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1,1'-Carbonyldiimidazole as a cyclodehydrating agent for the Castagnoli–Cushman reaction of dicarboxylic acids and imines

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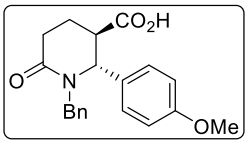
Experimental part

General considerations

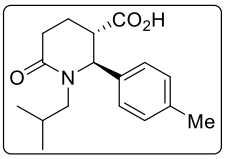
All commercial reagents were used without further purification. NMR spectra were recorded using Bruker Avance III spectrometer (^{1}H: 400.13 MHz; ^{13}C: 100.61 MHz; chemical shifts are reported as parts per million (δ, ppm); the solvent was DMSO-d_6 (99.9% atom D), the residual solvent peaks were used as internal standards: 2.50 ppm for ^{1}H and 39.52 ppm for ^{13}C spectra; multiplicities are abbreviated as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad; coupling constants, *J*, are reported in Hz. Mass spectra were recorded using Bruker microTOF spectrometer (electrospray ionization, positive ions detection). Melting points were determined in open capillary tubes on Stuart SMP50 Automatic Melting Point Apparatus. Analytical HPLC was carried out on "Milichrom A-02" chromatograph, equipped with spectrophotometric detector. Column: Khromasil 100 C18, 5 μm, 10 cm×3mm. Gradient: TFA (trifluoroacetic acid) (0.1 %) in water, TFA (trifluoroacetic acid) (0.1 %) in acetonitrile, 5−95 % B (0−15 min), 95 % B (15−20 min). Flow rate (200 μl min^{-1}), temperature – 40 °C, detection UV at 254 and 380 nm, injection 20 μl. Chlorobenzene and 1,2-dichloroethane were distilled from P_2O_5 (phosphorus pentoxide) and stored over MS 4Å. 2-Phenylsuccinic acid[S1] **4b** and 2,2'-[(methylsulfonyl)azanediyl]diacetic acid[S2] **1b** were prepared according to published procedures. Other diacids were obtained from commercial sources.

General procedure for the Castagnoli–Cushman reaction (Schemes 2-4). Synthesis of lactams 3a-c, 5a-c, 7a-e

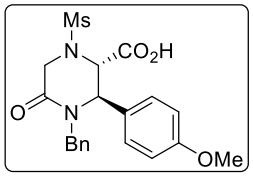
To a stirred mixture of imine **2a-g** (0.9 mmol), dicarboxylic acid **1a,b, 4a,c or 6** (1 mmol) and dry 1,2-dichloroethane) or PhCl (3 ml), 1,1'-carbonyldiimidazole (1.1 mmol) was added in one portion (gas evolution!). The reaction mixture was heated at required temperature (65 or 130 °C) for 16 h in a sealed screw-cap vial. After cooling to room temperature, the mixture was diluted with CH_2Cl_2 (5 ml) and extracted with saturated sodium bicarbonate solution (5 ml). The aqueous layer was separated, and HCl_{conc} was added slowly at 0°C to adjust pH to 1. After 1 h of standing at the same temperature, the precipitate formed was filtered, washed with water and crystallized from aqueous MeCN to afford pure title compounds.



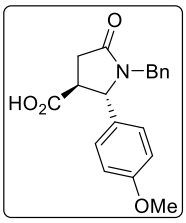
(2*RS*,3*RS*)-1-Benzyl-2-(4-methoxyphenyl)-5-oxopyrrolidine-3-carboxylic acid (3a)[S3]. Prepared according to the general procedure, yield 130 mg (40 %), d.r. 88:12; white powder, mp 191.3–191.7 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ (signals of major diastereomer) 12.63 (br. s, 1H, COOH), 7.34 – 7.23 (m, 3H, 3CH(Ar)), 7.12 (d, *J* = 8.5 Hz, 2H, 2CH(Ar)), 7.02 (d, *J* = 7.2 Hz, 2H, 2CH(Ar)), 6.94 (d, *J* = 8.6 Hz, 1H, 2CH(Ar)), 4.80 (d, *J* = 15.2 Hz, 1H, PhC<u>H</u>), 4.50 (d, *J* = 5.8 Hz, 1H, 2-CH), 3.77 (s, 3H, CH_3), 3.44 (d, *J* = 15.1 Hz, 1H, PhC<u>H</u>), 3.09 – 2.98 (m, 1H, 3-CH), 2.83 (dd, *J* = 17.0, 9.7 Hz, 1H, 4-CH), 2.63 (dd, *J* = 16.9, 7.0 Hz, 1H, 3-CH). ^{13}C NMR (101 MHz, DMSO-d_6) δ (signals of major diastereomer) 174.3, 172.7, 159.6, 136.8, 131.6, 128.9, 128.8, 128.1, 127.7, 114.7, 63.5, 55.6, 45.9, 43.9, 33.7. HRMS (ESI), *m/z* calcd for $C_{19}H_{20}NO_4$ $[M+H]^+$ 326.1387, found 326.1399.



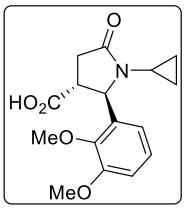
(2*RS*,3*RS*)-1-Isobutyl-6-oxo-2-(*p*-tolyl)piperidine-3-carboxylic acid (3b). Prepared according to the general procedure, yield 173 mg (60 %); white powder, mp 202.3–202.7 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.74 (br.s, 1H, COOH), 7.20 (d, *J* = 7.9 Hz, 2H, 2CH), 7.08 (d, *J* = 8.0 Hz, 2H, 2CH), 4.94 (d, *J* = 3.9 Hz, 1H, 2-CH), 3.73 (dd, *J* = 13.2, 8.7 Hz, 1H, CH), 2.79 (q, *J* = 4.2 Hz, 1H, CH), 2.43 – 2.37 (m, 2H, 2CH), 2.30 (s, 3H, 4'-CH_3), 2.05 (dd, *J* = 13.2, 6.1 Hz, 1H, CH), 1.97 – 1.81 (m, 2H, 2CH), 1.79 – 1.67 (m, 1H, CH), 0.80 (d, *J* = 6.6 Hz, 3H, CHC$\underline{H}_3$), 0.75 (d, *J* = 6.6 Hz, 3H, CHC$\underline{H}_3$). ^{13}C NMR (101 MHz, DMSO-d_6) δ 173.9, 169.3, 138.2, 137.2, 129.7, 127.0, 61.8, 52.0, 46.3, 29.8, 26.3, 21.1, 20.6, 20.5, 19.6. HRMS (ESI), *m/z* calcd for $C_{17}H_{24}NO_3$ $[M+H]^+$ 290.1751, found 290.1745



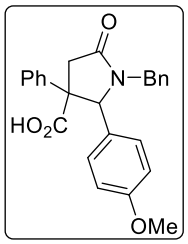
(2*SR*,3*RS*)-4-Benzyl-3-(4-methoxyphenyl)-1-(methylsulfonyl)-5-oxopiperazine-2-carboxylic acid (3c). Prepared according to the general procedure, yield 217 mg (52 %); white powder, mp 205.1–205.4 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.65 (br.s, 1H, COOH), 7.33 – 7.27 (m, 3H, 3CH(Ar)), 7.25 – 7.19 (m, 2H, 2CH(Ar)), 7.19 – 7.11 (m, 2H, 2CH(Ar)), 6.98 (d, *J* = 8.7 Hz, 2H, 2CH(Ar)), 5.18 (d, *J* = 15.0 Hz, 1H, PhC$\underline{H}$), 4.94 (d, *J* = 1.6 Hz, 1H, 3-CH), 4.46 (d, *J* = 1.8 Hz, 1H, 2-CH), 4.29 (d, *J* = 16.9 Hz, 1H, 6-CH), 4.21 (d, *J* = 16.9 Hz, 1H, 6-CH), 3.77 (s, 3H, OCH_3), 3.57 (d, *J* = 15.0 Hz, 1H, PhC$\underline{H}$), 2.70 (s, 3H, SO_2CH_3). ^{13}C NMR (101 MHz, DMSO-d_6) δ 170.4, 164.6, 159.6, 136.5, 129.8, 129.3, 128.8, 128.7, 128.3, 128.2, 127.8, 114.6, 61.0, 60.7, 55.6, 48.5, 46.1, 38.8. HRMS (ESI), *m/z* calcd for $C_{20}H_{23}N_2O_6S$ $[M+H]^+$ 419.1271, found 419.1274.



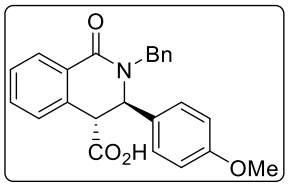
(2*RS*,3*RS*)-1-Benzyl-2-(4-methoxyphenyl)-6-oxopiperi-dine-3-carboxylic acid (5a)[S4]**.** Prepared according to the general procedure, yield 135 mg (40 %), d.r. 90:10; white powder, mp 198.3–198.7 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ (signals of major diastereomer) 12.68 (br.s, 1H, COOH), 7.33 – 7.19 (m, 3H, 3CH(Ar)), 7.11 – 7.08 (m, 4H, 4CH(Ar)), 6.92 (d, *J* = 8.5 Hz, 2H, 2CH(Ar)), 5.15 (d, *J* = 15.2 Hz, 1H, PhC$\underline{H}$), 4.74 (d, *J* = 5.5 Hz, 1H, 2-CH), 3.76 (s, 3H, OCH_3), 3.38 (d, *J* = 15.2 Hz, 1H, PhC$\underline{H}$), 2.72 (q, *J* = 5.6 Hz, 1H, CH), 2.58 – 2.42 (m, 2H, 4-CH_2), 1.91 – 1.82 (m, 2H, 5-CH_2). ^{13}C NMR (101 MHz, DMSO-d_6) δ (signals of major diastereomer) 174.2, 169.7, 159.1, 137.7, 133.1, 128.6, 128.6, 127.9, 127.2, 114.5, 61.8, 55.5, 47.81, 47.5, 30.6, 21.2. HRMS (ESI), *m/z* calcd for $C_{20}H_{22}NO_4$ $[M+H]^+$ 340.1543, found 340.1556.



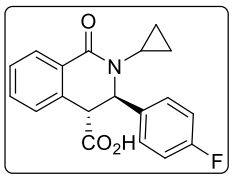
(2*RS*,3*RS*)-1-Cyclopropyl-2-(2,3-dimethoxyphenyl)-5-oxopyrrolidine-3-carboxylic acid (5b). Prepared according to the general procedure, yield 158 mg (52 %); white powder, mp 174.1–174.4 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.66 (br.s, 1H, COOH), 6.95 (d, *J* = 8.2 Hz, 1H, CH(Ar)), 6.88 (d, *J* = 2.0 Hz, 1H, CH(Ar)), 6.82 (dd, *J* = 8.2, 2.0 Hz, 1H, CH(Ar)), 4.66 (d, *J* = 4.9 Hz, 1H, 3-CH), 3.78 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 3.01 – 2.93 (m, 1H, 4-CH), 2.71 (dd, *J* = 16.6, 9.9 Hz, 1H, CH), 2.46 (dd, *J* = 16.9, 6.2 Hz, 1H, 5-CH$\underline{H}$), 2.25 – 2.13 (m, 1H, 5-C$\underline{H}$H), 0.73 – 0.59 (m, 2H, CH_2), 0.55 – 0.47 (m, 1H, CH), 0.43 – 0.33 (m, 1H, CH). ^{13}C NMR (101 MHz, DMSO-d_6) δ 174.39, 173.32, 149.53, 148.94, 133.61, 119.46, 112.21, 110.52, 65.14, 56.01, 55.97, 45.76, 39.38, 34.13, 24.58, 6.97, 4.85. HRMS (ESI), *m/z* calcd for $C_{16}H_{20}NO_5$ $[M+H]^+$ 306.1336, found 306.1351.



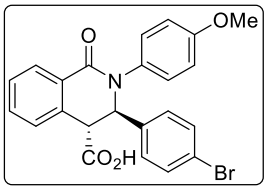
1-Benzyl-2-(4-methoxyphenyl)-5-oxo-3-phenyl-pyrrolidine-3-carboxylic acid (5c). Prepared according to the general procedure, yield 252 mg (63 %), d.r. 56:44; white powder, mp 192.3–192.7 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.18 (br.s, 0.50H, COOH major), 12.62 (s, 0.44H, COOH minor), 7.35 – 7.26 (m, 3H, 3CH(Ar)), 7.26 – 7.19 (m, 2H, 2CH(Ar)), 7.17 – 7.06 (m, 5H, 5CH(Ar)), 7.05 – 7.00 (m, 1H, CH(Ar)), 6.96 (d, *J* = 8.7 Hz, 1H, CH(Ar)), 6.90 (d, *J* = 8.6 Hz, 1H, CH(Ar)), 6.68 (d, *J* = 8.7 Hz, 2H, CH(Ar)), 5.39 (s, 0.56H, 2-CH), 4.93 (s, 0.44H, 2-CH), 4.89 (d, *J* = 14.7 Hz, 0.44H, PhC<u>H</u>(minor)), 4.87 (d, *J* = 15.3 Hz, 0.56H, PhC<u>H</u>(major)), 3.78 (s, 1.32H, OCH_3(minor)), 3.64 (s, 1.68H, OCH_3(major)), 3.59 (d, *J* = 17.1 Hz 0.44H, 4-CH(minor)), 3.46 – 3.40 (m, 1.56H, PhC<u>H</u>(major), PhC<u>H</u>(minor), 4-CH(major)), 3.23 (d, *J* = 16.6 Hz, 0.56H, 4-CH(major)), 2.59 (d, *J* = 17.1 Hz, 0.44H, 4-CH(minor)). ^{13}C NMR (101 MHz, DMSO-d_6) δ 175.3, 172.6, 172.4, 171.7, 159.7, 159.0, 142.8, 137.1, 136.8, 136.4, 130.0, 128.9, 128.9, 128.9, 128.8, 128.2, 128.2, 128.06, 128.05, 127.7, 127.6, 127.5, 126.3, 114.3, 114.0, 67.4, 66.8, 57.7, 57.6, 55.6, 55.3, 44.5, 44.4, 44.1, 37.3. HRMS (ESI), *m/z* calcd for $C_{25}H_{24}NO_4$ $[M+H]^+$ 402.1700, found 402.1720.



(3*RS*,4*RS*)-2-Benzyl-3-(4-methoxyphenyl)-1-oxo-1,2,3,4-tetra-hydroisoquinoline-4-carboxylic acid (7a)[S5]**.** Prepared according to the general procedure, yield 263 mg (68 %); white powder, mp 217.7–217.9 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.91 (br.s, 1H, COOH), 8.02 (d, *J* = 7.1 Hz, 1H, CH(Ar)), 7.49 – 7.40 (m, 2H, 2CH(Ar)), 7.32 – 7.15 (m, 6H, 6CH(Ar)), 6.96 (d, *J* = 8.3 Hz, 2H, 2CH(Ar)), 6.81 (d, *J* = 8.3 Hz, 2H, 2CH(Ar)), 5.29 (d, *J* = 14.9 Hz, 1H, PhC<u>H</u>), 5.21 (s, 1H, 3-CH), 4.06 (s, 1H, 4-CH), 3.86 (d, *J* = 15.0 Hz, 1H, PhC<u>H</u>), 3.67 (s, 3H, OCH_3). ^{13}C NMR (101 MHz, DMSO-d_6) δ 172.5, 163.8, 159.1, 137.7, 134.2, 132.4, 131.3, 130.0, 129.4, 128.6, 128.4, 127.7, 127.5, 127.4, 114.5, 61.1, 55.5, 51.4, 49.6. HRMS (ESI), *m/z* calcd for $C_{24}H_{22}NO_4$ $[M+H]^+$ 388.1543, found 388.1559.

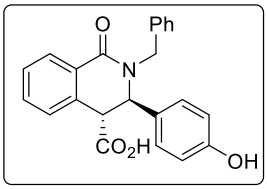


(3*RS*,4*RS*)-2-Cyclopropyl-3-(4-fluorophenyl)-1-oxo-1,2,3,4-tetra-hydroisoquinoline-4-carboxylic acid (7b). Prepared according to the general procedure, yield 243 mg (75 %); white powder, mp 212.3–212.7 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.01 (br.s, 1H, COOH), 7.94 (d, *J* = 7.5 Hz, 1H, CH(Ar)), 7.40 (dt, *J* = 20.5, 7.3 Hz, 2H, 2CH(Ar)), 7.24 (d, *J* = 7.3 Hz, 1H, CH(Ar)), 7.16 (t, *J* = 7.1 Hz, 2H, 2CH(Ar)), 7.09 (t, *J* = 8.7 Hz, 2H, 2CH(Ar)), 5.30 (s, 1H, 3-CH), 4.16 (s, 1H, 4-CH), 2.85 – 2.72 (m, 1H, CH), 0.91 (p, *J* = 6.8 Hz, 1H), 0.77 (q, *J* = 7.7, 4.5 Hz, 1H), 0.72 – 0.53 (m, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 172.3, 164.9, 161.7 (d, *J* = 243.6 Hz), 136.4 (d, *J* = 2.8 Hz), 133.8, 132.4, 130.2, 129.5, 128.4, 128.3 (d, *J* = 8.3 Hz), 127.3, 115.9 (d, *J* = 21.5 Hz), 61.3, 51.1, 30.2, 8.6, 5.7. HRMS (ESI), *m/z* calcd for $C_{19}H_{17}FNO_3$ $[M+H]^+$ 326.1187, found 326.1179.

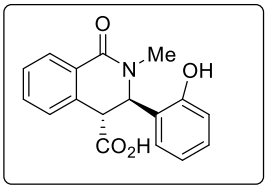


(3*RS*,4*RS*)-3-(4-Bromophenyl)-2-(4-methoxyphenyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid (7c)[S6]**.** Prepared according to the general procedure, yield 307 mg (65 %); white powder, mp 224.1–224.3 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.13 (br.s, 1H, COOH), 8.00 (d, *J* = 7.4 Hz, 1H, CH(Ar)), 7.53 – 7.47 (m, 2H, 2CH(Ar)), 7.44 (d, *J* = 8.4 Hz, 2H, 2CH(Ar)), 7.31 (d, *J* = 7.4 Hz, 1H, CH(Ar)), 7.26 (d, *J* = 8.9 Hz, 2H, 2CH(Ar)), 7.17 (d, *J* = 8.5 Hz, 2H, 2CH(Ar)), 6.95 (d, *J* = 9.0 Hz, 2H, 2CH(Ar)), 5.64 (s, 1H, 3-CH), 4.22

(s, 1H, 4-CH), 3.74 (s, 3H, OCH_3). ^{13}C NMR (101 MHz, DMSO-d_6) δ 172.4, 163.0, 158.1, 139.2, 135.4, 134.0, 132.8, 131.9, 130.1, 129.5, 129.1, 128.6, 128.2, 127.8, 121.2, 114.5, 64.4, 55.7, 51.2. HRMS (ESI), *m/z* calcd for $C_{23}H_{18}BrNNaO_4$ $[M+Na]^+$ 474.0311, found 474.0310.

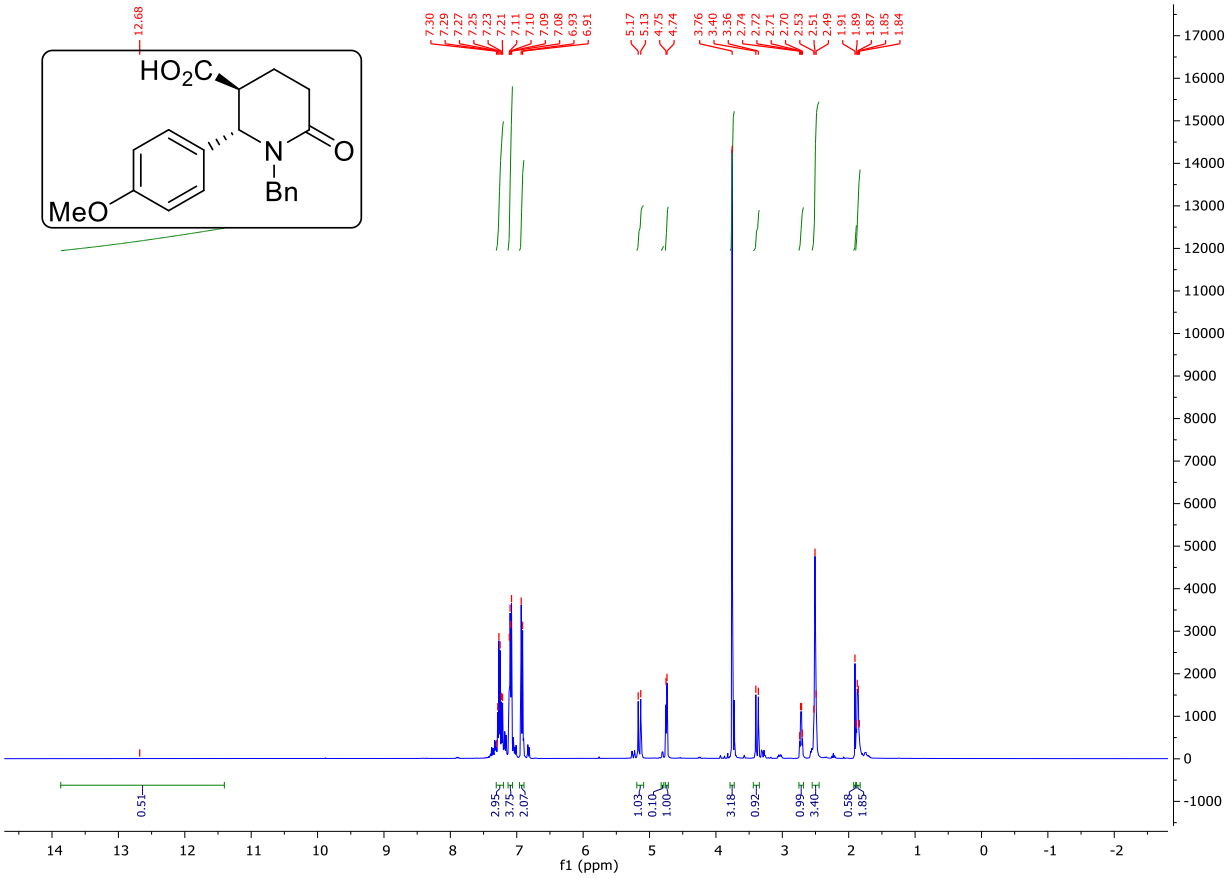


(3*RS*,4*RS*)-2-Benzyl-3-(4-hydroxyphenyl)-1-oxo-1,2,3,4-tetrahydro-isoquinoline-4-carboxylic acid (7d). Prepared according to the general procedure, yield 239 mg (64%); white powder, mp 235-237 °C (decomp.). ^1H NMR (400 MHz, DMSO-d_6) δ 12.89 (s, 1H), 9.39 (s, 1H), 8.21 – 7.78 (m, 1H), 7.54 – 7.34 (m, 2H), 7.34 – 7.06 (m, 6H), 6.83 (d, *J* = 8.5 Hz, 2H), 6.63 (d, *J* = 8.5 Hz, 2H), 5.28 (d, *J* = 15.1 Hz, 1H), 5.14 (s, 1H), 4.03 (s, 1H), 3.83 (d, *J* = 15.1 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 172.6, 163.8, 157.3, 137.8, 134.3, 132.4, 130.0, 129.6, 129.5, 128.6, 128.3, 128.3, 127.6, 127.5, 127.4, 115.8, 61.2, 51.5, 49.5. HRMS (ESI), *m/z* calcd for $C_{23}H_{20}NO_4$ $[M+H]^+$ 374.1387, found 374.1396.



(3*RS*,4*RS*)-3-(2-Hydroxyphenyl)-2-methyl-1-oxo-1,2,3,4-tetrahydro-isoquinoline-4-carboxylic acid (7e). Prepared according to the general procedure, yield 135 mg (45%); white powder, mp 220-221°C (decomp.). ^1H NMR (400 MHz, DMSO-d_6) δ 12.91 (s, 1H), 9.96 (s, 1H), 7.94 (d, *J* = 6.4 Hz, 1H), 7.56 – 7.29 (m, *J* = 5.3 Hz, 2H), 7.24 (d, *J* = 6.3 Hz, 1H), 7.03 (t, *J* = 7.2 Hz, 1H), 6.86 (d, *J* = 7.8 Hz, 1H), 6.60 (t, *J* = 7.3 Hz, 1H), 6.45 (d, *J* = 7.3 Hz, 1H), 5.45 (s, 1H), 4.07 (s, 1H), 2.98 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 172.8, 163.9, 154.9, 134.4, 132.2, 130.2, 129.0, 129.0, 128.2, 127.3, 125.9, 124.5, 119.4, 115.9, 58.6, 48.1, 34.5. HRMS (ESI), *m/z* calcd for $C_{17}H_{16}NO_4$ $[M+H]^+$ 298.1074, found 298.1093.

Figure S1, copies of ^{1}H and ^{13}C NMR of compound **3a**



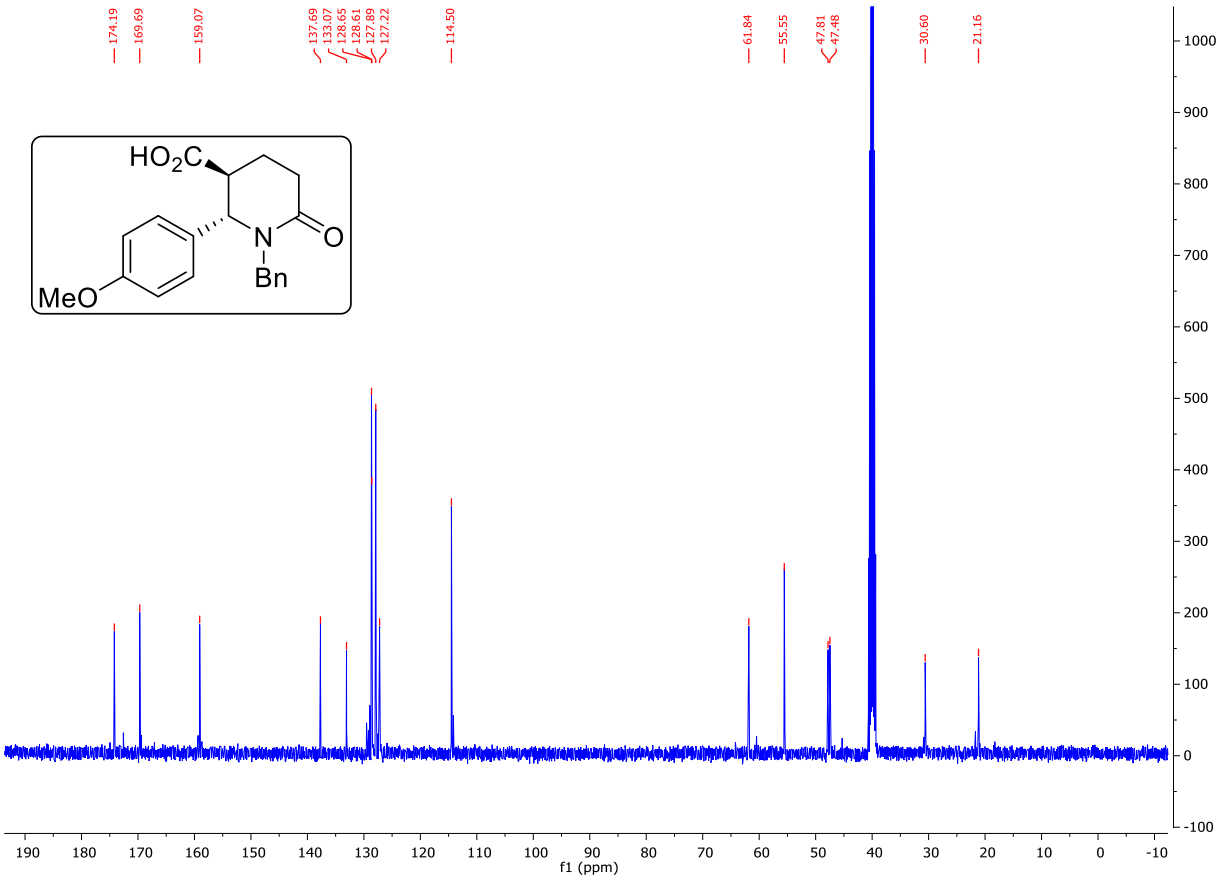
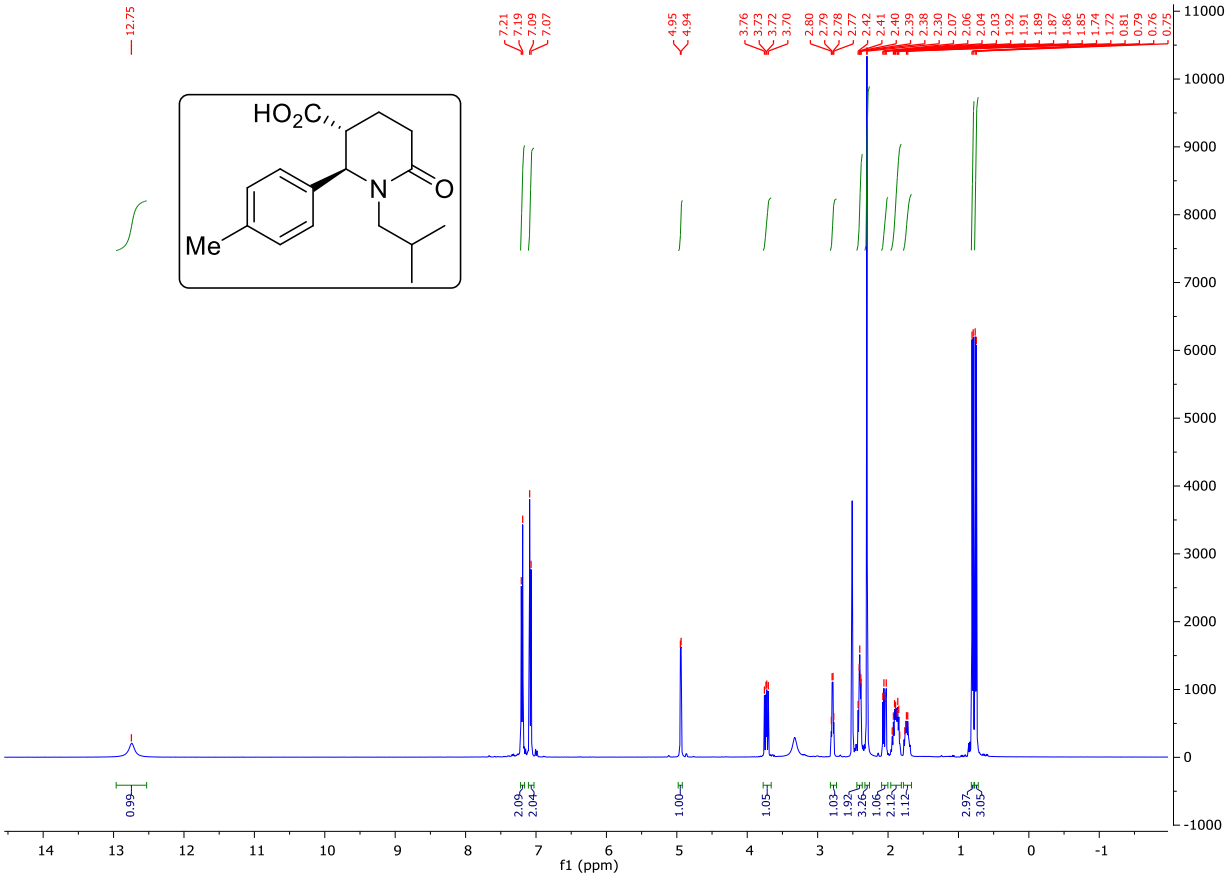


Figure S2, copies of ^{1}H and ^{13}C NMR of compound **3b**



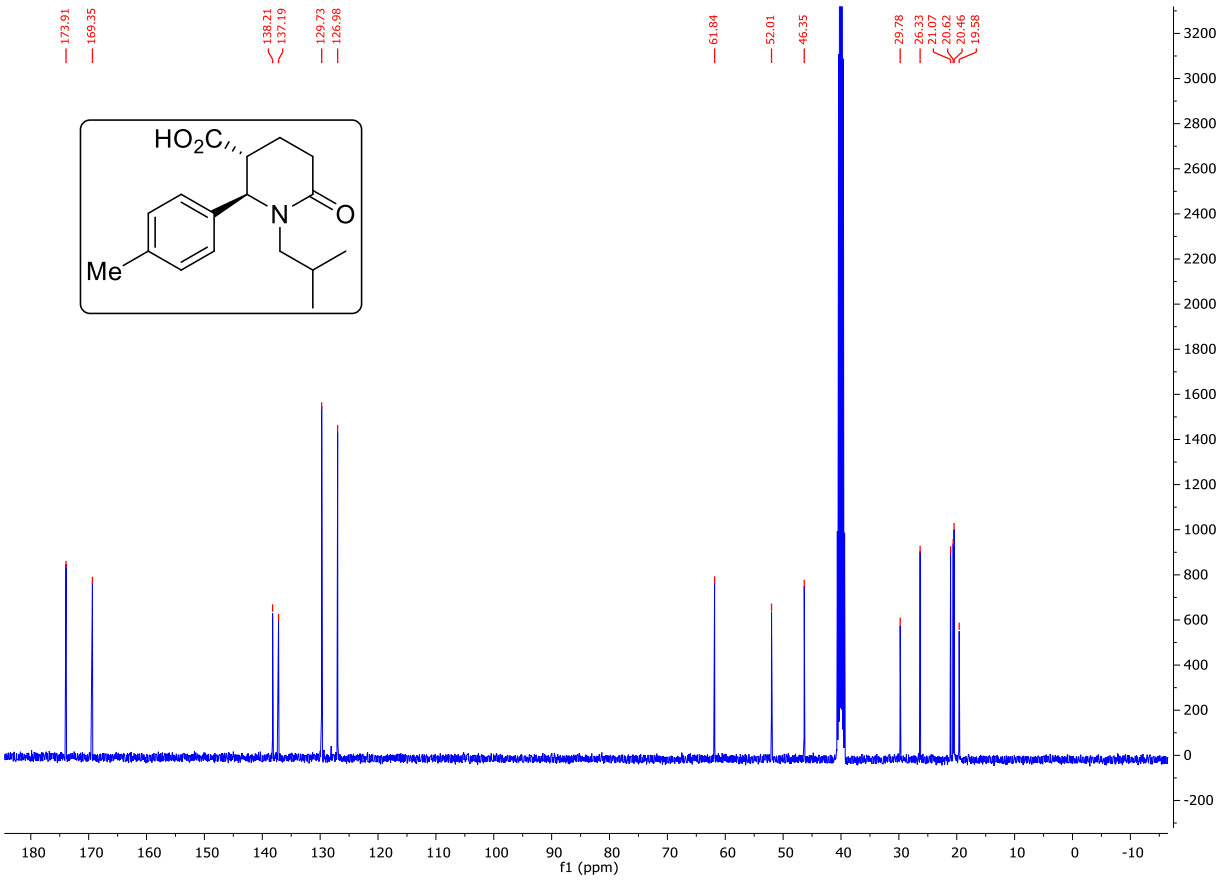
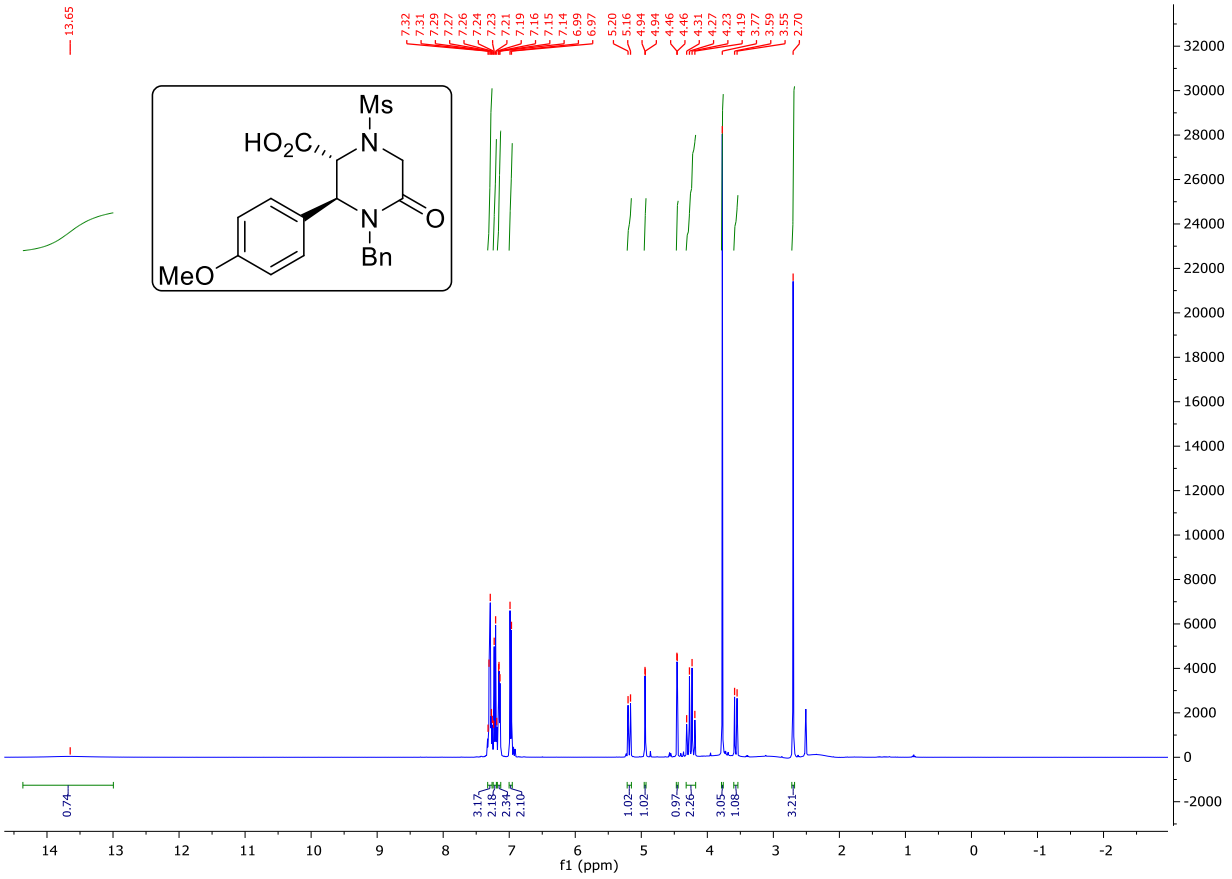


Figure S3, copies of ^{1}H and ^{13}C NMR of compound **3c**



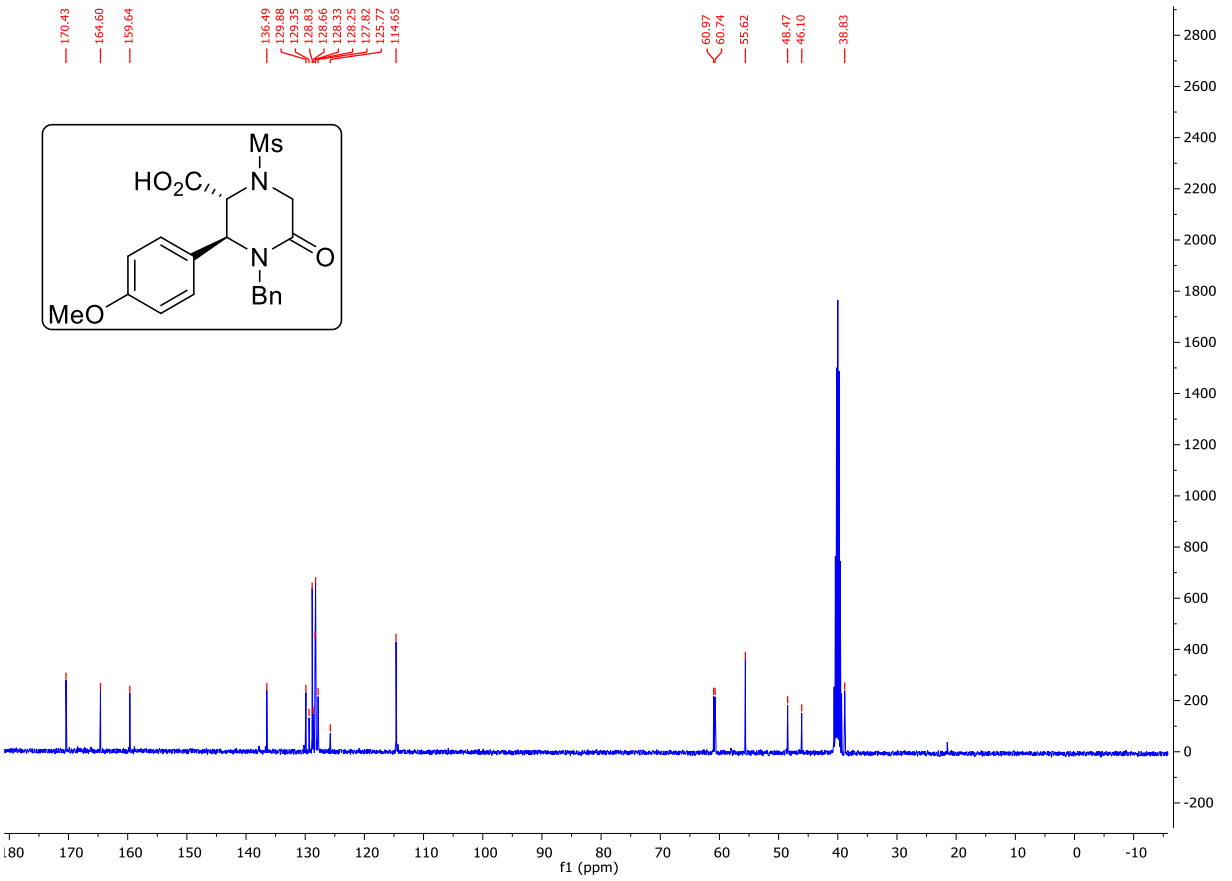


Figure S4, copies of ^{1}H and ^{13}C NMR of compound **5a**

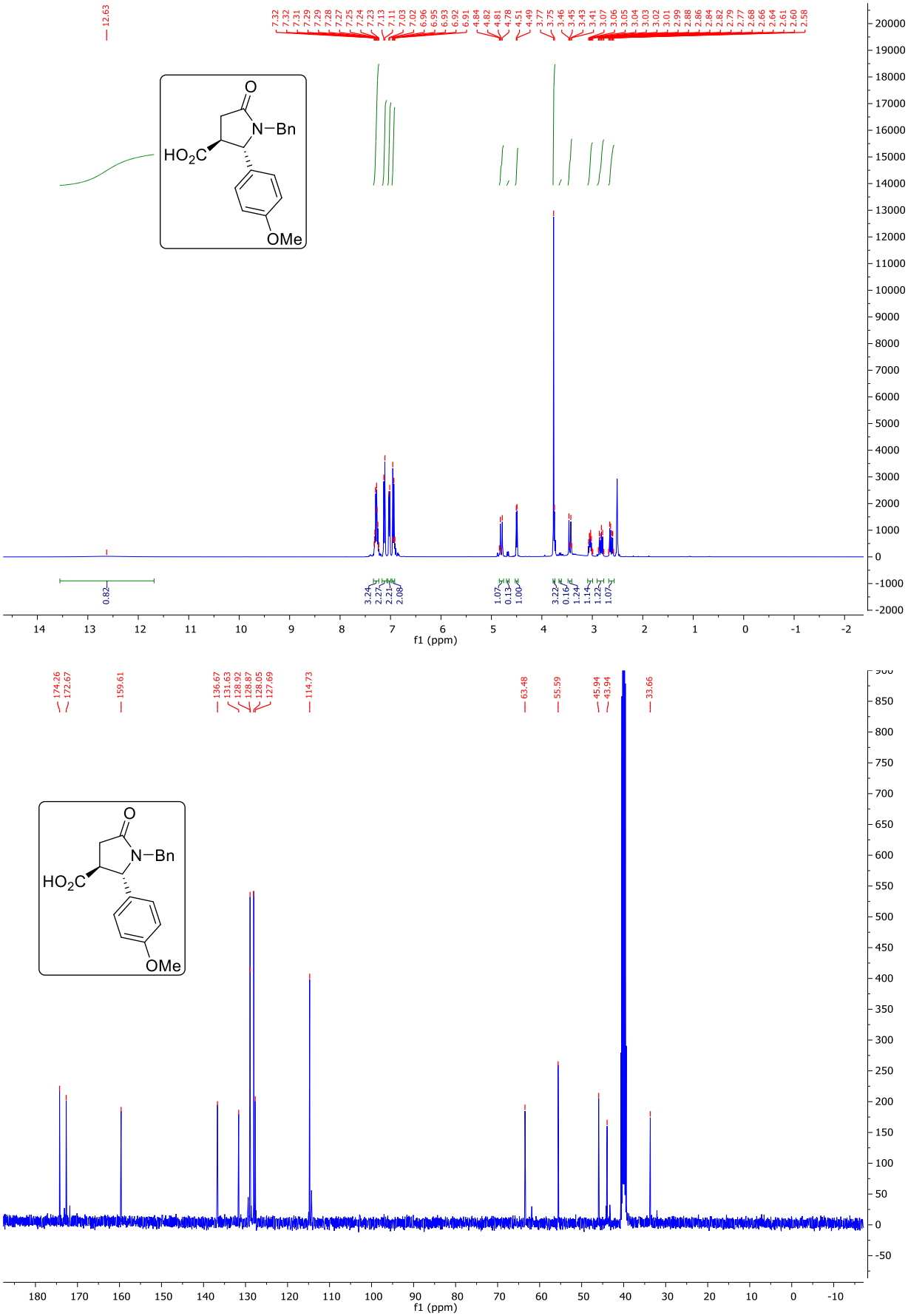
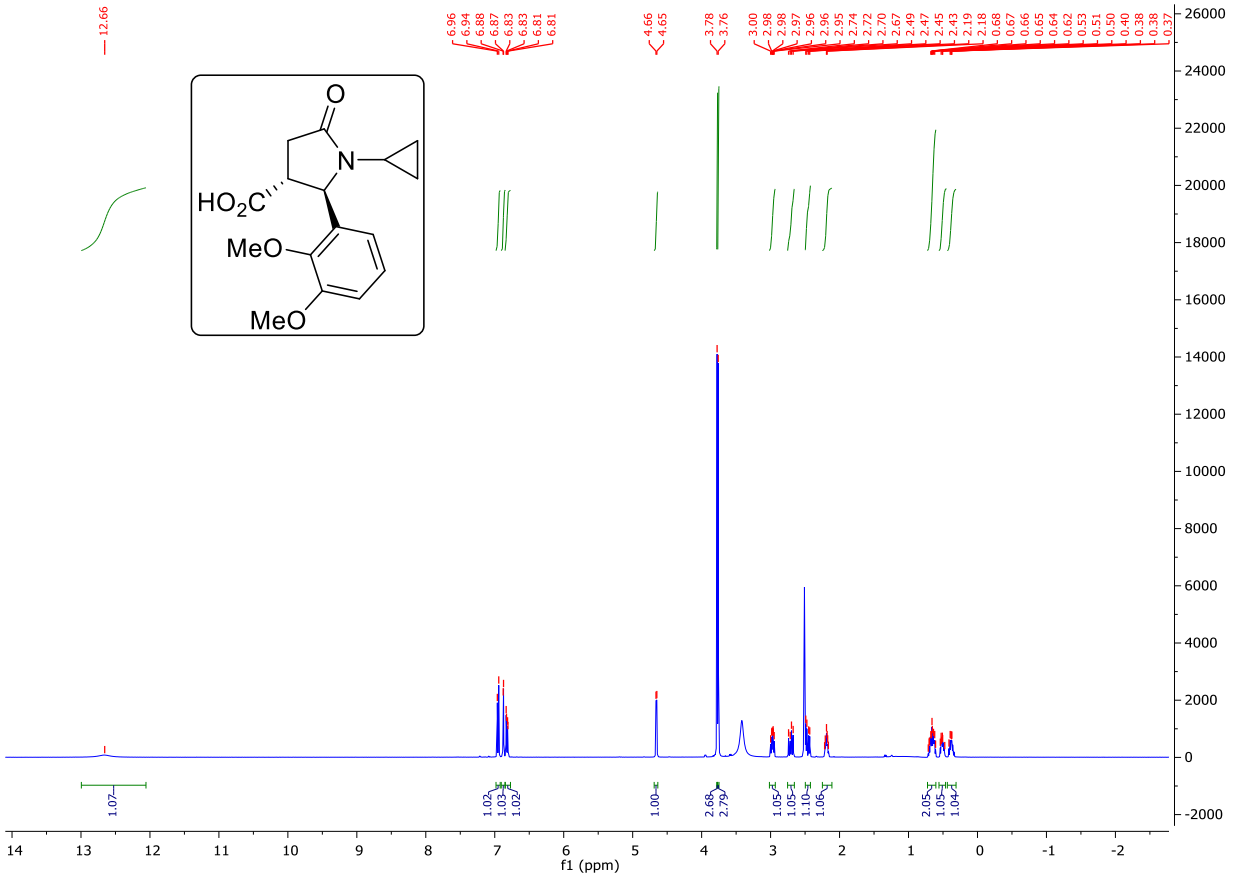


Figure S5, copies of ^{1}H and ^{13}C NMR of compound **5b**



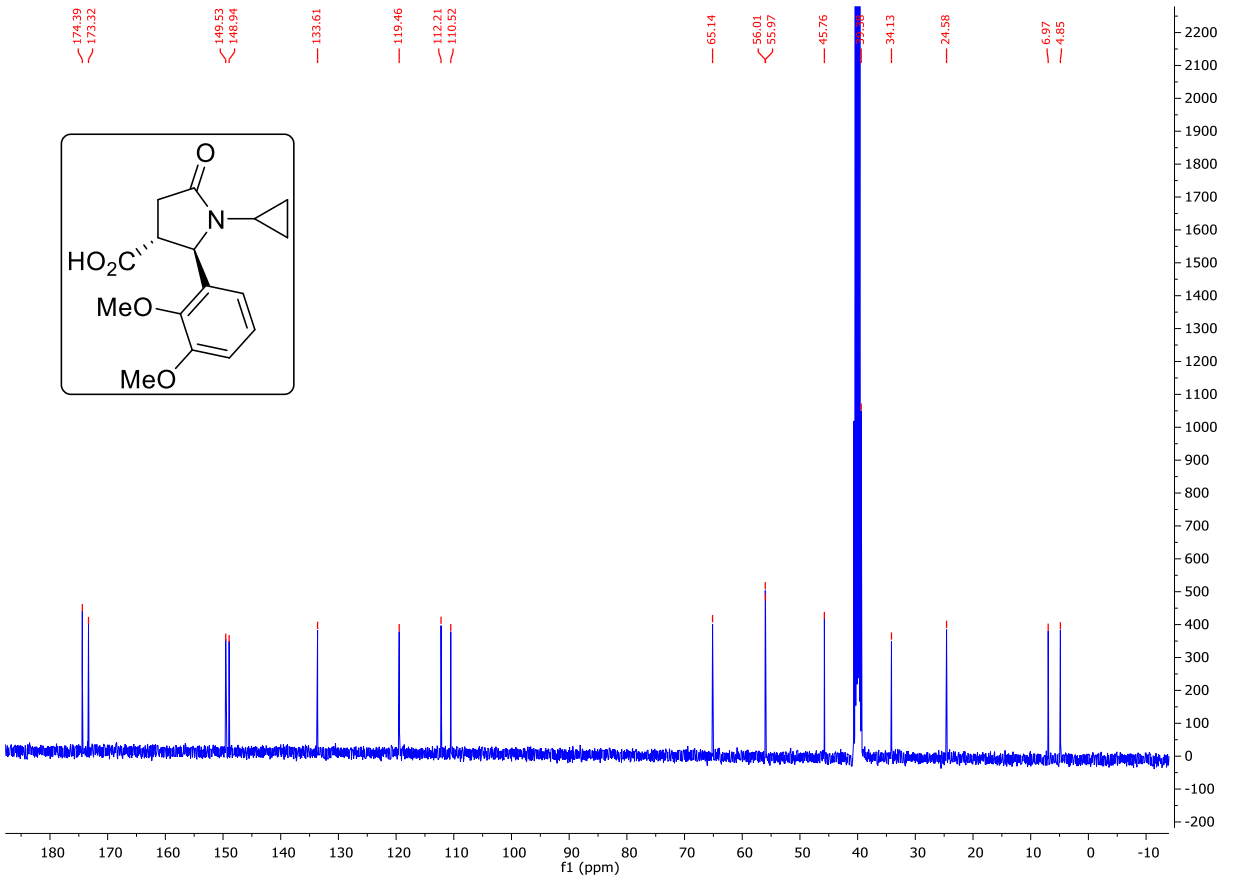
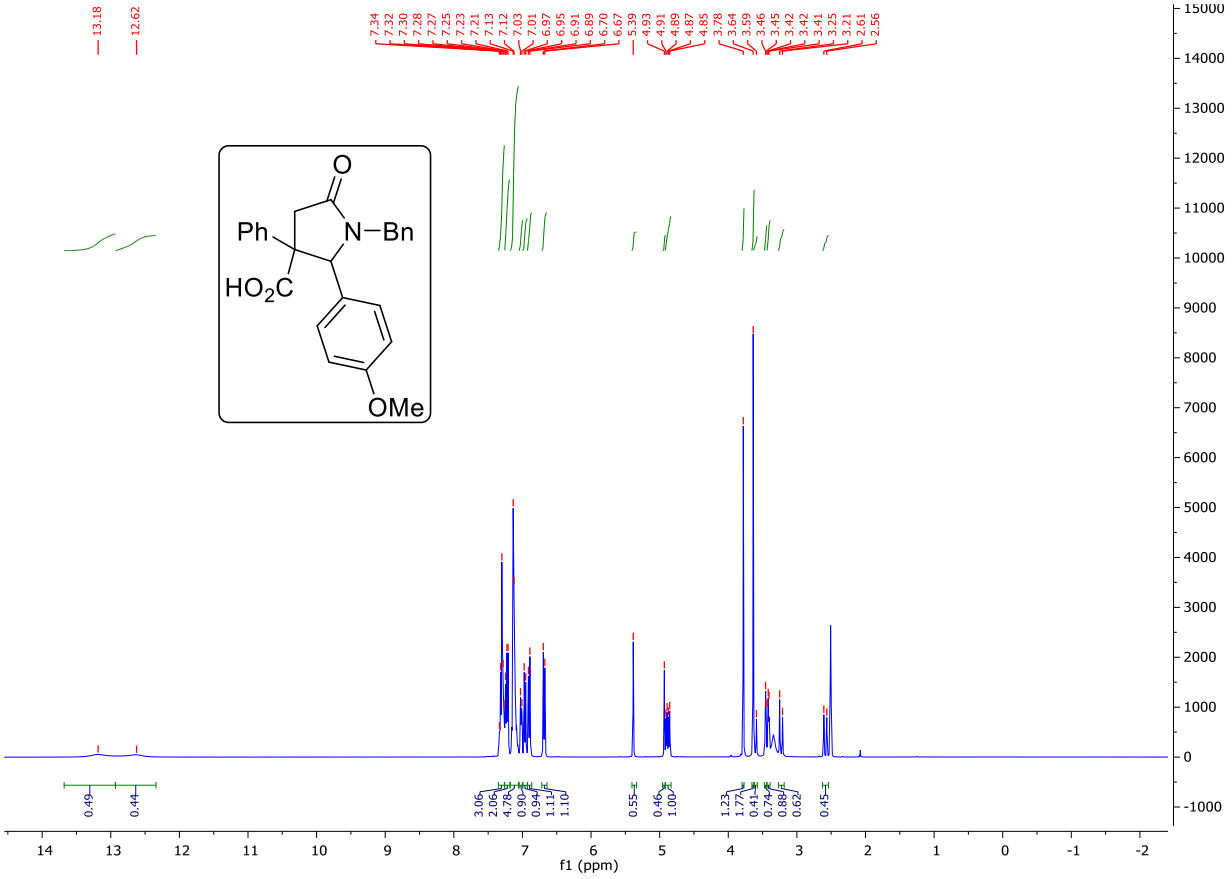


Figure S6, copies of ^{1}H and ^{13}C NMR of compound **5c**



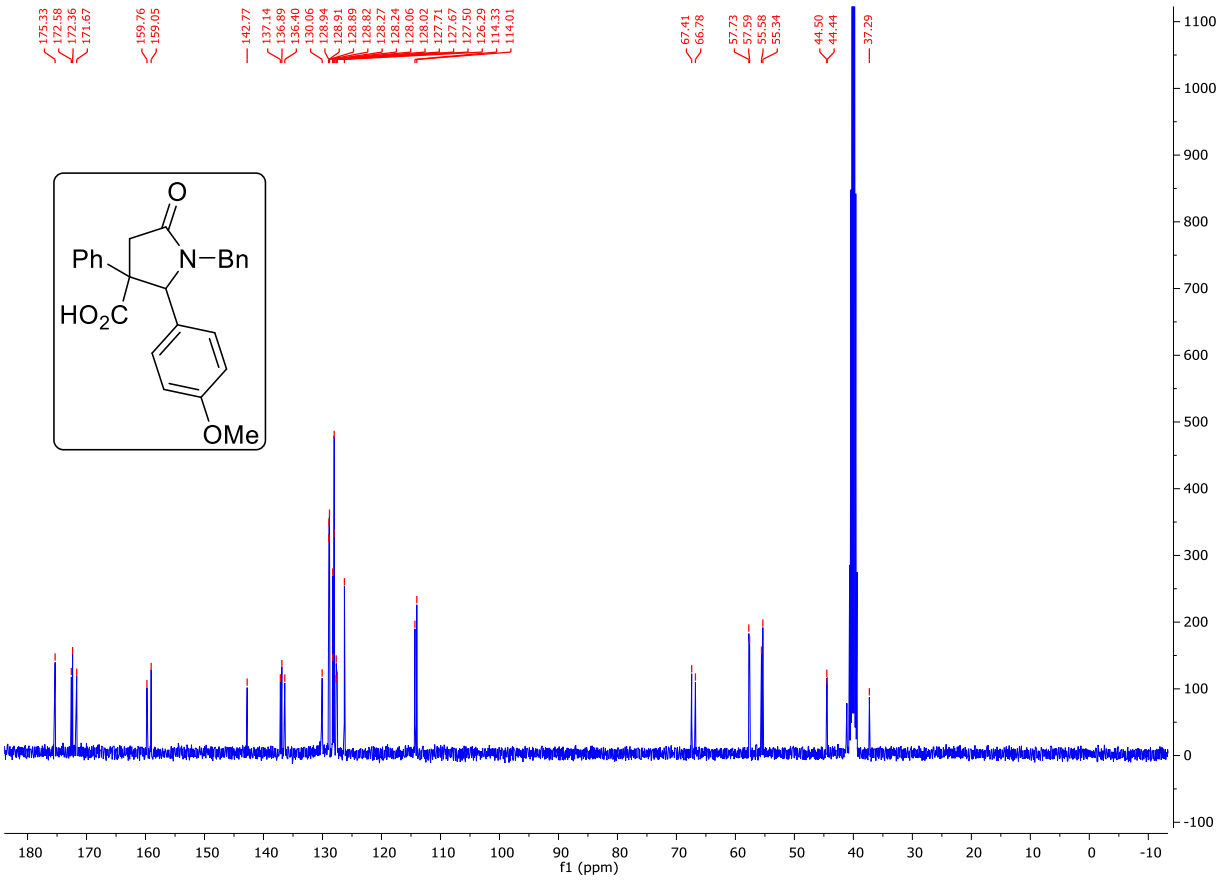
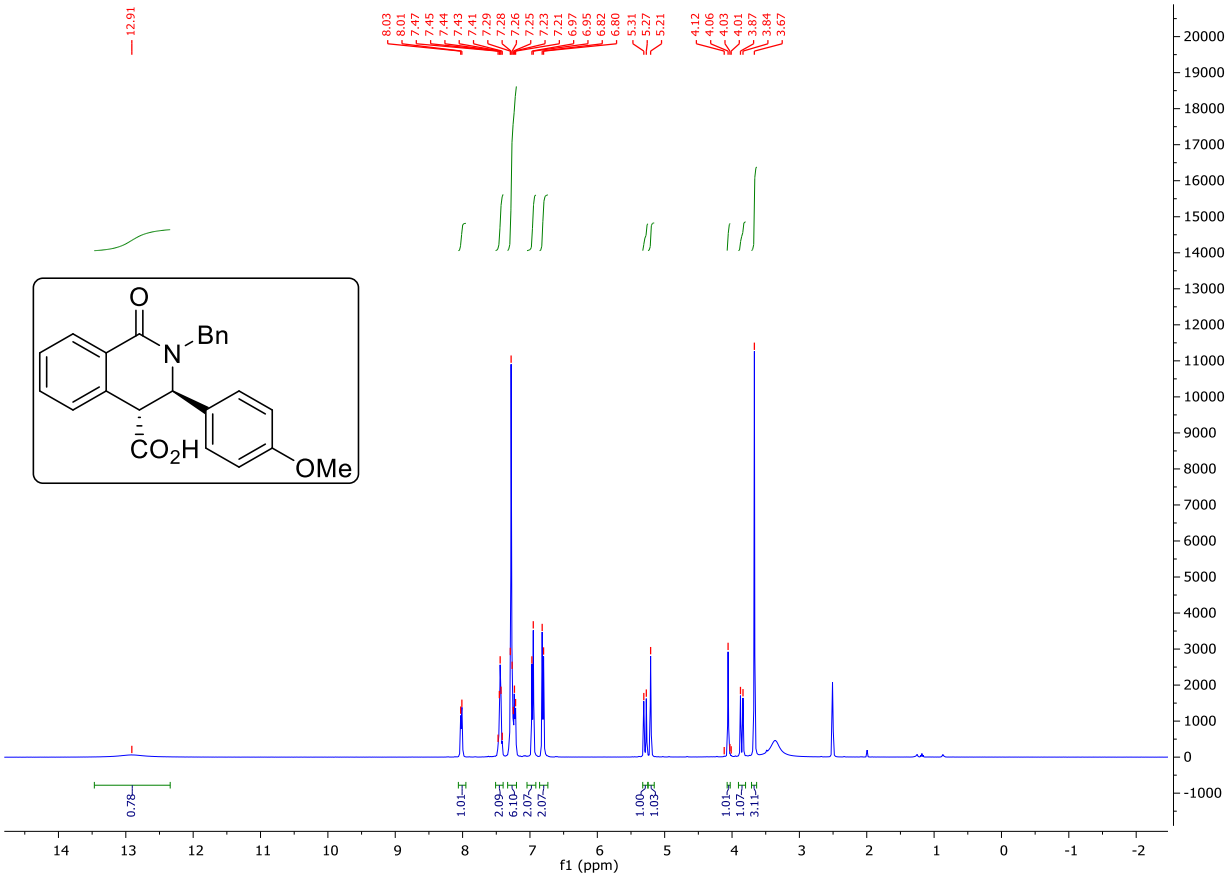


Figure S7, copies of ^{1}H and ^{13}C NMR of compound **7a**



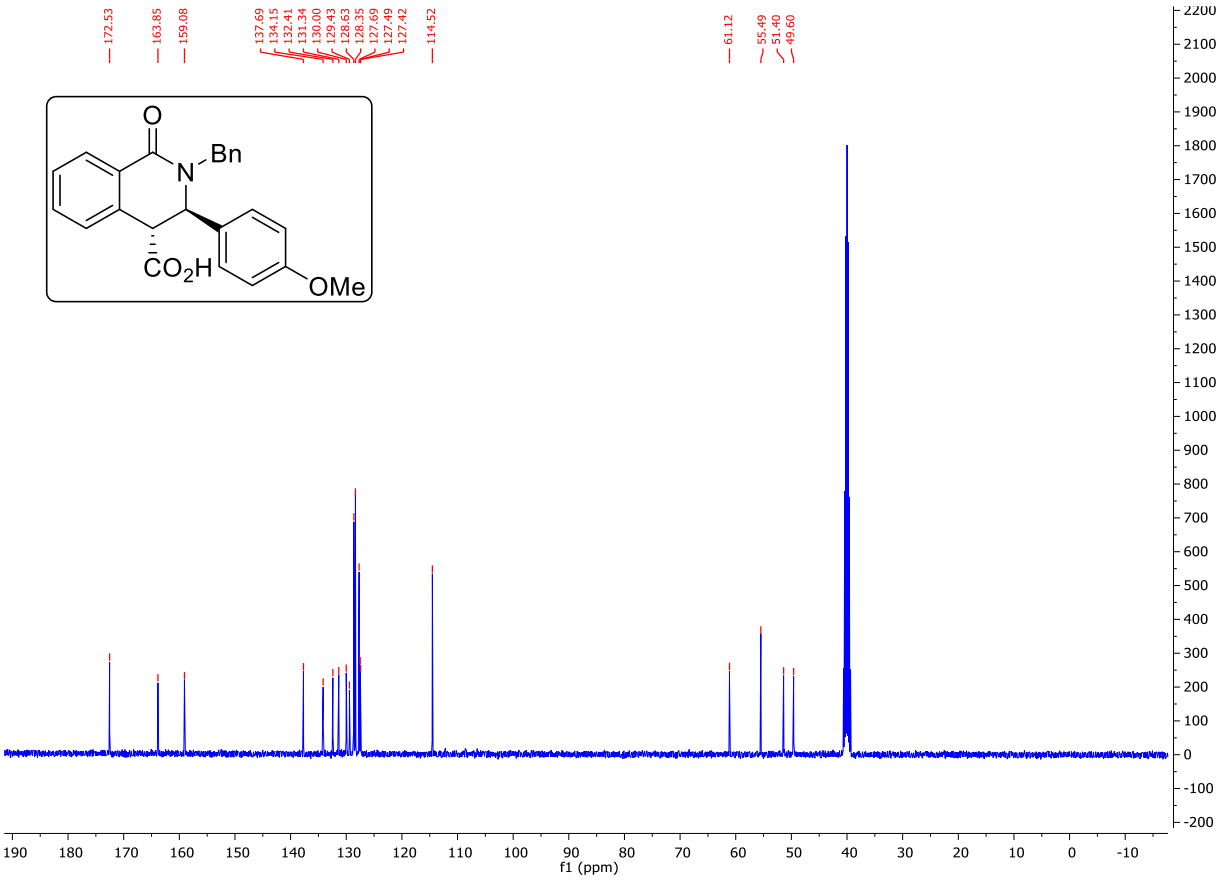
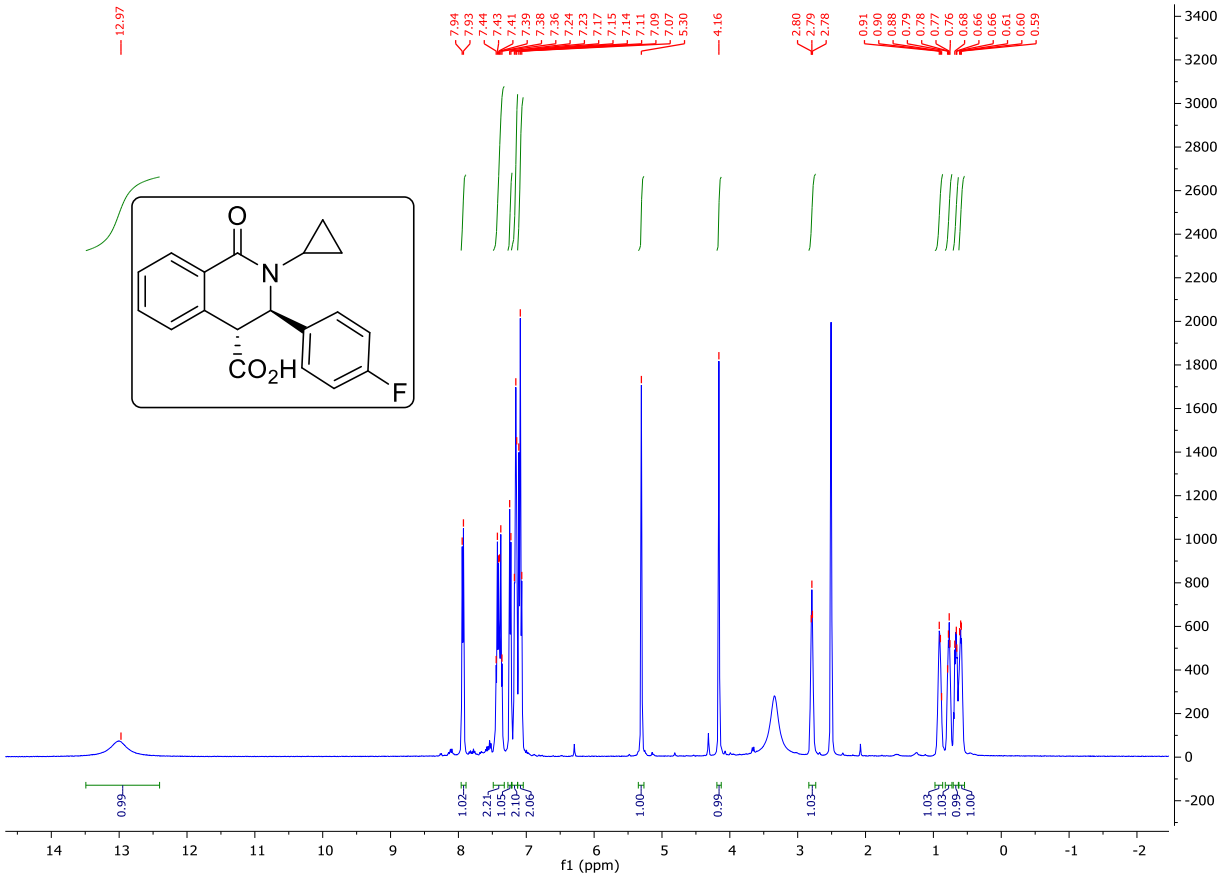


Figure S8, copies of ^{1}H and ^{13}C NMR of compound **7b**



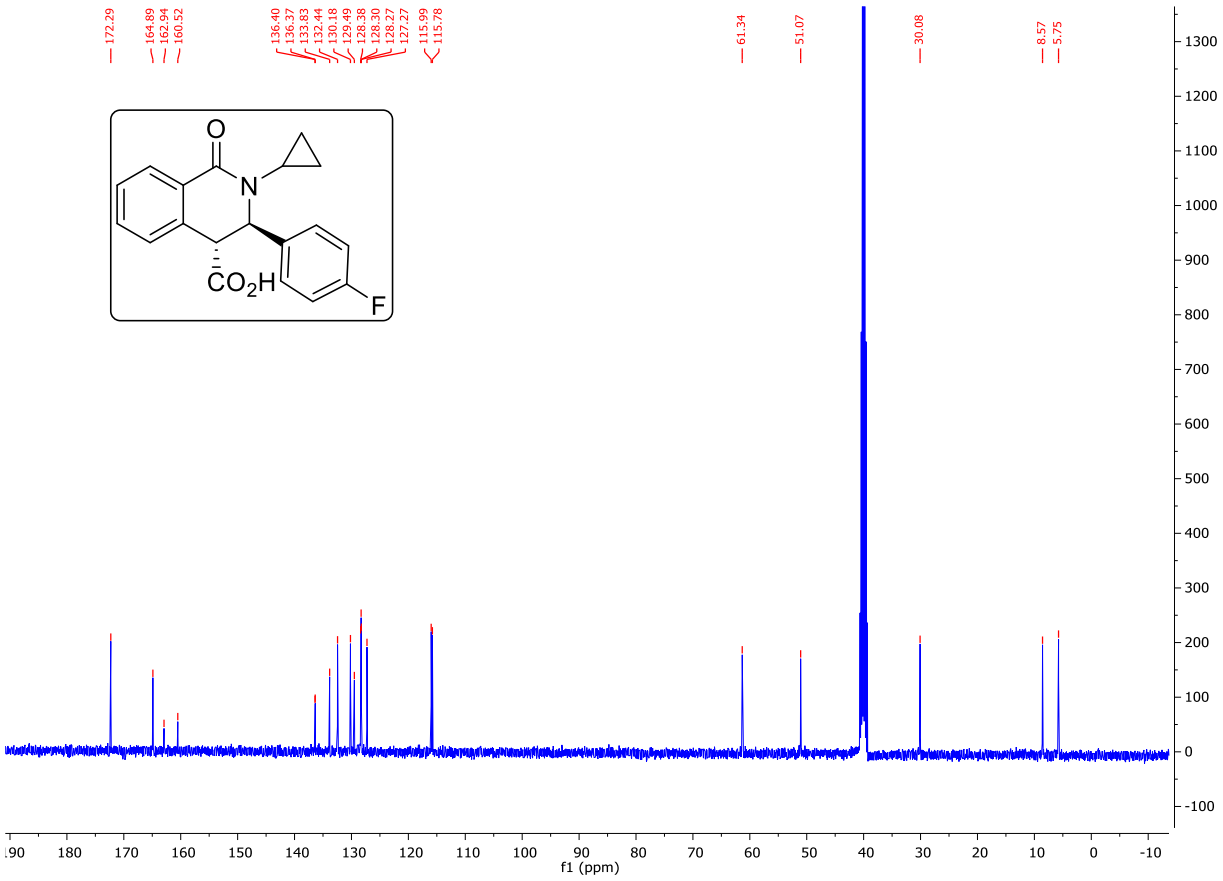


Figure S9, copies of ^{1}H and ^{13}C NMR of compound **7c**

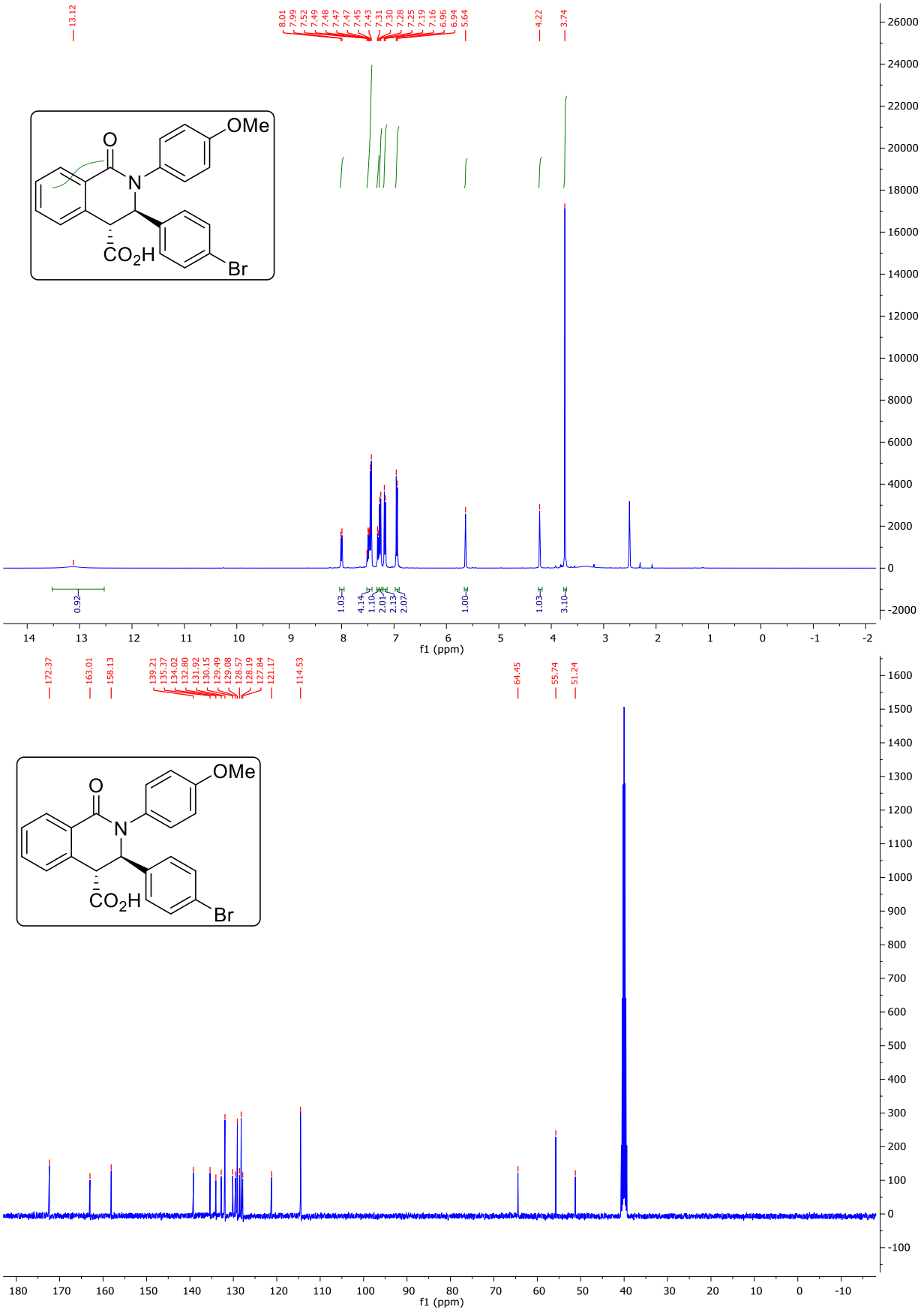


Figure S10, copies of ^{1}H and ^{13}C NMR of compound **7d**

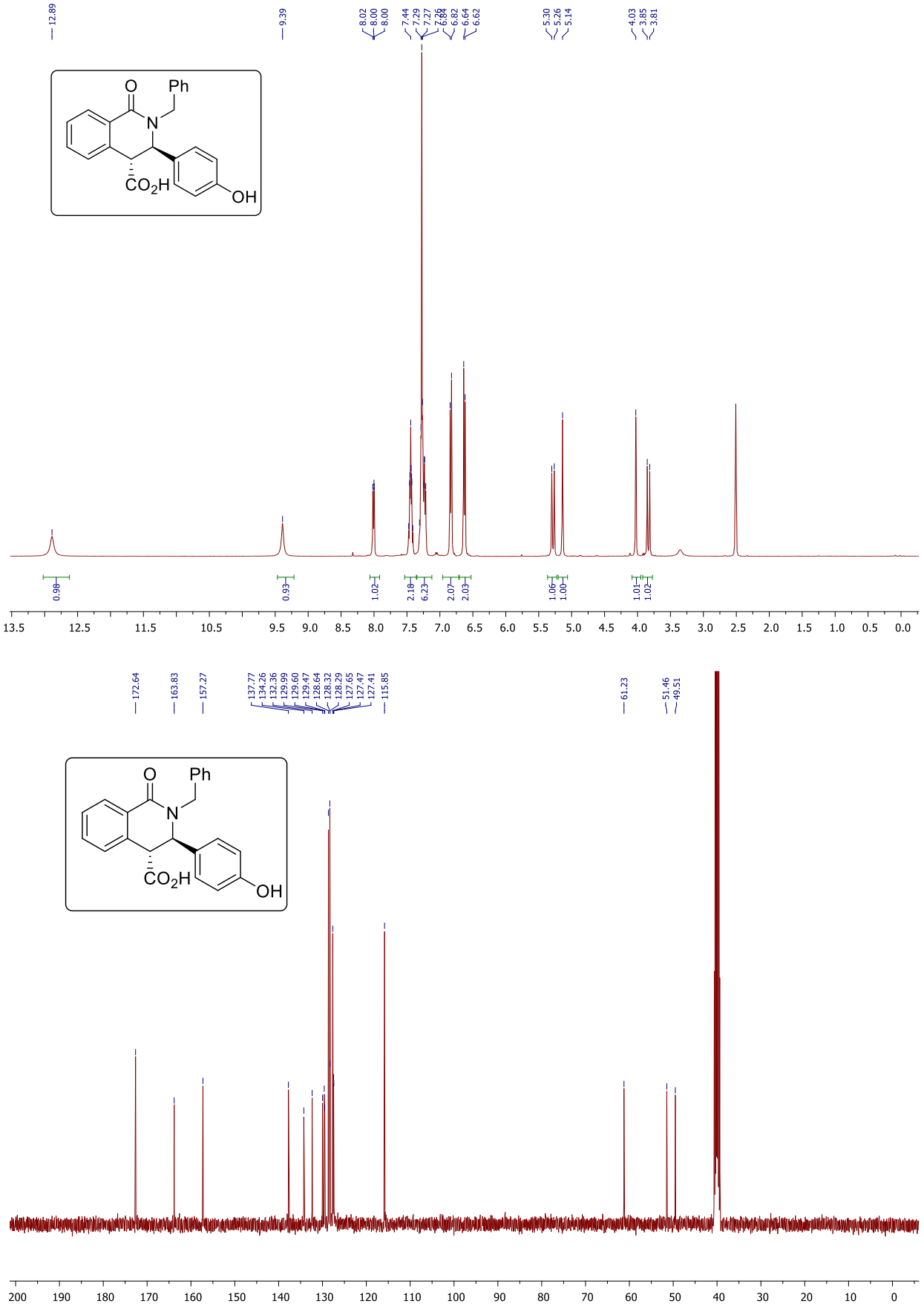
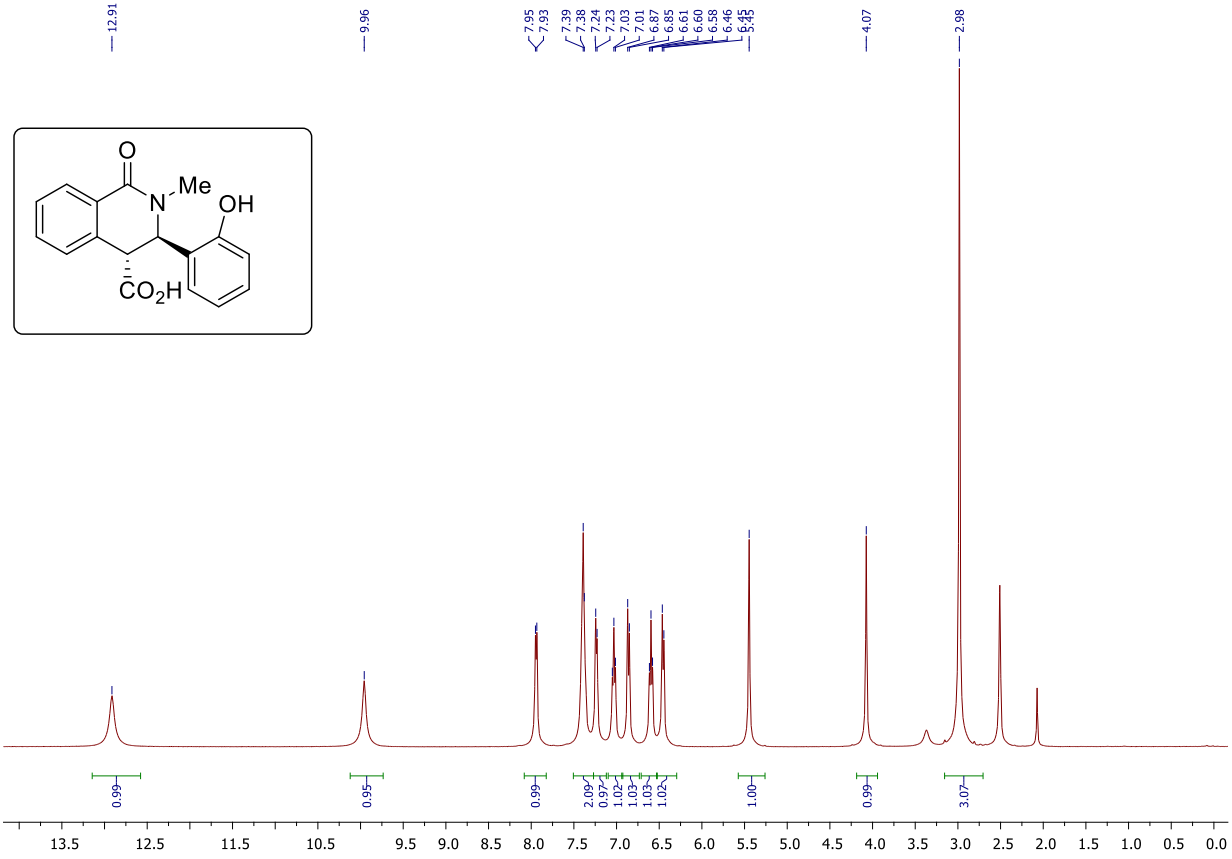
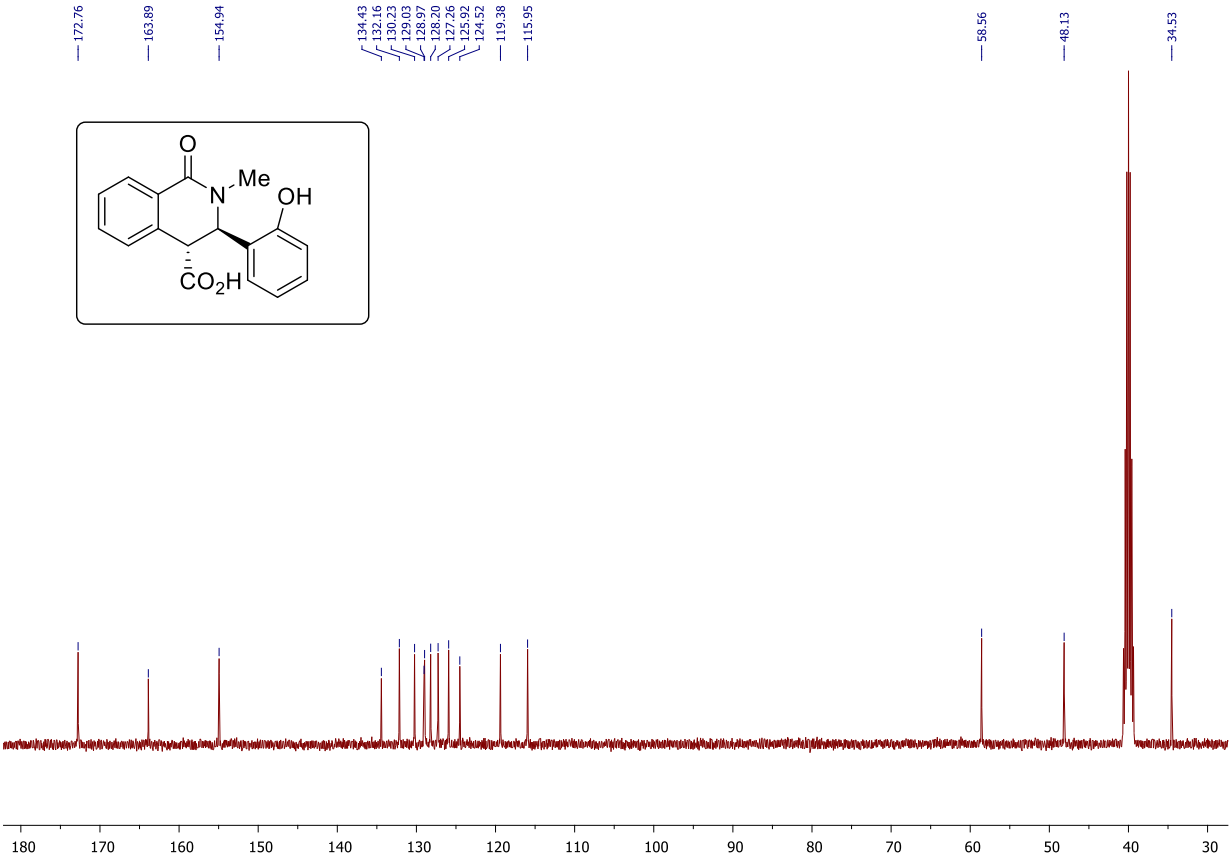


Figure S11, copies of ^{1}H and ^{13}C NMR of compound **7e**





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