Synthesis of 2-(2-Nitrophenyl)indoline-3-acetic Acid Derivatives via Base-Catalyzed Cyclization of *N*-(2-Nitrobenzyl)-2-aminocinnamic Acid Derivatives

Ju Hyeon Park,[1] Jinjae Park[1] and Cheol-Hong Cheon[1,*]

[1] *Department of Chemistry, Korea University, 145 Anam-ro, Seongbuk-gu, Seoul 02841, Republic of Korea*

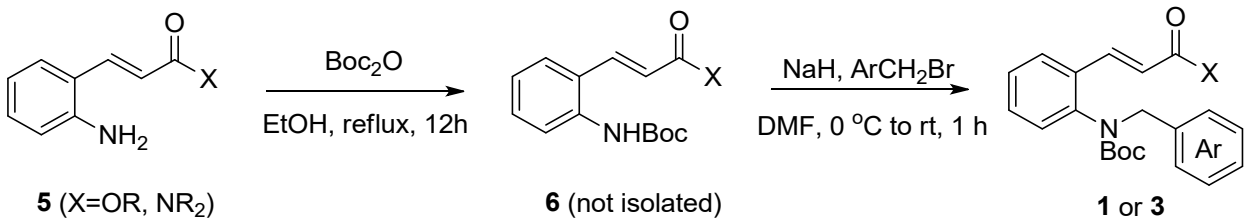
Table of Contents

1. General Information

All reactions were carried out in an oven-dried glassware under an argon atmosphere unless otherwise noted. Except as otherwise indicated, all reactions were magnetically stirred and monitored by analytical thin layer chromatography (TLC) using precoated silica gel glass plates (0.25 mm) with F254 indicator. Visualization was accomplished by UV light (254 nm). Flash column chromatography was performed using silica gel 60 (230 - 400 mesh). Yields refer to chromatographically and spectroscopically pure compounds, unless otherwise noted. ^{1}H NMR and ^{13}C NMR spectra were recorded on 500 MHz and 125 MHz spectrometers, respectively. Residual NMR solvents {either $CDCl_3$ (δ_H: 7.26 ppm, δ_C: 77.16 ppm) or MeOD (δ_H: 3.31 ppm, δ_C: 49.00 ppm) or DMSO (δ_H: 2.50 ppm, δ_C: 39.52 ppm} were used as internal standards for ^{1}H NMR and ^{13}C NMR spectra, respectively. The proton spectra are reported as follows δ (multiplicity, coupling constant *J*, number of protons). Multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), p (quintet), h (septet), m (multiplet) and br (broad). High resolution mass spectra (HRMS) were recorded on quadrupole time-of-flight mass spectrometer (QTOF-MS) using electrospray ionization (ESI) as an ionization method.

2. Preparation of *N*-Benzyl-2-aminocinnamic Acid Derivatives 1 or 3

2-1. Preparation of N-Boc-N-Benzyl-2-Aminocinnamic Acid Derivatives 1 or 3

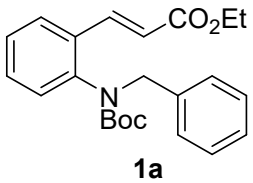


5 (X=OR, NR_2) **6** (not isolated) **1** or **3**

2-Aminocinnamic acid derivative **5** (1.0 mmol) was added to a 50 mL two-neck round bottom flask equipped with a reflux condenser and dissolved in EtOH (10.0 mL). Di-*tert*-butyl-dicarbonate (Boc_2O, 0.65 g, 3.0 mmol) was added dropwise to the above mixture at room temperature. The reaction mixture was allowed to reflux with an oil bath and monitored by TLC. After the complete consumption of **5**, the reaction mixture was cooled to room temperature, quenched with H_2O, and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure to provide a crude product of **6**, which was directly used in the next step without further isolation.

The resulting **6** was added to a 50 mL one-neck round bottom flask and dissolved in dimethylformamide (DMF, 10.0 mL). To the above mixture was added NaH (60% dispersion in mineral oil, 0.049 g, 1.2 mmol) at 0 °C and the resulting mixture was stirred at the same temperature. After 30 min, a benzyl bromide derivative (1.2 mmol) was added to the reaction mixture. The resulting mixture was stirred at room temperature and monitored by TLC. After the complete consumption of **6**, the reaction mixture was carefully quenched with H_2O and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using a mixture of ethyl acetate and hexanes as the eluent to provide the desired product **1** or **3**.

(*E*)-Ethyl 3-(2-(benzyl(*tert*-butoxycarbonyl)amino)phenyl)acrylate (1a)



1a

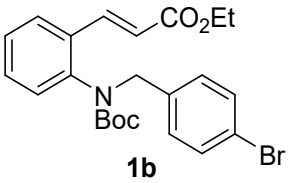
A white solid; 0.38 g (99%);

^{1}H NMR (500 MHz, MeOD) δ 7.64 (d, *J* = 6.1 Hz, 1H), 7.44 (d, *J* = 16.0 Hz, 1H), 7.36 (t, *J* = 5.3 Hz, 1H), 7.30 (d, *J* = 4.9 Hz, 1H), 7.21 (br, 3H), 7.17-7.15 (m, 2H), 7.12 (s, 1H), 6.30 (d, *J* = 16.0 Hz, 1H), 4.89 (d, *J* = 14.2 Hz, 1H) 4.86 (d, *J* = 14.2 Hz, 1H) 4.22-4.17 (m, 2H), 1.31 (t, *J* = 7.2 Hz, 12H).

^{13}C NMR (125 MHz, MeOD) δ 168.1, 156.2, 142.4, 141.8, 138.4, 133.9, 132.0, 130.0, 129.6, 129.4, 128.8, 128.7, 127.7, 120.1, 81.8, 61.5, 54.9, 28.4, 14.6.

HRMS (ESI): *m/z*; $[M+Na]^+$ Calcd for $C_{23}H_{27}NO_4Na$ 404.18323; Found: 404.1833.

(*E*)-Ethyl 3-(2-((4-bromobenzyl)(*tert*-butoxycarbonyl)amino)phenyl)acrylate (1b)



1b

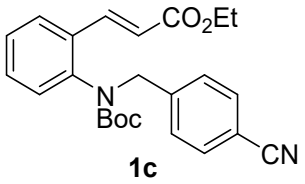
A white solid; 0.39 g (85%);

^{1}H NMR (500 MHz, MeOD) δ 7.67 (d, *J* = 7.0 Hz, 1H), 7.41-7.31 (m, 5H), 7.16 (s, 1H), 7.10 (dt, *J* = 8.4, 2.4 Hz, 2H), 6.31 (d, *J* = 16.0 Hz, 1H), 4.93 (d, *J* = 14.5 Hz, 1H), 4.57 (d, *J* = 14.5 Hz, 1H), 4.24-4.18 (m, 2H), 1.32 (t, *J* = 7.2 Hz, 12H).

^{13}C NMR (125 MHz, MeOD) δ 168.1, 156.2, 142.4, 141.6, 137.8, 134.0, 132.6, 132.2, 132.0, 129.7, 129.0, 127.8, 122.6, 120.3, 82.0, 61.6, 54.3, 28.5, 14.6,

HRMS (ESI): *m/z*; $[M+Na]^+$ Calcd for $C_{23}H_{26}BrNO_4Na$ 482.09374; Found: 482.0942.

(*E*)-Ethyl 3-(2-((*tert*-butoxycarbonyl)(4-cyanobenzyl)amino)phenyl)acrylate (1c)



1c

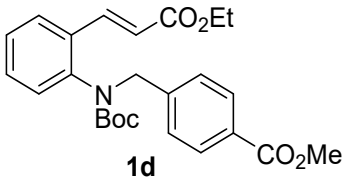
A white solid; 0.33 g (81%);

^{1}H NMR (500 MHz, MeOD) δ 7.68 (d, *J* = 7.5 Hz, 1H), 7.62 (d, *J* = 7.0 Hz, 2H), 7.43 (t, *J* = 56.9 Hz, 1H), 7.38 (d, *J* = 8.2 Hz, 3H), 7.33 (br, 1H), 7.19 (br, 1H), 6.32 (d, *J* = 16.0 Hz, 1H), 5.02 (d, *J* = 13.6 Hz, 1H) 4.69 (d, *J* = 13.6 Hz, 1H) 4.24-4.19 (m, 2H), 1.32 (t, *J* = 7.2 Hz, 12H).

^{13}C NMR (125 MHz, MeOD) δ 168.0, 156.2, 144.2, 142.4, 141.4, 133.9, 133.4, 132.3, 130.9, 129.6, 129.1, 127.9, 120.5, 119.5, 112.5, 82.3, 61.7, 54.6, 28.4, 14.6.

HRMS (ESI): *m/z*; $[M+Na]^+$ Calcd for $C_{24}H_{26}N_2O_4Na$ 429.17848; Found: 429.1783.

(*E*)-Methyl 4-(((*tert*-butoxycarbonyl)(2-(3-ethoxy-3-oxoprop-1-en-11)phenyl)amino)methyl)benzoate (1d)



1d

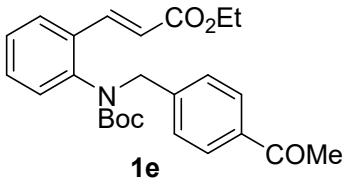
A white solid; 0.39 g (89%);

^{1}H NMR (500 MHz, MeOD) δ 7.89 (d, *J* = 6.9 Hz, 2H), 7.65 (d, *J* = 6.4 Hz, 1H), 7.40-7.32 (m, 3H), 7.30 (d, *J* = 8.2 Hz, 2H), 7.18 (br, 1H), 6.27 (d, *J* = 16.0 Hz, 1H), 5.02 (d, *J* = 14.0 Hz, 1H), 4.67 (d, *J* = 14.0 Hz, 1H), 4.20 (q, *J* = 7.2 Hz, 2H), 3.87 (s, 3H) 1.31 (t, *J* = 7.2 Hz, 12H).

^{13}C NMR (125 MHz, MeOD) δ 168.1, 168.0, 156.2, 144.0, 142.4, 141.6, 134.0, 132.2, 130.7, 130.6, 130.2, 129.6, 129.0, 127.8, 120.3, 82.1, 61.6, 54.6, 52.6, 28.4, 14.6.

HRMS (ESI): *m/z*; $[M+Na]^+$ Calcd for $C_{25}H_{29}NO_6Na$ 462.18871; Found: 462.1883.

(*E*)-Ethyl 3-(2-((4-acetylbenzyl)(*tert*-butoxycarbonyl)amino)phenyl)acrylate (1e)



1e

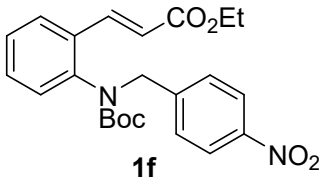
A white solid; 0.29 g (69%);

^{1}H NMR (500 MHz, MeOD) δ 7.88 (d, *J* = 7.0 Hz, 2H), 7.66 (d, *J* = 7.3 Hz, 1H), 7.42-7.36 (m, 3H), 7.33 (d, *J* = 8.2 Hz, 2H), 7.19 (br, 1H), 6.28 (d, *J* = 16.0 Hz, 1H), 5.03 (d, *J* = 14.5 Hz, 1H) 4.69 (d, *J* = 14.5 Hz, 1H) 4.20 (q, *J* = 7.2 Hz, 2H), 2.56 (s, 3H), 1.32 (t, *J* = 7.2 Hz, 12H).

^{13}C NMR (125 MHz, MeOD) δ 199.9, 168.0, 156.2, 144.1, 142.4, 141.6, 137.6, 134.0, 132.3, 130.3, 129.71, 129.66, 129.0, 127.9, 120.3, 82.2, 61.6, 54.6, 28.4, 26.7, 14.6.

HRMS (ESI): *m/z*; $[M+Na]^+$ Calcd for $C_{25}H_{29}NO_5Na$ 446.19379; Found: 446.1939.

(*E*)-Ethyl 3-(2-((*tert*-butoxycarbonyl)(4-nitrobenzyl)amino)phenyl)acrylate (1f)



1f

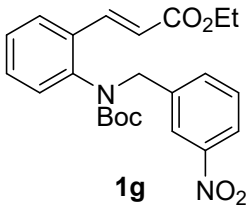
A white solid; 0.30 g (70%);

^{1}H NMR (500 MHz, MeOD) δ 8.11 (d, *J* = 7.6 Hz, 2H), 7.67 (d, *J* = 7.6 Hz, 1H), 7.44 (d, *J* = 8.7 Hz, 3H), 7.37-7.33 (m, 2H), 7.22 (br, 1H), 6.29 (d, *J* = 16.0 Hz, 1H), 5.07 (d, *J* = 14.0 Hz, 1H), 4.72 (d, *J* = 14.0 Hz, 1H), 4.20 (q, *J* = 7.2 Hz, 2H), 1.32 (s, 9H), 1.29 (t, *J* = 7.2 Hz, 12H).

^{13}C NMR (125 MHz, MeOD) δ 168.0, 156.1, 148.8, 146.1, 142.3, 141.4, 133.9, 132.4, 131.0, 129.6, 129.1, 127.9, 124.6, 120.5, 82.3, 61.7, 54.3, 28.4, 14.6.

HRMS (ESI): *m/z*; $[M+Na]^+$ Calcd for $C_{23}H_{26}N_2O_6Na$ 449.16831; Found: 449.1685.

(*E*)-Ethyl 3-(2-((*tert*-butoxycarbonyl)(3-nitrobenzyl)amino)phenyl)acrylate (1g)



1g

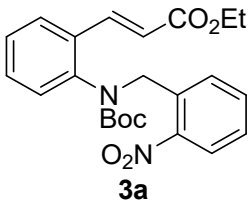
A white solid; 0.42 g (99%);

^{1}H NMR (500 MHz, MeOD) δ 8.13 (d, *J* = 7.2 Hz, 2H), 7.67 (d, *J* = 7.5 Hz, 1H), 7.49-7.45 (m, 3H), 7.34 (d, *J* = 16.0 Hz, 2H), 7.24 (br, 1H), 6.26 (d, *J* = 16.0 Hz, 1H), 5.15 (d, *J* = 12.8 Hz, 1H) 4.69 (d, *J* = 12.8 Hz, 1H) 4.18-4.11 (m, 2H), 1.32 (s, 9H), 1.28 (t, *J* = 7.2 Hz, 12H).

^{13}C NMR (125 MHz, MeOD) δ 167.9, 156.1, 149.7, 142.2, 141.3, 140.8, 136.3, 133.9, 132.4, 130.7, 129.5, 129.2, 127.9, 124.8, 123.6, 120.4, 82.3, 61.7, 54.3, 28.4, 26.7, 14.5.

HRMS (ESI): *m/z*; $[M+Na]^+$ Calcd for $C_{23}H_{26}N_2O_6Na$ 449.16831; Found: 449.1682.

(*E*)-Ethyl 3-(2-((*tert*-butoxycarbonyl)(2-nitrobenzyl)amino)phenyl)acrylate (3a)



3a

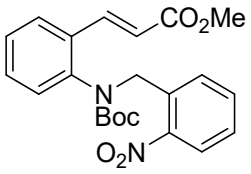
A white solid; 0.42 g (99%);

^{1}H NMR (500 MHz, MeOD) δ 7.86 (d, *J* = 8.1 Hz, 1H), 7.66 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.60 (t, *J* = 7.2 Hz, 1H), 7.48-7.44 (m, 2H), 7.40 (t, *J* = 7.3 Hz, 1H), 7.33 (t, *J* = 7.3 Hz, 1H), 7.18 (br, 1H), 6.32 (d, *J* = 15.9 Hz, 1H), 5.21 (d, *J* = 14.0 Hz, 1H), 5.12 (d, *J* = 14.0 Hz, 1H), 4.24 (q, *J* = 7.2 Hz, 2H), 1.33 (t, *J* = 7.2 Hz, 12H).

^{13}C NMR (125 MHz, MeOD) δ 168.1, 156.1, 150.6, 142.2, 141.2, 134.2, 134.0, 132.95, 132.86, 132.3, 130.0, 129.5, 129.2, 128.0, 125.6, 120.7, 82.5, 61.7, 50.9, 28.4, 14.6.

HRMS (ESI): *m/z*; $[M+Na]^+$ Calcd for $C_{23}H_{26}N_2O_6Na$ 449.16831; Found: 449.1688.

(*E*)-Methyl 3-(2-((*tert*-butoxycarbonyl)(2-nitrobenzyl)amino)phenyl)acrylate (3e)



3e

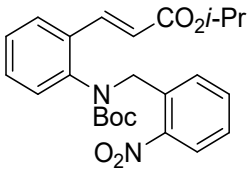
A white solid; 0.35 g (85%);

^{1}H NMR (500 MHz, MeOD) δ 7.86 (d, *J* = 7.9 Hz, 1H), 7.67 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.61 (t, *J* = 7.2 Hz, 1H), 7.49-7.44 (m, 2H), 7.39 (t, *J* = 7.2 Hz, 1H), 7.33 (t, *J* = 7.2 Hz, 1H), 7.16 (br, 1H), 6.35 (d, *J* = 16.0 Hz, 1H), 5.15 (d, *J* = 3.8 Hz, 2H), 3.77 (s, 3H), 1.33 (s, 9H).

^{13}C NMR (125 MHz, MeOD) δ 168.5, 156.2, 150.6, 142.2, 141.4, 134.2, 133.9, 133.0, 132.8, 132.3, 129.9, 129.6, 129.2, 128.1, 125.6, 120.3, 82.3, 52.2, 51.0, 28.4.

HRMS (ESI): *m/z*; $[M+Na]^+$ Calcd for $C_{22}H_{24}N_2O_6Na$ 435.15266; Found: 435.1530.

(*E*)-Isopropyl 3-(2-((*tert*-butoxycarbonyl)(2-nitrobenzyl)amino)phenyl)acrylate (3f)



3f

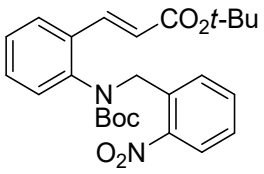
A white solid; 0.26 g (60%);

^{1}H NMR (500 MHz, MeOD) δ 7.85 (d, *J* = 7.8 Hz, 1H), 7.64 (dd, *J* = 7.8, 1.1 Hz, 1H), 7.59 (t, *J* = 7.3 Hz, 1H), 7.48-7.43 (m, 2H), 7.39 (t, *J* = 7.3 Hz, 1H), 7.32 (t, *J* = 7.3 Hz, 1H), 7.19 (br, 1H), 6.29 (d, *J* = 16.0 Hz, 1H), 5.22 (d, *J* = 13.0 Hz, 1H), 5.11 (d, *J* = 13.0 Hz, 1H), 5.09 (h, *J* = 6.3 Hz, 1H), 1.33 (s, 9H), 1.30 (d, *J* = 6.3 Hz, 6H).

^{13}C NMR (125 MHz, MeOD) δ 167.5, 156.0, 150.5, 142.1, 141.0, 134.2, 134.0, 133.0, 132.7, 132.2, 129.9, 129.3, 129.1, 128.0, 125.6, 121.2, 82.4, 69.2, 50.9, 28.7, 28.4, 22.2.

HRMS (ESI): *m/z*; $[M+Na]^+$ Calcd for $C_{24}H_{28}N_2O_6Na$ 463.18396; Found: 463.1842.

(*E*)-*tert*-Butyl 3-(2-((*tert*-butoxycarbonyl)(2-nitrobenzyl)amino)phenyl)acrylate (3g)



3g

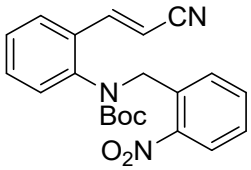
A white solid; 0.44 g (96%);

^{1}H NMR (500 MHz, MeOD) δ 7.87 (d, *J* = 7.6 Hz, 1H), 7.63 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.48 (t, *J* = 8.4 Hz, 1H), 7.39-7.36 (m, 2H), 7.32 (t, *J* = 7.3 Hz, 1H), 7.19 (br, 1H), 5.22 (d, *J* = 14.8 Hz, 1H), 5.12 (d, *J* = 14.8 Hz, 1H), 1.52 (s, 9H), 1.33 (s, 9H).

^{13}C NMR (125 MHz, MeOD) δ 167.3, 156.1, 150.6, 142.1, 140.3, 134.2, 134.1, 133.0, 132.8, 132.0, 129.9, 129.2, 129.1, 127.9, 125.6, 122.5, 82.3, 81.8, 51.0, 28.6, 28.4.

HRMS (ESI): *m/z*; $[M+Na]^+$ Calcd for $C_{25}H_{30}N_2O_6Na$ 477.19961; Found: 477.1984.

(*E*)-*tert*-Butyl (2-(2-cyanovinyl)phenyl)(2-nitrobenzyl)carbamate (3h)



3h

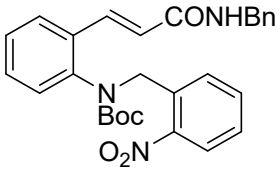
A white solid; 0.27 g (70%);

^{1}H NMR (500 MHz, MeOD) δ 7.87 (d, *J* = 7.9 Hz, 1H), 7.64 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.81 (d, *J* = 7.8 Hz, 1H), 7.51 (t, *J* = 8.1 Hz, 2H), 7.44 (td, *J* = 7.5, 1.2 Hz, 1H), 7.34 (t, *J* = 7.5 Hz, 1H), 7.20 (s, 1H), 7.18 (d, *J* = 16.6 Hz, 1H), 6.07 (d, *J* = 16.6, 1H), 5.22 (d, *J* = 14.6 Hz, 1H), 5.11 (d, *J* = 14.6 Hz, 1H), 1.39 (s, 9H).

^{13}C NMR (125 MHz, MeOD) δ 156.0, 150.9, 147.3, 141.7, 134.2, 133.6, 133.1, 133.0, 132.6, 130.3, 129.6, 129.3, 127.4, 125.6, 119.0, 99.1, 82.9, 54.8, 28.4.

HRMS (ESI): *m/z*; $[M+Na]^+$ Calcd for $C_{21}H_{21}N_3O_4Na$ 402.14243; Found: 402.1419.

(*E*)-*tert*-Butyl (2-(3-(benzylamino)-3-oxoprop-1-en-1-yl)phenyl)(2-nitrobenzyl)carbamate (3i)



3i

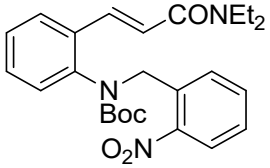
A white solid; 0.44 g (90%);

^{1}H NMR (500 MHz, MeOD) δ 7.83 (d, *J* = 7.0 Hz, 1H), 7.63 (br, 2H), 7.61 (t, *J* = 7.5 Hz, 1H), 7.55 (d, *J* = 15.6 Hz, 1H), 7.42 (t, *J* = 6.7 Hz, 1H), 7.35 (d, *J* = 1.8 Hz, 1H), 7.33 (s, 3H), 7.28-7.25 (m, 3H), 7.06 (br, 1H), 6.51 (d, *J* = 15.6 Hz, 1H), 5.30 (d, *J* = 16.0 Hz, 1H), 5.00 (d, *J* = 16.0 Hz, 1H), 4.48 (s, 2H), 1.32 (br, 9H).

^{13}C NMR (125 MHz, MeOD) δ 167.7, 156.3, 150.5, 142.1, 139.9, 137.6, 137.4, 134.5, 134.3, 133.3, 132.3, 132.3, 131.4, 129.7, 129.6, 129.0, 128.7, 128.6, 128.3, 128.0, 125.5, 123.9, 82.3, 50.9, 44.3, 28.4.

HRMS (ESI): *m/z*; $[M+Na]^+$ Calcd for $C_{28}H_{29}N_3O_5Na$ 510.19994; Found: 510.2005.

(*E*)-*tert*-Butyl (2-(3-(diethylamino)-3-oxoprop-1-en-1-yl)phenyl)(2-nitrobenzyl)carbamate (3j)



3j

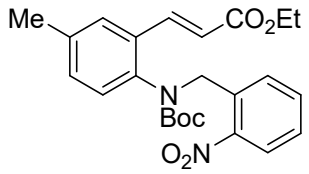
A white solid; 0.45 g (99%);

^{1}H NMR (500 MHz, MeOD) δ 7.86 (d, *J* = 5.8 Hz, 1H), 7.71 (d, *J* = 4.0 Hz, 1H), 7.65 (t, *J* = 7.0 Hz, 2H), 7.58 (d, *J* = 15.4 Hz, 1H), 7.47 (t, *J* = 7.9 Hz, 1H), 7.30 (br, 2H), 7.045(br, 1H), 6.91 (d, *J* = 15.4 Hz, 1H), 5.32 (d, *J* = 14.6 Hz, 1H), 4.95 (d, *J* = 14.6 Hz, 1H), 3.57 (q, *J* = 7.2 Hz, 2H), 3.51(q, *J* = 7.2 Hz, 2H), 1.34 (br, 9H), 1.28 (t, *J* = 7.2 Hz, 3H), 1.21 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (125 MHz, MeOD) δ 167.3, 156.3, 150.4, 142.0, 139.2, 134.3, 133.4, 132.3, 131.4, 129.7, 129.6, 129.1, 128.5, 125.5, 120.9, 82.3, 50.9, 43.6, 42.4, 28.7, 28.4, 15.4, 13.4.

HRMS (ESI): *m/z*; $[M+Na]^+$ Calcd for $C_{25}H_{31}N_3O_5Na$ 476.21559; Found: 476.2159.

(*E*)-Ethyl 3-(2-((*tert*-butoxycarbonyl)(2-nitrobenzyl)amino)-5-methylphenyl)acrylate (3k)



3k

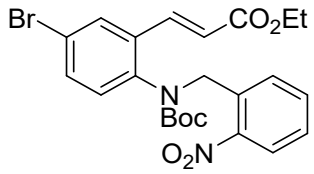
A light brown solid; 0.35 g (80%);

^{1}H NMR (500 MHz, MeOD) δ 7.84 (d, *J* = 7.8 Hz, 1H), 7.59 (t, *J* = 7.2 Hz, 1H), 7.45-7.41 (m, 3H), 7.19 (d, *J* = 7.8 Hz, 1H), 7.04 (br, 1H), 6.30 (d, *J* = 16.0 Hz, 1H), 5.13 (br, 1H), 5.10 (br, 1H), 4.24-4.19 (m, 2H), 2.33 (s, 3H), 1.33 (t, *J* = 7.2 Hz, 12H).

^{13}C NMR (125 MHz, MeOD) δ 168.1, 156.3, 150.7, 142.0, 141.1, 139.7, 139.3, 137.0, 134.2, 133.0, 132.9, 129.9, 129.2, 128.3, 125.6, 120.4, 82.4, 61.7, 50.9, 28.4, 21.0, 14.6.

HRMS (ESI): *m/z*; $[M+Na]^+$ Calcd for $C_{24}H_{28}N_2O_6Na$ 463.18396; Found: 463.1833.

(*E*)-Ethyl 3-(5-bromo-2-((*tert*-butoxycarbonyl)(2-nitrobenzyl)amino)phenyl)acrylate (3l)



3l

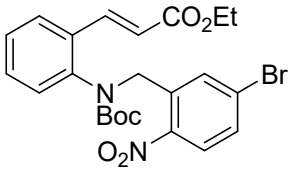
A light brown solid; 0.30 g (60%);

^{1}H NMR (500 MHz, MeOD) δ 7.85 (d, *J* = 8.1 Hz, 1H), 7.78 (d, *J* = 2.3 Hz, 1H), 7.61 (td, *J* = 7.6, 1.1 Hz, 1H), 7.52 (dd, *J* = 8.4, 2.1 Hz, 2H), 7.47 (td, *J* = 8.2,1.2 Hz, 1H), 7.36 (d, *J* = 16.0 Hz, 1H), 7.12 (d, *J* = 8.1 Hz, 1H), 6.32 (d, *J* = 16.0 Hz, 1H), 5.19 (br, 1H), 5.07 (br, 1H), 5.09 (h, *J* = 6.3 Hz, 1H), 4.23 (d, *J* = 6.3 Hz, 2H), 1.35 (s, 9H), 1.32 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (125 MHz, MeOD) δ 167.6, 155.7, 150.6, 141.2, 139.7, 136.3, 135.0, 134.3, 132.9, 132.7, 131.3, 130.8, 130.1, 125.7, 122.6, 122.1, 82.7, 61.8, 50.8, 28.4, 14.6.

HRMS (ESI): *m/z*; $[M+Na]^+$ Calcd for $C_{22}H_{25}BrN_2O_6Na$ 527.07882; Found: 527.0782.

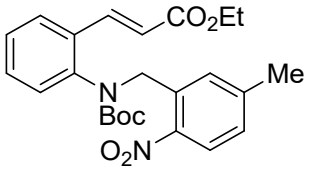
(*E*)-Ethyl 3-(2-((5-bromo-2-nitrobenzyl)(*tert*-butoxycarbonyl)amino)phenyl)acrylate (3m)



3m

Compound **3m** could not be obtained under the benzylation conditions. Instead, **3m** underwent the cyclization to afford the corresponding indoline-3-acetate **4m**. Thus, the spectroscopic data of **3m** could not be obtained.

(*E*)-Ethyl 3-(2-((*tert*-butoxycarbonyl)(5-methyl-2-nitrobenzyl)amino)phenyl)acrylate (3n)



3n

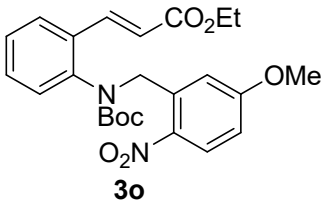
A white solid; 0.43 g (97%);

^{1}H NMR (500 MHz, MeOD) δ 7.77 (d, *J* = 7.5 Hz, 1H), 7.65 (d, *J* = 7.6 Hz, 1H), 7.51 (d, *J* = 16.0 Hz, 1H), 7.41 (t, *J* = 7.2 Hz, 1H), 7.35 (br, 1H), 7.32 (t, *J* = 7.3 Hz, 1H), 7.25 (d, *J* = 8.4 Hz, 1H), 7.20 (br, 1H), 6.32 (d, *J* = 16.0 Hz, 1H), 5.26 (d, *J* = 15.4 Hz, 1H), 5.08 (d, *J* = 15.4 Hz, 1H), 4.24-4.19 (m, 2H), 2.36 (s, 3H), 1.33 (br, 9H), 1.32 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (125 MHz, MeOD) δ 168.1, 156.1, 148.3, 145.8, 142.3, 141.4, 134.0, 133.3, 133.1, 132.3, 130.3, 129.3, 129.1, 127.9, 125.9, 120.5, 82.5, 61.7, 51.0, 28.4, 21.4, 14.6.

HRMS (ESI): *m/z*; $[M+Na]^+$ Calcd for $C_{24}H_{28}N_2O_6Na$ 463.18396; Found: 463.1845.

(*E*)-Ethyl 3-(2-((*tert*-butoxycarbonyl)(5-methoxy-2-nitrobenzyl)amino)phenyl)acrylate (3o)



3o

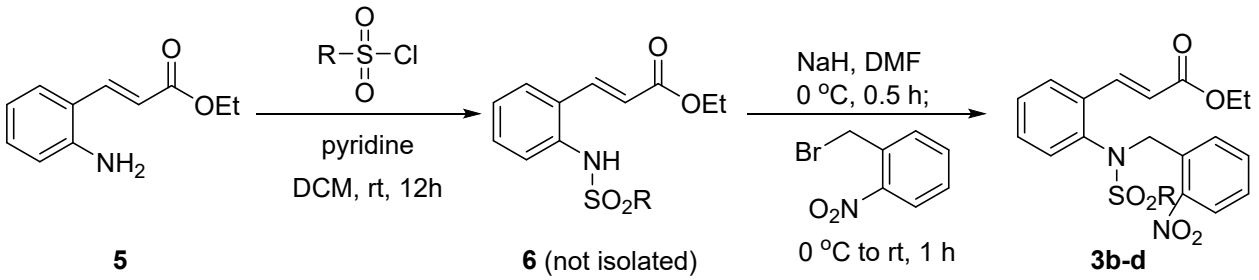
A white solid; 0.31 g (69%);

^{1}H NMR (500 MHz, MeOD) δ 7.95 (d, *J* = 8.2 Hz, 1H), 7.66 (d, *J* = 7.8, 0.92 Hz, 1H), 7.51 (d, *J* = 16.0 Hz, 1H), 7.42 (t, *J* = 7.3 Hz, 1H), 7.33 (t, *J* = 7.5 Hz, 1H), 7.23 (br, 1H), 7.07 (br, 1H), 6.95 (dd, *J* = 9.0, 2.4 Hz, 1H), 6.33 (d, *J* = 15.8 Hz, 1H), 5.27 (d, *J* = 14.5 Hz, 1H), 5.15 (d, *J* = 14.5 Hz, 1H), 4.25-4.20 (m, 2H), 3.85 (s, 3H), 1.50 (br, 9H), 1.33 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (125 MHz, MeOD) δ 168.1, 164.8, 156.2, 143.2, 142.3, 141.3, 136.2, 133.9, 132.3, 129.3, 129.1, 128.6, 127.9, 120.7, 117.4, 114.7, 82.6, 61.7, 56.5, 28.6, 28.4, 14.6.

HRMS (ESI): *m/z*; $[M+Na]^+$ Calcd for $C_{24}H_{28}N_2O_7Na$ 479.17887; Found: 479.1785.

2-2. Preparation of N-Sulfonyl-N-(2-Nitrobenzyl)-2-Aminocinnamic Acid Derivatives 3b-d

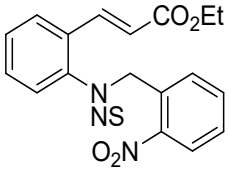


5 **6** (not isolated) **3b-d**

Ethyl 2-aminocinnamate (**5**, 0.19 g, 1.0 mmol) was placed in a one-neck round bottom flask and dissolved in dichloromethane (DCM, 10.0 mL). To the solution were added sulfonyl chloride (1.5 mmol) and pyridine (0.080 mL, 2.0 mmol) at room temperature, and the reaction mixture was monitored by TLC. After the complete consumption of **5**, the reaction mixture was quenched with H_2O, and extracted with DCM. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure to provide a crude product of **6**, which was directly used in the next step without further isolation.

The resulting **6** was added to a 50 mL one-neck round bottom flask and dissolved in dimethylformamide (DMF, 10.0 mL). To the above mixture was added NaH (60% dispersion in mineral oil, 0.049 g, 1.2 mmol) at 0 °C and the resulting mixture was stirred at the same temperature. After 30 min, 2-nitrobenzyl bromide (0.26 g, 1.2 mmol) was added to the reaction mixture. The reaction mixture was stirred at room temperature and monitored by TLC. After the complete consumption of **6**, the reaction mixture was carefully quenched with H_2O and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using a mixture of ethyl acetate and hexanes as the eluent to provide the desired product **3**.

(*E*)-Ethyl 3-(2-(4-nitro-N-(2-nitrobenzyl)phenylsulfonamido)phenyl)acrylate (3b)



3b

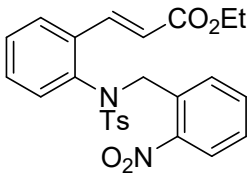
A white solid; 0.26 g (70%);

^{1}H NMR (500 MHz, MeOD) δ 8.44 (dt, *J* = 8.8, 2.6 Hz, 2H), 7.98 (d, *J* = 9.0, 2.1 Hz, 2H), 7.80 (dd, *J* = 8.1, 1.1 Hz, 1H), 7.63 (td, *J* = 7.0, 1.8 Hz, 2H), 7.58 (td, *J* = 7.3, 1.2 Hz, 1H), 7.47 (td, *J* = 8.1, 1.5 Hz, 1H), 7.39 (d, *J* = 16.0 Hz, 1H), 7.37 (dd, *J* = 7.6, 1.4 Hz, 1H), 7.36 (td, *J* = 7.3, 1.7 Hz, 1H), 6.96 (dd, *J* = 7.6, 1.4 Hz, 1H), 6.13 (d, *J* = 16.0 Hz, 1H), 5.45 (br, 1H), 5.01 (br, 1H), 4.21(q, *J* = 7.2 Hz, 2H), 1.34 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (125 MHz, MeOD) δ 167.8, 152.0, 150.8, 145.1, 140.7, 138.4, 136.7, 134.31, 134.28, 132.2, 131.6, 130.9, 130.8, 130.6, 130.5, 128.4, 125.69, 125.67, 121.2, 61.8, 53.1, 14.6.

HRMS (ESI): *m/z*; $[M+Na]^+$ Calcd for $C_{24}H_{21}N_3O_8SNa$ 534.09416; Found: 534.0946.

(*E*)-Ethyl 3-(2-(4-methyl-N-(2-nitrobenzyl)phenylsulfonamido)phenyl)acrylate (3c)



3c

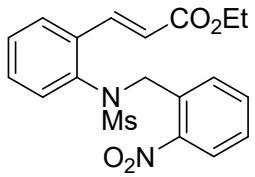
A white solid; 0.41 g (86%);

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 (dd, *J* = 7.8, 0.9 Hz, 1H), 7.76 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.61-7.55(m, 4H), 7.51 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.38 (td, *J* = 8.2, 1.4 Hz, 1H), 7.31-7.28 (m, 3H), 7.27 (td, *J* = 7.5, 1.7 Hz, 1H), 6.88 (dd, *J* = 7.8, 1.2 Hz, 1H), 6.10 (d, *J* = 16.0 Hz, 1H), 5.16 (br, 2H), 4.26 (q, *J* = 7.2 Hz, 2H), 2.44 (s, 3H), 1.36 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 166.2, 149.0, 144.4, 139.7, 138.2, 135.7, 135.1, 133.4, 132.5, 131.2, 130.7, 130.0, 129.9, 129.3, 128.9, 128.1, 127.3, 124.6, 120.5, 60.6, 52.0, 21.7, 14.5.

HRMS (ESI): *m/z*; $[M+Na]^+$ Calcd for $C_{25}H_{24}N_2O_6SNa$ 503.12473; Found: 503.1247.

(*E*)-Ethyl 3-(2-(N-(2-nitrobenzyl)methylsulfonamido)phenyl)acrylate (3d)



3d

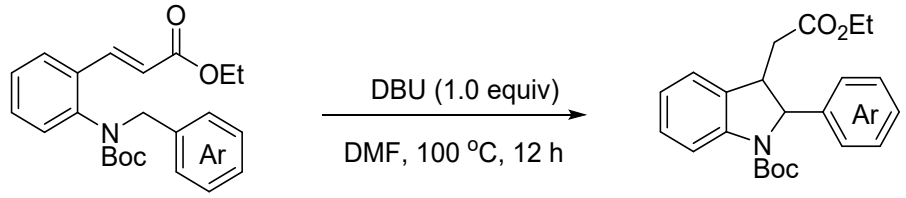
A white solid; 0.37 g (91%);

^{1}H NMR (500 MHz, MeOD) δ 7.77 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.75 (d, *J* = 16.0 Hz, 1H), 7.64 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.61 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.55 (td, *J* = 7.5, 1.2 Hz, 1H), 7.54 (dd, *J* = 8.1, 1.2 Hz, 1H), 7.49 (td, *J* = 7.3, 1.5 Hz, 1H), 7.44 (td, *J* = 8.1, 1.5 Hz, 1H), 7.39 (td, *J* = 7.9, 0.76 Hz, 1H), 6.19 (d, *J* = 16.0 Hz, 1H), 5.20 (br, 2H), 4.24 (q, *J* = 7.2 Hz, 2H), 3.15 (s, 3H), 1.35 (t, *J* = 7.2 Hz, 3H),

^{13}C NMR (125 MHz, MeOD) δ 168.0, 150.8, 141.7, 139.6, 137.1, 134.4, 134.2, 132.5, 131.3, 130.5, 130.43, 130.40, 128.3, 125.5, 120.9, 61.7, 52.6, 38.4, 14.6.

HRMS (ESI): *m/z*; $[M+Na]^+$ Calcd for $C_{19}H_{20}N_2O_6SNa$ 427.09343; Found: 427.0941.

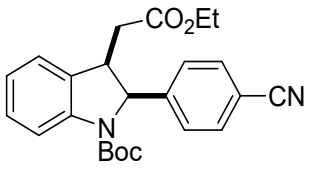
3. Synthesis of Indoline-3-acetic Acid Derivatives 2 (Table 1)



1 **2**

To a solution of **1** 0.40 mmol) in dimethylformamide (DMF, 4.0 mL) was added 1,8-diazabicyclo(5.4.0)undec-7-ene (DBU, 0.060 g, 0.40 mmol). The reaction mixture was stirred at 100 °C with an oil bath and monitored by TLC. After the complete consumption of the staring material **1,** the reaction mixture was cooled to room temperature, quenched with H_2O, and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using a mixture of ethyl acetate and hexanes as the eluent to provide the desired indoline product **2**. The diastereomeric ratio of the resulting indoline-3-acetate **2** depends on the choice of a substituent on the benzyl moiety at the *para*-position.

***tert*-Butyl 2-(4-Cyanophenyl)-3-(2-ethoxy-2-oxoethyl)indoline-1-carboxylate (2c)**



2c

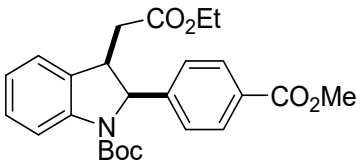
A white solid; 0.13 g (81%); *cis: trans* = 5:1.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 (br, 1H), 7.58* (d, *J* = 8.2 Hz, 0.4H), 7.54 (d, *J* = 8.5 Hz, 2H), 7.34* (d, *J* = 7.6 Hz, 0.4H), 7.30 (t, *J* = 7.5 Hz, 1H+0.4H), 7.16 (d, *J* = 8.2 Hz, 2H), 7.12* (d, *J* = 7.5 Hz, 0.2H), 7.06-6.99 (m, 2H + 0.2H), 5.63 (d, *J* = 9.6 Hz, 1H), 5.14* (br, 0.2H), 4.30 (td, *J* = 10.5, 4.4 Hz, 1H), 4.22* (q, *J* = 7.2 Hz, 0.4H), 4.11-4.02 (m, 2H), 3.47* (t, *J* = 5.8 Hz, 0.2H), 2.72-2.68 (m, 1H + 0.4H), 1.97 (dd, *J* = 17.5, 10.8 Hz, 1H), 1.28 (t, *J* = 7.2 Hz, 9H + 1.8H), 1.21 (t, *J* = 7.2 Hz, 3H+0.6H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 172.0, 171.6, 151.8, 144.8, 143.0, 132.6, 132.2, 131.0, 128.9, 128.8, 128.0, 126.4, 123.5, 123.4, 123.1, 118.9, 118.7, 115.0, 114.6, 111.8, 111.3, 81.5, 66.2, 61.0, 60.9, 41.1, 40.7, 34.5, 28.2, 14.34, 14.26.

HRMS (ESI): *m/z*; $[M+Na]^+$ Calcd for $C_{24}H_{26}N_2O_4Na$ 429.17848; Found: 429.1785.

***tert* -Butyl 3-(2-ethoxy-2-oxoethyl)-2-(4-(methoxycarbonyl)phenyl)indoline-1-carboxylate (2d)**



2d

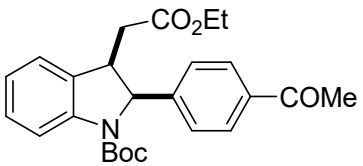
A white solid; 0.17 g (50%); *cis: trans* = 5:1.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.2 Hz, 1H + 0.4H), 7.91 (d, *J* = 8.5 Hz, 2H + 0.2H), 7.29 (t, *J* = 7.6 Hz, 1H + 0.4H), 7.13* (d, *J* = 7.6 Hz, 0.2H) 7.10 (d, *J* = 7.9 Hz, 2H), 7.05-7.00 (m, 2H + 0.4H), 5.62 (d, *J* = 9.5 Hz, 1H), 5.13* (br, 0.2H), 4.30 (td, *J* = 10.4, 4.7 Hz, 1H), 4.21* (q, *J* = 7.0 Hz, 0.4H), 4.09-4.03 (m, 2H), 3.89 (s, 3H + 0.6H), 3.51 (t, *J* = 5.9 Hz, 0.2H), 2.71-2.63 (m, 1H + 0.4H), 2.00 (dd, *J* = 17.5, 10.5 Hz, 1H), 1.27 (t, *J* = 7.0 Hz, 9H + 1.8H), 1.19 (t, *J* = 7.2 Hz, 3H + 0.6H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 172.2, 171.6, 166.9, 152.0, 144.6, 143.3, 131.5, 130.1, 129.7, 128.8, 128.6, 127.3, 125.5, 124.8, 123.5, 123.1, 122.9, 114.9, 114.6, 81.3, 66.4, 60.95, 60.86, 52.2, 41.3, 40.8, 34.6, 29.8, 28.2, 14.2.

HRMS (ESI): *m/z*; $[M+Na]^+$ Calcd for $C_{25}H_{29}NO_6Na$ 462.18871; Found: 462.1885.

***tert* -Butyl 3-(2-Ethoxy-2-oxoethyl)-2-(4-(methoxycarbonyl)phenyl)indoline-1-carboxylate (2e)**



2e

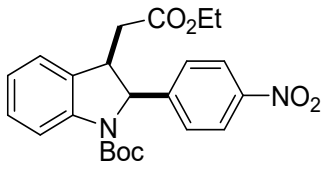
A white solid; 0.17 g (70%); *cis: trans* = 5:1.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 (br, 1H), 7.88 *(dt, *J* = 8.4, 1.8 Hz, 0.4H), 7.83 (d, *J* = 8.5 Hz, 2H + 0.2H), 7.29 (t, *J* = 7.5 Hz, 1H + 0.4H) 7.13 (d, *J* = 8.1 Hz, 2H + 0.2H), 7.05-6.99 (m, 2H + 0.4H), 5.63 (d, *J* = 9.6 Hz, 1H), 5.15* (br, 0.2H), 4.31 (td, *J* = 10.2, 4.7 Hz, 1H), 4.22* (q, *J* = 7.0 Hz, 0.4H), 4.09-4.05 (m, 2H), 3.51* (t, *J* = 5.9 Hz, 0.2H), 2.72-2.63 (m, 1H + 0.4H), 2.56 (s, 3H + 0.6H), 2.01 (dd, *J* = 17.5, 10.4 Hz, 1H), 1.28 (t, *J* = 7.2 Hz, 9H + 1.8H), 1.19 (t, *J* = 7.2 Hz, 3H + 0.6H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 197.8, 197.7, 172.2, 171.6, 152.0, 144.7, 143.3, 136.7, 136.4, 131.5, 128.9, 128.6, 128.5, 127.5, 125.7, 123.5, 123.2, 123.0, 115.0, 114.6, 81.3, 66.4, 61.0, 60.9, 41.3, 40.8, 34.6, 29.8, 28.3, 26.7, 14.4, 14.3.

HRMS (ESI): *m/z*; $[M+Na]^+$ Calcd for $C_{25}H_{29}NO_5Na$ 446.19379; Found: 446.1941.

***tert* -Butyl 3-(2-Ethoxy-2-oxoethyl)-2-(4-nitrophenyl)indoline-1-carboxylate (2f)**



2f

A light yellow solid; 0.16 g (91%); *cis*: *trans* = 7:1.

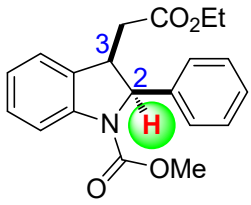
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15* (d, *J* = 8.8 Hz, 0.30H), 8.11 (d, *J* = 8.8 Hz, 2H), 7.94 (br, 1H), 7.41* (d, *J* = 8.5 Hz, 0.30H), 7.31 (t, *J* = 7.8 Hz, 1H + 0.30H) 7.22 (d, *J* = 8.5 Hz, 2H), 7.13* (d, *J* = 7.5 Hz, 0.15H), 7.07-7.01 (m, 2H + 0.15H), 5.70 (d, *J* = 9.6 Hz, 1H), 5.22* (br, 0.15H), 4.33 (td, *J* = 10.7, 4.6 Hz, 1H), 4.23* (q, *J* = 7.2 Hz, 0.30H), 4.12-4.03 (m, 2H), 3.50 (t, *J* = 6.4 Hz, 0.15H), 2.74-2.69 (m, 1H + 0.30H), 1.97 (dd, *J* = 17.5, 10.8 Hz, 1H), 1.31 (t, *J* = 7.2 Hz, 9H + 1.35H), 1.20 (t, *J* = 7.2 Hz, 3H+0.45H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 172.0, 171.6, 151.8, 147.7, 146.8, 143.0, 131.1, 129.0, 128.9, 128.2, 126.5, 124.1, 123.7, 123.6, 123.5, 123.2, 115.1, 114.7, 81.7, 66.0, 61.1, 61.0, 41.2, 40.8, 34.5, 29.8, 28.3, 14.4 14.2.

HRMS (ESI): *m/z*; $[M+Na]^+$ Calcd for $C_{23}H_{26}N_2O_6Na$ 449.16831; Found: 449.1682.

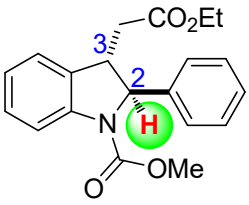
4. Determination of Stereochemistry of Indoline-3-acetic Acid Derivatives

The cis/trans ratios of indoline-3-acetic acid derivatives **2** or **4** were determined by the comparison of ^{1}H NMR spectrum of the synthesized compounds with one reported in the literature.[1] The proton at the C2-position of *cis*- and *trans*-ethyl *N*-methoxycarbonyl-2-phenylindoline-3-acetate displayed unique features. The chemical shift of the proton at the C2-position of the *cis*-isomer was at 5.63 ppm (d, J = 10.0 Hz, 1H), while one of the proton at the same position of the *trans*-isomer was at 5.22 ppm (s, 1H).



cis-isomer

^{1}H Spectral data of H^2:
δ 5.63 ppm (d, J = 10.0 Hz)



trans-isomer

^{1}H Spectral data of H^2:
δ 5.22 ppm (s)

Similar trends were observed in the newly synthesized indoline-3-acetic acid derivatives **2** or **4**. As depicted below, indoline **2c** also exhibited a characteristic peaks in its ^{1}H NMR spectrum. *cis*-**2c** has peaks at 5.61 ppm (d, 1H) and 4.27 ppm (ddd, 1H), while *trans*-**2c** has 5.14 ppm (br (s), 1H) and 3.47 ppm (d, 1H). Based on these characteristic peaks of *cis*- and *trans*-isomers of **2c** from its ^{1}H NMR spectrum, we were able to determine the *cis*:*trans* ratio of **2c** as 5:1.

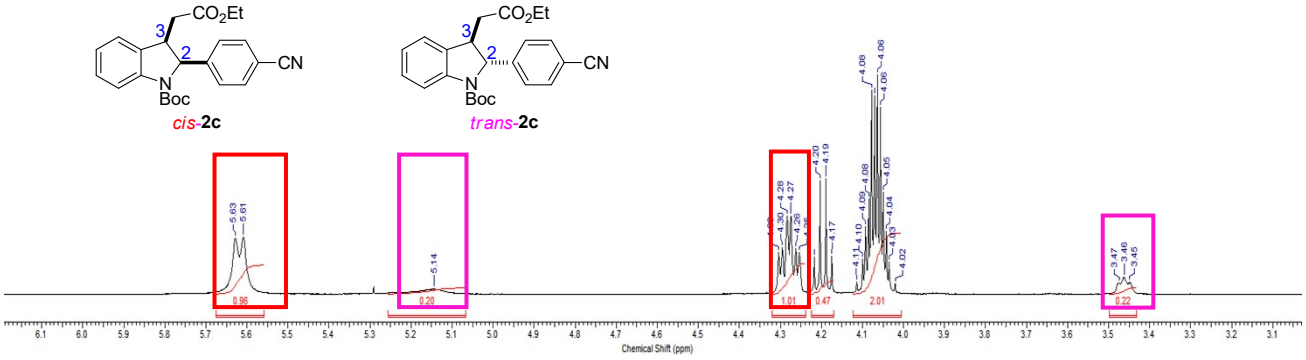


Figure S 1. ^{1}H NMR Spectrum of 2c.

Accordingly, the stereochemistry of the resulting 2-(2-nitropheyl)indoline-3-acetic acid derivatives **4** generated the cyclization reaction of *N*-(2-nitrobenzyl)-2-aminocinnamic acid derivatives **3** using ^{1}H NMR spectra. As shown in the below spectrum, there were peaks from the *cis*-isomer (*cis*-**4a**) and no

peaks was observed from *trans*-isomer (trans-**4a**).Furthermore, we concluded that only the *cis*-isomer of indoline-3-acetic acid derivatives **4** was obtained from the cyclization of of *N*-(2-nitrobenzyl)-2-aminocinnamic acid derivatives **3**.

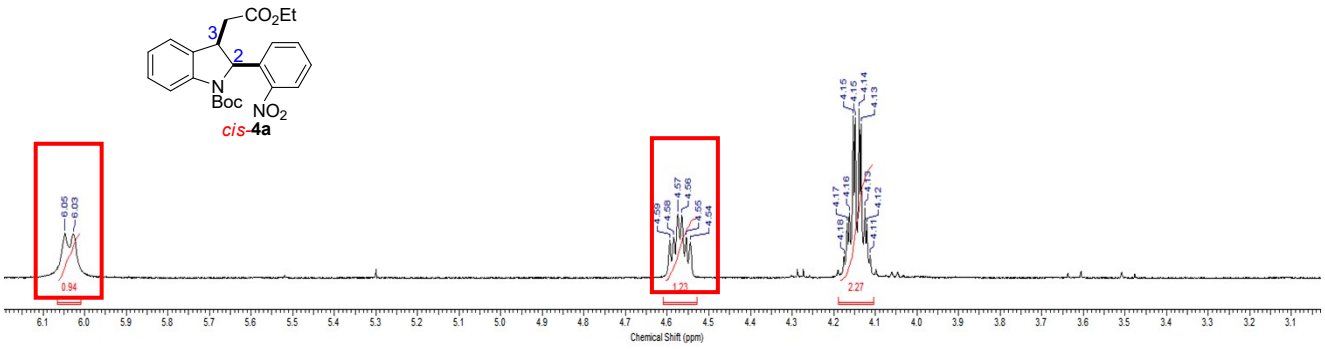
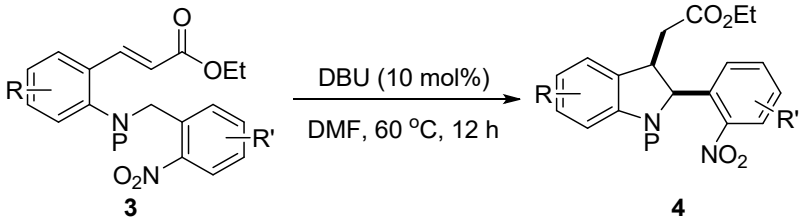


Figure S 2. 1H NMR Spectrum of 4a

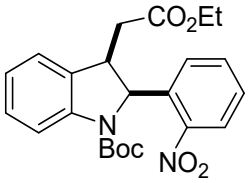
5. Synthesis of 2-(2-Nitrophenyl)indoline-3-acetic Acid Derivatives 4 (Table 3)



3 **4**

To a solution of **3** (0.40 mmol) in dimethylformamide (DMF, 4.0 mL) was added 1,8-diazabicyclo (5.4.0)undec-7-ene (DBU, 0.0060 g, 0.040 mmol). The reaction mixture was stirred at 60 °C with an oil bath and monitored by TLC. After the complete consumption of the staring material **3**, the reaction mixture was cooled to room temperature, quenched with H_2O, and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using a mixture of ethyl acetate and hexanes as the eluent to provide the desired indoline product **4**.

***tert*-Butyl 3-(2-Ethoxy-2-oxoethyl)-2-(2-nitrophenyl)indoline-1-carboxylate (4a)**



4a

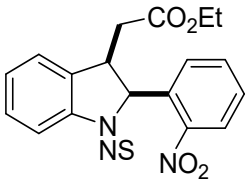
A light yellow solid; 0.16 g (97%); *cis: trans* = 1:0.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (d, *J* = 7.8, 1H), 7.52 (td, *J* = 7.5, 1.2 Hz, 1H), 7.45 (td, *J* = 8.2, 1.4 Hz, 1H), 7.30 (t, *J* = 8.4 Hz, 2H) 7.13 (d, *J* = 7.6 Hz, 1H), 7.04 (td, *J* = 7.5, 0.9 Hz, 1H), 6.05 (d, *J* = 10.2 Hz, 1H), 4.59 (td, *J* = 9.6, 4.9 Hz, 1H), 4.18-4.11 (m, 2H), 2.42 (dd, *J* = 16.3, 4.9 Hz, 1H), 2.24 (dd, *J* = 16.3, 9.3 Hz, 1H), 1.25(t, *J* = 7.2 Hz, 3H), 1.19(br, 9H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 171.9, 151.6, 149.1, 142.8, 136.3, 133.6, 132.4, 128.62, 128.6, 128.1, 124.5, 124.4, 123.4, 114.5, 81.5, 61.4, 61.0, 40.6, 36.9, 28.0, 14.3.

HRMS (ESI): *m/z*; $[M+Na]^+$ Calcd for $C_{23}H_{26}N_2O_6Na$ 449.16831; Found: 449.1685.

Ethyl 2-(2-(2-nitrophenyl)-1-thionitrosoindolin-3-yl)acetate (4b)



4b

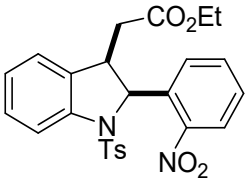
A light yellow solid; 0.14 g (68%);

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.30 (d, *J* = 8.8 Hz, 2H), 8.08 (d, *J* = 8.1 Hz, 1H), 7.92 (d, *J* = 8.8 Hz, 2H), 7.82 (d, *J* = 8.2 Hz, 1H), 7.60 (td, *J* = 8.1, 1.1 Hz, 1H), 7.54 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.52 (td, *J* = 8.4, 1.4 Hz, 1H), 7.37 (t, *J* = 7.6 Hz, 1H), 7.15 (t, *J* = 7.0 Hz, 1H), 7.06 (d, *J* = 7.5Hz, 1H), 6.21 (d, *J* = 10.4 Hz, 1H), 4.25 (q, *J* = 9.2 Hz, 1H), 4.06-4.01 (m, 2H), 2.23 (dd, *J* = 16.6, 5.8 Hz, 1H), 2.16 (dd, *J* = 16.6, 8.5 Hz, 1H), 1.17 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 171.2, 150.8, 148.0, 142.5, 140.9, 134.1, 134.0, 133.6, 129.9, 129.4, 129.2, 128.7, 126.0, 125.3, 125.1, 124.6, 115.7, 63.4, 61.2, 41.5, 36.4, 14.2.

HRMS (ESI): *m/z*; $[M+Na]^+$ Calcd for $C_{24}H_{21}N_3O_8SNa$ 534.09416; Found: 534.0950.

Ethyl 2-(2-(2-nitrophenyl)-1-tosylindolin-3-yl)acetate (4c)



4c

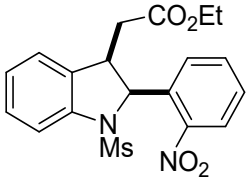
A light yellow solid; 0.18 g (95%);

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (d, *J* = 8.2 Hz, 1H), 7.82 (d, *J* = 7.9 Hz, 1H), 7.64 (d, *J* = 7.6 Hz, 1H), 7.60-7.57 (m, 3H), 7.48 (td, *J* = 8.4, 1.5 Hz, 1H), 7.33 (t, *J* = 7.5 Hz, 1H), 7.23 (d, *J* = 7.9 Hz, 2H), 7.09 (td, *J* = 7.5, 0.9 Hz, 1H), 7.02 (d, *J* = 7.6 Hz, 1H), 6.10 (d, *J* = 10.4 Hz, 1H), 4.25 (td, *J* = 9.2, 5.3 Hz, 1H), 4.07-4.00 (m, 2H), 2.38 (m, 3H), 2.21 (dd, *J* = 16.3, 5.0 Hz, 1H), 2.10 (dd, *J* = 16.3, 9.0 Hz, 1H), 1.17 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 171.5, 148.0, 144.8, 141.8, 135.0, 133.86, 133.84, 133.73, 133.68, 130.3, 130.0, 129.0, 128.9, 127.5, 125.2, 124.9, 116.0, 63.4, 61.0, 41.4, 36.9, 21.7, 14.2.

HRMS (ESI): *m/z*; $[M+Na]^+$ Calcd for $C_{25}H_{24}N_2O_6SNa$ 503.12473; Found: 503.1238.

Ethyl 2-(1-(methylsulfonyl)-2-(2-nitrophenyl)indolin-3-yl)acetate (4d)



4d

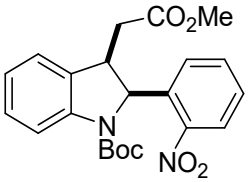
A light yellow solid; 0.12 g (77%);

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (d, *J* = 8.1 Hz, 1H), 7.68 (d, *J* = 7.8 Hz, 1H), 7.61 (t, *J* = 7.8 Hz, 1H), 7.57 (t, *J* = 7.9 Hz, 1H), 7.48 (td, *J* = 8.4, 1.2 Hz, 1H), 7.33 (t, *J* = 7.5 Hz, 1H), 7.20 (d, *J* = 7.5 Hz, 1H), 7.14 (t, *J* = 7.5 Hz, 1H), 6.13 (d, *J* = 10.4 Hz, 1H), 4.73 (td, *J* = 9.6, 5.3 Hz, 1H), 4.11-4.05 (m, 2H), 2.86 (S, 3H), 2.30 (dd, *J* = 16.5, 5.0 Hz, 1H), 2.19 (dd, *J* = 16.5, 9.2 Hz, 1H), 1.22 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 171.4, 147.9, 141.4, 134.8, 133.8, 133.1, 129.9, 129.2, 129.1, 125.3, 125.2, 125.0, 114.5, 64.2, 61.1, 41.6, 37.3, 35.5, 14.2.

HRMS (ESI): *m/z*; $[M+Na]^+$ Calcd for $C_{19}H_{20}N_2O_6SNa$ 427.09343; Found: 427.0935.

***tert* -Butyl 3-(2-methoxy-2-oxoethyl)-2-(2-nitrophenyl)-1H-indoline-1-carboxylate (4e)**



4e

A light yellow solid; 0.14 g (87%);

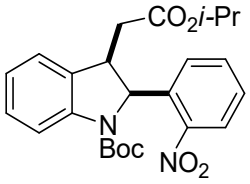
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (d, *J* = 7.9 Hz, 1H), 7.92 (br, 1H), 7.52 (td, *J* = 7.5, 1.2 Hz, 1H), 7.45 (td, *J* = 8.2, 1.4 Hz, 1H), 7.30 (t, *J* = 8.7 Hz, 2H), 7.11 (d, *J* = 7.5 Hz, 1H), 7.04 (td, *J* = 7.5, 1.1 Hz, 1H),

6.05 (d, *J* = 10.4 Hz, 1H), 4.58 (td, *J* = 9.6, 5.2 Hz, 1H), 3.68 (s, 3H), 2.41 (dd, *J* = 16.2, 5.0 Hz, 1H), 2.27 (dd, *J* = 16.4, 9.0 Hz, 1H), 1.19 (br, 9H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 172.3, 151.6, 149.1, 142.8, 136.2, 133.6, 132.2, 128.7, 128.6, 128.1, 124.5, 124.4, 123.4, 114.5, 81.6, 61.4, 52.1, 40.7, 36.6, 28.0.

HRMS (ESI): *m/z*; $[M+Na]^+$ Calcd for $C_{22}H_{22}N_2O_6Na$ 435.15266; Found: 435.1529.

***tert* -Butyl 3-(2-isopropoxy-2-oxoethyl)-2-(2-nitrophenyl)-1H-indoline-1-carboxylate (4f)**



4f

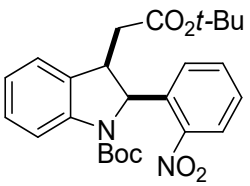
A light yellow solid; 0.18 g (94%);

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.1 Hz, 1H), 7.91 (br, 1H), 7.50 (td, *J* = 7.5, 1.1 Hz, 1H), 7.44 (td, *J* = 8.2, 1.4 Hz, 1H), 7.28 (t, *J* = 7.6 Hz, 2H), 7.12 (d, *J* = 7.5 Hz, 1H), 7.02 (td, *J* = 7.5, 0.9 Hz, 1H), 6.03 (d, *J* = 10.2 Hz, 1H), 5.05 (p, *J* = 6.3 Hz, 1H), 4.58 (td, *J* = 10.1, 4.4 Hz, 1H), 2.39 (dd, *J* = 16.2, 4.4 Hz, 1H), 2.17 (dd, *J* = 16.2, 9.6 Hz, 1H), 1.23 (d, *J* = 6.3 Hz, 15H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 171.4, 151.6, 149.0, 142.8, 136.4, 133.6, 132.48, 132.46, 128.5, 128.0, 124.4, 123.3, 114.4, 81.5, 68.5, 61.4, 40.6, 37.2, 28.0, 21.9, 21.8.

HRMS (ESI): *m/z*; $[M+Na]^+$ Calcd for $C_{24}H_{26}N_2O_6Na$ 463.18396; Found:. 463.1843.

***tert* -Butyl 3-(2-(*tert*-,butoxy)-2-oxoethyl)-2-(2-nitrophenyl)-1H-indoline-1-carboxylate (4g)**



4g

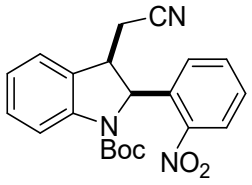
A light yellow solid; 0.16 g (88%);

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (d, *J* = 8.1 Hz, 1H), 7.92 (br, 1H), 7.51 (td, *J* = 7.6, 1.2 Hz, 1H), 7.44 (td, *J* = 7.9, 1.4 Hz, 1H), 7.29 (t, *J* = 8.0 Hz, 2H), 7.16 (d, *J* = 7.5 Hz, 1H), 7.03 (td, *J* = 7.5, 0.9 Hz, 1H), 6.02 (d, *J* = 10.4 Hz, 1H), 4.55 (td, *J* = 10.2, 4.1 Hz, 1H), 2.39 (dd, *J* = 16.2, 3.8 Hz, 1H), 2.07 (dd, *J* = 16.2, 10.1 Hz, 1H), 1.45 (s, 9H), 1.19 (br, 9H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 171.2, 151.6, 149.0, 142.8, 136.6, 133.6, 132.82, 132.80, 128.5, 128.1, 124.5, 124.4, 123.3, 114.4, 81.5, 81.2, 61.4, 40.6, 38.2, 28.2, 28.1.

HRMS (ESI): *m/z*; $[M+Na]^+$ Calcd for $C_{25}H_{28}N_2O_6Na$ 477.19961; Found: 477.1999.

***tert* -Butyl 3-(cyanomethyl)-2-(2-nitrophenyl)-1H-indoline-1-carboxylate (4h**



4h

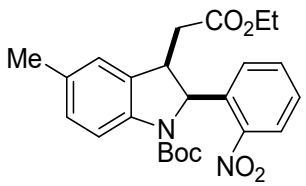
A light yellow solid; 0.11 g (75%);

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (dd, *J* = 8.1, 1.1 Hz, 1H), 7.95 (br, 1H), 7.60 (td, *J* = 7.6, 1.2 Hz, 1H), 7.55 (d, *J* = 7.6 Hz, 1H), 7.52 (td, *J* = 8.2, 1.4 Hz, 1H), 7.42 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.37 (t, *J* = 7.8 Hz, 1H), 7.13 (td, *J* = 7.5, 0.9 Hz, 1H), 5.93 (d, *J* = 10.5 Hz, 1H), 4.38 (td, *J* = 9.8, 4.9 Hz, 1H), 2.64 (dd, *J* = 16.9, 4.9 Hz, 1H), 2.27 (dd, *J* = 16.9, 8.7 Hz, 1H), 1.19 (br, 9H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 151.4, 149.3, 142.7, 134.6, 133.8, 129.6, 129.2, 128.6, 124.71, 124.66, 123.8, 118.1, 114.9, 81.9, 61.7, 40.5, 29.8, 28.0, 20.2.

HRMS (ESI): *m/z*; $[M+Na]^+$ Calcd for $C_{21}H_{19}N_3O_4Na$ 402.14243; Found: 402.1428.

***tert* -Butyl 3-(2-ethoxy-2-oxoethyl)-5-methyl-2-(2-nitrophenyl)-1H-indoline-1-carboxylate (4k)**



4k

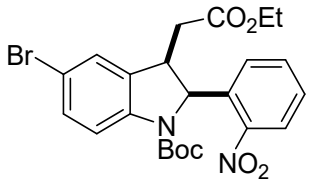
A light yellow solid; 0.18 g (89%);

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (d, *J* = 8.1 Hz, 1H), 7.80 (br, 1H), 7.51 (td, *J* = 7.6, 1.1 Hz, 1H), 7.44 (td, *J* = 8.2, 1.4 Hz, 1H), 7.28 (d, *J* = 1.2 Hz, 1H), 7.09 (d, *J* = 8.1 Hz, 1H), 6.92 (s, 1H), 6.03 (d, *J* = 9.6 Hz, 1H), 4.56 (td, *J* = 9.6, 4.9 Hz, 1H), 4.20 (m, 2H), 2.40 (dd, *J* = 16.3, 5.0 Hz, 1H), 2.31 (s, 3H), 2.23 (dd, *J* = 16.3, 9.2 Hz, 1H), 1.26 (t, *J* = 7.2 Hz, 3H), 1.18 (br, 9H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 172.0, 151.6, 149.1, 140.5, 136.5, 133.6, 132.9, 132.4, 129.0, 128.5, 128.1, 125.1, 124.4, 114.2, 81.4, 61.5, 61.0, 40.7, 36.9, 28.1, 21.2, 14.3.

HRMS (ESI): *m/z*; $[M+Na]^+$ Calcd for $C_{24}H_{26}N_2O_6Na$ 463.18396; Found: 463.1843.

***tert* -Butyl 5-bromo-3-(2-ethoxy-2-oxoethyl)-2-(2-nitrophenyl)-1H-indoline-1-carboxylate (4l)**



4l

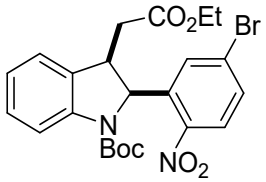
A light yellow solid; 0.19 g (96%);

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (d, *J* = 8.1 Hz, 1H), 7.82 (br, 1H), 7.56 (t, *J* = 7.3 Hz, 1H), 7.49 (t, *J* = 7.6 Hz, 1H), 7.40 (d, *J* = 7.9 Hz, 1H), 7.26 (d, *J* = 6.7 Hz, 2H), 6.05 (d, *J* = 9.6 Hz, 1H), 4.58 (td, *J* = 9.9, 4.4 Hz, 1H), 4.20 (m, 2H), 2.43 (dd, *J* = 16.5, 4.6 Hz, 1H), 2.23 (dd, *J* = 16.5, 9.3 Hz, 1H), 1.27 (t, *J* = 7.0 Hz, 3H), 1.19 (br, 9H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 172.0, 151.6, 149.1, 140.5, 136.5, 133.6, 132.9, 132.4, 129.0, 128.5, 128.1, 125.1, 124.4, 114.2, 81.4, 61.5, 61.0, 40.7, 36.9, 28.1, 21.2, 14.3.

HRMS (ESI): *m/z*; $[M+Na]^+$ Calcd for $C_{23}H_{23}BrN_2O_6Na$ 527.07882; Found: 527.0789.

***tert* -Butyl 2-(5-bromo-2-nitrophenyl)-3-(2-ethoxy-2-oxoethyl)-1H-indoline-1-carboxylate (4m)**



4m

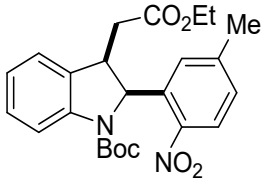
A light yellow solid; 0.17 g (83%);

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (br, 1H), 7.88 (d, *J* = 8.7 Hz, 1H), 7.59 (dd, *J* = 8.7, 2.1 Hz, 1H), 7.43 (d, *J* = 2.0 Hz, 1H), 7.31 (t, *J* = 7.6 Hz, 1H), 7.15 (d, *J* = 7.5 Hz, 1H), 7.05 (td, *J* = 7.5, 0.9 Hz, 1H), 6.02 (d, *J* = 10.7 Hz, 1H), 4.59 (td, *J* = 9.6, 5.2 Hz, 1H), 4.16 (m, 2H), 2.36 (dd, *J* = 16.2, 5.2 Hz, 1H), 2.28 (dd, *J* = 16.2, 9.0 Hz, 1H), 1.24 (t, *J* = 7.2 Hz, 12H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 171.6, 151.5, 147.8, 142.4, 142.3, 138.4, 131.9, 131.1, 128.8, 128.7, 126.1, 124.5, 123.6, 114.8, 81.9, 61.5, 61.1, 40.6, 37.3, 28.1, 14.2.

HRMS (ESI): *m/z*; $[M+Na]^+$ Calcd for $C_{23}H_{23}BrN_2O_6Na$ 527.07882; Found: 527.0786.

***tert* -Butyl 3-(2-ethoxy-2-oxoethyl)-2-(5-methyl-2-nitrophenyl)-1H-indoline-1-carboxylate (4n)**



4n

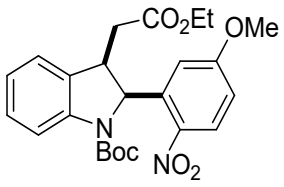
A light yellow solid; 0.17 g (95%);

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 (br, 1H), 7.91 (d, *J* = 8.4 Hz, 1H), 7.30 (t, *J* = 7.8 Hz, 1H), 7.22 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.14 (d, *J* = 7.6 Hz, 1H), 7.04 (td, *J* = 7.5, 0.9 Hz, 2H), 6.06 (d, *J* = 10.7 Hz, 1H), 4.59 (td, *J* = 10.1, 4.7 Hz, 1H), 4.16 (m, 2H), 2.39 (dd, *J* = 16.2, 4.7 Hz, 1H), 2.31 (s, 3H), 2.23 (dd, *J* = 16.2, 9.5 Hz, 1H), 1.25 (t, *J* = 7.2 Hz, 3H), 1.19 (br, 9H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 171.8, 163.6, 151.6, 142.6, 142.0, 139.3, 132.3, 128.5, 127.3, 124.3, 123.2, 114.3, 113.1, 112.8, 81.4, 61.6, 60.9, 55.8, 40.5, 36.8, 28.0, 14.1

HRMS (ESI): *m/z*; $[M+Na]^+$ Calcd for $C_{24}H_{26}N_2O_6Na$ 463.18396; Found: 463.1842.

***tert* -Butyl 3-(2-ethoxy-2-oxoethyl)-2-(5-methoxy-2-nitrophenyl)-1H-indoline-1-carboxylate (4o)**



4o

A light yellow solid; 0.17 g (94%);

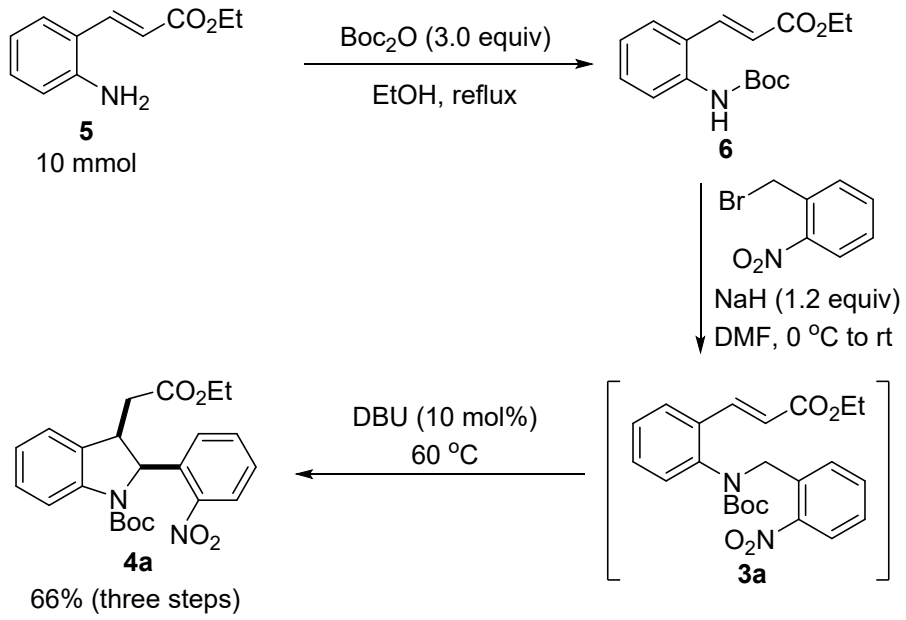
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (d, *J* = 9.2 Hz, 1H), 7.91 (br, 1H), 7.28 (t, *J* = 7.8 Hz, 1H), 7.12 (d, *J* = 7.5 Hz, 1H), 7.03 (td, *J* = 7.5, 0.9 Hz, 1H), 6.89 (dd, *J* = 9.2, 2.7 Hz, 2H), 6.71 (d, *J* = 2.7 Hz, 1H), 6.19 (d, *J* = 10.4 Hz, 1H), 4.60 (td, *J* = 9.9, 4.9 Hz, 1H), 4.16 (m, 2H), 3.73 (s, 3H), 2.41 (dd, *J* = 16.3, 4.9 Hz, 1H), 2.26 (dd, *J* = 16.3, 9.3 Hz, 1H), 1.25 (t, *J* = 7.2 Hz, 12H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 171.9, 163.7, 151.7, 142.8, 142.2, 139.5, 132.4, 128.6, 127.5, 124.5, 123.4, 114.5, 113.3, 112.9, 81.5, 61.7, 61.0, 55.9, 40.6, 36.9, 28.1, 14.3.

HRMS (ESI): *m/z*; $[M+Na]^+$ Calcd for $C_{24}H_{26}N_2O_7Na$ 479.17887; Found: 479.1783.

6. Synthetic Utilities (Scheme 2)

6-1. Telescope Synthesis of 4a on a Large-scale (Scheme 2a)



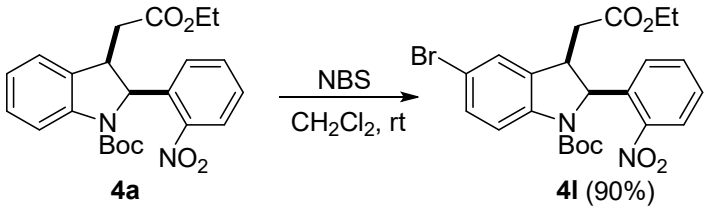
Ethyl 2-aminocinnamate (**5**, 1.9 g, 10.0 mmol) was added to a 250 mL two-neck round bottom flask equipped with a reflux condenser and dissolved in EtOH (100.0 mL). To the above mixture was added a solution of di-*tert*-butyl dicarbonate (Boc_2O, 6.9 mL, 30.0 mmol) dropwise at room temperature. The reaction mixture was allowed to reflux with an oil bath and monitored by TLC. After the complete consumption of **5**, the reaction mixture was cooled to room temperature, quenched with H_2O, and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure to provide a crude product of **6**, which was directly used in the next step without further isolation.

The resulting **6** was added to a 250 mL one-neck round bottom flask and dissolved in dimethylformamide (DMF, 100.0 mL) at 0 °C. To the above mixture was added a NaH (60% dispersion in mineral oil, 0.49 g, 12.0 mmol). After 30 min, the reaction mixture was cooled to room temperature. To the reaction mixture was added 2-nitrobenzyl bromide (2.6 g, 12.0 mmol) and the reaction mixture was stirred and monitored by TLC at room temperature. After the complete consumption of the starting material **6**, the resulting mixture of **3a** was directly subjected to base-catalyzed cyclization. To the above reaction mixture was added 1,8-diazabicyclo (5.4.0)undec-7-ene (DBU, 0.15 mL, 1.0 mmol). The reaction mixture was

stirred at 60 °C with an oil bath and monitored by TLC. After the complete consumption of **3a**, the reaction mixture was carefully quenched with H_2O and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using a mixture of ethyl acetate and hexanes as the eluent to provide product **4a** as a light yellow solid in 66% yield (2.8 g) over three steps.

Spectroscopic data were in good agreement with ones reported in Table 1.

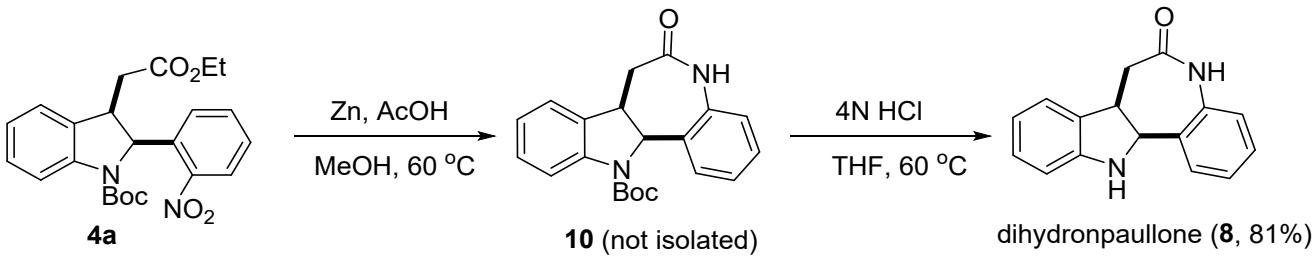
6-2. Divergent Approach for Synthesis of 4l from 4a (Scheme 2b)



In a one neck round bottom flask was placed **4a** (0.42 g, 1.0 mmol) and NBS (0.53 g, 3.0 mmol). The mixture was dissolved with dichloromethane (DCM, 10.0 mL), stirred at room temperature and monitored by TLC. After the complete consumption of **4a,** the reaction mixture was carefully quenched with H_2O, and extracted with dichloromethane. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure The residue was purified by column chromatography on silica gel using a 1:3 mixture of ethyl acetate and hexanes as the eluent to provide product **4l** as a light yellow solid (0.45 g, 90% yield).

Spectroscopic data were identical to ones reported in Table **3**.

6-3. Total Synthesis of Dihydropaullone (8) (Scheme 2b)



In a one neck round bottom flask were placed indoline **4a** (0.42 g, 1.0 mmol) and Zn (0.33 g, 5.0 mmol). To the flask were added MeOH (10.0 mL) and AcOH (0.57 mL, 10.0 mmol) and the reaction mixture was heated to 60 °C with an oil bath. After 12 h, the reaction mixture was cooled to room temperature, quenched with H_2O, and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure to provide a crude product of **10**, which was directly used in the next step without further isolation.

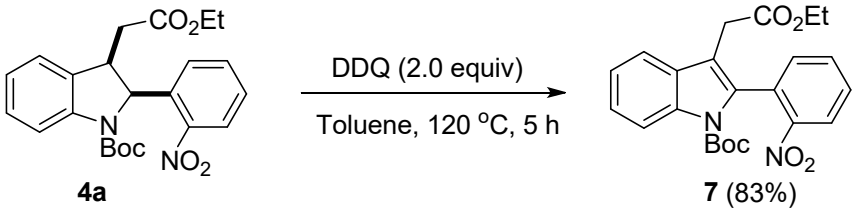
The resulting **10** was added to a 25 mL one-neck round bottom flask and dissolved in tetrahydrofuran (THF, 10.0 mL) at 60 °C. 4N HCl (5ml, 20.0 mmol) was added to the above mixture and the resulting mixture was monitored by TLC at the same temperature. After the complete consumption of **10**, the reaction mixture was carefully quenched with H_2O and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using a 1:3 mixture of ethyl acetate and hexanes as the eluent to provide the desired dihydropaullone (**8**) as a white solid in 81% yield (0.20 g).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (s, 1H), 7.33 (d, *J* = 7.8 Hz, 1H), 7.29 (td, *J* = 7.6, 1.4 Hz, 1H), 7.18 (td, *J* = 7.6, 1.2 Hz, 1H), 7.11 (t, *J* = 7.6 Hz, 1H), 7.03 (d, *J* = 7.3 Hz, 1H), 6.97 (dd, *J* = 7.8, 0.92 Hz, 1H), 6.78 (td, *J* = 7.5, 0.92 Hz, 1H), 6.74 (d, *J* = 7.8 Hz, 1H), 5.07 (d, *J* = 9.3 Hz, 1H), 4.25 (td, *J* = 9.6, 5.3 Hz, 1H), 2.86 (dd, *J* = 12.4, 5.2 Hz, 1H), 2.47 (td, *J* = 12.4, 9.6 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 173.9, 149.9, 137.1, 133.9, 129.3, 128.6, 127.93, 127.92, 125.8, 124.0, 123.0, 119.6, 109.3, 63.1, 48.6, 36.2.

HRMS (ESI): *m/z*; $[M+Na]^+$ Calcd for $C_{16}H_{14}N_2ONa$ 273.09983; Found: 273.0998.

6-4. Synthesis of Indole 7 from Indoline 4a (Scheme 2b)



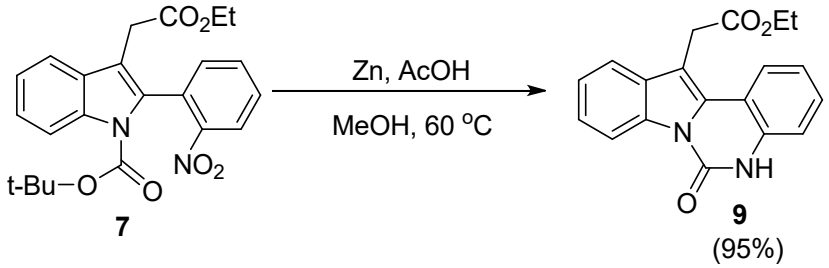
To a solution of indoline **4a** (0.43 g, 1.0 mmol) in toluene (10.0 mL) was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ, 0.45 g, 2.0 mmol). The reaction mixture was stirred at 120 °C with an oil bath and monitored by TLC. After the complete consumption of **4a**, the reaction mixture was cooled to room temperature, quenched with H_2O, and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using a 1:3 mixture of ethyl acetate and hexanes as the eluent to provide the desired indole product **7** as yellow solid (0.35 g, 83% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.28 (d, *J* = 8.2 Hz, 1H), 8.24 (d, *J* = 8.2 Hz, 1H), 7.73 (t, *J* = 7.5 Hz, 1H), 7.64 (t, *J* = 7.5 Hz, 1H), 7.59 (d, *J* = 7.8 Hz, 1H), 7.55 (d, *J* = 7.3 Hz, 1H), 7.40 (t, *J* = 7.3 Hz, 1H), 7.31 (t, *J* = 7.5 Hz, 1H), 4.07 (q, *J* = 7.2 Hz, 2H), 3.45 (d, *J* = 15.4 Hz, 1H), 3.34 (d, *J* = 15.4 Hz, 1H), 1.28 (s, 9H), 1.18(t, *J* = 7.2 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 170.7, 149.7, 148.8, 136.3, 133.2, 133.1, 132.7, 129.6, 129.4, 129.2, 125.3, 124.8, 123.1, 119.1, 116.0, 114.0, 83.7, 61.2, 30.9, 27.7, 14.2.

HRMS (ESI): *m/z*; $[M+Na]^+$ Calcd for $C_{23}H_{24}N_2O_6Na$ 447.15266; Found: 447.1524.

6-5. Synthesis of Indoloquinazolinone 9 from 7 (Scheme 2b)



In a one neck round bottom flask was placed indole **7** (0.42 g, 1.0 mmol) and Zn (0.33 g, 5.0 mmol). To the flask were added MeOH (10.0 mL) and AcOH (0.57 mL, 10.0 mmol) and the reaction mixture was heated to 60 °C with an oil bath. After 12 h, the reaction mixture was cooled to room temperature, quenched with H_2O, and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using a 1:3 mixture of ethyl acetate and hexanes as the eluent to provide indoloquinazolinone **9** as a white solid (0.32 g, 95% yield).

^{1}H NMR (500 MHz, DMSO) δ 11.41 (s, 1H), 8.62-8.58 (m, 1H), 8.05 (d, *J* = 7.3 Hz, 1H), 7.84-7.80 (m, 1H), 7.46 (td, *J* = 8.2, 1.1 Hz, 1H), 7.42-7.38 (m, 2H), 7.31 (d, *J* = 8.2 Hz, 1H), 7.27 (td, *J* = 8.2, 1.1 Hz, 1H), 4.29 (s, 2H), 4.13 (q, *J* = 7.0 Hz, 2H), 1.18 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (125 MHz, DMSO) δ 170.5, 147.0, 134.7, 132.2, 130.5, 129.9, 129.1, 124.0, 123.7, 123.3, 122.9, 118.4, 115.5, 115.4, 114.1, 106.5, 60.6, 30.5, 14.1.

HRMS (ESI): *m/z*; $[M+Na]^+$ Calcd for $C_{19}H_{16}N_2O_3Na$ 343.1053; Found: 343.1058.

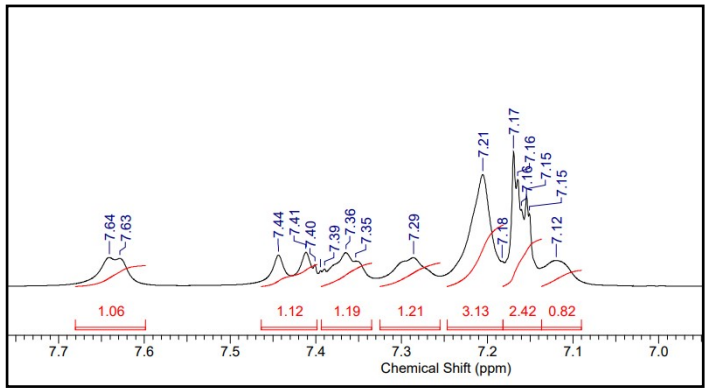
7. References

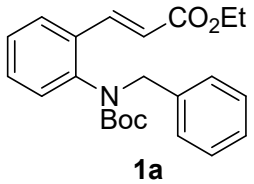
1. (a) I. Prediger, T. Weiss and O. Reiser, *Synthesis* **2008**, *14*, 2191–2198. (b) S. K. Pagire and O. Reiser, *Green. Chem.* **2017**, *19*, 1721–1725.

8. Spectroscopic Data

8-1. NMR Spectra of (*E*)-Ethyl 3-(2-(Benzyl(*tert*-butoxycarbonyl)amino)phenyl)acrylate (1a)

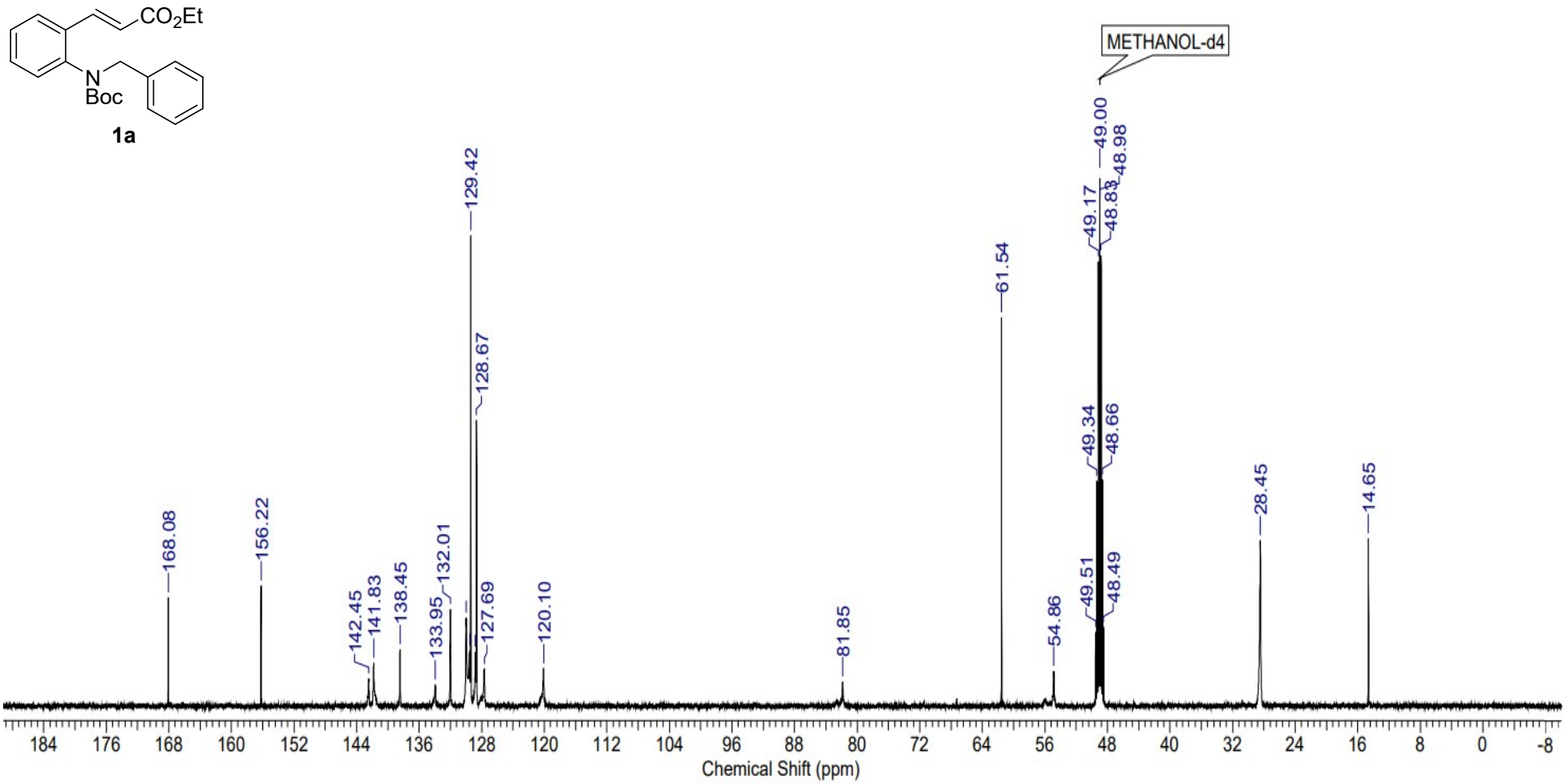
a) ^{1}H NMR Spectrum (500 MHz, MeOD)





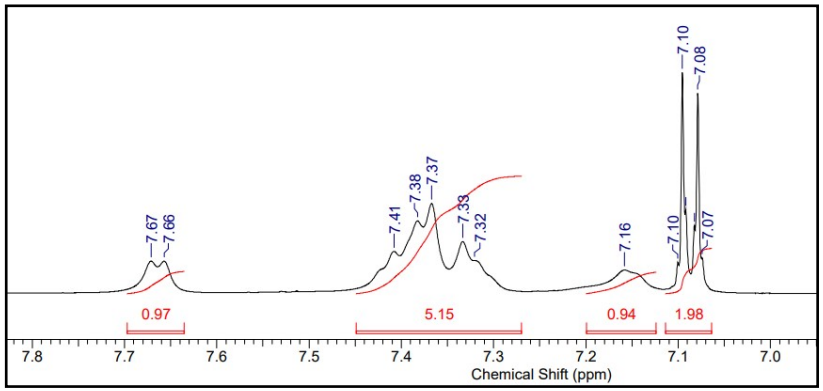
1a

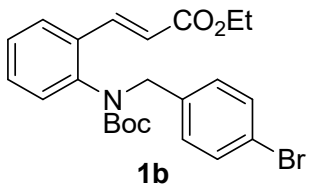
b) ^{13}C NMR Spectrum (125 MHz, MeOD)

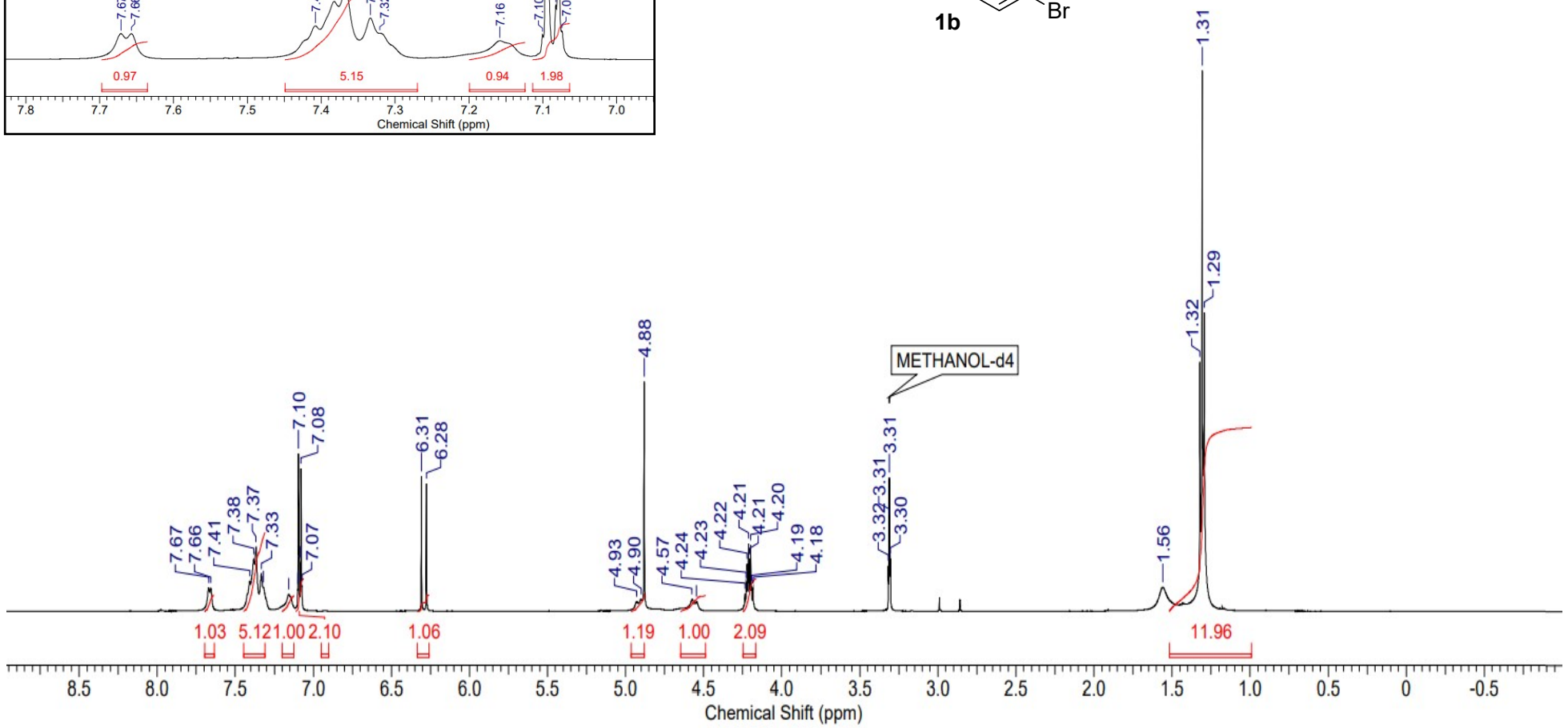


8-2. NMR Spectra of (*E*)-Ethyl 3-(2-((4-Bromobenzyl)(*tert*-butoxycarbonyl)amino)phenyl)acrylate (1b)

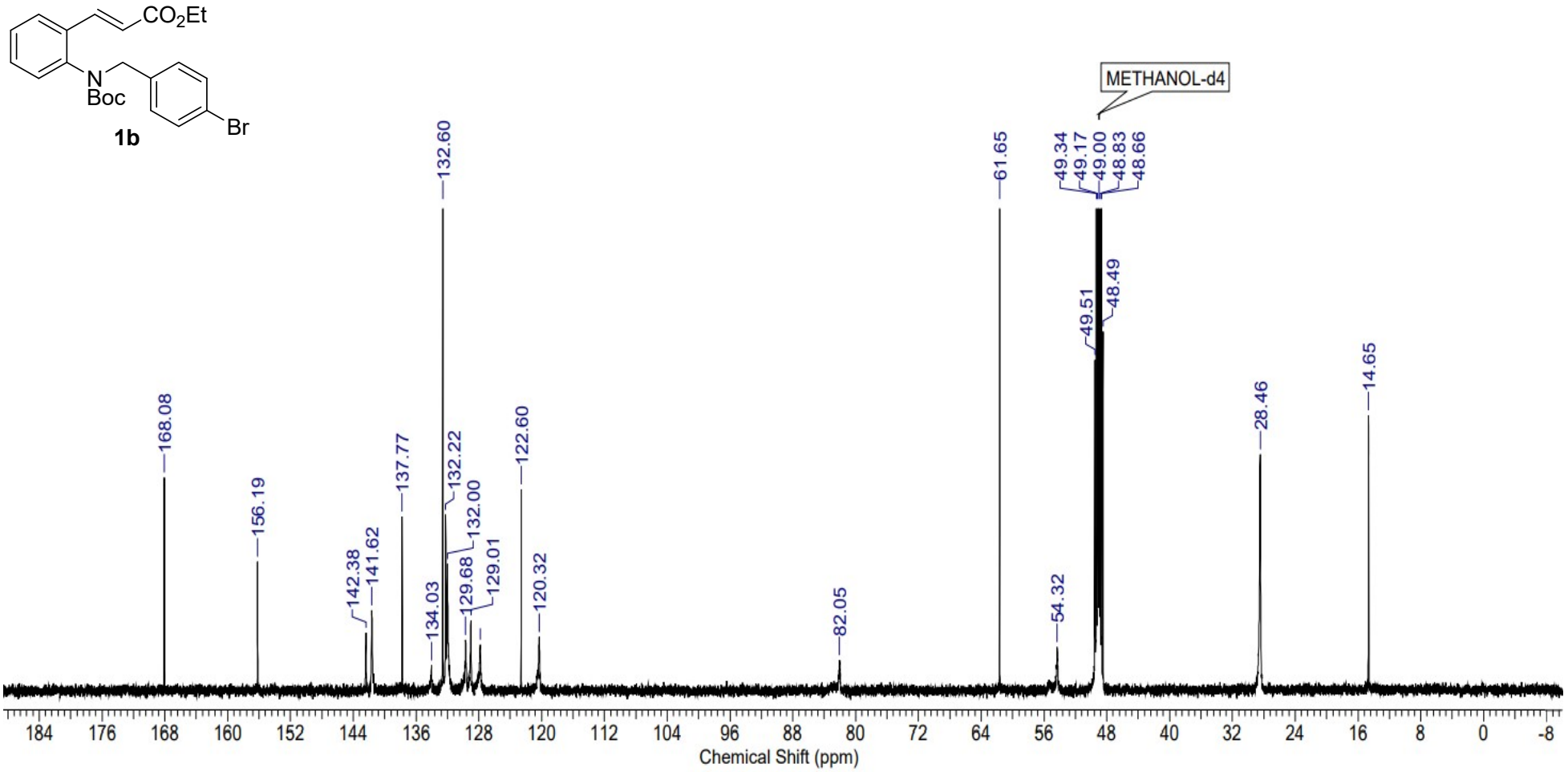
a) ^{1}H NMR Spectrum (500 MHz, MeOD)





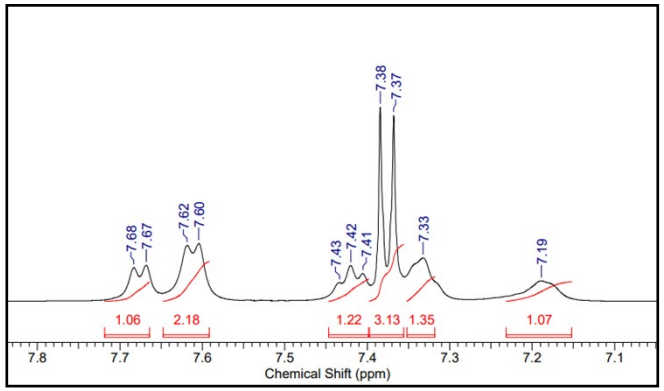


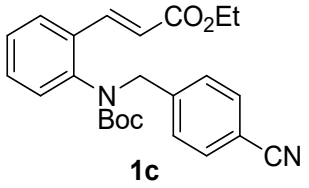
b) ^{13}C NMR Spectrum (125 MHz, MeOD)

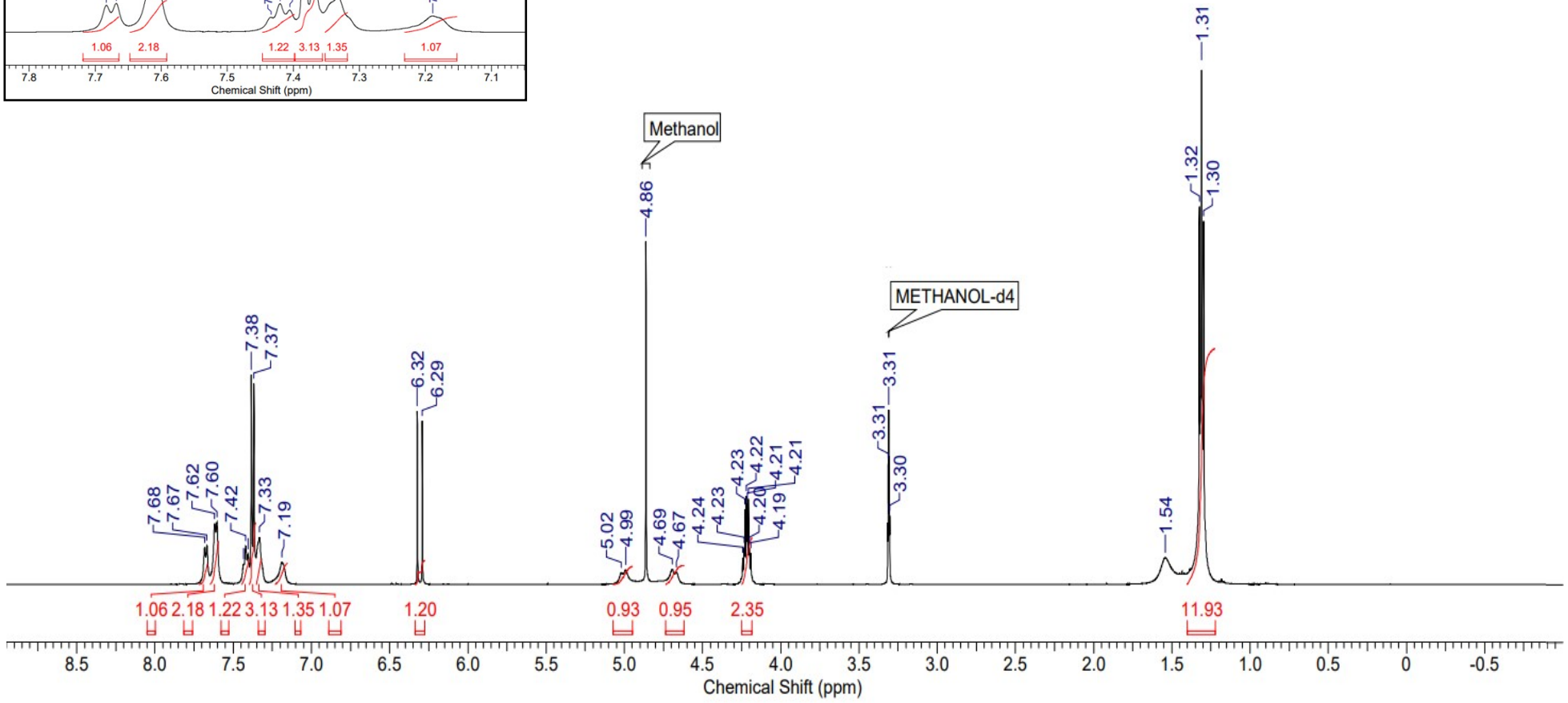


8-3. NMR Spectra of (*E*)-Ethyl 3-(2-((*tert*-Butoxycarbonyl)(4-cyanobenzyl)amino)phenyl)acrylate (1c)

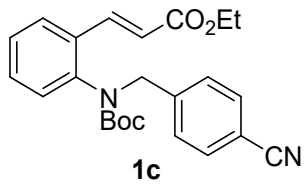
a) ^{1}H NMR Spectrum (500 MHz, MeOD)



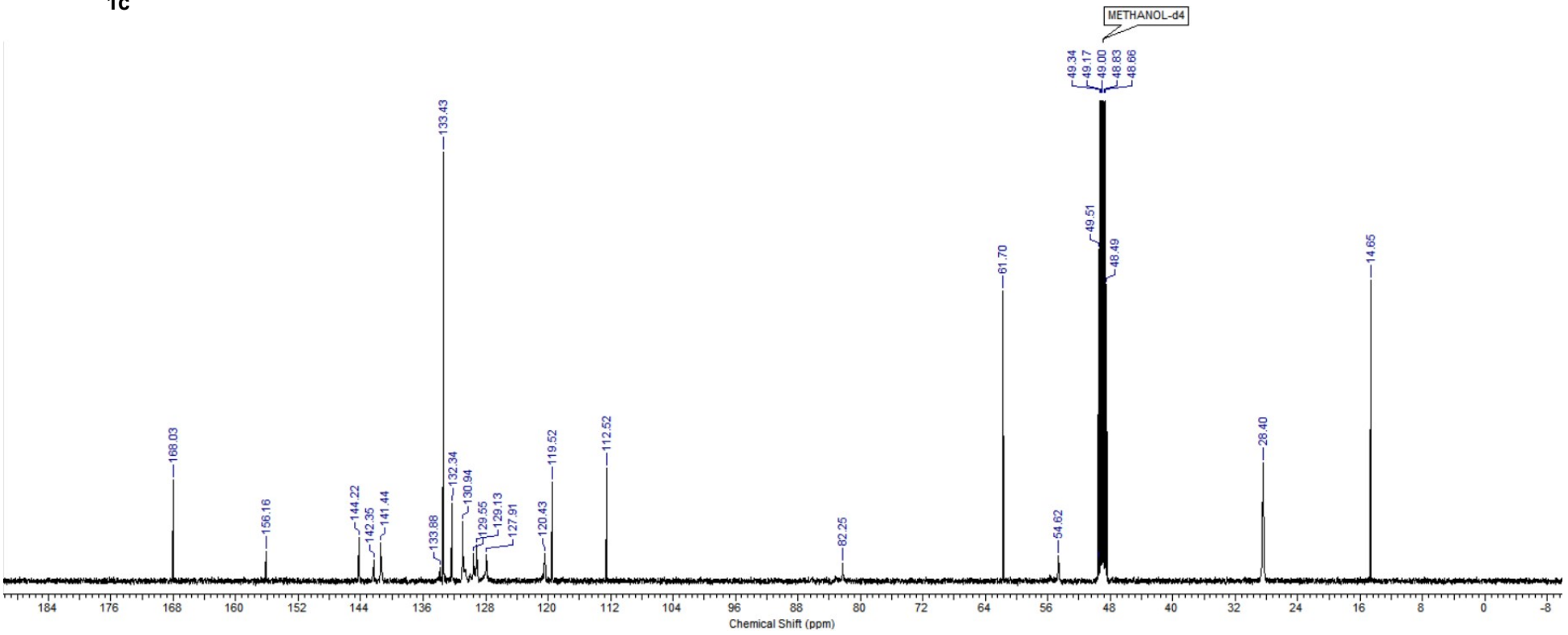




b) ^{13}C NMR Spectrum (125 MHz, MeOD)

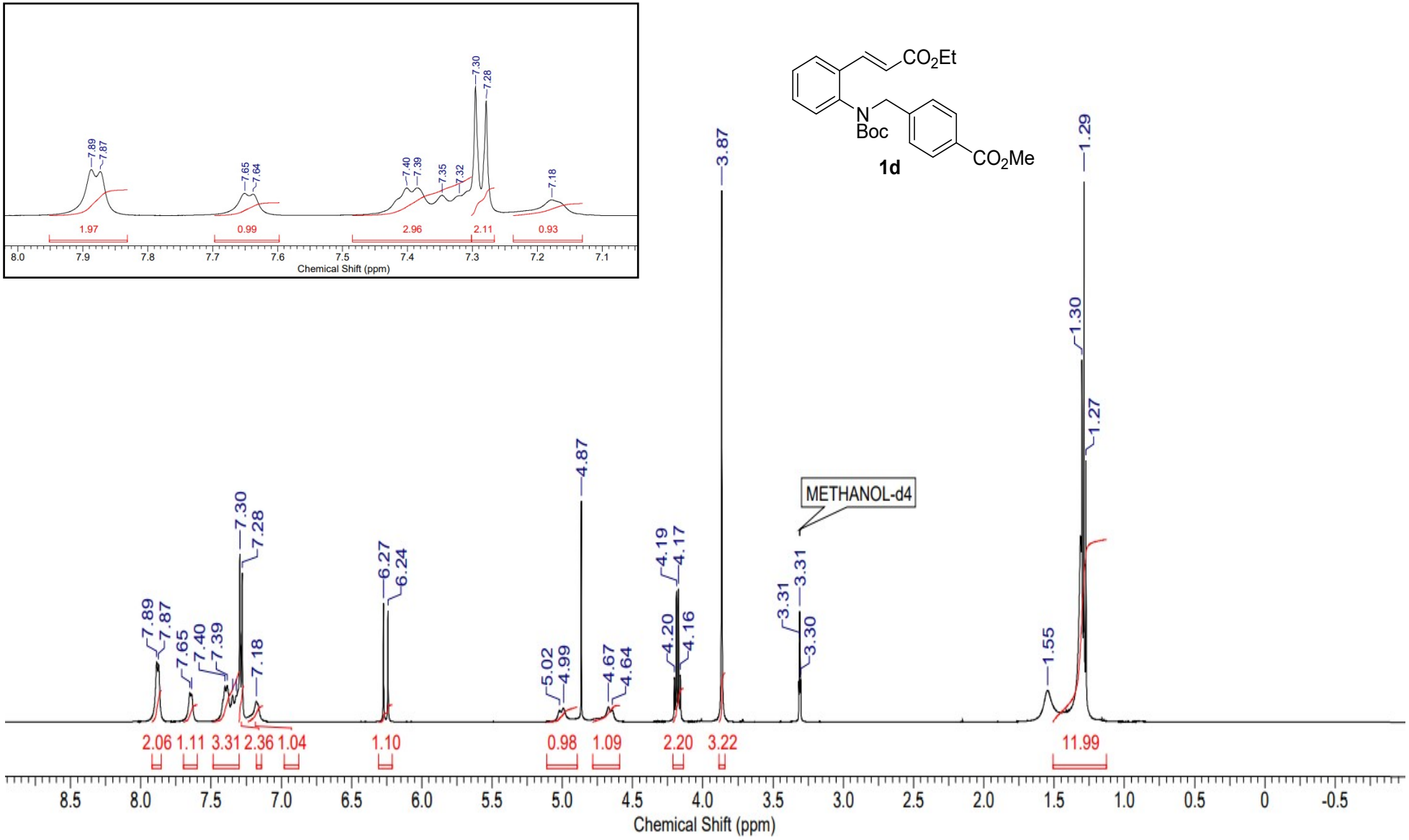


1c

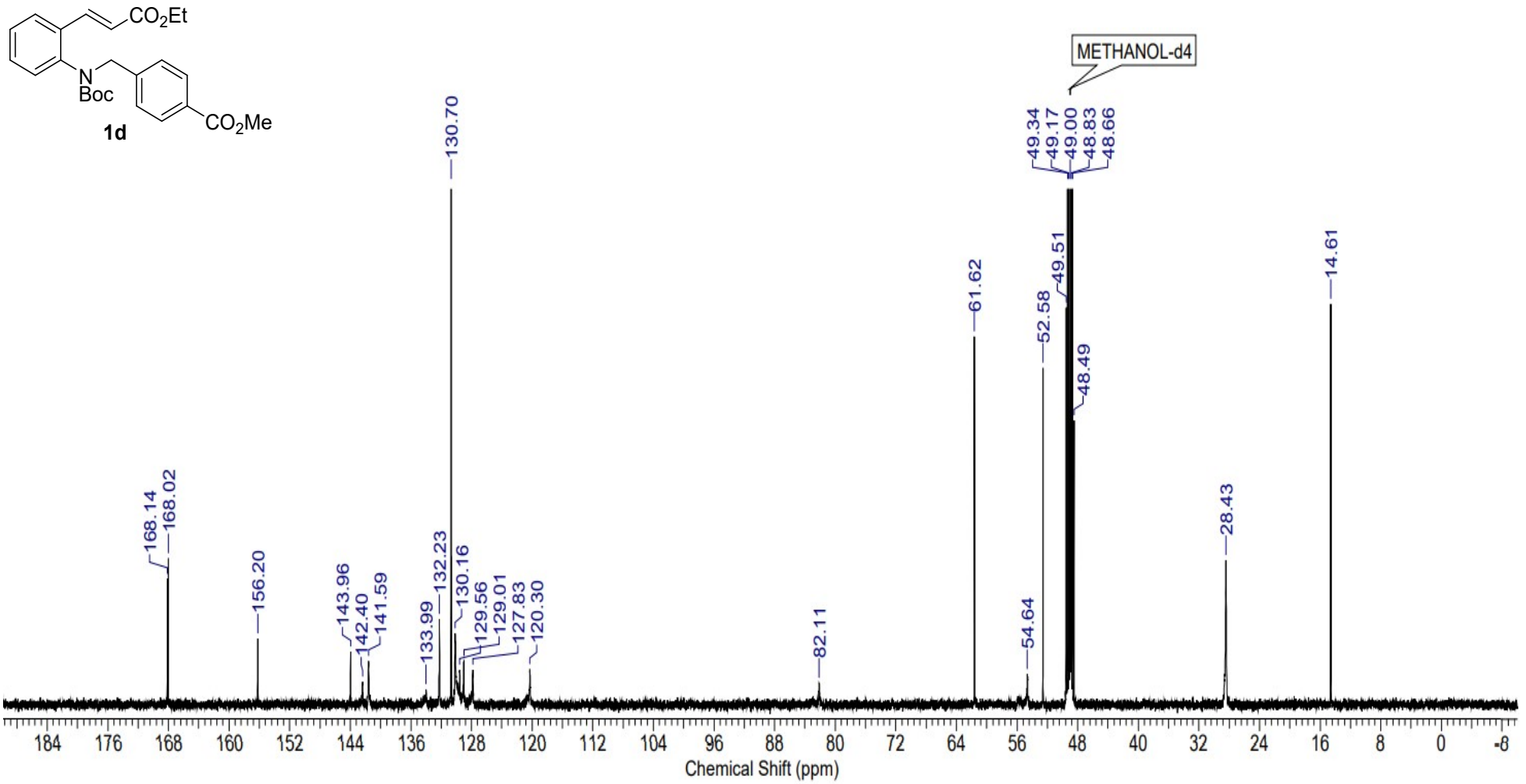


8-4. NMR Spectra of (*E*)-Methyl 4-(((*tert*-Butoxycarbonyl)(2-(3-ethoxy-3-oxoprop-1-en-1 1)phenyl)amino)methyl)benzoate (1d)

a) ^{1}H NMR Spectrum (500 MHz, MeOD)

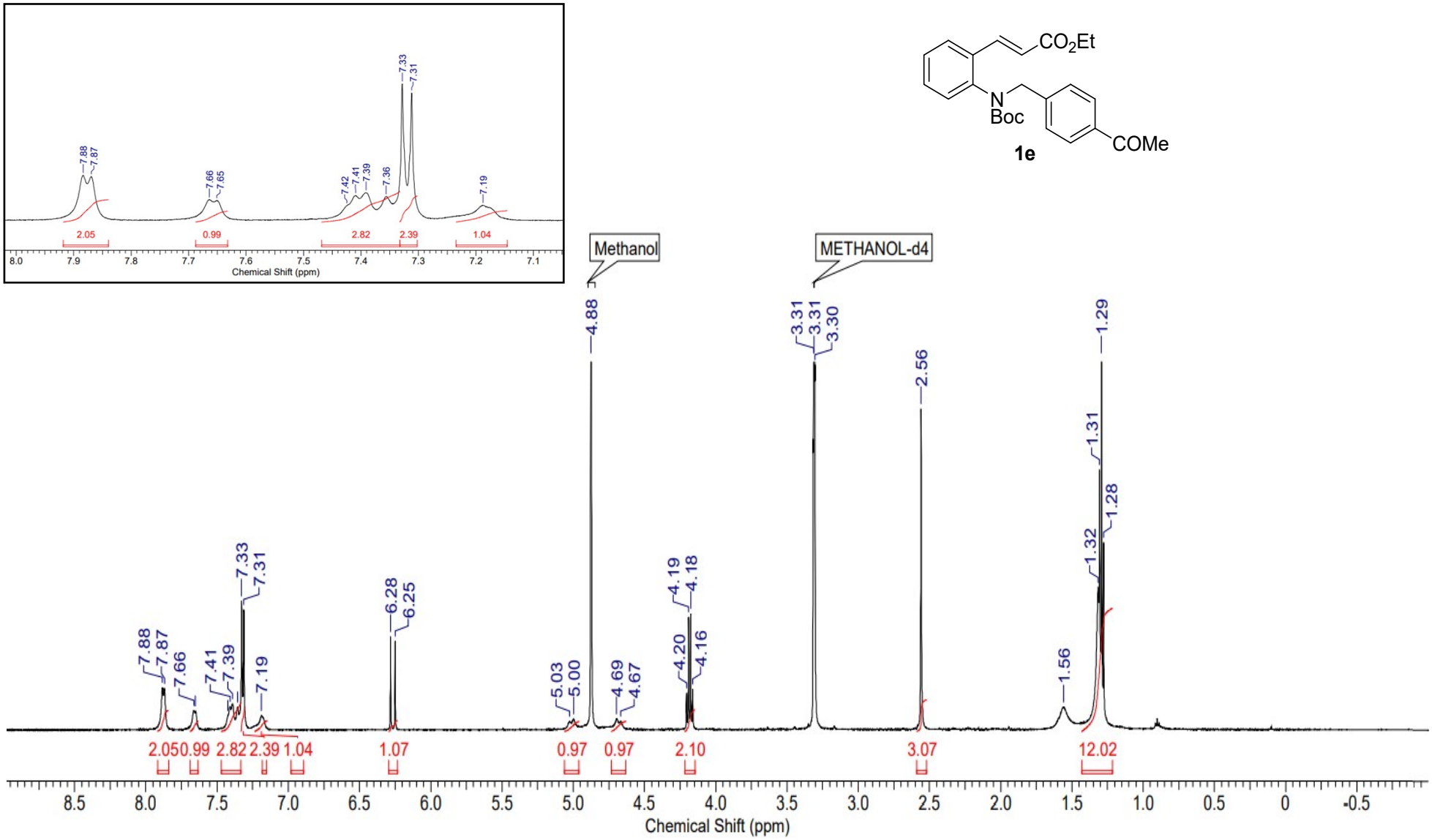


b) ^{13}C NMR Spectrum (125 MHz, MeOD)

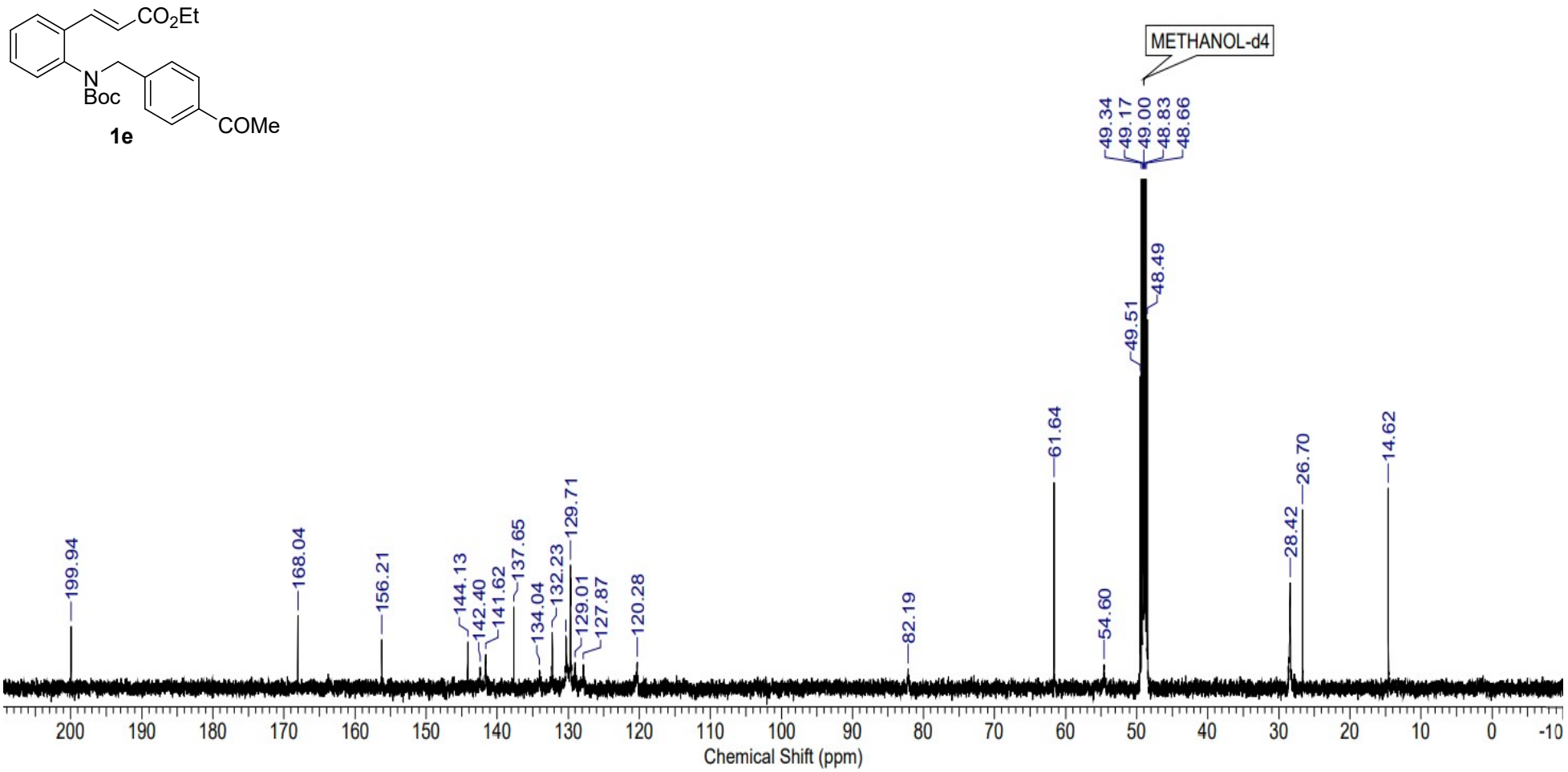


8-5. NMR Spectra of (*E*)-Ethyl 3-(2-((4-Acetylbenzyl)(*tert*-butoxycarbonyl)amino)phenyl)acrylate (1e)

a) ^{1}H NMR Spectrum (500 MHz, MeOD)

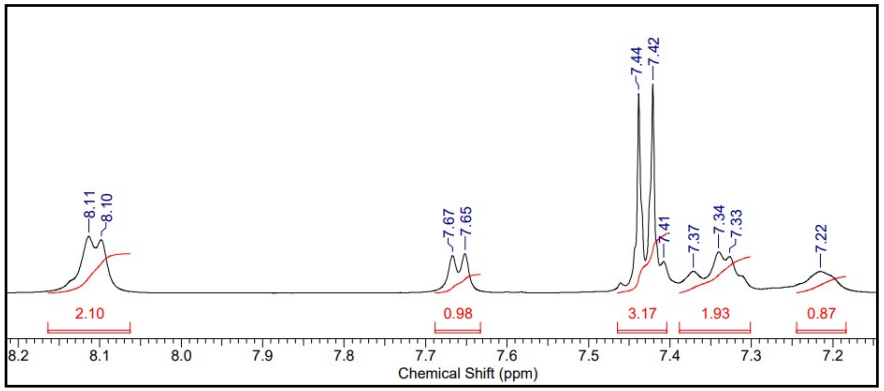


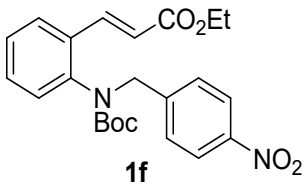
b) ^{13}C NMR Spectrum (125 MHz, MeOD)

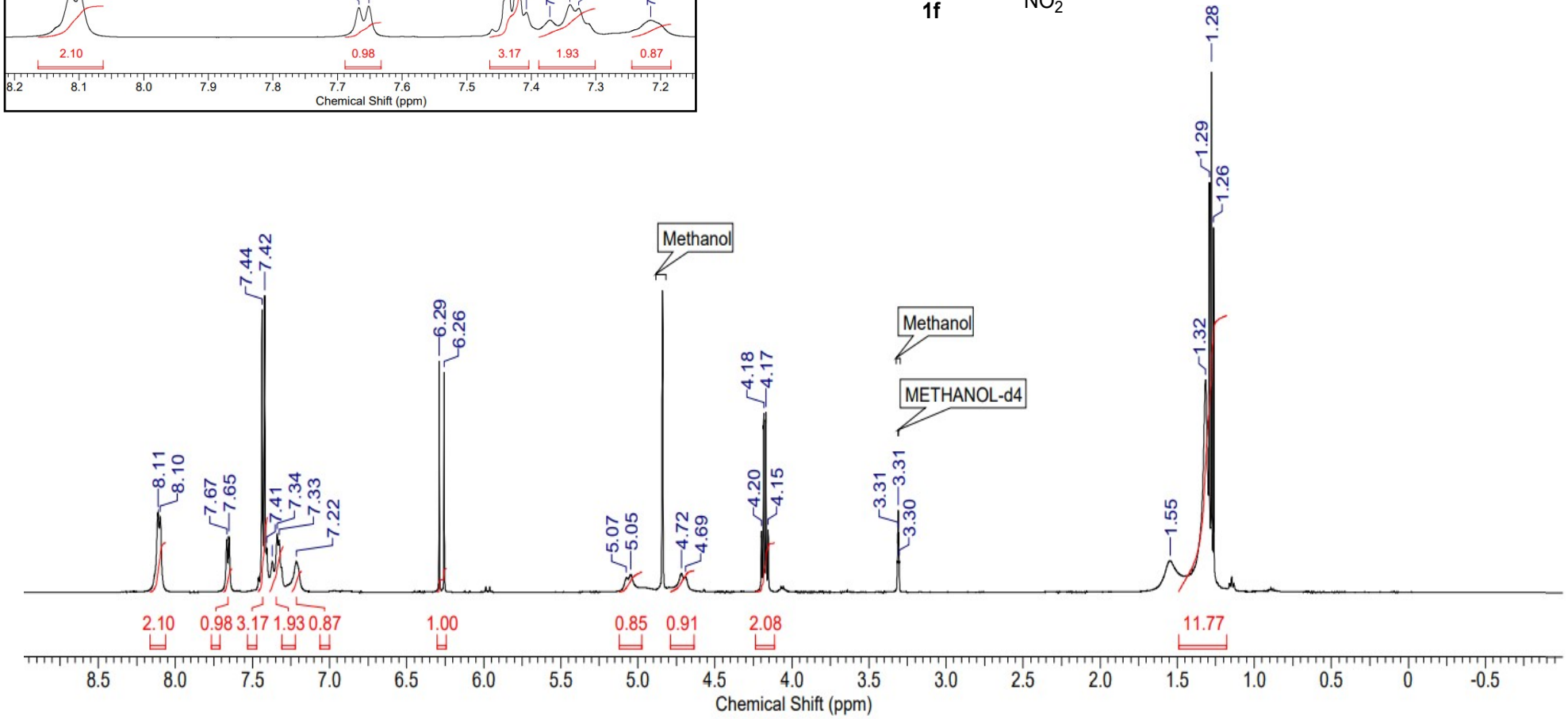


8-6. NMR Spectra of (*E*)-Ethyl 3-(2-((*tert*-Butoxycarbonyl)(4-nitrobenzyl)amino)phenyl)acrylate (1f)

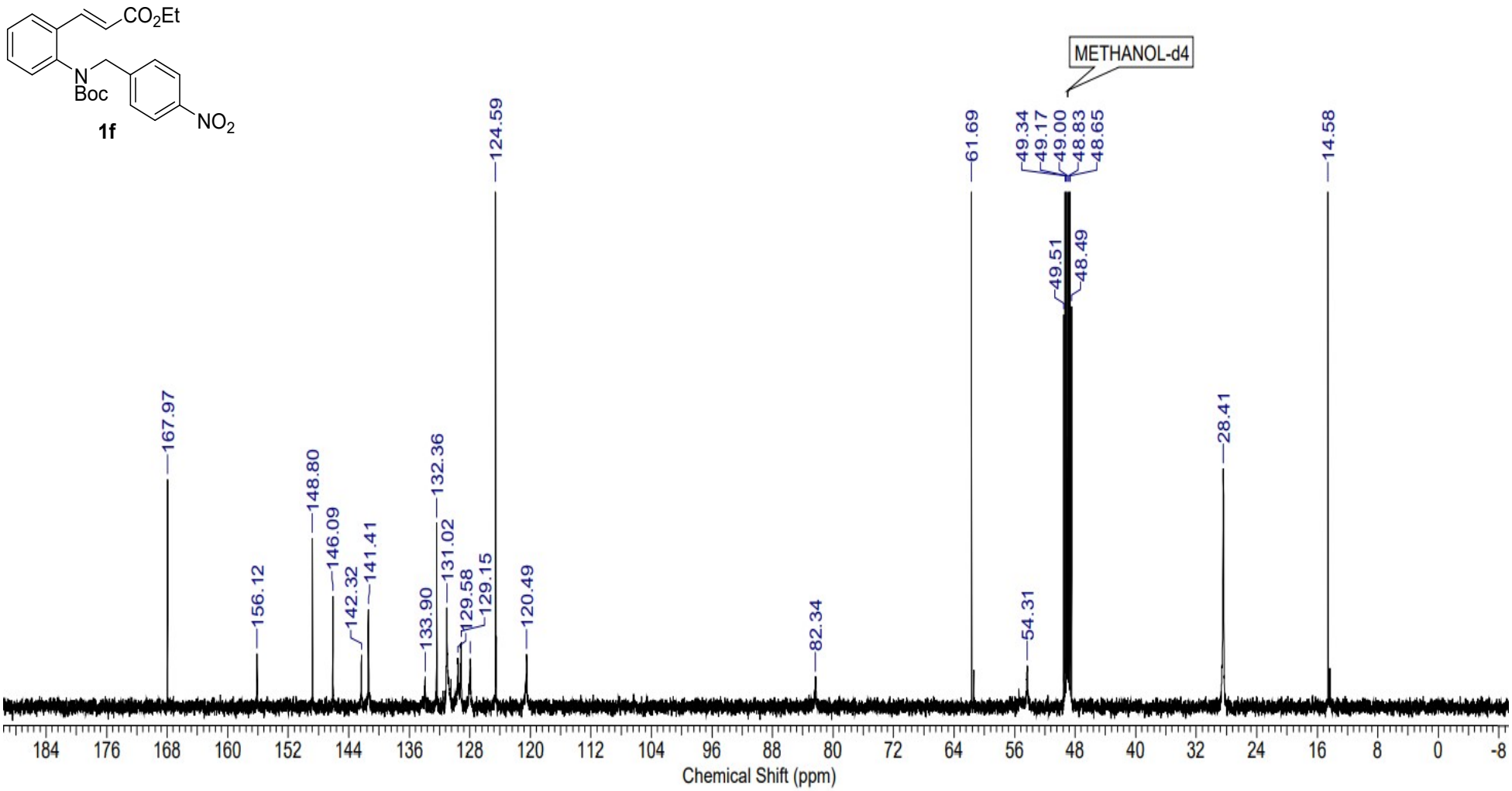
a) ^{1}H NMR Spectrum (500 MHz, MeOD)





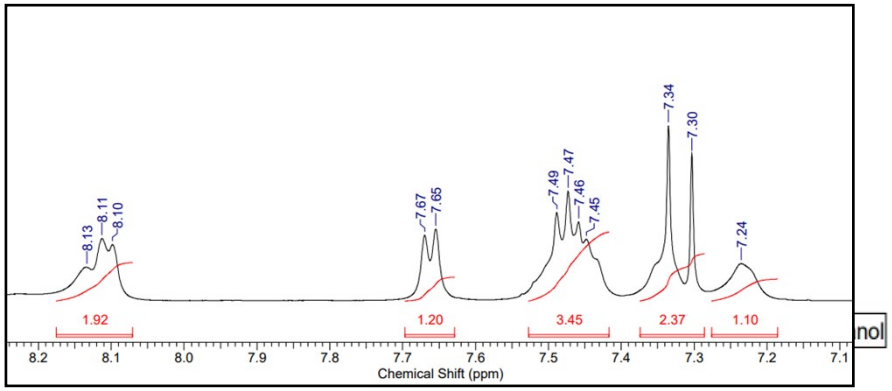


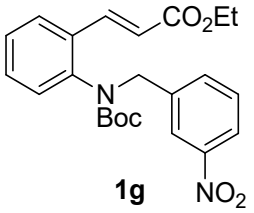
b) ^{13}C NMR Spectrum (125 MHz, MeOD)

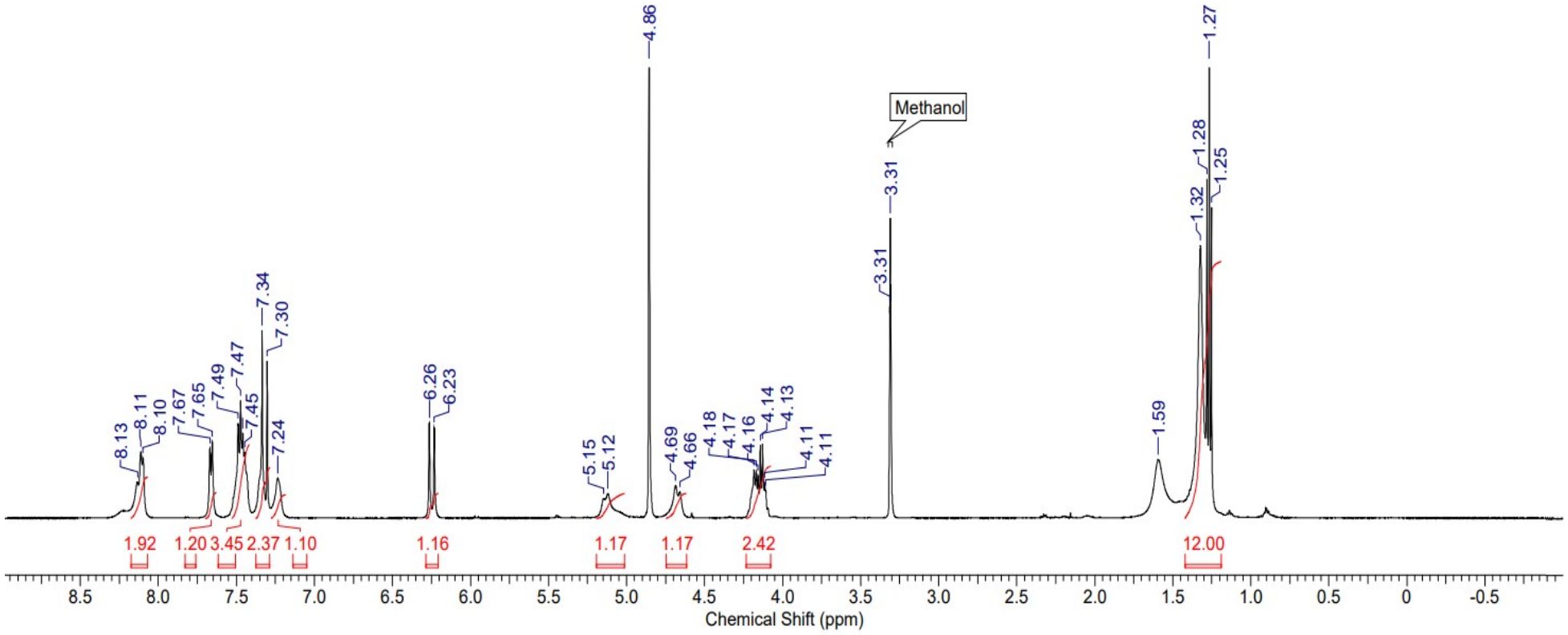


8-7. NMR Spectra of (*E*)-Ethyl 3-(2-((*tert*-Butoxycarbonyl)(3-nitrobenzyl)amino)phenyl)acrylate (1g)

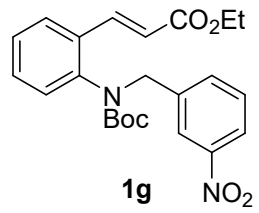
a) ^{1}H NMR Spectrum (500 MHz, MeOD)



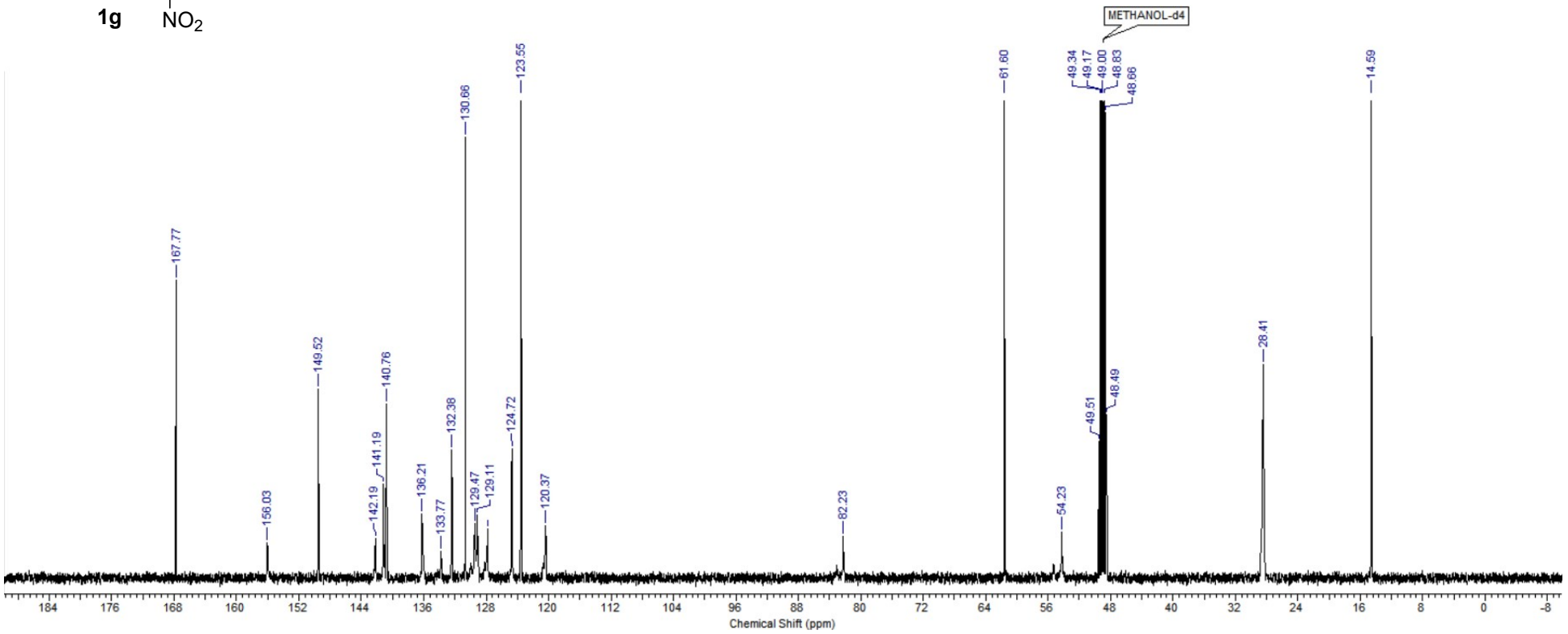




b) ^{13}C NMR Spectrum (125 MHz, MeOD)

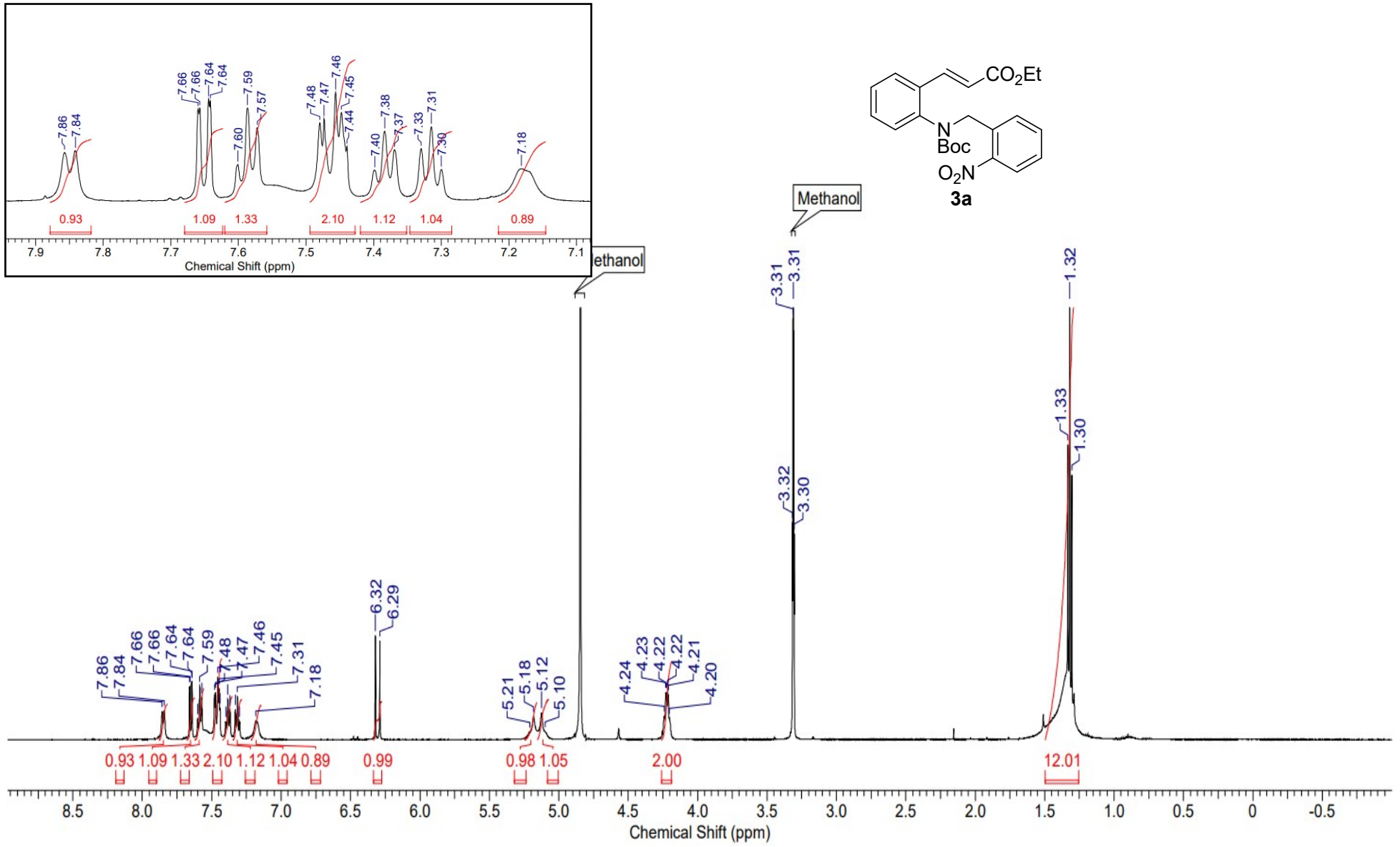


1g

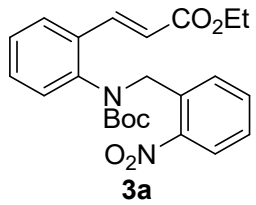


8-8. NMR Spectra of (*E*)-Ethyl 3-(2-((*tert*-Butoxycarbonyl)(2-nitrobenzyl)amino)phenyl)acrylate (3a)

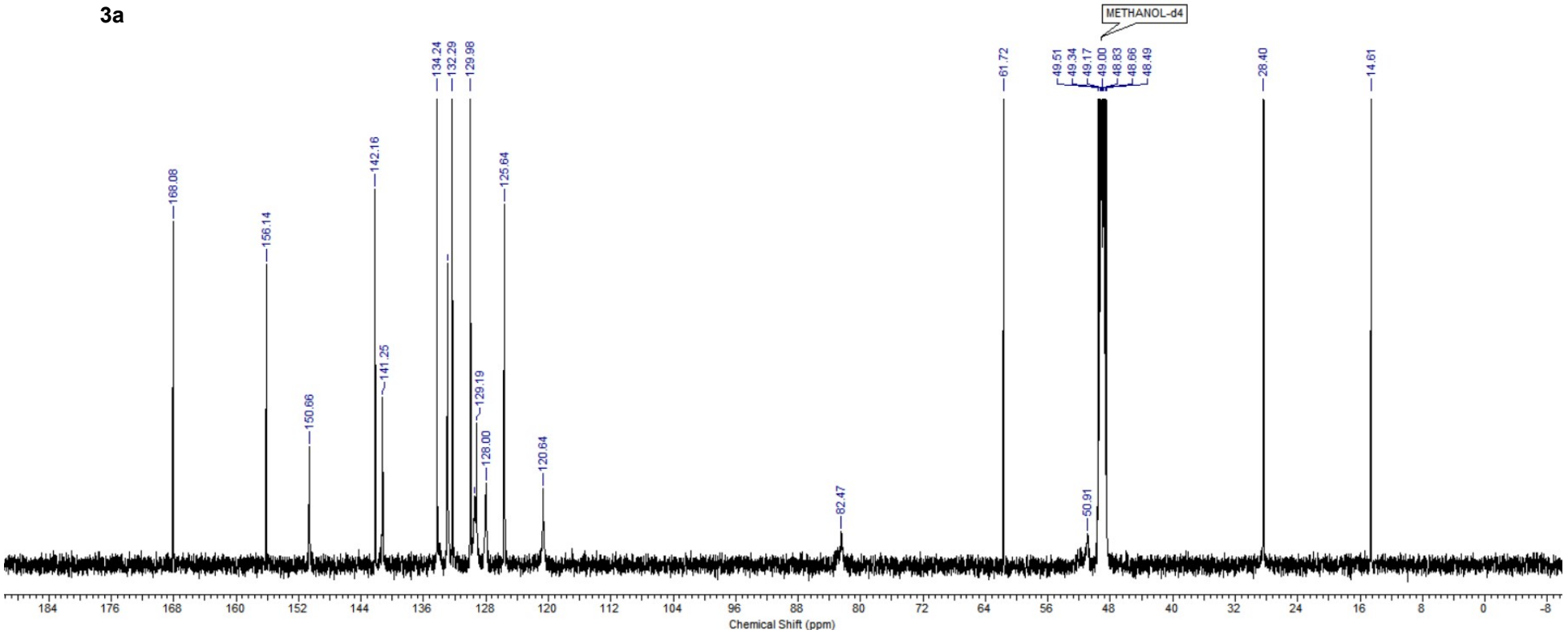
a) ^{1}H NMR Spectrum (500 MHz, MeOD)



b) ^{13}C NMR Spectrum (125 MHz, MeOD)

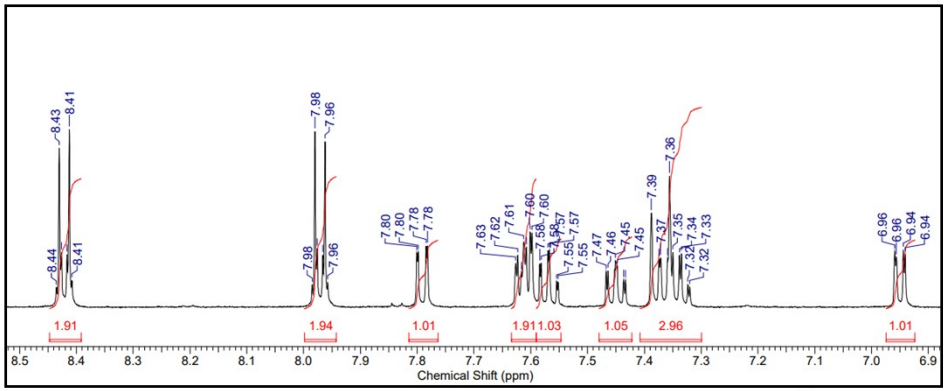


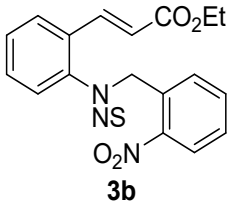
3a

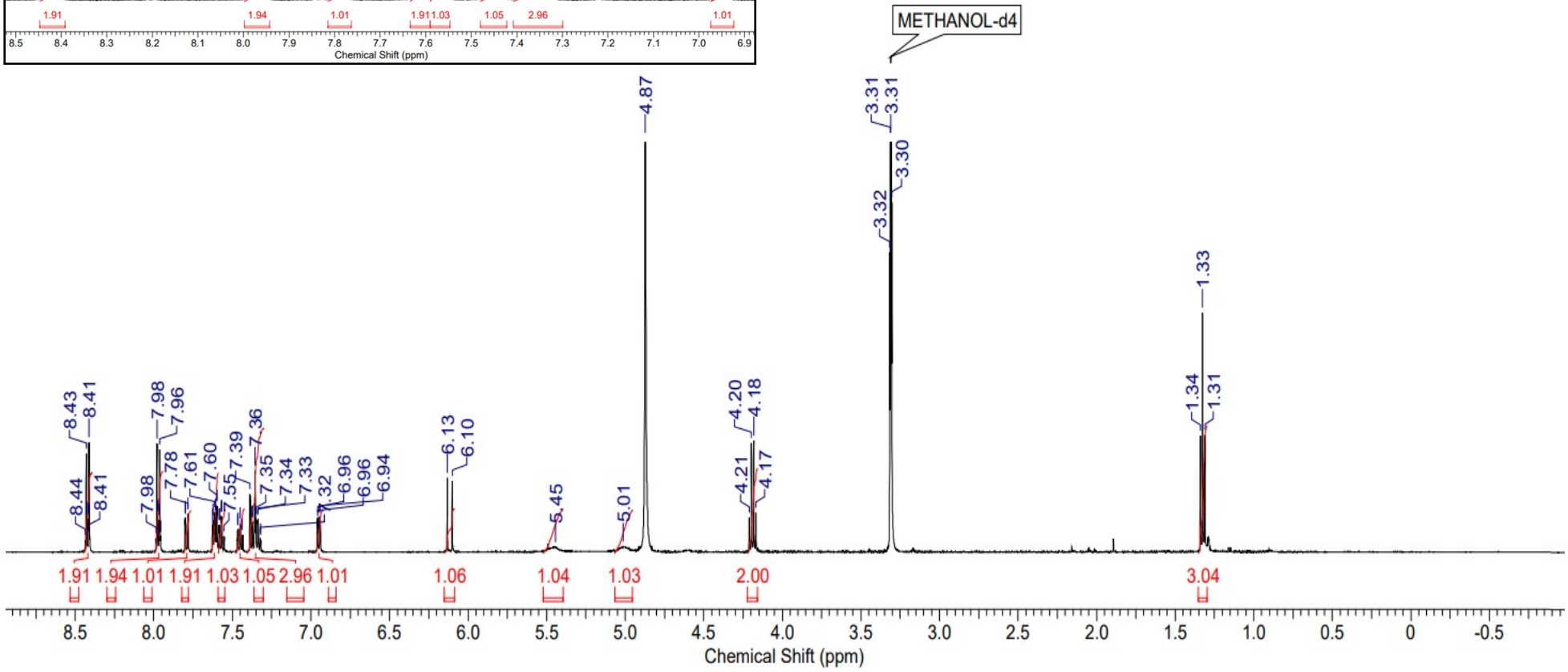


8-9. NMR Spectra of (*E*)-Ethyl 3-(2-((2-Nitrobenzyl)(thionitroso)amino)phenyl)acrylate (3b)

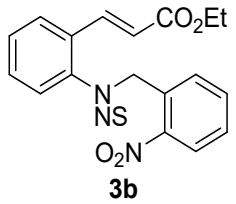
a) ^{1}H NMR Spectrum (500 MHz, MeOD)







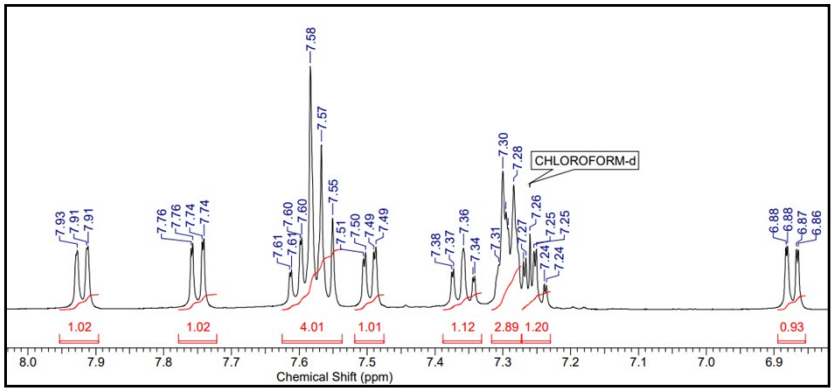
b) ^{13}C NMR Spectrum (125 MHz, MeOD)

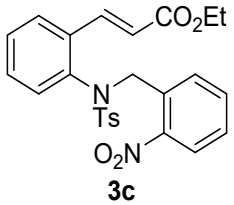


3b

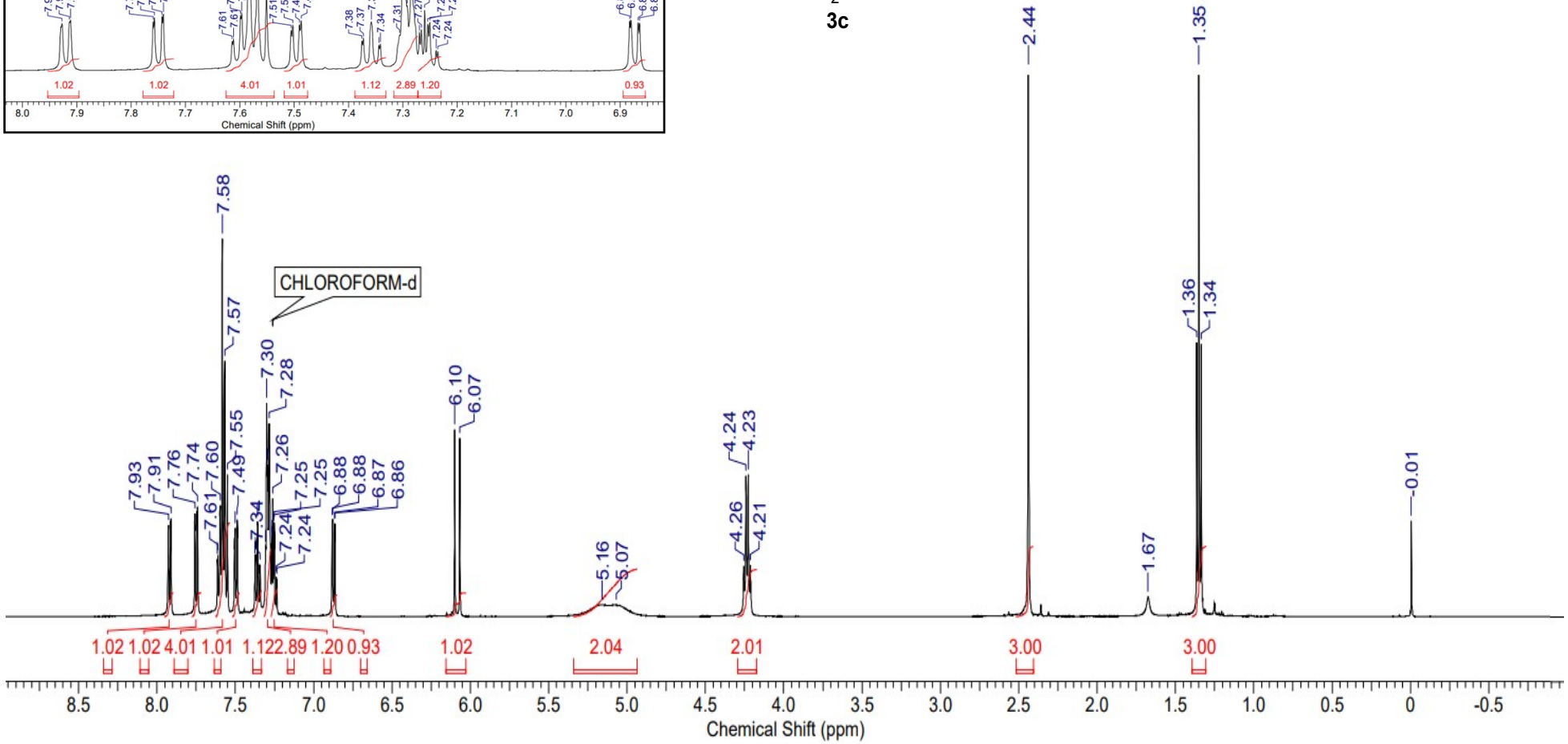
8-10. NMR Spectra of (*E*)-Ethyl 3-(2-(4-Methyl-N-(2-nitrobenzyl)phenylsulfonamido)phenyl)acrylate (3c)

a) ^{1}H NMR Spectrum (500 MHz, $CDCl_3$)

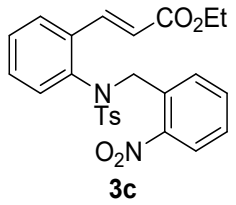




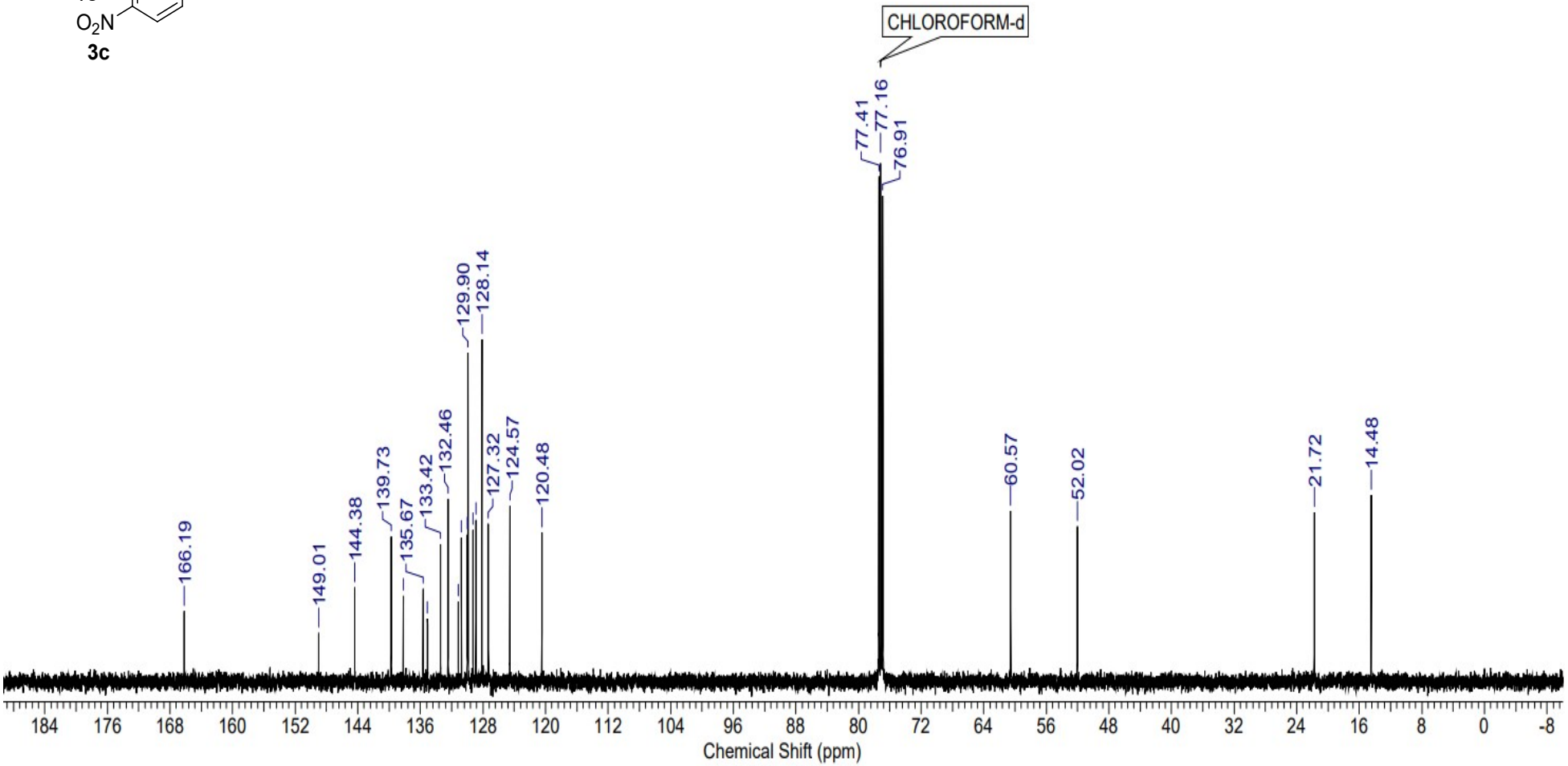
3c



b) ^{13}C NMR Spectrum (125 MHz, $CDCl_3$)

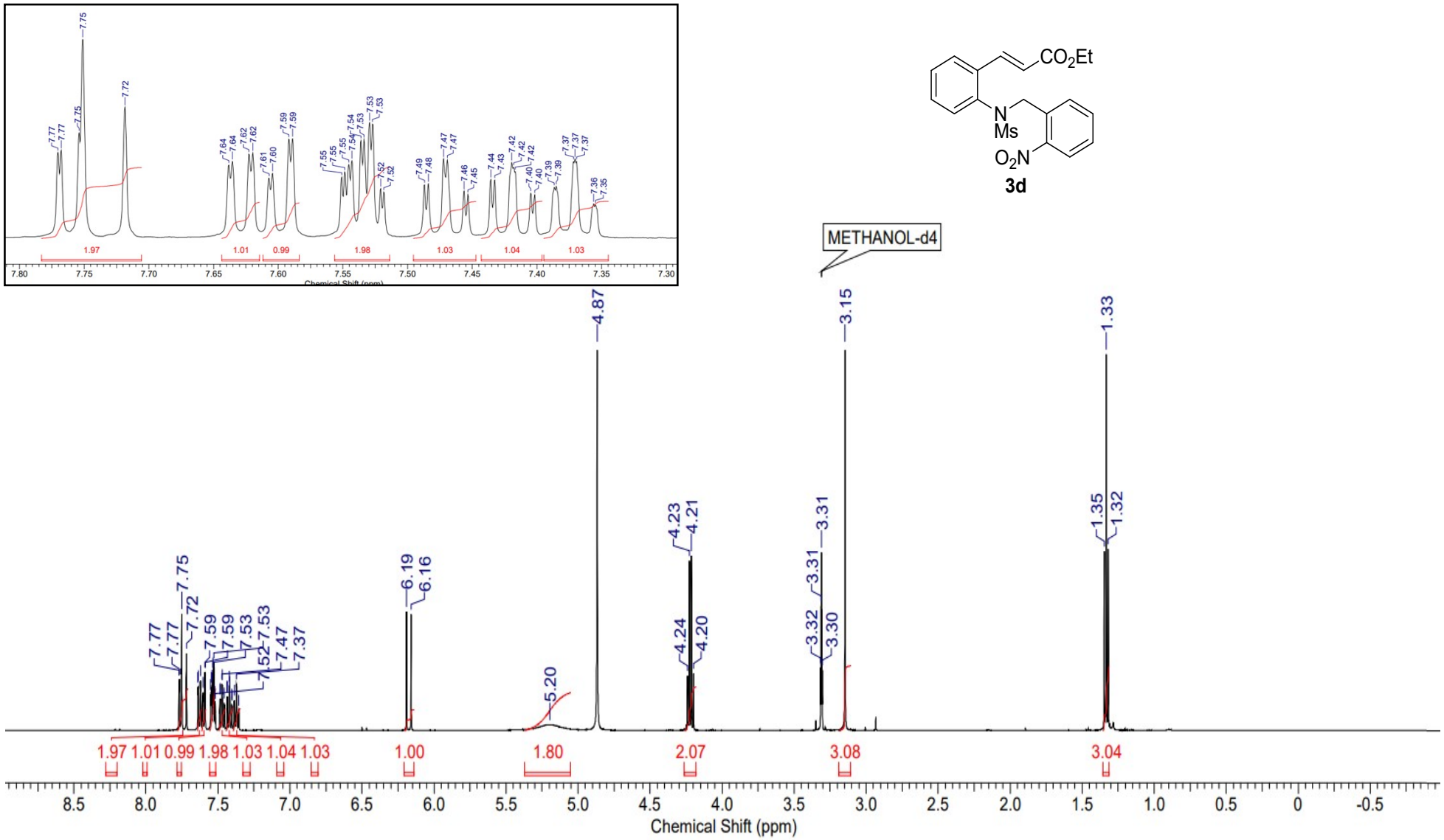


3c

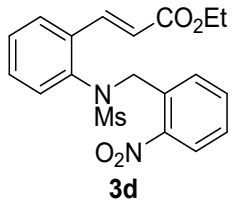


8-11. NMR Spectra of (*E*)-Ethyl 3-(2-(N-(2-Nitrobenzyl)methylsulfonamido)phenyl)acrylate (3d)

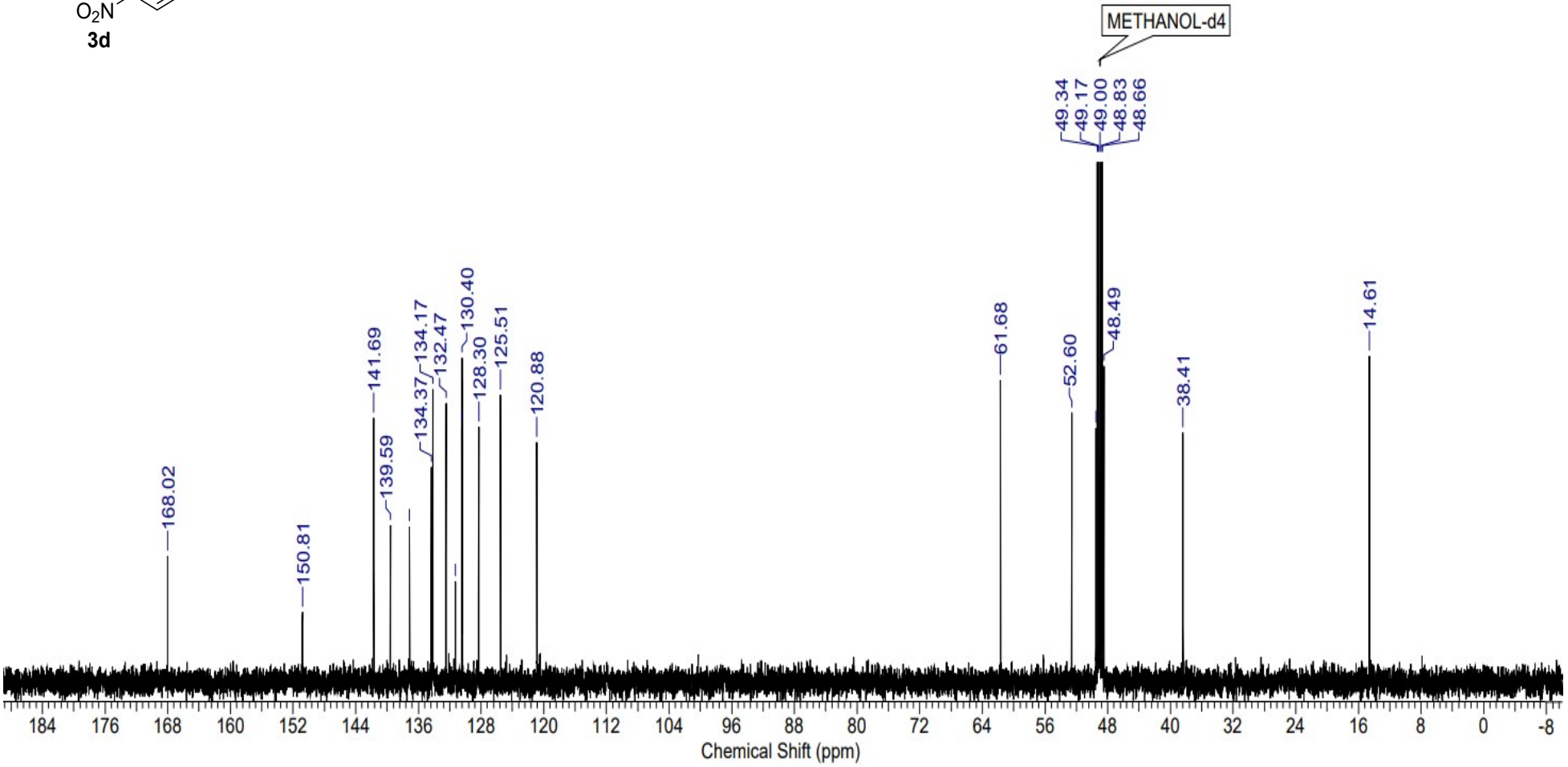
a) ^{1}H NMR Spectrum (500 MHz, $CDCl_3$)



b) ^{13}C NMR Spectrum (125 MHz, MeOD)

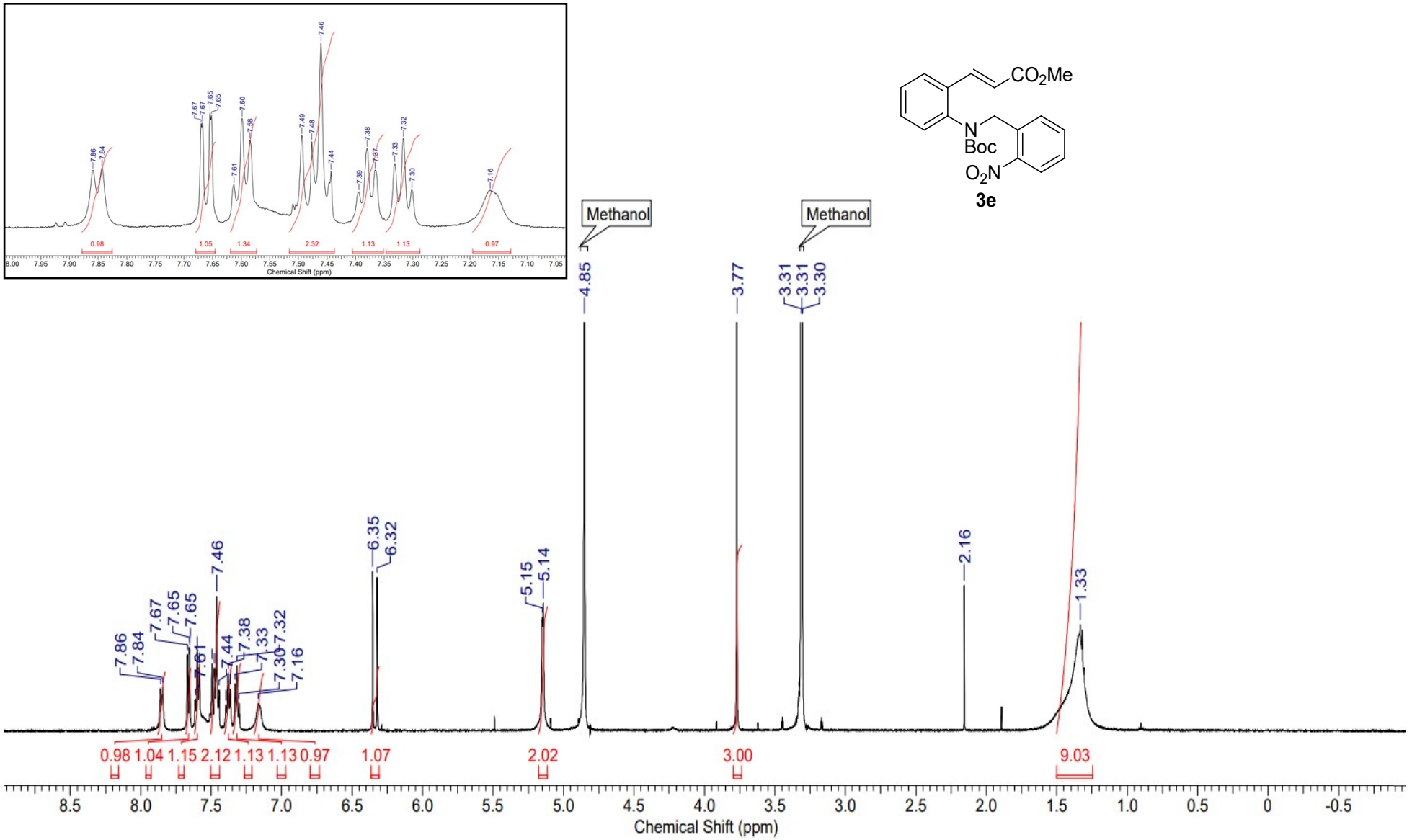


3d

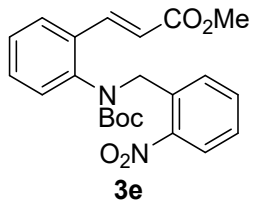


8-12. NMR Spectra of (*E*)-Methyl 3-(2-((*tert*-Butoxycarbonyl)(2-nitrobenzyl)amino)phenyl)acrylate (3e)

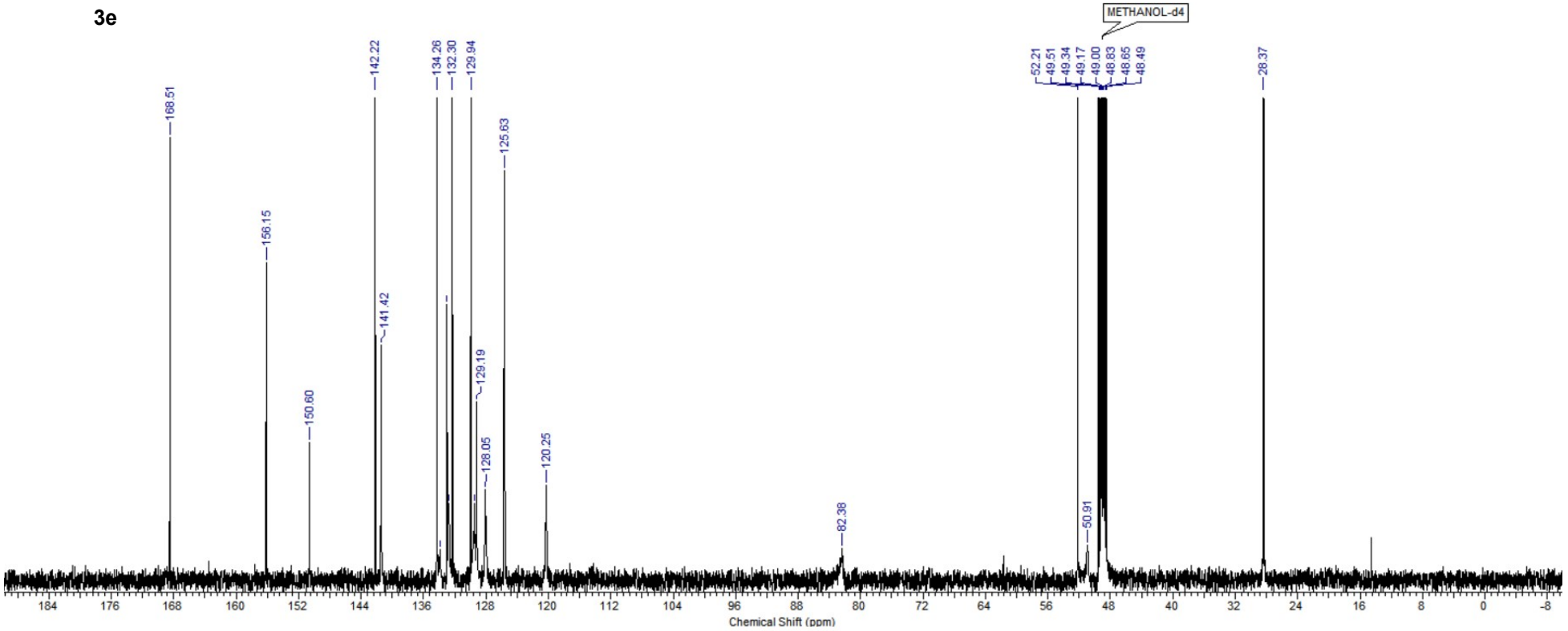
a) ^{1}H NMR Spectrum (500 MHz, MeOD)



b) ^{13}C NMR Spectrum (125 MHz, MeOD)

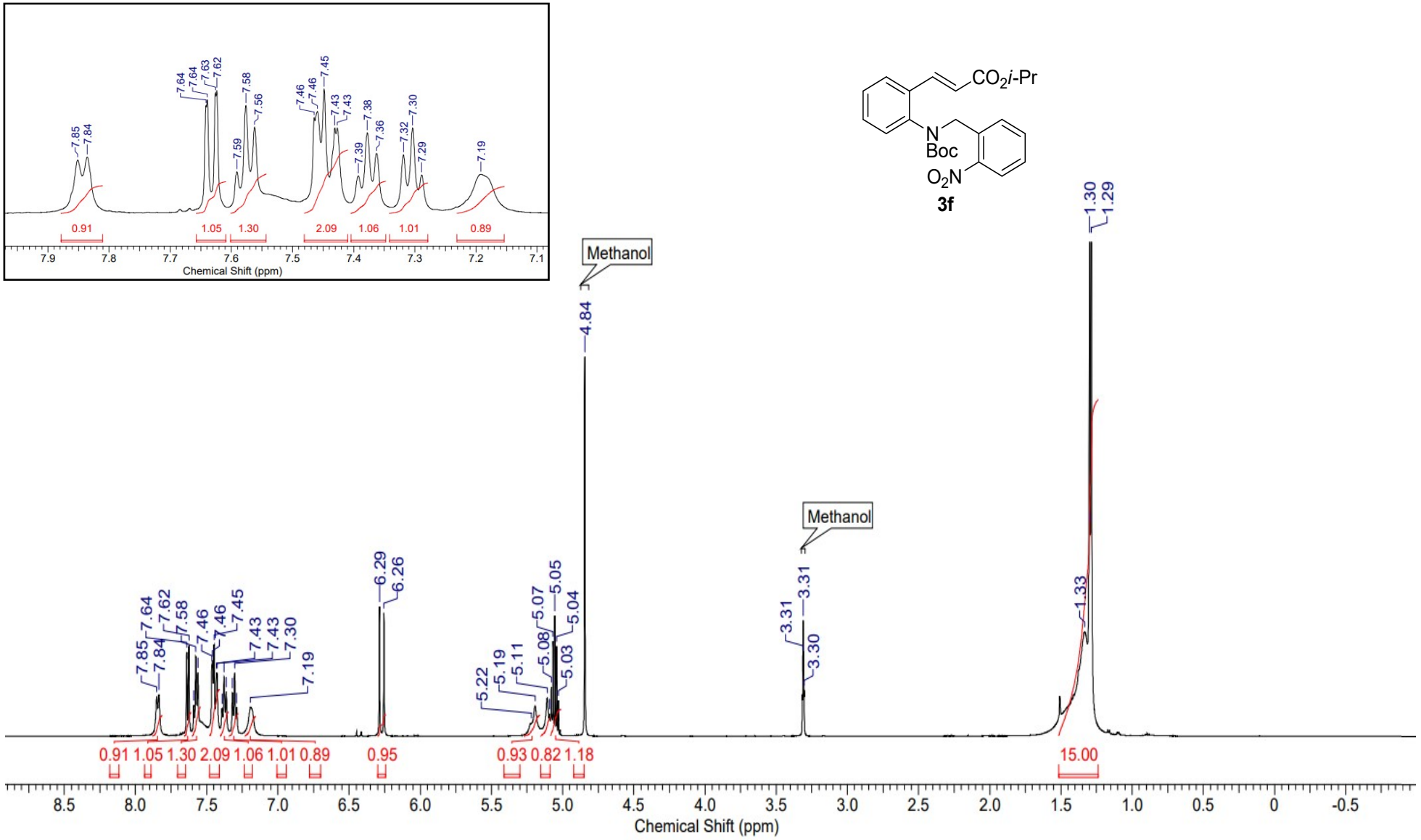


3e

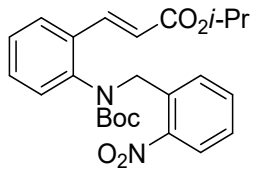


8-13. NMR Spectra of (*E*)-Isopropyl 3-(2-((*tert*-Butoxycarbonyl)(2-nitrobenzyl)amino)phenyl)acrylate (3f)

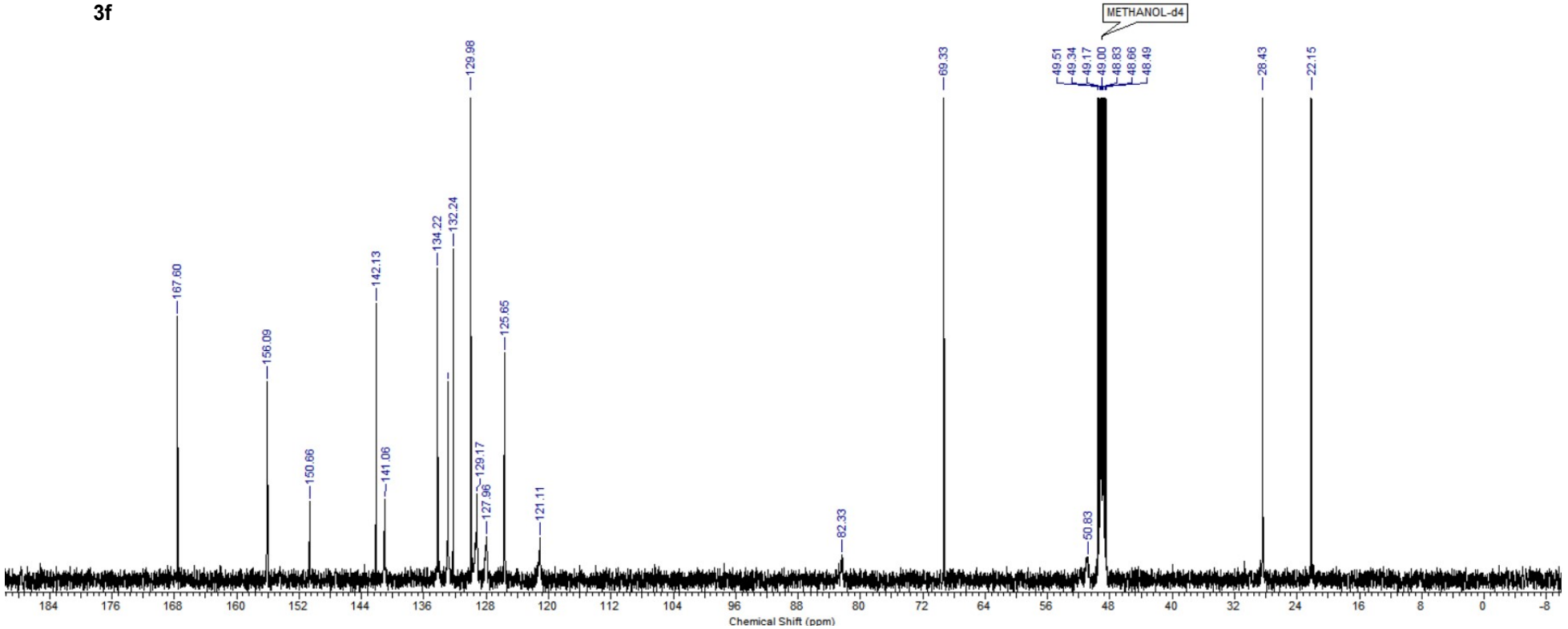
a) ^{1}H NMR Spectrum (500 MHz, MeOD)



b) ^{13}C NMR Spectrum (125 MHz, MeOD)

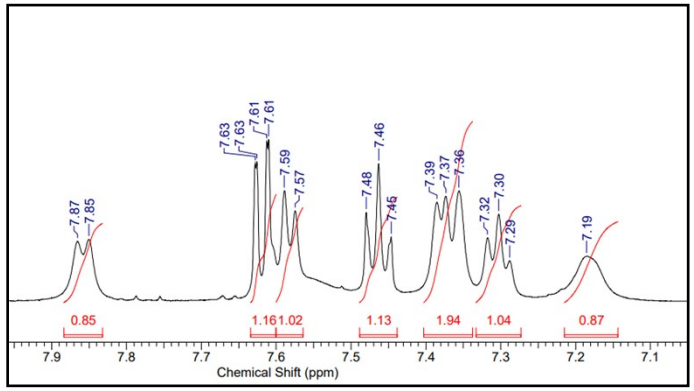


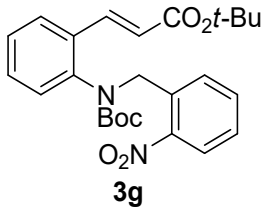
3f

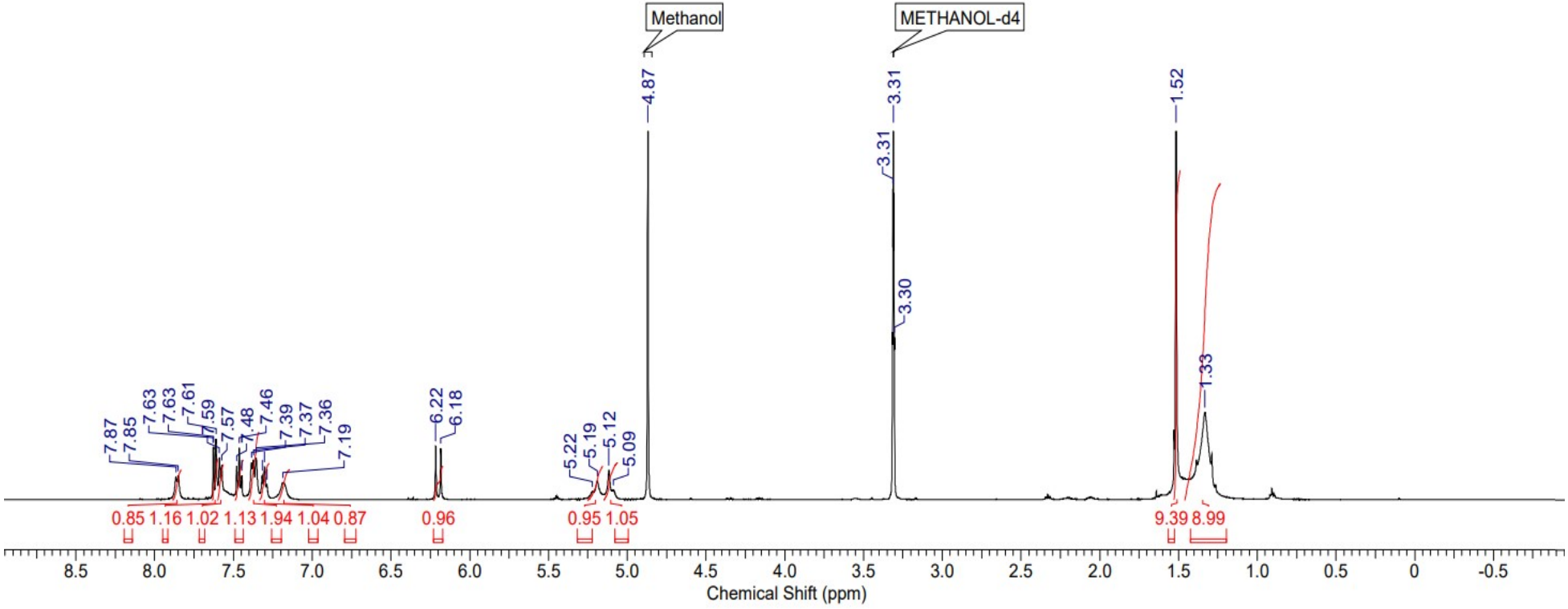


8-14. NMR Spectra of (*E*)-*tert*-Butyl 3-(2-((*tert*-Butoxycarbonyl)(2-nitrobenzyl)amino)phenyl)acrylate (3g)

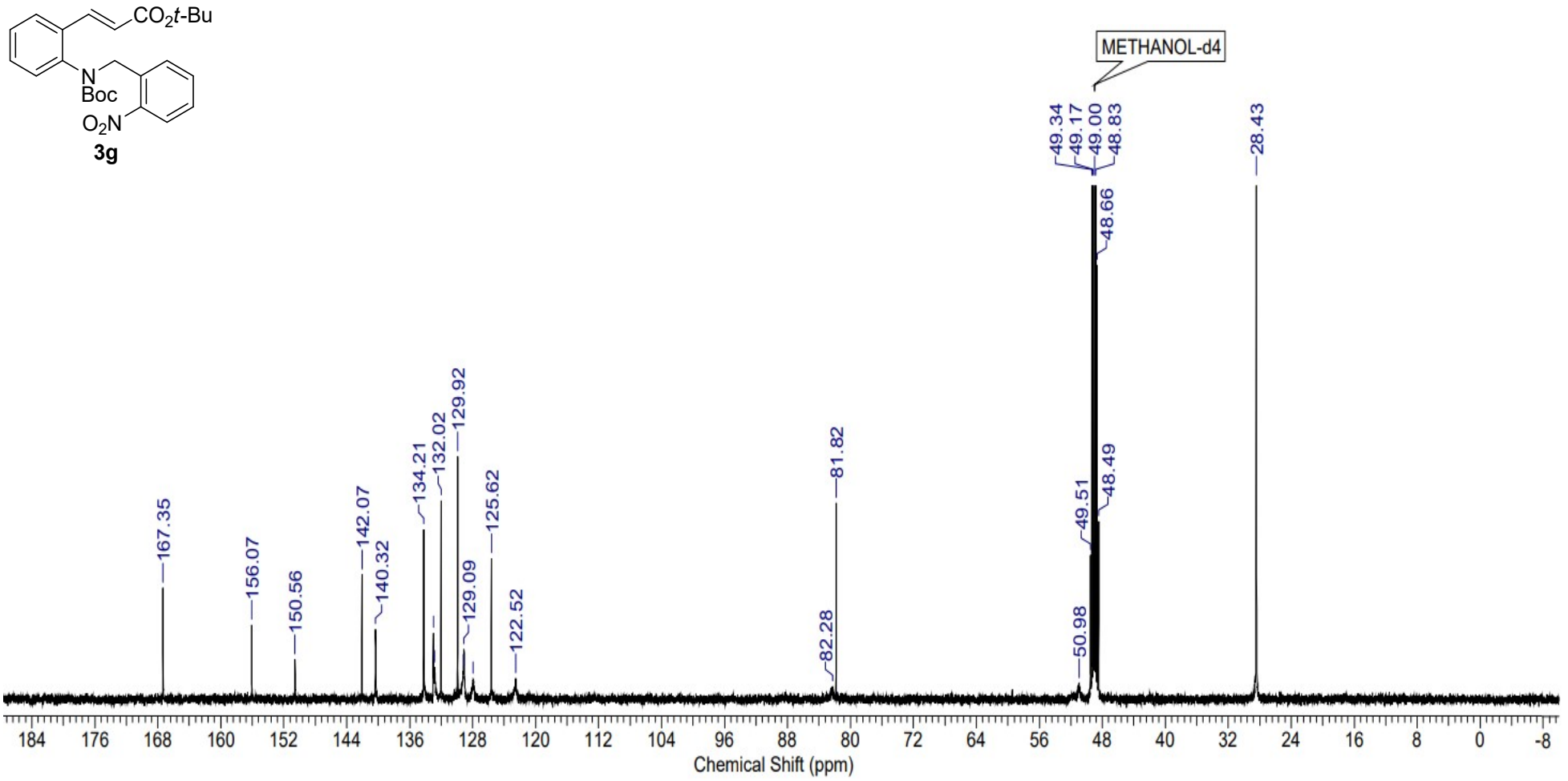
a) ^{1}H NMR Spectrum (500 MHz, MeOD)





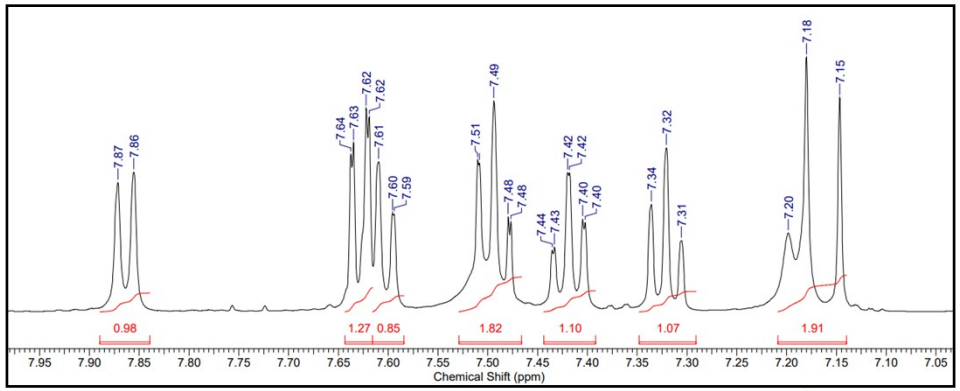


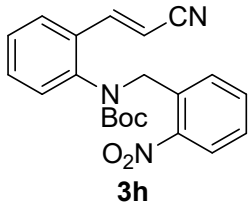
b) ^{13}C NMR Spectrum (125 MHz, MeOD)



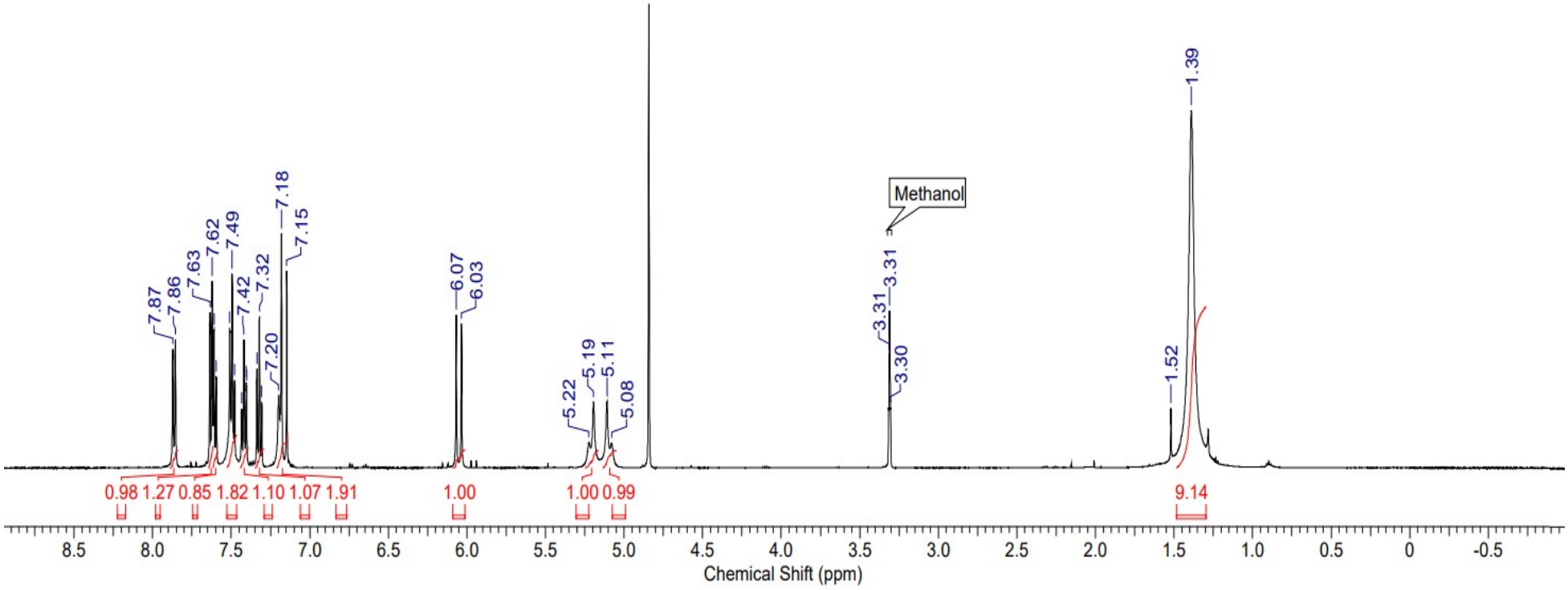
8-15. NMR Spectra of (*E*)-*tert*-Butyl (2-(2-Cyanovinyl)phenyl)(2-nitrobenzyl)carbamate (3h)

a) ^{1}H NMR Spectrum (500 MHz, MeOD)

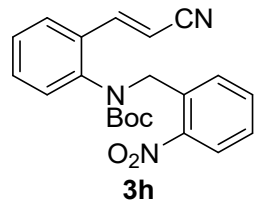




3h



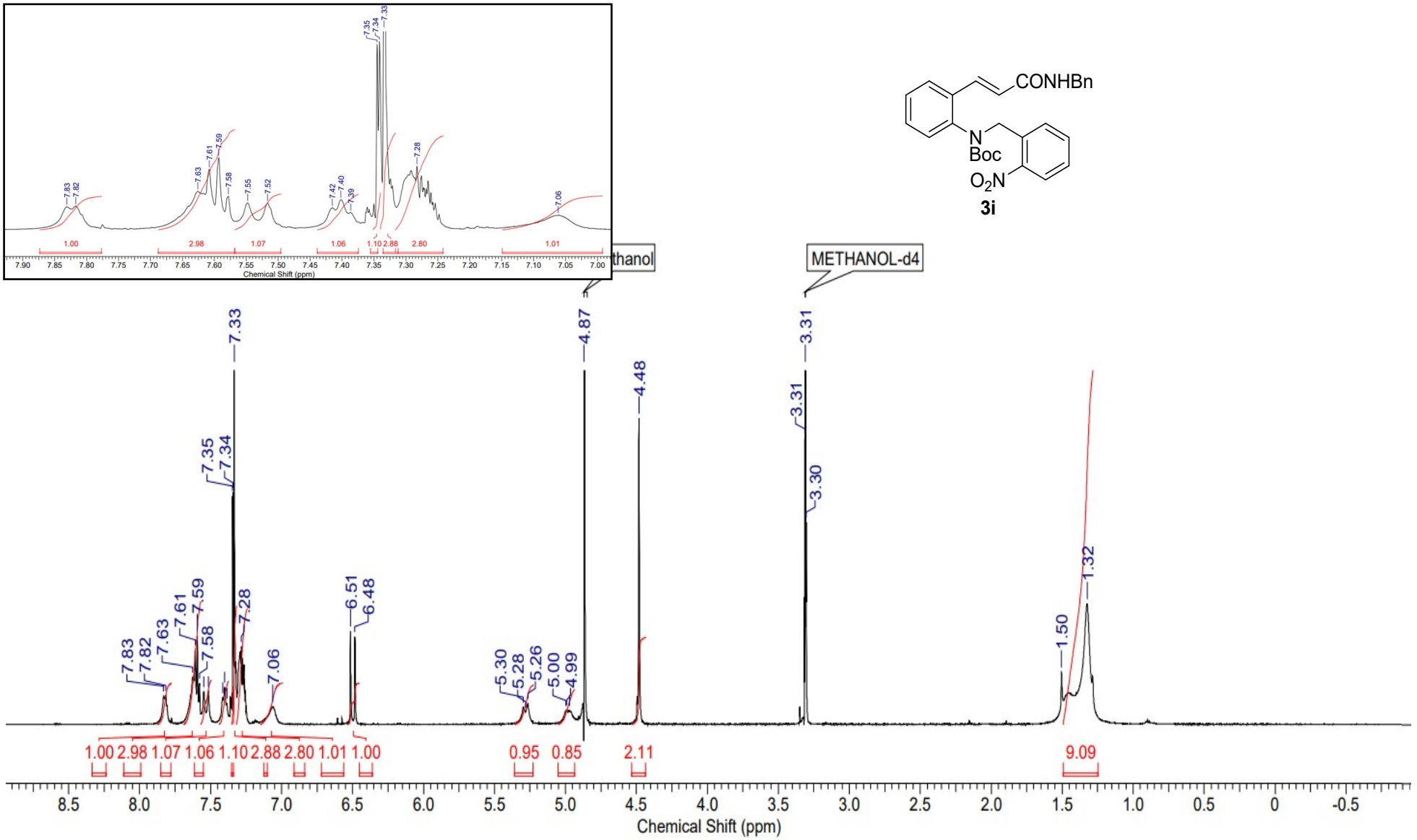
b) ^{13}C NMR Spectrum (125 MHz, MeOD)



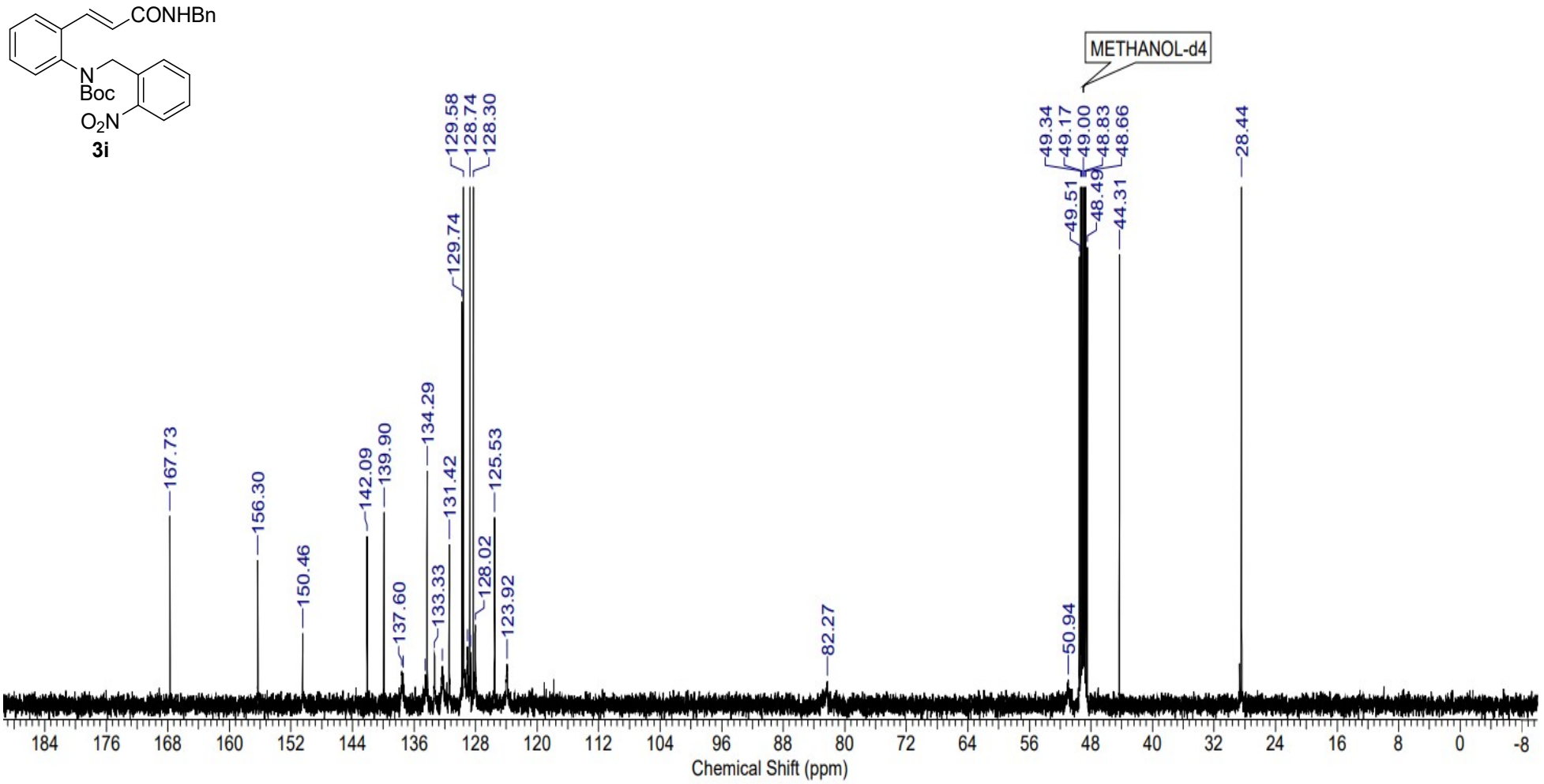
3h

8-16. NMR Spectra of (*E*)-*tert*-Butyl (2-(3-(Benzylamino)-3-oxoprop-1-en-1-yl)phenyl)(2-nitrobenzyl)carbamate (3i)

a) ^{1}H NMR Spectrum (500 MHz, MeOD)

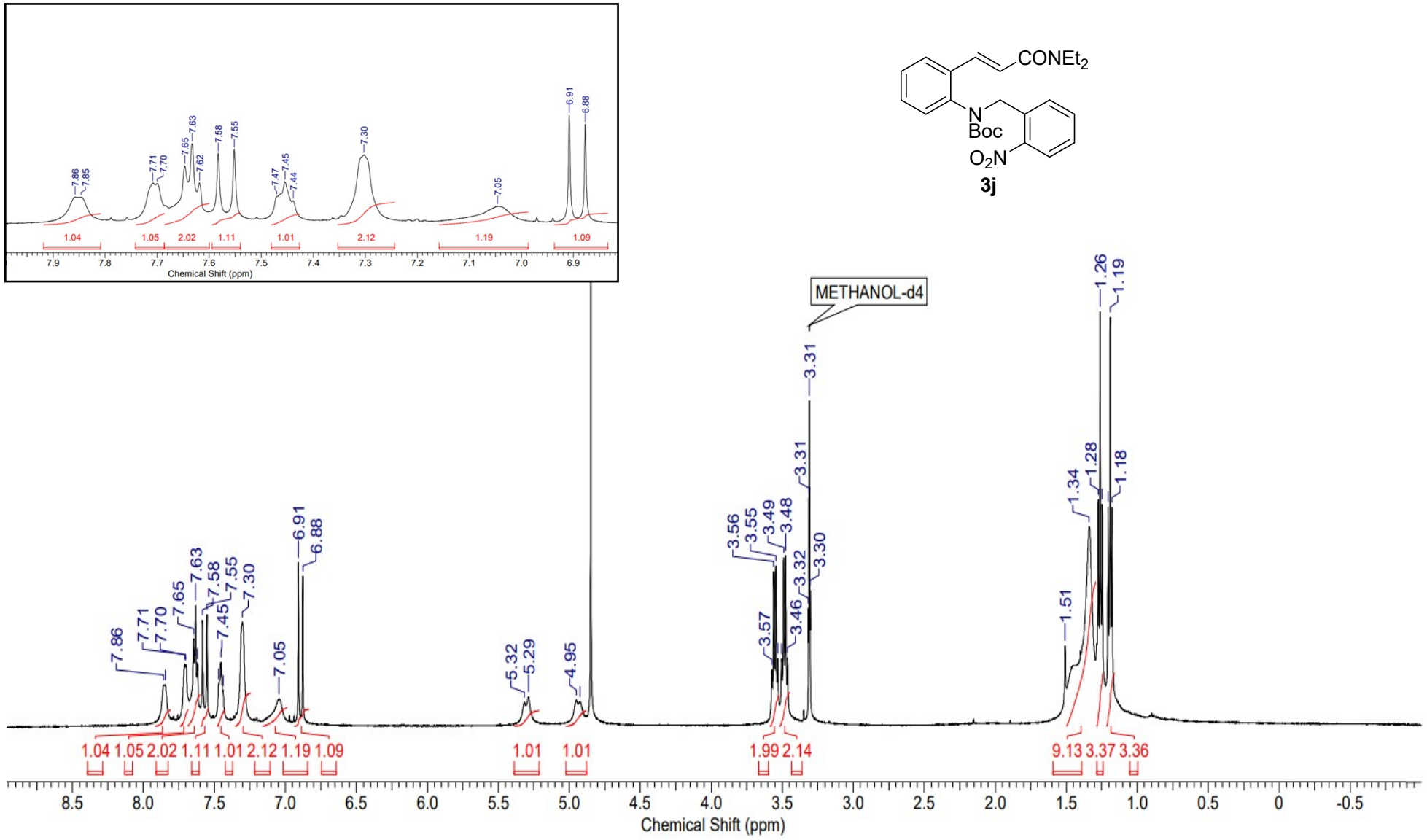


b) ^{13}C NMR Spectrum (125 MHz, MeOD)

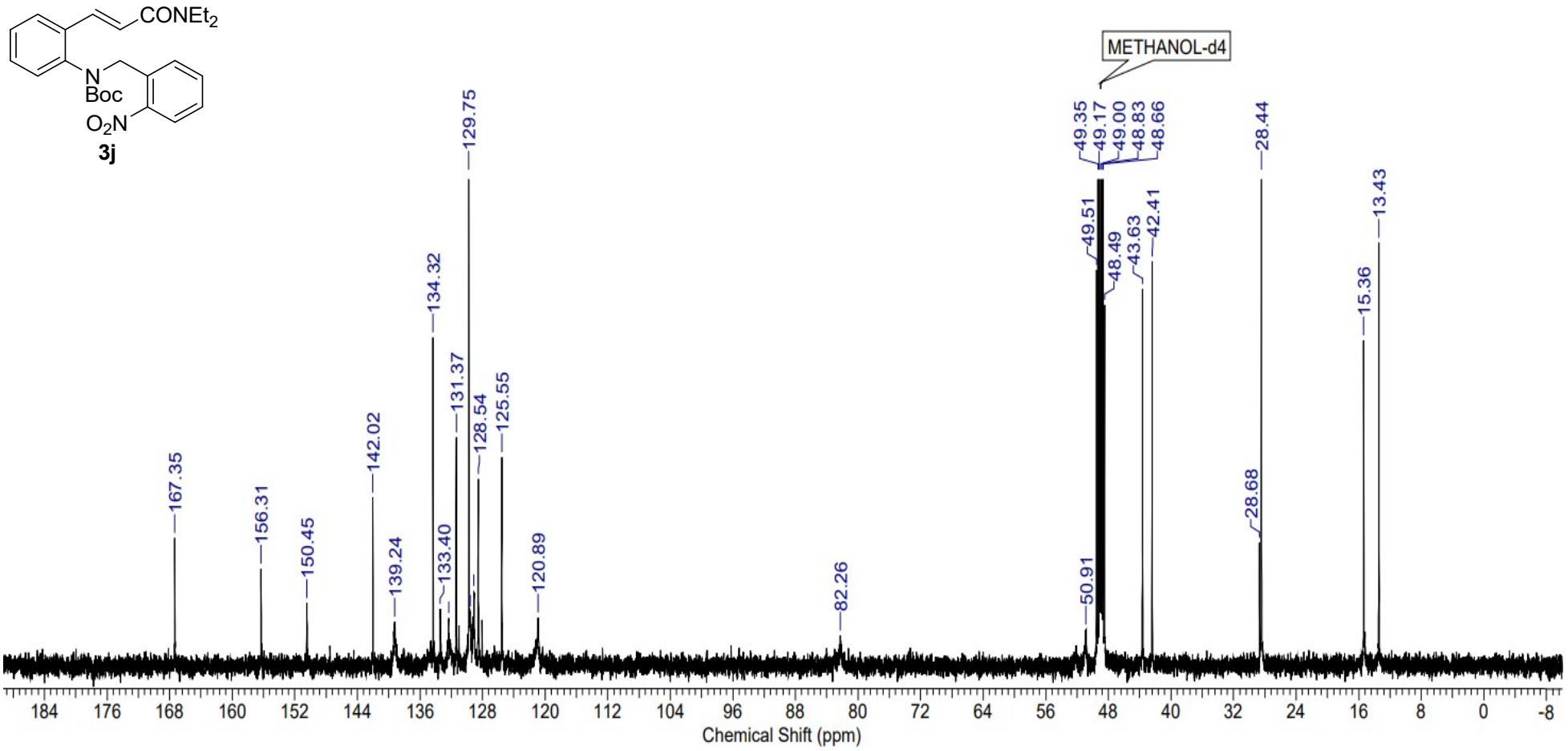


8-17. NMR Spectra of (*E*)-*tert*-Butyl (2-(3-(Diethylamino)-3-oxoprop-1-en-1-yl)phenyl)(2-nitrobenzyl)carbamate (3j)

a) ^{1}H NMR Spectrum (500 MHz, MeOD)

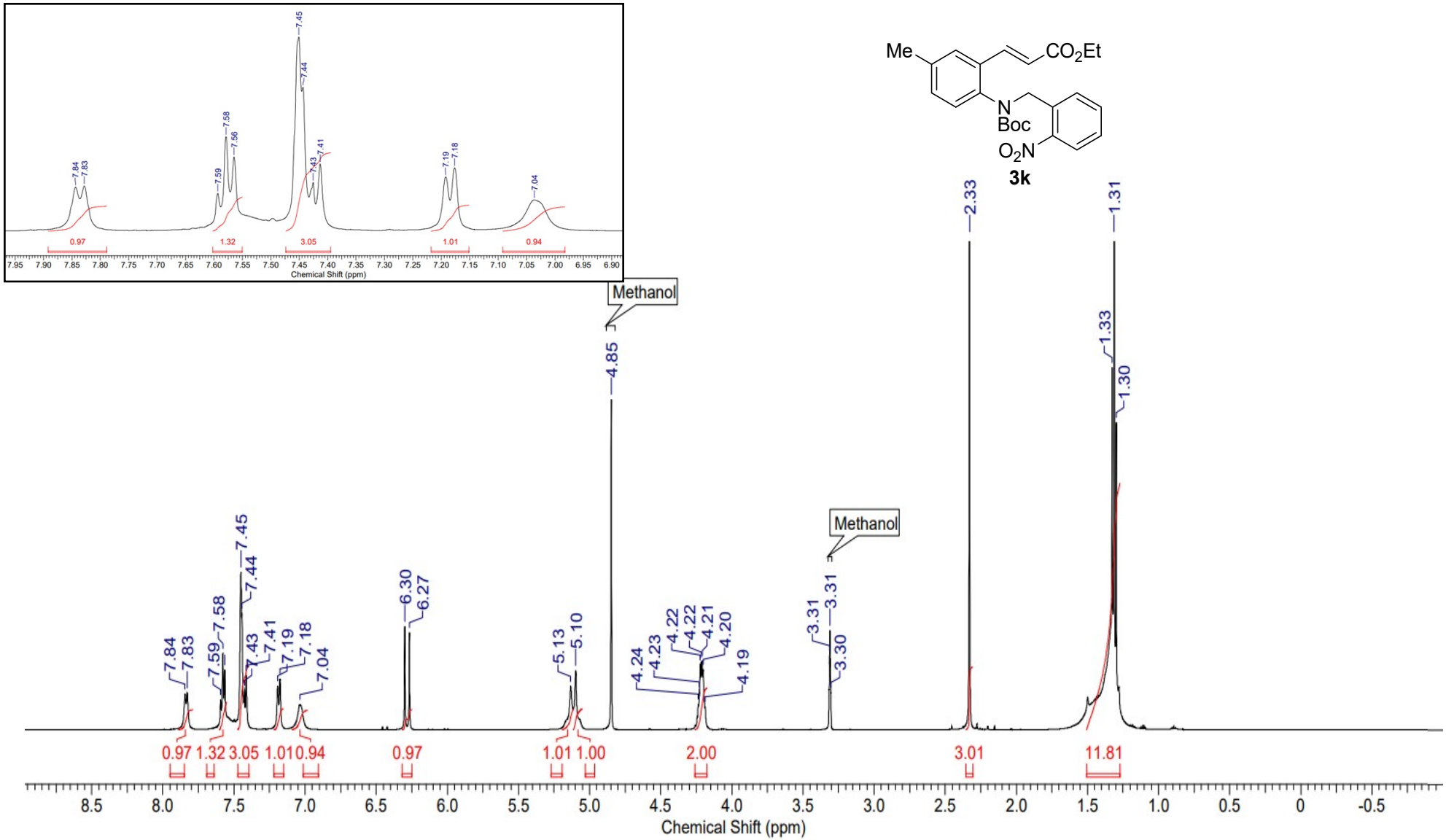


b) ^{13}C NMR Spectrum (125 MHz, MeOD)

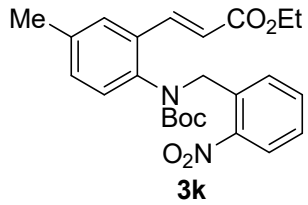


8-18. NMR Spectra of (*E*)-Ethyl 3-(2-((*tert*-Butoxycarbonyl)(2-nitrobenzyl)amino)-5-methylphenyl)acrylate (3k)

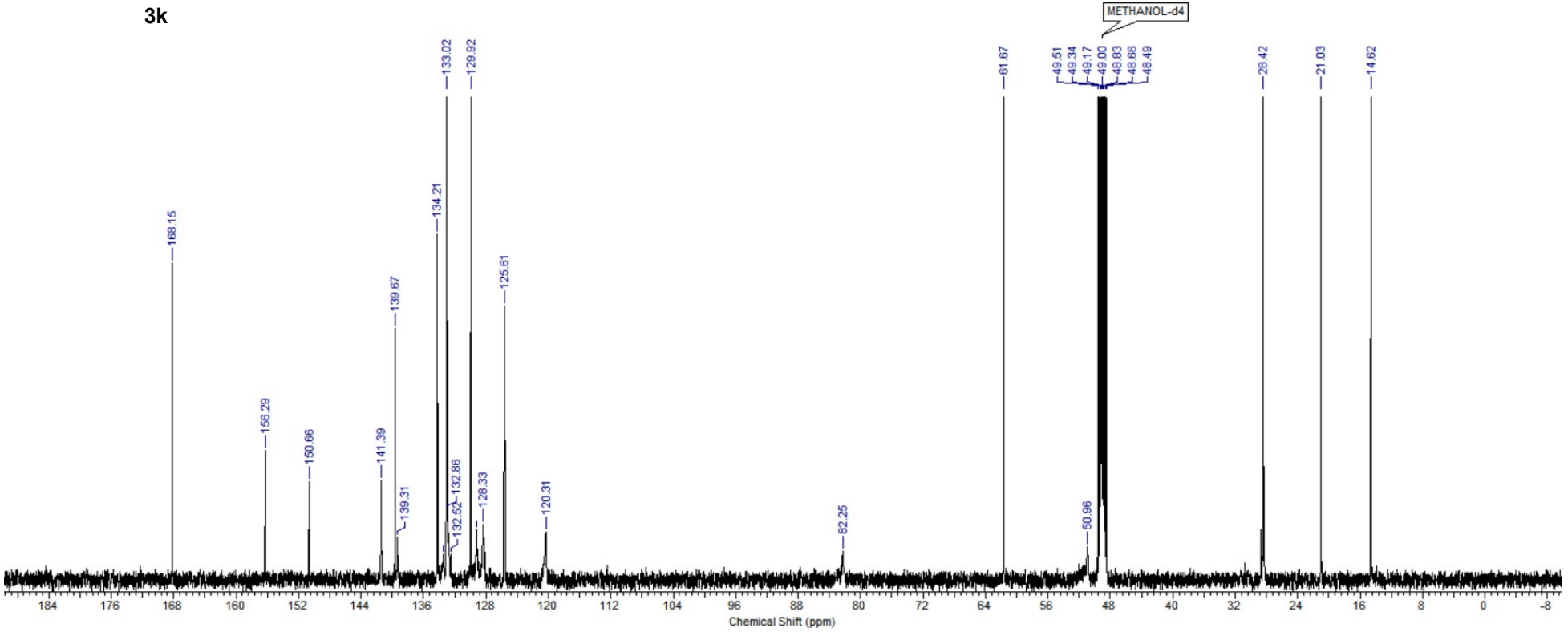
a) ^{1}H NMR Spectrum (500 MHz, MeOD)



b) ^{13}C NMR Spectrum (125 MHz, MeOD)

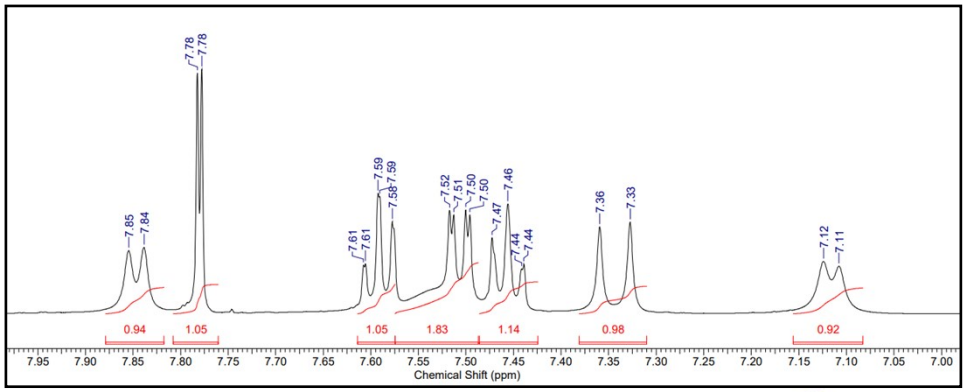


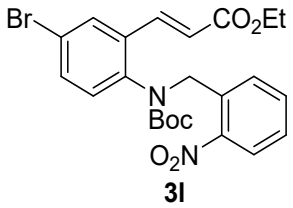
3k

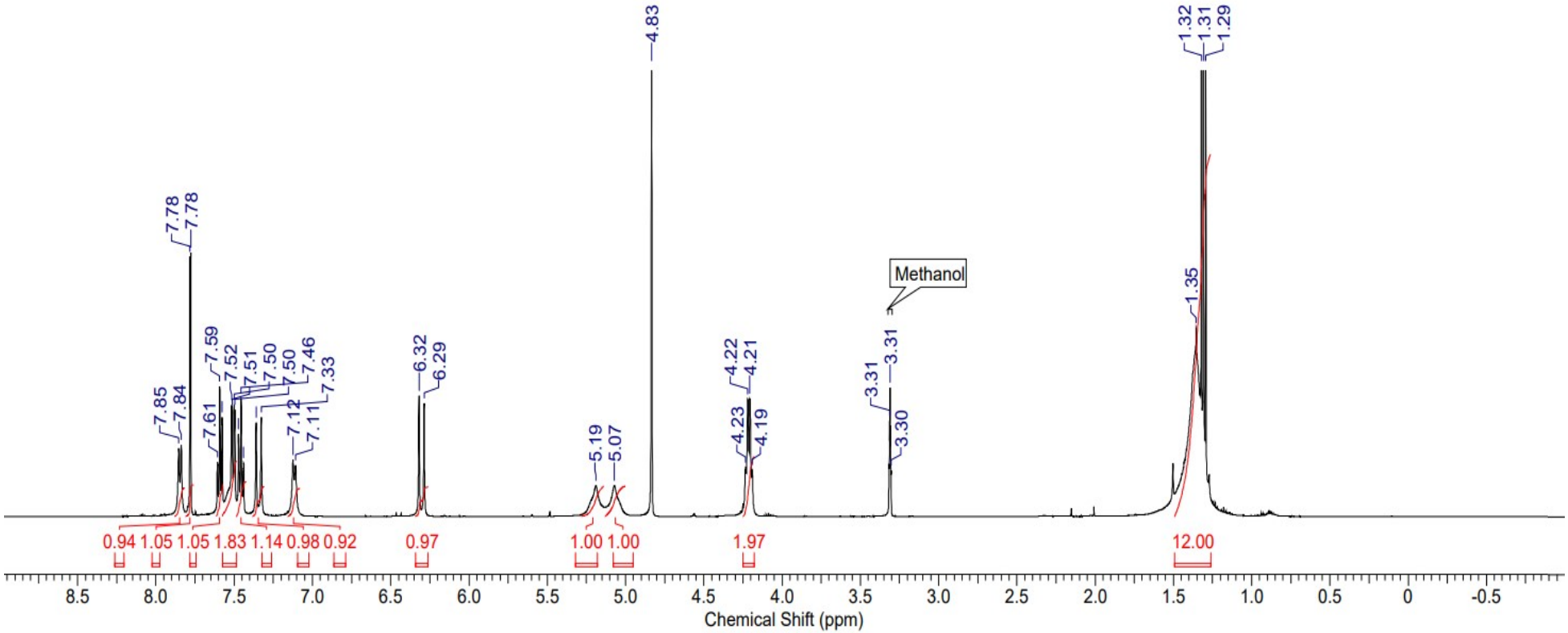


8-19. NMR Spectra of *(E)*-Ethyl 3-(5-Bromo-2-((*tert*-butoxycarbonyl)(2-nitrobenzyl)amino)phenyl)acrylate (3l)

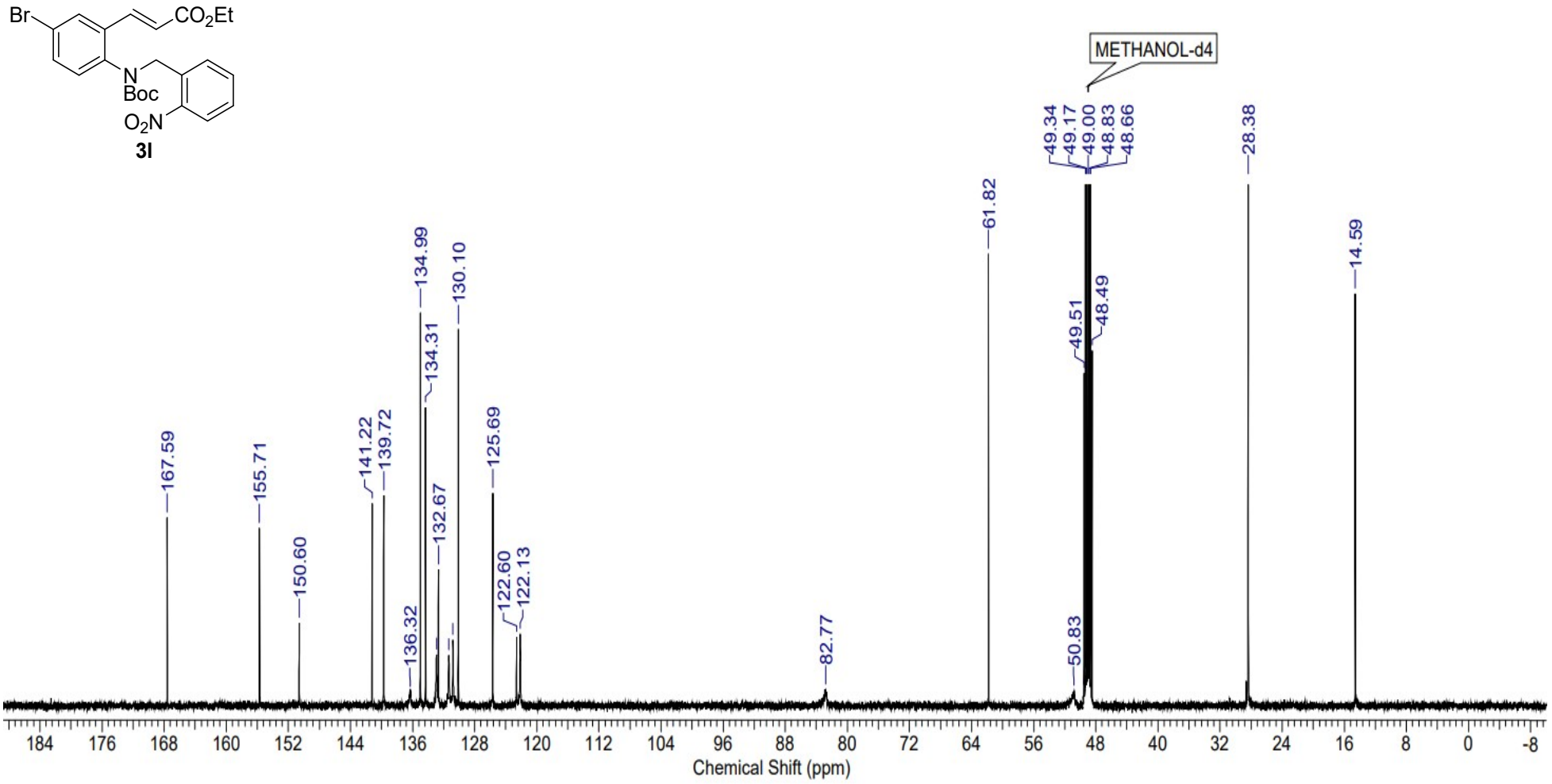
a) ^{1}H NMR Spectrum (500 MHz, MeOD)





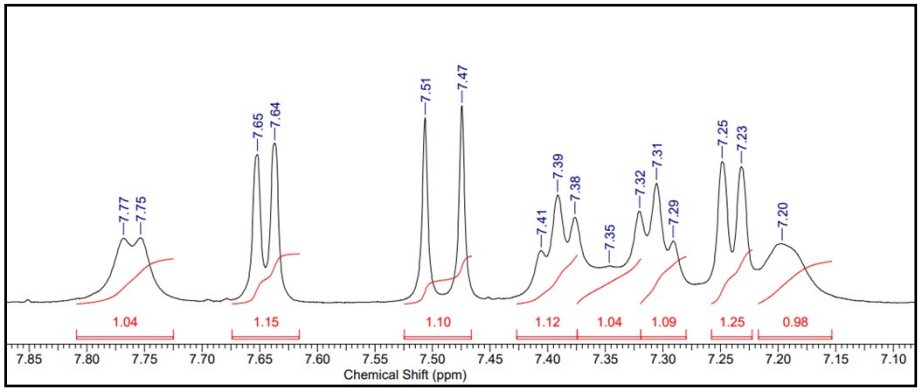


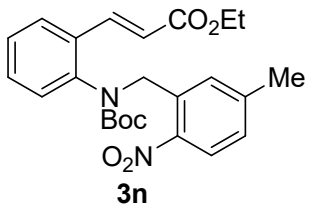
b) ^{13}C NMR Spectrum (125 MHz, MeOD)

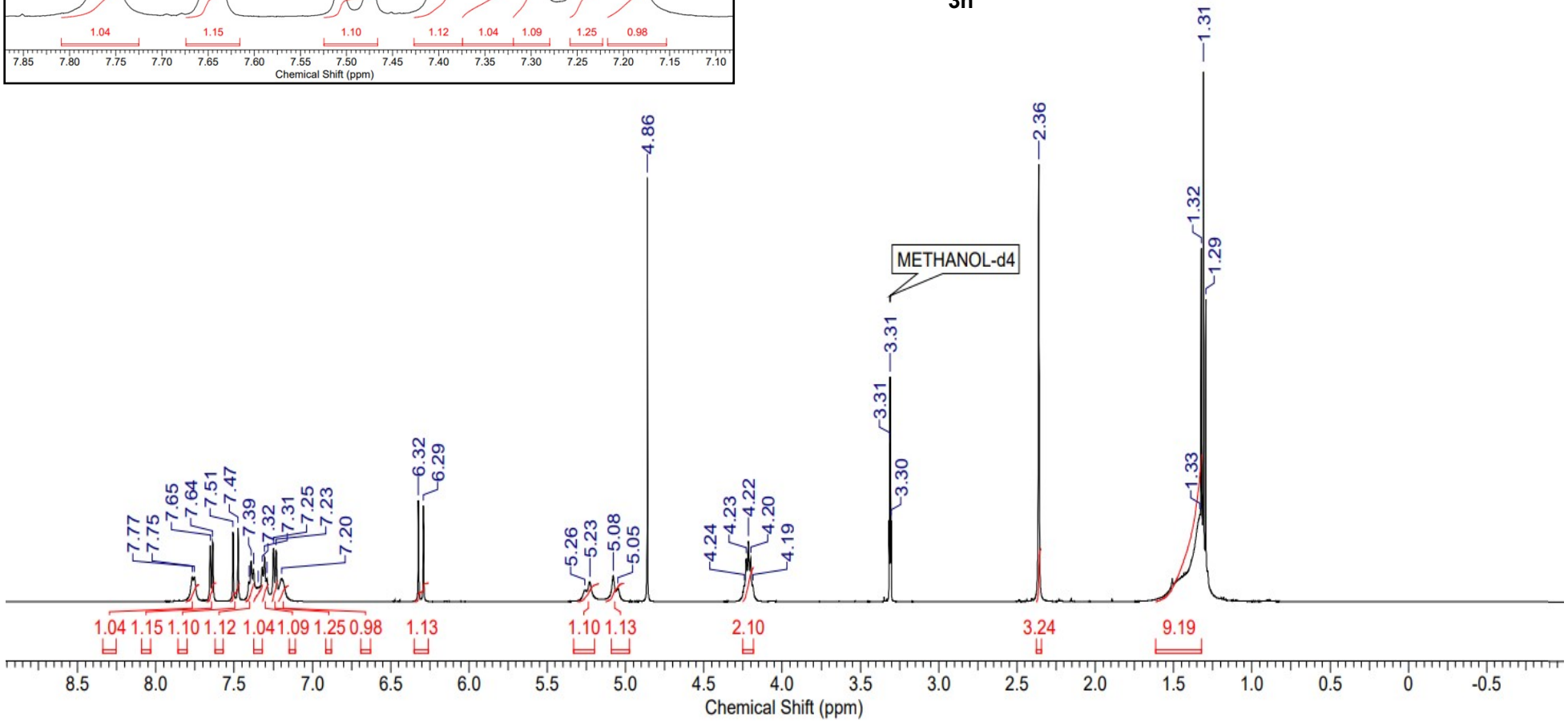


8-20. NMR Spectra of (*E*)-Ethyl 3-(2-((*tert*-Butoxycarbonyl)(5-methyl-2-nitrobenzyl)amino)phenyl)acrylate (3n)

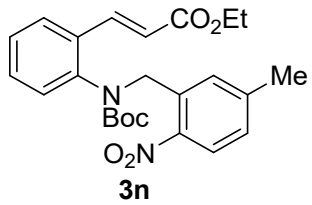
a) ^{1}H NMR Spectrum (500 MHz, MeOD)



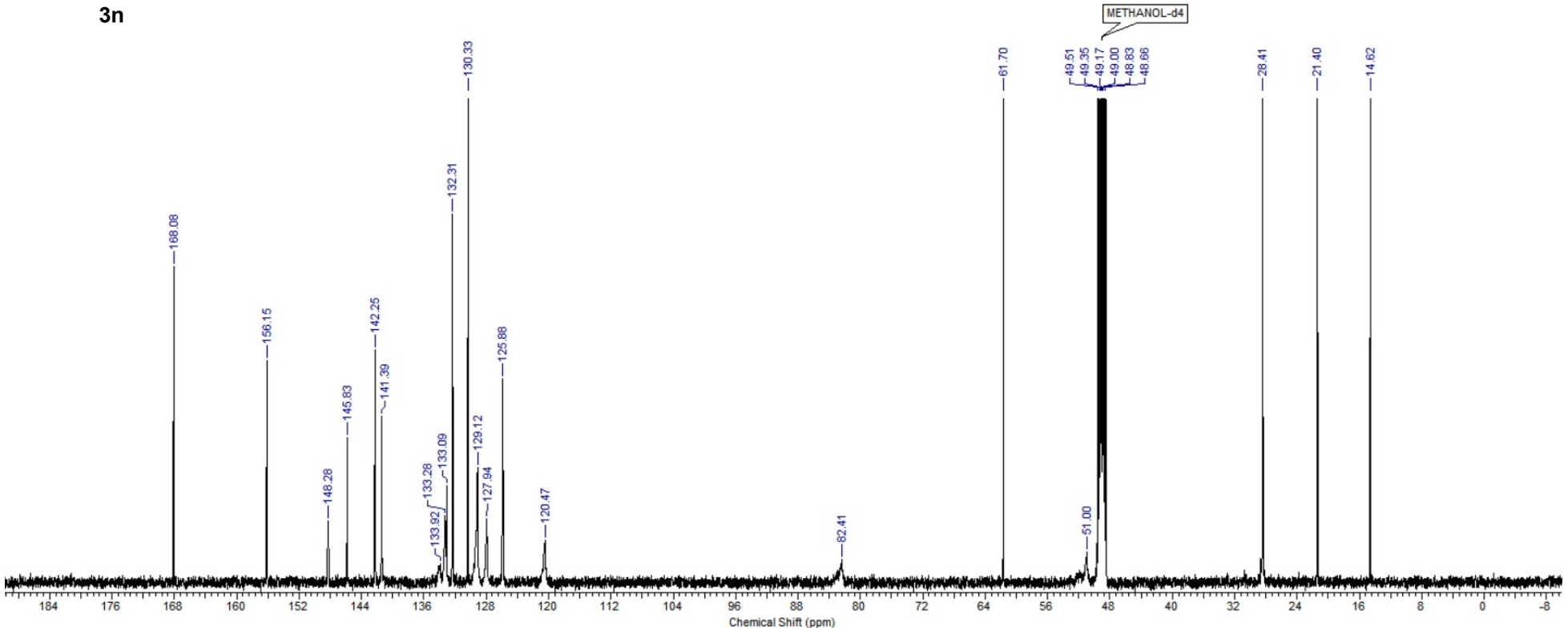




b) ^{13}C NMR Spectrum (125 MHz, MeOD)

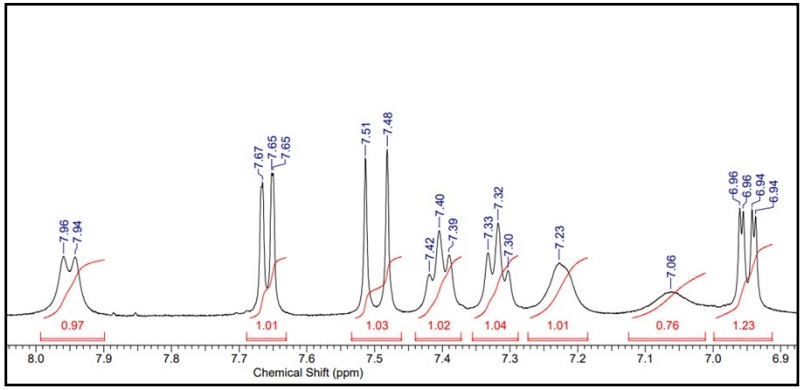


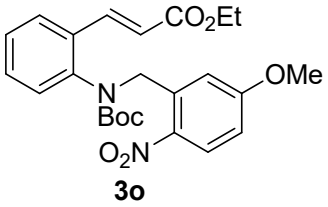
3n



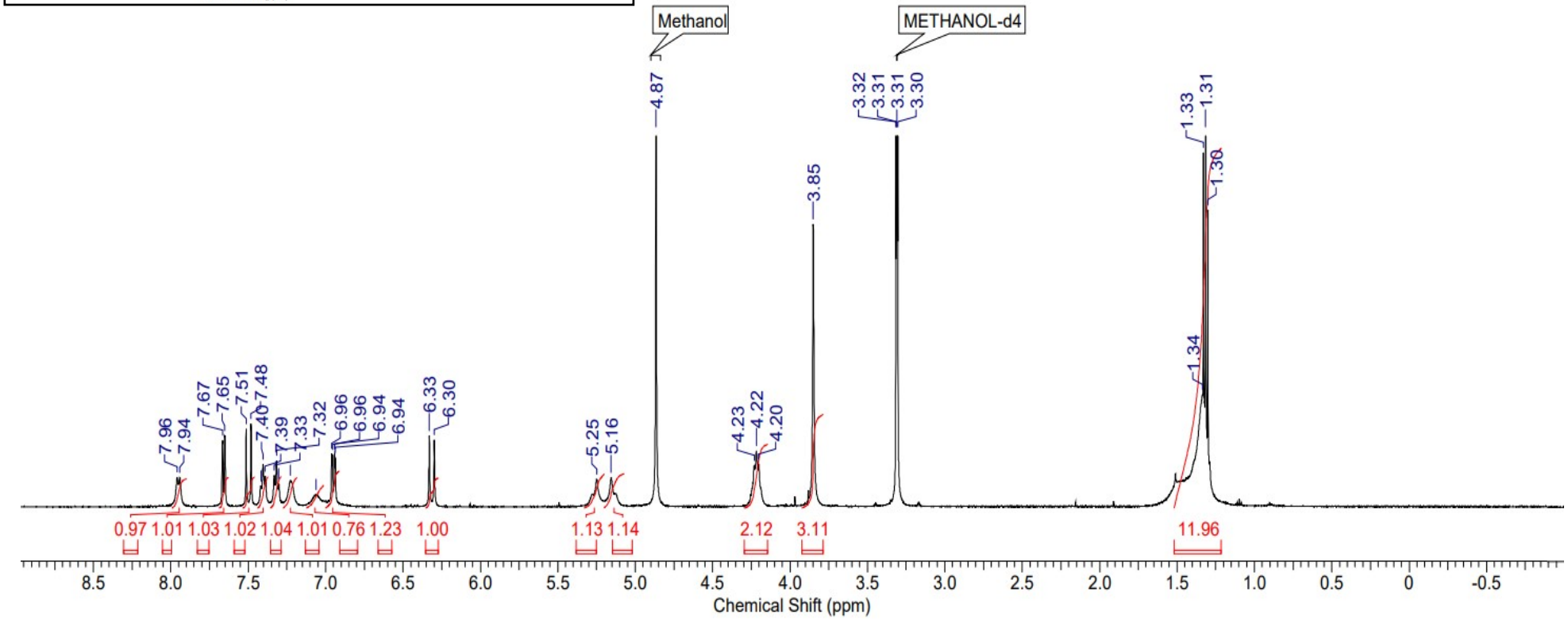
8-21. NMR Spectra of (*E*)-Ethyl 3-(2-((*tert*-Butoxycarbonyl)(5-methoxy-2-nitrobenzyl)amino)phenyl)acrylate (3o)

a) ^{1}H NMR Spectrum (500 MHz, MeOD)

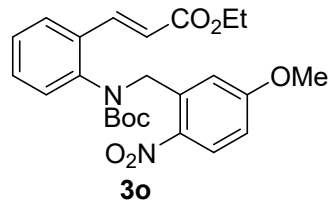




3o



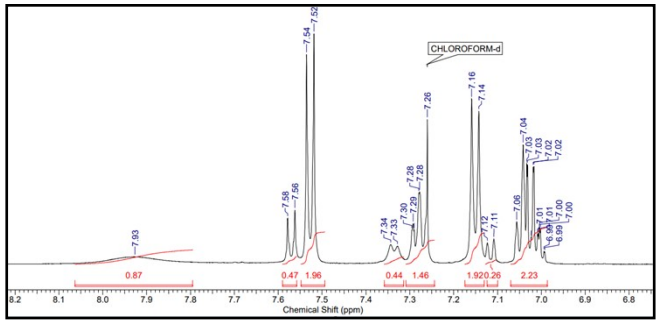
b) ^{13}C NMR Spectrum (125 MHz, MeOD)

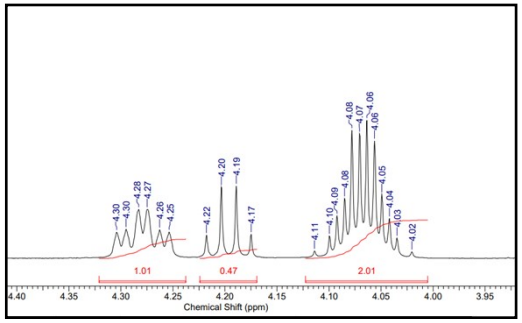


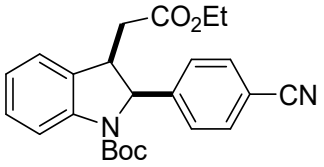
3o

8-22. NMR Spectra of *tert*-Butyl 2-(4-Cyanophenyl)-3-(2-ethoxy-2-oxoethyl)indoline-1-carboxylate (2c)

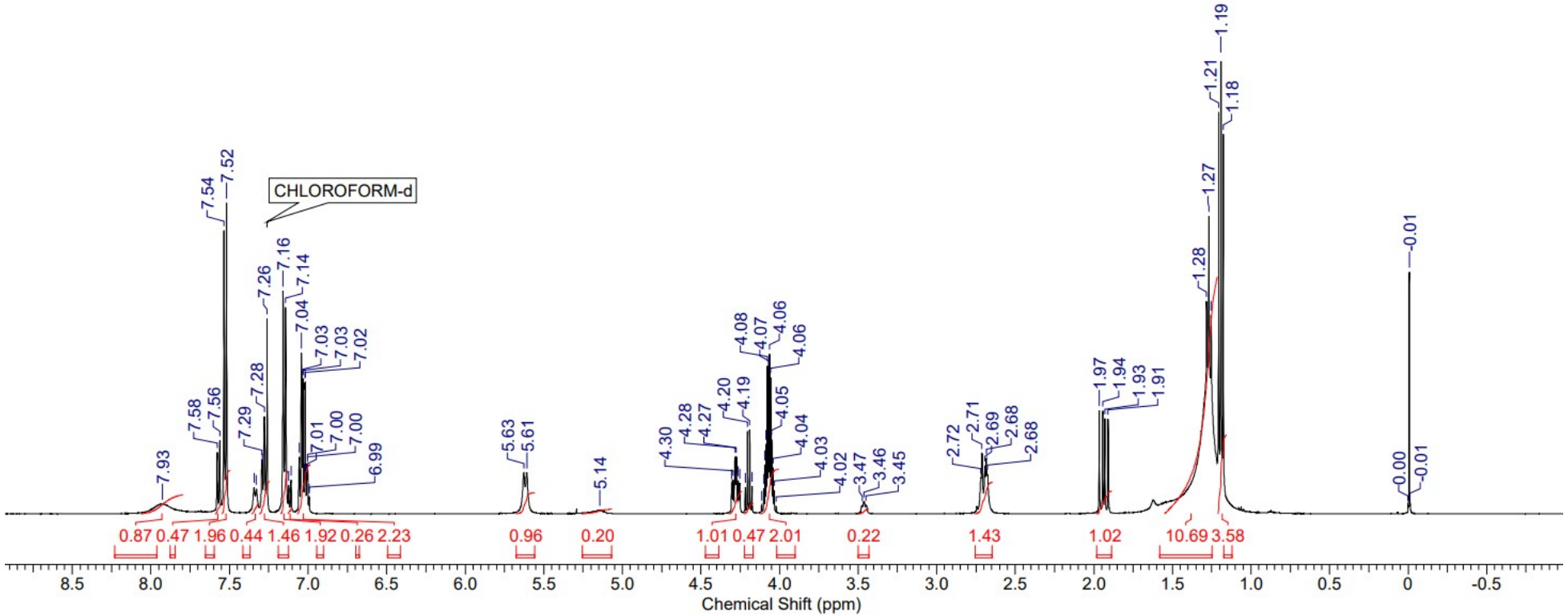
a) ^{1}H NMR Spectrum (500 MHz, $CDCl_3$)



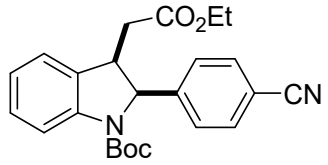




2c



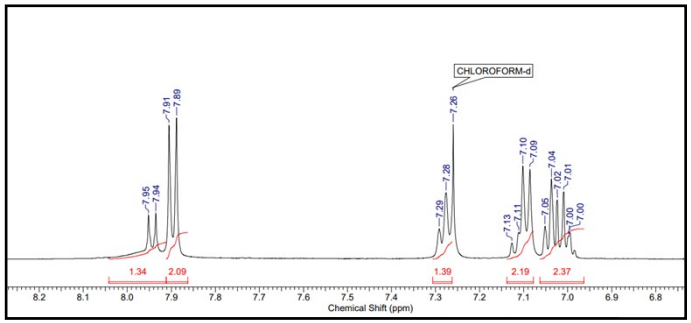
b) ^{13}C NMR Spectrum (125 MHz, $CDCl_3$)

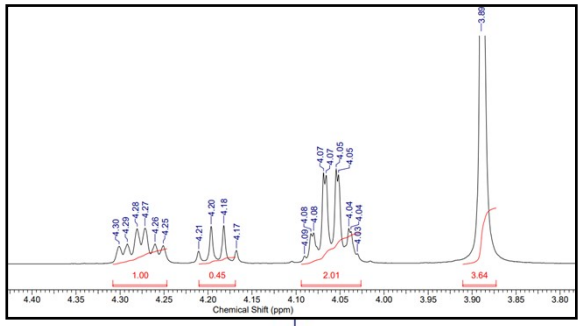


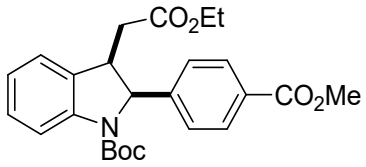
2c

8-23. NMR Spectra of *tert*-Butyl 3-(2-Ethoxy-2-oxoethyl)-2-(4-(methoxycarbonyl)phenyl)indoline-1-carboxylate (2d)

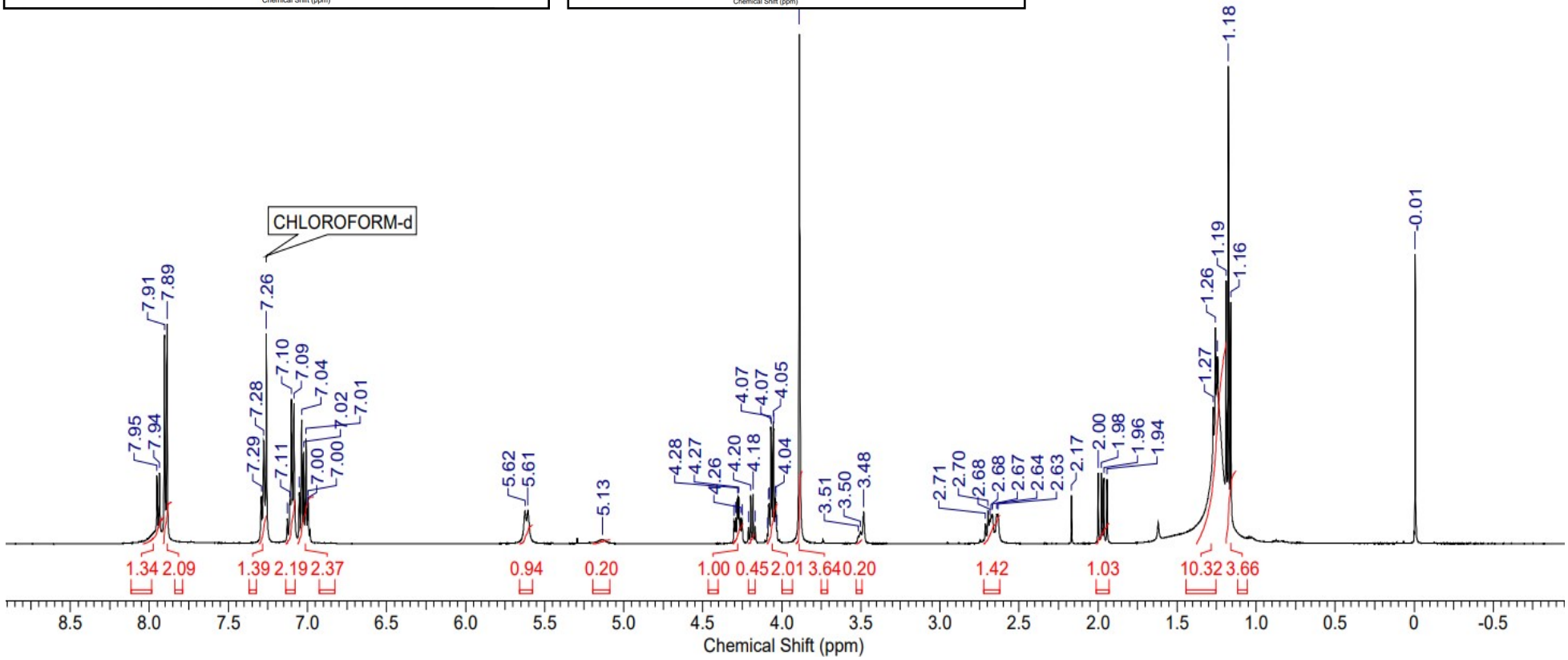
a) ^{1}H NMR Spectrum (500 MHz, $CDCl_3$)



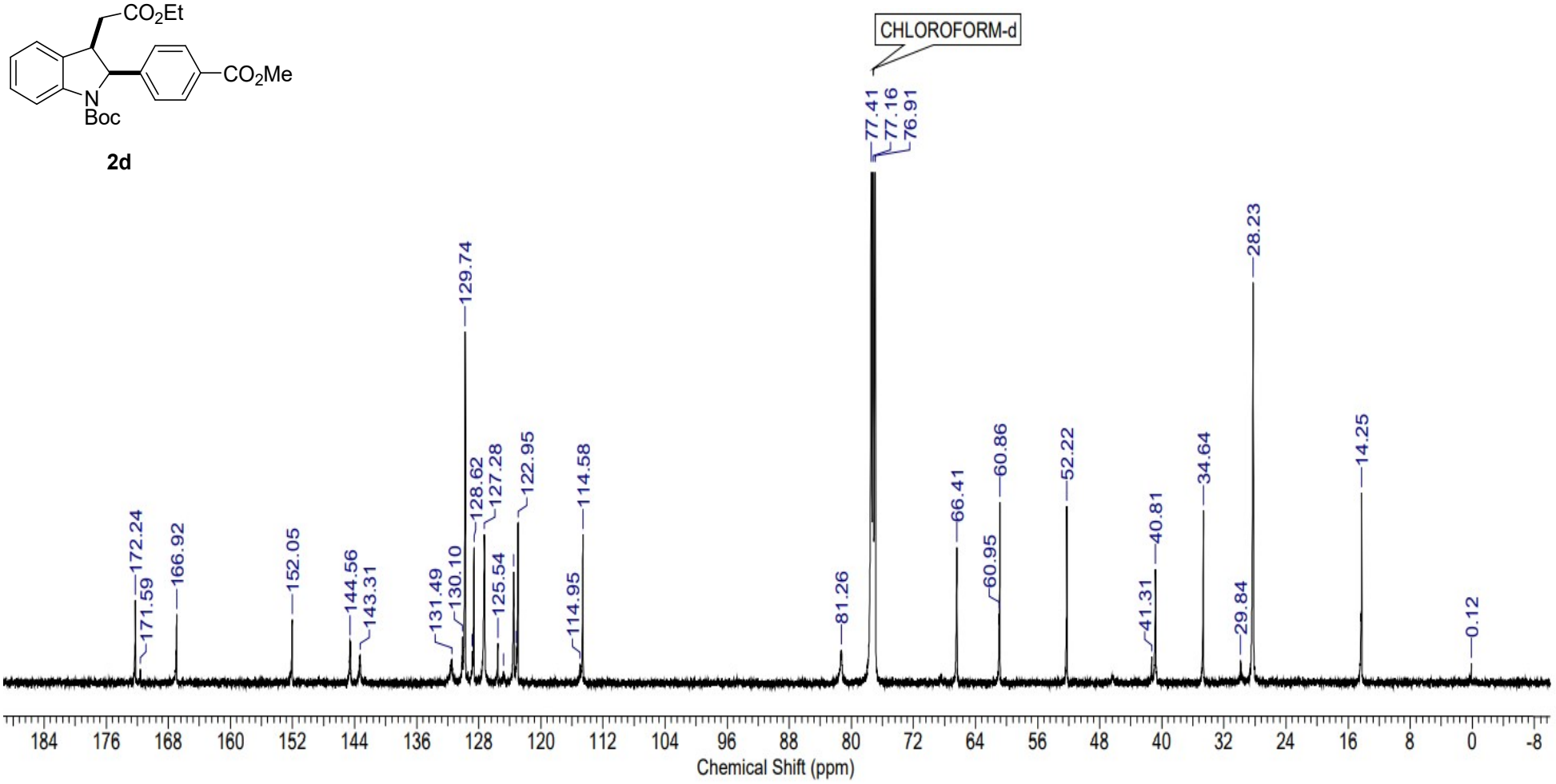




2d

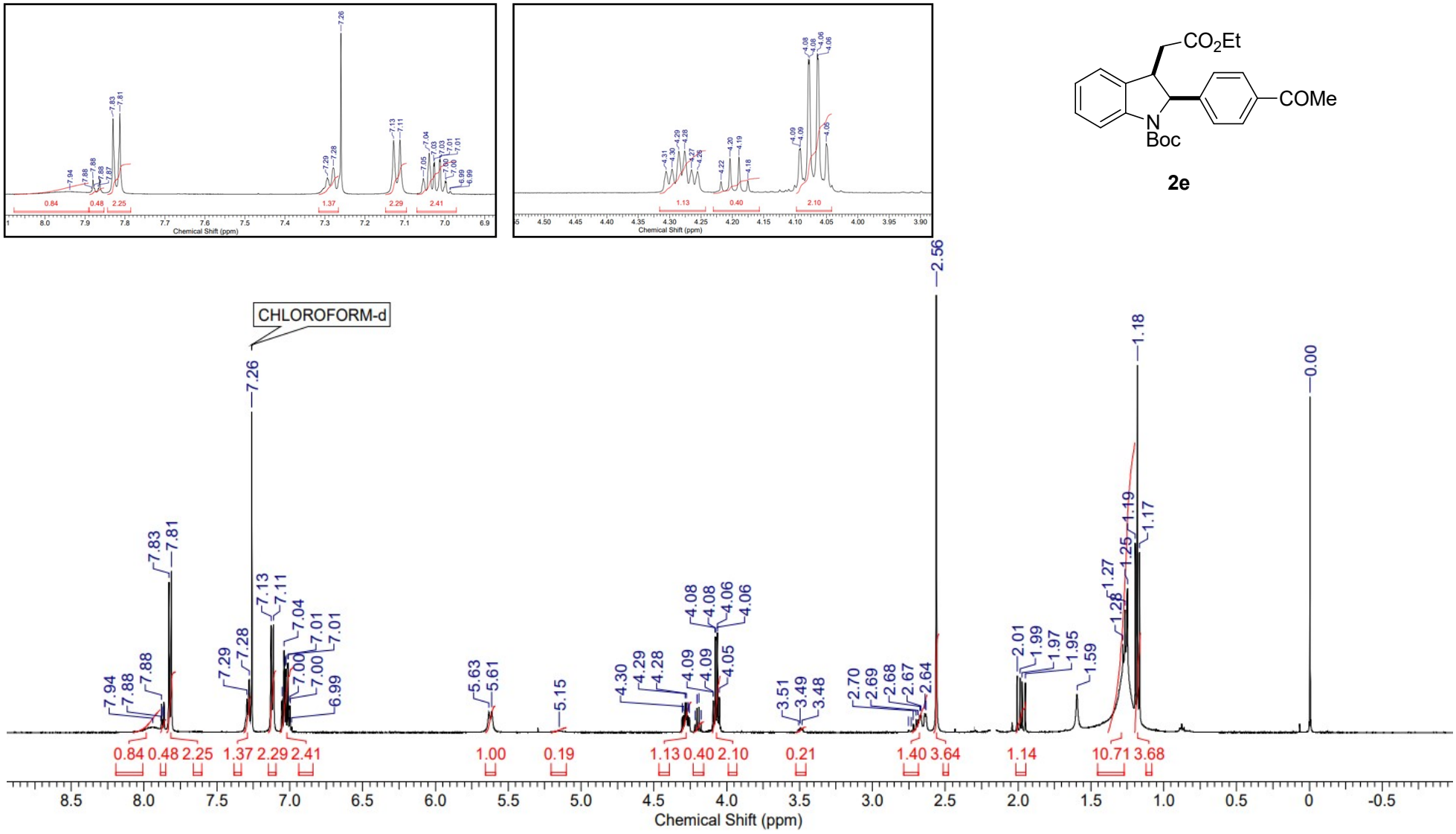


b) ^{13}C NMR Spectrum (125 MHz, $CDCl_3$)

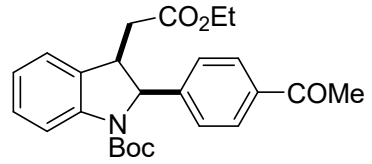


8-24. NMR Spectra of *tert*-Butyl 3-(2-Ethoxy-2-oxoethyl)-2-(4-(methoxycarbonyl)phenyl)indoline-1-carboxylate (2e)

a) ^{1}H NMR Spectrum (500 MHz, $CDCl_3$)



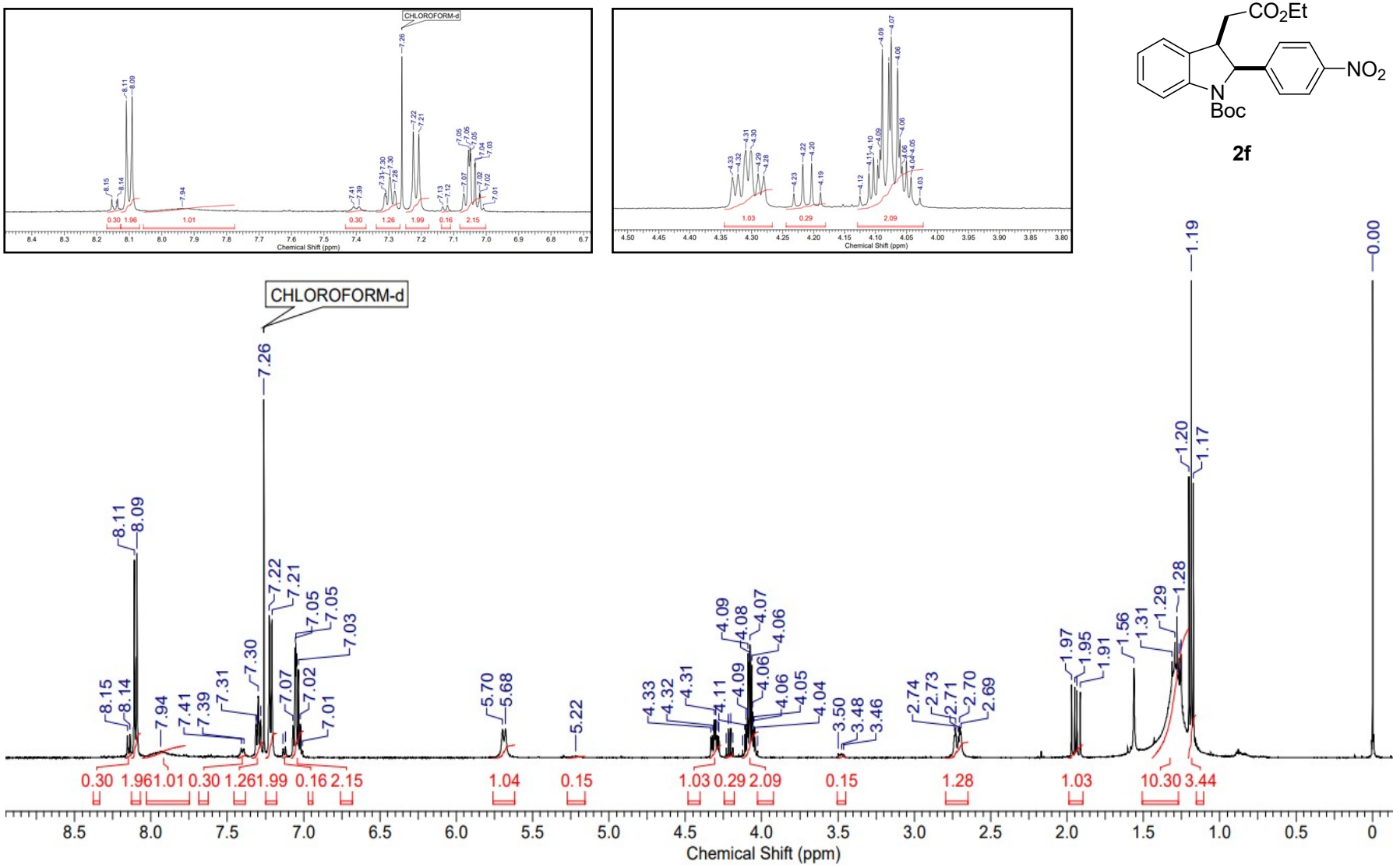
b) ^{13}C NMR Spectrum (125 MHz, $CDCl_3$)



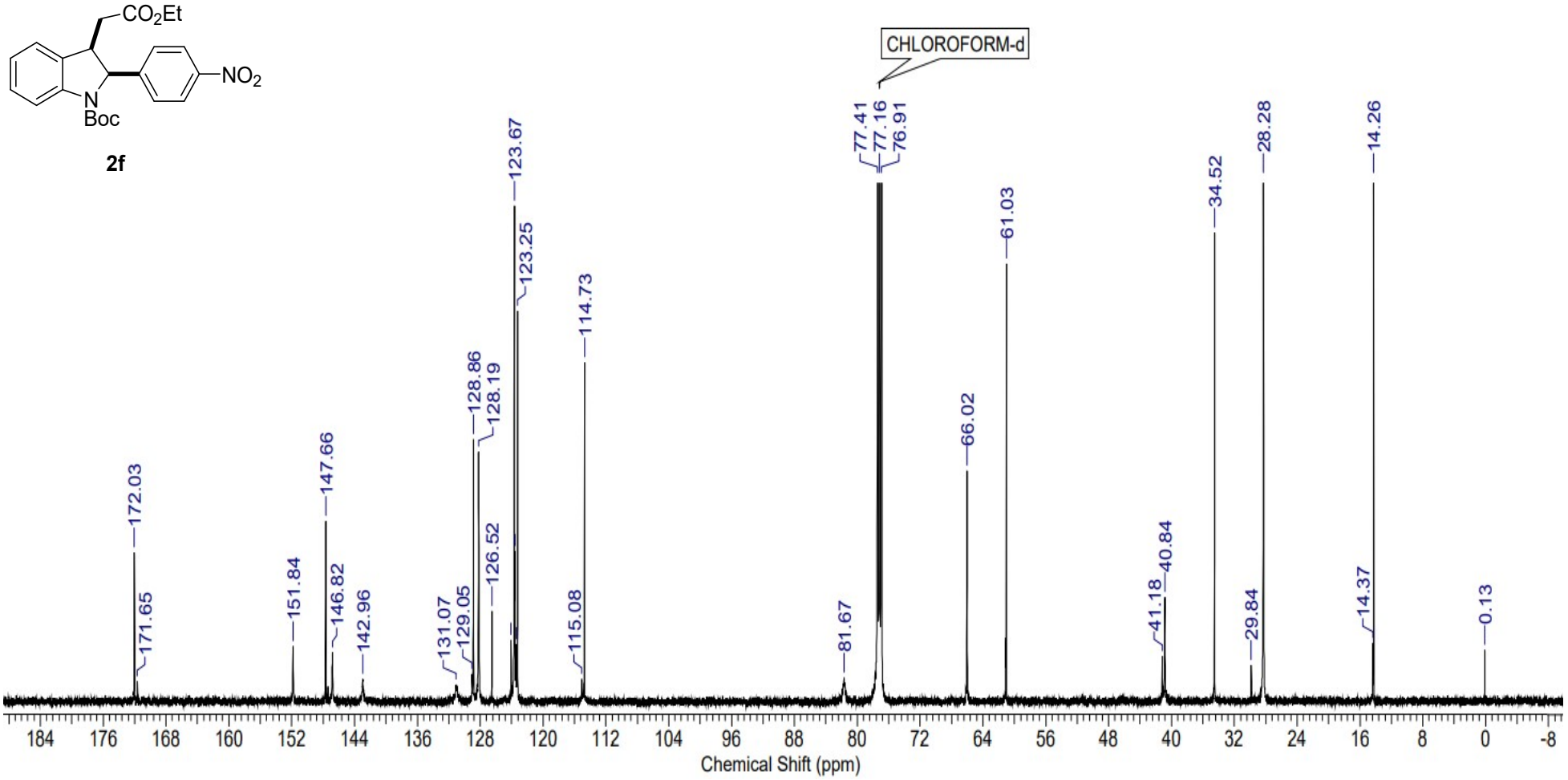
2e

8-25. NMR Spectra of *tert*-Butyl 3-(2-Ethoxy-2-oxoethyl)-2-(4-nitrophenyl)indoline-1-carboxylate (2f)

a) ^{1}H NMR Spectrum (500 MHz, $CDCl_3$)

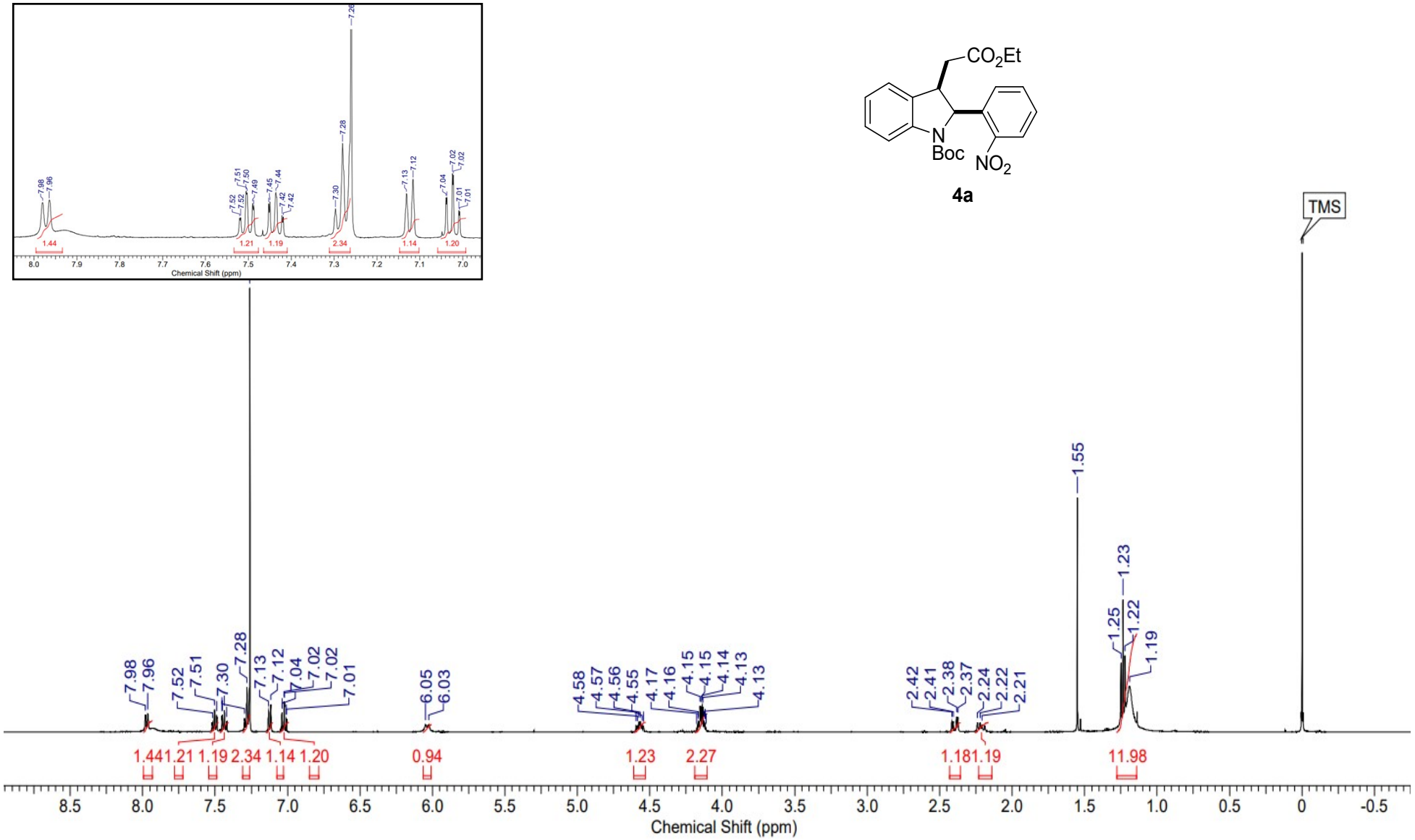


b) ^{13}C NMR Spectrum (125 MHz, $CDCl_3$)

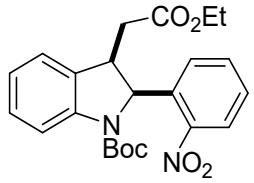


8-26. NMR Spectra of *tert*-Butyl 3-(2-Ethoxy-2-oxoethyl)-2-(2-nitrophenyl)indoline-1-carboxylate (4a)

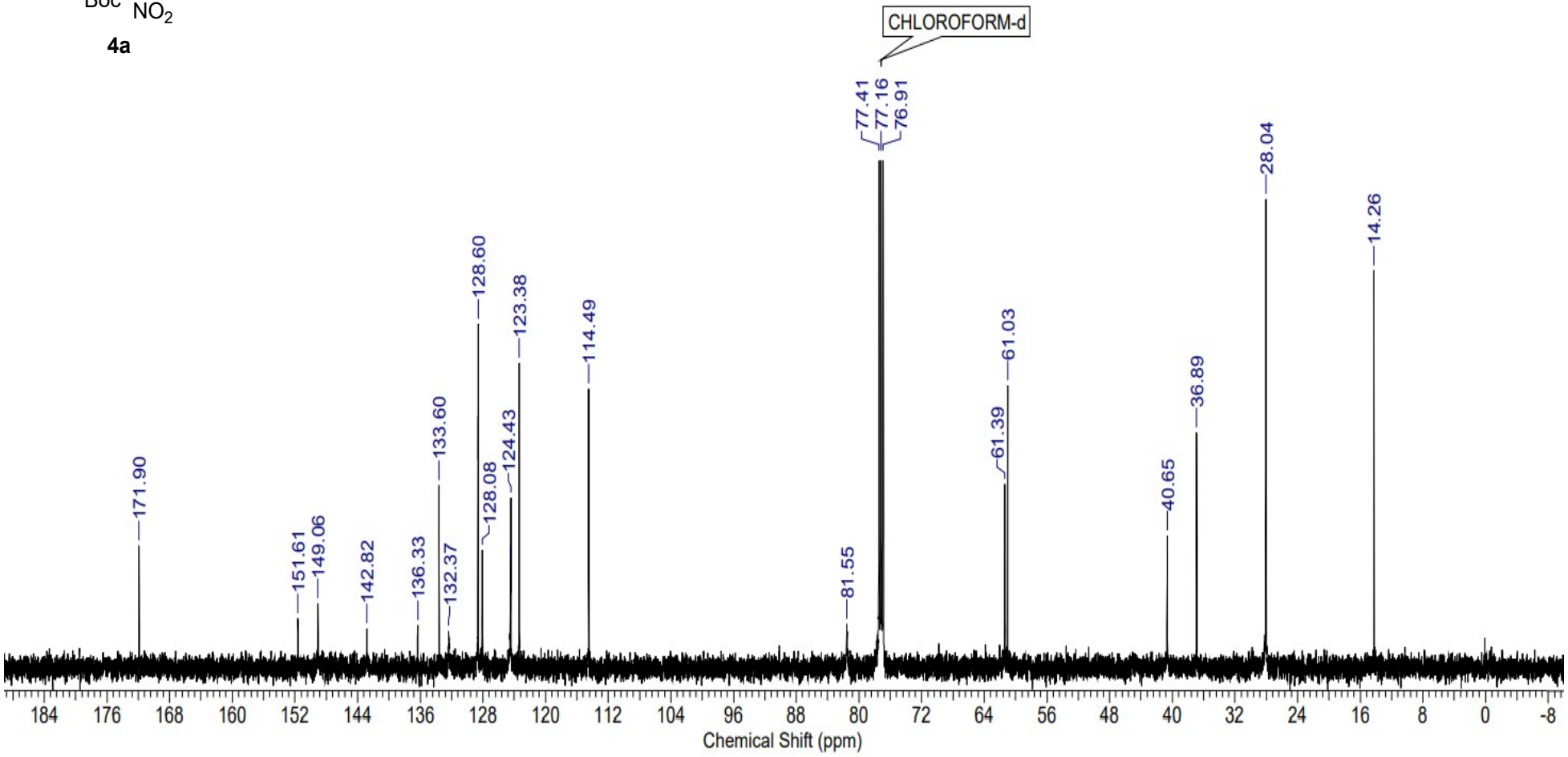
a) ^{1}H NMR Spectrum (500 MHz, $CDCl_3$)



b) ^{13}C NMR Spectrum (125 MHz, $CDCl_3$)

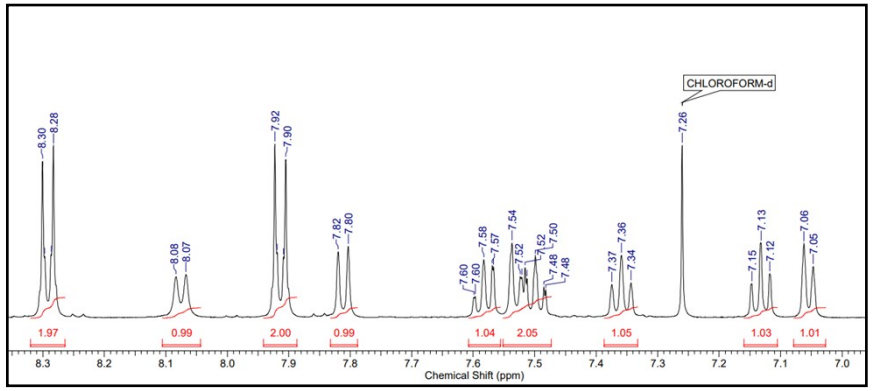


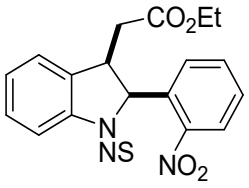
4a



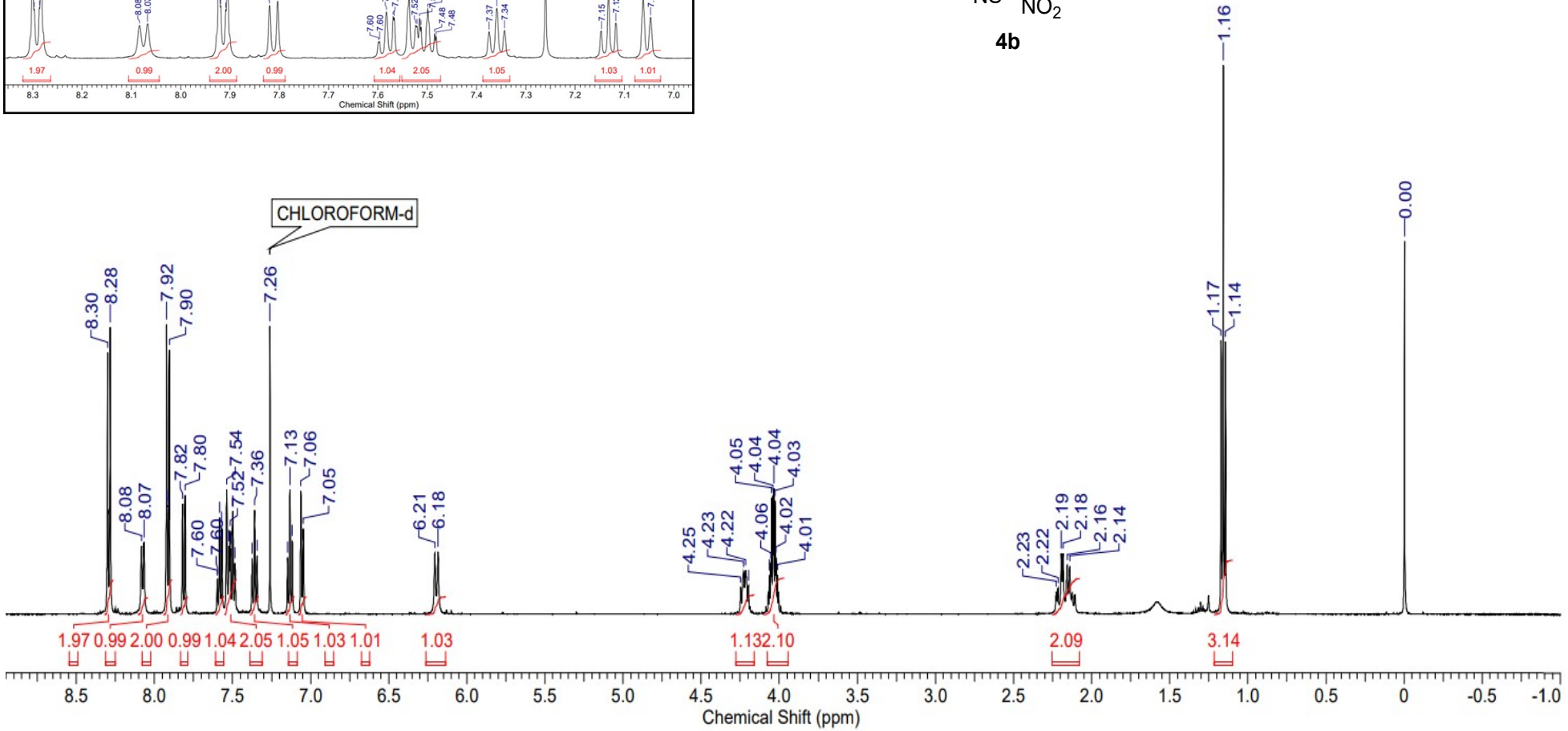
8-27. NMR Spectra of Ethyl 2-(2-(2-Nitrophenyl)-1-thionitrosoindolin-3-yl)acetate (4b)

a) ^{1}H NMR Spectrum (500 MHz, $CDCl_3$)

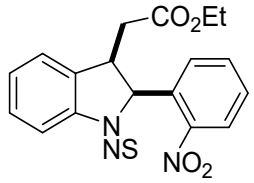




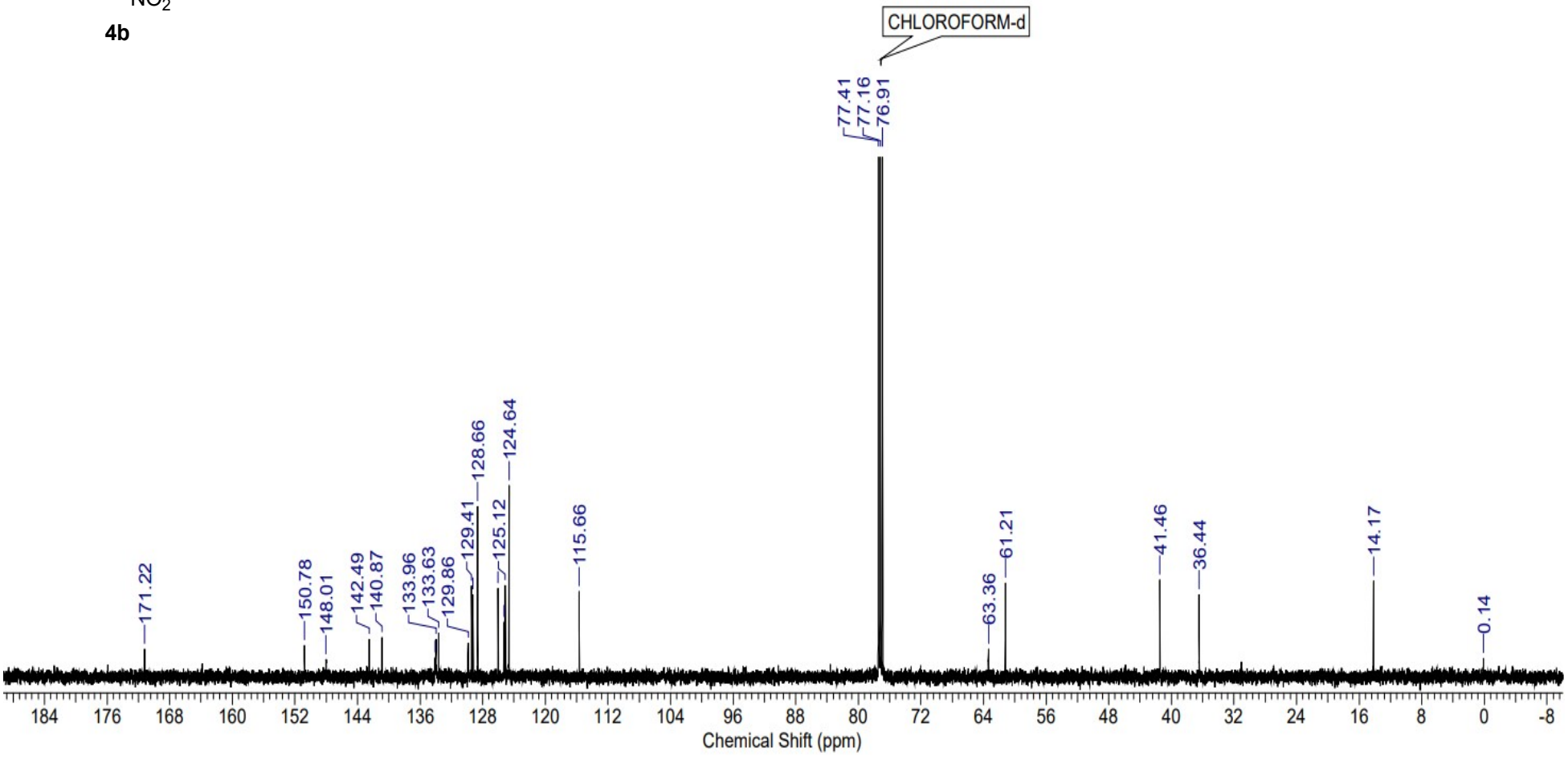
4b



b) ^{13}C NMR Spectrum (125 MHz, $CDCl_3$)

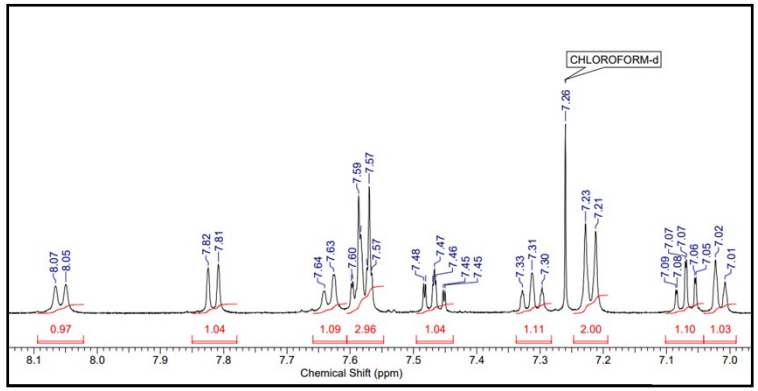


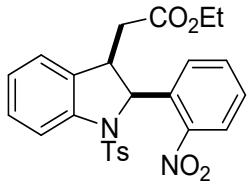
4b



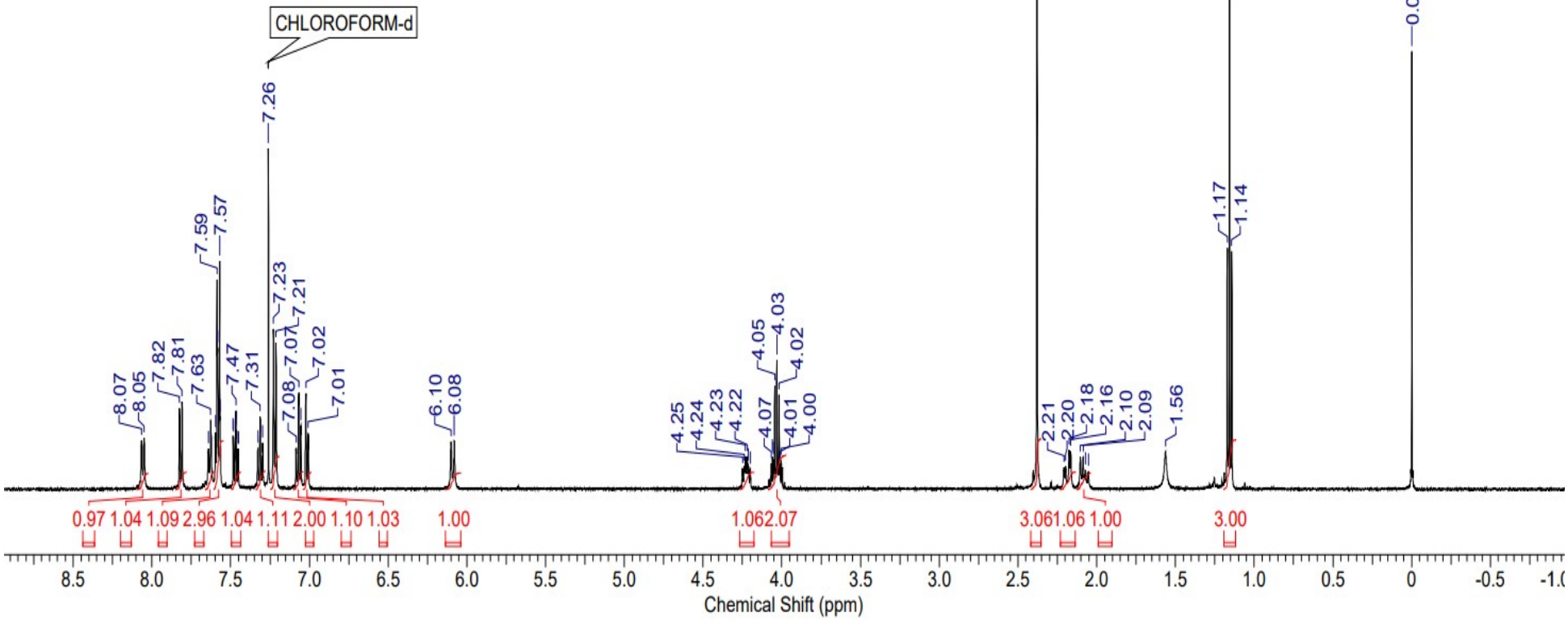
8-28. NMR Spectra of Ethyl 2-(2-(2-Nnitrophenyl)-1-tosylindolin-3-yl)acetate (4c)

a) ^{1}H NMR Spectrum (500 MHz, $CDCl_3$)

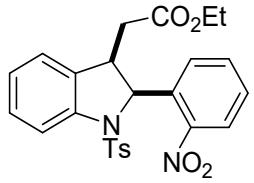




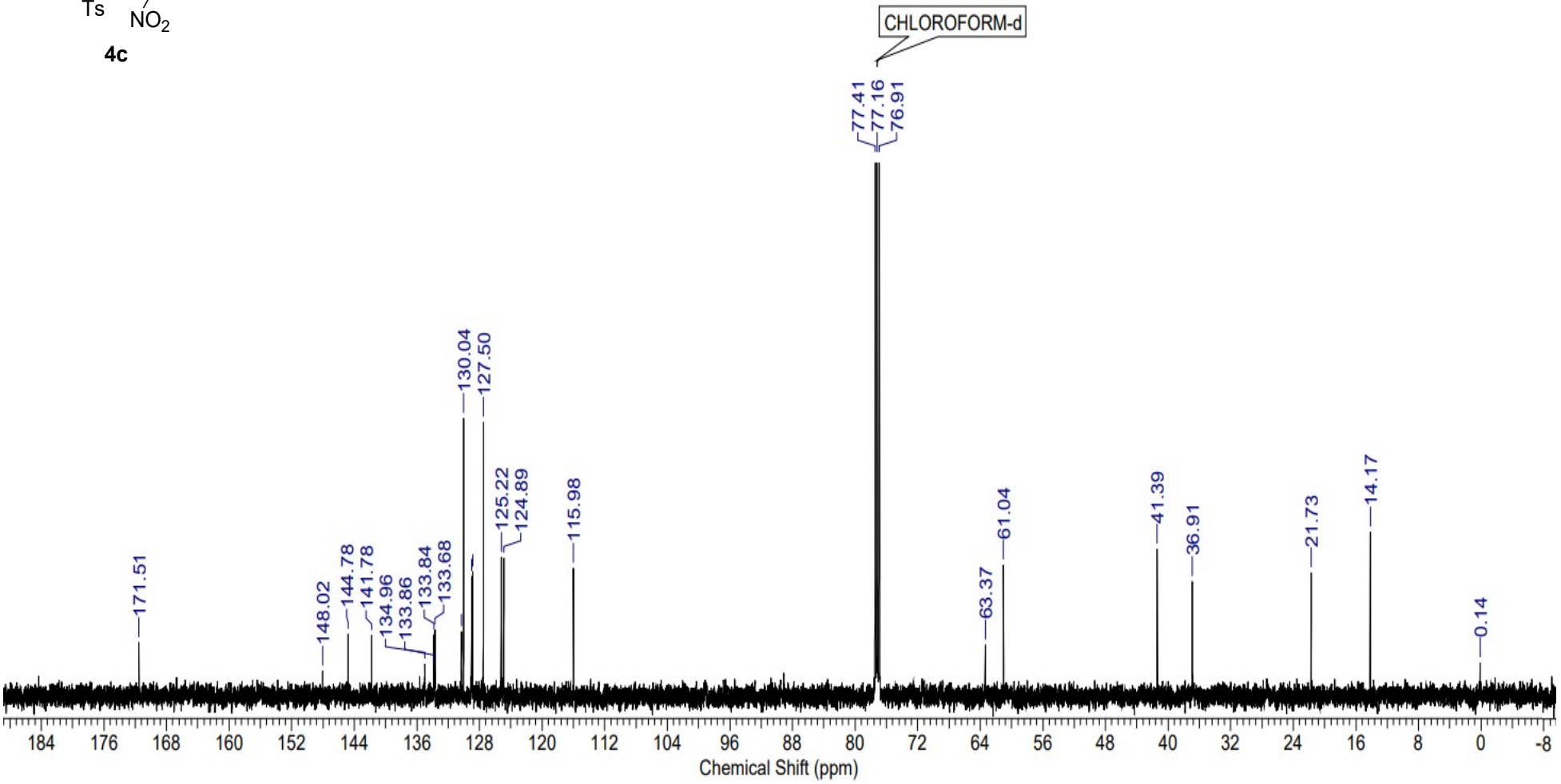
4c



b) ^{13}C NMR Spectrum (125 MHz, $CDCl_3$)

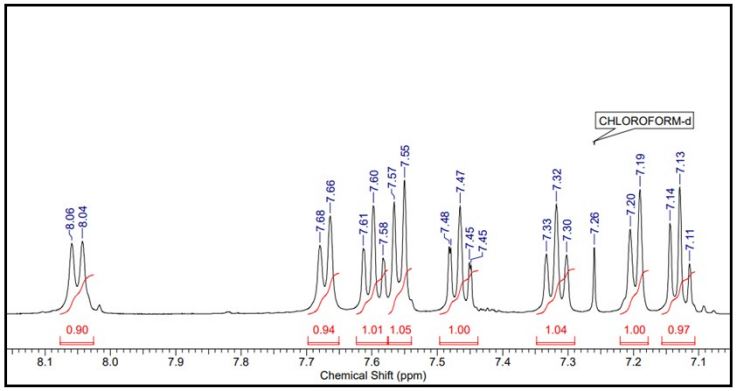


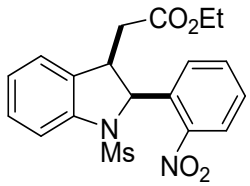
4c



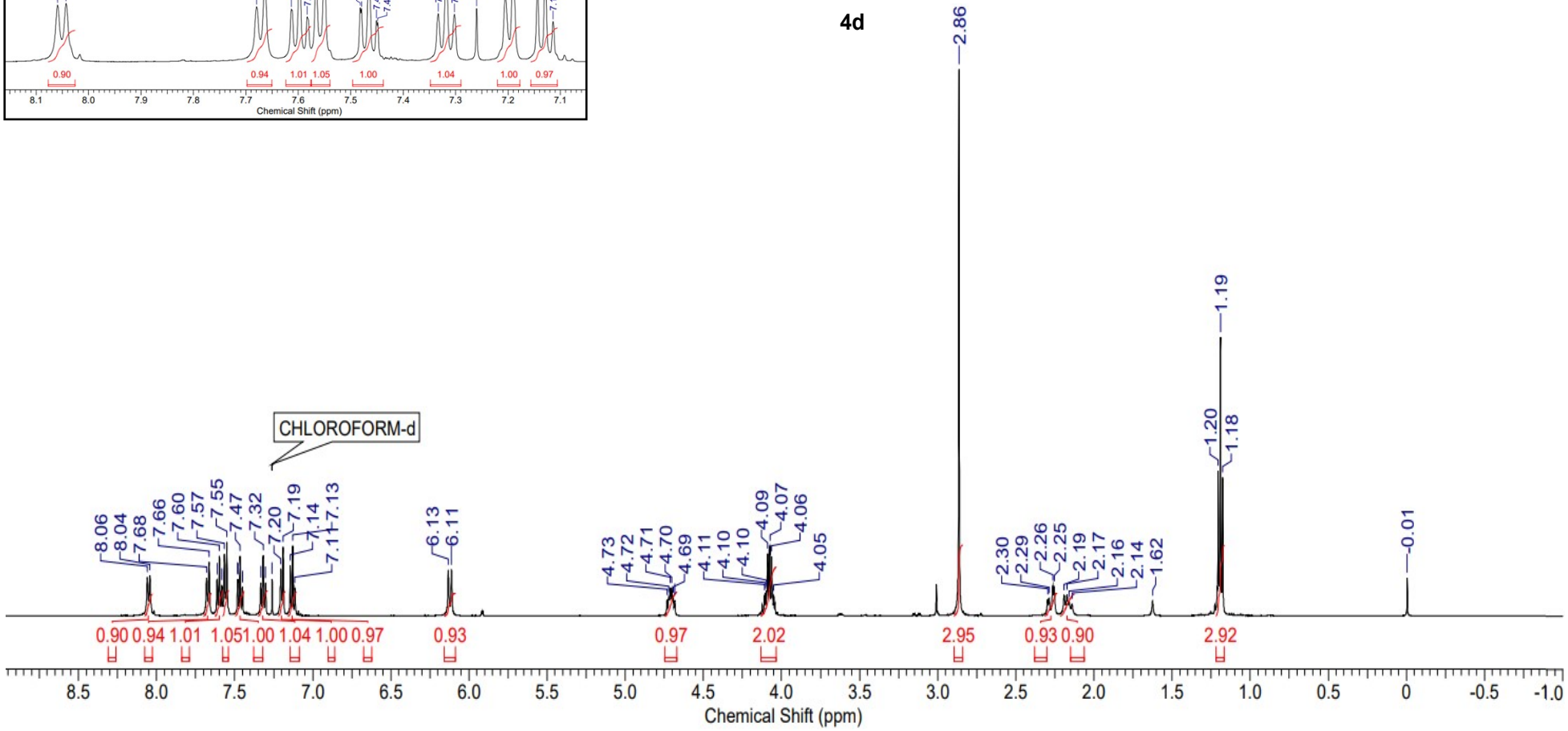
8-29. NMR Spectra of Ethyl 2-(1-(Methylsulfonyl)-2-(2-nitrophenyl)indolin-3-yl)acetate (4d)

a) ^{1}H NMR Spectrum (500 MHz, $CDCl_3$)

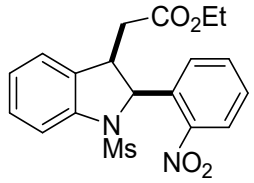




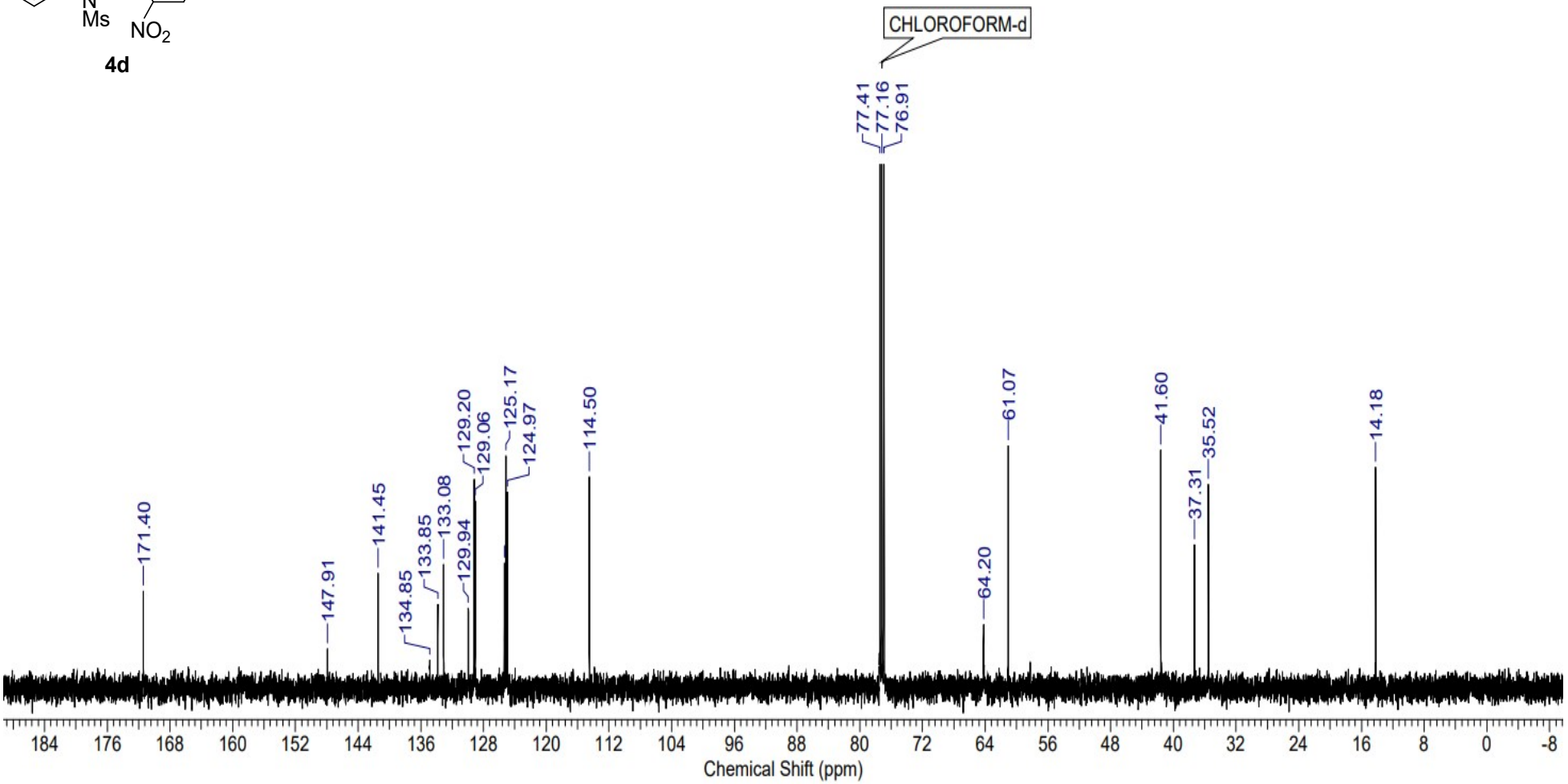
4d



b) ^{13}C NMR Spectrum (125 MHz, $CDCl_3$)

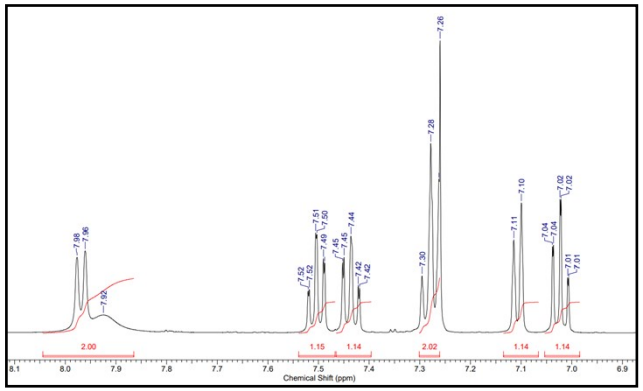


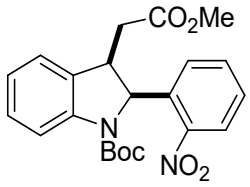
4d



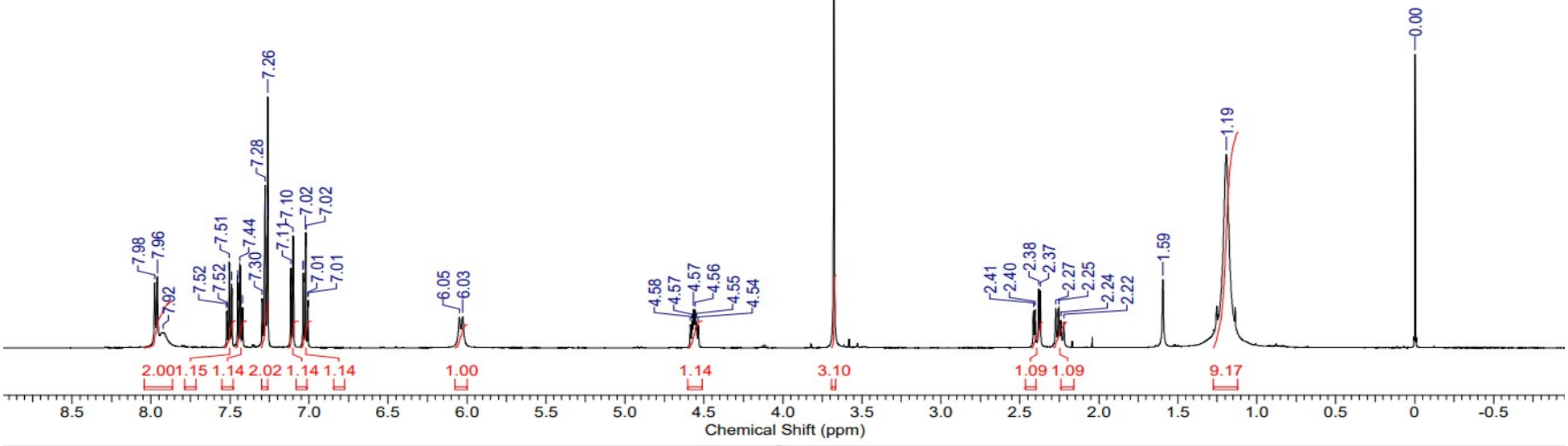
8-30. NMR Spectra of *tert*-Butyl 3-(2-Methoxy-2-oxoethyl)-2-(2-nitrophenyl)-1H-indoline-1-carboxylate (4e)

a) ^{1}H NMR Spectrum (500 MHz, $CDCl_3$)

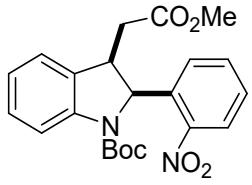




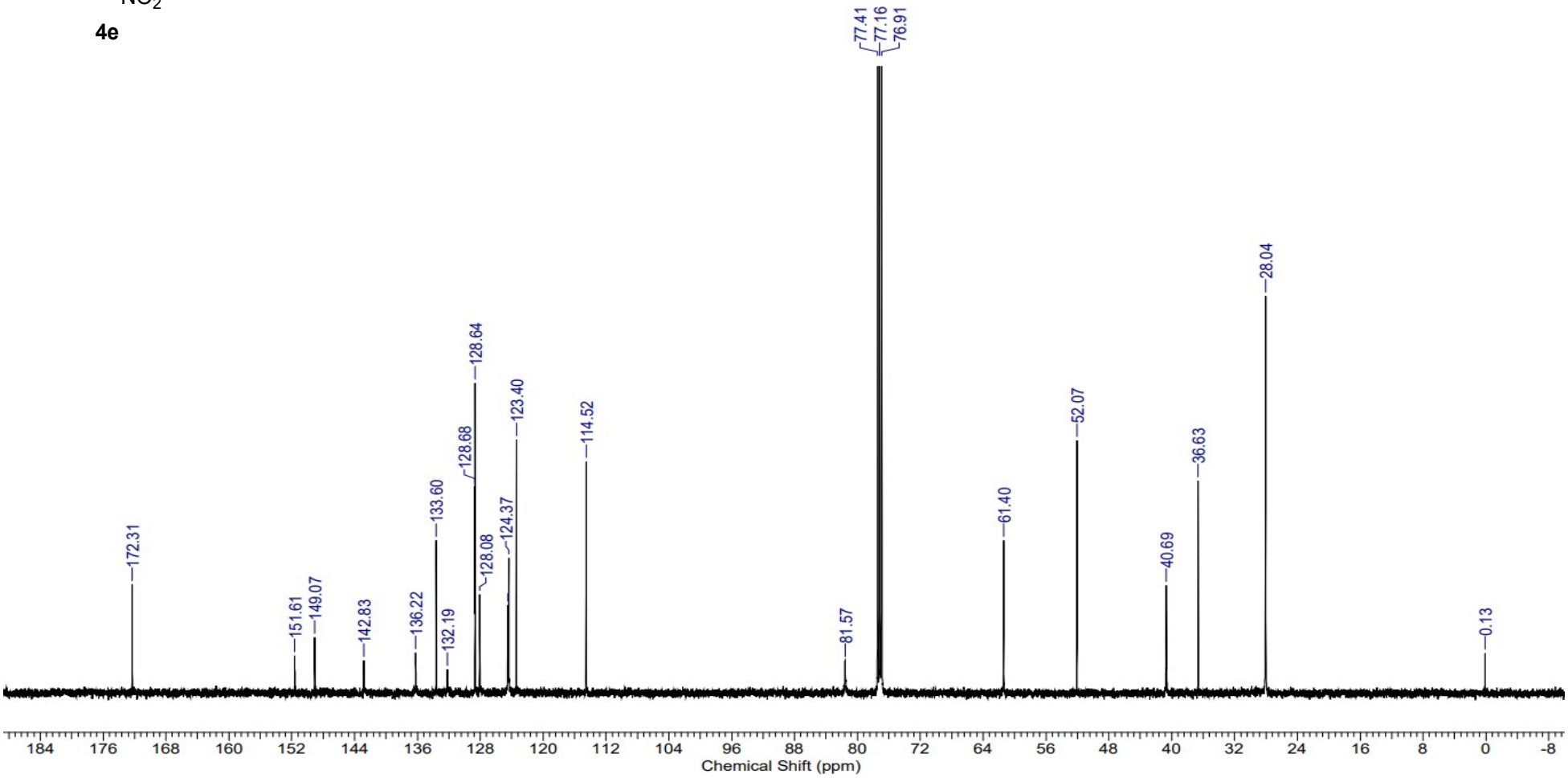
4e



b) ^{13}C NMR Spectrum (125 MHz, $CDCl_3$)

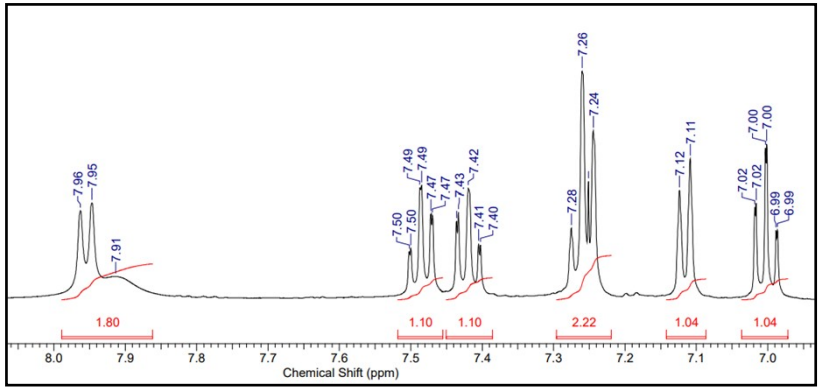


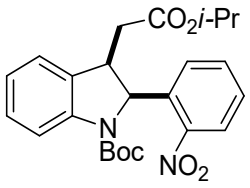
4e



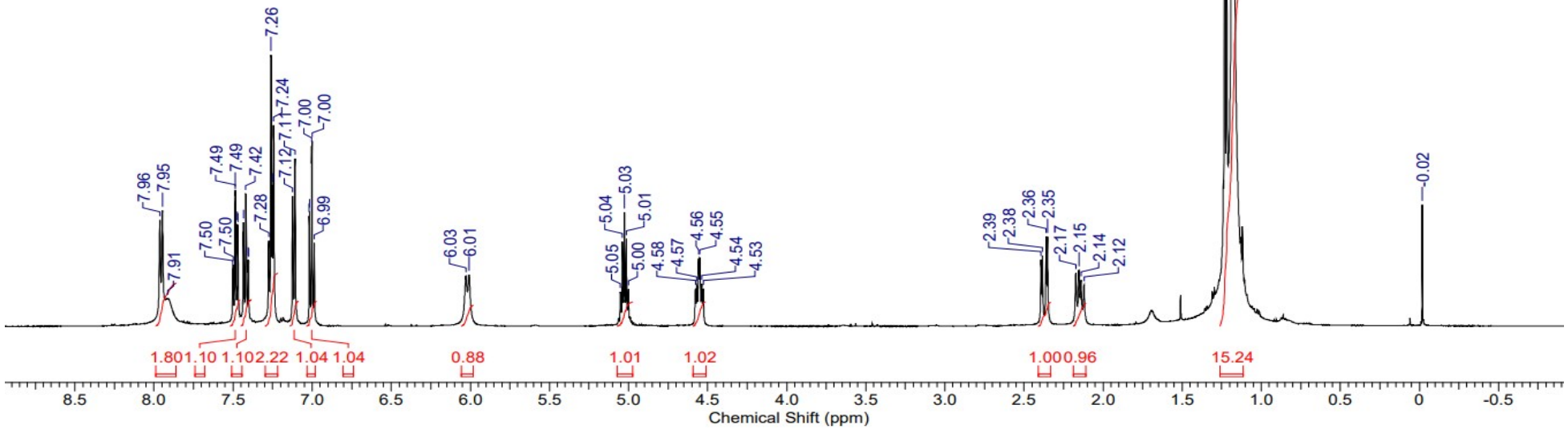
8-31. NMR Spectra of *tert*-Butyl 3-(2-Isopropoxy-2-oxoethyl)-2-(2-nitrophenyl)-1H-indoline-1-carboxylate (4f)

a) ^{1}H NMR Spectrum (500 MHz, $CDCl_3$)

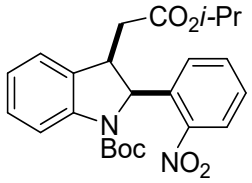




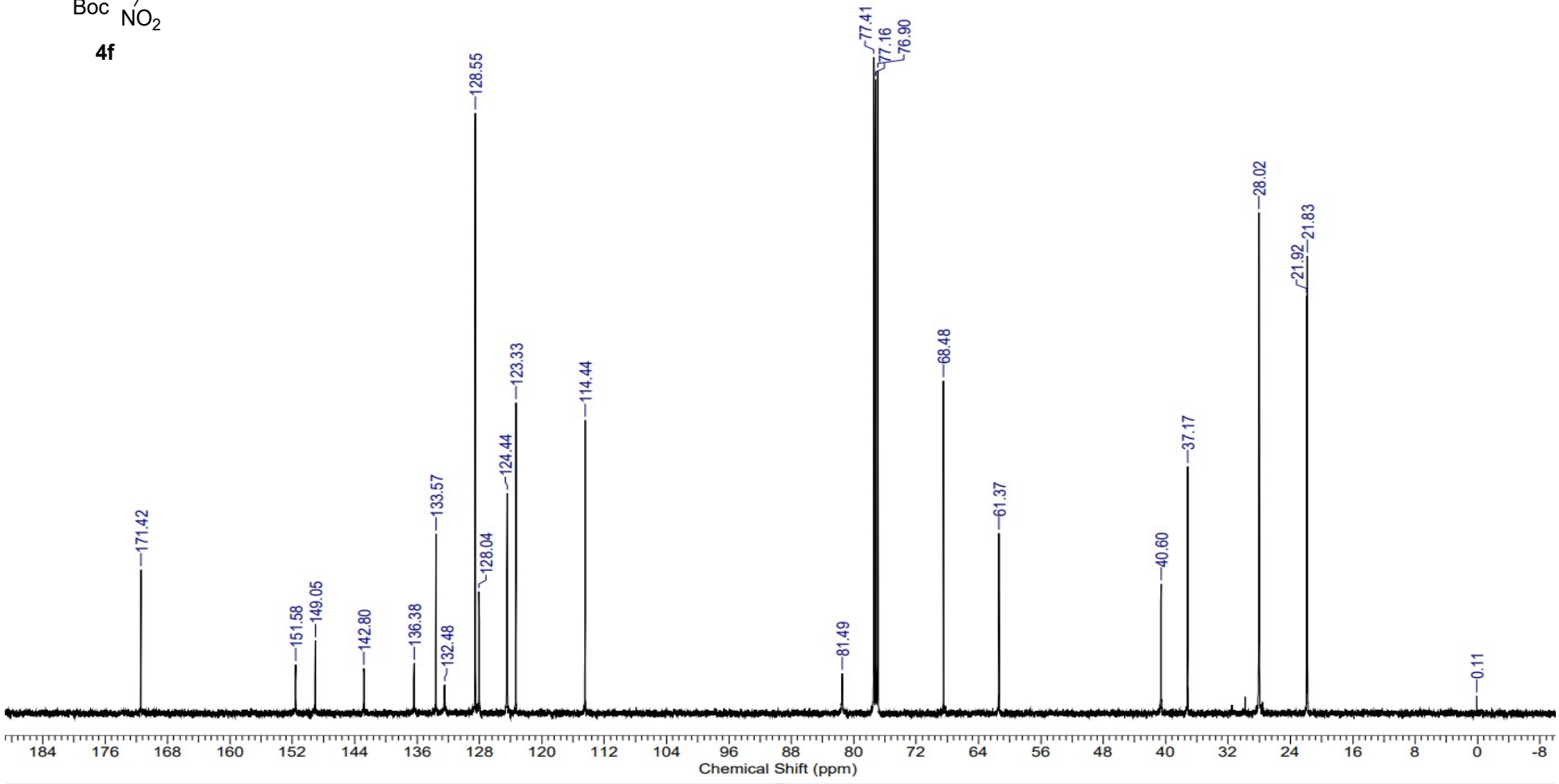
4f



b) ^{13}C NMR Spectrum (125 MHz, $CDCl_3$)

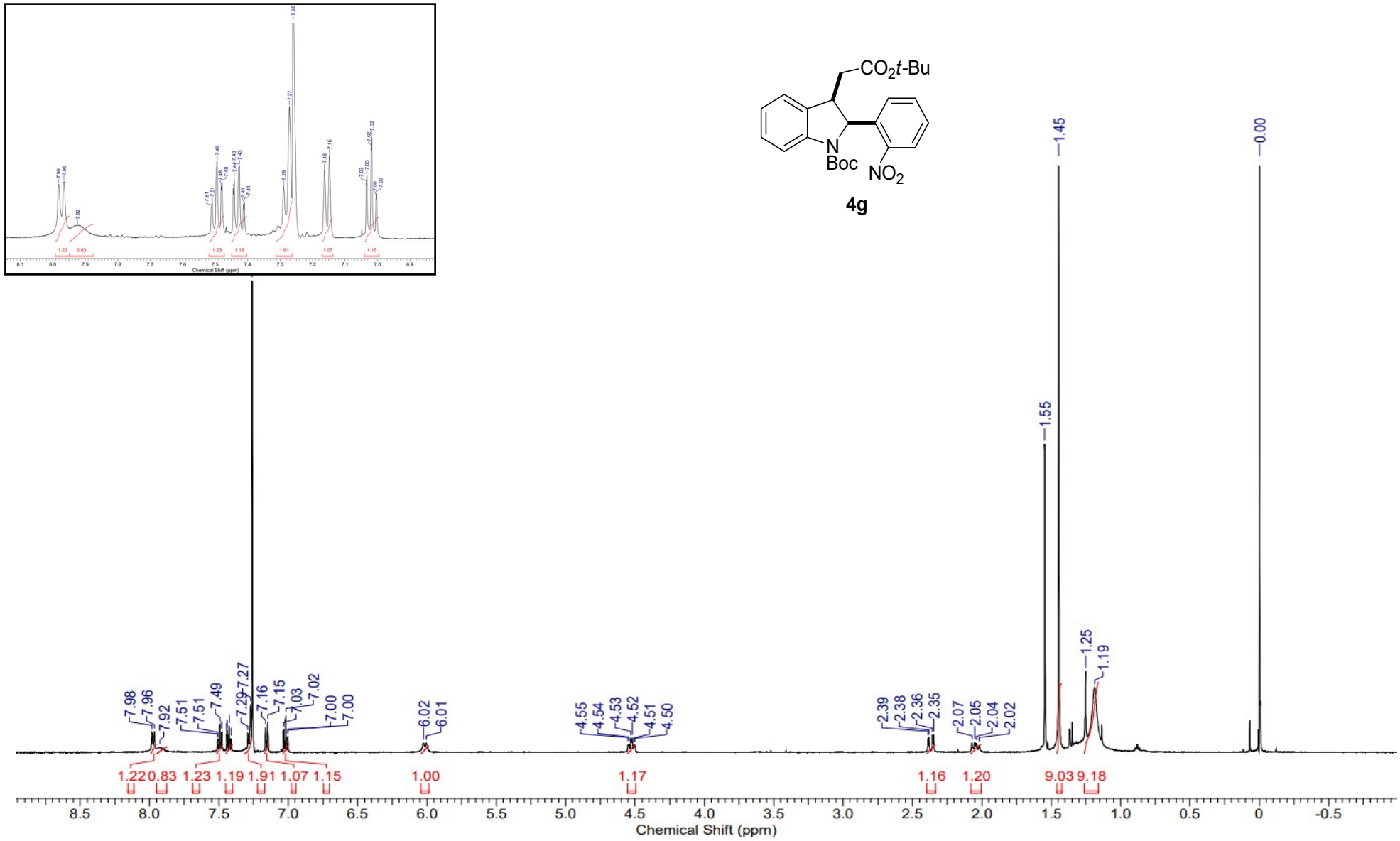


4f

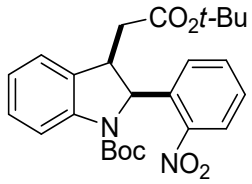


8-32. NMR Spectra of *tert*-Butyl 3-(2-(*tert*-Butoxy)-2-oxoethyl)-2-(2-nitrophenyl)-1H-indoline-1-carboxylate (4g)

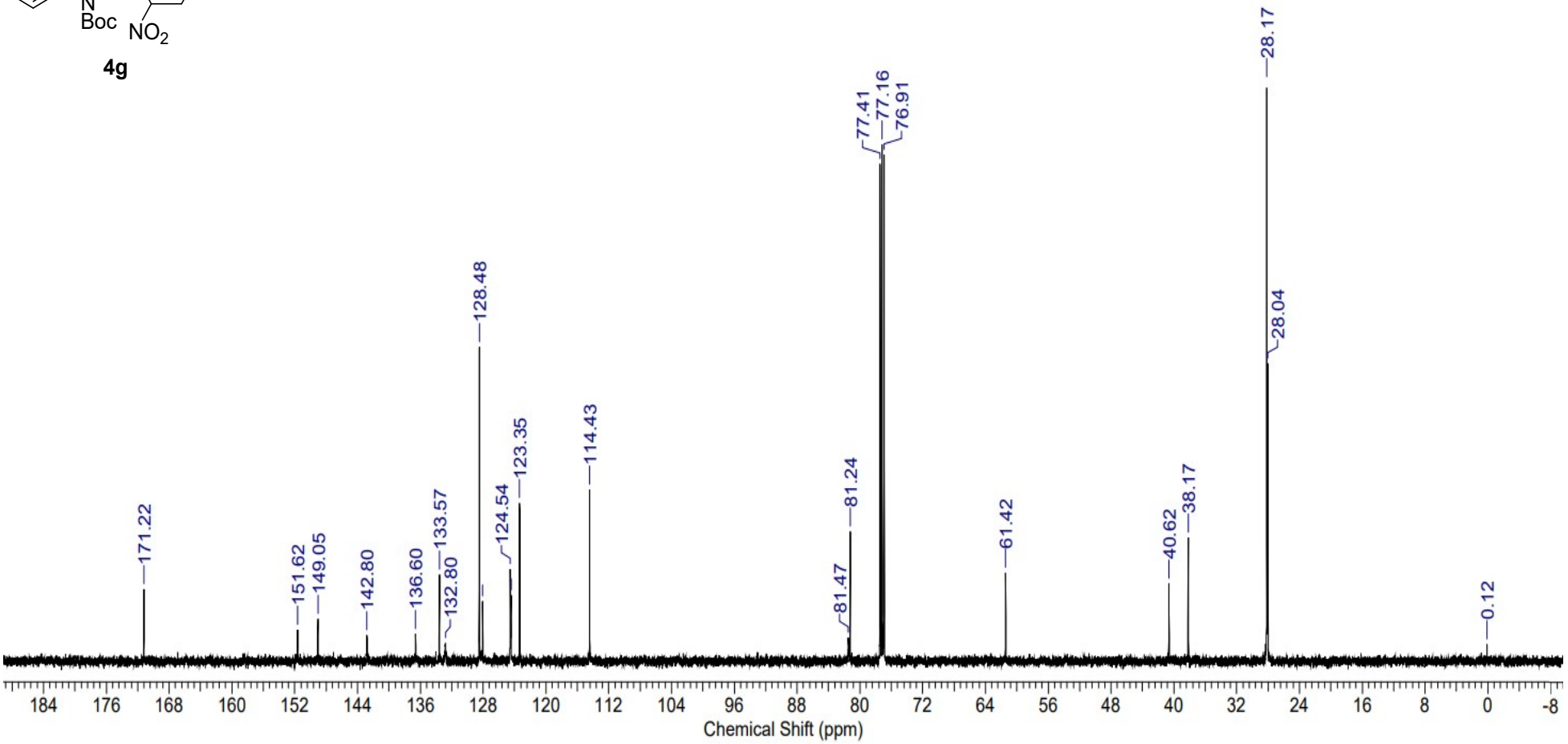
a) ^{1}H NMR Spectrum (500 MHz, $CDCl_3$)



b) ^{13}C NMR Spectrum (125 MHz, $CDCl_3$)

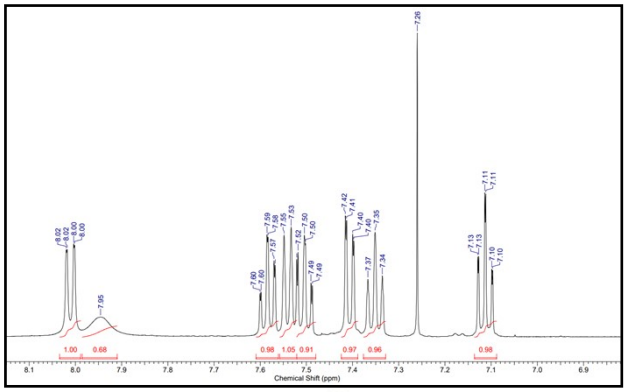


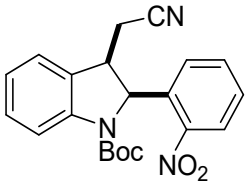
4g



8-33. NMR Spectra of *tert*-Butyl 3-(Cyanomethyl)-2-(2-nitrophenyl)-1H-indoline-1-carboxylate (4h)

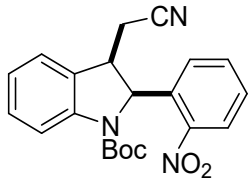
a) ^{1}H NMR Spectrum (500 MHz, $CDCl_3$)





4h

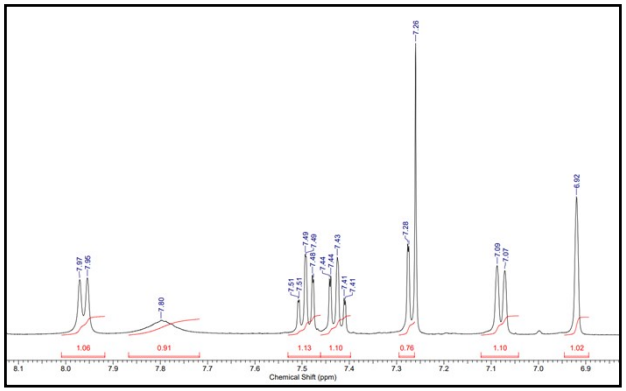
b) ^{13}C NMR Spectrum (125 MHz, $CDCl_3$)

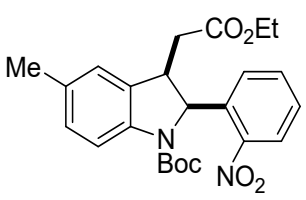


4h

8-34. NMR Spectra of *tert*-Butyl 3-(2-Ethoxy-2-oxoethyl)-5-methyl-2-(2-nitrophenyl)-1H-indoline-1-carboxylate (4k)

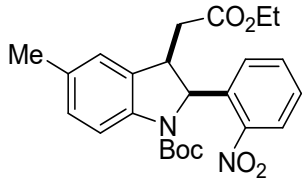
a) ^{1}H NMR Spectrum (500 MHz, $CDCl_3$)



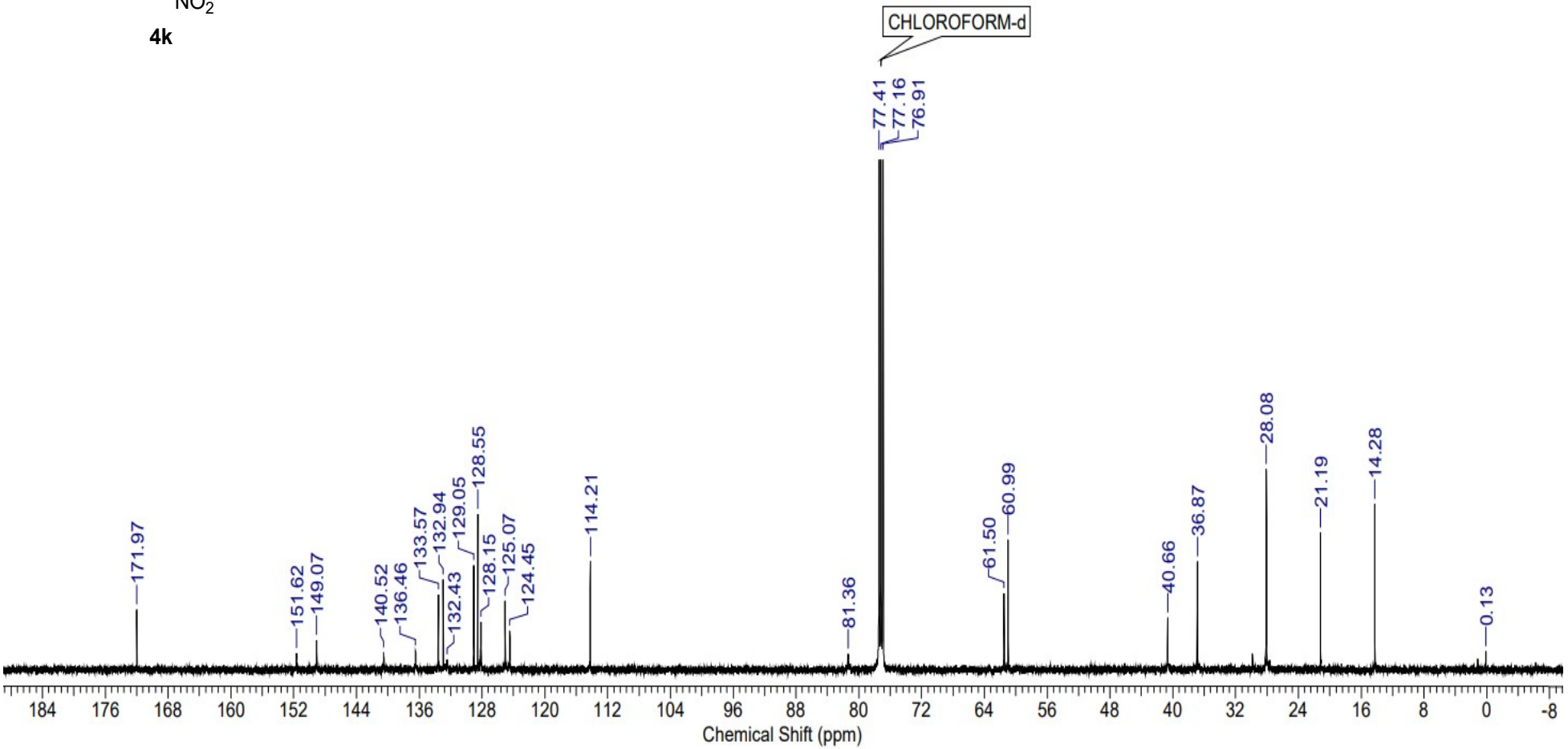


4k

b) ^{13}C NMR Spectrum (125 MHz, $CDCl_3$)

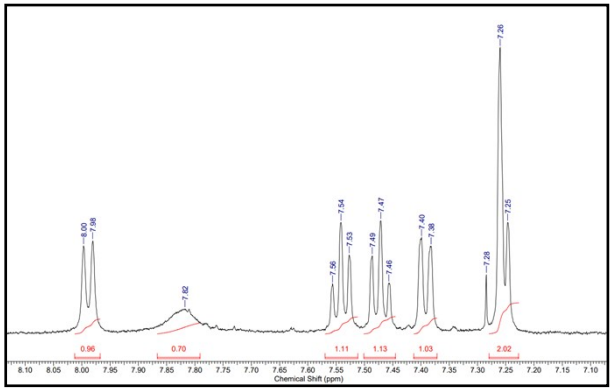


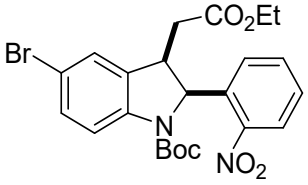
4k



8-35. NMR Spectra of *tert*-Butyl 5-Bromo-3-(2-ethoxy-2-oxoethyl)-2-(2-nitrophenyl)-1H-indoline-1-carboxylate (4l)

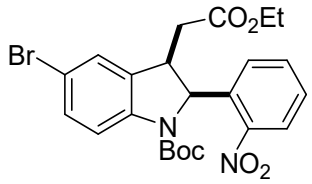
a) ^{1}H NMR Spectrum (500 MHz, $CDCl_3$)





4l

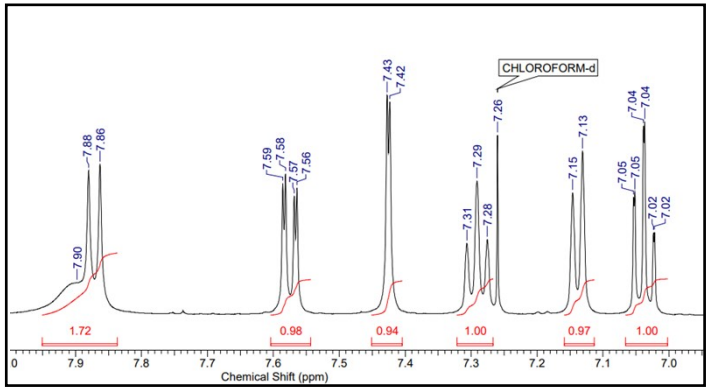
b) ^{13}C NMR Spectrum (125 MHz, $CDCl_3$)

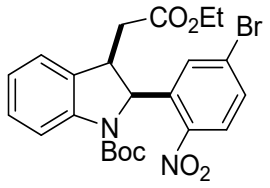


4l

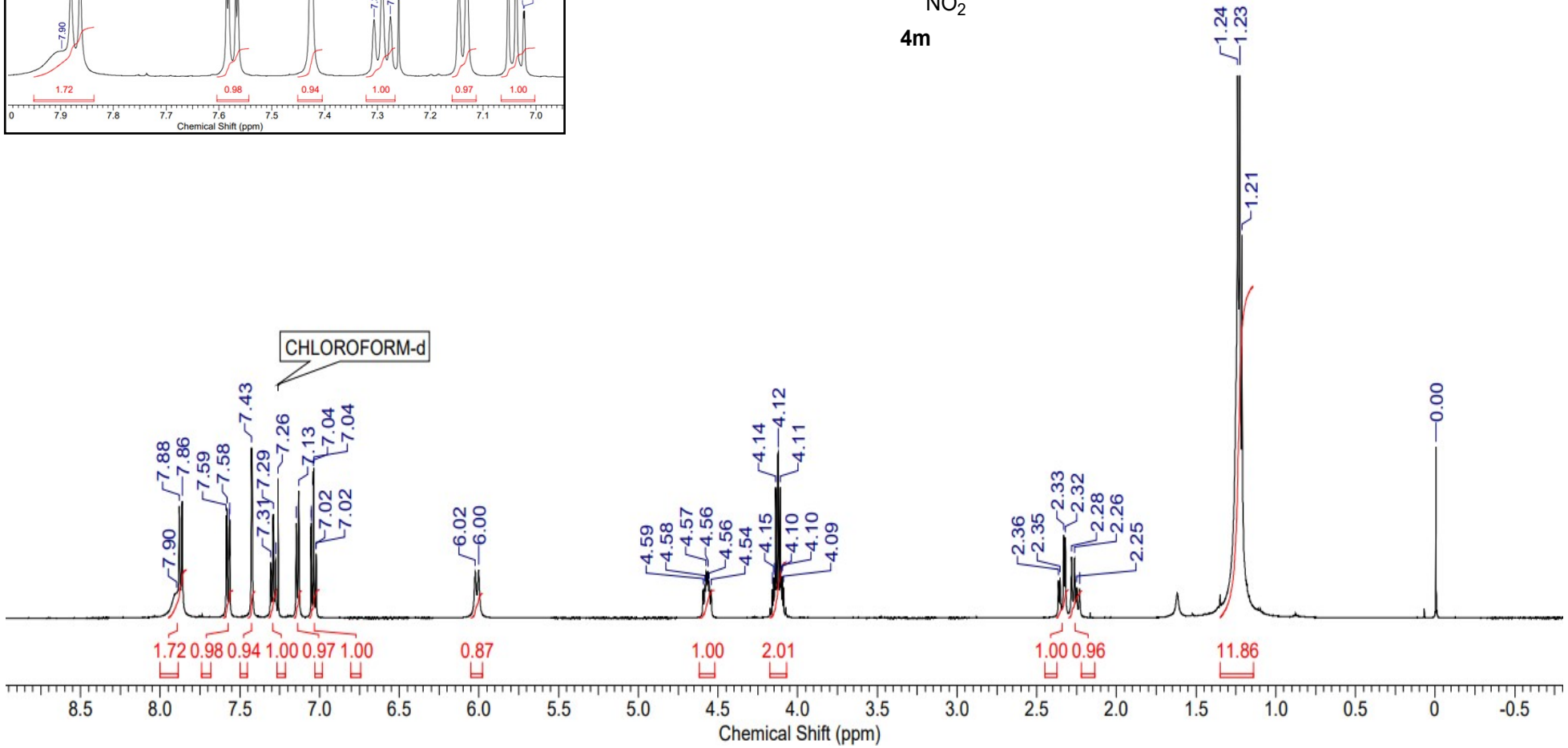
8-36. NMR Spectra of *tert*-Butyl 2-(5-Bromo-2-nitrophenyl)-3-(2-ethoxy-2-oxoethyl)-1H-indoline-1-carboxylate (4m)

a) ^{1}H NMR Spectrum (500 MHz, $CDCl_3$)

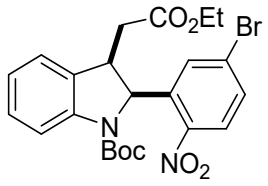




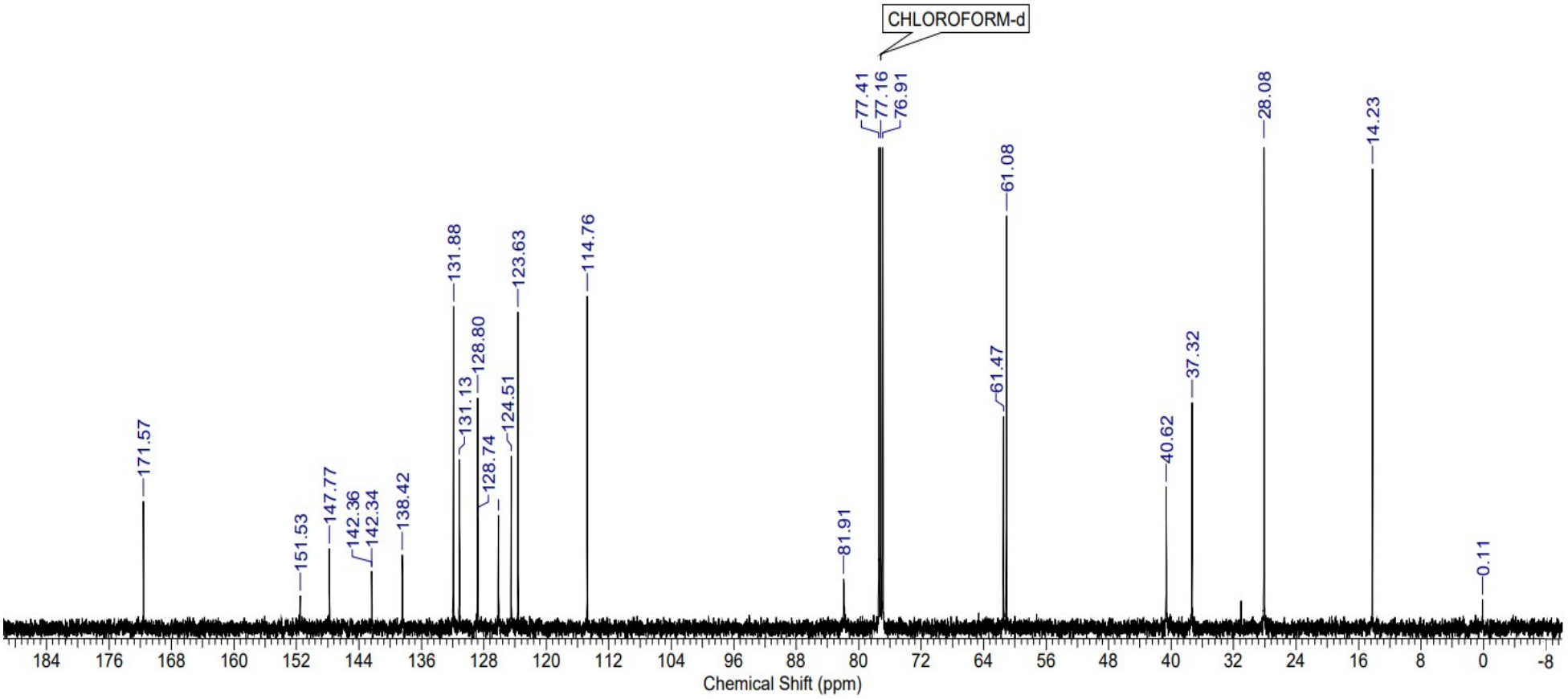
4m



b) ^{13}C NMR Spectrum (125 MHz, $CDCl_3$)

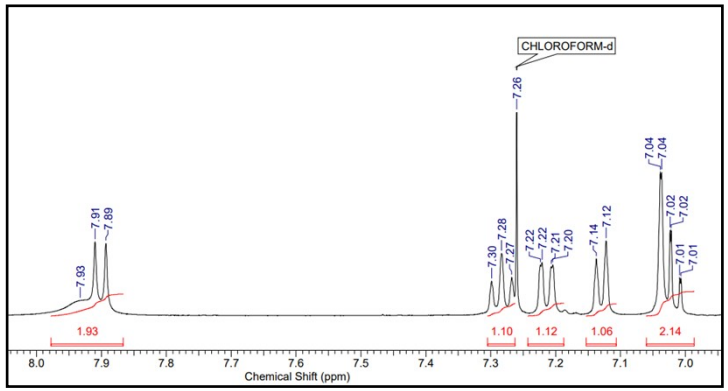


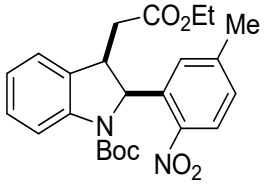
4m



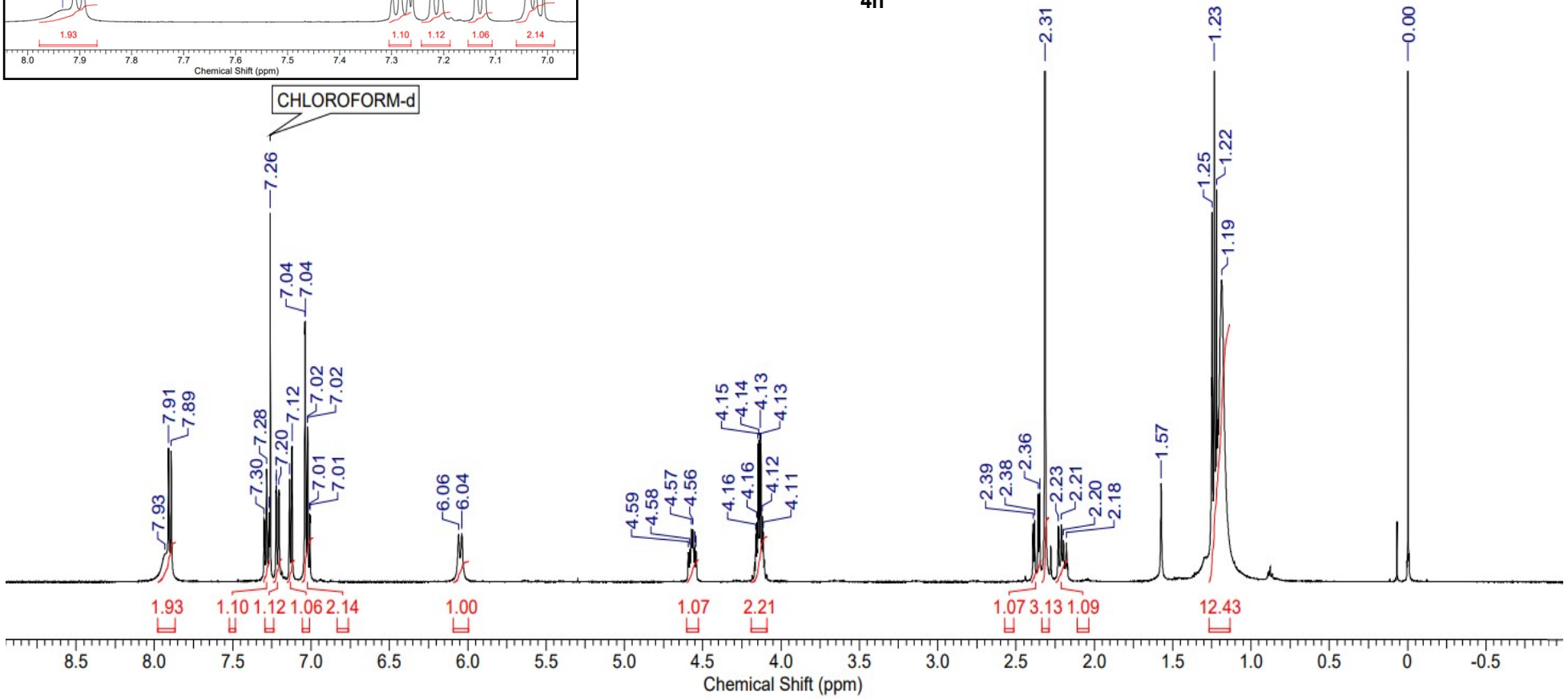
8-37. NMR Spectra of *tert*-Butyl 3-(2-Ethoxy-2-oxoethyl)-2-(5-methyl-2-nitrophenyl)-1H-indoline-1-carboxylate (4n)

a) ^{1}H NMR Spectrum (500 MHz, $CDCl_3$)

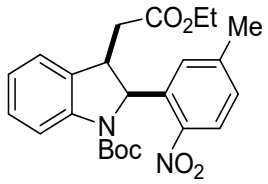




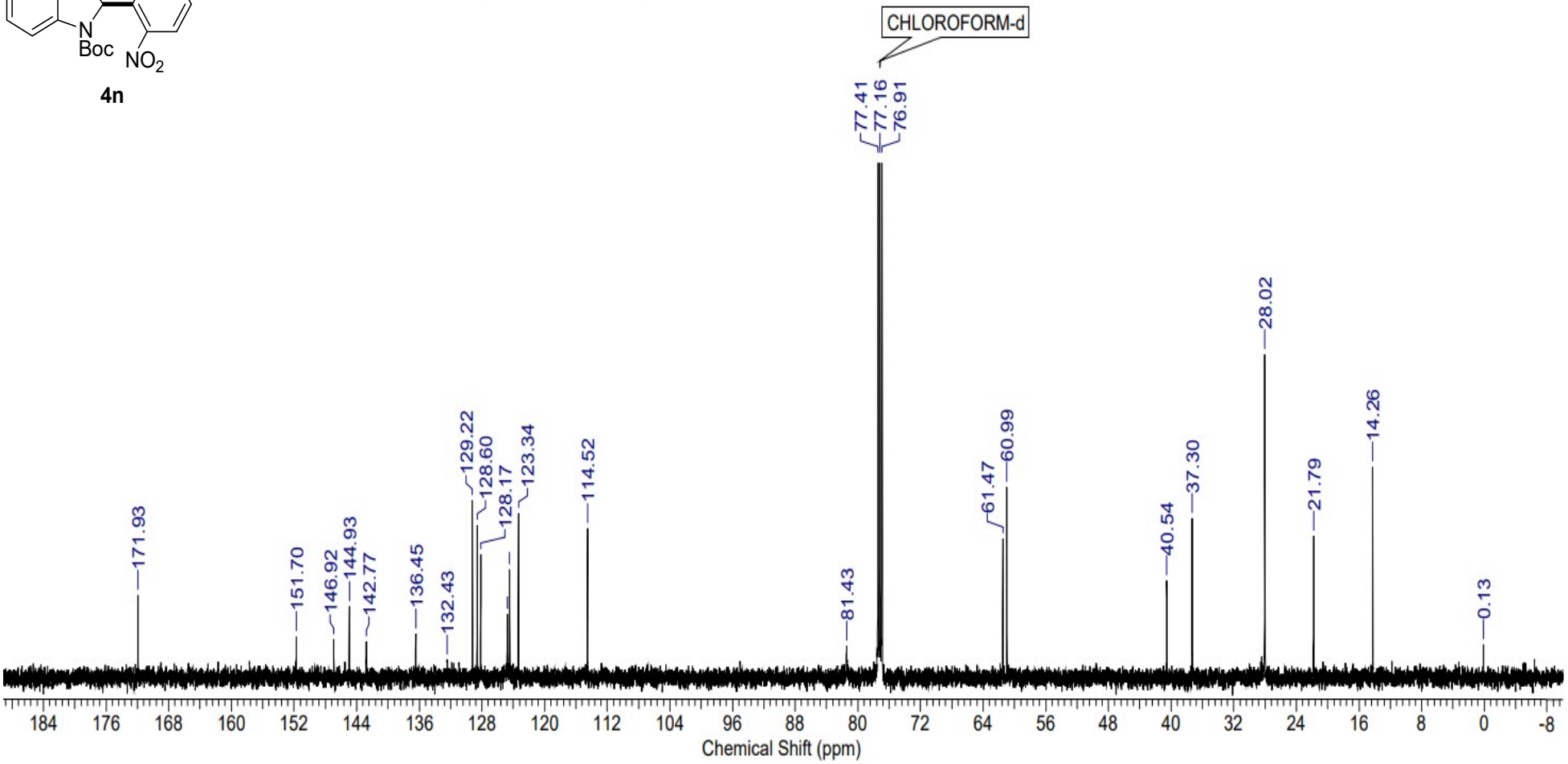
4n



b) ^{13}C NMR Spectrum (125 MHz, $CDCl_3$)

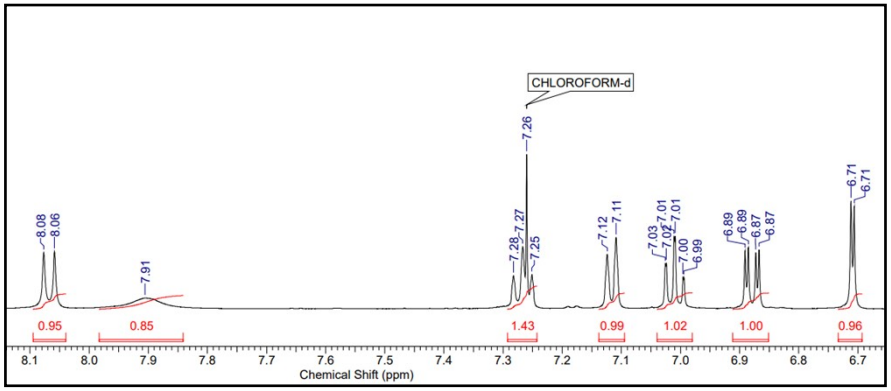


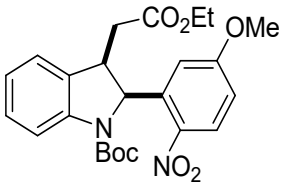
4n



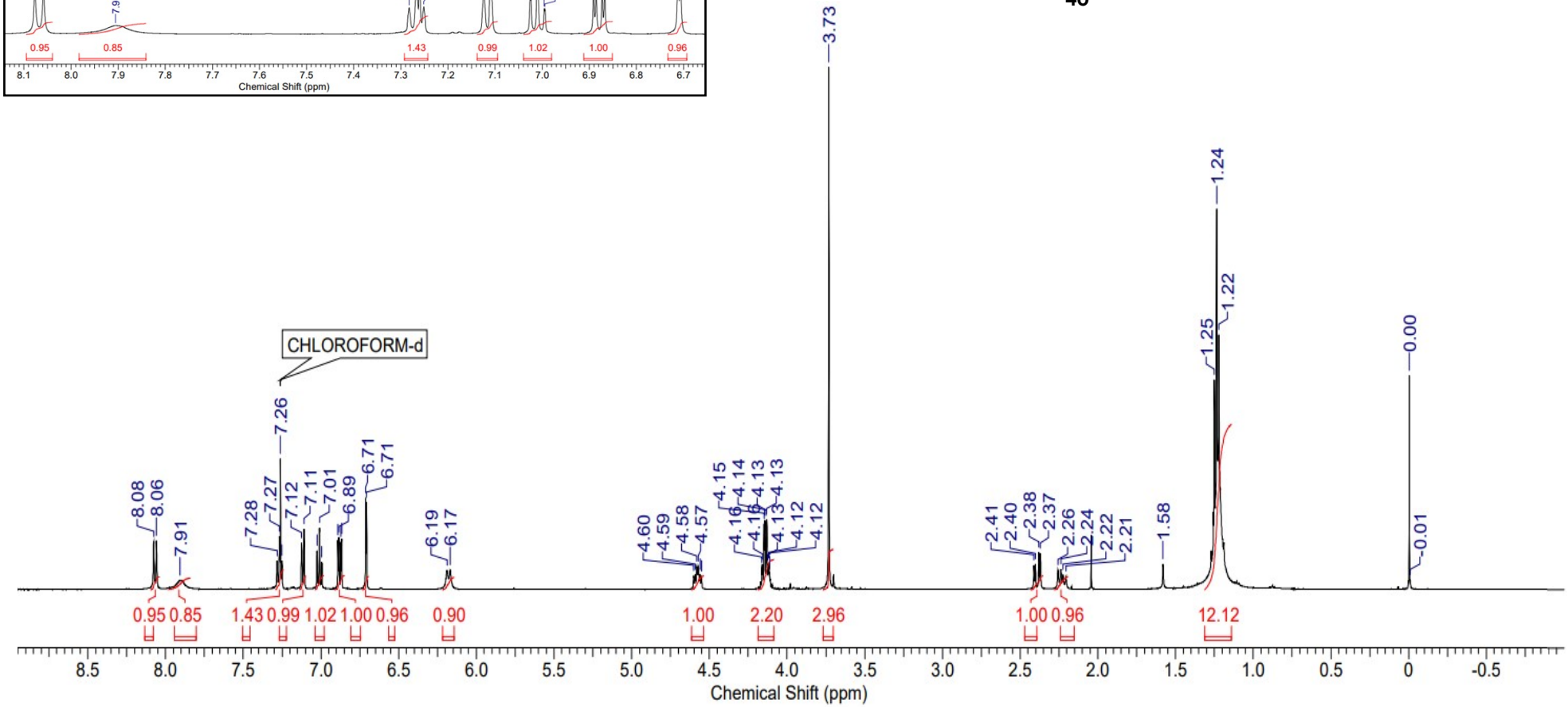
8-38. NMR Spectra of *tert*-Butyl 3-(2-Ethoxy-2-oxoethyl)-2-(5-methoxy-2-nitrophenyl)-1H-indoline-1-carboxylate (4o)

a) ^{1}H NMR Spectrum (500 MHz, $CDCl_3$)

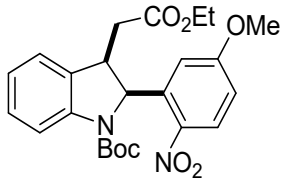




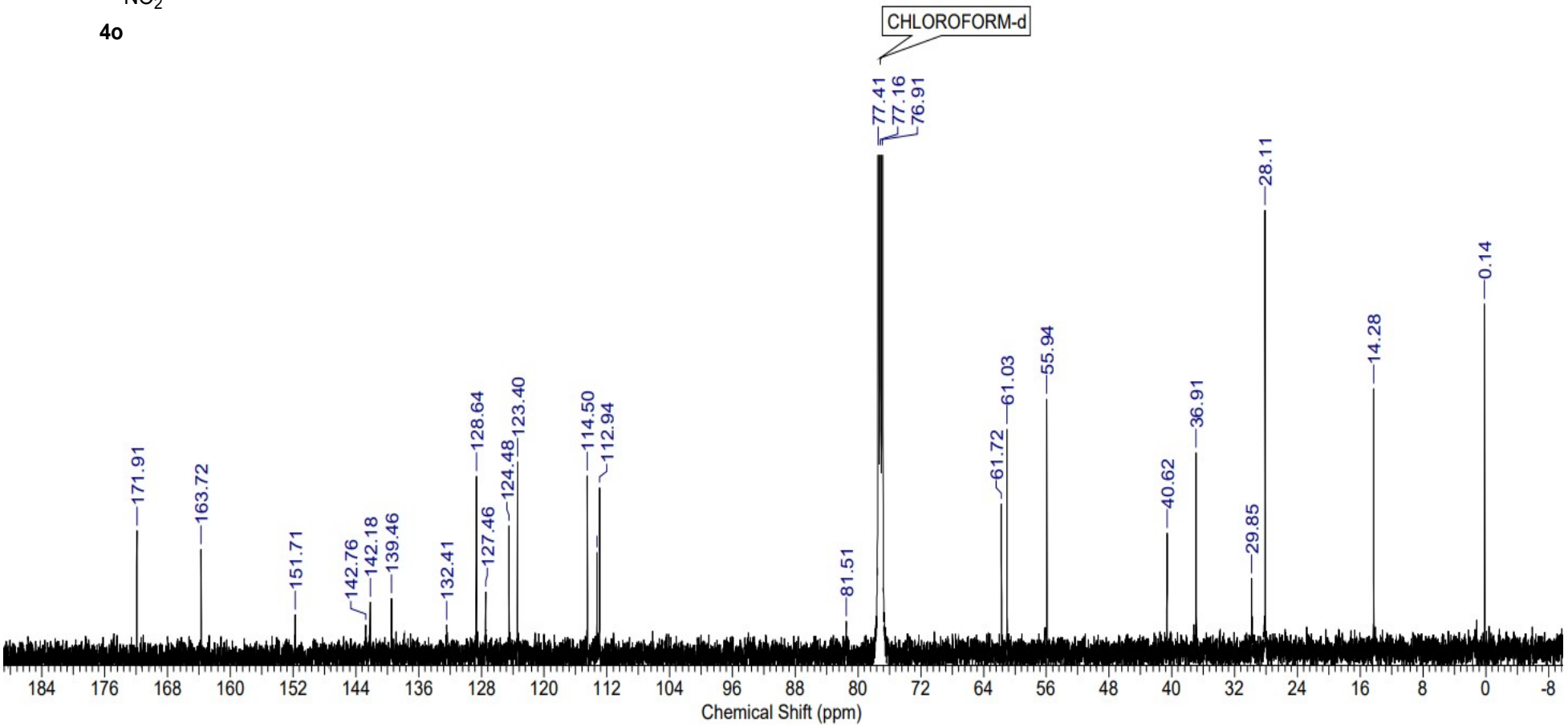
4o



b) ^{13}C NMR Spectrum (125 MHz, $CDCl_3$)

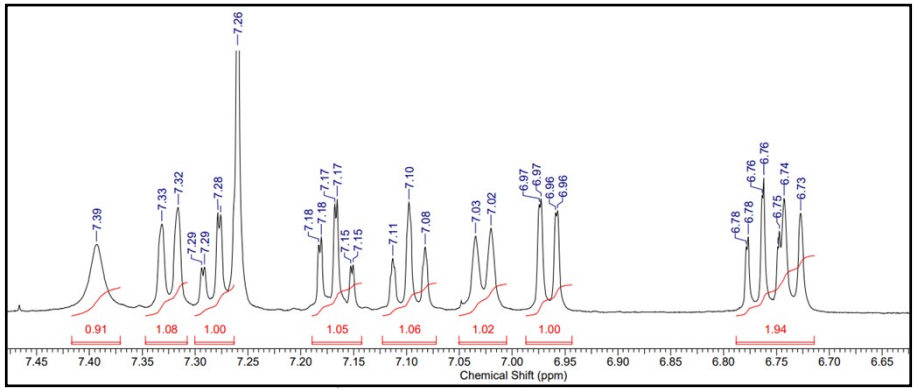


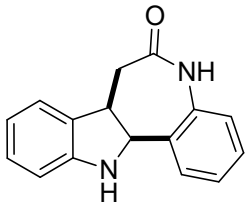
4o



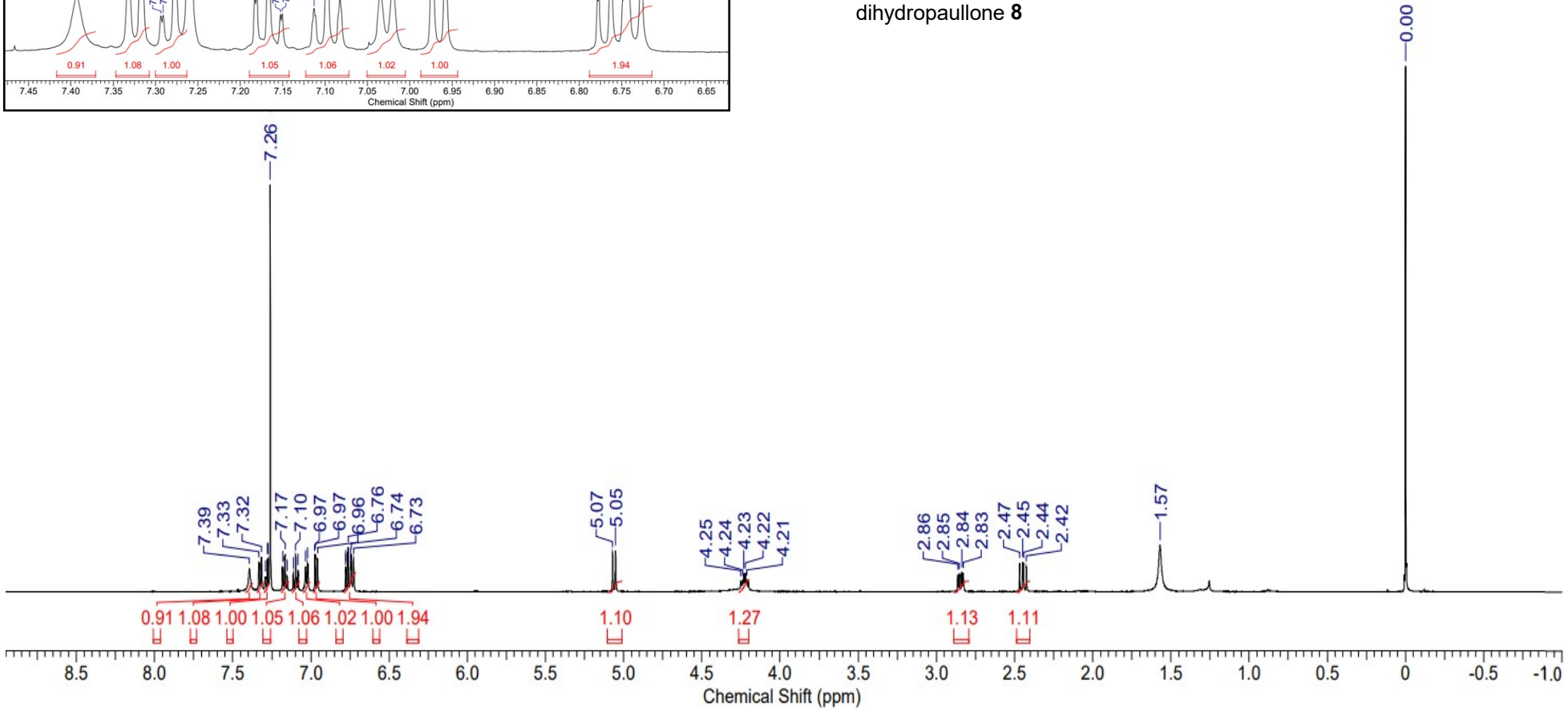
8-39. NMR Spectra of Dihydropaullone (8)

a) ^{1}H NMR Spectrum (500 MHz, $CDCl_3$)

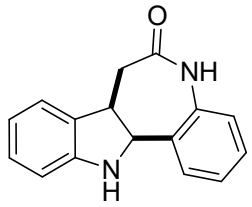




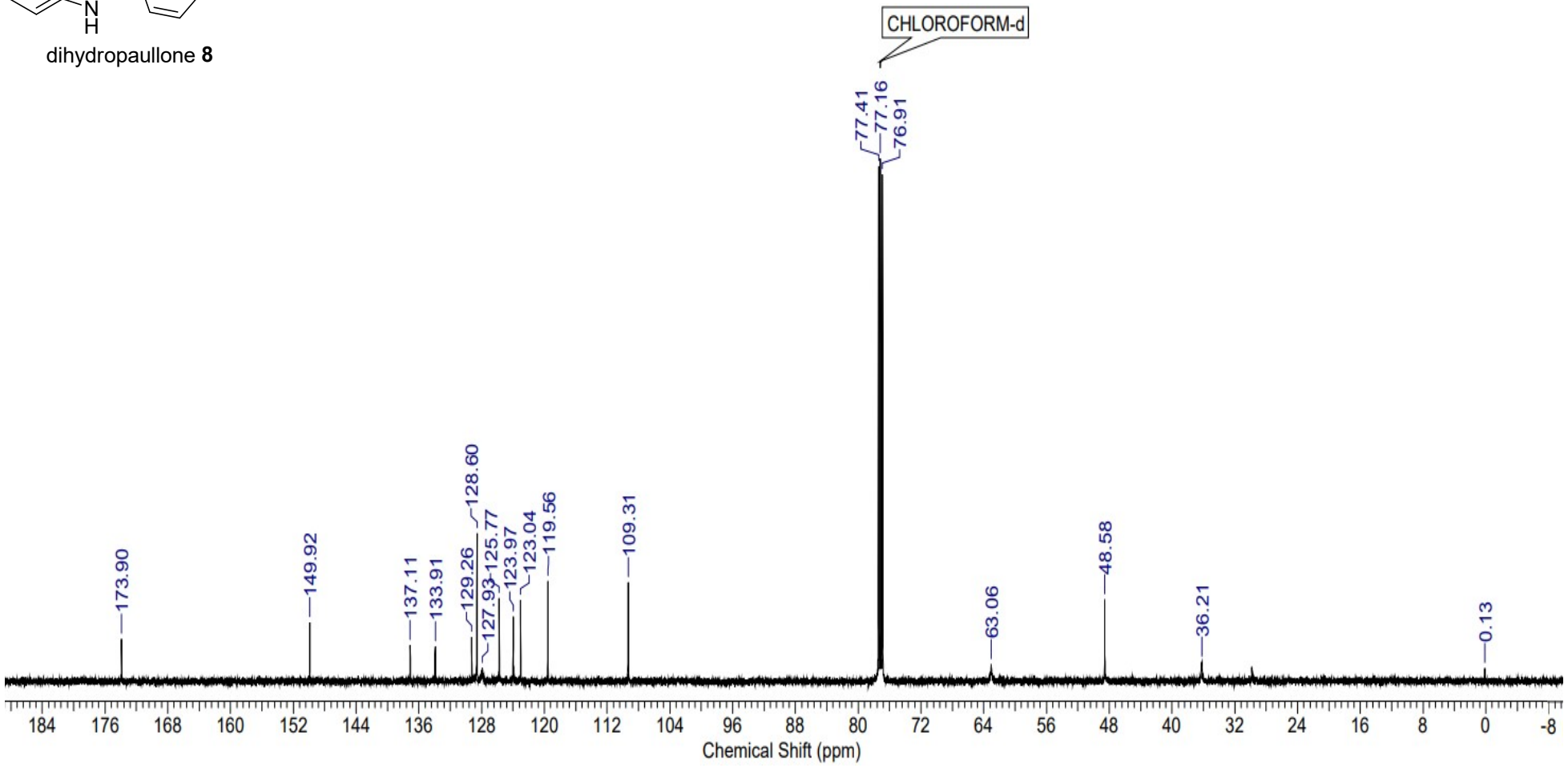
dihydropaullone **8**



b) ^{13}C NMR Spectrum (125 MHz, $CDCl_3$)

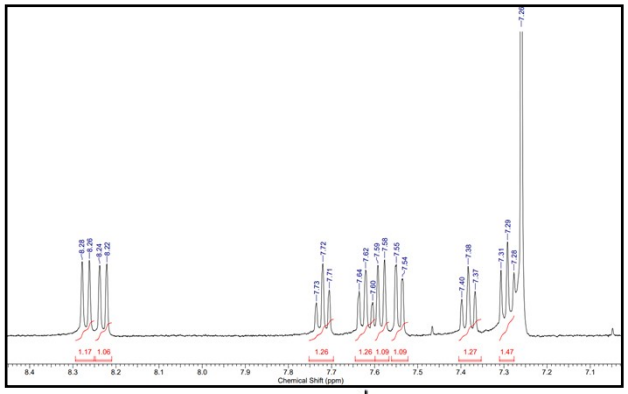


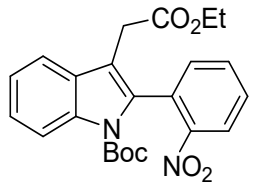
dihydropaullone **8**



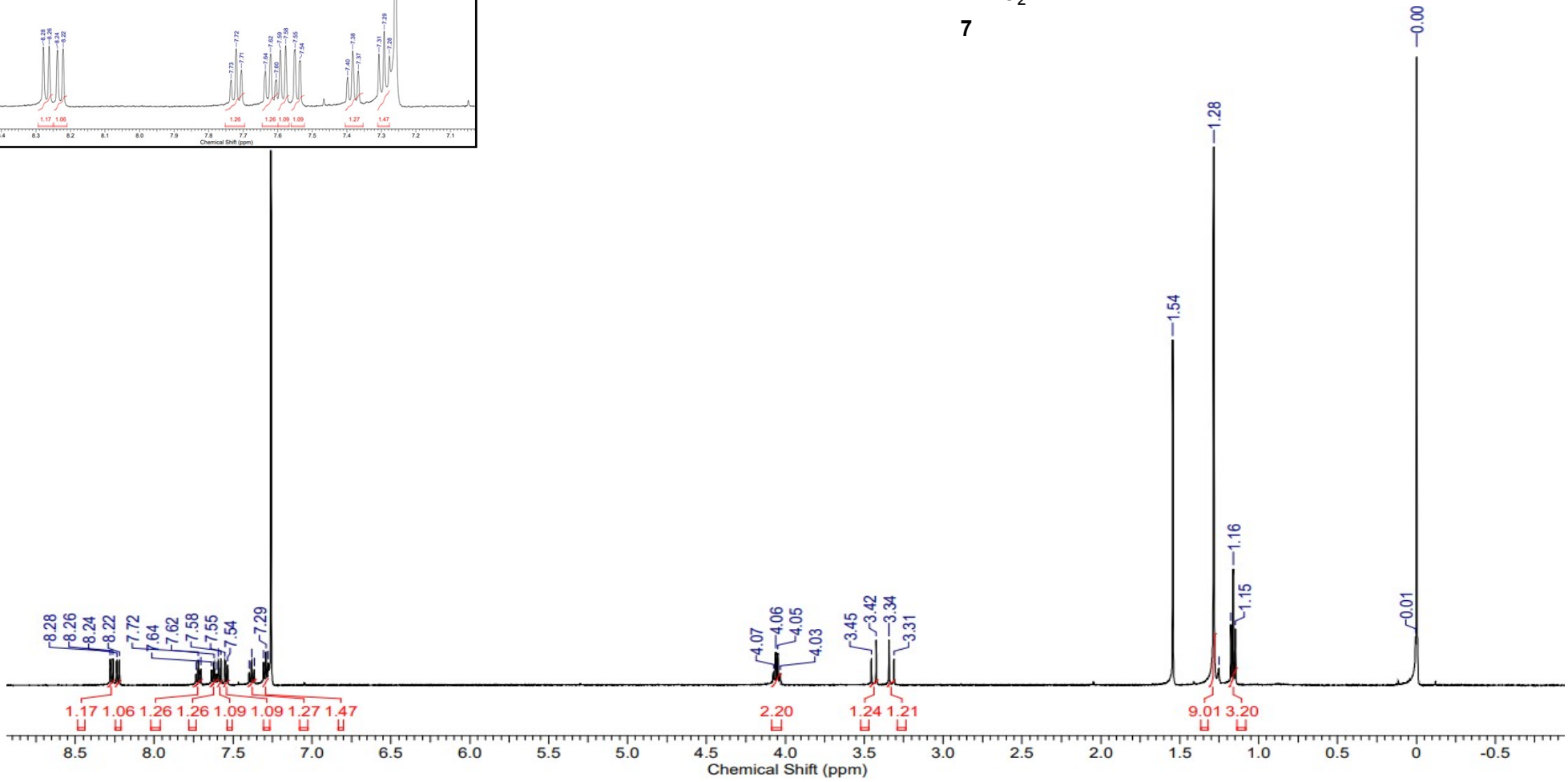
8-40. NMR Spectra of *tert*-Butyl 3-(2-Ethoxy-2-oxoethyl)-2-(2-nitrophenyl)-1H-indole-1-carboxylate (7)

a) ^{1}H NMR Spectrum (500 MHz, $CDCl_3$)

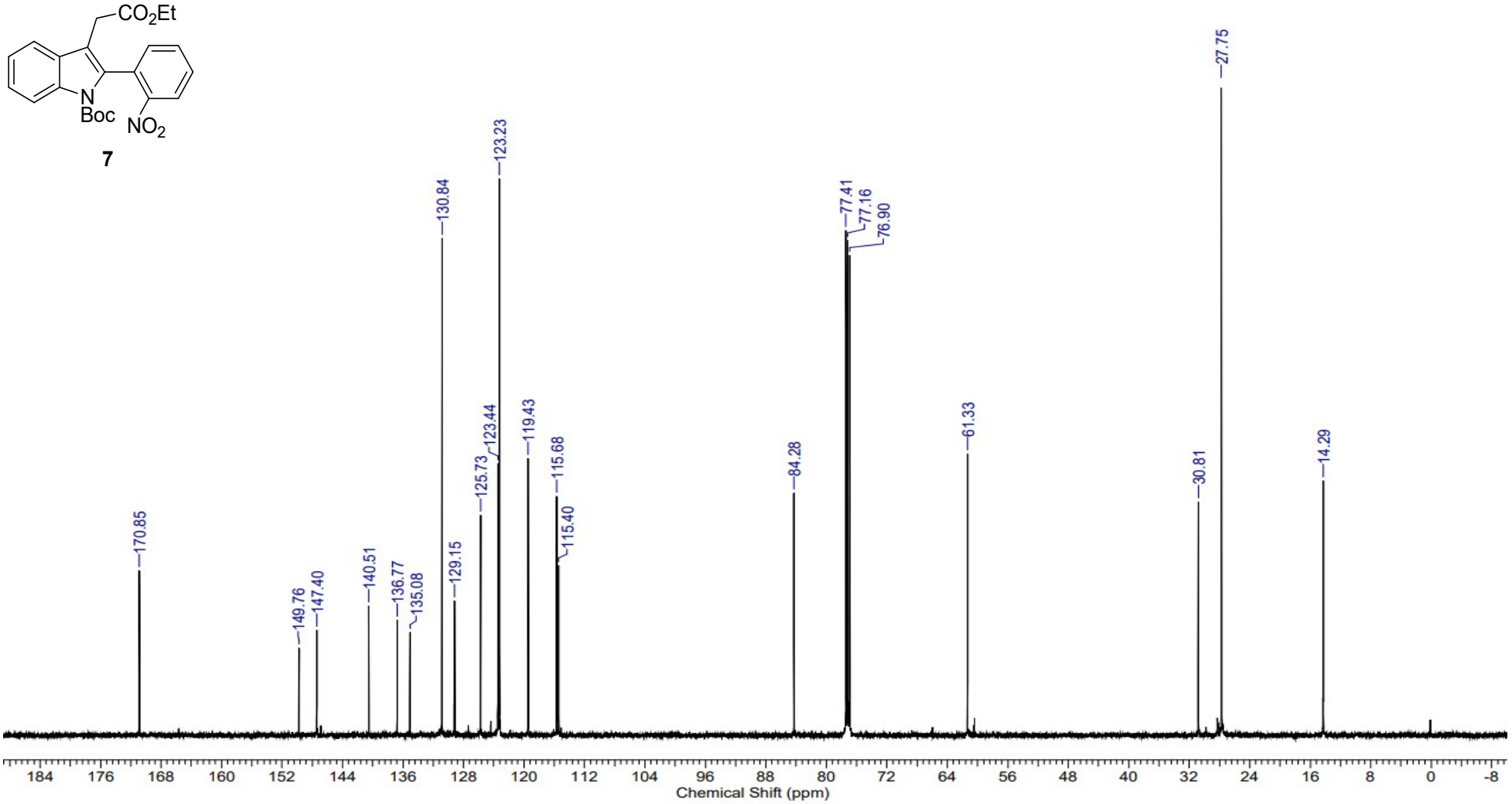




7

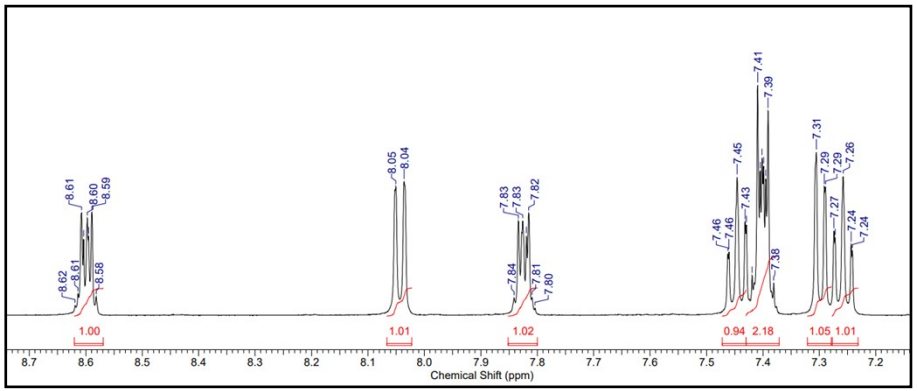


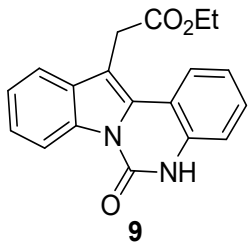
b) ^{13}C NMR Spectrum (125 MHz, $CDCl_3$)



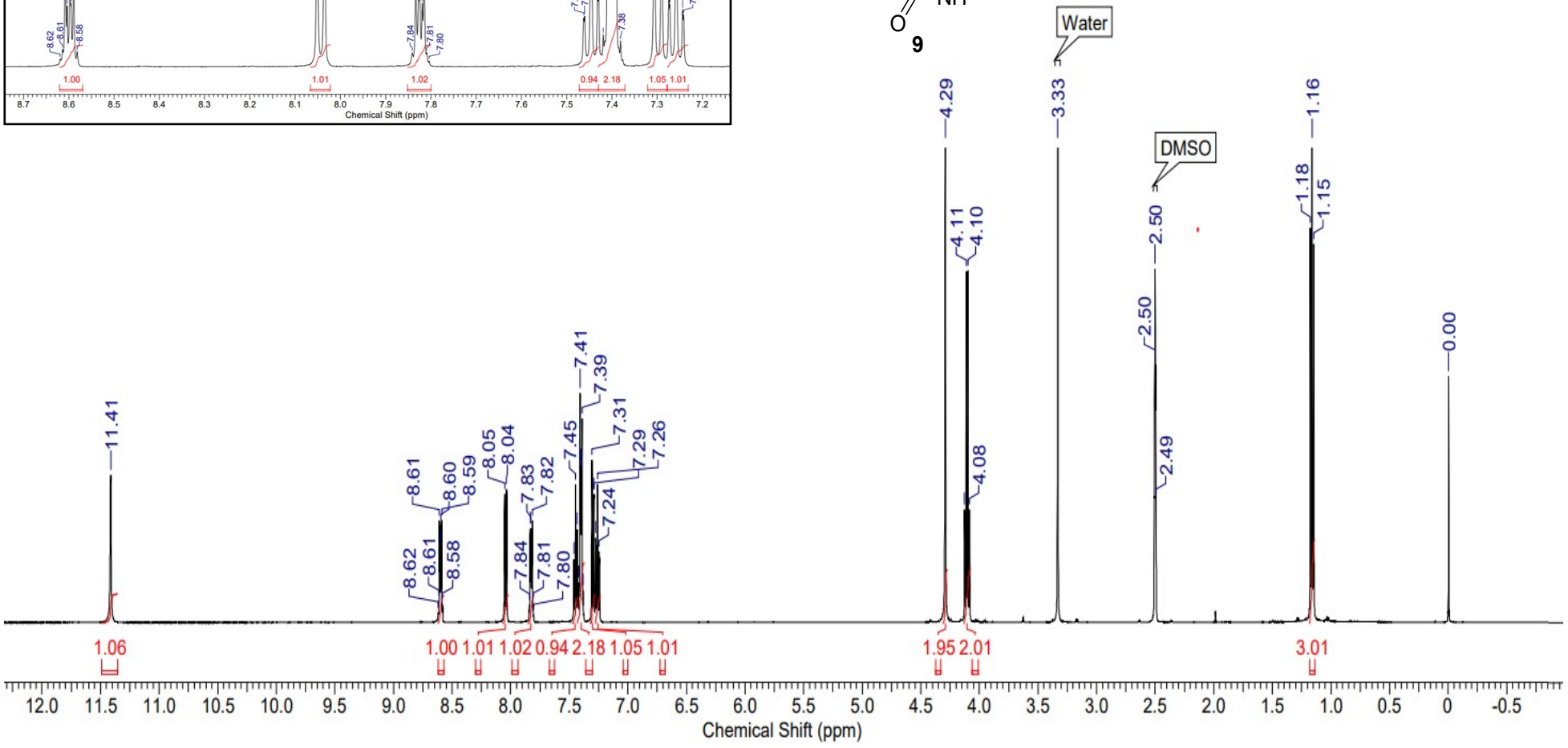
8-41. NMR Spectra of Ethyl 2-(6-Oxo-5,6-dihydroindolo[1,2-c]quinazolin-12-yl)acetate (9)

a) ^{1}H NMR Spectrum (500 MHz, DMSO)

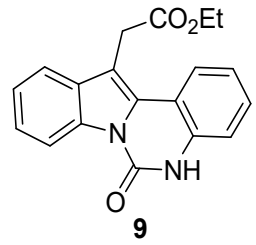




9



b) ^{13}C NMR Spectrum (125 MHz, DMSO)



9