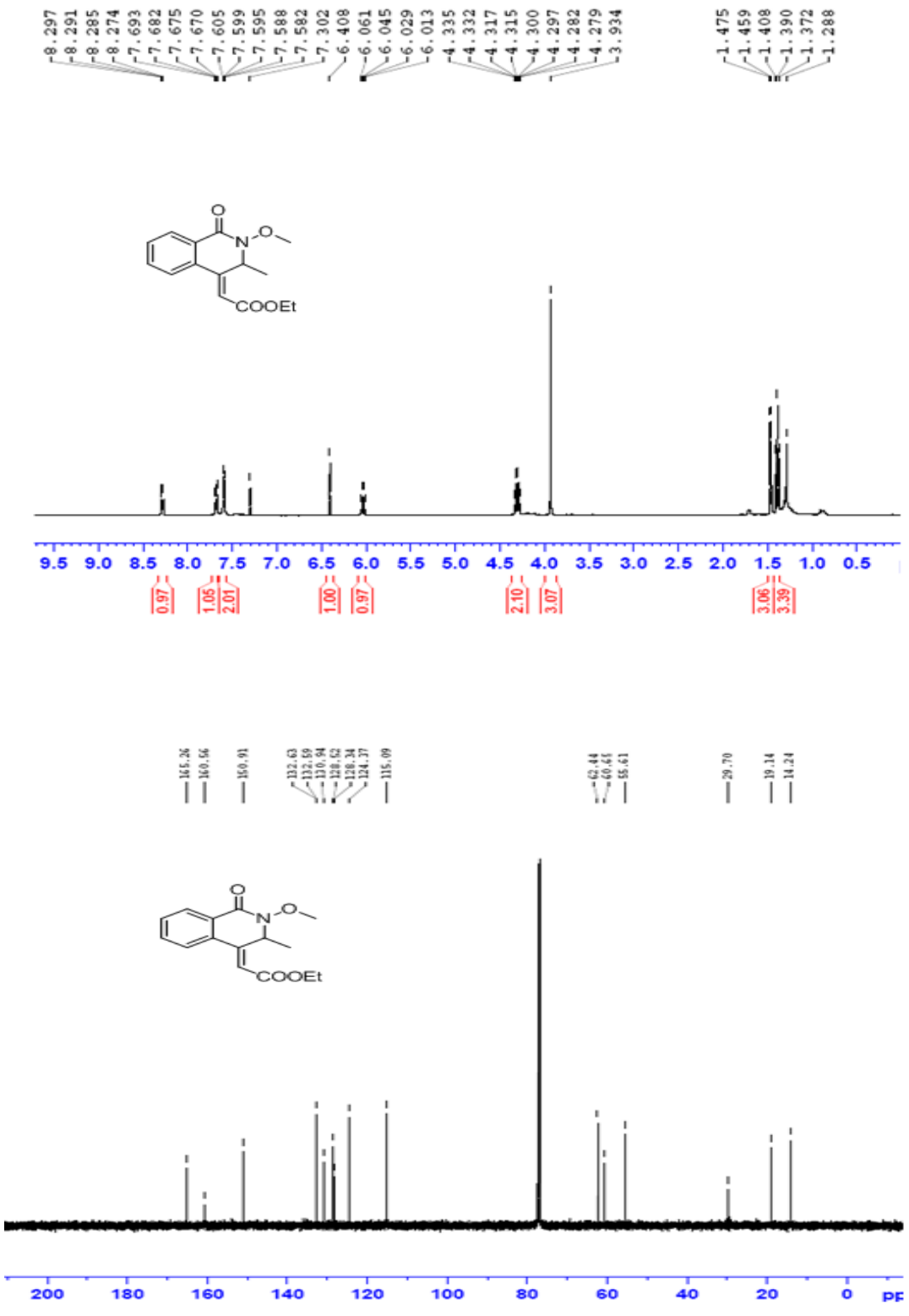
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
O
N
OMe
CO2Et





Ethyl (Z)-2-(2-methoxy-3-methyl-1-oxo-2,3-dihydroisoquinolin-4(1H)-ylidene)acetate, 3a


8.297
8.291
8.285
8.274
7.693
7.682
7.675
7.670
7.605
7.599
7.595
7.588
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7.302
6.408
6.061
6.045
6.029
6.013
4.335
4.332
4.317
4.315
4.300
4.297
4.282
4.279
3.934
1.475
1.459
1.408
1.390
1.372
1.288
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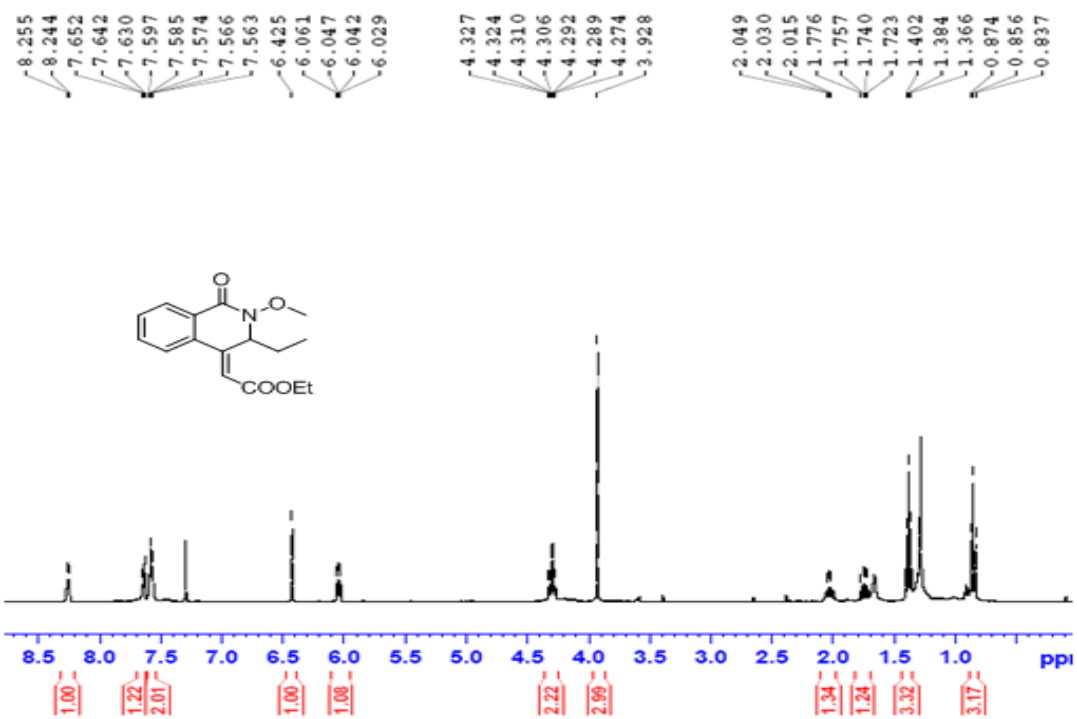
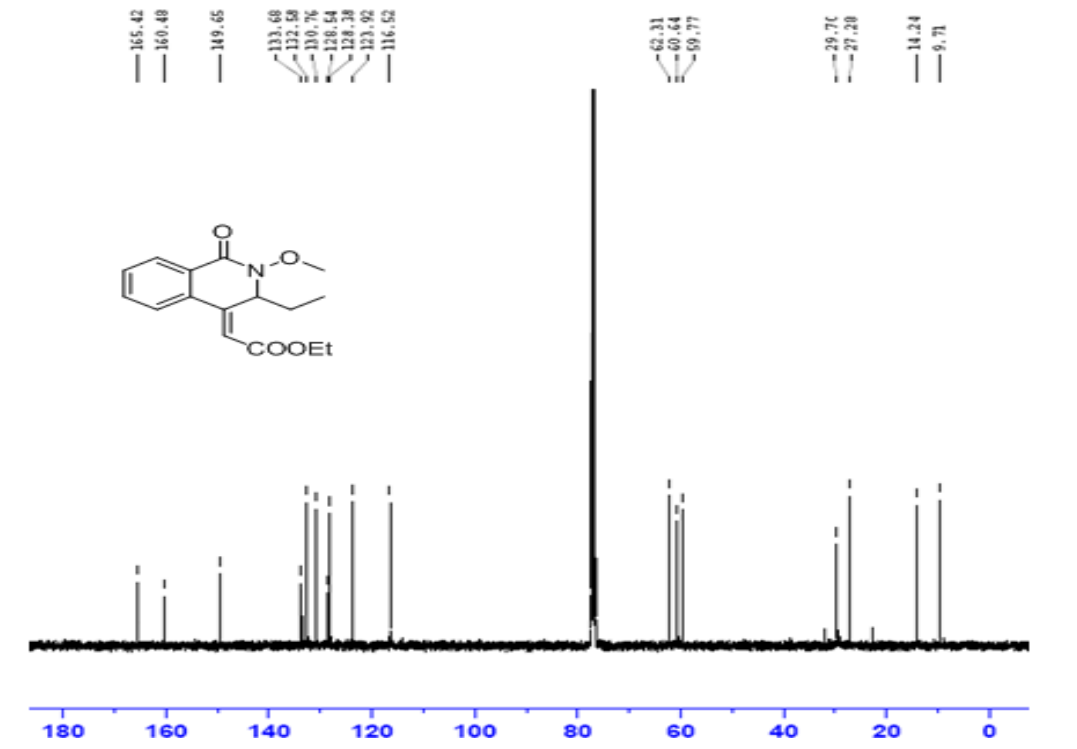
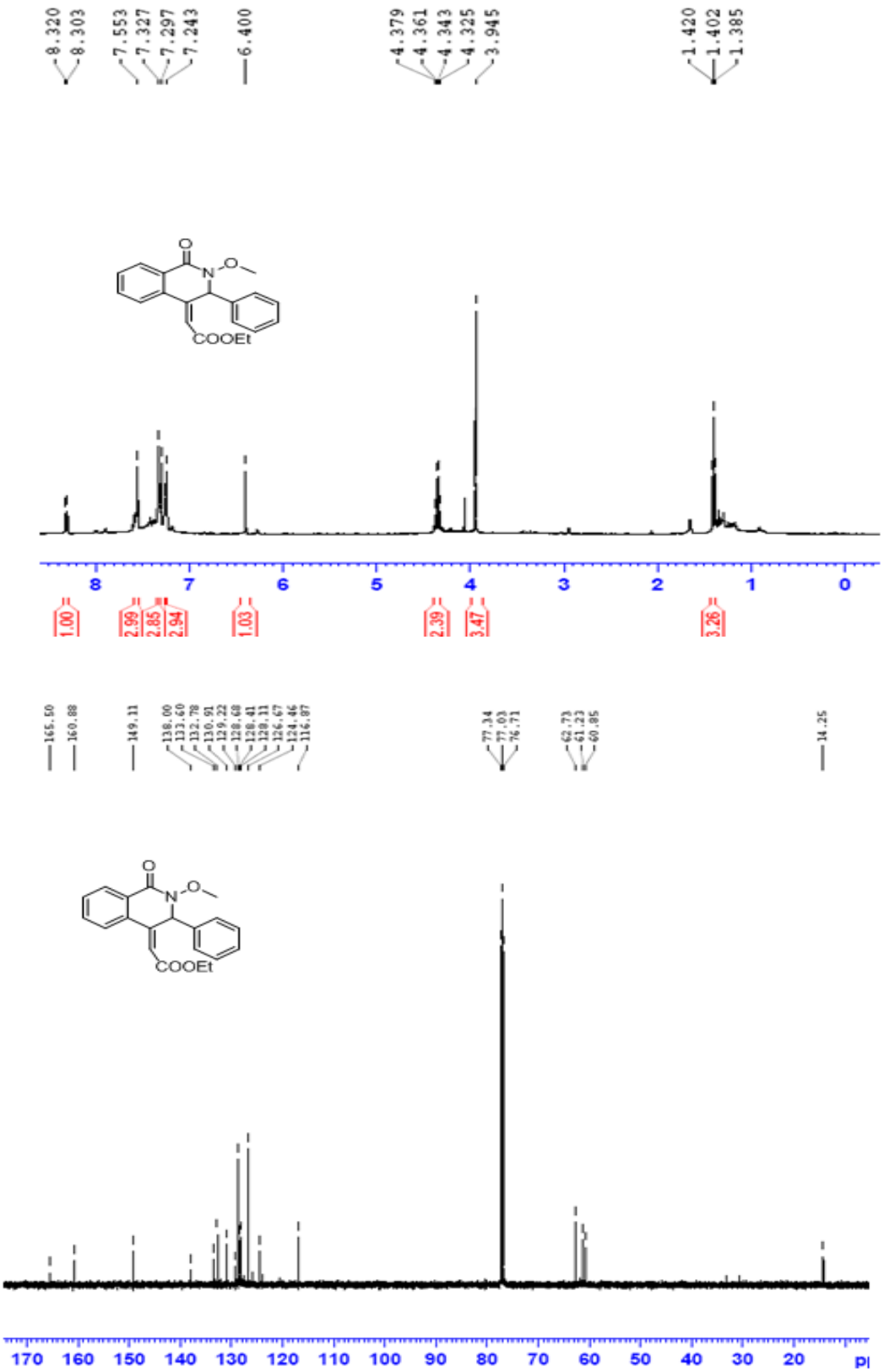
N
O
COOEt
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
0.97
1.06
2.01
1.00
0.97
2.10
3.07
3.06
3.39
165.26
160.56
150.91
132.63
132.59
130.94
128.62
128.34
124.37
115.09
62.44
60.61
55.61
29.70
19.14
14.24
O
N
O
COOEt
200 180 160 140 120 100 80 60 40 20 0 pp

Ethyl (Z)-2-(3-ethyl-2-methoxy-1-oxo-2,3-dihydroisoquinolin-4(1H)-ylidene)acetate, 3b





Ethyl (Z)-2-(2-methoxy-1-oxo-3-phenyl-2,3-dihydroisoquinolin-4(1H)-ylidene)acetate, 3c



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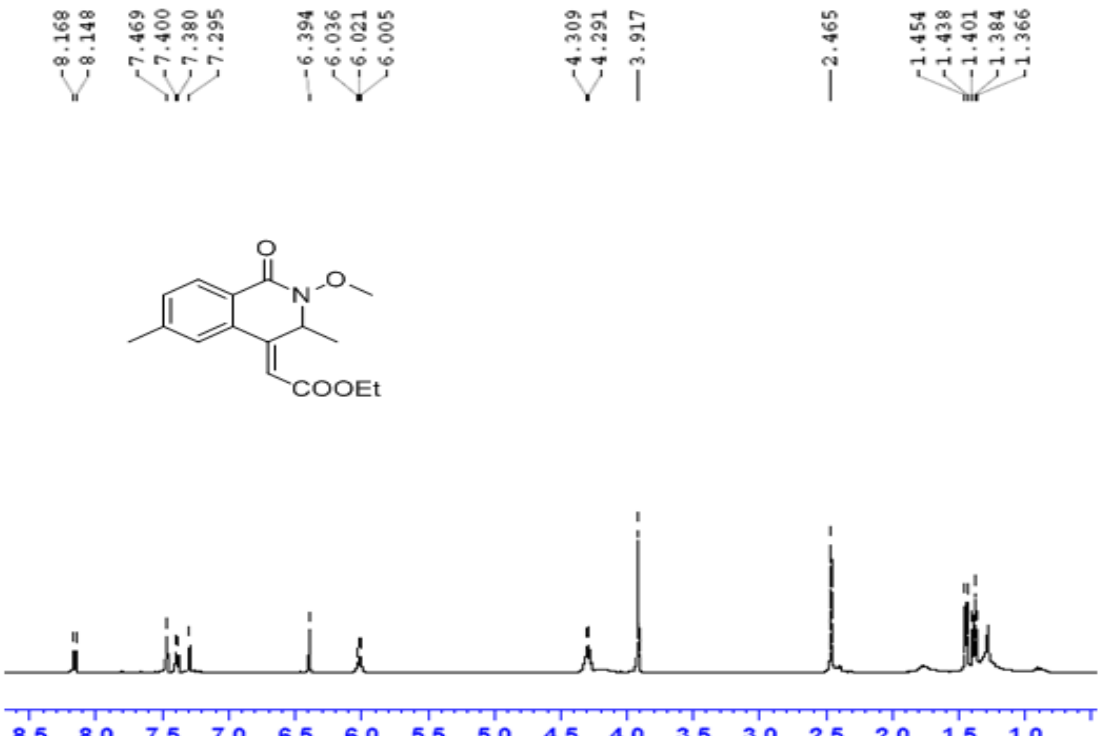

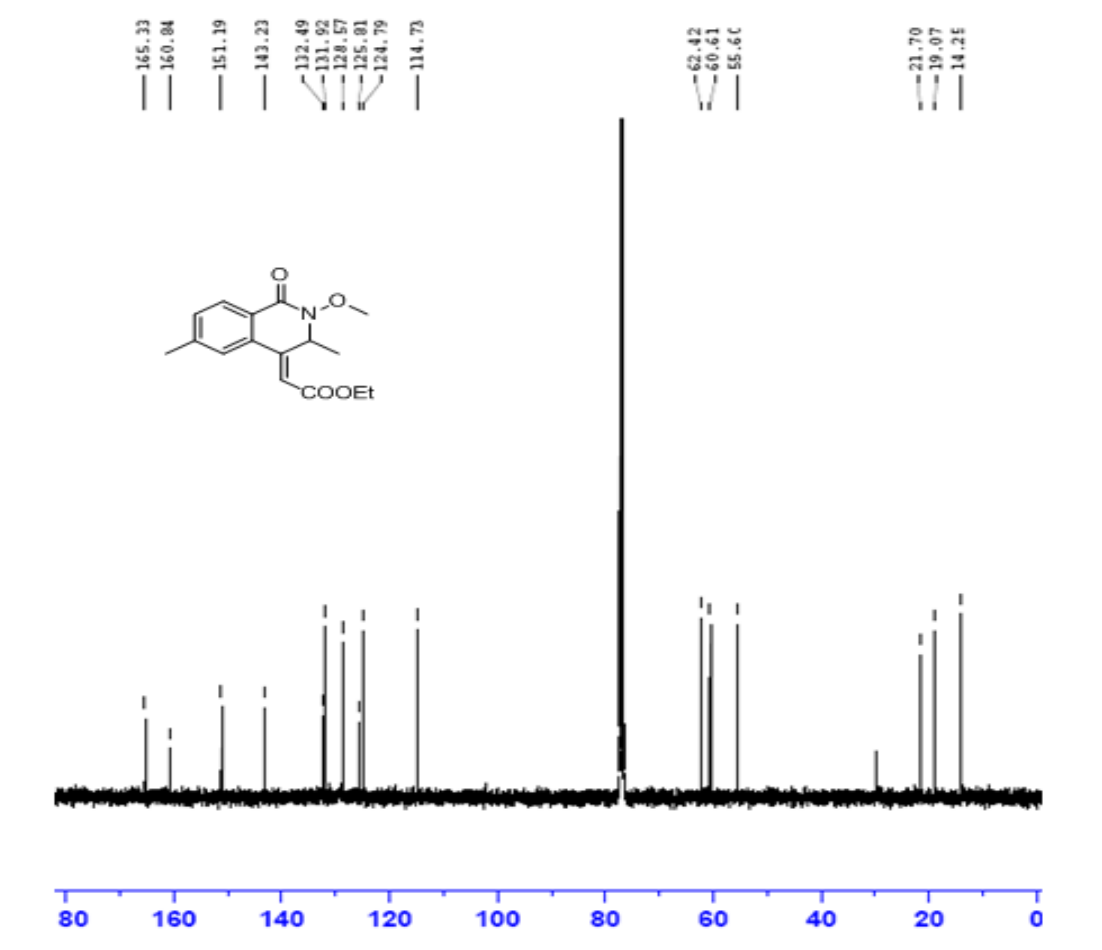

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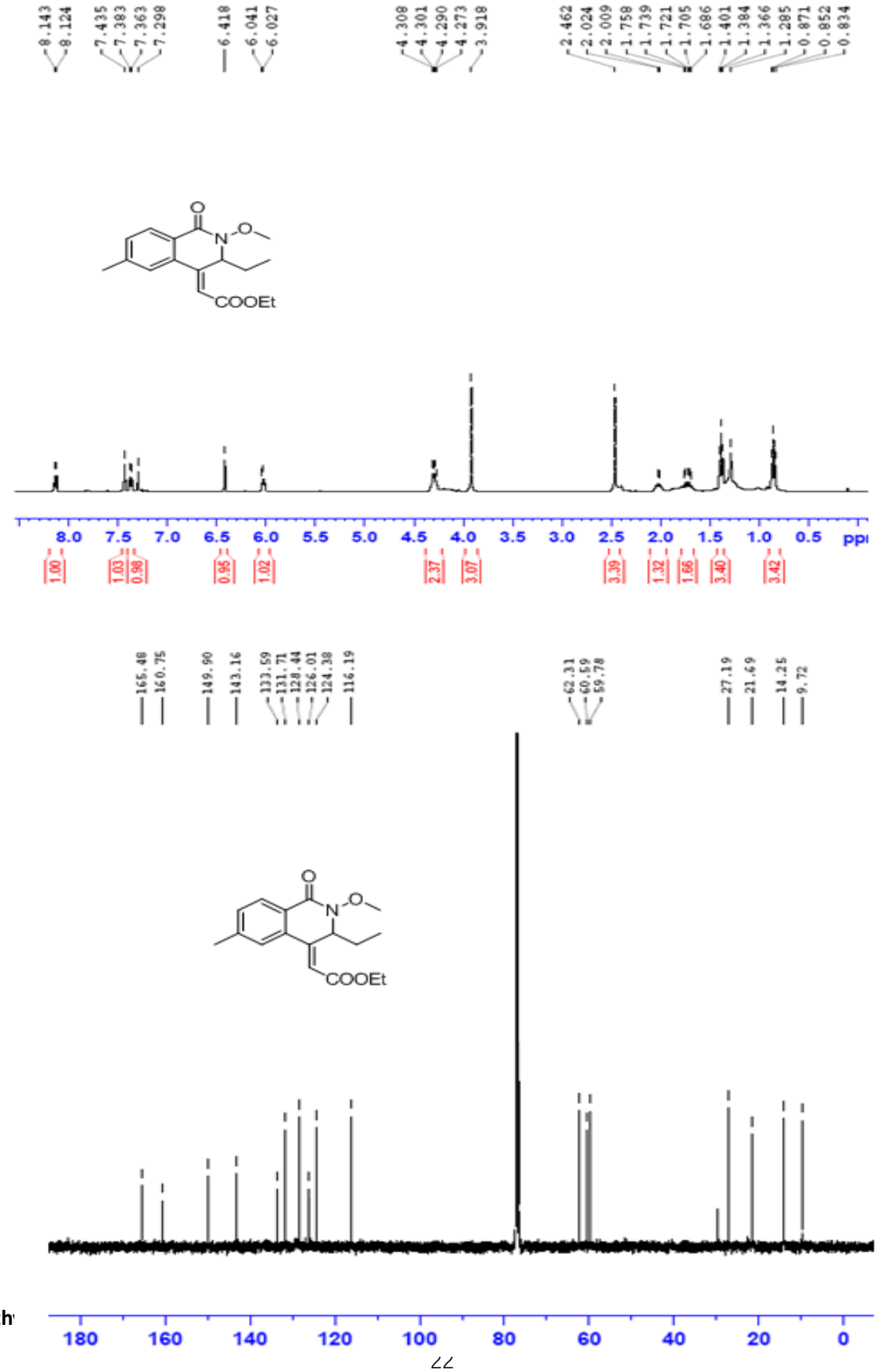

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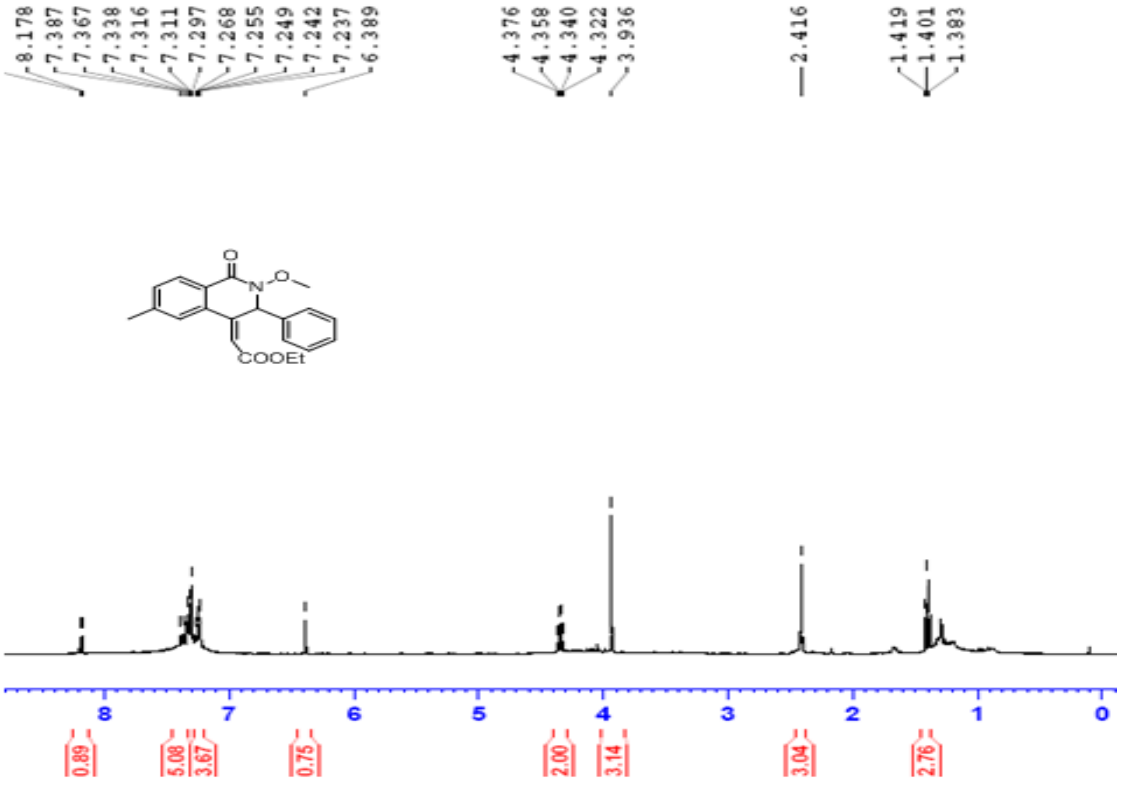
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4.340
4.322
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1.419
1.401
1.383
O
N
O
COOEt
8
7
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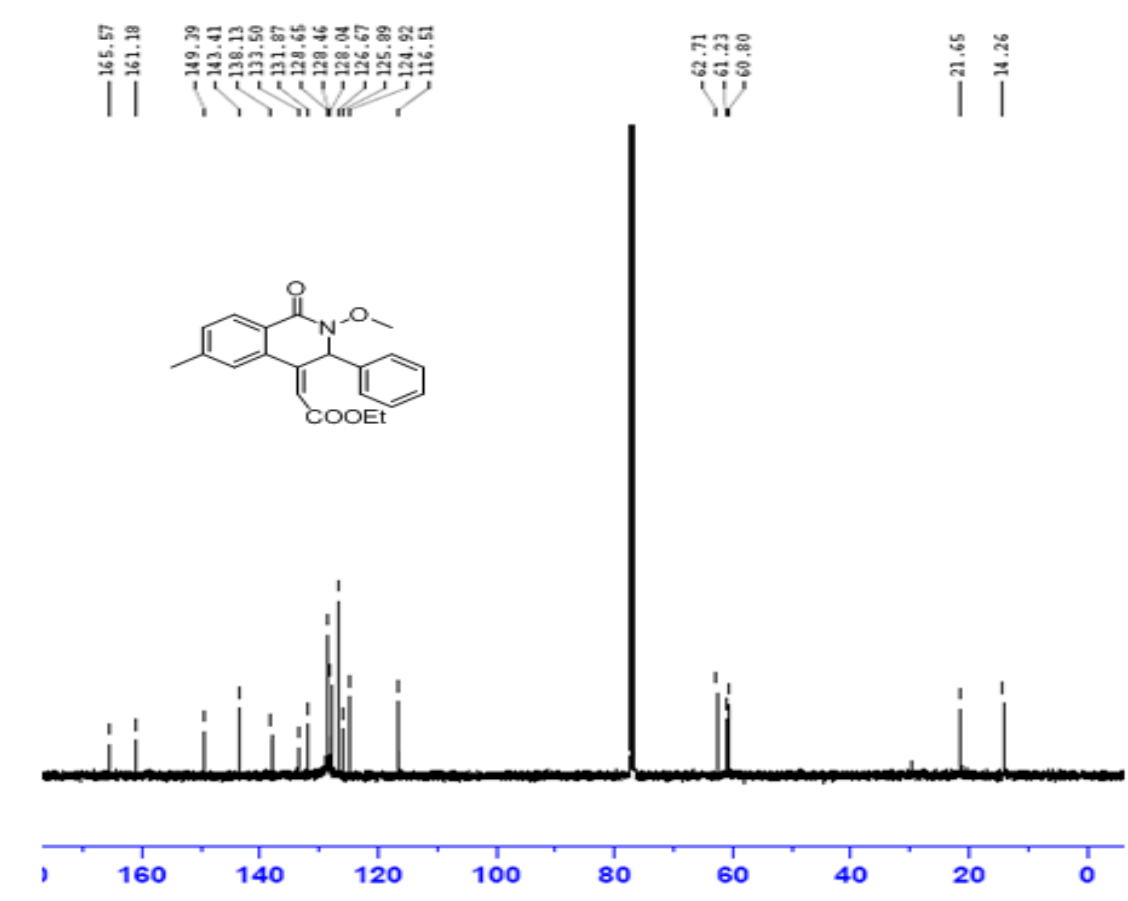
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61.23
60.80
21.65
14.26
O
N
O
COOEt
160
140
120
100
80
60
40
20
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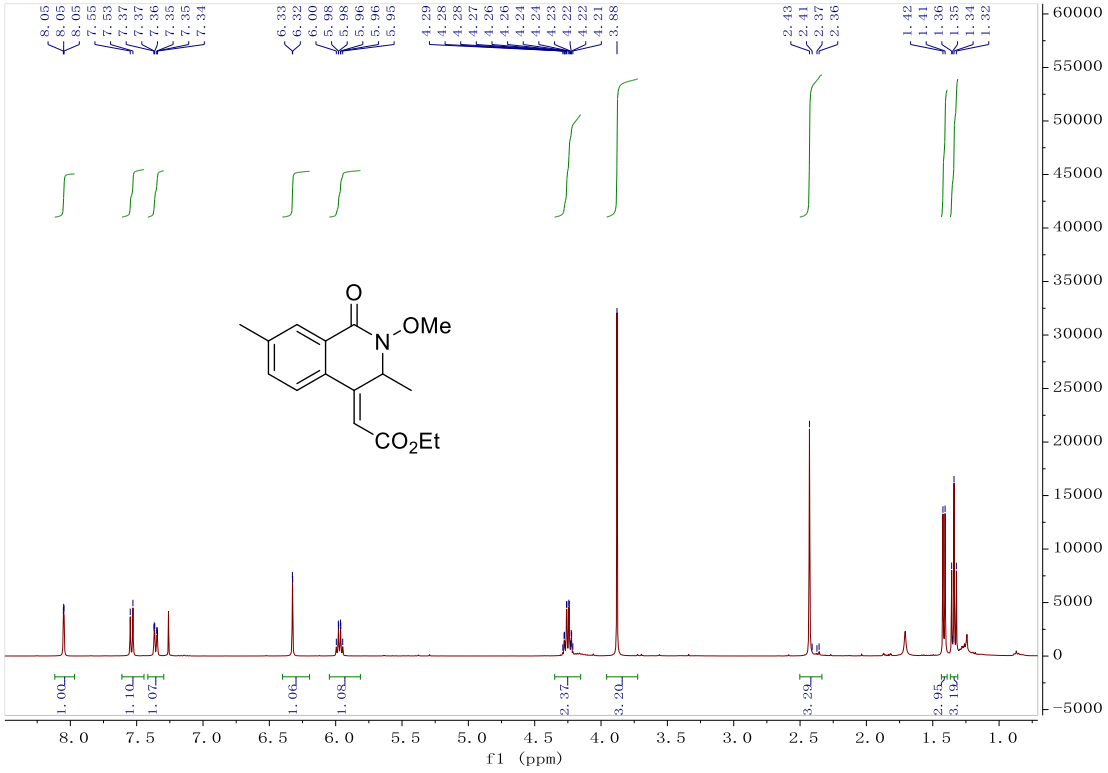
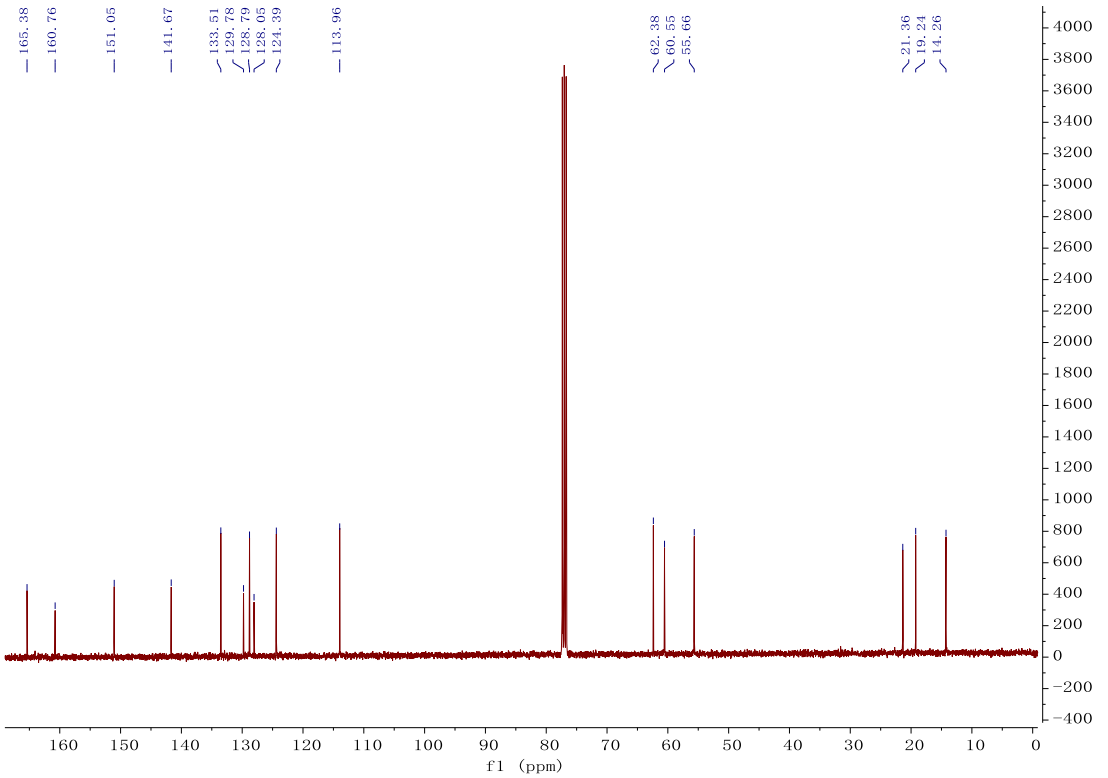
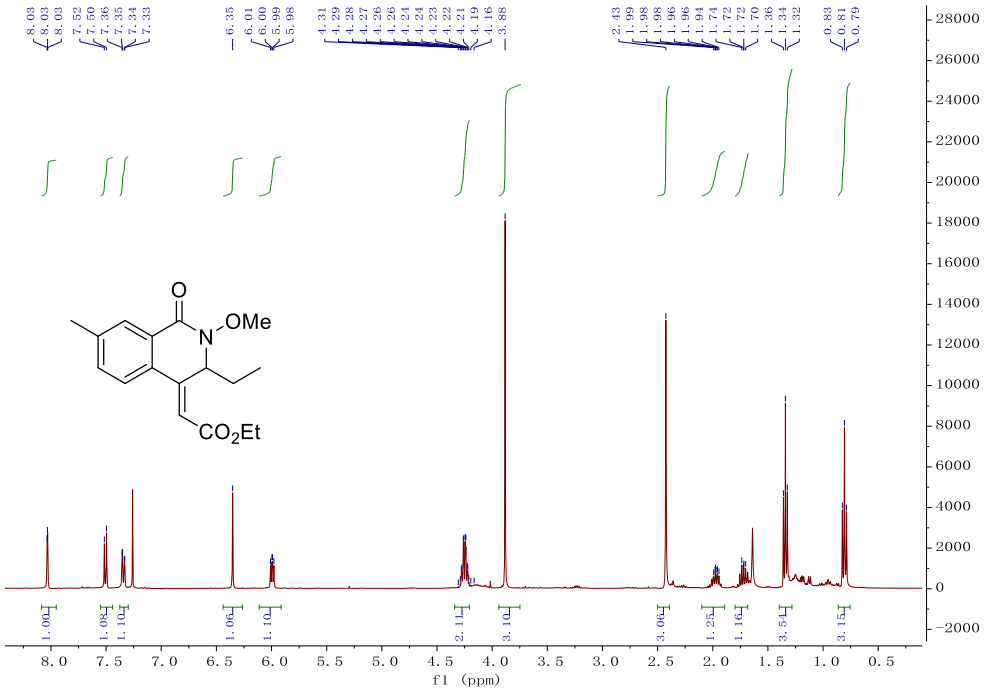
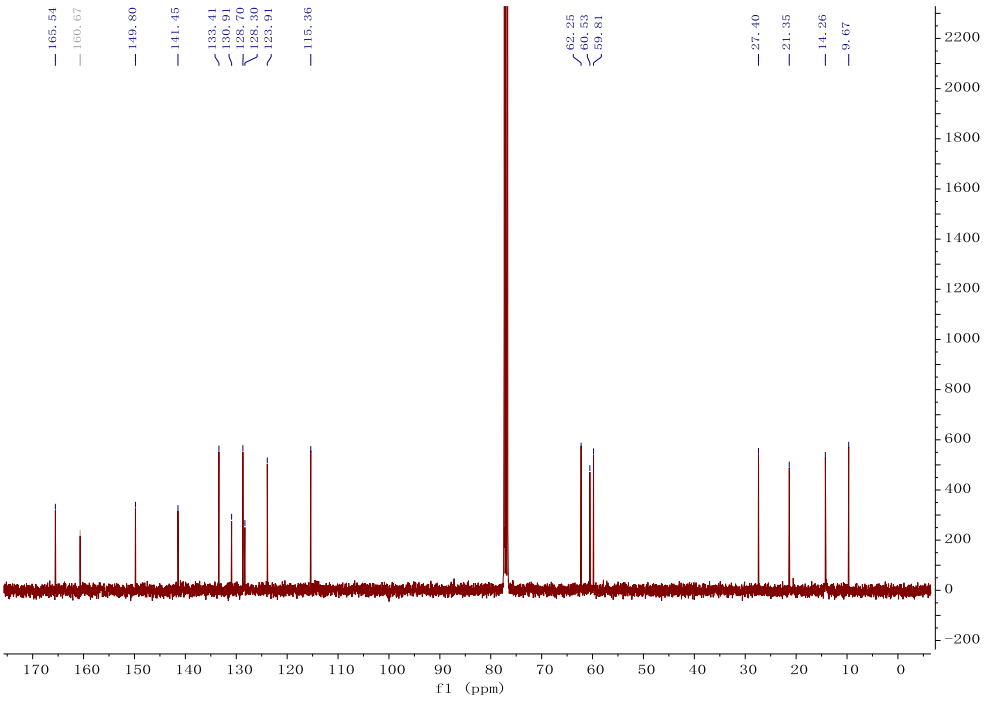


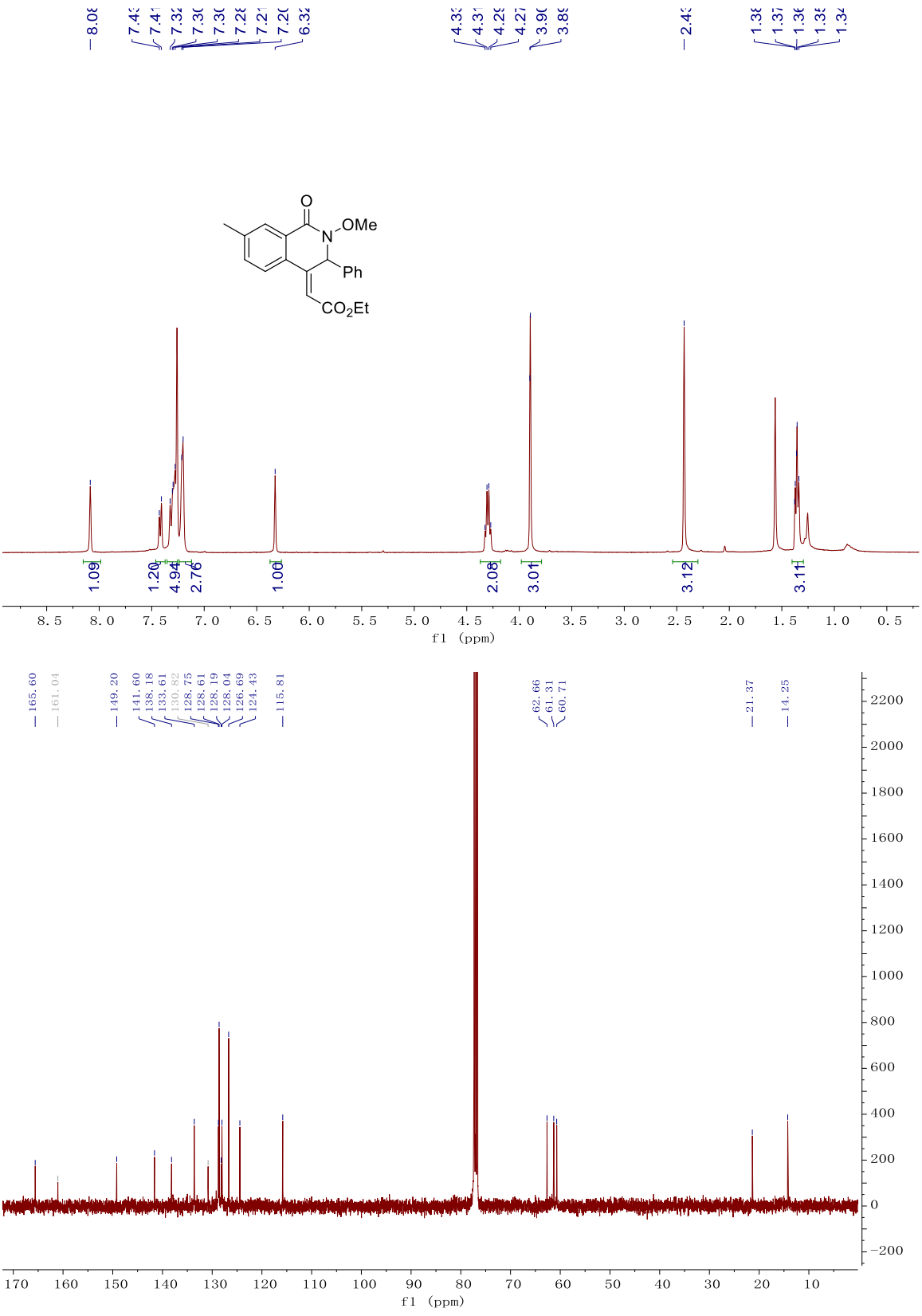


Ethyl (Z)-2-(3-ethyl-2-methoxy-7-methyl-1-oxo-2,3-dihydroisoquinolin-4(1H)-ylidene)acetate, 3h

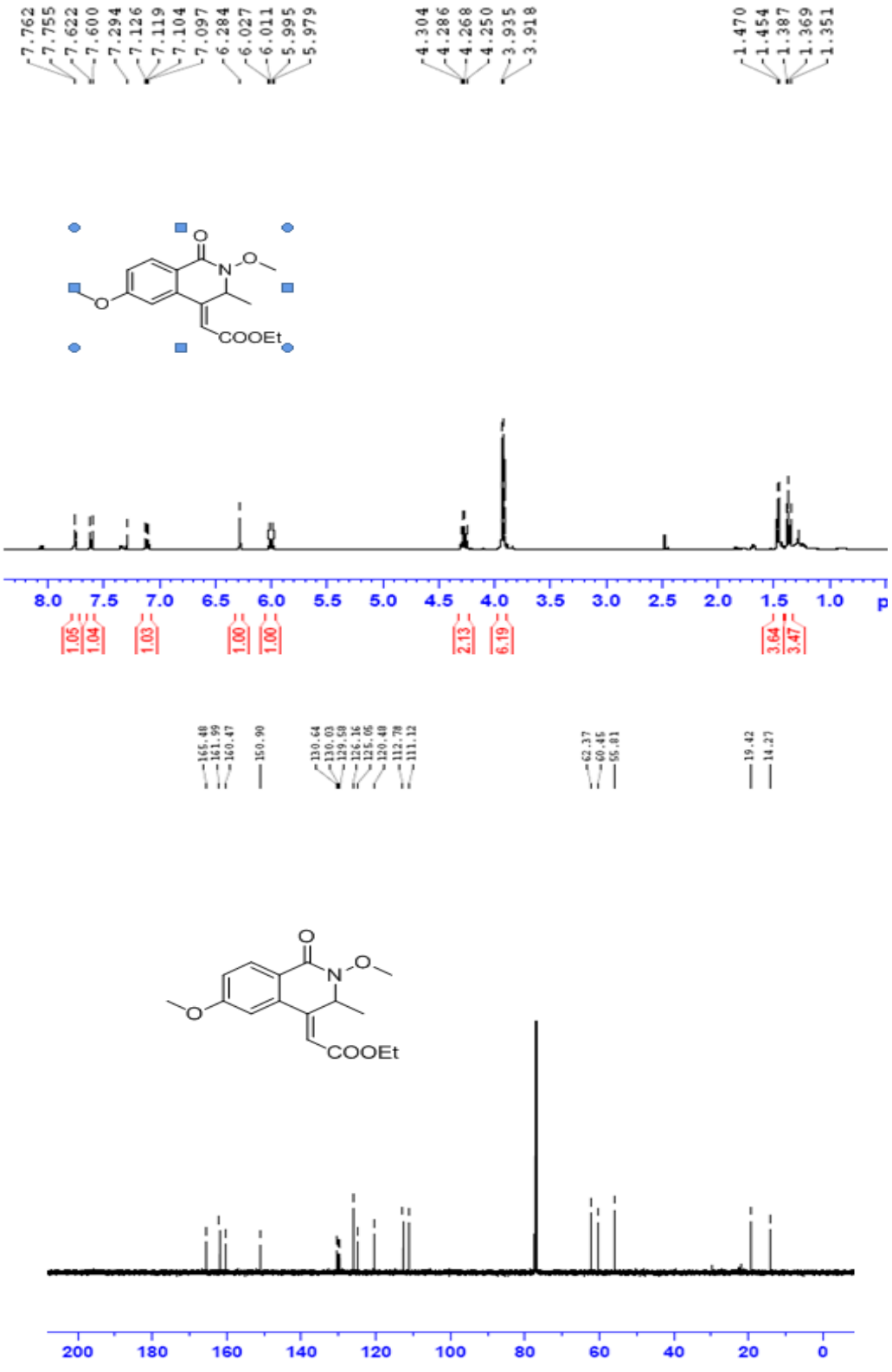




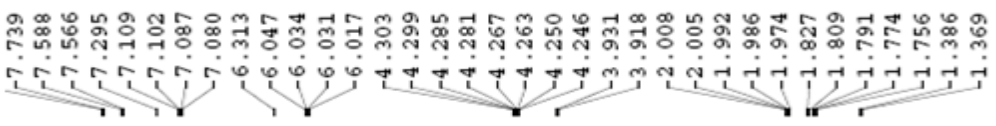
Ethyl (Z)-2-(2-methoxy-7-methyl-1-oxo-3-phenyl-2,3-dihydroisoquinolin-4(1H)-ylidene)acetate, 3i

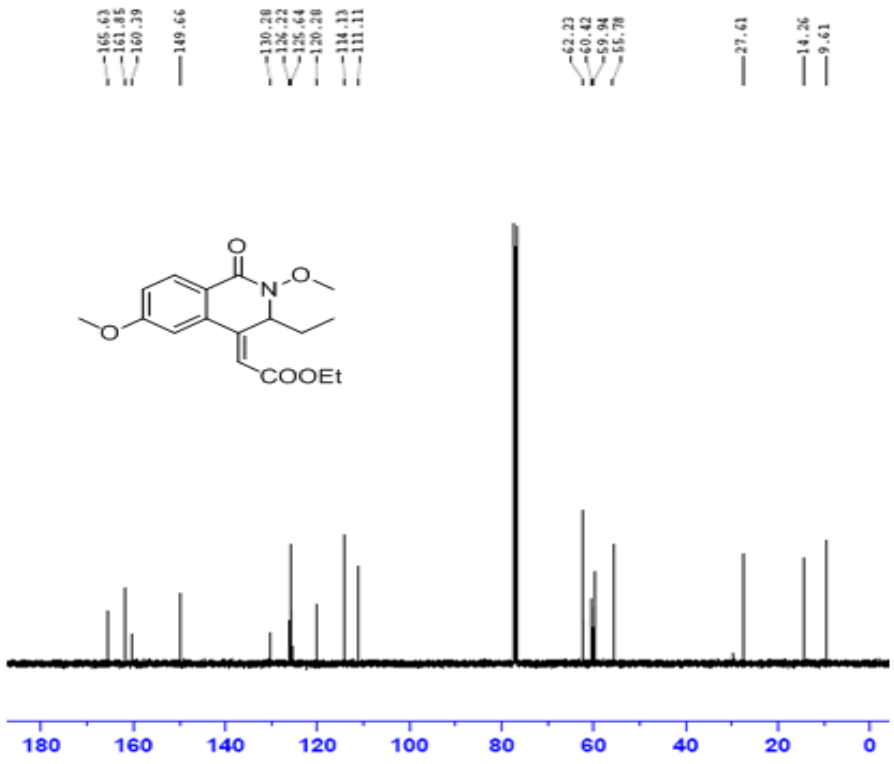


Ethyl (Z)-2-(2,6-dimethoxy-3-methyl-1-oxo-2,3-dihydroisoquinolin-4(1H)-ylidene)acetate, 3j

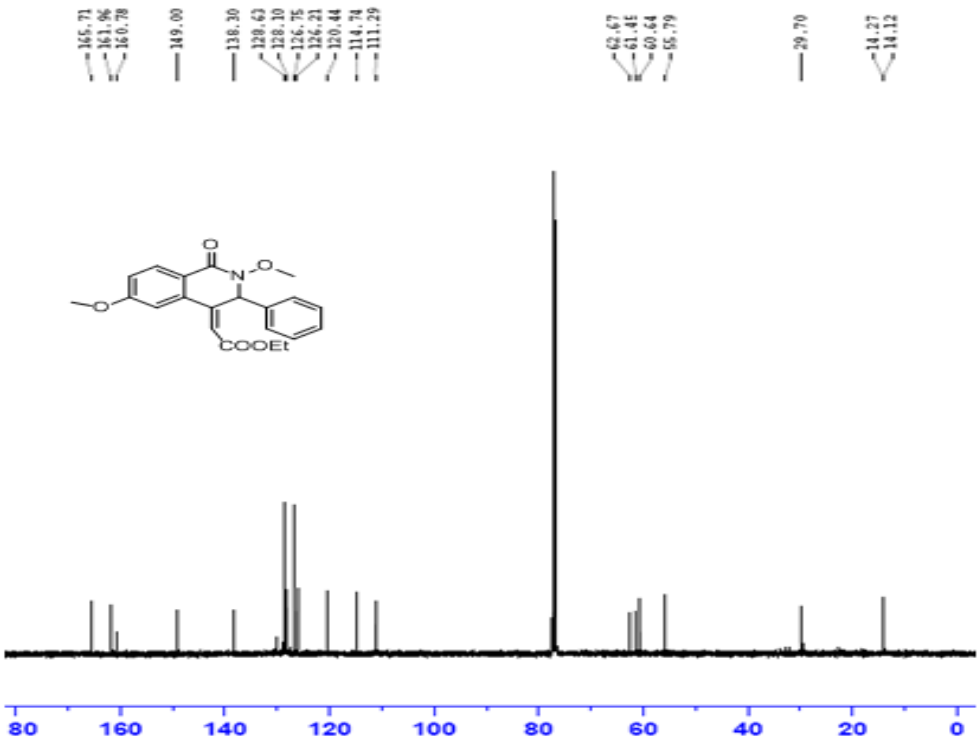


Ethyl (Z)-2-(3-ethyl-2,6-dimethoxy-1-oxo-2,3-dihydroisoquinolin-4(1H)-ylidene)acetate, 3k

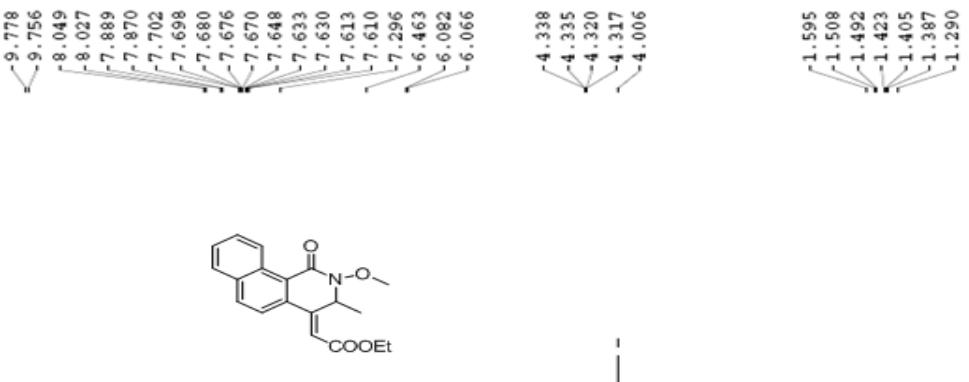


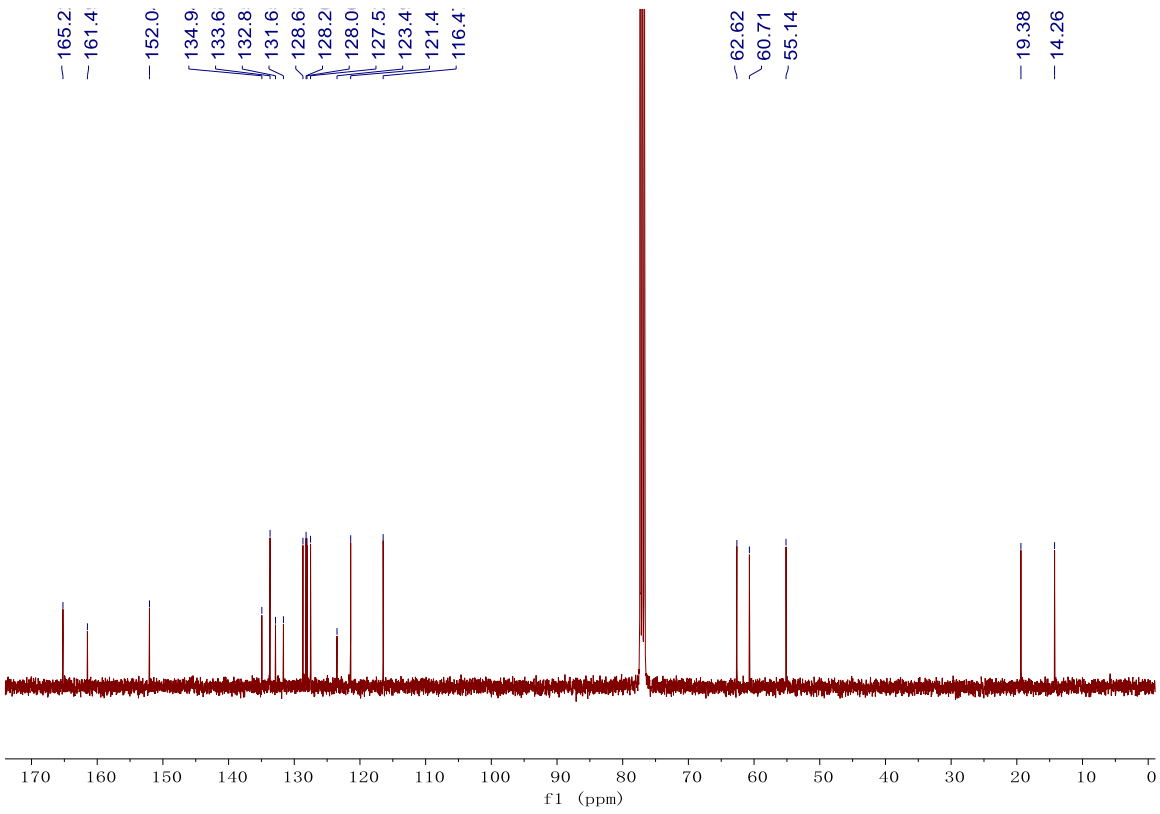


Ethyl (Z)-2-(2,6-dimethoxy-1-oxo-3-phenyl-2,3-dihydroisoquinolin-4(1H)-ylidene)acetate, 3l

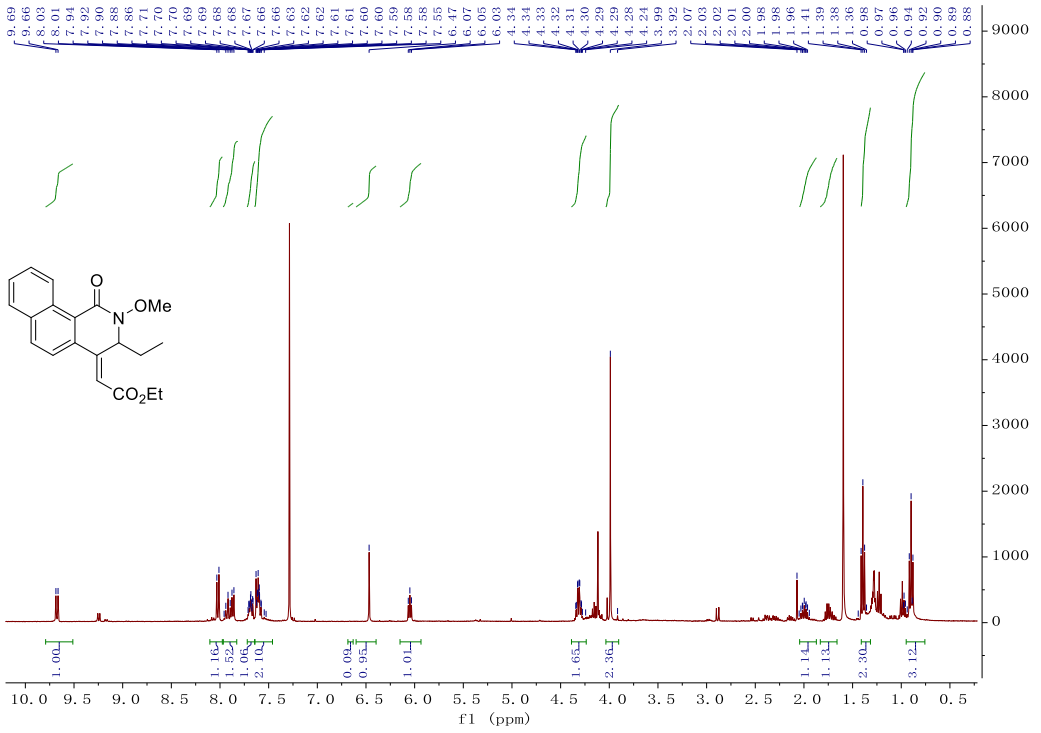


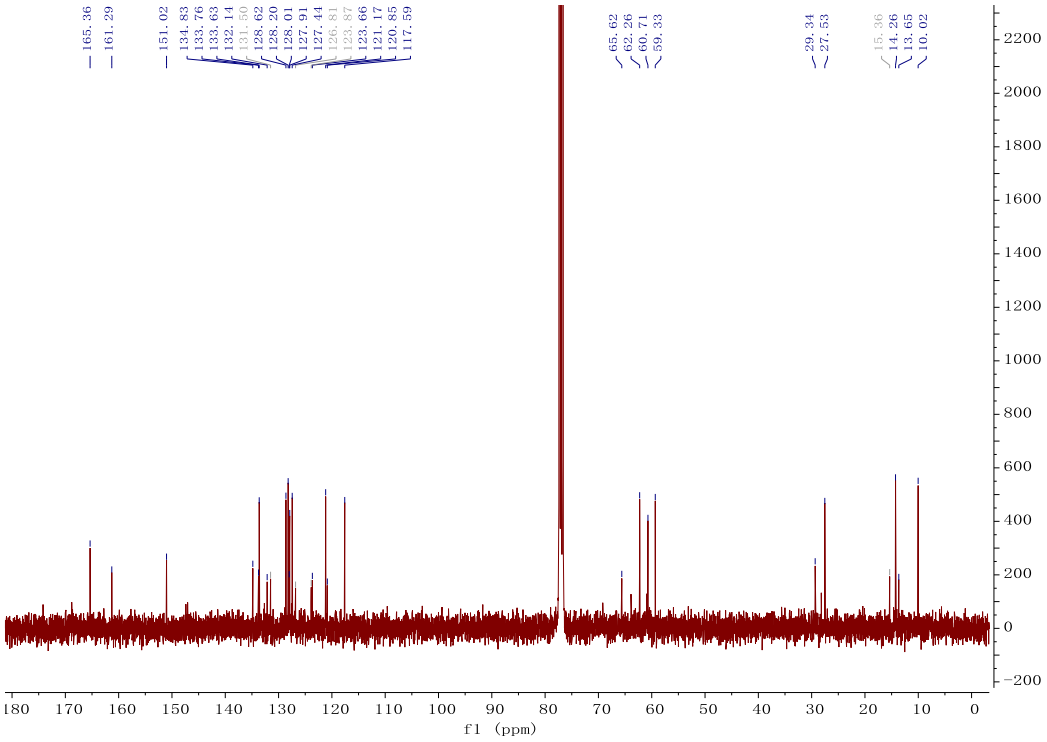
Ethyl (Z)-2-(2-methoxy-3-methyl-1-oxo-2,3-dihydrobenzo[h]isoquinolin-4(1H)-ylidene)acetate, 3m



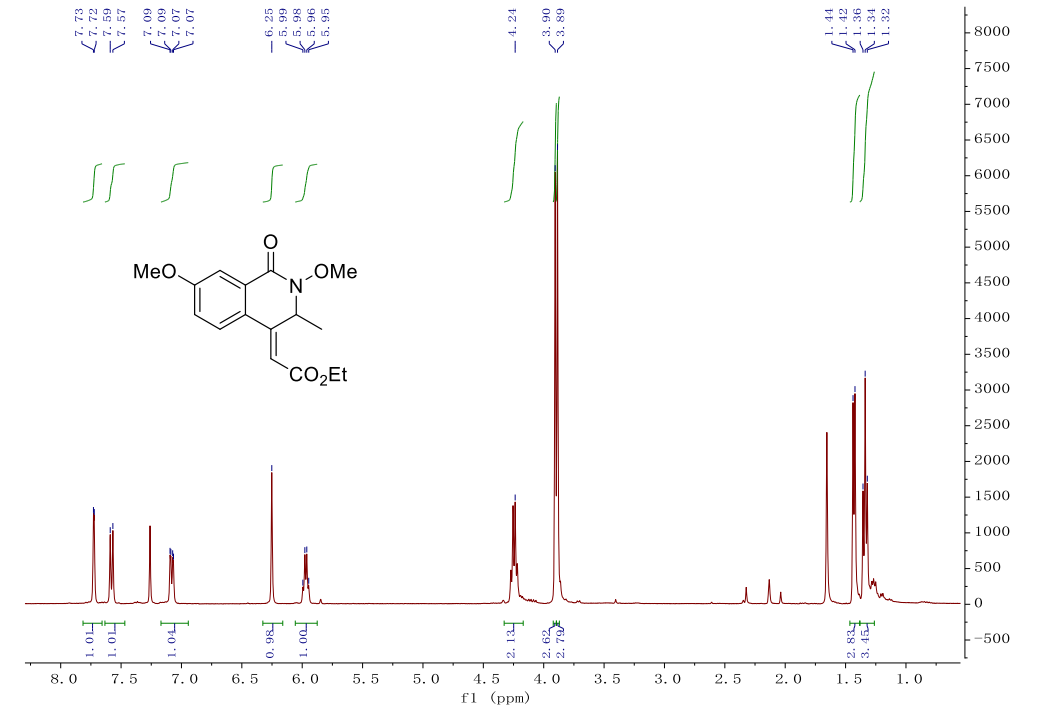


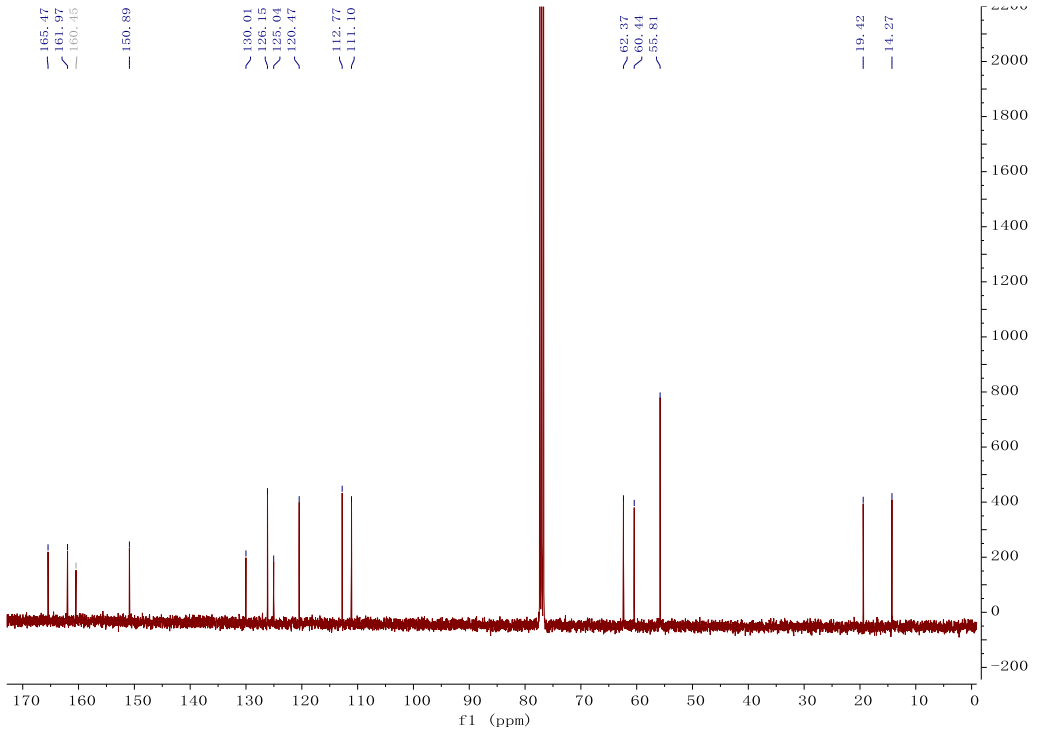
Ethyl (Z)-2-(3-ethyl-2-methoxy-1-oxo-2,3-dihydrobenzo[h]isoquinolin-4(1H)-ylidene)acetate, 3n



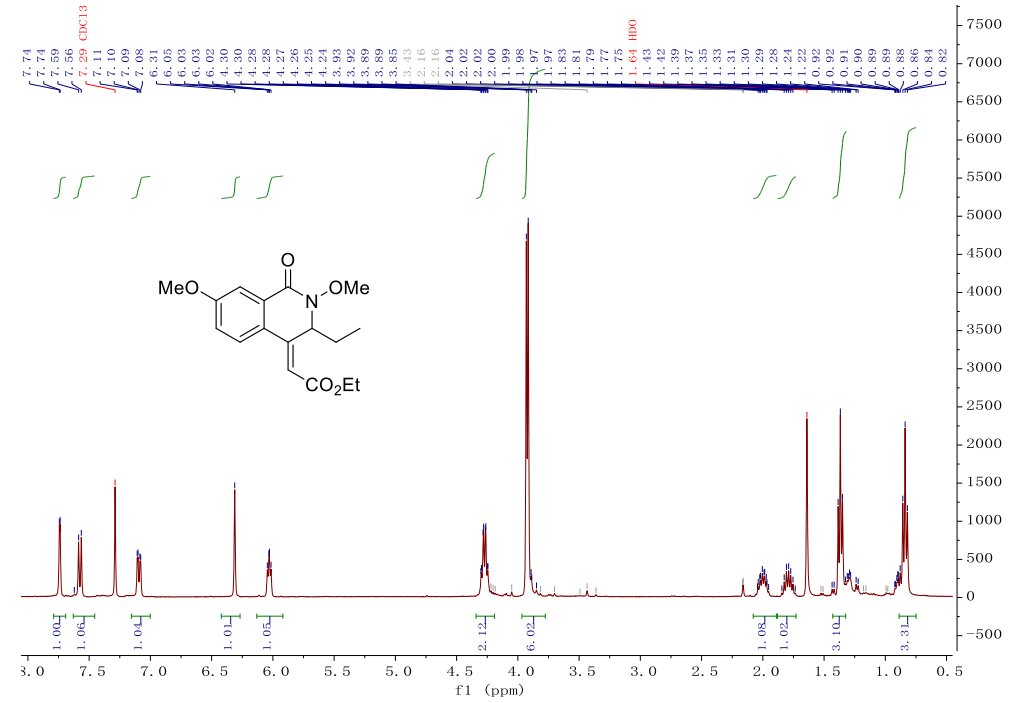


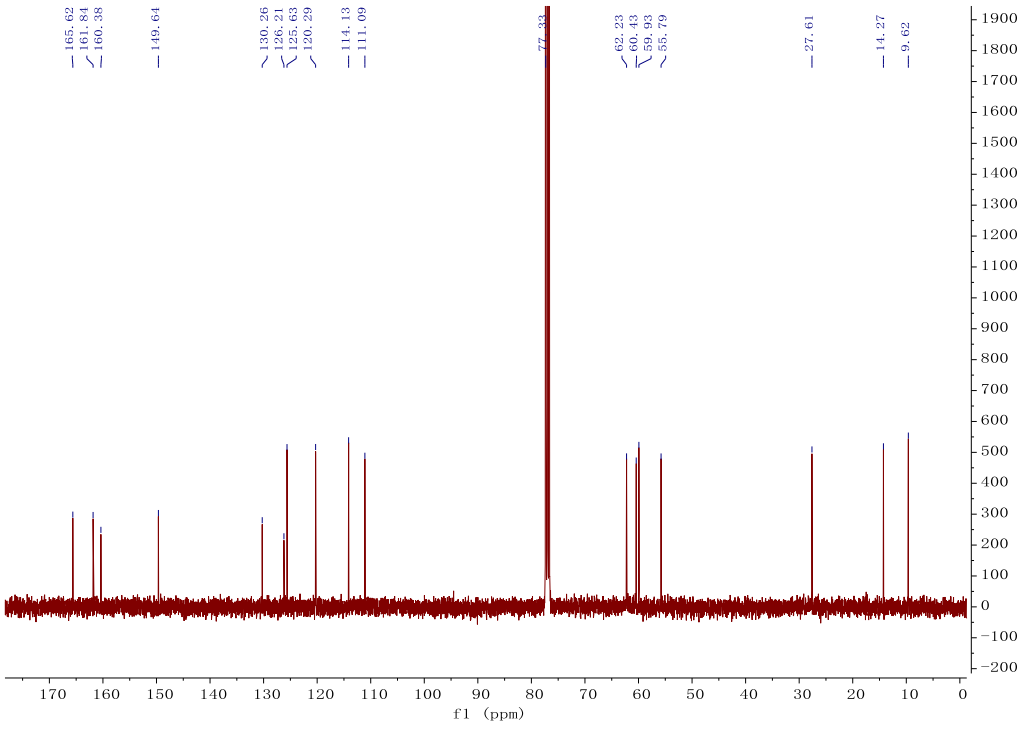
Ethyl (Z)-2-(2,7-dimethoxy-3-methyl-1-oxo-2,3-dihydroisoquinolin-4(1H)-ylidene)acetate, 3o



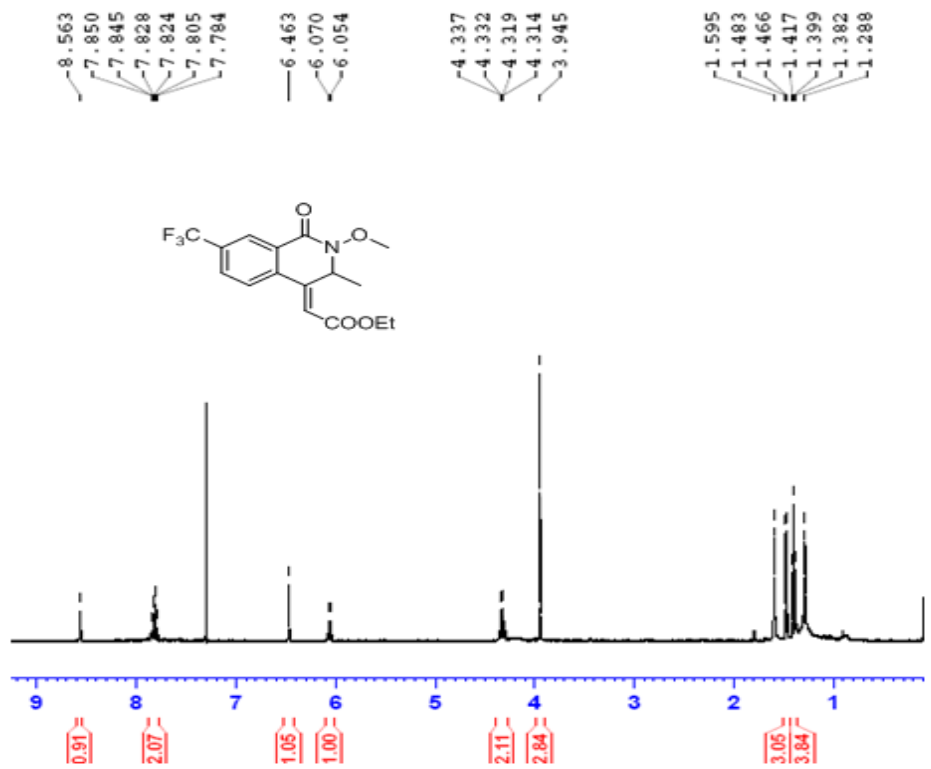


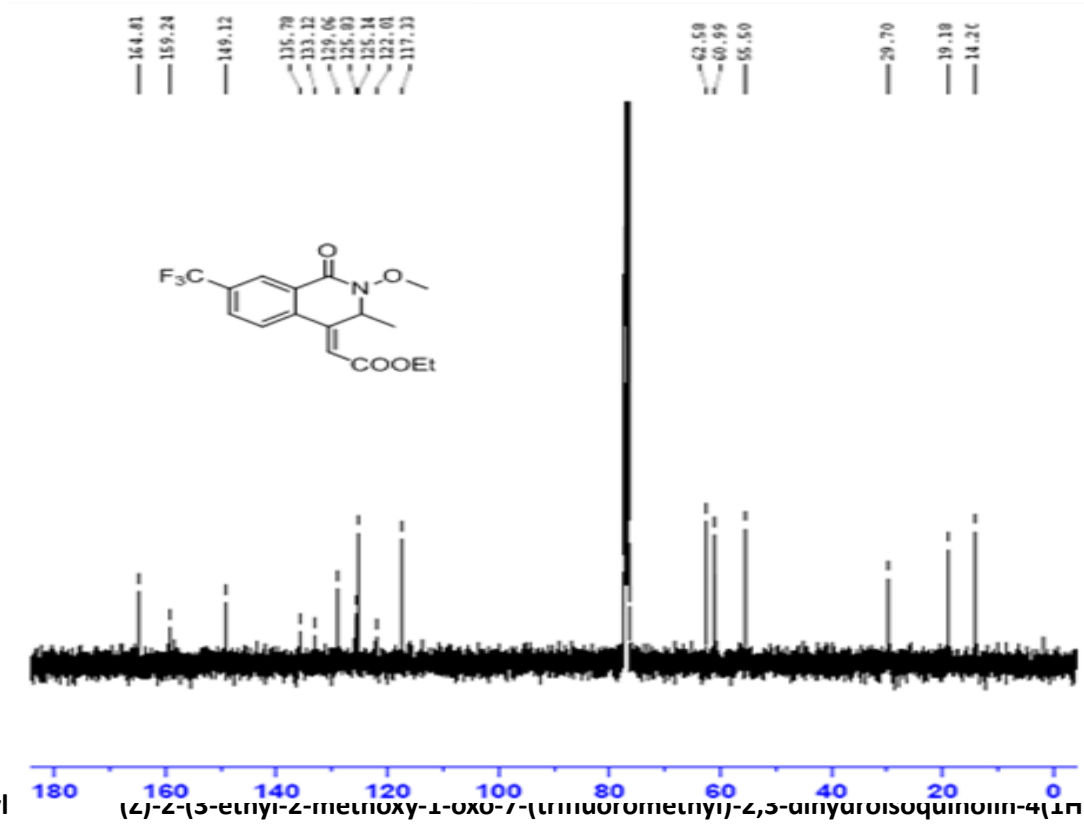
Ethyl (Z)-2-(3-ethyl-2,7-dimethoxy-1-oxo-2,3-dihydroisoquinolin-4(1H)-ylidene)acetate, 3p



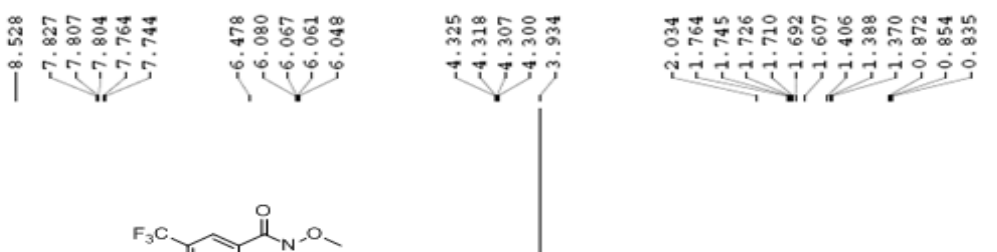


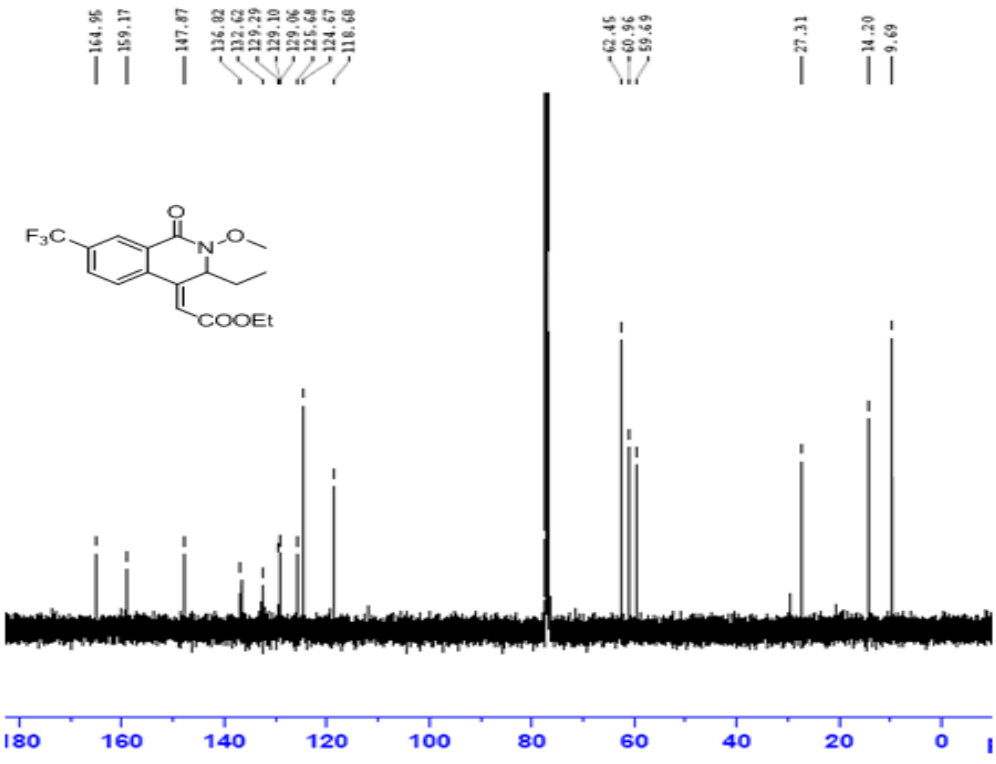
Ethyl (Z)-2-(2-methoxy-3-methyl-1-oxo-7-(trifluoromethyl)-2,3-dihydroisoquinolin-4(1H)-ylidene)acetate, 3q



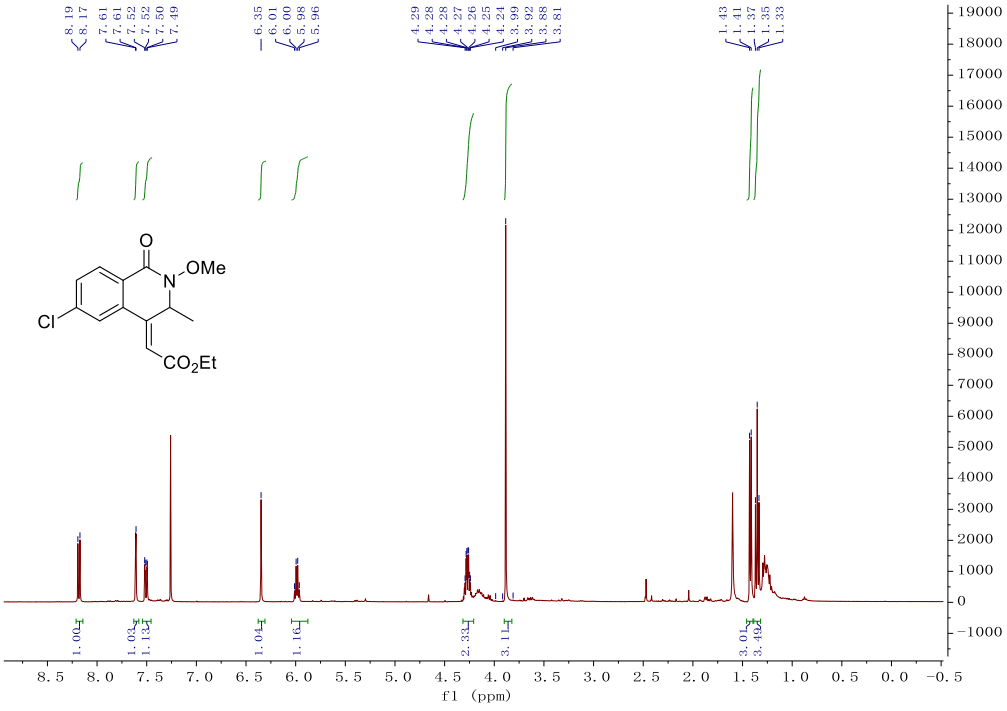


Ethyl (Z)-2-(3-ethyl-2-methoxy-1-oxo-7-(trifluoromethyl)-2,3-dihydroisoquinolin-4(1H)-ylidene)acetate, 3r





Ethyl (Z)-2-(6-chloro-2-methoxy-3-methyl-1-oxo-2,3-dihydroisoquinolin-4(1H)-ylidene)acetate, 3s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4.25
4.24
3.99
3.92
3.88
3.81
1.43
1.41
1.37
1.35
1.33
O
N
OMe
Cl
CO2Et
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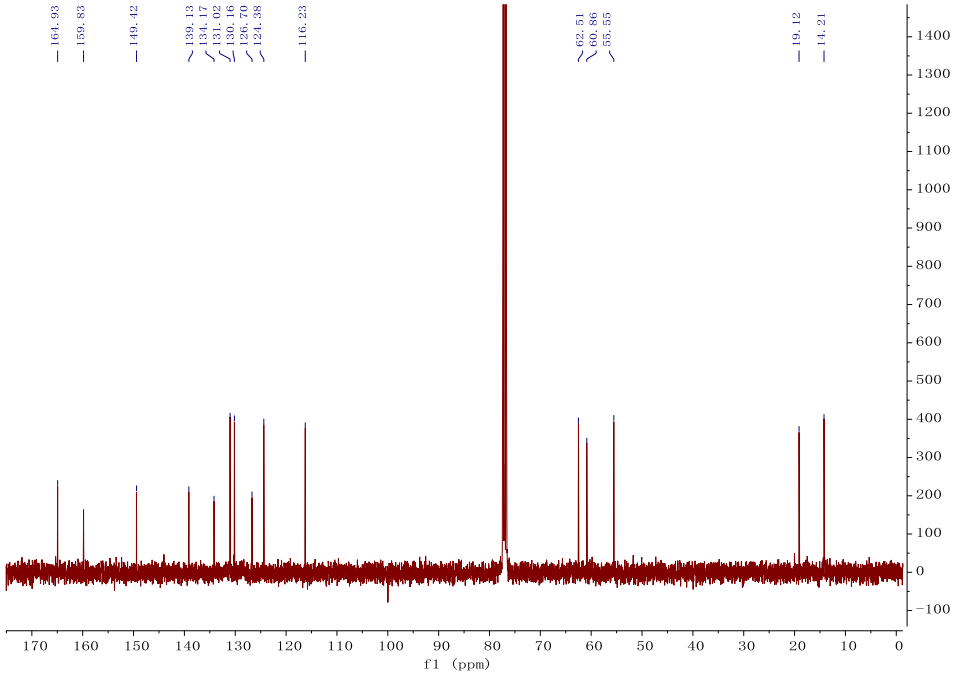
1.04
1.16
2.33
3.11
3.01
3.48
f1 (ppm)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19.12
14.21
f1 (ppm)

Reference:

1. Wrigglesworth, J.W.; Cox, B.; Lloyd-Jones, G.C.; Booker-Milburn, K.I. New heteroannulation reactions of n-alkoxybenzamides by pd(ii) catalyzed c-h activation. *Org Lett* **2011**, *13*, 5326-5329.
2. Castellano, S.; Fiji, H.D.; Kinderman, S.S.; Watanabe, M.; Leon, P.; Tamanoi, F.; Kwon, O. Small-molecule inhibitors of protein geranylgeranyltransferase type i. *J Am Chem Soc* **2007**, *129*, 5843-5845.