Electronic Supplementary Information for

Synthesis of 5,6-dihydropyrrolo[2,1-*a*]isoquinolines featuring an intramolecular radical-oxidative cyclization of polysubstituted pyrroles, and evaluation of their cytotoxic activity.

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General

^{1}H NMR spectra were recorded on Varian Gemini-200 MHz and Eclipse 300 MHz JEOL spectrometers in deuterated chloroform ($CDCl_3$) solutions with internal standard TMS (0 ppm) or in deuterated dimethyl sulfoxide (DMSO-d_6), and the chemical shifts were reported in parts per million (δ/ppm). The peak patterns are indicated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. The coupling constants (*J*) are reported in Hertz (Hz). ^{13}C NMR spectra were recorded at 50 MHz and 75 MHz on the same instruments. Assignments of ^{13}C spectra were performed by DEPT experiments. The X-ray crystallography was carried out on a Bruker Smart Apex CCD diffractometer.

2-(2-bromo-4,5-dimethoxyphenyl)ethanol A solution of commercially available 2-(3,4-dimetoxyphenyl)ethanol (1.0 g, 5.5 mmol) in dry DMF (18 mL) was cooled at 0°C, and *N*-bromosuccinimide (1.5 g, 8.2 mmol) was added portionwise. The mixture was warmed at room temperature (RT), stirred overnight, diluted with AcOEt (20 mL), and washed with a solution of $Na_2S_2O_3$ (5wt%, 3 x 10 mL), with H_2O, then with brine (3 x 10 mL). The organic layer was dried with anhydrous Na_2SO_4 then evaporated *in vacuo*. The residue was purified by flash column chromatography on silica gel, to furnish **17** (0.89 g) as yellow oil, yield 62%. TLC (hexane:EtOAc, 60:40 v/v): R_f = 0.16; ^{1}H-NMR (200 MHz, $CDCl_3$) δ/ppm: 1.67 (brs, 1H, -OH), 2.95 (t, *J*= 6.6 Hz, 2H), 3.82-3.89 (m, 8H), 6.78 (s, 1H), 7.01 (s, 1H); ^{13}C-NMR (50 MHz, $CDCl_3$) δ/ppm: 148.2, 129.6, 115.6, 114.3, 113.7, 62.3, 56.1, 56.0, 38.9; IR (Film, cm^{-1}) 3491, 3384, 3081, 3001, 2954, 2937, 2879, 2843, 1723, 1603, 1574, 1509, 1464, 1442; MS (EI) m/z 260 (M^+, 40%), 262 ([M^+]+2, 38%), 229 (M^+-31, 100%), 231 ([M^+-31]+2, 98%).

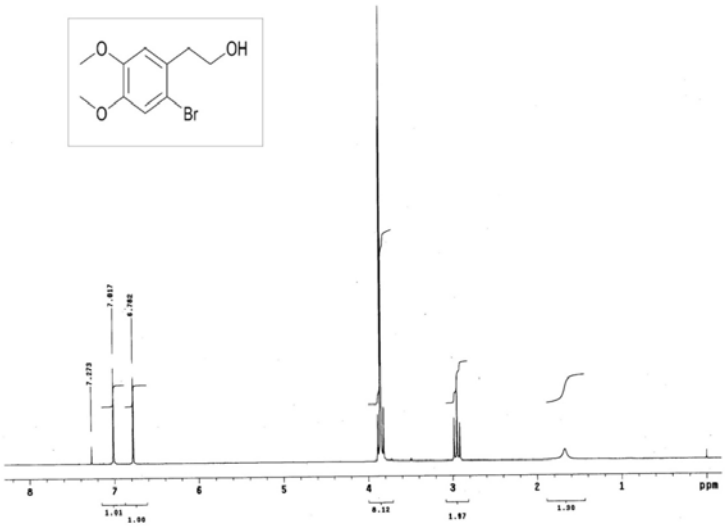

Figure 1. ^{1}H NMR Spectrum of 2-(2-bromo-4,5-dimethoxyphenyl)ethanol (200 MHz, $CDCl_3$) *δ*(ppm).

2-(2-bromo-4,5-dimethoxyphenyl)ethyl *p*-toluenesulfonate (8) *p*-toluenesulfonyl chloride (0.88 g, 4.6 mmol) was added portionwise to a solution of 2-(2-bromo-4,5-dimethoxyphenyl)ethanol (**17**, 1.0 g, 3.8 mmol), 4-(dimethylamino)pyridine (0.55 g, 4.6 mmol), and pyridine (0.9 mL, 11.2 mmol) in CH_2Cl_2 (6 mL) at 5°C. The mixture was warmed at room temperature and stirred for 4 h. After that time, H_2O (3 x 6 mL) was added dropwise, and the organic layer was washed with a solution of HCl (20%, 3 x 6 mL), dried with anhydrous Na_2SO_4, and evaporated *in vacuo*. The residue was purified by flash column chromatography on silica gel, to furnish **8** (0.86 g) as a white solid, melting point (m.p.) 66°C, yield 55%. TLC (hexane:EtOAc, 60:40): R_f = 0.31; ^{1}H-NMR (300 MHz, $CDCl_3$) δ/ppm: 2.43 (s, 3H), 3.02 (t, *J*= 6.6 Hz, 2H), 3.82 (s, 3H), 3.84 (s, 3H), 4.24 (t, *J*= 6.6 Hz, 2H), 6.70 (s, 1H), 6.92 (s, 1H), 7.27 (d, *J*= 8.1 Hz, 2H), 7.69 (d, *J*= 8.1 Hz, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ/ppm: 148.6, 148.4, 133.0, 129.7, 127.8, 127.5, 115.5, 114.1, 113.9, 69.1, 56.1, 56.0, 35.3, 21.6; IR (KBr, cm^{-1}) 3086, 3060, 3000, 2965, 2940, 2913, 2843, 2603, 1599, 1508, 1467, 1438; MS (EI) m/z 414 (M^+, 30%), 416 ([M^+]+2, 27%), 242 (M^+-172, 100%), 244 ([M^+-172]+2, 98%).

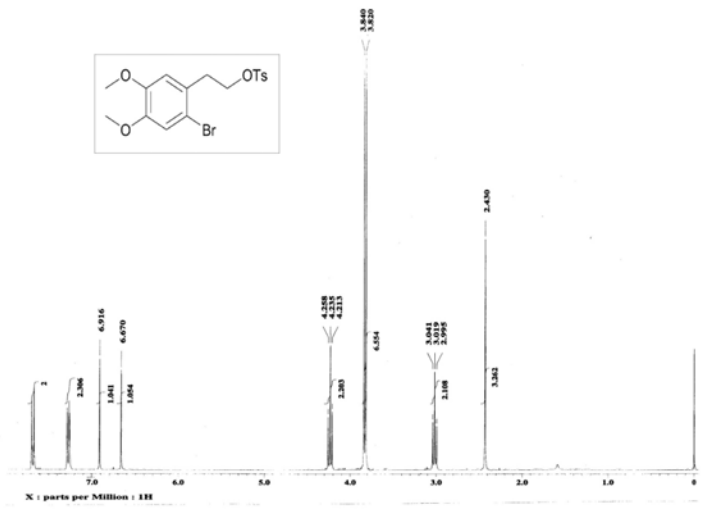

Figure 2. ^{1}H NMR Spectrum of **8** (300 MHz, $CDCl_3$) δ(ppm).

1-(1-isocyanoethylsulfonyl)-4-methylbenzene (10) A solution of commercially available *p*-toluenesulfonylmethylisocyanide (1.0 g, 5.1 mmol) and tetrabutylammonium iodide (2.8 g, 7.7 mmol) in CH_2Cl_2 (10 mL) was cooled at 0°C, then NaOH (30%, 10 mL) was added and the solution was stirred for 15 minutes. Subsequently, MeI (0.73 mL, 10.2 mmol) was added dropwise, and the mixture was stirred for 3 h. After that time, H_2O (50 mL) was added and the compound was extracted with CH_2Cl_2 (2 x 10 mL). The organic layer was dried over anhydrous Na_2SO_4 and evaporated *in vacuo*. The residue was purified by flash column chromatography on silica gel, to furnish **10** (0.77 g) as a yellow solid, m.p. 46°C, yield 90%. TLC (hexane:EtOAc, 70:30 v/v): R_f = 0.41; ^{1}H-NMR (200 MHz, $CDCl_3$) δ/ppm: 1.74 (d, *J*= 6.8 Hz, 3H), 2.49 (s, 3H), 4.61 (q, *J*= 6.8 Hz, 1H), 7.44 (d, *J*= 8.6 Hz, 2H), 7.87 (d, 8.4 Hz, 2H); ^{13}C-NMR (50 MHz, $CDCl_3$) δ/ppm: 146.7, 130.5, 130.1, 129.8, 68.3, 21.7, 15.4; IR (KBr, cm^{-1}) 3068, 2924, 2872, 2133, 1930, 1814, 1698, 1660, 1593, 1448, 1325; MS (EI) m/z 209 (M^+, 10%), 155 (M^+ -54, 70%), 91 (M^+- 118, 100%).

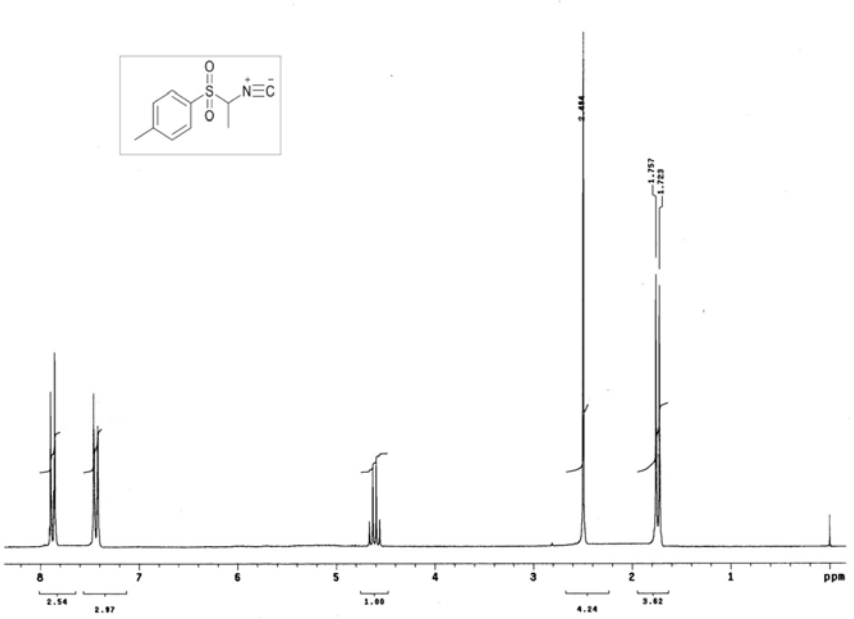

Figure 3. ^{1}H NMR Spectrum of **10** (200 MHz, $CDCl_3$) δ(ppm).

Piperazine-1-carbaldehyde To ethyl formate (1 mL, 12.4 mmol), piperazine (1.0 g, 11.6 mmol) was added portionwise, and the resulting solution was warmed at 85°C for 5 h. After that time, the solution was cooled at room temperature, and EtOAc (10 mL) was added to remove the insoluble remaining piperazine. The solvent was evaporated *in vacuo*, and the residue was purified by distillation at 100°C/0.5 mmHg to furnish **18** (0.8 g, lit.[ref] 94–97°C/0.5 mmHg) as a yellow oil, yield 61%. ^{1}H-NMR (200 MHz, $CDCl_3$) δ/ppm: 1.99 (s, 1H), 2.77-2.86 (m, 3H), 3.29-3.52 (m, 5H), 7.99 (s, 1H (60%)), 8.08 (s, 1H (40%)); ^{13}C-NMR (50 MHz, $CDCl_3$) δ/ppm: 160.8, 46.7, 46.6, 45.3, 41.1; IR (Film, cm^{-1}) 3423, 3313, 2956, 2923, 2866, 1659, 1445, 1401; MS (EI) m/z 114 (M^+, 85%), 69 (M^+ -45, 100%).

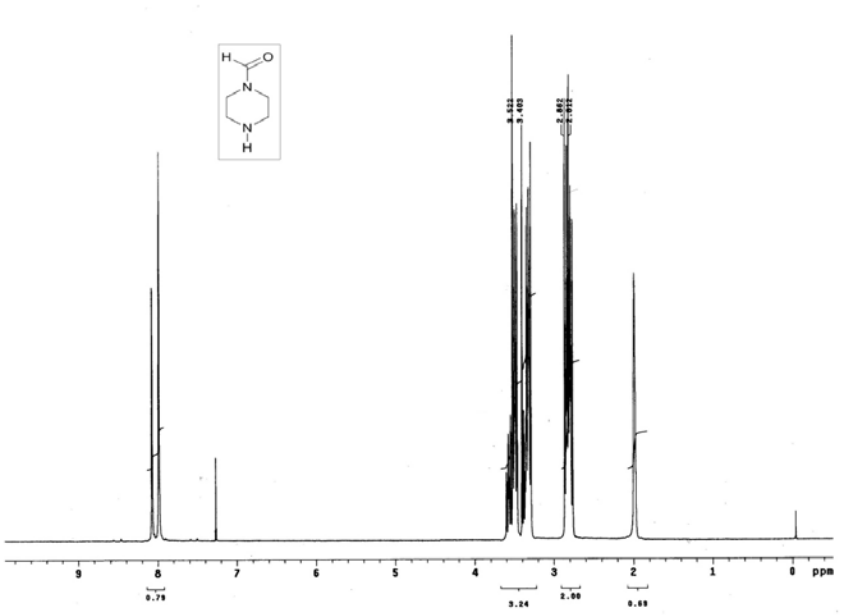

Figure 4. ^{1}H NMR Spectrum of the piperazine-1-carbaldehyde (200 MHz, $CDCl_3$) δ(ppm).

1-(cyclohexylmethyl)piperazine (12) A mixture of (bromomethyl)cyclohexane (1.21 mL, 8.8 mmol), piperazine-1-carbaldehyde (**18**, 1.0 g, 8.8 mmol), K_2CO_3 (1.21 g, 8.8 mmol), and KI (0.02 g, 0.12 mmol) in CH_3CN (10 mL) was refluxed for 23 h. After that time, the

reaction was cooled at room temperature, filtered, and concentrated *in vacuo*. The residue was diluted with EtOH (5 mL), NaOH 5 N (5 mL) was added, and the solution was refluxed for 4 h. Finally, the EtOH was removed under reduced pressure, and the residue was diluted with CH_2Cl_2 (10 mL) and washed with H_2O and brine (3 x 5 mL). The organic layer was dried with anhydrous Na_2SO_4 and evaporated *in vacuo*. The residue was purified by distillation to furnish **12** at 80°C/0.5 mmHg (1.0 g, lit.[ref] 104–112°C/1.2 mmHg) as a yellow oil, yield 62%. ^{1}H-NMR (300 MHz, $CDCl_3$) δ/ppm: 0.80-0.92 (m, 2H), 1.13-1.28 (m, 3H), 1.43-1.53 (m, 1H), 1.68-1.78 (m, 5H), 2.09 (d, *J*= 6.9 Hz, 2H), 2.18 (s, 1H), 2.35 (brs, 4H), 2.88 (t, *J*= 5.1 Hz, 4H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ/ppm: 66.1, 54.2, 45.5, 34.7, 31.8, 26.7, 26.1. IR (Film, cm^{-1}) 3382, 2922, 2849, 2805, 1636, 1548, 1449, 1416.

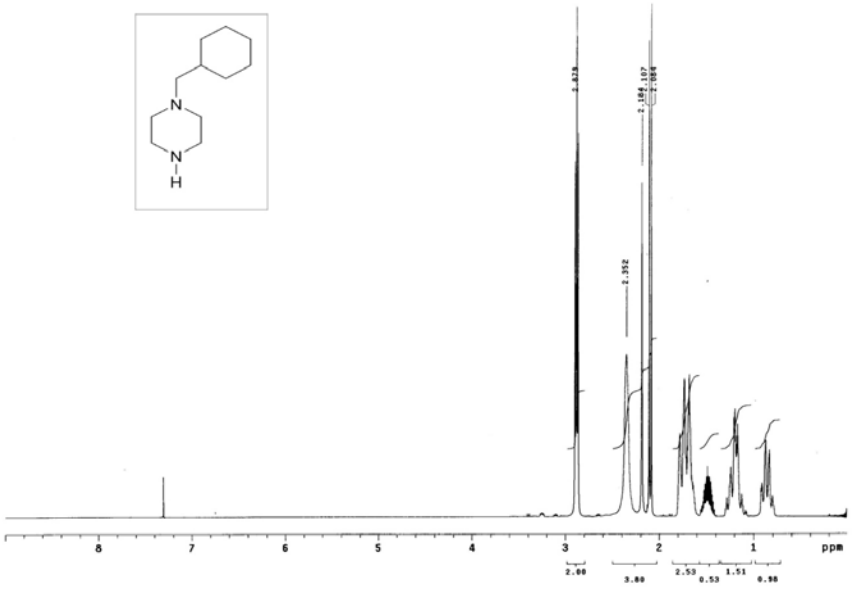

Figure 5. ^{1}H NMR Spectrum of **12** (200 MHz, $CDCl_3$) δ(ppm).

Experimental procedure for the Heck reaction

A mixture of the corresponding iodo compound (4.0 mmol), palladium(II) acetate (0.01 g, 0.06 mmol), triphenylphosphine (0.06 g, 0.24 mmol), Et_3N (0.67 mL, 4.8 mmol), and the corresponding alkene (4.8 mmol) was refluxed in dry acetonitrile (10 mL) for 5–6 h. After that time, the mixture was cooled at room temperature. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (hexane:EtOAc, 90:10) to furnish the respective coupling product.

Ethyl cinnamate (9b) From iodobenzene (0.44 mL, 4.0 mmol) and ethylacrylate (0.52 mL, 4.8 mmol), to furnish 0.68 g of **9b** as a yellow oil, yield 97%. ^{1}H-NMR (200 MHz, $CDCl_3$) δ/ppm: 1.34 (t, *J*= 7.0 Hz, 3H), 4.27 (q, *J*= 7.2 Hz, 2H), 6.44 (d, *J*= 16.0 Hz, 1H), 6.37-7.41 (m, 3H), 7.50-7.55 (m, 2H), 7.69 (d, *J*= 16.0 Hz, 1H); ^{13}C-NMR (50 MHz, $CDCl_3$) δ/ppm: 167.0, 144.6, 134.5, 130.2, 128.9, 128.0, 118.3, 60.4, 14.2. IR (Film, cm^{-1}) 3061, 3029, 2982, 2936, 2904, 1712, 1638, 1449, 1311.

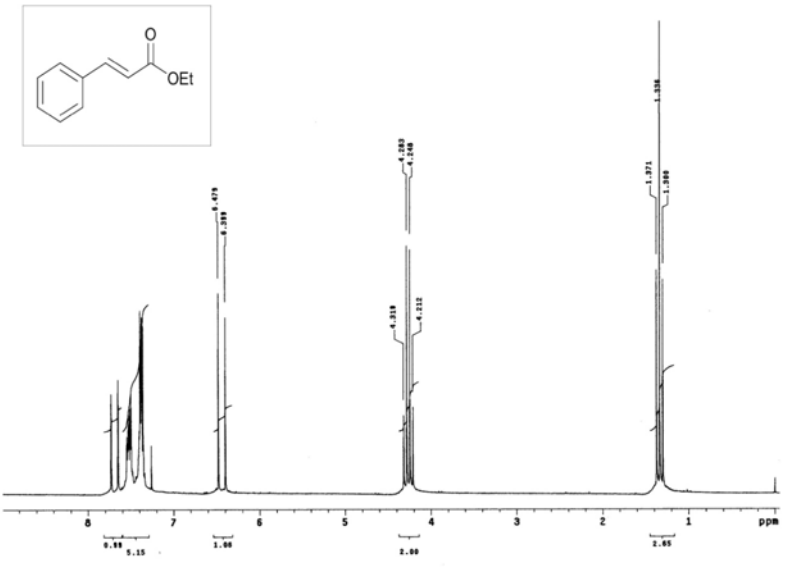

Figure 6. ^{1}H NMR Spectrum of **9b** (200 MHz, $CDCl_3$) δ(ppm).

(*E*)-ethyl 3-(3-aminophenyl)acrylate (9c) From 3-iodoaniline (0.48 mL, 4.0 mmol) and ethylacrylate (0.52 mL, 4.8 mmol), to furnish 0.48 g of **9c** as a brown solid, m.p. 48°C, yield 80%. ^{1}H-NMR (200 MHz, $CDCl_3$) δ/ppm: 1.33 (t, *J*= 7.2 Hz, 3H), 3.74 (brs, 2H, -$N\underline{H}_2$), 4.26 (q, *J*= 7.2 Hz, 2H), 6.38 (d, *J*= 16.0 Hz, 1H), 6.67-6.94 (m, 3H), 7.17 (t, *J*= 7.6 Hz, 1H), 7.60 (d, *J*= 16.0 Hz, 1H).

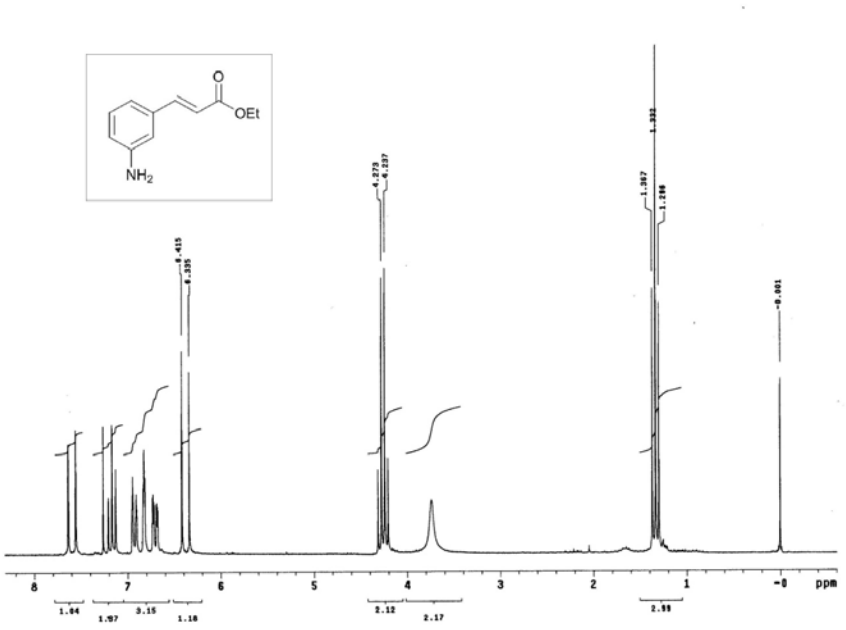

Figure 7. ^{1}H NMR Spectrum of **9c** (200 MHz, $CDCl_3$) *δ*(ppm).

(*E*)-ethyl 3-(thiophen-3-yl)acrylate (9d) From 3-iodothiophene (0.45 mL, 4 mmol) and ethylacrylate (0.52 mL, 4.8 mmol), to furnish 0.38 g of **9d** as a brown oil, yield 65%. ^{1}H-NMR (200 MHz, $CDCl_3$) δ/ppm: 1.33 (t, *J*= 7.2 Hz, 3H), 4.25 (q, *J*= 7.2 Hz, 2H), 6.24 (d, *J*= 16.0 Hz, 1H), 7.05 (dd, *J*= 3.8 y 5.0 Hz, 1H), 7.25 (d, *J*= 3.8 Hz, 1H), 7.37 (d, *J*= 5.0 Hz, 1H), 7.79 (d, *J*= 16.0 Hz, 1H).

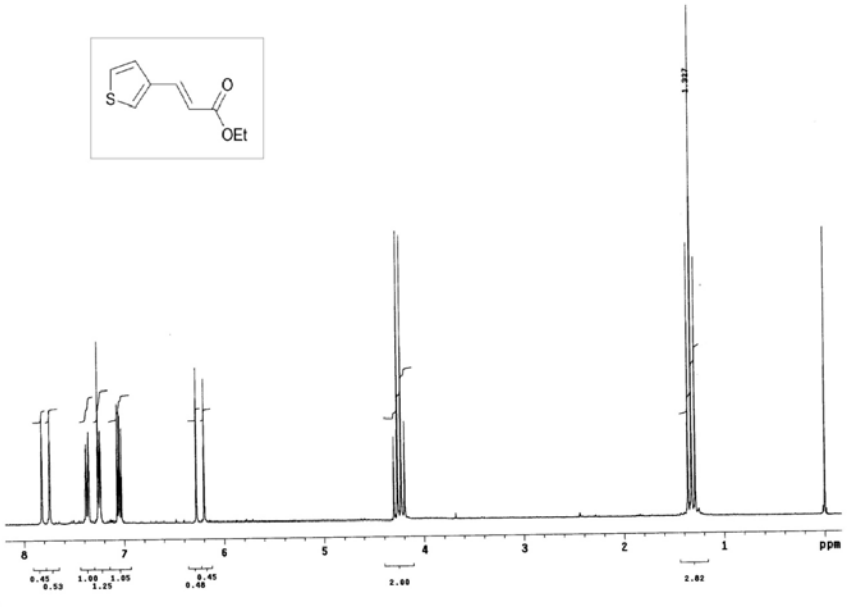

Figure 8. ^{1}H NMR Spectrum of **9d** (200 MHz, $CDCl_3$) δ(ppm).

(*E*)/(*Z*)-3-phenylacrilonitrile (65:35, 9e) From iodobenzene (0.44 mL, 4 mmol) and acrylonitrile (0.31 mL, 4.8 mmol), to furnish 0.45 g of **9e** as a yellow oil, yield 88%. ^{1}H-NMR (200 MHz, $CDCl_3$) δ/ppm: 5.45 (d, *J*= 12.0 Hz, 1H (35%)), 5.88 (d, *J*= 16.0 Hz, 1H (65%)), 7.13 (d, *J*= 12.0 Hz, 1H (35%)), 7.36-7.48 (m, 5H + 1H(65%)).

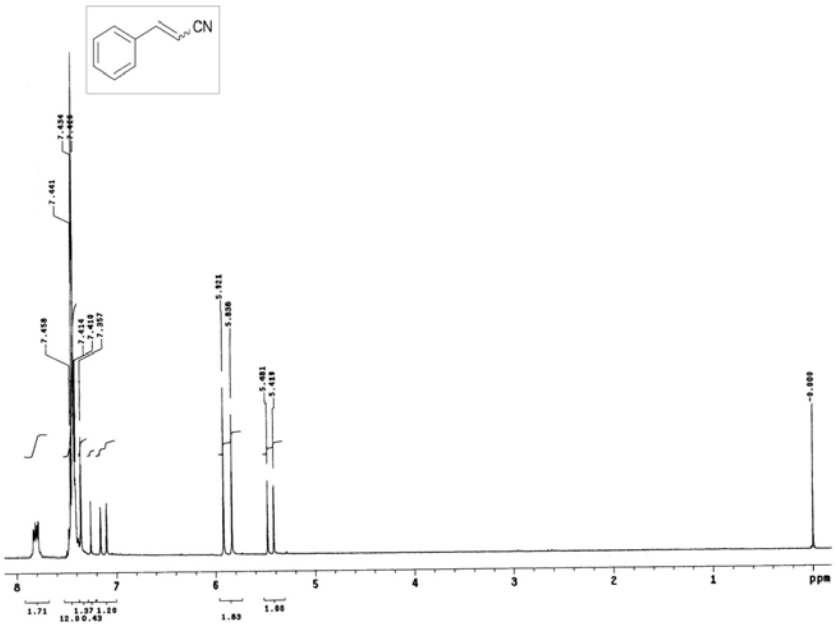

Figure 9. ^{1}H NMR Spectrum of **9e** (200 MHz, $CDCl_3$) δ(ppm).

(*E*)-3-(2-ethoxycarbonyl-vinyl)benzoic acid (11) From 3-iodobenzoic acid (1.0 g, 4 mmol) and ethylacrylate (0.52 mL, 4.8 mmol). After 5 h refluxing, the mixture was cooled at room temperature. The solvent was removed under reduced pressure and the remaining solid was washed with absolute MeOH to furnish 0.58 g of **11** as a white solid, m.p. 159^{o}C, yield 66%. ^{1}H-NMR (200 MHz, DMSO-d_6) δ/ppm: 1.25 (t, *J*= 7.2 Hz, 3H), 4.18 (q, *J*= 7.0 Hz, 2H), 6.67 (d, *J*= 16.0 Hz, 1H), 7.53 (t, *J*= 7.8 Hz, 1H), 7.71 (d, *J*= 16.0 Hz, 1H), 7.94-8.0 (m, 2H), 8.17 (s, 1H), 13.15 (brs, 1H); ^{13}C-NMR (50 MHz, $CDCl_3$) δ/ppm: 166.9, 166.0, 143.4, 134.5, 132.0, 131.6, 131.0, 129.3, 119.4, 60.2, 14.2; IR (KBr, cm^{-1}) 3069, 2985, 2939, 2909, 2821, 2671, 2565, 1963, 1897, 1794, 1726, 1695, 1641, 1605, 1585, 1445; MS (EI) m/z 220 (M^+, 40%), 175 (M^+-45, 100%).

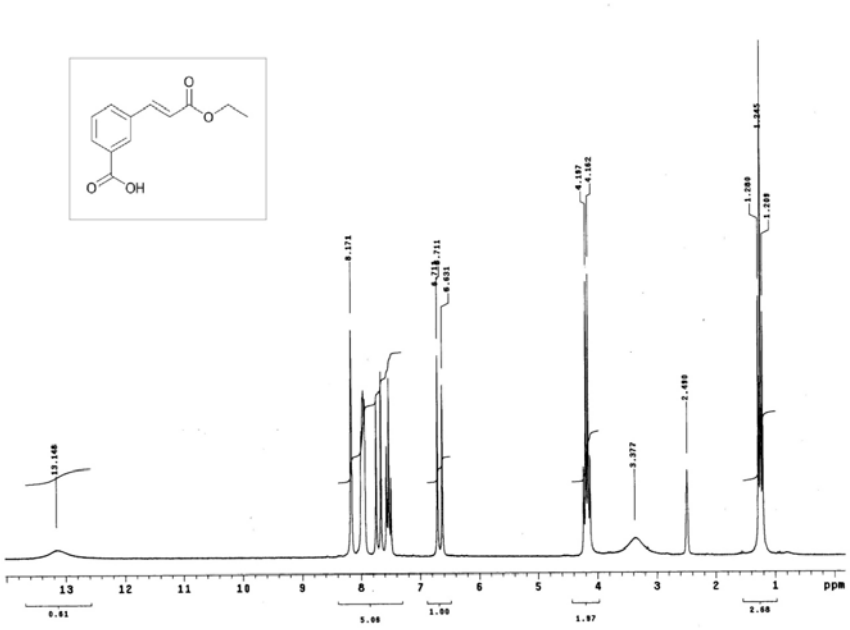

Figure 10. ^{1}H NMR Spectrum of **11** (200 MHz, $CDCl_3$) δ(ppm).

(*E*)-ethyl 3-(3-(4-(cyclohexylmethyl)piperazine-1-carbonyl)phenyl)acrylate (13)

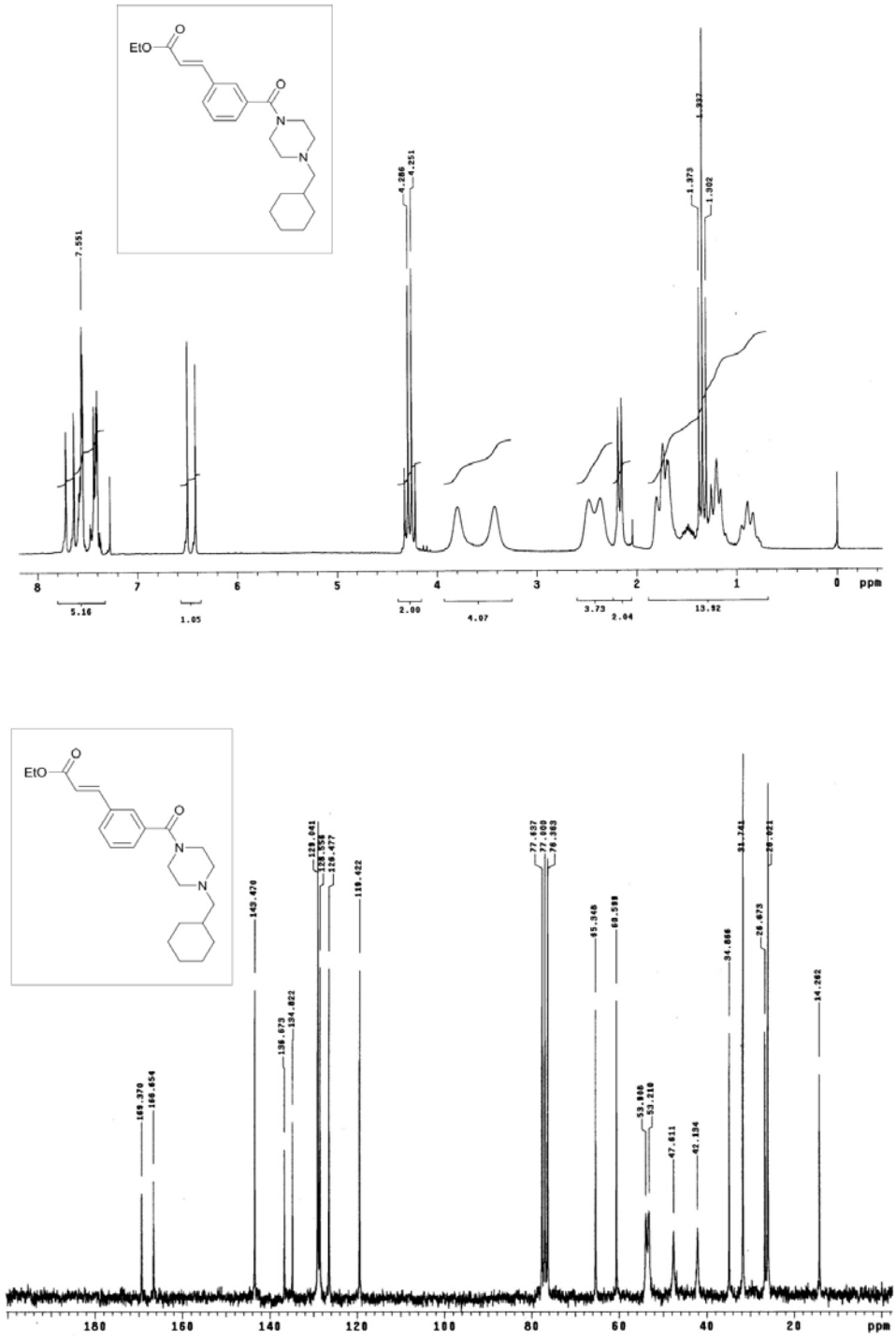

Figure 11. ^{1}H and ^{13}C NMR Spectrum of **13** (200 and 50 MHz, $CDCl_3$) δ(ppm).

NMR Spectrums of the Pyrroles 7a-e and 14

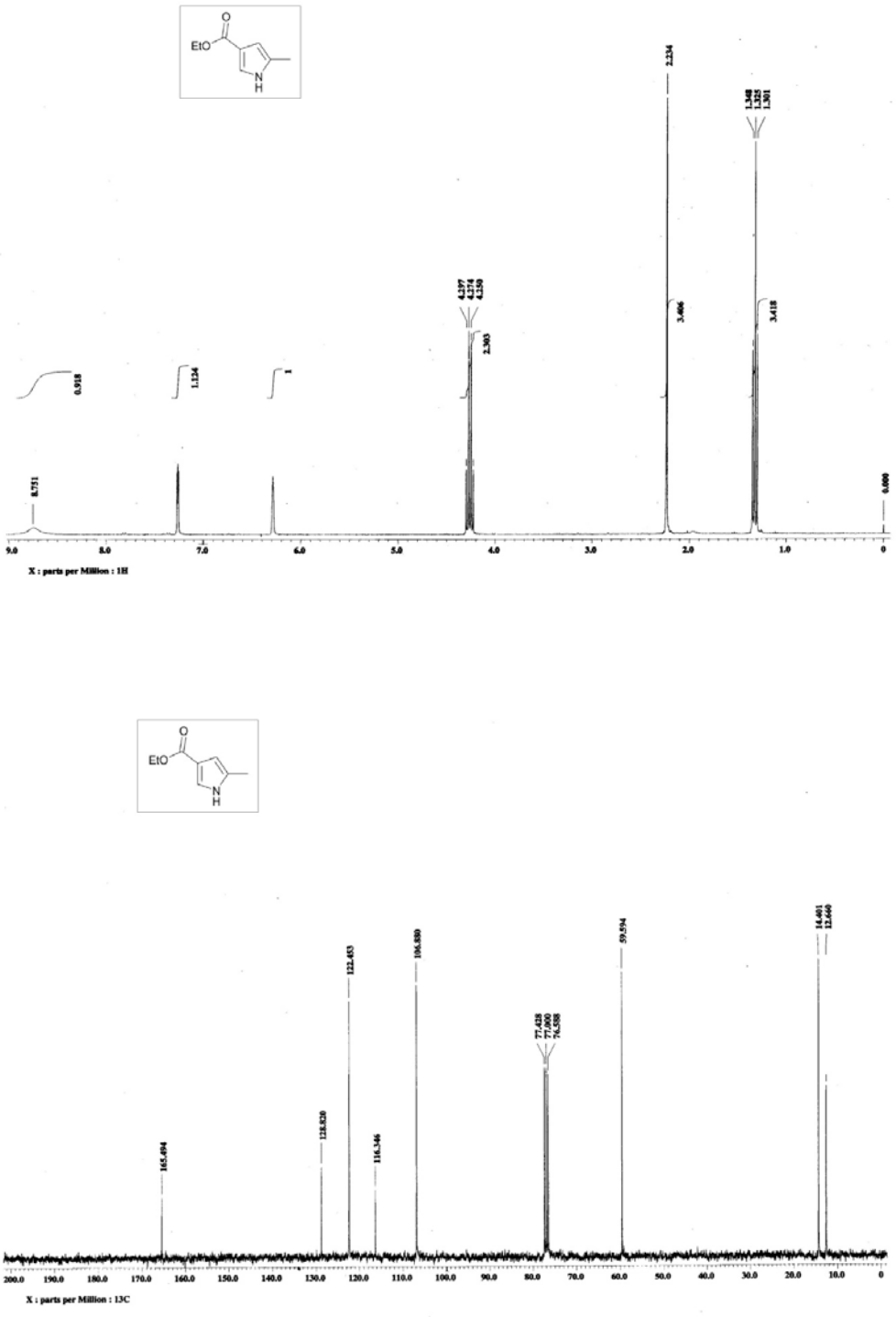

Figure 12. ^{1}H and ^{13}C NMR Spectrum of **7b** (300 and 75 MHz, $CDCl_3$) δ(ppm).

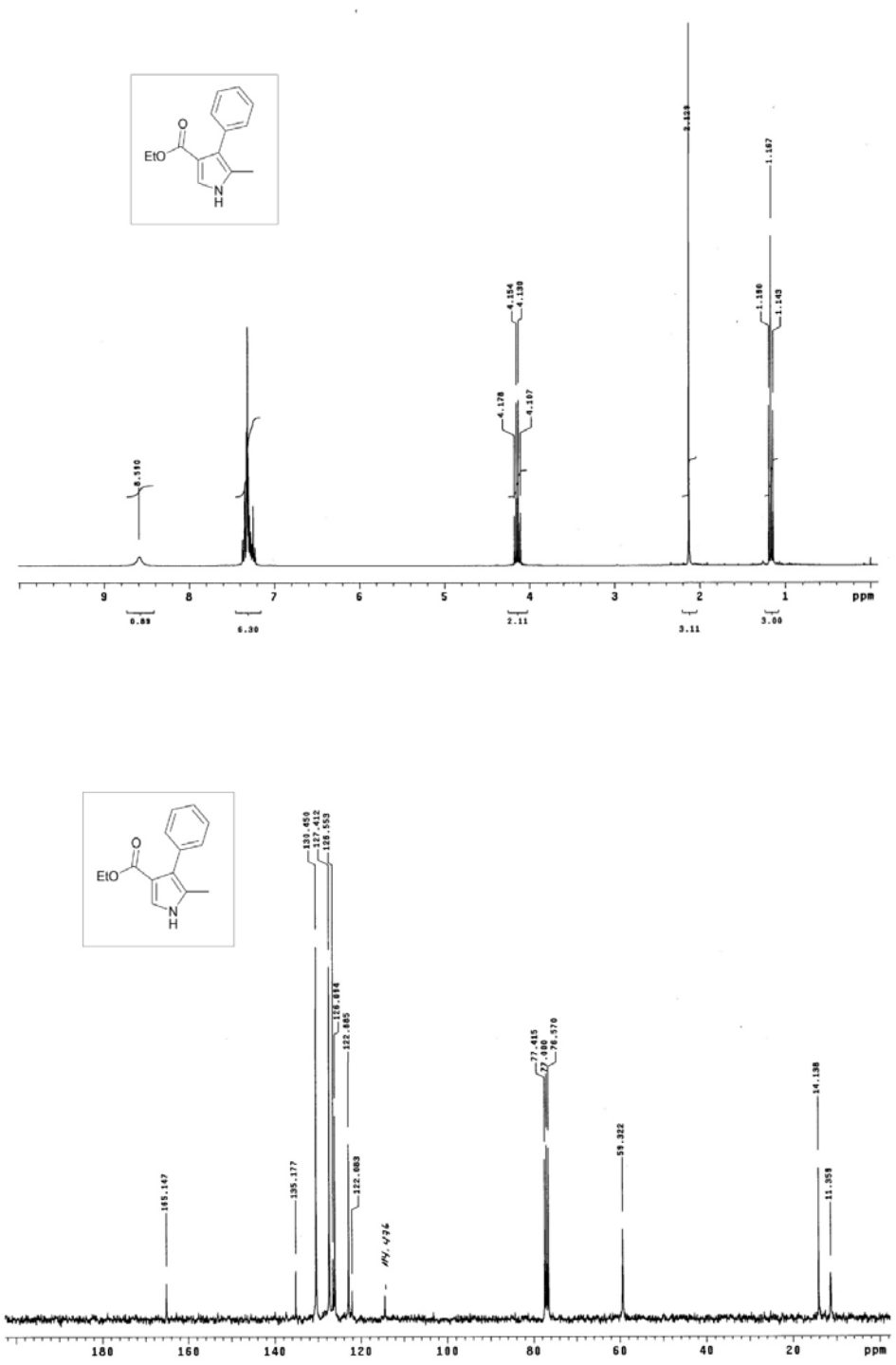

Figure 13. ^{1}H and ^{13}C NMR Spectrum of **7b** (300 and 75 MHz, $CDCl_3$) δ(ppm)

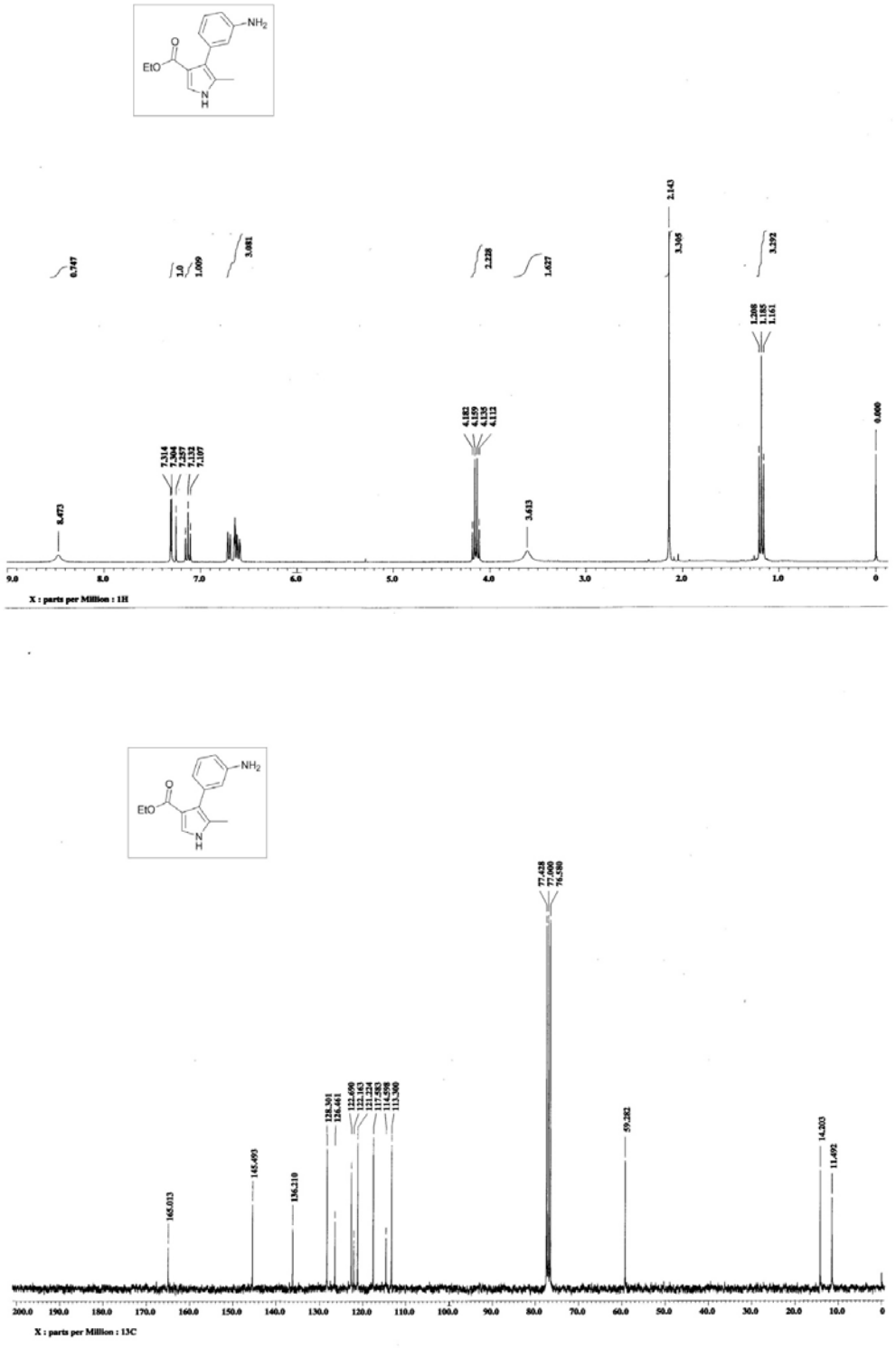

Figure 14. ^{1}H and ^{13}C NMR Spectrum of **7c** (300 and 75 MHz, $CDCl_3$) δ(ppm).

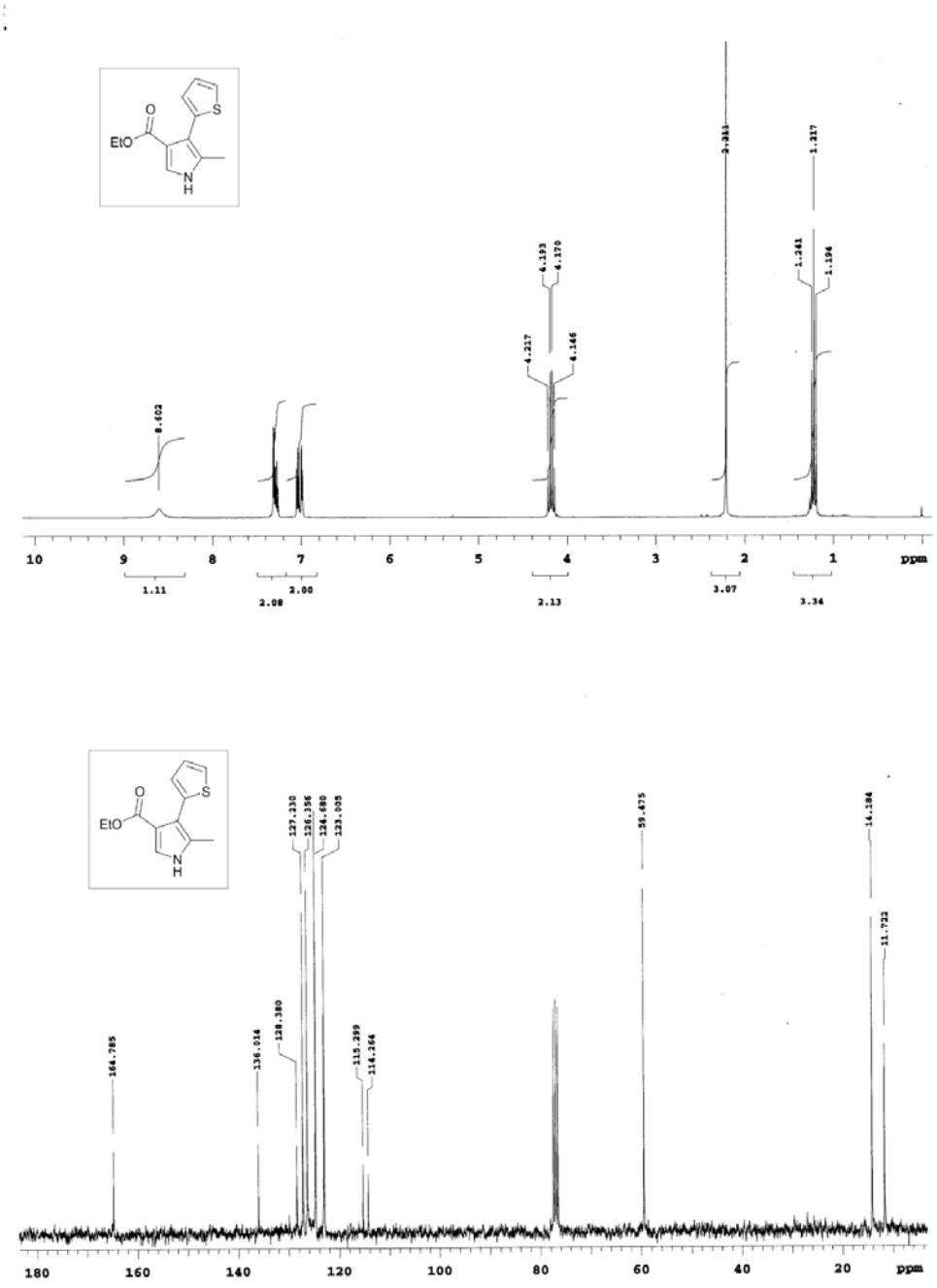

Figure 15. ^{1}H and ^{13}C NMR Spectrum of **7d** (300 and 75 MHz, $CDCl_3$) δ(ppm).

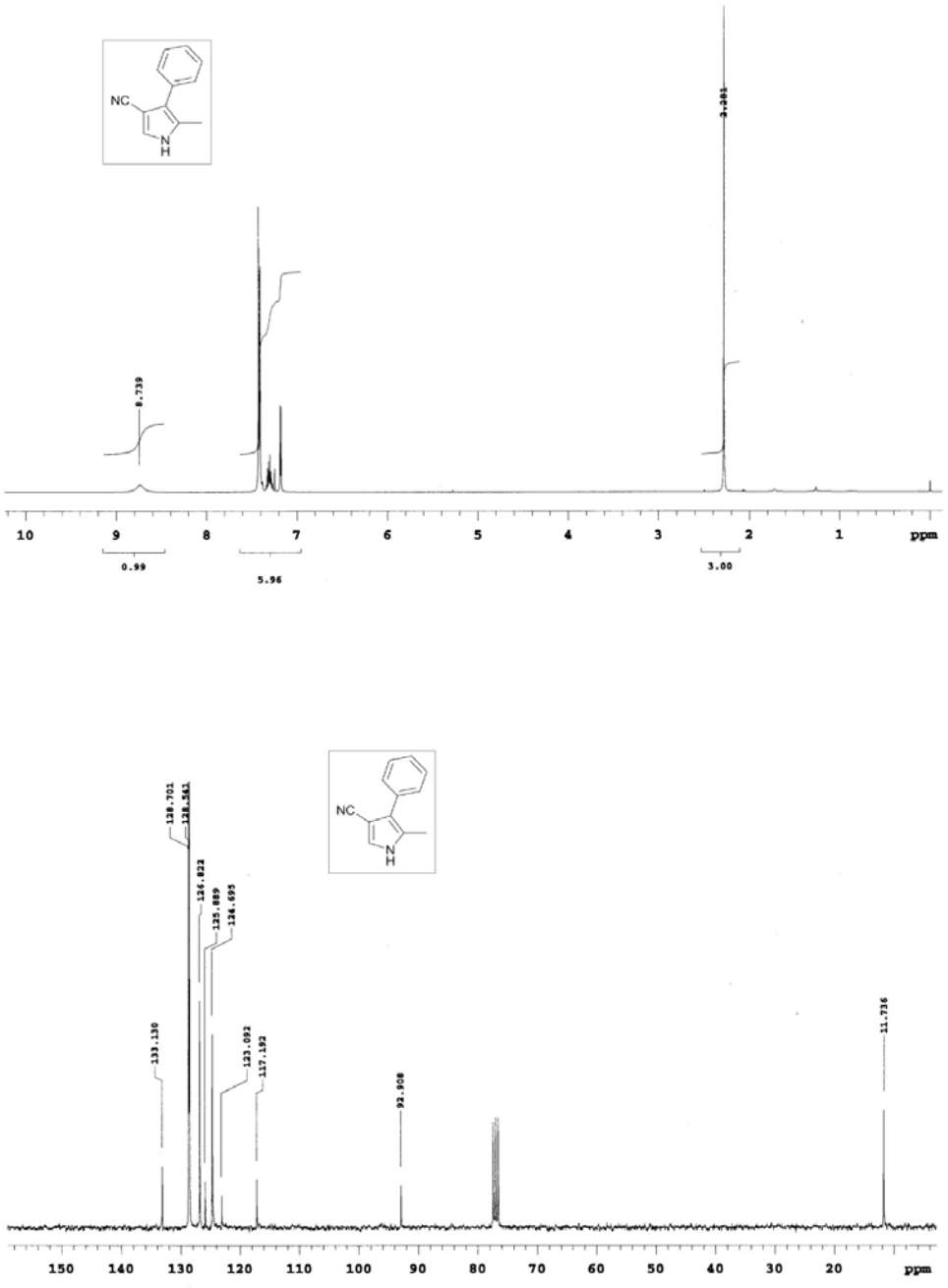

Figure 16. ^{1}H and ^{13}C NMR Spectrum of **7e** (300 and 75 MHz, $CDCl_3$) δ(ppm).

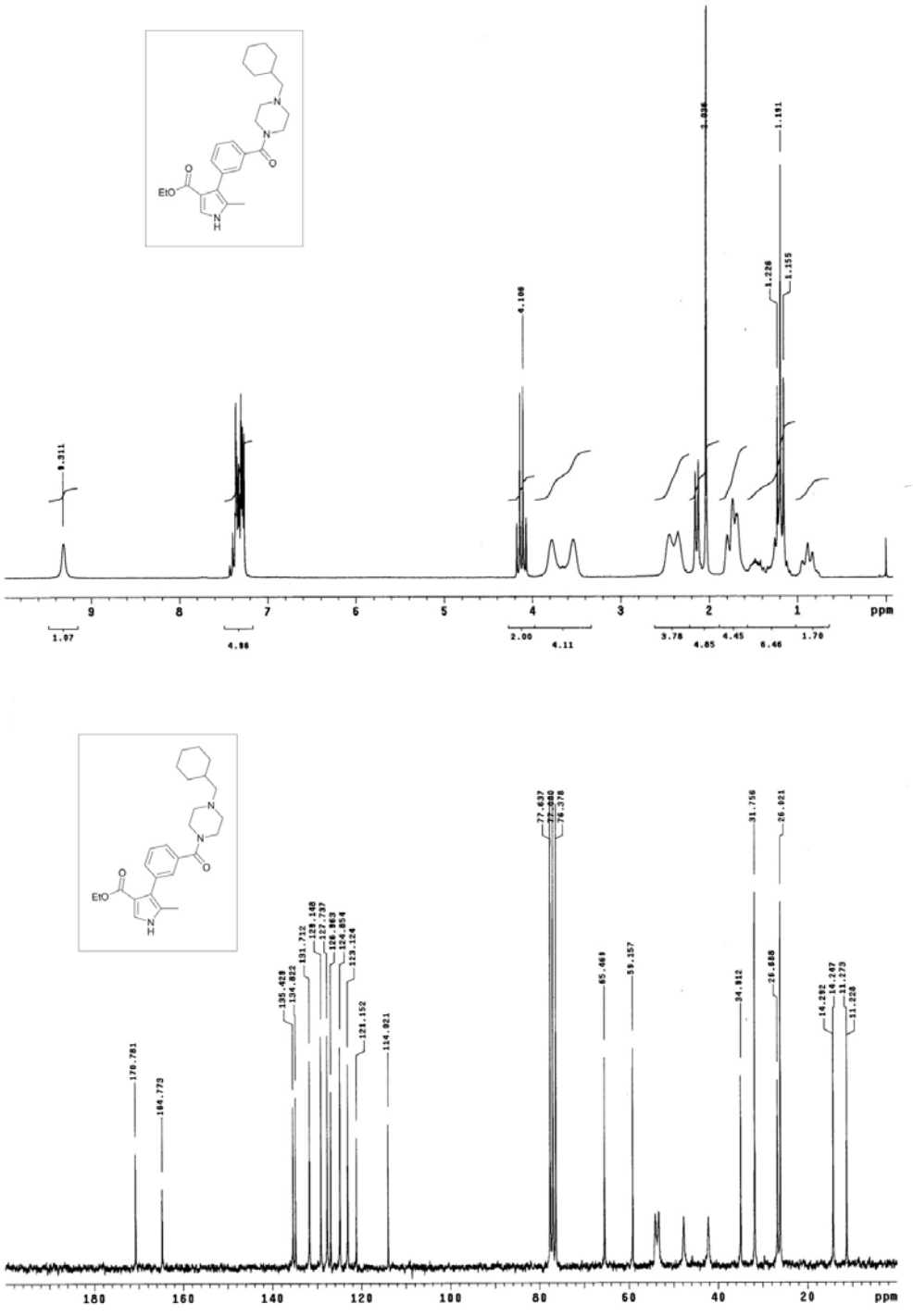

Figure 17. ^{1}H and ^{13}C NMR Spectrum of **14** (200 and 50 MHz, $CDCl_3$) δ(ppm).

NMR Spectrums of the *N*-alkylpyrroles 6a-e and 15

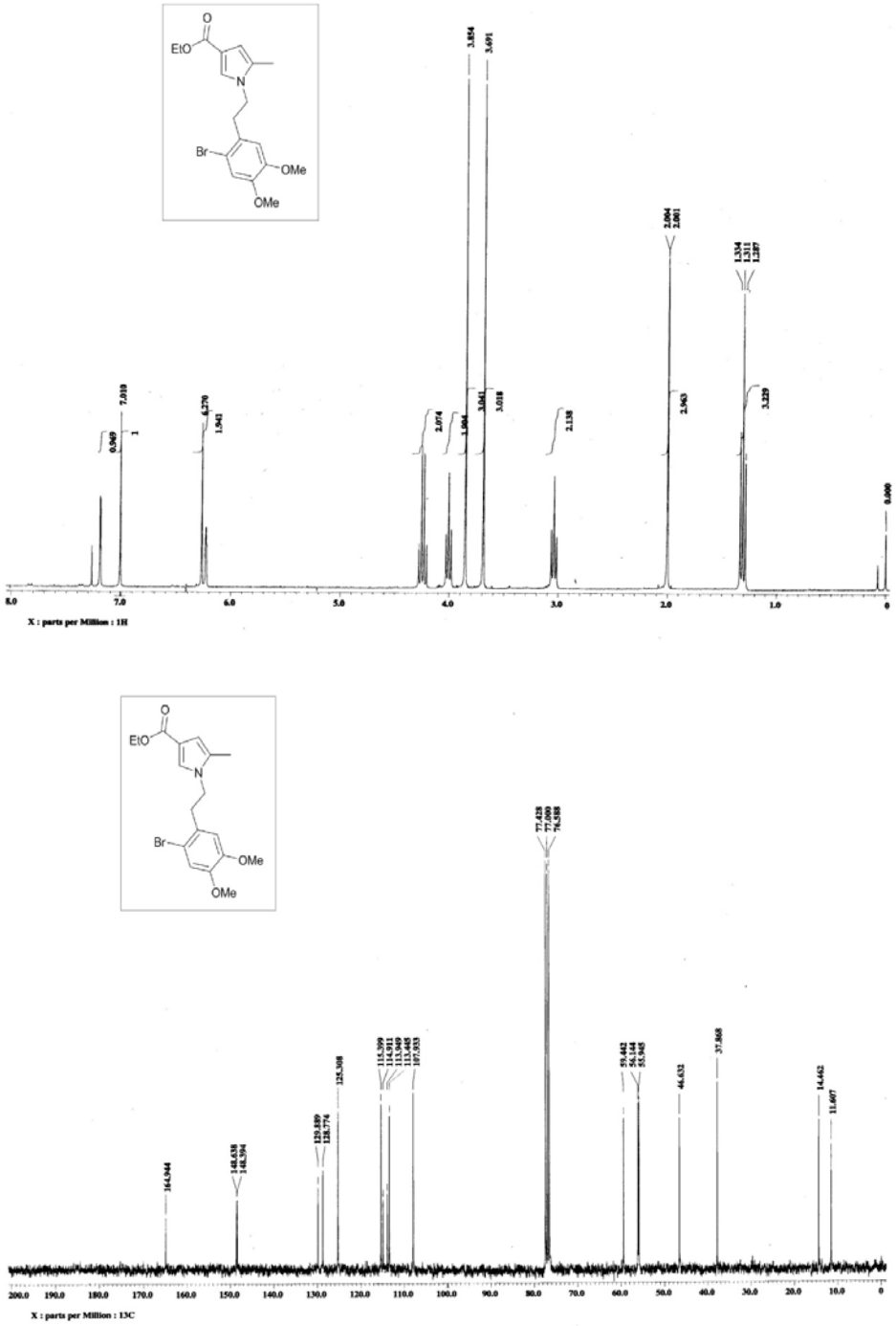

Figure 18. ^{1}H and ^{13}C NMR Spectrum of **6a** (300 and 75 MHz, $CDCl_3$) δ(ppm).

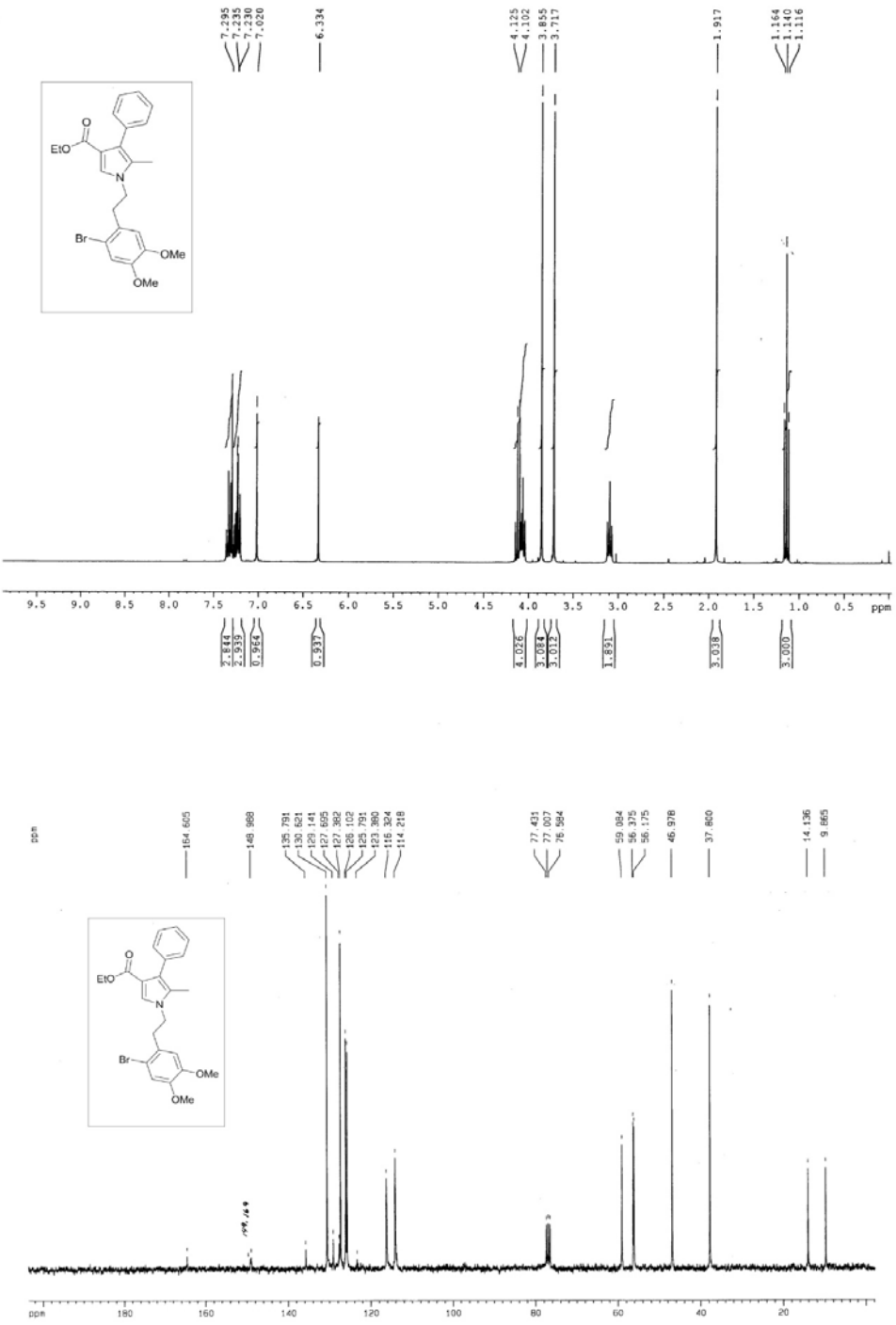

Figure 19. ^{1}H and ^{13}C NMR Spectrum of **6b** (300 and 75 MHz, $CDCl_3$) δ(ppm).

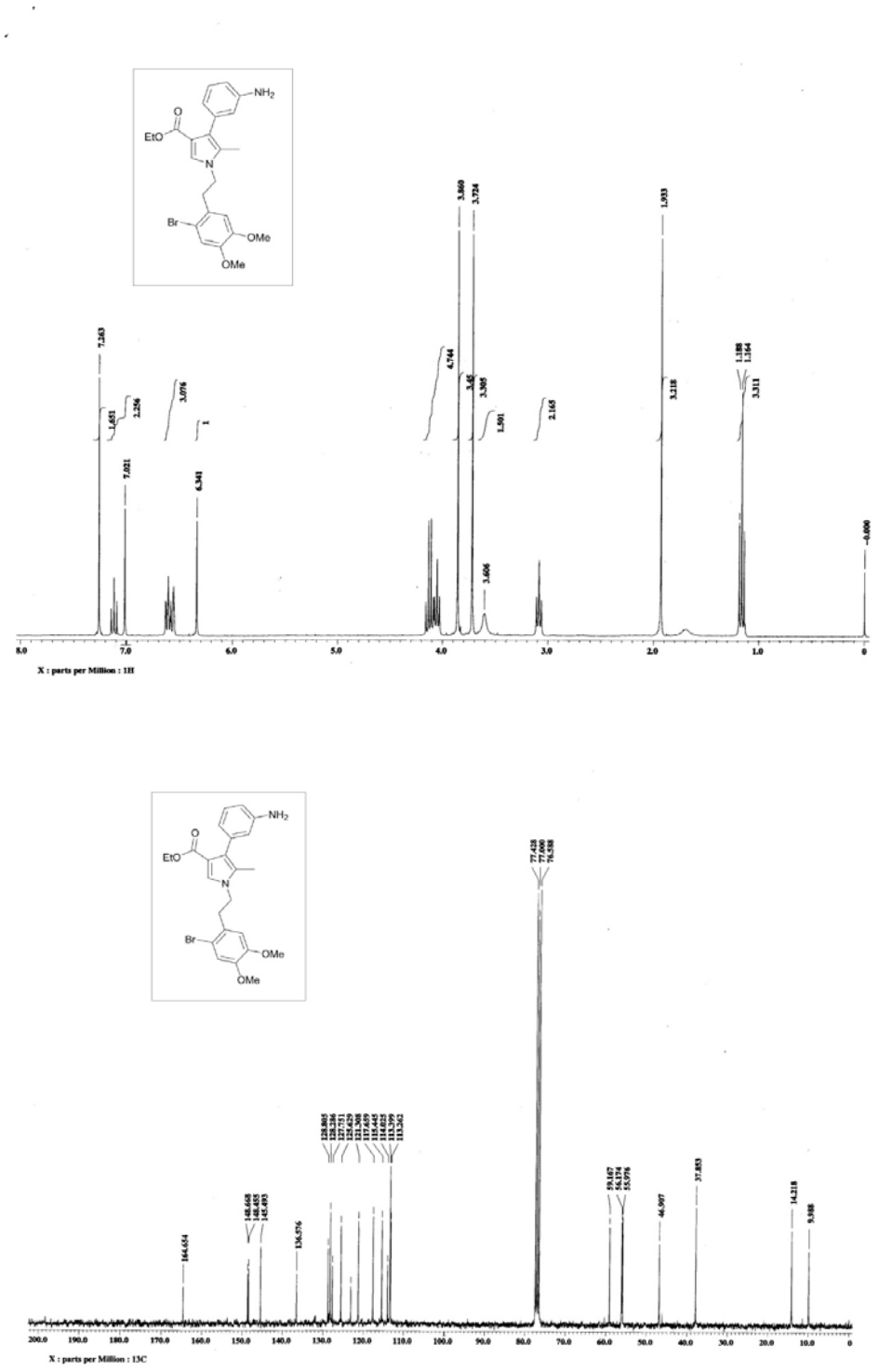

Figure 20. ^{1}H and ^{13}C NMR Spectrum of **6c** (300 and 75 MHz, $CDCl_3$) δ(ppm).

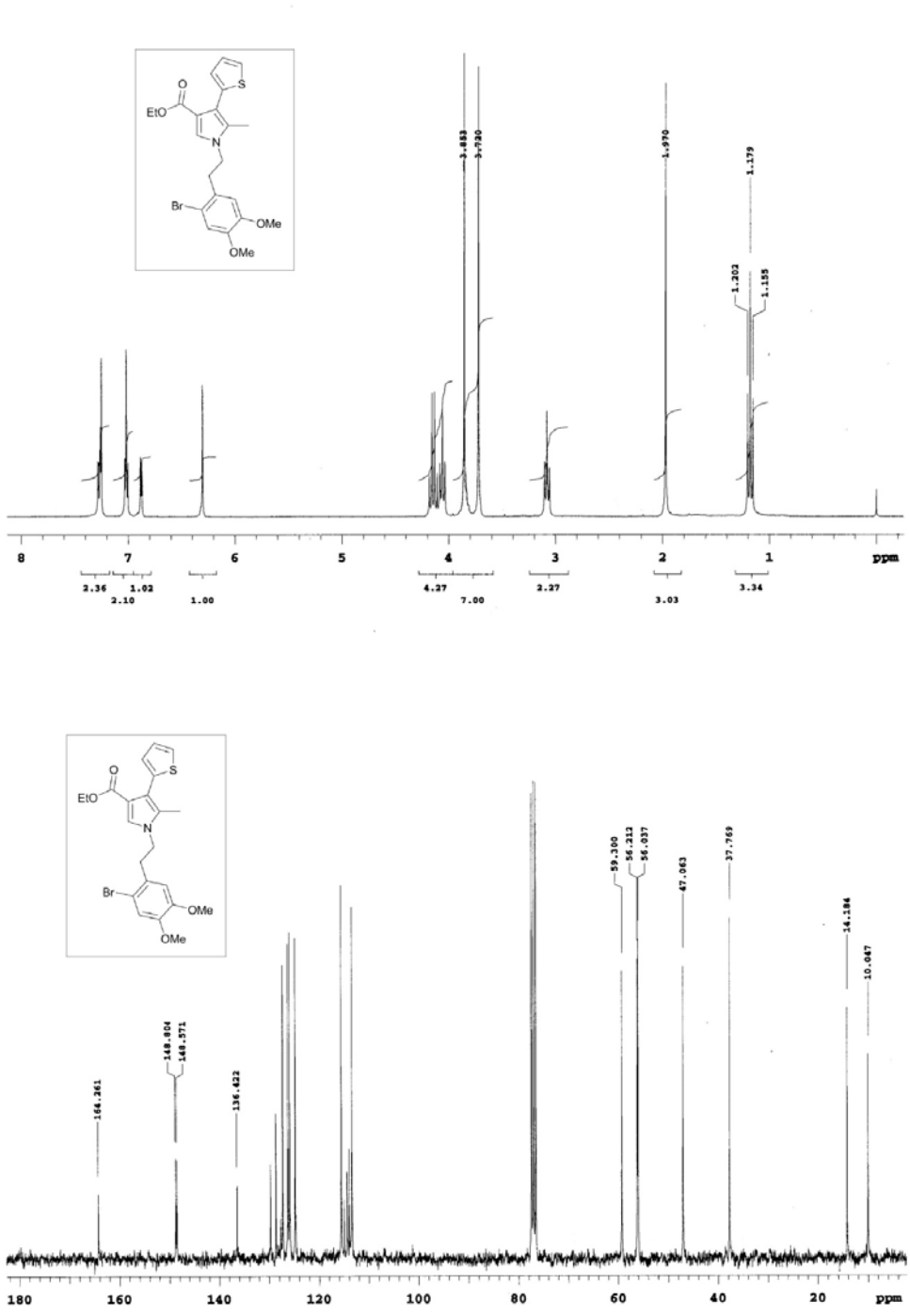

Figure 21. ^{1}H and ^{13}C NMR Spectrum of **6d** (300 and 75 MHz, $CDCl_3$) δ(ppm).

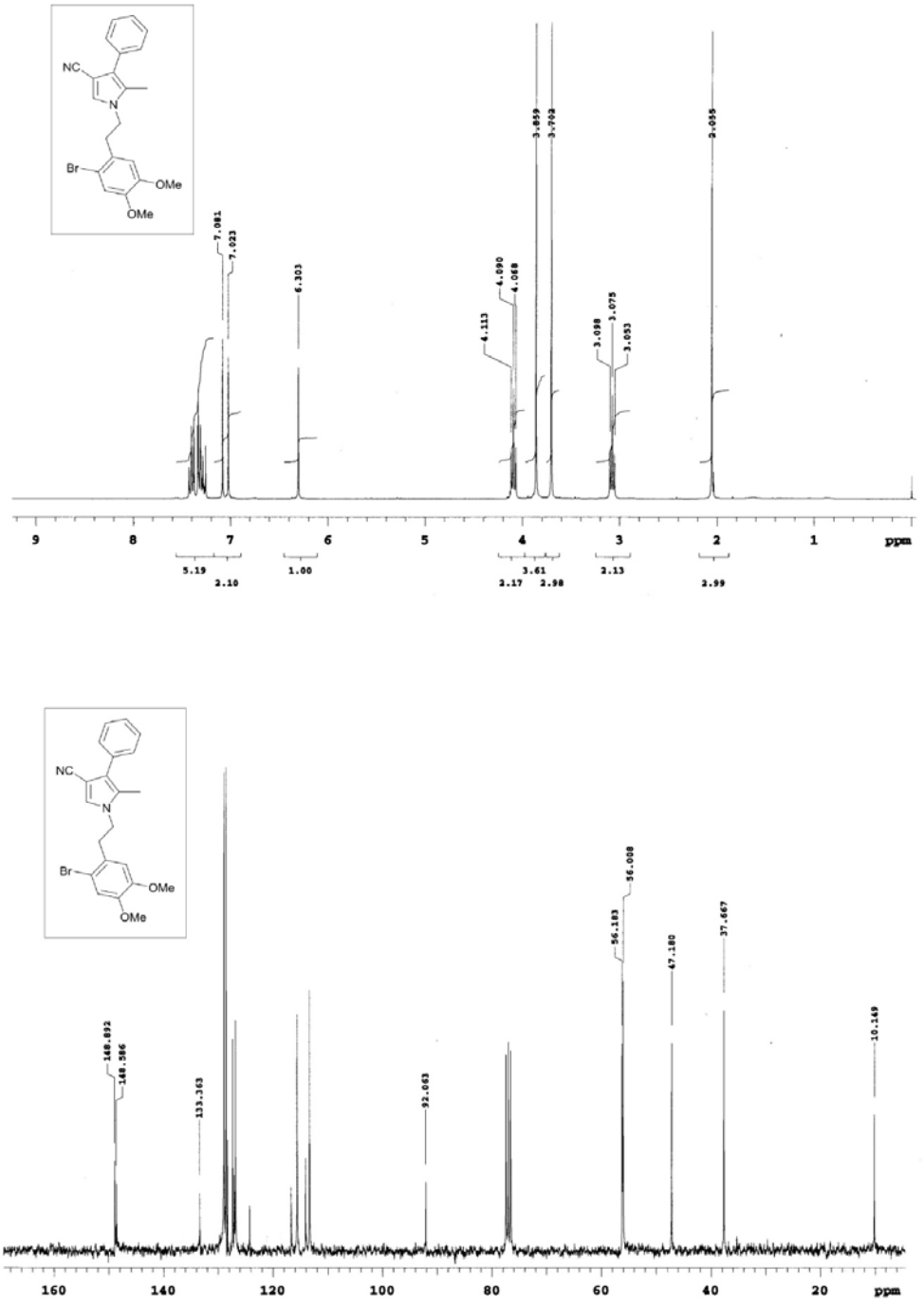

Figure 22. ^{1}H and ^{13}C NMR Spectrum of **6e** (300 and 75 MHz, $CDCl_3$) δ(ppm).

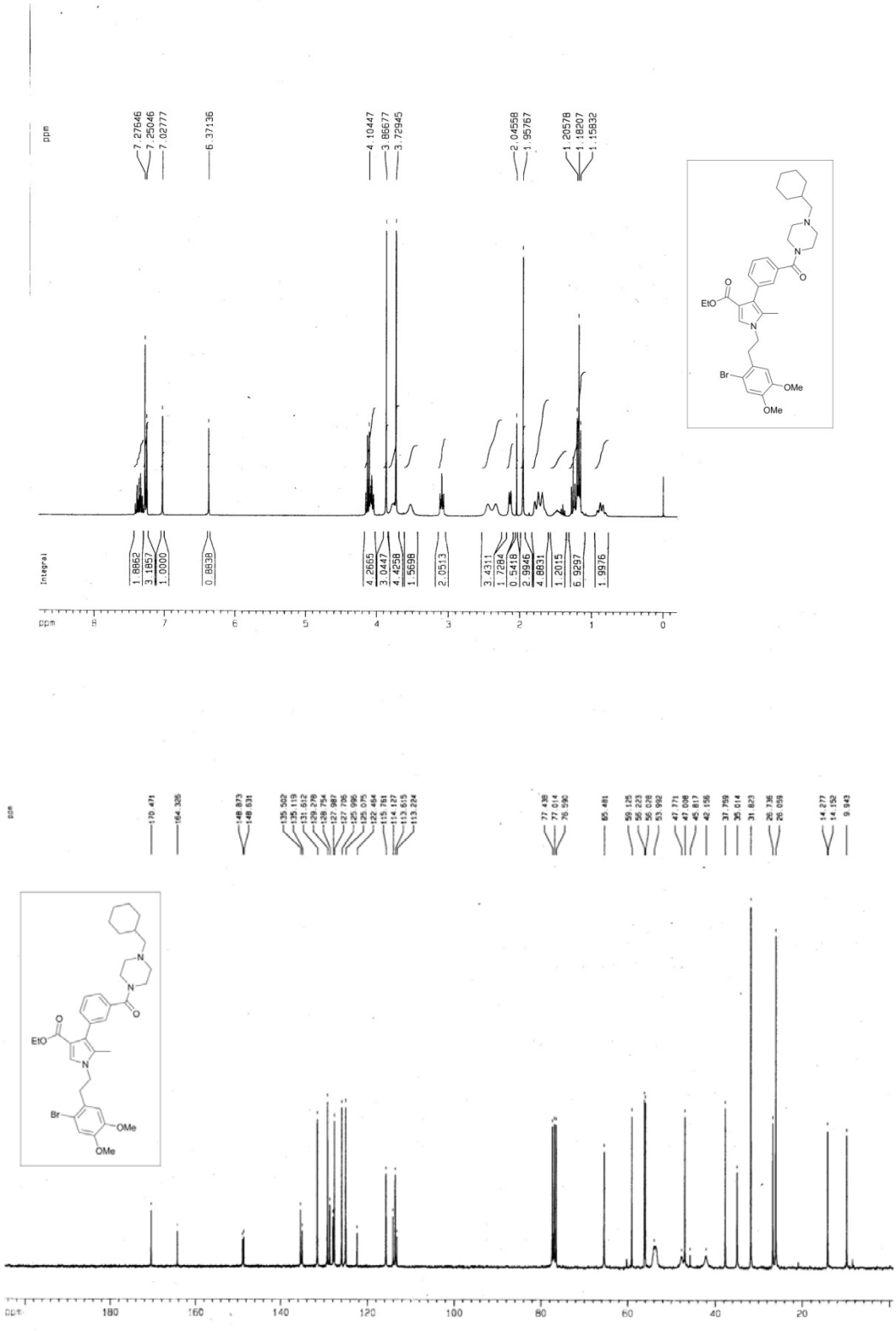

Figure 23. ^{1}H and ^{13}C NMR Spectrum of **15** (300 and 75 MHz, $CDCl_3$) δ(ppm).

NMR Spectrums of the 5,6-dihydropyrrolo[2,1-*a*]isoquinolines 5a-e and 16

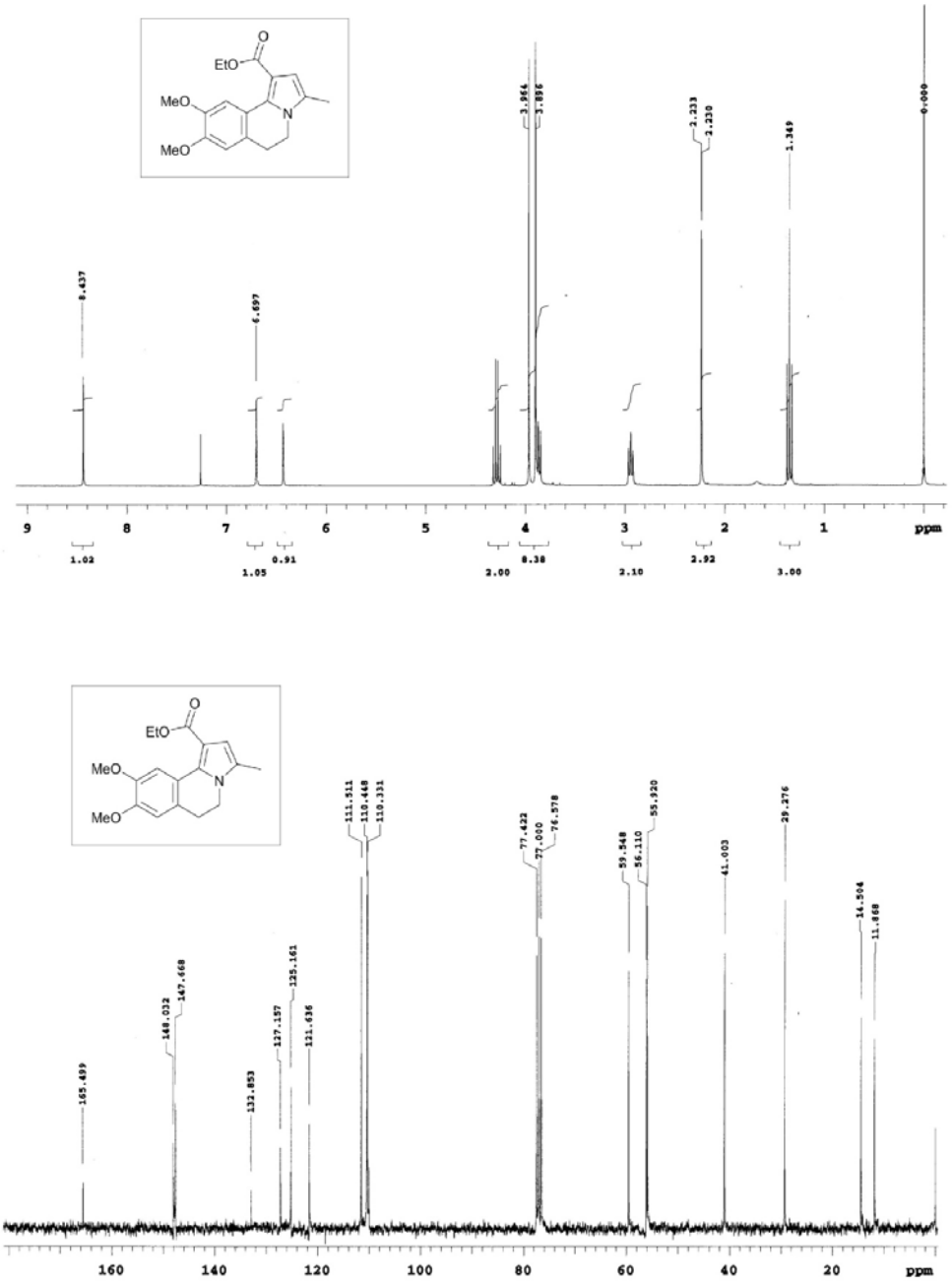

Figure 24. ^{1}H and ^{13}C NMR Spectrum of **5a** (300 and 75 MHz, $CDCl_3$) δ(ppm).

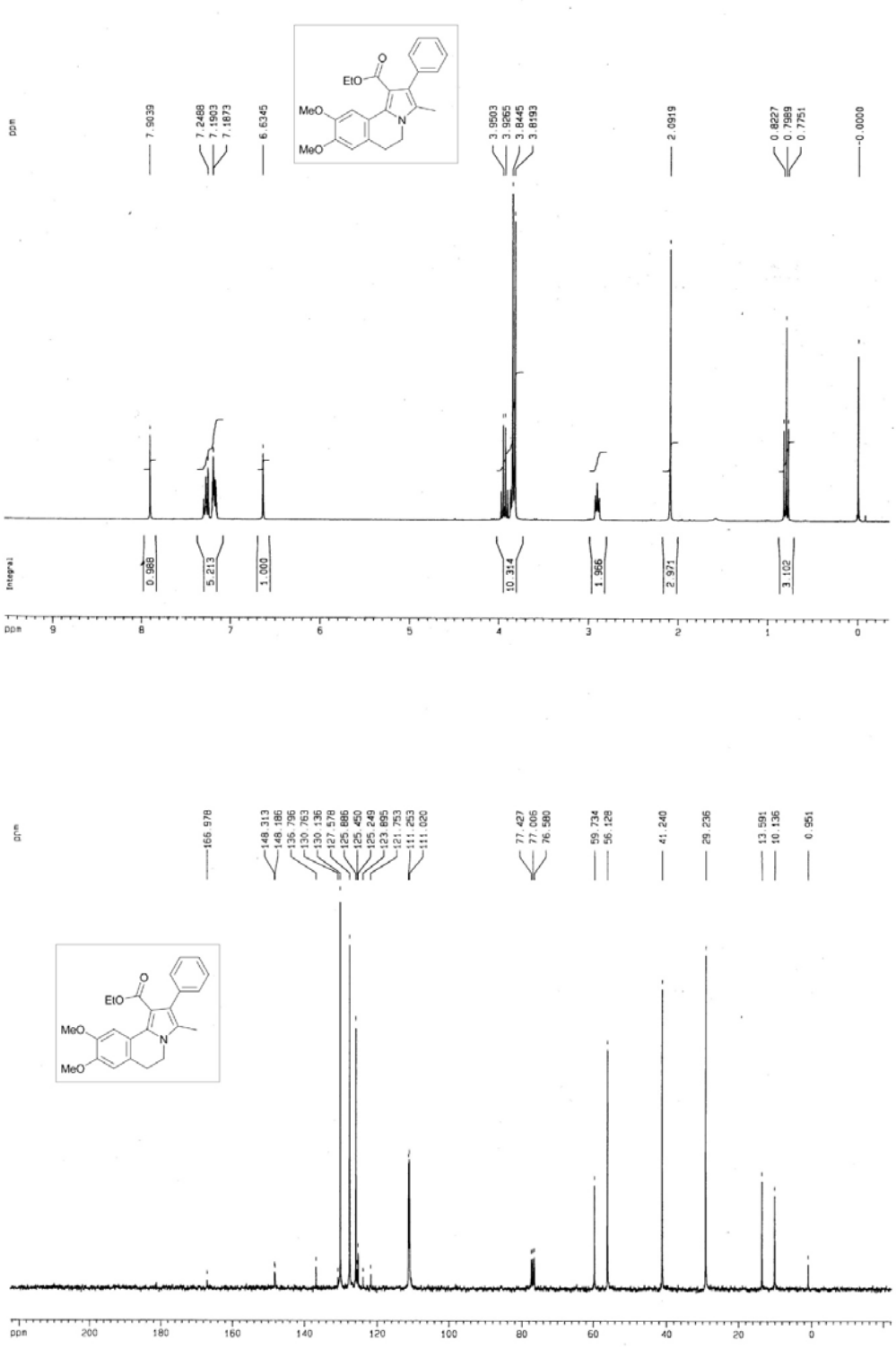

Figure 25. ^{1}H and ^{13}C NMR Spectrum of **5b** (300 and 75 MHz, $CDCl_3$) δ(ppm).

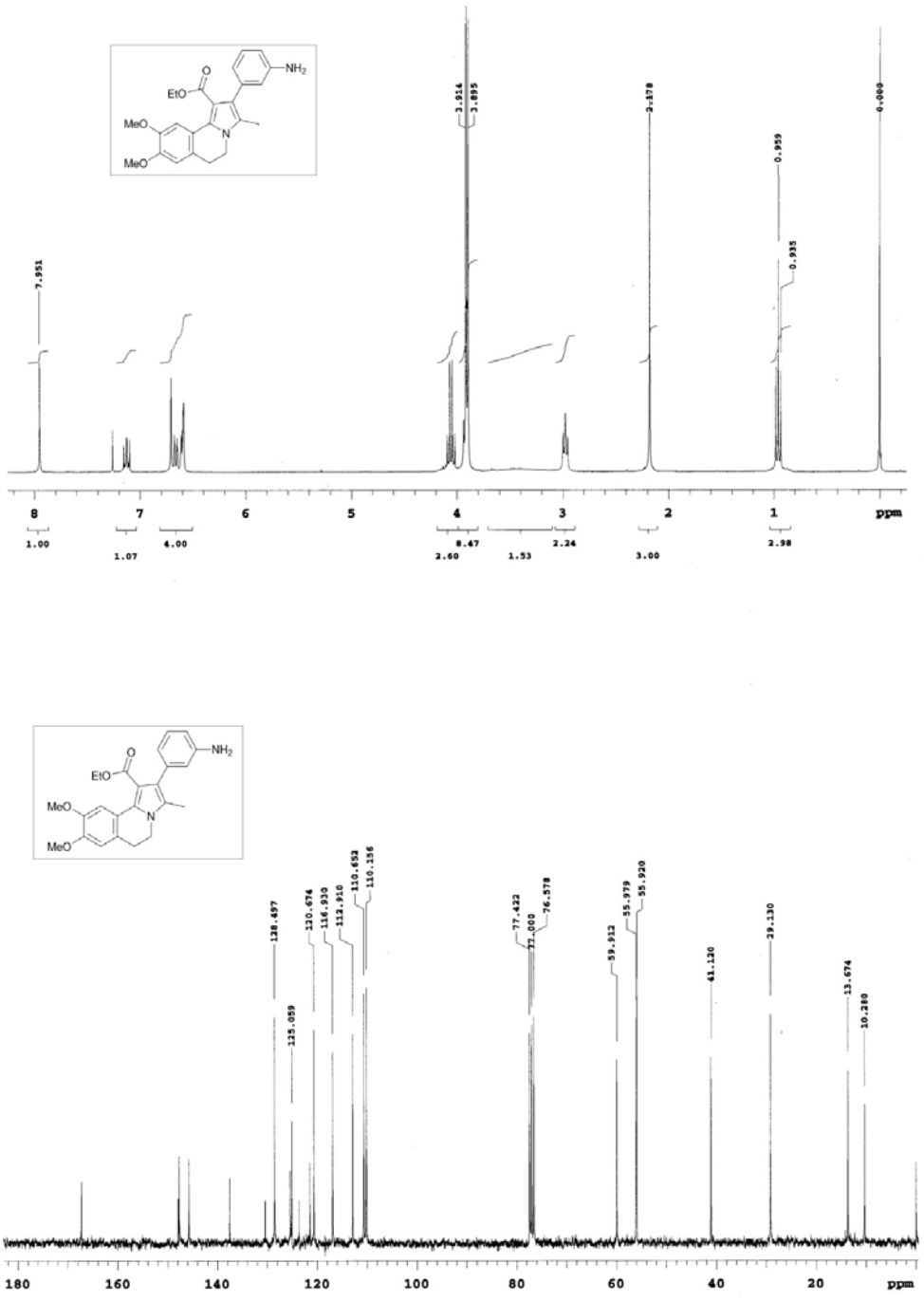

Figure 26. ^{1}H and ^{13}C NMR Spectrum of **5c** (300 and 75 MHz, $CDCl_3$) δ(ppm).

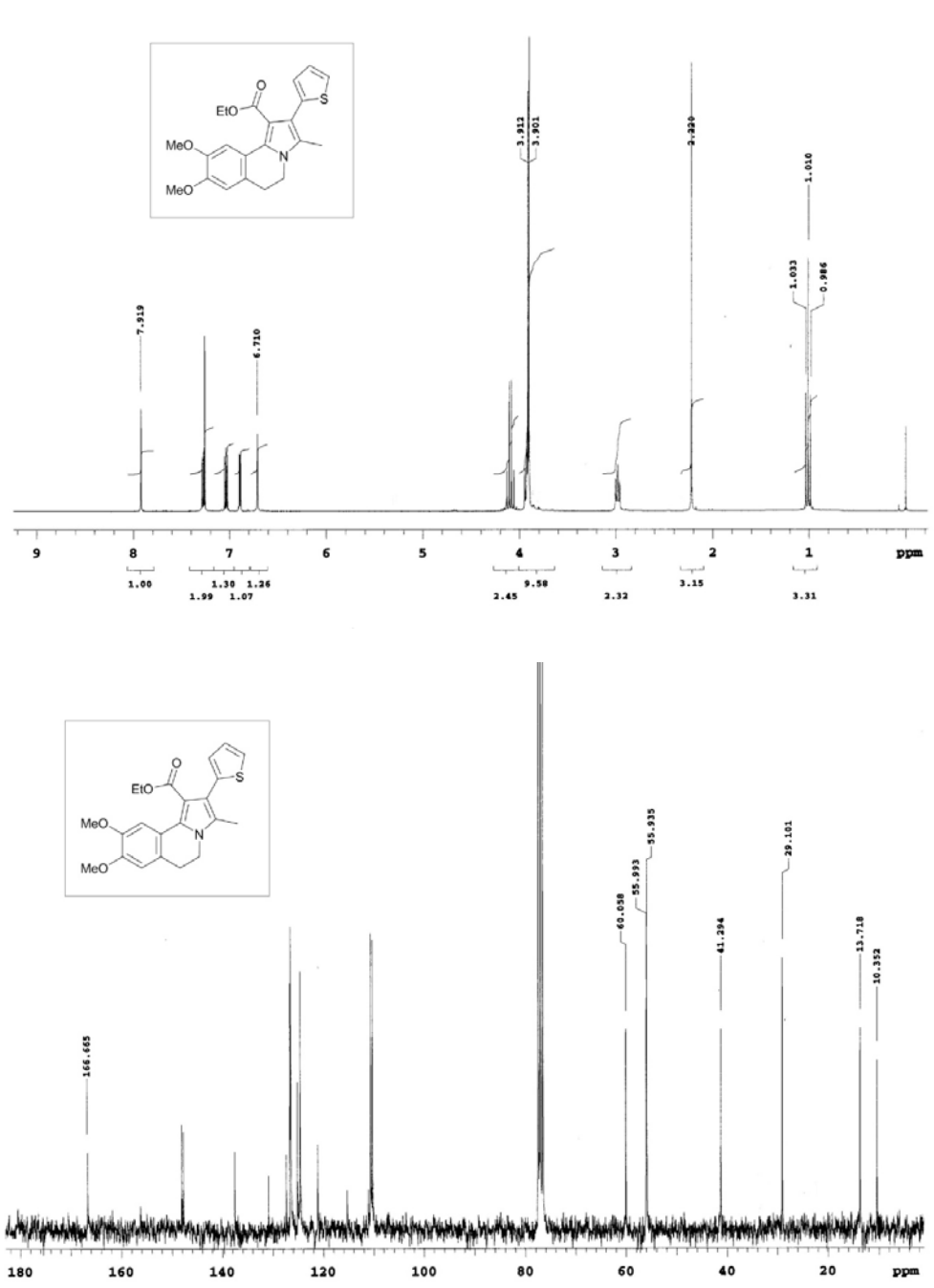

Figure 27. ^{1}H and ^{13}C NMR Spectrum of **5d** (300 and 75 MHz, $CDCl_3$) δ(ppm).

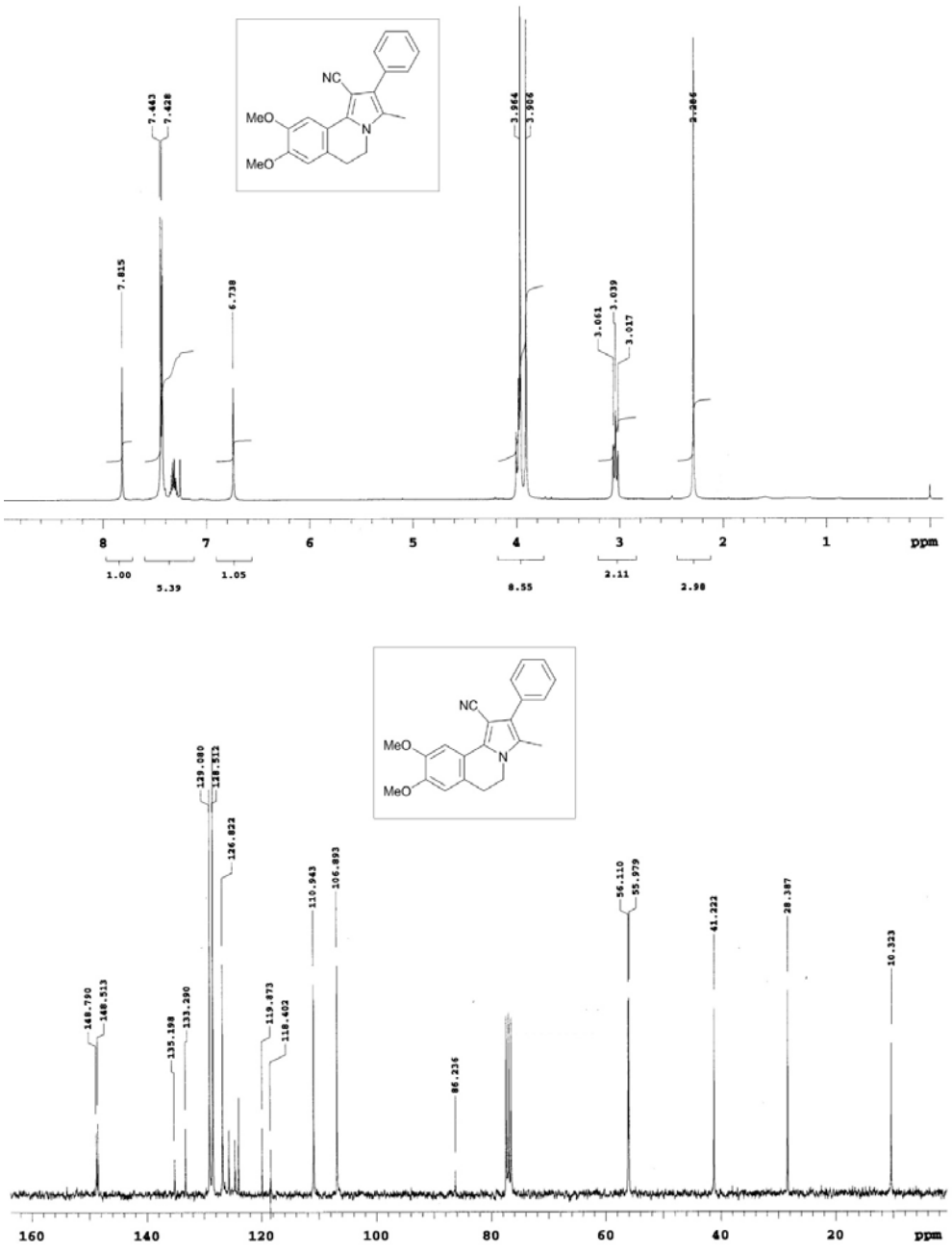

Figure 28. ^{1}H and ^{13}C NMR Spectrum of **5e** (300 and 75 MHz, $CDCl_3$) δ(ppm).

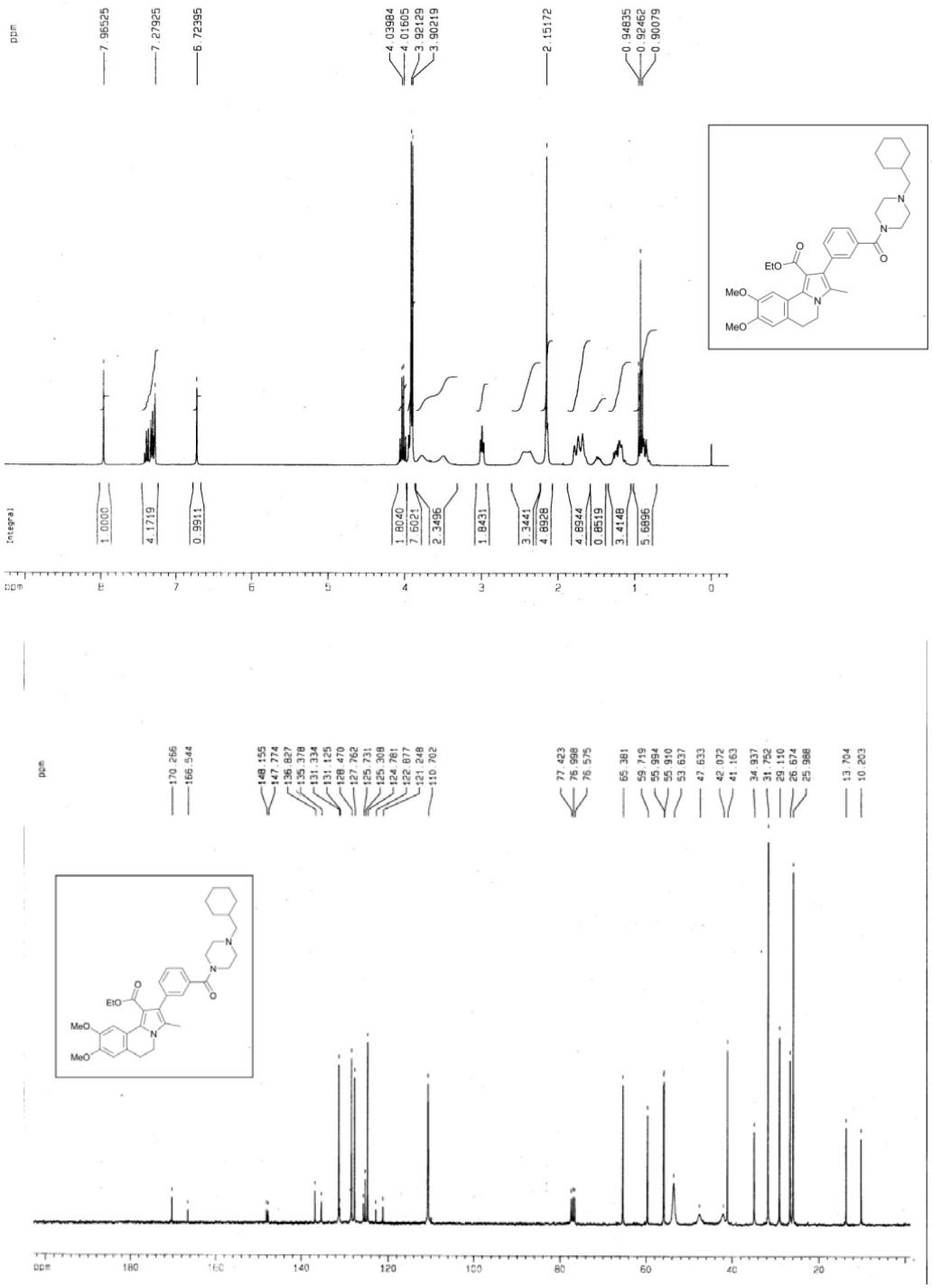

Figure 29. ^{1}H and ^{13}C NMR Spectrum of **16** (300 and 75 MHz, $CDCl_3$) δ(ppm).