Supplementary Material (ESI) for Green Chemistry

Three-Component Solvent-Free Synthesis of Highly Substituted Bicyclic Pyridines Containing a Ring-Junction Nitrogen

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Supporting Information

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General Information

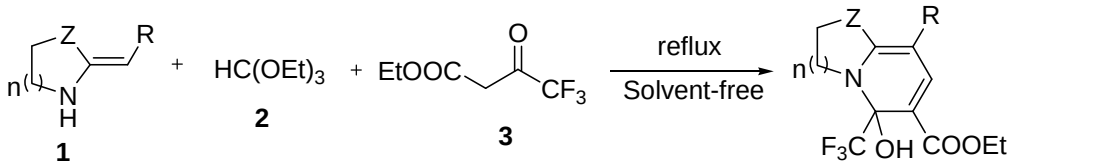
All compounds were fully characterized by spectroscopic data. The NMR spectra were recorded on a Bruker DRX500 (^{1}H: 500 MHz, ^{13}C: 125 MHz), chemical shifts (δ) are expressed in ppm, and J values are given in Hz, $CDCl_3$ and DMSO-d_6 were used as solvent. IR spectra were recorded on a FT-IR Thermo Nicolet Avatar 360 using KBr pellet. The reactions were monitored by thin layer chromatography (TLC) using silica gel GF_{254}. The melting points were determined on XT-4A melting point apparatus and are uncorrected. HRMs were performed on a Agllent LC/Msd TOF instrument.

All chemicals and solvents were used as received without further purification unless otherwise stated. Column chromatography was performed on silica gel (200–300 mesh).

The raw materials **1a**~**1w** were synthesized according to the literature.[1~4]

4,4,4-trifluoro-3-oxo-butanoate **3a** is lower acute toxicity (LD_{50}=1260 mg/kg) in the mice tested according to the literature.[5] Safety phrases of **3a** is S61 (Avoid release to the environment) in the safety description; Diethyl malonate **5a** is lower acute toxicity (ORL-RAT LD_{50}=15000 mg/kg, ORL-MUS LD_{50}=6400mg/kg); Safety phrases of Ethyl 2-cyanoacetate **5b** is S23-26-37 in the safety description.

General Procedure for the Preparation of Bicyclic Pyridines 4 *via* One-pot Three-component Reactions



1 **2** **3**

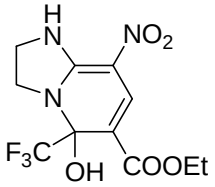
n = 1, 2, 3; Z = NH, O, S
R = COOEt, NO_2, MeCO, ArCO

4

HKAs **1** (2.5mmol), triethoxymethane **2** (3 mmol) and ethyl 4,4,4-trifluoro-3 -oxobutanoate **3** (3mmol) were charged into a 25 mL round-bottom flask and the mixture was refluxed. The resulting solution was stirred for 0.5–1 h until the HKAs **1** were completely consumed. The mixture was diluted with EtOAc (50 mL x 2) and quenched with water (50 mL). The organic layer was dried by Na_2SO_4, concentrated, and purified by flash column chromatography (Petro/AcOEt = 6/1) to afford product **4** with 78-94% yield.

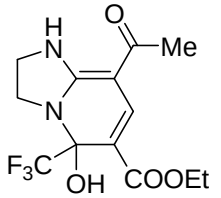
Spectroscopic Data of Bicyclic Pyridines 4

Ethyl 5-hydroxy-8-nitro-5-(trifluoromethyl)-1,2,3,5-tetrahydroimidazo[1,2-*a*] pyridine-6-carboxylate (4a)



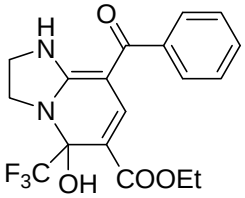
Yellow solid; Mp 187–192 °C; IR (KBr): 3358, 3086, 1675, 1597, 1460, 1385, 1207, 1078, 763 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 1.35 (t, J = 7.1 Hz, 3H, CH_3), 3.92–4.16 (m, 4H, NCH_2CH_2N), 4.28–4.30 (m, 2H, OCH_2), 7.74 (s, 1H, CH), 8.32 (br, 1H, OH), 8.36 (br, 1H, NH); ^{13}C HMR (125 MHz, $CDCl_3$): δ = 14.5, 43.9, 44.8, 62.2, 84.5 (d, J = 35.0 Hz), 101.5, 108.9, 124.4 (d, J = 292.5 Hz), 135.6, 155.2, 168.2; HRMS (TOF ES^+): *m/z* calcd for $C_{11}H_{13}F_3N_3O_5$ $[(M+H)^+]$, 324.0802; found, 324.0804.

Ethyl 8-acetyl-5-hydroxy-5-(trifluoromethyl)-1,2,3,5-tetrahydroimidazo[1,2-*a*] pyridine-6-carboxylate (4b)



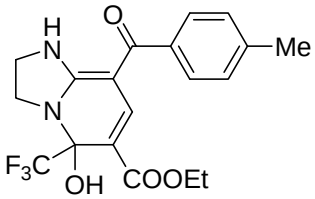
White solid; Mp 107–108 °C; IR (KBr): 3347, 2990, 1664, 1586, 1497, 1388, 1210, 1114 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 1.35 (t, J = 7.1 Hz, 3H, CH_3), 2.25 (s, 3H, $COCH_3$), 3.81–4.00 (m, 4H, NCH_2CH_2N), 4.25–4.29 (m, 2H, OCH_2), 7.81 (s, 1H, CH), 7.95 (br, 1H, OH), 9.05 (br, 1H, NH); ^{13}C HMR (125 MHz, $CDCl_3$): δ = 14.7, 25.4, 43.6, 43.6, 61.2, 84.3 (d, J = 32.5 Hz), 92.4, 96.9, 125.0 (d, J = 293.8 Hz), 141.9, 159.3, 168.8, 192.6; HRMS (TOF ES^+): *m/z* $C_{13}H_{16}F_3N_2O_4$ $[(M+H)^+]$, 321.1057; found, 321.1058.

Ethyl 8-benzoyl-5-hydroxy-5-(trifluoromethyl)-1,2,3,5-tetrahydroimidazo[1,2-*a*] pyridine-6-carboxylate (4c)



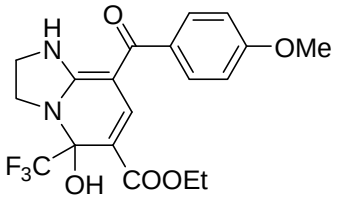
White solid; Mp 163–166 °C; IR (KBr): 3294, 2987, 1662, 1591, 1499, 1089, 1025, 752, 706 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 1.21 (t, J = 7.0 Hz, 3H, CH_3), 3.80–4.10 (m, 4H, NCH_2CH_2N), 4.11–4.18 (m, 2H, OCH_2), 7.42–7.54 (m, 5H, PhH), 7.84 (s, 1H, CH), 7.92 (br, 1H, OH), 9.33 (br, 1H, NH); ^{13}C HMR (125 MHz, $CDCl_3$): δ = 14.5, 43.8, 44.2, 61.2, 84.2 (d, J = 33.8 Hz), 91.7, 97.3, 125.1 (d, J = 295.0 Hz), 128.6, 128.7, 131.0, 139.7, 143.6, 160.4, 168.8, 191.0; HRMS (TOF ES^+): *m/z* calcd for $C_{18}H_{18}F_3N_2O_4$ [$(M+H)^+$], 383.1213; found, 383.1216.

Ethyl 5-hydroxy-8-(4-methylbenzoyl)-5-(trifluoromethyl)-1,2,3,5-tetrahydro-imidazo[1,2-*a*]pyridine-6-carboxylate (4d)



White solid; Mp 168–171 °C; IR (KBr): 3322, 2977, 1656, 1582, 1498, 1401, 1309, 1083, 766 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 1.25 (t, J = 7.0 Hz, 3H, CH_3), 2.44 (s, 3H, $ArCH_3$), 3.85–4.19 (m, 4H, NCH_2CH_2N), 4.08–4.22 (m, 2H, OCH_2), 7.27 (t, J = 7.6 Hz, 2H, ArH), 7.47 (d, J = 7.6 Hz, 2H, ArH), 7.90 (s, 1H, CH), 7.97 (br, 1H, OH), 9.34 (br, 1H, NH); ^{13}C HMR (125 MHz, $CDCl_3$): δ = 14.6, 21.9, 43.8, 43.8, 61.2, 84.2 (d, J = 33.8 Hz), 91.7, 97.1, 125.6 (d, J = 295.0 Hz), 128.9, 129.3, 136.9, 141.4, 143.7, 160.5, 168.9, 191.0; HRMS (TOF ES^+): *m/z* calcd for $C_{19}H_{20}F_3N_2O_4$ [$(M+H)^+$], 397.1370; found, 397.1372.

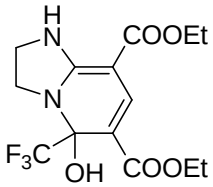
Ethyl 5-hydroxy-8-(4-methoxybenzoyl)-5-(trifluoromethyl)-1,2,3,5-tetrahydro-imidazo[1,2-*a*]pyridine-6-carboxylate (4e)



White solid; Mp 1801–185 °C; IR (KBr): 3288, 2987, 1654, 1594, 1400, 1253, 1170, 1088, 843 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 1.24 (t, J = 7.1 Hz, 3H, CH_3), 3.89 (s, 3H, OCH_3), 3.88–4.07 (m, 4H, NCH_2CH_2N), 4.19 (q, J = 7.1 Hz, 2H, OCH_2), 6.95 (d, J = 8.5 Hz, 2H, ArH), 7.54 (d, J = 8.5 Hz, 2H, ArH), 7.88 (s, 1H, CH), 7.97 (br,

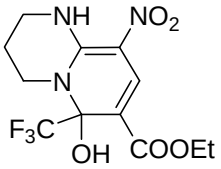
1H, OH), 9.28 (br, 1H, NH); ^{13}C HMR (125 MHz, $CDCl_3$): δ = 14.6, 43.5, 43.8, 55.8, 61.1, 84.2 (d, J = 33.8 Hz), 91.6, 96.8, 113.9, 125.7 (d, J = 293.8 Hz), 130.8, 132.2, 143.8, 160.5, 162.1, 168.9, 190.3; HRMS (TOF ES$^+$): *m/z* calcd for $C_{19}H_{20}F_3N_2O_5$ [(M+H)$^+$], 413.1319; found, 413.1322.

Diethyl 5-hydroxy-5-(trifluoromethyl)-1,2,3,5-tetrahydroimidazo[1,2-*a*]pyridine -6,8-dicarboxylate (4f)



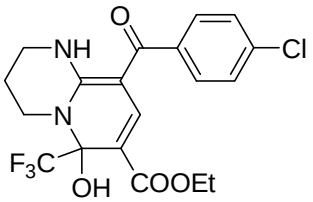
White solid; Mp 146–149 °C; IR (KBr): 3398, 3308, 2988, 1638, 1575, 1411, 1332, 1216, 768 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.18–1.47 (m, 6H, CH_3), 3.74–4.05 (m, 4H, NCH_2CH_2N), 4.19–4.29 (m, 4H, OCH_2), 7.83 (s, 1H, CH), 7.91 (br, 1H, OH), 8.02 (br, 1H, NH); ^{13}C HMR (125 MHz, $CDCl_3$): δ = 14.5, 14.7, 43.5, 44.1, 60.0, 61.0, 80.5, 84.7 (q, J = 33.8 Hz), 96.2, 125.7 (q, J = 295.0 Hz), 141.5, 159.4, 166.8, 169.0; HRMS (TOF ES$^+$): *m/z* calcd for $C_{14}H_{18}F_3N_2O_5$ [(M+H)$^+$], 351.1162; found, 351.1164.

Ethyl 6-hydroxy-9-nitro-6-(trifluoromethyl)-2,3,4,6-tetrahydro-1*H*-pyrido [1,2-*a*]pyrimidine-7-carboxylate (4g)



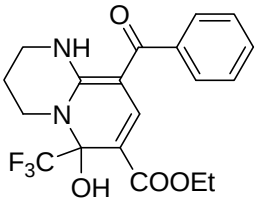
Yellow solid; Mp 147–151 °C; IR (KBr): 3182, 2982, 1668, 1607, 1539, 1474, 1370, 1018, 752 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.31 (t, J = 7.2 Hz, 3H, CH_3), 1.94–1.98 (m, 1H, CH_2), 2.08–2.13 (m, 1H, CH_2), 3.46–3.54 (m, 2H, CH_2), 3.61–3.65 (m, 1H, CH_2), 3.64–3.97 (m, 1H, CH_2), 4.22–4.27 (m, 2H, OCH_2), 8.40 (s, 1H, CH), 8.42 (br, 1H, OH), 10.70 (br, 1H, NH); ^{13}C HMR (125 MHz, $CDCl_3$): δ = 14.5, 19.7, 39.7, 40.5, 62.2, 84.4 (q, J = 33.8 Hz), 100.2, 111.3, 124.5 (q, J = 293.8 Hz), 135.9, 151.8, 168.5; HRMS (TOF ES$^+$): *m/z* calcd for $C_{12}H_{15}F_3N_3O_5$ [(M+H)$^+$], 338.0958; found, 338.0959.

Ethyl 9-(4-chlorobenzoyl)-6-hydroxy-6-(trifluoromethyl)-2,3,4,6-tetrahydro-1*H*-pyrido[1,2-*a*]pyrimidine-7-carboxylate (4h)



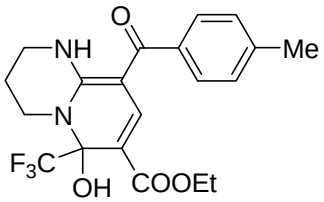
Yellow solid; Mp 168–173 °C; IR (KBr): 3429, 2979, 1657, 1595, 1508, 1239, 1174, 1099, 816 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 1.21 (t, J = 6.9 Hz, 3H, CH_3), 1.99–2.08 (m, 2H, CH_2), 3.40–3.43 (m, 1H, NCH_2), 3.54–3.58 (d, m, 2H, NCH_2), 3.94–3.98 (m, 1H, NCH_2),), 4.17 (q, J = 6.9 Hz, 2H, OCH_2), 7.4 (d, J = 8.1 Hz, 2H, ArH), 7.43 (d, J = 8.1 Hz, 2H, ArH), 7.70 (s, 1H, CH), 8.63 (br, 1H, OH), 11.79 (br, 1H, NH); ^{13}C HMR (125 MHz, $CDCl_3$): δ = 14.6, 20.1, 39.2, 39.9, 61.2, 84.0 (d, J = 32.5 Hz), 94.1, 95.5, 125.3 (d, J = 295.0 Hz), 128.7, 130.5, 136.7, 139.0, 143.7, 156.5, 169.0, 190.2; HRMS (TOF ES^+): *m/z* calcd for $C_{19}H_{19}ClF_3N_2O_4$ $[(M+H)^+]$, 431.0980; found, 431.0984.

Ethyl 9-benzoyl-6-hydroxy-6-(trifluoromethyl)-2,3,4,6-tetrahydro-1*H*-pyrido [1,2-*a*]pyrimidine-7-carboxylate (4i)



Yellow solid; Mp 149–151 °C; IR (KBr): 3427, 2983, 1645, 1598, 1509, 1395, 1241, 1181, 751, 703 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 1.20 (t, J = 7.0 Hz, 3H, CH_3), 1.99–2.08 (m, 2H, CH_2), 3.41–3.45 (m, 1H, NCH_2), 3.55–3.59 (m, 2H, NCH_2), 3.96–3.99 (m, 1H, NCH_2), 4.16 (q, J = 7.0 Hz, 2H, OCH_2), 7.42–7.51 (m, 5H, PhH), 7.78 (s, 1H, CH), 8.66 (br, 1H, OH), 11.88 (br, 1H, NH); ^{13}C HMR (125 MHz, $CDCl_3$): δ = 14.5, 20.2, 39.2, 39.9, 61.1, 84.1 (d, J = 33.8 Hz), 94.2, 95.0, 125.4 (d, J = 295.0 Hz), 128.4, 129.0, 130.6, 140.7, 144.3, 156.6, 169.1, 191.8; HRMS (TOF ES^+): *m/z* calcd for $C_{19}H_{20}F_3N_2O_4$ $[(M+H)^+]$, 397.1370; found, 397.1369.

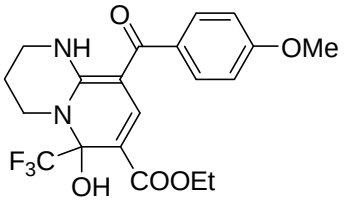
Ethyl 6-hydroxy-9-(4-methylbenzoyl)-6-(trifluoromethyl)-2,3,4,6-tetrahydro-1*H*-pyrido[1,2-*a*]pyrimidine-7-carboxylate (4j)



Yellow solid; Mp 165–170 °C; IR (KBr): 3374, 2984, 1651, 1601, 1503, 1373, 1236, 1176, 776 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 1.20 (t, J = 7.1 Hz, 3H, CH_3),

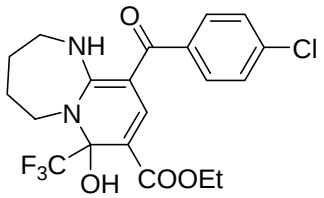
1.78–2.08 (m, 2H, CH_2), 2.42 (s, 3H, $ArCH_3$), 3.40–3.98 (m, 3H, NCH_2CH_2N), 4.16 (q, J = 7.1 Hz, 2H, OCH_2), 7.23 (d, J = 7.8 Hz, 2H, ArH), 7.40 (d, J = 7.8 Hz, 2H, ArH), 7.81 (s, 1H, CH), 8.68 (br, 1H, OH), 11.91 (br, 1H, NH); ^{13}C HMR (125 MHz, $CDCl_3$): δ = 14.6, 20.2, 21.9, 39.2, 39.9, 61.1, 84.1 (q, J = 32.5 Hz), 94.2, 94.7, 125.4 (q, J = 293.8 Hz), 129.1, 129.2, 137.9, 141.0, 144.5, 156.6, 169.1, 191.7; HRMS (TOF ES^+): *m/z* calcd for $C_{20}H_{22}F_3N_2O_4$ [$(M+H)^+$], 411.1526; found, 411.1525.

Ethyl 6-hydroxy-9-(4-methoxybenzoyl)-6-(trifluoromethyl)-2,3,4,6-tetrahydro-1*H*-pyrido[1,2-*a*]pyrimidine-7-carboxylate (4k)



Yellow solid; Mp: 148–150 °C; IR (KBr): 3428, 2980, 1645, 1597, 1506, 1372, 1249, 1173, 837 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.20–1.23 (m, 3H, CH_3), 1.98–2.08 (m, 2H, CH_2), 3.40–3.56 (m, 3H, NCH_2CH_2N), 3.87 (s, 3H, OCH_3), 3.89–3.96 (m, 1H, NCH_2), 4.15–4.19 (m, 2H, OCH_2), 6.95 (d, J = 6.4 Hz, 2H, ArH), 7.49 (d, J = 6.4 Hz, 2H, ArH), 7.83 (s, 1H, CH), 8.71 (br, 1H, OH), 11.88 (br, 1H, NH); ^{13}C HMR (125 MHz, $CDCl_3$): δ = 14.6, 20.2, 39.2, 39.9, 55.8, 61.0, 84.1 (d, J = 32.5 Hz), 94.1, 94.4, 113.7, 125.5 (d, J = 295.0 Hz), 131.1, 133.2, 144.5., 156.5, 161.9, 169.1, 191.1; HRMS (TOF ES^+): *m/z* calcd for $C_{20}H_{22}F_3N_2O_5$ [$(M+H)^+$], 427.1475; found, 427.1473.

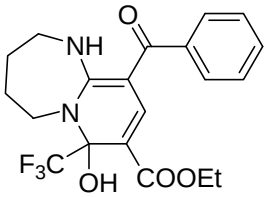
Ethyl 10-(4-chlorobenzoyl)-7-hydroxy-7-(trifluoromethyl)-1,2,3,4,5,7,8,9-octahydropyrido[1,2-*a*][1,3]diazepine-8-carboxylate (4l)



White solid; Mp 145–146 °C; IR (KBr): 3421, 2946, 1654, 1589, 1367, 1236, 1167, 1097, 807 cm^{-1}: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.21 (t, J = 7.0 Hz, 3H, CH_3), 1.81–1.90 (m, 2H, CH_2), 2.02–2.05 (m, 2H, CH_2), 3.49–3.55 (m, 2H, NCH_2), 3.68–3.73 (m, 1H, NCH_2), 4.15–4.20 (m, 2H, OCH_2), 4.47–4.51(m, 1H, NCH_2), 7.38–7.67 (m, 4H, ArH), 7.66 (s, 1H, CH), 9.05 (br, 1H, OH), 11.59 (br, 1H, NH); ^{13}C HMR (125 MHz, $CDCl_3$): δ = 14.6, 25.4, 25.5, 43.5, 45.2, 61.4, 84.3 (d, J = 32.5 Hz), 96.4, 96.7, 125.1 (d, J = 292.5 Hz), 128.7, 130.7, 137.0, 139.1, 144.0, 163.1, 169.1,

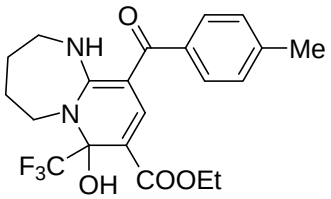
190.6; HRMS (TOF ES$^+$): *m/z* calcd for $C_{20}H_{21}ClF_3N_2O_4$ [(M+H)$^+$], 445.1136; found, 445.1145.

Ethyl 10-benzoyl-7-hydroxy-7-(trifluoromethyl)-1,2,3,4,5,7,8,9-octahydropyrido [1,2-*a*][1,3]diazepine-8-carboxylate (4m)



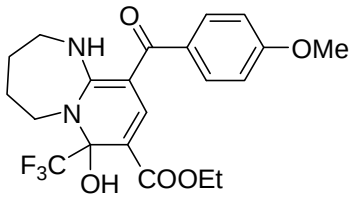
White solid; Mp 119−121 °C; IR (KBr): 3433, 2969, 1647, 1578, 1496, 1364, 1096, 759, 699 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.18 (t, *J* = 7.2 Hz, 3H, CH_3), 1.79−1.95 (m, 2H, CH_2), 2.01−2.07 (m, 2H, CH_2), 3.48−3.54 (m, 2H, NCH_2), 3.67−3.72 (m, 1H, CH_2), 4.10−4.16 (m, 2H, OCH_2), 4.47−4.51 (m, 1H, NCH_2), 7.40−7.50 (m, 5H, PhH), 7.73 (s, 1H, CH), 9.06 (br, 1H, OH), 11.66 (br, 1H, NH); ^{13}C HMR (125 MHz, $CDCl_3$): δ = 14.5, 25.4, 25.5, 43.4, 45.2, 61.2,84.3 (d, *J* = 32.5 Hz), 96.2, 96.6, 125.1 (d, *J* = 292.5 Hz), 128.4, 129.2, 130.9, 140.6, 144.6, 163.2, 169.3, 192.2; HRMS (TOF ES$^+$): *m/z* calcd for $C_{20}H_{22}F_3N_2O_4$ [(M+H)$^+$], 411.1526; found, 411.1533.

Ethyl 7-hydroxy-10-(4-methylbenzoyl)-7-(trifluoromethyl)-1,2,3,4,5,7,8,9-octahydropyrido[1,2-*a*][1,3]diazepine-8-carboxylate (4n)



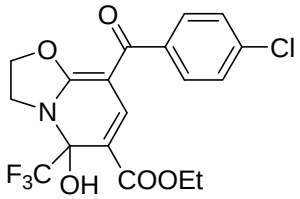
White solid; Mp 138−139 °C; IR (KBr): 3427, 2933, 1650, 1589, 1369, 1236, 1169, 1098, 821 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.20 (t, *J* = 6.9 Hz, 3H, CH_3), 1.80−1.88 (m, 2H, CH_2), 2.00−2.03 (m, 2H, CH_2), 2.41 (s, 3H, $ArCH_3$), 3.46−3.52 (m, 2H, NCH_2), 3.67−3.70 (m, 1H, NCH_2), 4.16 (t, *J* = 6.9 Hz, 2H, OCH_2), 4.48−4.51 (m, 1H, NCH_2), 7.22 (d, *J* = 7.5 Hz, 2H, ArH), 7.40 (d, *J* = 7.5 Hz, 2H, ArH), 7.76 (s, 1H, CH), 9.09 (br, 1H, OH), 11.65 (br, 1H, NH); ^{13}C HMR (125 MHz, $CDCl_3$): δ = 14.6, 21.9, 25.4, 25.6, 43.5, 45.3, 61.2, 84.4 (q, *J* = 33.8 Hz), 96.0, 96.6, 125.0 (q, *J* = 292.5 Hz), 129.1, 129.4, 137.9, 141.3, 144.7, 163.3, 169.3, 192.2; HRMS (TOF ES$^+$): *m/z* calcd for $C_{21}H_{24}F_3N_2O_4$ [(M+H)$^+$], 425.1683; found, 425.1691.

Ethyl 7-hydroxy-10-(4-methoxybenzoyl)-7-(trifluoromethyl)-1,2,3,4,5,7,8,9-octahydropyrido[1,2-*a*][1,3]diazepine-8-carboxylate (4o)



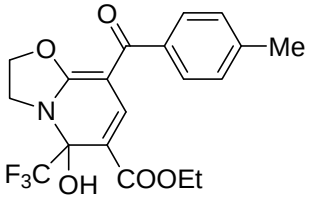
White solid; Mp 138–140 °C; IR (KBr): 3176, 2945, 1652, 1595, 1494, 1366, 1164, 1031, 836 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 1.21 (t, J = 7.0 Hz, 3H, CH_3), 1.78–1.87 (m, 2H, CH_2), 1.99–2.04 (m, 2H, CH_2), 3.45–3.48 (m, 2H, NCH_2), 3.67–3.70 (m, 1H, NCH_2), 3.86 (s, 3H, OCH_3), 4.17 (q, J = 7.0 Hz, 2H, OCH_2), 4.48–4.52 (m, 1H, NCH_2), 6.93 (d, J = 8.3 Hz, 2H, ArH), 7.49 (d, J = 8.3 Hz, 2H, ArH), 7.77 (s, 1H, CH), 9.11 (br, 1H, OH), 11.59 (br, 1H, NH); ^{13}C HMR (125 MHz, $CDCl_3$): δ = 14.6, 25.4, 25.6, 43.4, 45.3, 55.8, 61.2, 84.4 (d, J = 32.5 Hz), 95.7, 96.6, 113.7, 125.2 (d, J = 293.8 Hz), 131.4, 133.2, 144.8, 162.1, 163.2, 169.3, 191.5; HRMS (TOF ES^+): *m/z* calcd for $C_{21}H_{24}F_3N_2O_5$ $[(M+H)^+]$, 441.1632; found, 441.1644.

Ethyl 8-(4-chlorobenzoyl)-5-hydroxy-5-(trifluoromethyl)-3,5-dihydro-2*H*-oxazolo[3,2-*a*]pyridine-6-carboxylate (4p)



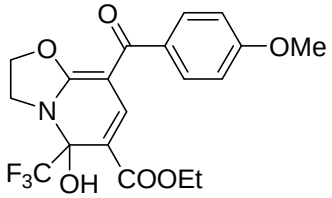
White solid; Mp: 156–158 °C; IR (KBr): 3178, 2980, 1663, 1600, 1529, 1345, 1262, 1179, 843 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 1.32 (t, J = 7.2 Hz, 3H, CH_3), 4.03–4.08 (m, 2H, NCH_2), 4.25–4.29 (m, 2H, OCH_2), 4.63–4.72 (m, 2H, OCH_2), 7.37 (d, J = 8.3 Hz, 2H, ArH), 7.49 (d, J = 8.3 Hz, 2H, ArH), 7.94 (s, 1H, CH), 8.13 (br, 1H, OH); ^{13}C HMR (125 MHz, $CDCl_3$): δ = 14.6, 43.5, 61.9, 70.3, 85.8 (q, J = 33.8 Hz), 91.2, 99.9, 124.7 (q, J = 292.5 Hz), 128.6, 130.2, 137.6, 139.0, 142.7, 163.9, 168.7, 188.0; HRMS (TOF ES^+): *m/z* calcd for $C_{18}H_{16}ClF_3NO_5$ $[(M+H)^+]$, 418.0664; found, 418.0665.

Ethyl 5-hydroxy-8-(4-methylbenzoyl)-5-(trifluoromethyl)-3,5-dihydro-2*H*-oxazolo[3,2-*a*]pyridine-6-carboxylate (4q)



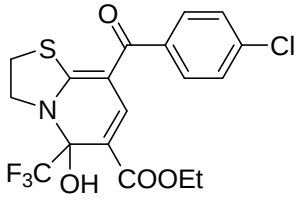
White solid; Mp 164–168 °C; IR (KBr): 3200, 2982, 1662, 1601, 1524, 1345, 1177, 1012, 838 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 1.29 (t, J = 7.1 Hz, 3H, CH_3), 2.39 (s, 3H, $ArCH_3$), 3.98–4.03 (m, 2H, NCH_2), 4.24 (d, J = 6.5 Hz, 2H, OCH_2), 4.62–4.68 (m, 2H, OCH_2), 7.19 (d, J = 7.5 Hz, 2H, ArH), 7.46 (d, J = 7.5 Hz, 2H, ArH), 7.94 (s, 1H, CH), 8.14 (br, 1H, OH); ^{13}C HMR (125 MHz, $CDCl_3$): δ = 14.6, 22.0, 43.5, 61.7, 70.3, 85.9 (q, J = 32.5, Hz), 91.4, 99.2, 124.8 (q, J = 293.8 Hz), 129.0, 129.1, 137.7, 142.1, 143.4, 163.8, 168.9, 189.2; HRMS (TOF ES^+): *m/z* calcd for $C_{19}H_{19}F_3NO_5$ $[(M+H)^+]$, 398.1210; found, 398.1213.

Ethyl 5-hydroxy-8-(4-methoxybenzoyl)-5-(trifluoromethyl)-3,5-dihydro-2*H*-oxazolo[3,2-*a*]pyridine-6-carboxylate (4r)



White solid; Mp 169–171 °C; IR (KBr): 3184, 3000, 1677, 1596, 1512, 1263, 1167, 1019, 852 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 1.31 (t, J = 7.2 Hz, 3H, CH_3), 3.85 (s, 3H, OCH_3), 4.01–4.06 (m, 2H, NCH_2), 4.23–4.28 (m, 2H, OCH_2), 4.63–4.70 (m, 2H, OCH_2), 6.90 (d, J = 8.6 Hz, 2H, ArH), 7.57 (d, J = 8.6 Hz, 2H, ArH), 7.95 (s, 1H, CH), 8.14 (br, 1H, OH); ^{13}C HMR (125 MHz, $CDCl_3$): δ = 14.6, 43.5, 55.7, 61.7, 70.2, 85.9 (q, J = 33.8 Hz), 91.3, 99.0, 113.6, 124.8 (q, J = 292.5 Hz), 131.1, 132.9, 143.5, 162.6, 163.6, 168.8, 188.3; HRMS (TOF ES^+): *m/z* calcd for $C_{19}H_{19}F_3NO_6$ $[(M+H)^+]$, 414.1159; found, 414.1157.

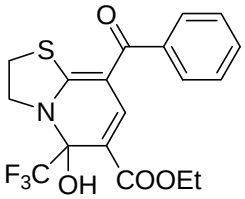
Ethyl 8-(4-chlorobenzoyl)-5-hydroxy-5-(trifluoromethiyl)-3,5-dihydro-2*H*-thiazolo[3,2-*a*]pyridine-6-carboxylate (4s)



Yellow solid; Mp 145–148 °C; IR (KBr): 3262, 2983, 1664, 1590, 1453, 1245, 1175, 1099, 845 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 1.26 (t, J = 7.0 Hz, 3H, CH_3), 3.19–3.24 (m, 1H, NCH_2), 3.32–3.39 (m, 1H, SCH_2), 4.00–4.06 (m, 1H, SCH_2), 4.24 (q, J = 7.0 Hz, 2H, OCH_2), 4.35–4.39 (m, 1H, NCH_2), 7.44 (d, J = 8.1 Hz, 2H, ArH), 7.54 (d, J = 8.1 Hz, 2H, ArH), 7.73 (s, 1H, CH), 8.20 (br, 1H, OH); ^{13}C HMR (125 MHz, $CDCl_3$): δ = 14.5, 29.4, 50.1, 62.0, 86.2 (q, J = 33.8 Hz), 100.2, 103.8, 124.8 (q,

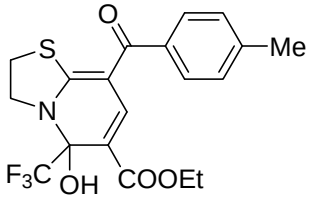
J = 293.8 Hz), 129.0, 130.6, 137.0, 137.9, 140.3, 168.0, 168.7, 188.7; HRMS (TOF ES$^+$): *m/z* calcd for $C_{18}H_{16}ClF_3NO_4S$ [(M+H)$^+$], 434.0435; found, 434.0434.

Ethyl 8-benzoyl-5-hydroxy-5-(trifluoromethyl)-3,5-dihydro-2*H*-thiazolo[3,2-*a*] pyridine-6-carb oxylate (4t)



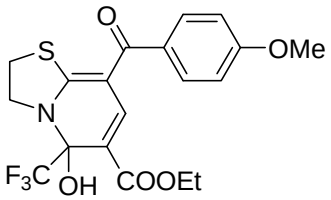
Yellow solid; Mp 129–132 °C; IR (KBr): 3441, 2987, 1658, 1583, 1498, 1397, 1252, 1182, 729 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.23 (t, *J* = 7.0 Hz, 3H, CH_3), 3.19–3.23 (m, 1H, NCH_2), 3.31–3.37 (m, 1H, SCH_2), 3.99–4.06 (m, 1H, SCH_2), 4.22 (q, *J* = 7.0 Hz, 2H, OCH_2), 4.33–4.37 (m, 1H, NCH_2), 7.44–7.60 (m, 5H, PhH), 7.79 (s, 1H, CH), 8.19 (br, 1H, OH); ^{13}C HMR (125 MHz, $CDCl_3$): δ = 14.5, 29.3, 50.1, 61.8, 86.2 (d, *J* = 33.8 Hz), 99.9, 104.1, 124.7 (d, *J* = 292.5 Hz), 128..7, 129.1, 131.7, 138.6, 140.8, 167.7, 168.8, 190.1; HRMS (TOF ES$^+$): *m/z* calcd for $C_{18}H_{17}F_3NO_4S$ [(M+H)$^+$], 400.0825; found, 400.0828.

Ethyl 5-hydroxy-8-(4-methylbenzoyl)-5-(trifluoromethyl)-3,5-dihydro-2*H*-thiazolo[3,2-*a*]pyridine-6-carboxylate (4u)



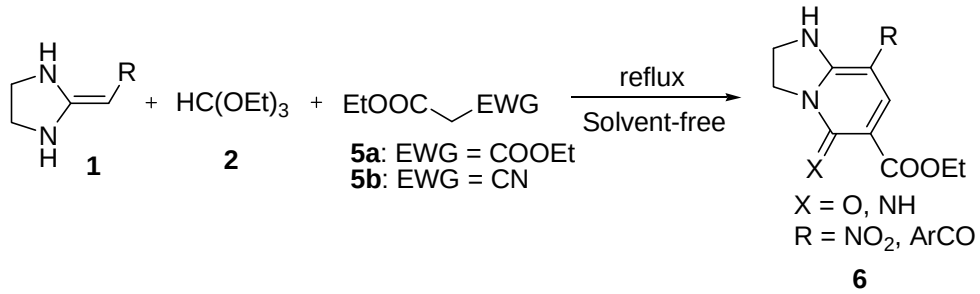
Yellow solid; Mp 122–123 °C; IR (KBr): 3273, 2986, 1664, 1581, 1453, 1248, 1176, 1102, 841 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.25 (t, *J* = 6.7 Hz, 3H, CH_3), 2.42 (s, 3H, $ArCH_3$), 3.18–3.20 (m, 1H, NCH_2), 3.30–3.33 (m, 1H, SCH_2), 3.99–4.04 (m, 1H, SCH_2), 4.22 (q, *J* = 6.7 Hz, 2H, OCH_2), 4.32–4.36 (m, 1H, NCH_2), 7.26 (d, *J* = 7.5 Hz, 2H, ArH), 7.51 (d, *J* = 7.4 Hz, 2H, ArH), 7.82 (s, 1H, CH), 8.21 (br, 1H, OH); ^{13}C HMR (125 MHz, $CDCl_3$): δ = 14.5, 21.9, 29.3, 50.0, 61.8, 86.2 (q, *J* = 33.8 Hz), 99.7, 104.2, 124.9 (q, *J* = 293.8 Hz), 129.3, 129.4, 135.8, 140.9, 142.3, 167.6, 168.9, 189.9; HRMS (TOF ES$^+$): *m/z* calcd for $C_{19}H_{19}F_3NO_4S$ [(M+H)$^+$], 414.0981; found, 414.0983.

Ethyl 5-hydroxy-8-(4-methoxybenzoyl)-5-(trifluoromethyl)-3,5-dihydro-2*H*-thiazolo[3,2-*a*]pyridine-6-carboxylate (4v)



Yellow solid; Mp 135−137 °C; IR (KBr): 3214, 2993, 1657, 1593, 1452, 1388, 1260, 1020, 847 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 1.26 (t, J = 7.0 Hz, 3H, CH_3), 3.17−3.21 (m, 1H, NCH_2), 3.30−3.34 (m, 1H, SCH_2), 3.87 (s, 3H, OCH_3), 3.97−4.01 (m, 1H, SCH_2), 4.23 (q, J = 7.0 Hz, 2H, OCH_2), 4.34−4.38 (m, 1H, NCH_2), 6.97 (d, J = 8.6 Hz, 2H, ArH), 7.60 (d, J = 8.6 Hz, 2H, ArH), 7.83 (s, 1H, CH), 8.23 (br, 1H, OH); ^{13}C HMR (125 MHz, $CDCl_3$): δ = 14.5, 29.4, 50.0, 55.8, 61.8, 86.2 (q, J = 33.8 Hz), 99.5, 104.1, 114.0, 124.9 (q, J = 293.8 Hz), 131.0, 131.4, 141.0, 162.7, 167.3, 168.9, 189.1; HRMS (TOF ES^+): *m/z* calcd for $C_{19}H_{19}F_3NO_5S$ $[(M+H)^+]$, 430.0931; found, 430.0930.

General Procedure for the Preparation of Bicyclic Pyridinone (-imine) 6 *via* One-pot Three-component Reactions

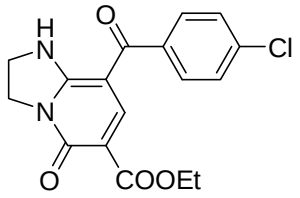


HKAs **1** (2.5mmol), triethoxymethane **2** (3 mmol) and diethyl malonate **5a** or ethyl 2-cyanoacetate **5b** (3mmol) was charged into a 25 mL round-bottom flask and the mixture was refluxed. The resulting solution was stirred for 1–3 h until the HKAs **1** were completely consumed. The mixture was diluted with EtOAc (50 mL x 2) and quenched with water (50 mL). The organic layer was dried by Na_2SO_4, concentrated,

and purified by flash column chromatography (Petro/AcOEt = 6/1) to afford product **6** with 89-94% yield.

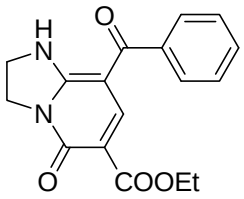
Spectroscopic Data of Bicyclic Pyridinone (-imine) 6

Ethyl 1,2,3,5-tetrahydro-8-(4-chlorobenzoyl)-5-oxoimidazo[1,2-*a*]pyridine-6-carboxylate (6a)



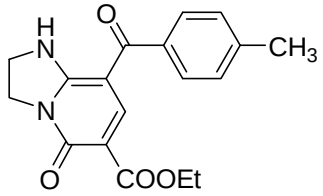
Yellow solid; Mp 280–281 °C; IR (KBr): 3494, 2981, 1727, 1568, 1224, 1171 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 1.31 (t, J = 6.6 Hz, 3H, CH_3), 4.01–4.06 (m, 2H, NCH_2), 4.25–4.28 (m, 4H, NCH_2 and OCH_2), 7.45 (d, J = 7.2 Hz, 2H, ArH), 7.63 (d, J = 7.2 Hz, 2H, ArH), 8.41 (s, 1H, CH), 8.80 (br, 1H, NH); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.8, 43.6, 44.0, 61.2, 97.8, 107.4, 129.3, 130.1, 137.0, 138.1, 149.5, 158.3, 158.6, 165.2, 191.7; HRMS (TOF ES^+): *m/z* calcd for $C_{17}H_{15}ClN_2NaO_4$ [$(M+Na)^+$], 369.0613; found, 369.0618.

Ethyl 1,2,3,5-tetrahydro-8-benzoyl-5-oxoimidazo[1,2-*a*]pyridine-6-carboxylate (6b)



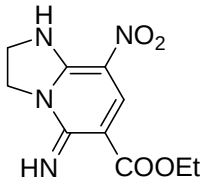
Yellow solid; Mp 234–236 °C; IR (KBr): 3302, 2981, 1727, 1568, 1224, 1171, 1105 cm^{-1}; ^1H NMR (500 MHz, CH_3OD+DMSO-d_6): δ = 0.74 (t, J = 6.7 Hz, 3H, CH_3), 3.68–3.72 (m, 2H, NCH_2), 3.77 (q, J = 6.7 Hz, 2H, OCH_2), 4.02–4.10 (m, 2H, NCH_2), 5.39 (s, 1H, CH), 7.18–7.30 (m, 5H, ArH and CH); ^{13}C NMR (125 MHz, CH_3OD+DMSO-d_6): δ = 12.3, 41.4, 43.7, 59.2, 85.1, 105.8, 126.2, 127.5, 127.5, 139.7, 153.6, 156.2, 158.2, 166.5, 194.0; HRMS (TOF ES^+): *m/z* calcd for $C_{17}H_{16}N_2NaO_4$ [$(M+Na)^+$], 335.1002; found, 335.1008.

Ethyl 1,2,3,5-tetrahydro-8-(4-methylbenzoyl)-5-oxoimidazo[1,2-*a*]pyridine-6-carboxylate (6c)



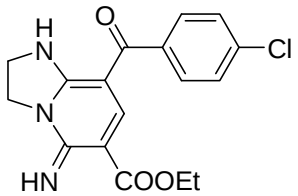
Yellow solid; Mp 203–205 °C; IR (KBr): 3266, 2978, 1694, 1632, 1571, 1275, 1120 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ = 0.86 (t, J = 6.9 Hz, 3H, CH_3), 2.32 (s, 3H, $ArCH_3$), 3.64–3.71 (m, 2H, NCH_2), 3.83 (q, J = 6.9 Hz, 2H, OCH_2), 4.02–4.07 (m, 2H, NCH_2), 5.29 (s, 1H, CH), 7.15 (d, J = 7.3 Hz, 2H, ArH), 7.20 (d, J = 7.3 Hz, 2H, ArH), 7.88 (br, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 14.0, 21.1, 42.3, 44.5, 59.9, 84.3, 107.4, 127.1, 129.2, 137.4, 138.1, 154.3, 155.2, 158.1, 167.2; HRMS (TOF ES^-): *m/z* calcd for $C_{18}H_{17}N_2O_4$ $[(M-H)^+]$, 325.1194; found, 325.1204.

Ethyl 1,2,3,5-tetrahydro-5-imino-8-nitroimidazo[1,2-*a*]pyridine-6-carboxylate (6d)



Yellow solid; Mp 213–216 °C; IR (KBr): 3493, 2984, 1688, 1535, 1376, 600 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ = 1.27–1.31 (m, 3H, CH_3), 3.70–4.00 (m, 4H, NCH_2CH_2N), 4.18–4.24 (m, 2H, OCH_2), 8.41 (s, 1H, CH), 8.81 (br, 1H, NH), 11.40 (br, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 14.5, 45.2, 47.1, 60.7, 98.9, 114.2, 137.7, 150.8, 153,4, 165.1; HRMS (TOF ES^+): *m/z* calcd for $C_{10}H_{13}N_4O_4$ $[(M+H)^+]$, 253.0931; found, 253.0915.

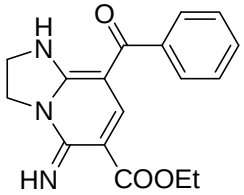
Ethyl 1,2,3,5-tetrahydro-5-imino-8-(4-chlorobenzoyl)imidazo[1,2-*a*]pyridine-6-carboxylate (6e)



Yellow solid; Mp 219–226 °C; IR (KBr): 3494, 2982, 1669, 1569, 1374, 1224, 717 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ = 1.22–1.25 (m, 3H, CH_3), 3.96–4.00 (m, 2H, NCH_2), 4.10-4.17 (m, 4H, NCH_2 and OCH_2), 7.61–7.66 (m, 4H, ArH), 7.96 (s, 1H,

CH), 8.08 (br, 1H, NH), 9.69 (br, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 14.9, 43.7, 43.8, 59.5, 98.6, 117.3, 118.4, 129.0, 130.4, 136.4, 137.2, 150.5, 157.2, 167.0, 189.6; HRMS (TOF ES$^+$): *m/z* calcd for $C_{17}H_{17}ClN_3O_3$ [(M+H)$^+$], 346.0953; found, 346.0974.

Ethyl 1,2,3,5-tetrahydro-5-imino-8-benzoylimidazo[1,2-*a*]pyridine-6- carboxylate (6f)



Yellow solid; Mp: 195–197 °C; IR (KBr): 3494, 2985, 1652, 1536, 1374, 1231, 759 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.24–1.27 (m, 3H, CH_3), 3.99–4.01 (m, 2H, NCH_2), 4.12-4.21 (m, 4H, NCH_2 and OCH_2), 7.59–7.65 (m, 5H, PhH), 7.89 (s, 1H, CH), 9.12 (br, 1H, NH), 9.60 (br, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 14.9, 43.7, 43.8, 59.5, 98.7, 117.3, 118.4, 128.4, 128.9, 131.5, 138.6, 150.4, 157.3, 167.0, 190.8; HRMS (TOF ES$^+$): *m/z* calcd for $C_{17}H_{18}N_3O_3$ [(M+H)$^+$], 312.1343; found, 312.1348.

Anti-cancer activities of compounds 4

The cytotoxic potential of the newly synthesized bicyclic pyridines **4** were evaluated in vitro against a series of human tumor cell lines according to the procedure described in the literature.[6] The tumor cell lines were myeloid leukaemia (HL-60 and K562). Cisplatin (DDP) was servered as the reference drug. (IC_{50} value, defined as the concentrations corresponding to 50% growth inhibition). The tested compounds showed moderate to excellent cellular cytotoxicity in the in vitro antitumor screening expressed by the IC_{50} values (Table S1).

Table S1. Cytotoxic activities of bicyclic pyridines **4** in vitro[a] (IC_{50}, μg/ml[b])

Compd.	K562	HL60
DDP	5.2	4.7
4a	>200	>200
4b	142	109
4c	55	11.7
4d	95	39.2
4e	>200	>200
4f	70	>200
4g	>200	>200
4h	>200	>200
4i	>200	>200
4j	>200	>200
4k	14	9.6
4l	24	9.3
4m	22	29.5
4n	144	11.9
4o	46	9.4
4p	12.1	>200
4q	>200	>200
4r	11.5	55.3
4s	6.1	2.5
4t	6.5	23.5
4u	8.1	14.3

4v	2.1	15.5

[a] Cytotoxicity as IC_{50} for each cell line, is the concentration of compound which reduced by 50% the optical density of treated cells with respect to untreated cells using the MTT assay.
[b] Data represent the mean values of three independent determinations.

X-ray Structure and Data[7] of 4m

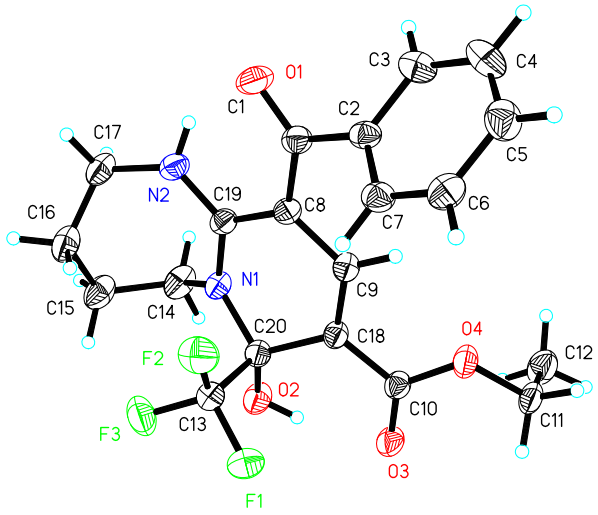


Figure S1 X-Ray crystal structure of **4m**

Table S2 Crystal data and structure refinement for 091209c

Identification code	091209c	
Empirical formula	$C_{20}\ H_{22}\ F_3\ N_2\ O_{4.5}$	
Formula weight	419.4	
Temperature	298(2) K	
Wavelength	0.71073 Å	
Crystal system, space group	Hexagonal, R-3	
Unit cell dimensions	a = 35.238(3) A	alpha = 90 deg.
	b = 35.238(3) A	beta = 90 deg.
	c = 8.3319(15) A	gamma = 120 deg.
Volume	8959.6(19) A^3	
Z, Calculated density	18, 1.399 Mg/m^3	
Absorption coefficient	0.117 mm^-1	

F(000)	3924
Crystal size	0.24x 0.14 x 0.10 mm
Theta range for data collection	2.00 to 28.32 deg.
Limiting indices	-29<=h<=47, -47<=k<=41, -11<=l<=9
Reflection collected/unique	19538/4676[R(int) = 0.0718]
Completeness to theta = 28.32	98.3%
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9884 and 0.9724
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	4676/ 186/ 271
Goodness-of-fit on F^2	0.952
Final R indices [I>2sigma(I)]	R1 = 0.0560, wR2 = 0.1364
R indices (all data)	R1 = 0.1294, wR2 = 0.1760
Extinction coefficient	0.00091(15)
Semi-empirical from equivalents	0.339 and -0.190 e.A^-3

Table S3 Bond lengths [A] and angles [deg] for 091209c

C(1)-O(1)	1.247(3)
C(1)-C(8)	1.437(3)
C(1)-C(2)	1.504(3)
C(2)-C(7)	1.389(3)
C(2)-C(3)	1.390(3)
C(3)-C(4)	1.380(4)
C(3)-H(3)	0.9300
C(4)-C(5)	1.375(4)
C(4)-H(4)	0.9300
C(5)-C(6)	1.383(4)
C(5)-H(5)	0.9300
C(6)-C(7)	1.382(4)
C(6)-H(6)	0.9300
C(7)-H(7)	0.9300
C(8)-C(9)	1.414(3)
C(8)-C(19)	1.433(3)
C(9)-C(18)	1.357(3)
C(9)-H(9)	0.9300
C(10)-O(3)	1.221(3)

C(10)-O(4)	1.334(3)
C(10)-C(18)	1.455(3)
C(11)-O(4)	1.454(3)
C(11)-C(12)	1.497(4)
C(11)-H(11A)	0.9700
C(11)-H(11B)	0.9700
C(12)-H(12A)	0.9600
C(12)-H(12B)	0.9600
C(12)-H(12C)	0.9600
C(13)-F(2)	1.328(3)
C(13)-F(3)	1.332(3)
C(13)-F(1)	1.344(3)
C(13)-C(20)	1.538(4)
C(14)-N(1)	1.470(3)
C(14)-C(15)	1.514(4)
C(14)-H(14A)	0.9700
C(14)-H(14B)	0.9700
C(15)-C(16)	1.514(4)
C(15)-H(15A)	0.9700
C(15)-H(15B)	0.9700
C(16)-C(17)	1.497(4)
C(16)-H(16A)	0.9700
C(16)-H(16B)	0.9700
C(17)-N(2)	1.466(3)
C(17)-H(17A)	0.9700
C(17)-H(17B)	0.9700
C(18)-C(20)	1.508(3)
C(19)-N(2)	1.329(3)
C(19)-N(1)	1.366(3)
C(20)-O(2)	1.400(3)
C(20)-N(1)	1.478(3)
N(2)-H(2)	0.8600
O(2)-H(2A)	0.8200
O(2W)-H(11D)	0.8900
O(2W)-H(11E)	0.8900
O(1W)-H(11D)	0.8451
O(1W)-H(10A)	0.8900
O(1W)-H(10B)	0.8900
O(1)-C(1)-C(8)	124.1(2)
O(1)-C(1)-C(2)	117.7(2)

C(8)-C(1)-C(2)	118.2(2)
C(7)-C(2)-C(3)	118.6(2)
C(7)-C(2)-C(1)	121.7(2)
C(3)-C(2)-C(1)	119.7(2)
C(4)-C(3)-C(2)	120.1(3)
C(4)-C(3)-H(3)	119.9
C(2)-C(3)-H(3)	119.9
C(5)-C(4)-C(3)	121.0(3)
C(5)-C(4)-H(4)	119.5
C(3)-C(4)-H(4)	119.5
C(4)-C(5)-C(6)	119.5(3)
C(4)-C(5)-H(5)	120.2
C(6)-C(5)-H(5)	120.2
C(7)-C(6)-C(5)	119.7(3)
C(7)-C(6)-H(6)	120.1
C(5)-C(6)-H(6)	120.1
C(6)-C(7)-C(2)	121.1(2)
C(6)-C(7)-H(7)	119.5
C(2)-C(7)-H(7)	119.5
C(9)-C(8)-C(19)	116.6(2)
C(9)-C(8)-C(1)	121.5(2)
C(19)-C(8)-C(1)	121.5(2)
C(18)-C(9)-C(8)	123.5(2)
C(18)-C(9)-H(9)	118.2
C(8)-C(9)-H(9)	118.2
O(3)-C(10)-O(4)	122.3(2)
O(3)-C(10)-C(18)	124.6(2)
O(4)-C(10)-C(18)	113.1(2)
O(4)-C(11)-C(12)	110.8(2)
O(4)-C(11)-H(11A)	109.5
C(12)-C(11)-H(11A)	109.5
O(4)-C(11)-H(11B)	109.5
C(12)-C(11)-H(11B)	109.5
H(11A)-C(11)-H(11B)	108.1
F(2)-C(13)-F(3)	106.9(2)
F(2)-C(13)-F(1)	106.2(2)
F(3)-C(13)-F(1)	106.4(2)
F(2)-C(13)-C(20)	113.1(2)
F(3)-C(13)-C(20)	113.1(2)
F(1)-C(13)-C(20)	110.8(2)

N(1)-C(14)-C(15)	113.7(2)
N(1)-C(14)-H(14A)	108.8
C(15)-C(14)-H(14A)	108.8
N(1)-C(14)-H(14B)	108.8
C(15)-C(14)-H(14B)	108.8
H(14A)-C(14)-H(14B)	107.7
C(16)-C(15)-C(14)	110.1(2)
C(16)-C(15)-H(15A)	109.6
C(14)-C(15)-H(15A)	109.6
C(16)-C(15)-H(15B)	109.6
C(14)-C(15)-H(15B)	109.6
H(15A)-C(15)-H(15B)	108.1
C(17)-C(16)-C(15)	113.7(2)
C(17)-C(16)-H(16A)	108.8
C(15)-C(16)-H(16A)	108.8
C(17)-C(16)-H(16B)	108.8
C(15)-C(16)-H(16B)	108.8
H(16A)-C(16)-H(16B)	107.7
N(2)-C(17)-C(16)	114.1(2)
N(2)-C(17)-H(17A)	108.7
C(16)-C(17)-H(17A)	108.7
N(2)-C(17)-H(17B)	108.7
C(16)-C(17)-H(17B)	108.7
H(17A)-C(17)-H(17B)	107.6
C(9)-C(18)-C(10)	122.5(2)
C(9)-C(18)-C(20)	117.7(2)
C(10)-C(18)-C(20)	119.8(2)
N(2)-C(19)-N(1)	120.3(2)
N(2)-C(19)-C(8)	120.0(2)
N(1)-C(19)-C(8)	119.6(2)
O(2)-C(20)-N(1)	107.70(18)
O(2)-C(20)-C(18)	114.33(19)
N(1)-C(20)-C(18)	110.06(19)
O(2)-C(20)-C(13)	105.9(2)
N(1)-C(20)-C(13)	107.79(18)
C(18)-C(20)-C(13)	110.8(2)
C(19)-N(1)-C(14)	118.9(2)
C(19)-N(1)-C(20)	119.94(18)
C(14)-N(1)-C(20)	120.98(19)
C(19)-N(2)-C(17)	130.2(2)

C(19)-N(2)-H(2)	114.9
C(17)-N(2)-H(2)	114.9
C(10)-O(4)-C(11)	117.27(18)
H(11D)-O(2W)-H(11E)	109.5
H(11D)-O(1W)-H(10A)	110.2
H(11D)-O(1W)-H(10B)	134.1
H(10A)-O(1W)-H(10B)	109.5

Symmetry transformations used to generate equivalent atoms:

Table S4 Torsion angles [deg] for 091209c

O(1)-C(1)-C(2)-C(7)	130.3(3)
C(8)-C(1)-C(2)-C(7)	-49.9(3)
O(1)-C(1)-C(2)-C(3)	-47.3(3)
C(8)-C(1)-C(2)-C(3)	132.5(2)
C(7)-C(2)-C(3)-C(4)	1.7(4)
C(1)-C(2)-C(3)-C(4)	179.4(2)
C(2)-C(3)-C(4)-C(5)	-1.9(4)
C(3)-C(4)-C(5)-C(6)	0.3(5)
C(4)-C(5)-C(6)-C(7)	1.4(4)
C(5)-C(6)-C(7)-C(2)	-1.6(4)
C(3)-C(2)-C(7)-C(6)	0.0(4)
C(1)-C(2)-C(7)-C(6)	-177.6(2)
O(1)-C(1)-C(8)-C(9)	163.4(2)
C(2)-C(1)-C(8)-C(9)	-16.4(3)
O(1)-C(1)-C(8)-C(19)	-9.1(4)
C(2)-C(1)-C(8)-C(19)	171.1(2)
C(19)-C(8)-C(9)-C(18)	-15.3(3)
C(1)-C(8)-C(9)-C(18)	171.9(2)
N(1)-C(14)-C(15)-C(16)	47.8(3)
C(14)-C(15)-C(16)-C(17)	39.3(3)
C(15)-C(16)-C(17)-N(2)	-76.7(3)
C(8)-C(9)-C(18)-C(10)	171.6(2)
C(8)-C(9)-C(18)-C(20)	-6.4(3)
O(3)-C(10)-C(18)-C(9)	-177.6(2)
O(4)-C(10)-C(18)-C(9)	2.0(3)
O(3)-C(10)-C(18)-C(20)	0.4(4)
O(4)-C(10)-C(18)-C(20)	180.0(2)
C(9)-C(8)-C(19)-N(2)	-168.4(2)
C(1)-C(8)-C(19)-N(2)	4.5(3)
C(9)-C(8)-C(19)-N(1)	8.1(3)
C(1)-C(8)-C(19)-N(1)	-179.0(2)

C(9)-C(18)-C(20)-O(2)	153.5(2)
C(10)-C(18)-C(20)-O(2)	-24.6(3)
C(9)-C(18)-C(20)-N(1)	32.1(3)
C(10)-C(18)-C(20)-N(1)	-145.9(2)
C(9)-C(18)-C(20)-C(13)	-87.0(3)
C(10)-C(18)-C(20)-C(13)	95.0(3)
F(2)-C(13)-C(20)-O(2)	-175.34(19)
F(3)-C(13)-C(20)-O(2)	-53.7(3)
F(1)-C(13)-C(20)-O(2)	65.6(3)
F(2)-C(13)-C(20)-N(1)	-60.3(3)
F(3)-C(13)-C(20)-N(1)	61.3(3)
F(1)-C(13)-C(20)-N(1)	-179.34(19)
F(2)-C(13)-C(20)-C(18)	60.2(3)
F(3)-C(13)-C(20)-C(18)	-178.2(2)
F(1)-C(13)-C(20)-C(18)	-58.9(3)
N(2)-C(19)-N(1)-C(14)	22.3(3)
C(8)-C(19)-N(1)-C(14)	-154.1(2)
N(2)-C(19)-N(1)-C(20)	-162.8(2)
C(8)-C(19)-N(1)-C(20)	20.7(3)
C(15)-C(14)-N(1)-C(19)	-85.0(3)
C(15)-C(14)-N(1)-C(20)	100.3(3)
O(2)-C(20)-N(1)-C(19)	-165.0(2)
C(18)-C(20)-N(1)-C(19)	-39.8(3)
C(13)-C(20)-N(1)-C(19)	81.1(2)
O(2)-C(20)-N(1)-C(14)	9.7(3)
C(18)-C(20)-N(1)-C(14)	134.9(2)
C(13)-C(20)-N(1)-C(14)	-104.2(2)
N(1)-C(19)-N(2)-C(17)	20.3(4)
C(8)-C(19)-N(2)-C(17)	-163.2(2)
C(16)-C(17)-N(2)-C(19)	20.5(4)
O(3)-C(10)-O(4)-C(11)	12.8(3)
C(18)-C(10)-O(4)-C(11)	-166.8(2)
C(12)-C(11)-O(4)-C(10)	79.6(3)

Table S5 Hydrogen bonds for 091209c [A and deg.].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)

C(14)-H(14A)...O(2)	0.97	2.19	2.670(3)	109.1
C(9)-H(9)...O(4)	0.93	2.37	2.709(3)	100.9
O(2)-H(2A)...O(3)	0.82	1.90	2.630(2)	147.2
N(2)-H(2)...O(1)	0.86	1.97	2.638(3)	134.2

^{1}H NMR and ^{13}C NMR Spectra for Bicyclic Pyridines 4, 6

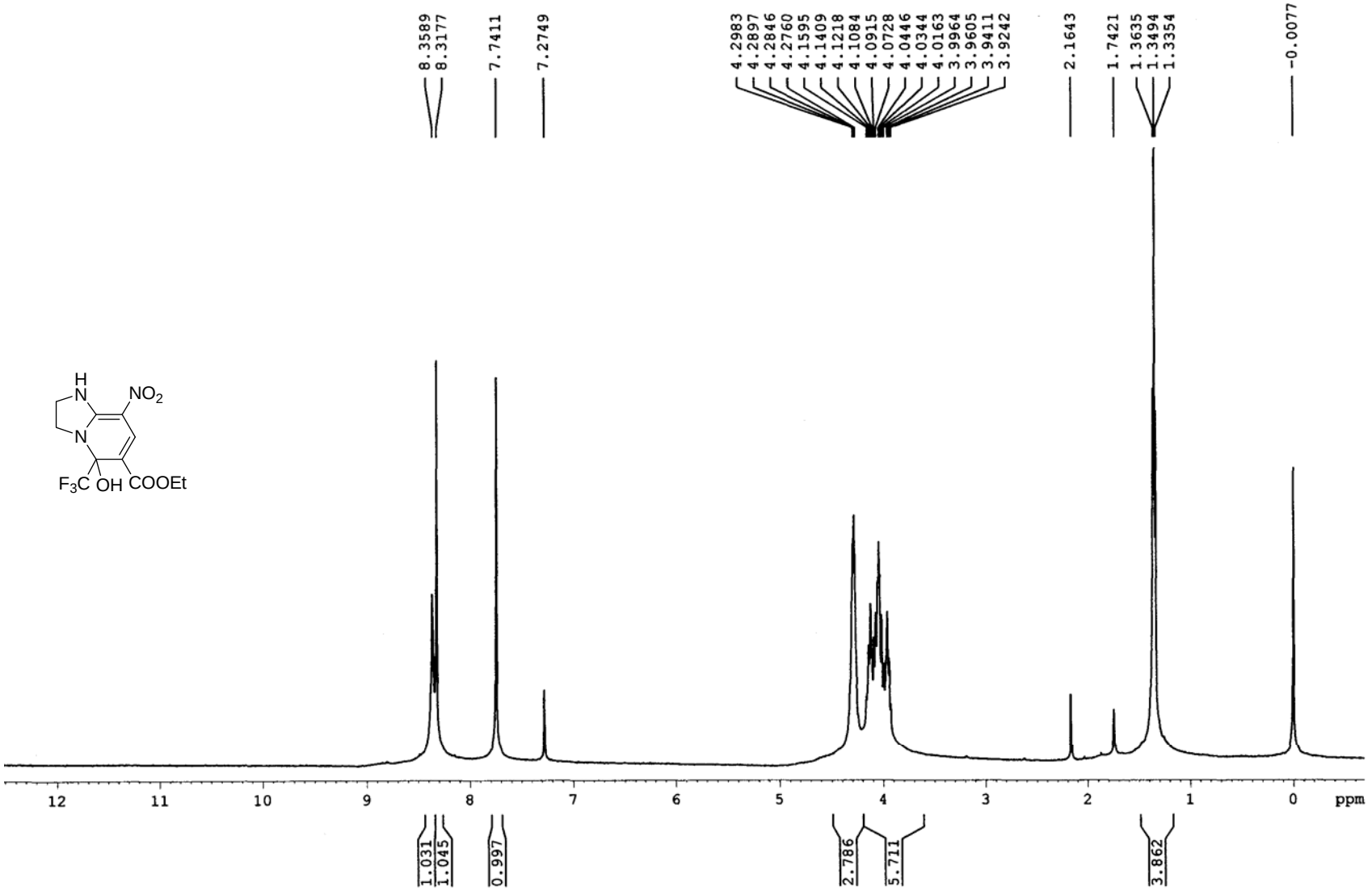


Figure 1. ^{1}H NMR (500 MHz, $CDCl_3$) spectra of compound **4a**

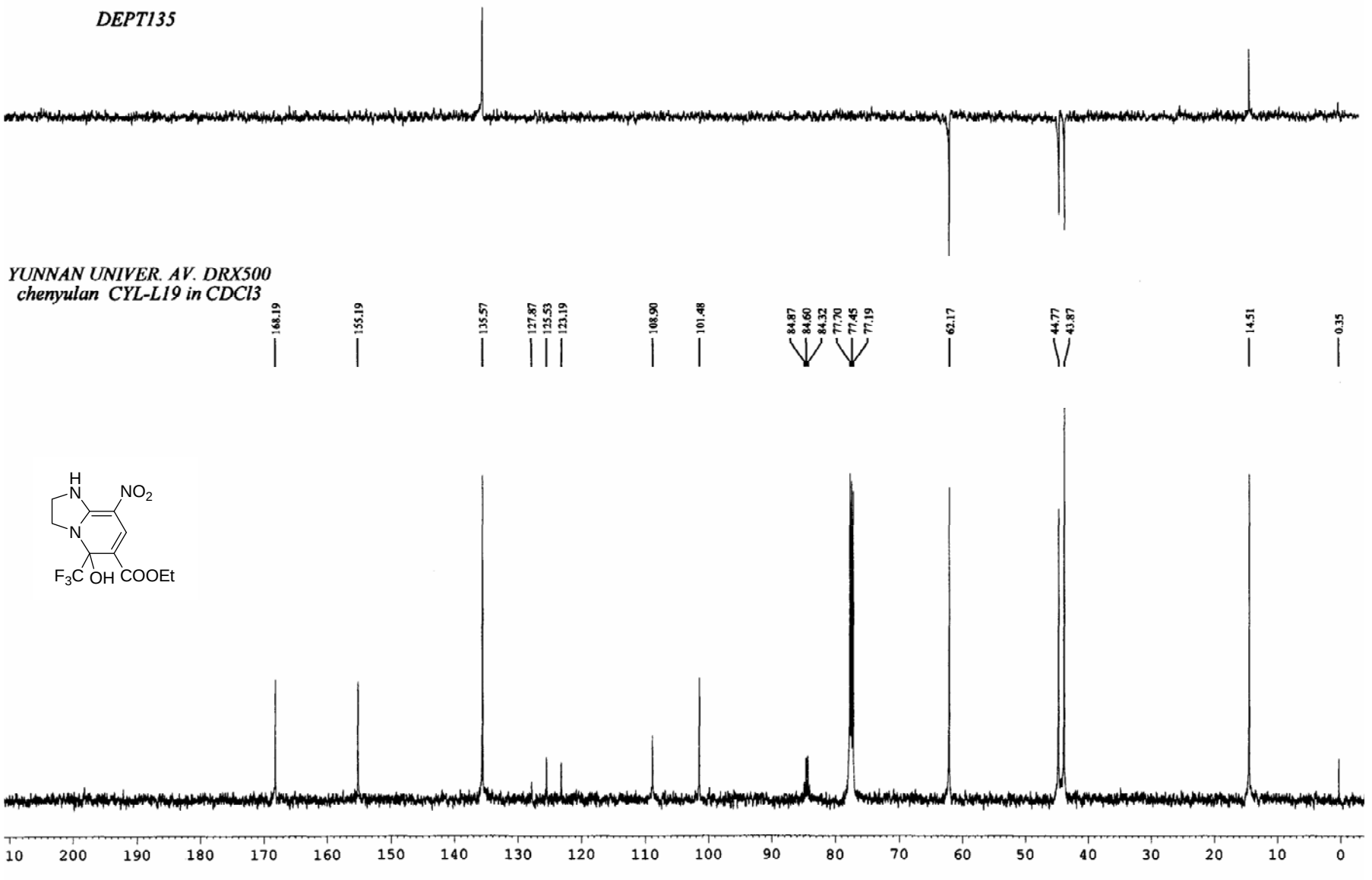


Figure 2. ^{13}C NMR (125 MHz, $CDCl_3$) spectra of compound **4a**

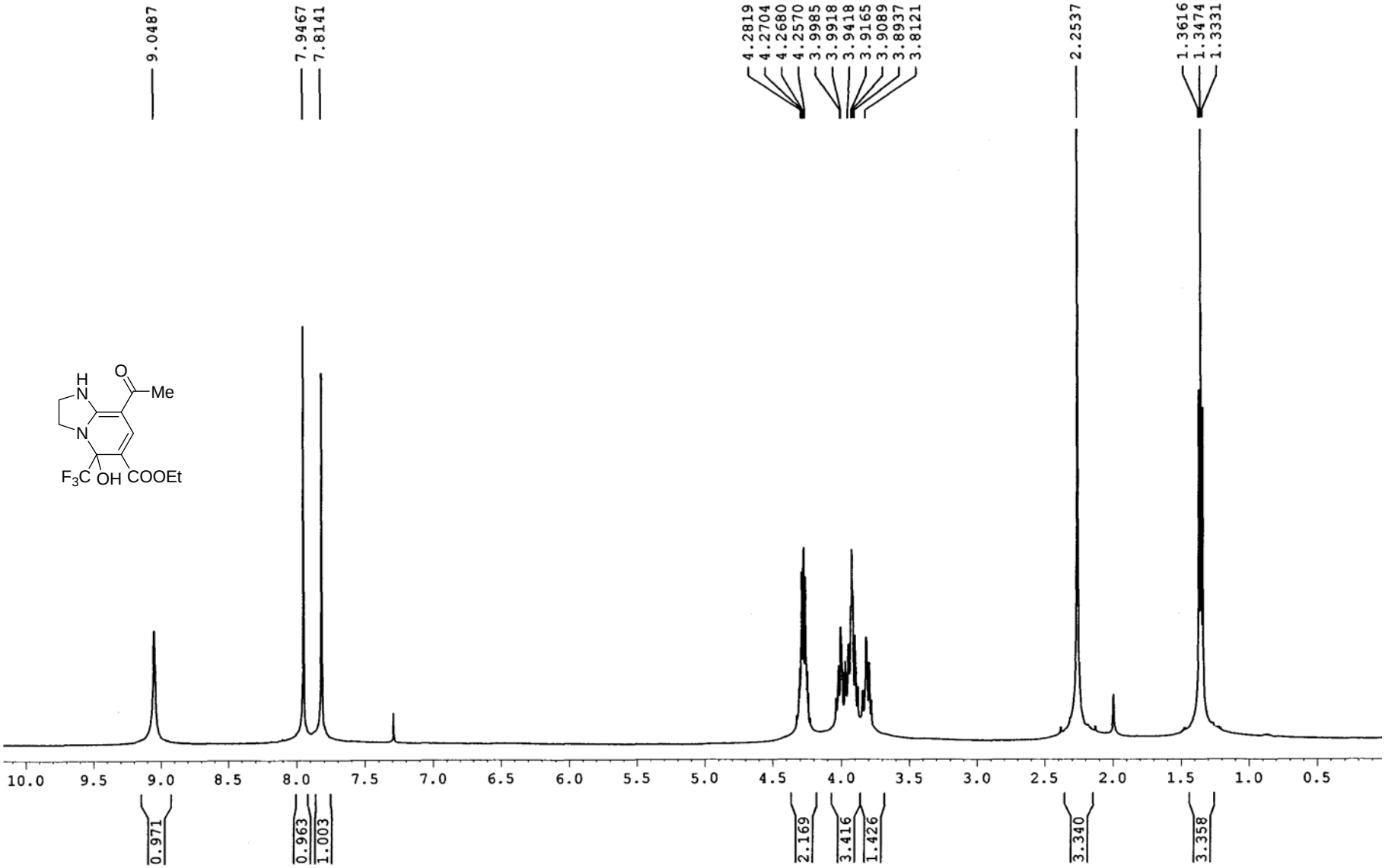


Figure 3. ^{1}H NMR (500 MHz, $CDCl_3$) spectra of compound **4b**

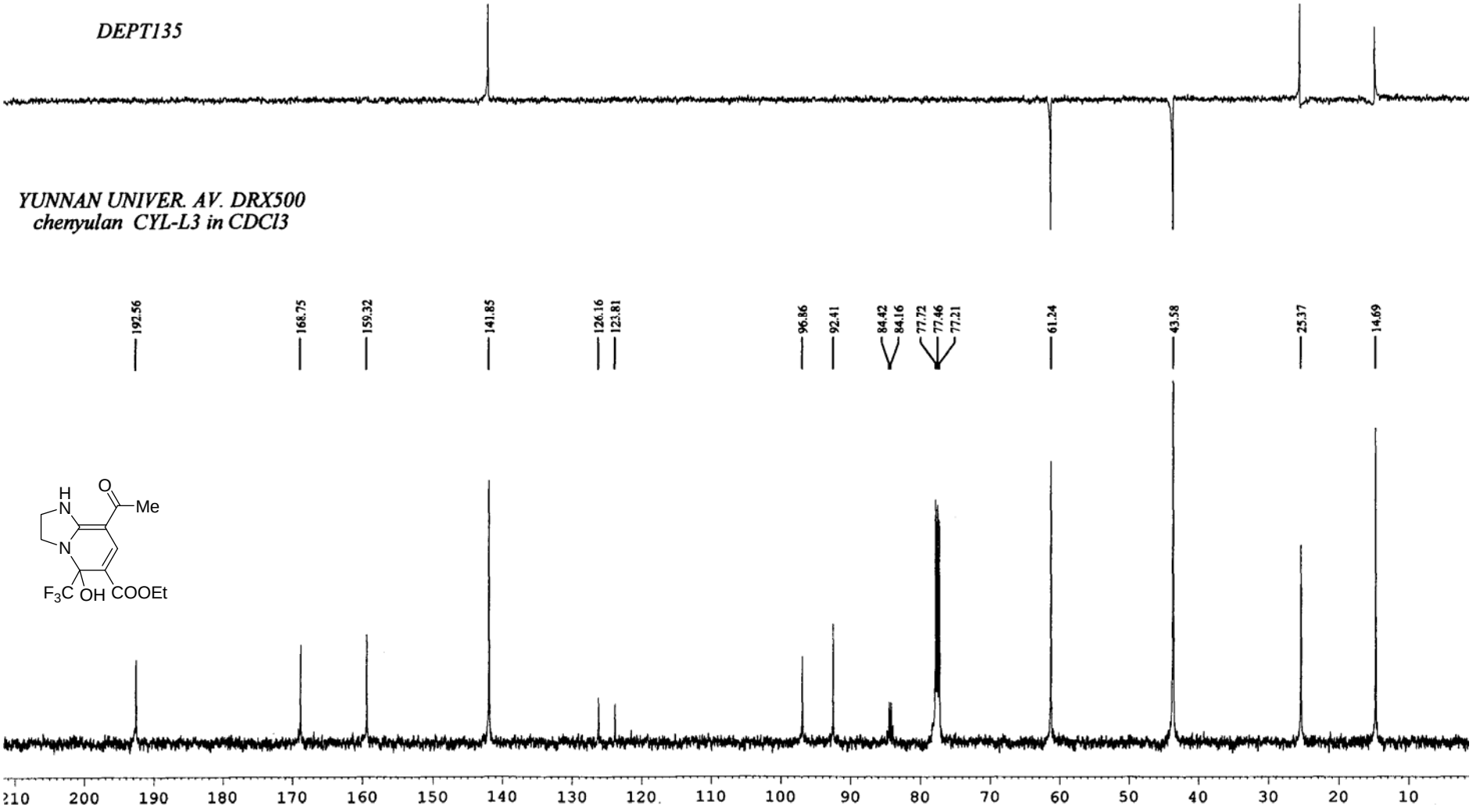


Figure 4. ^{13}C NMR (125 MHz, $CDCl_3$) spectra of compound **4b**

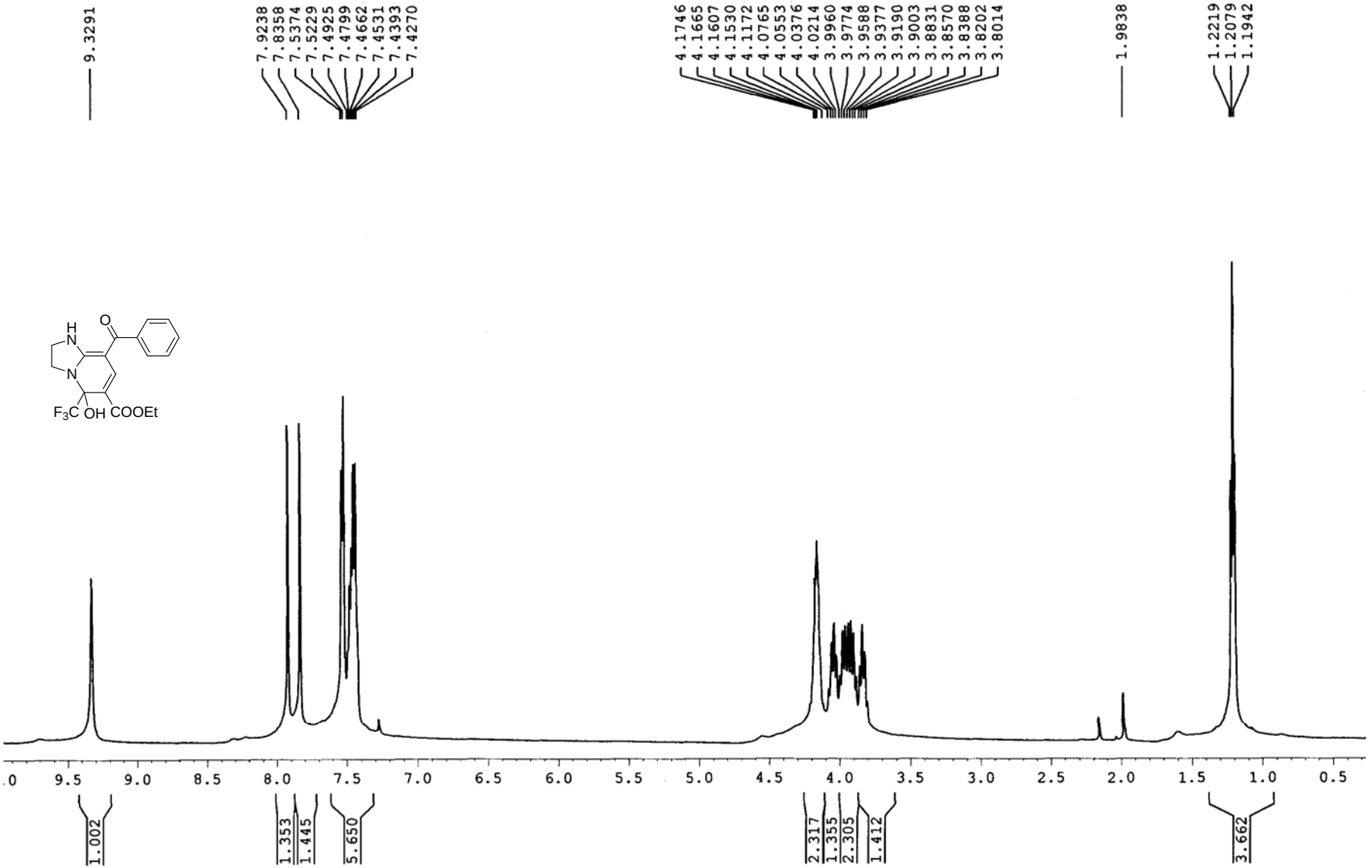


Figure 5. ^{1}H NMR (500 MHz, $CDCl_3$) spectra of compound **4c**

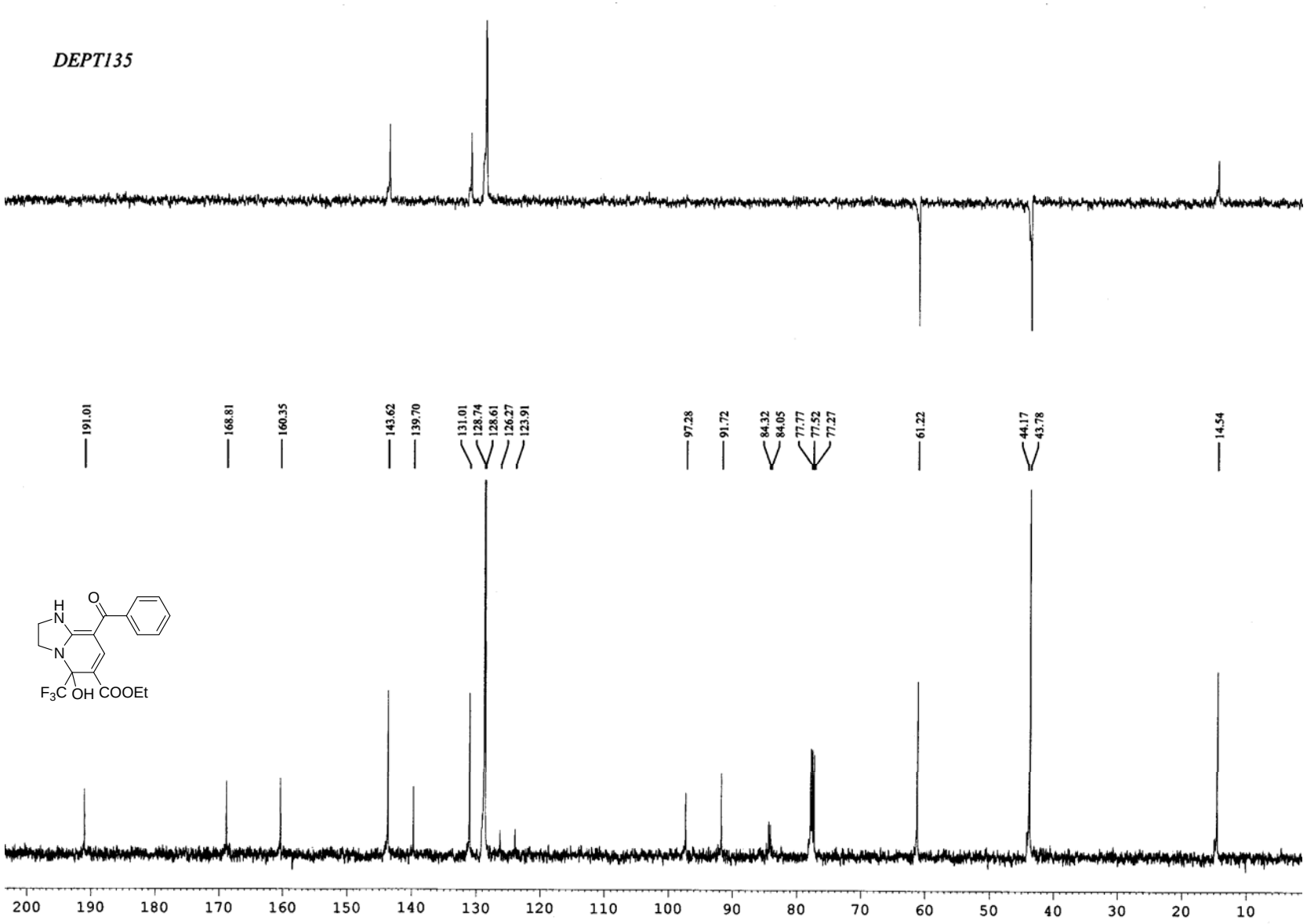


Figure 6. ^{13}C NMR (125 MHz, $CDCl_3$) spectra of compound **4c**

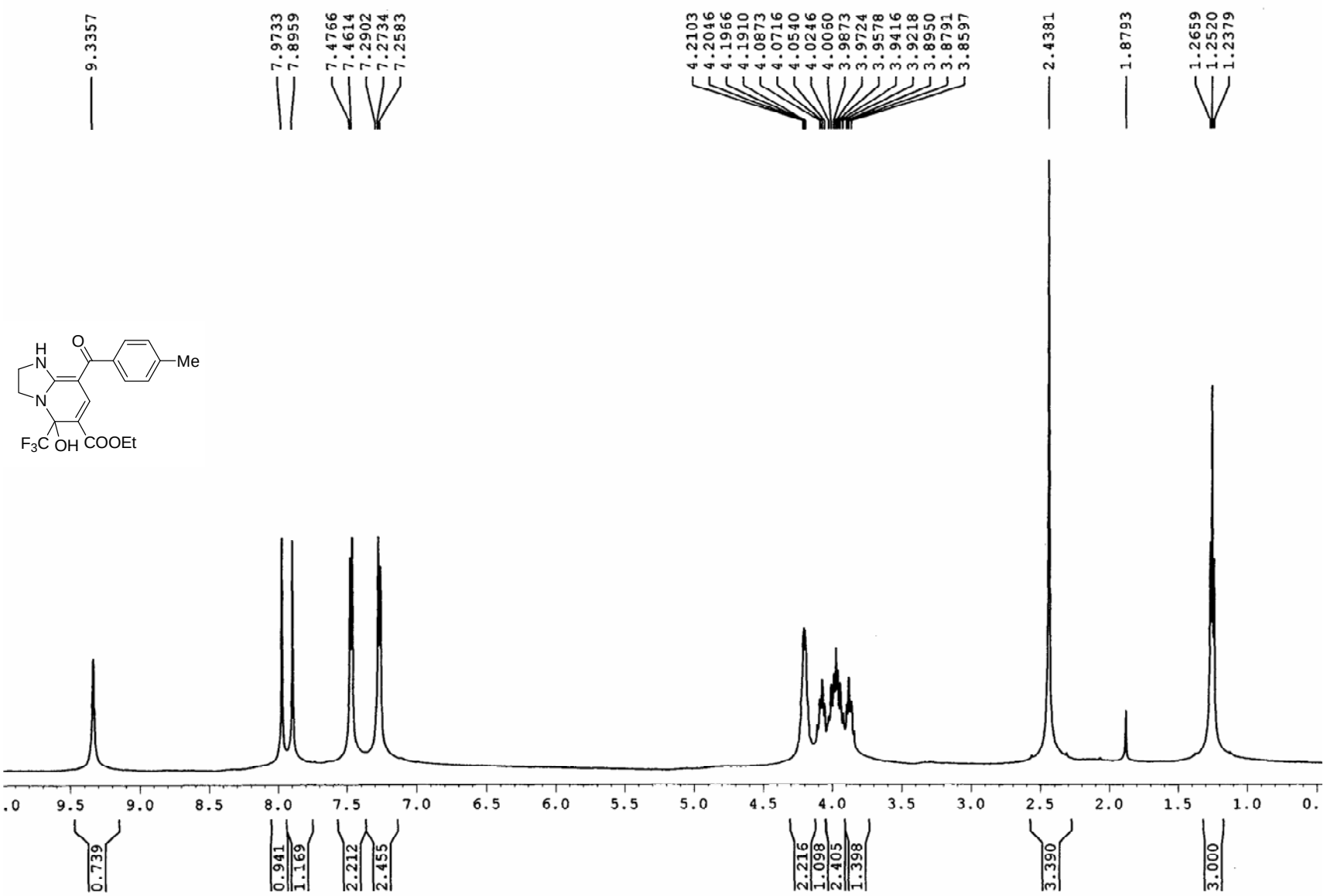


Figure 7. ^{1}H NMR (500 MHz, $CDCl_3$) spectra of compound **4d**

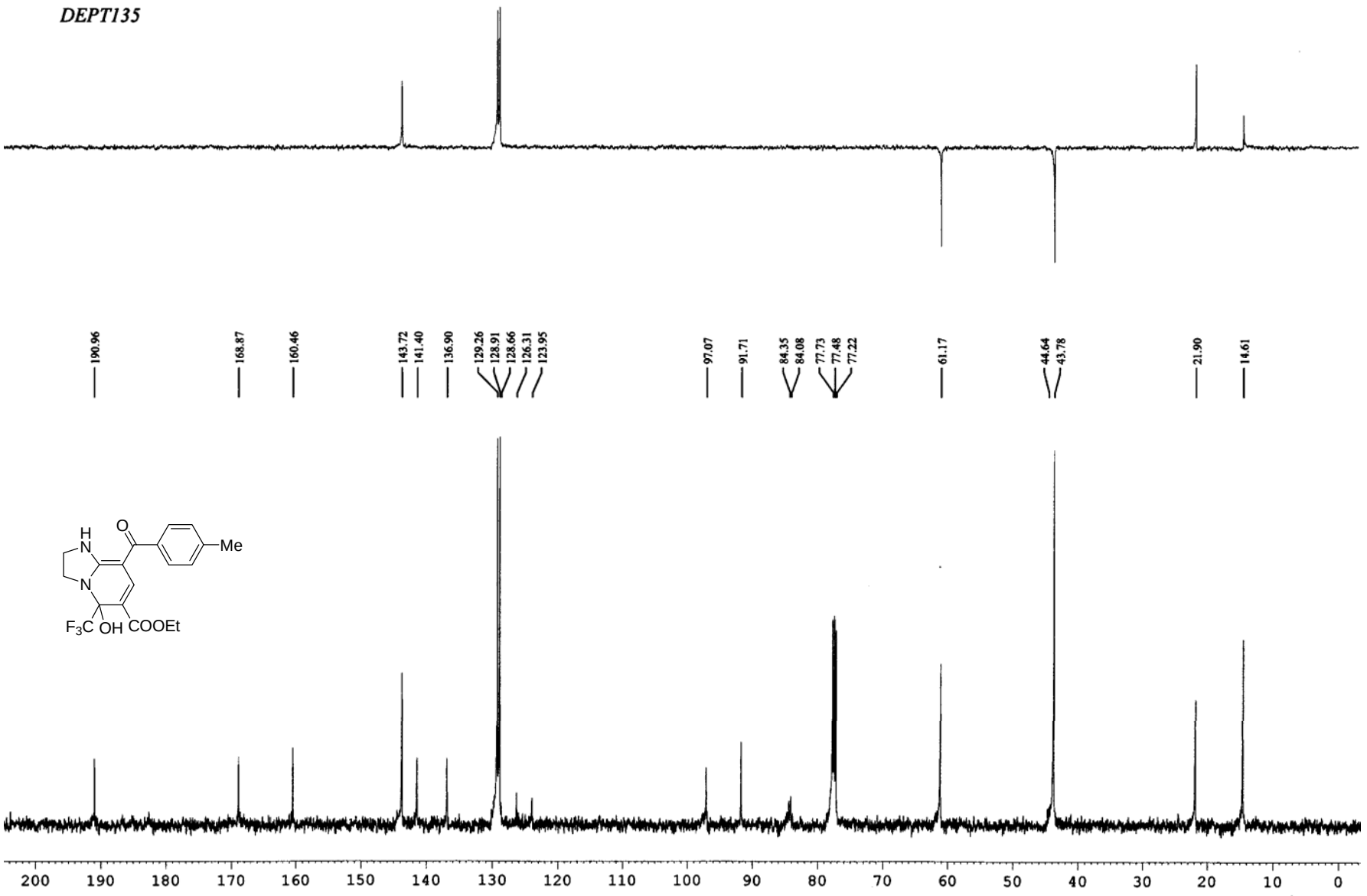


Figure 8. ^{13}C NMR (125 MHz, $CDCl_3$) spectra of compound **4d**

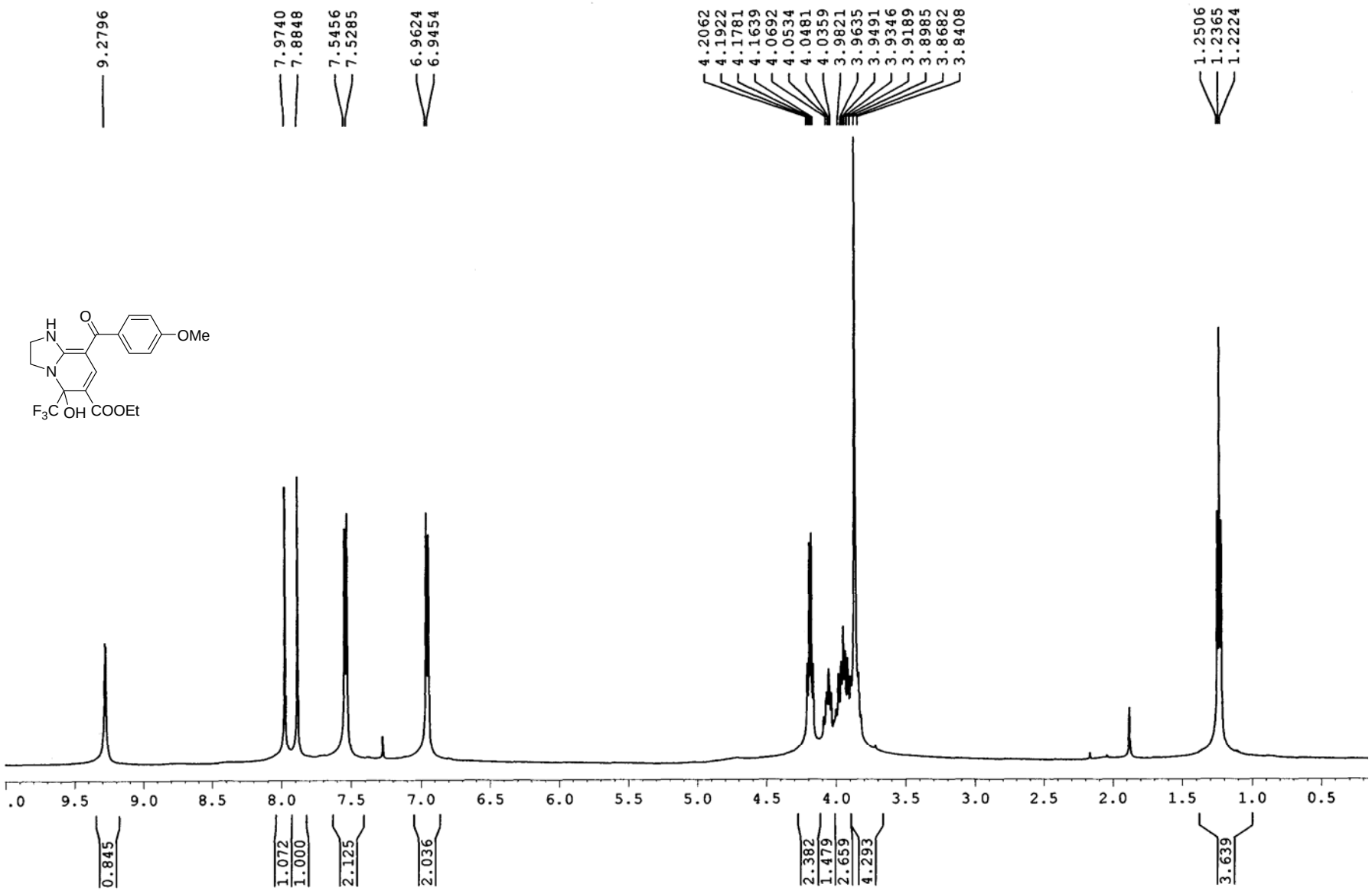


Figure 9. ^{1}H NMR (500 MHz, $CDCl_3$) spectra of compound **4e**

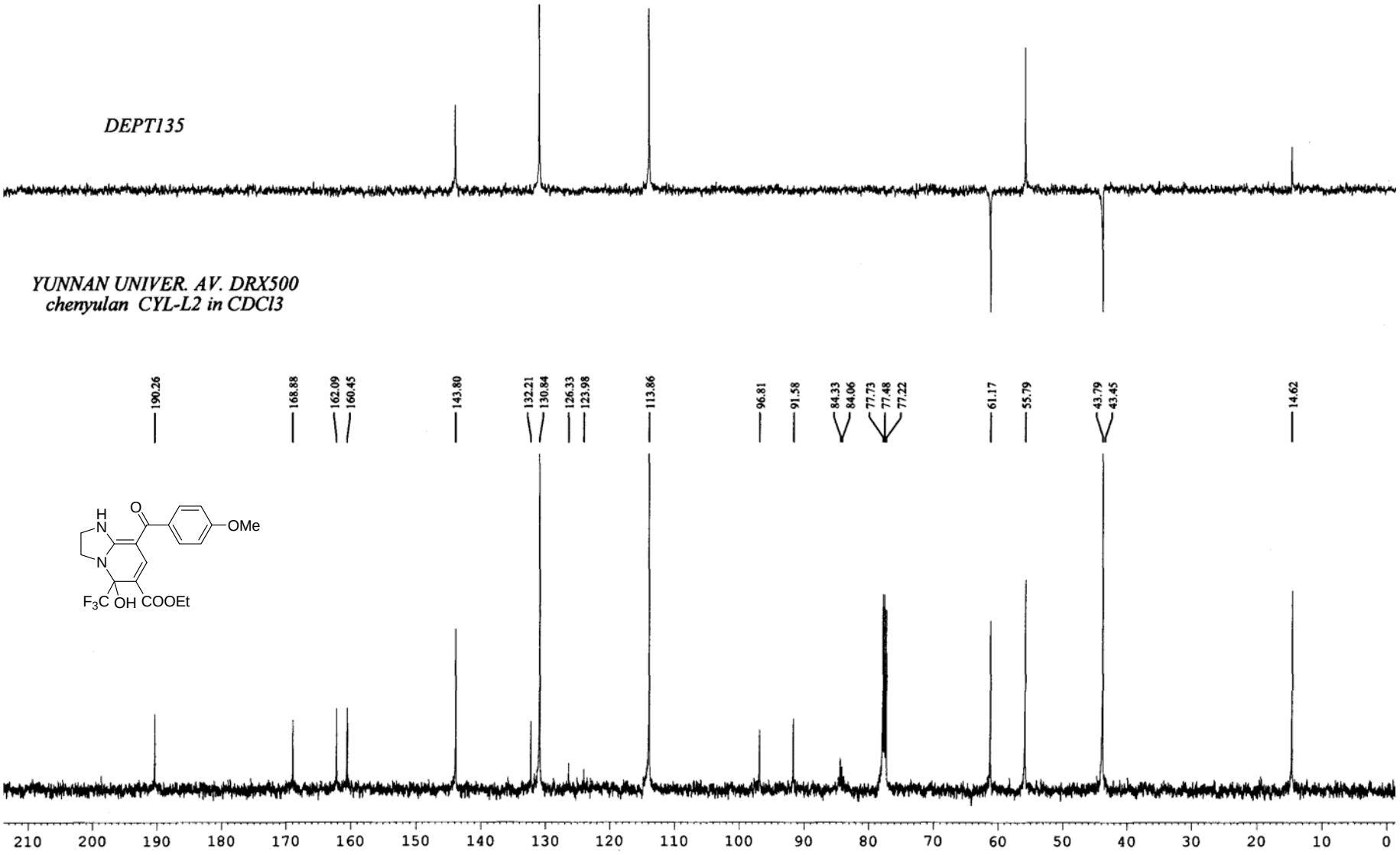


Figure 10. ^{13}C NMR (125 MHz, $CDCl_3$) spectra of compound **4e**

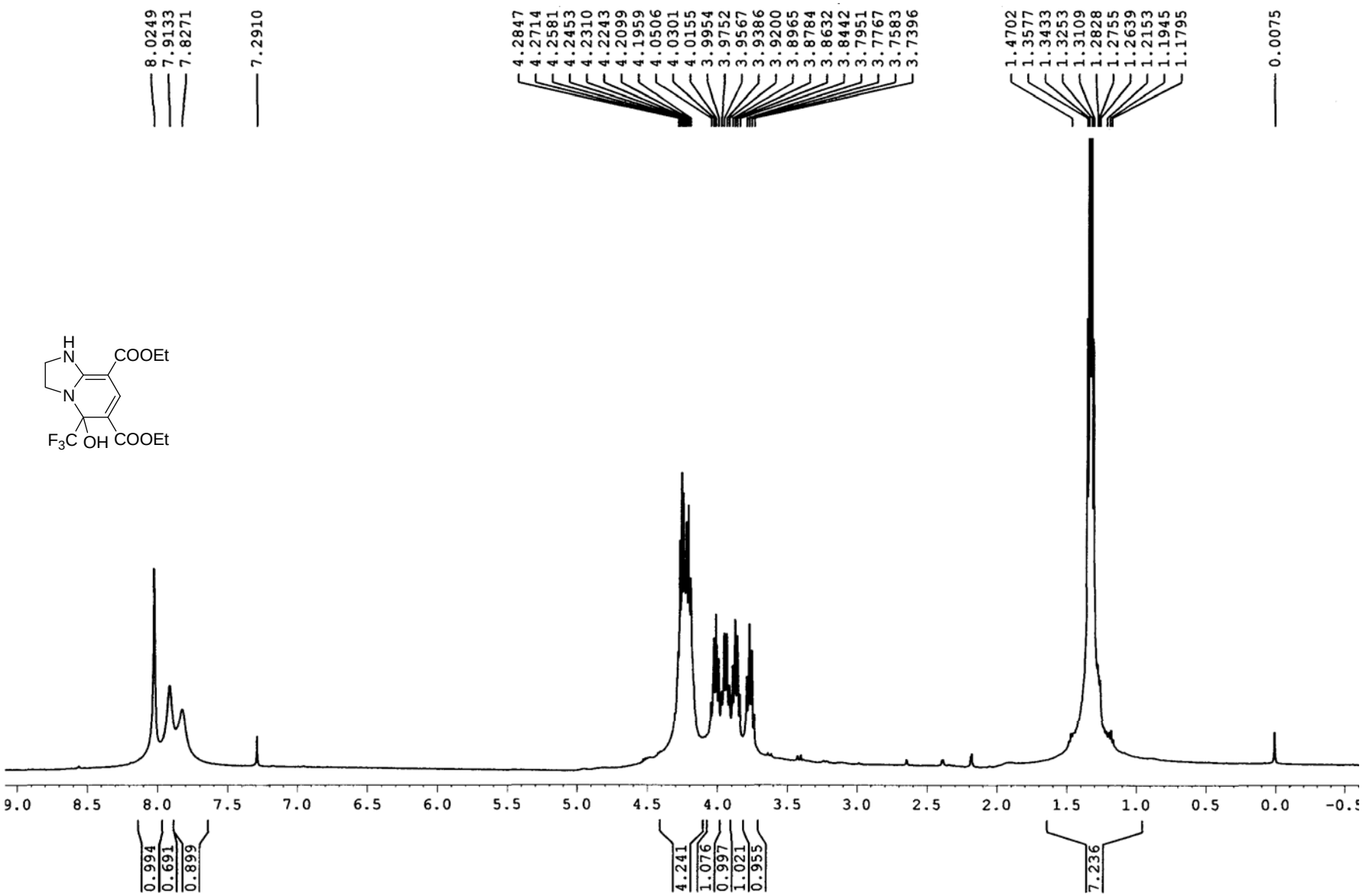


Figure 11. ^{1}H NMR (500 MHz, $CDCl_3$) spectra of compound **4f**

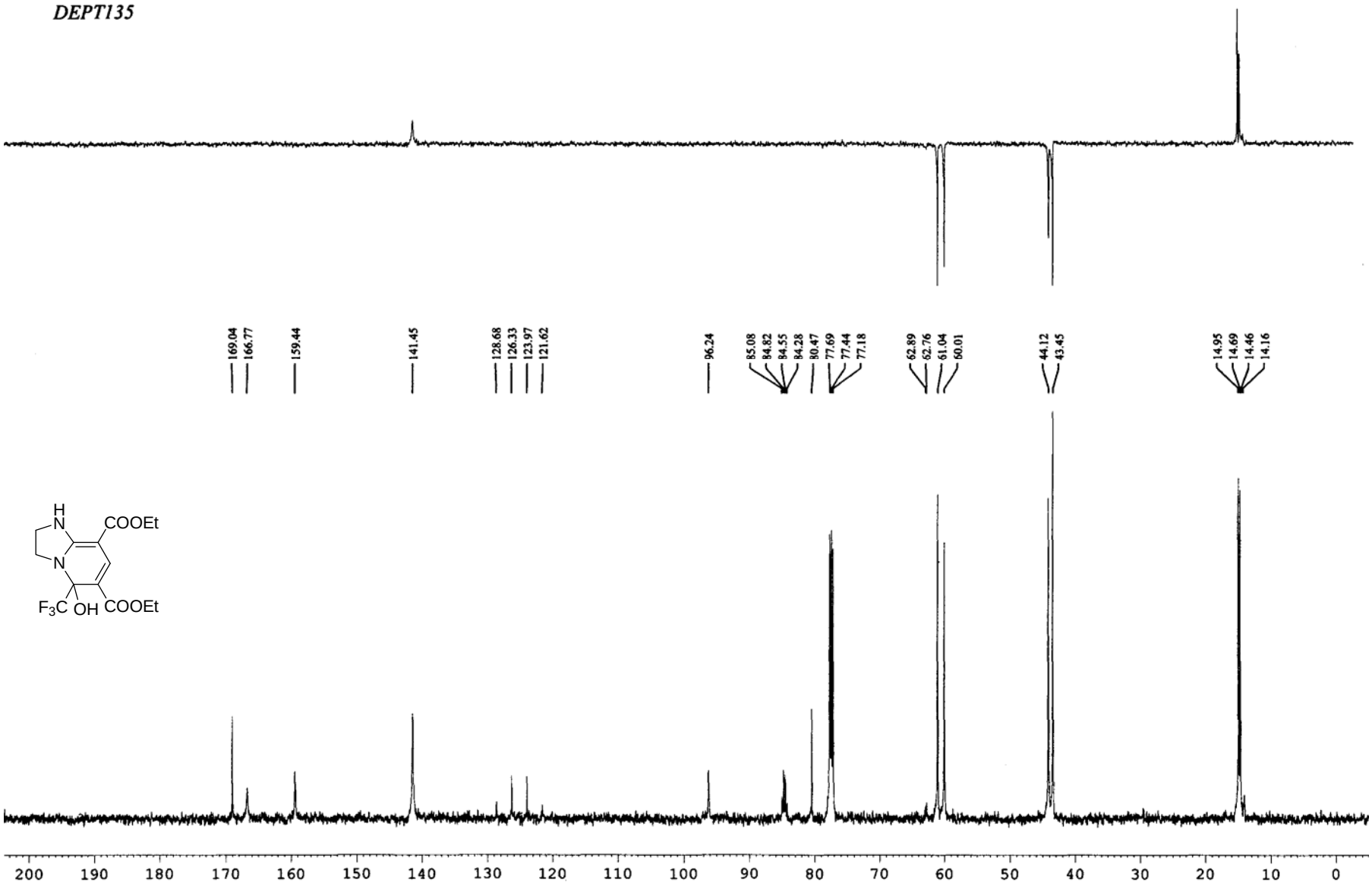


Figure 12. ^{13}C NMR (125 MHz, $CDCl_3$) spectra of compound **4f**

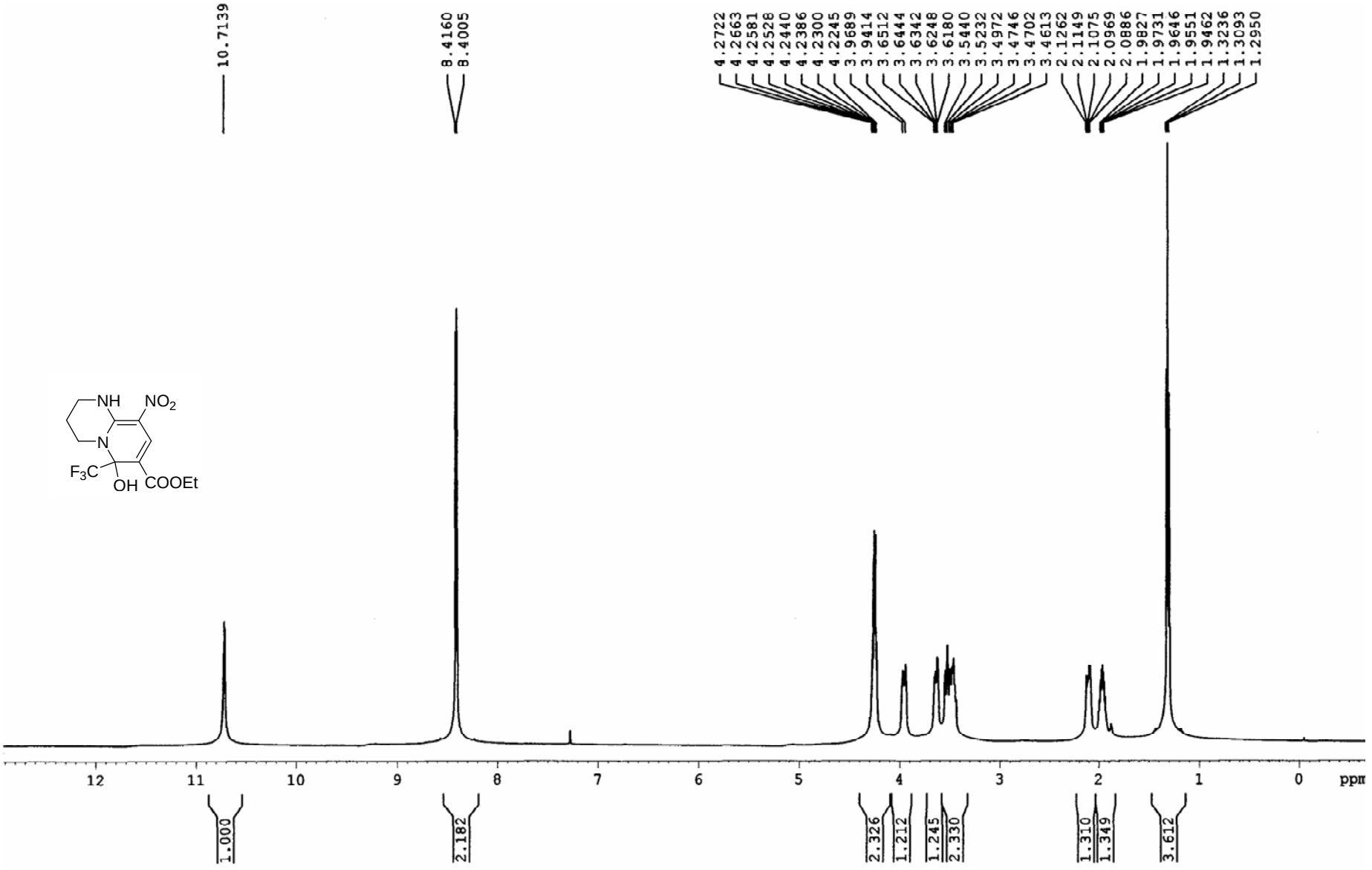


Figure 13. ^{1}H NMR (500 MHz, $CDCl_3$) spectra of compound **4g**

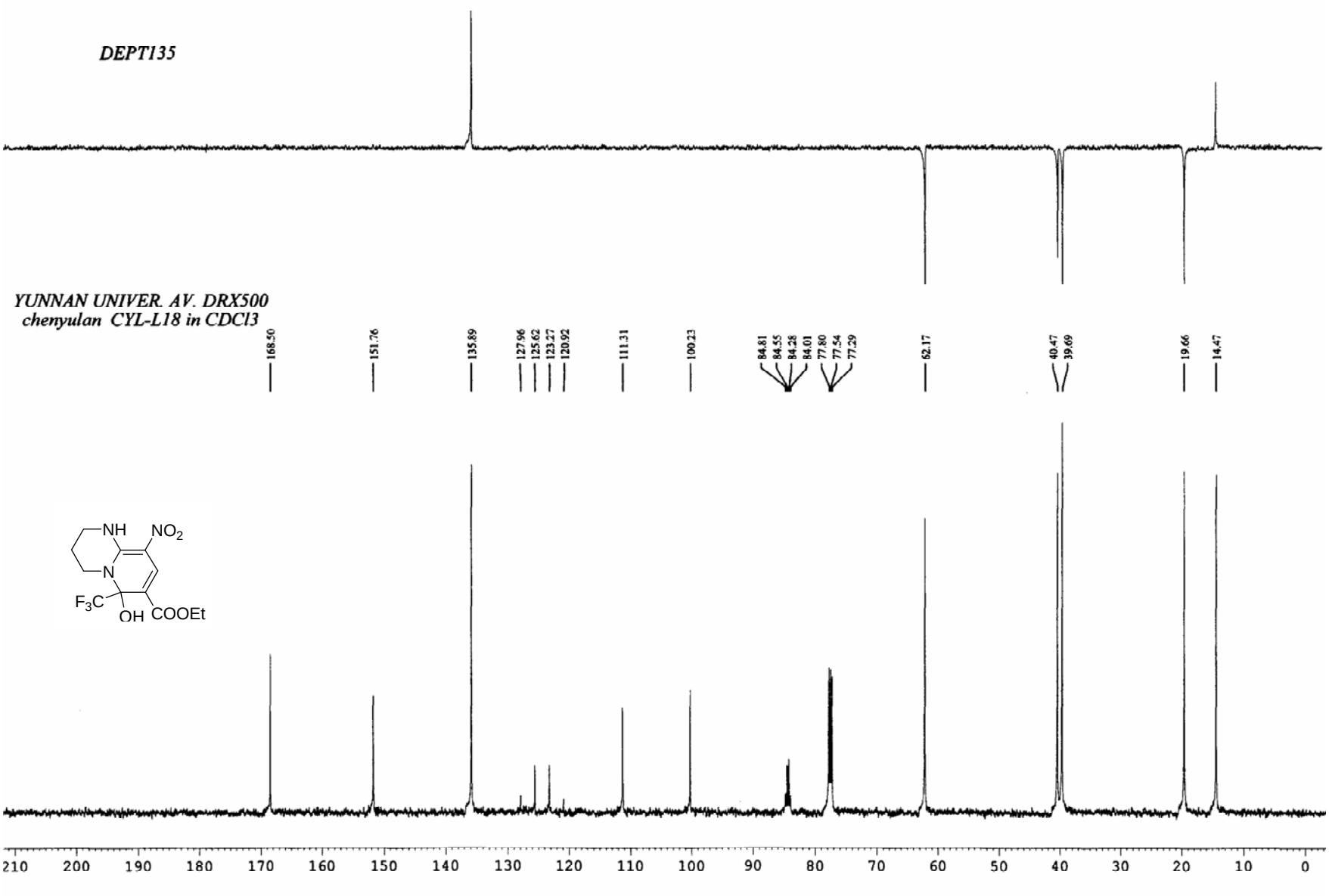


Figure 14. ^{13}C NMR (125 MHz, $CDCl_3$) spectra of compound **4g**

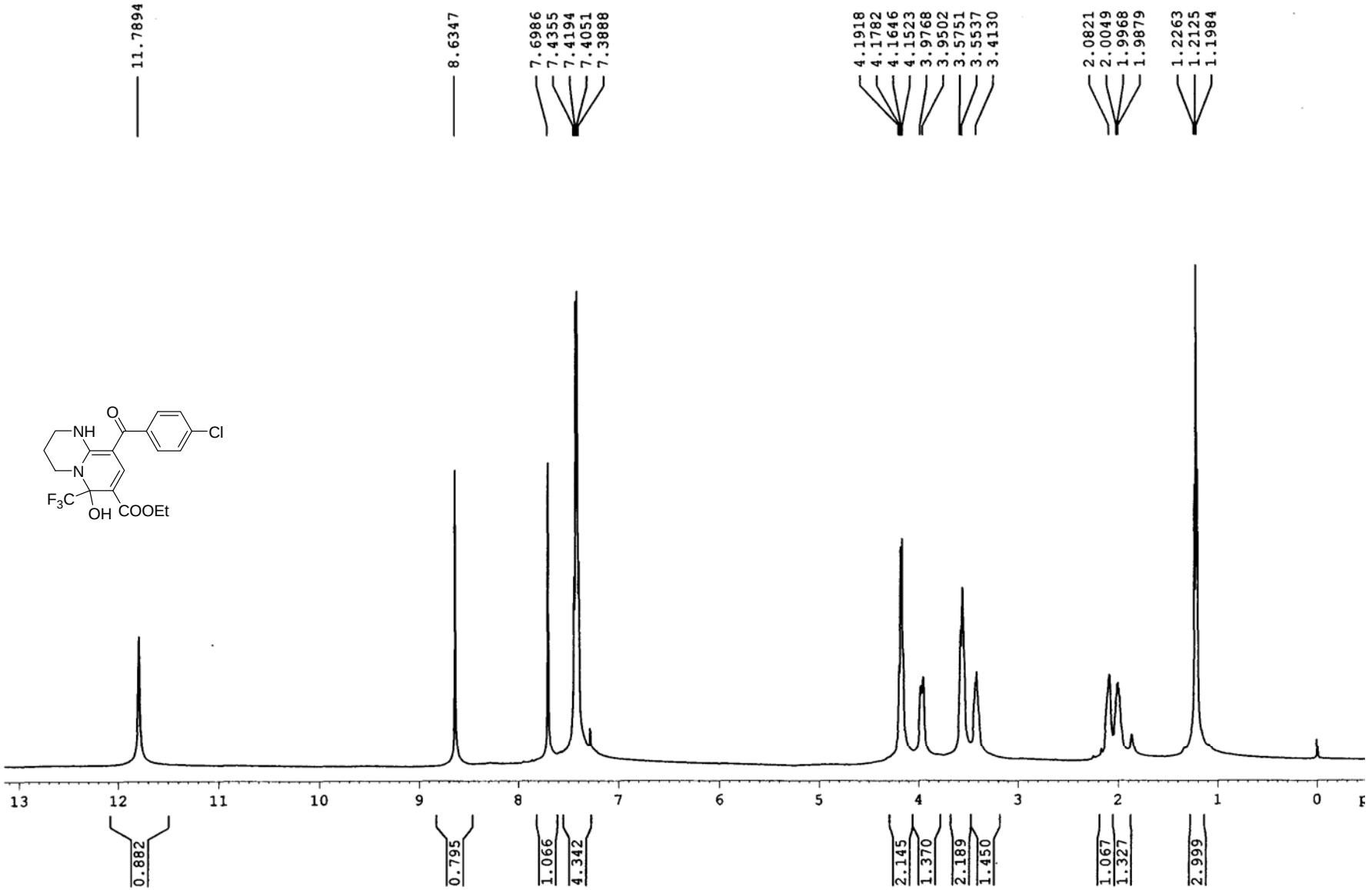


Figure 15. ^{1}H NMR (500 MHz, $CDCl_3$) spectra of compound **4h**

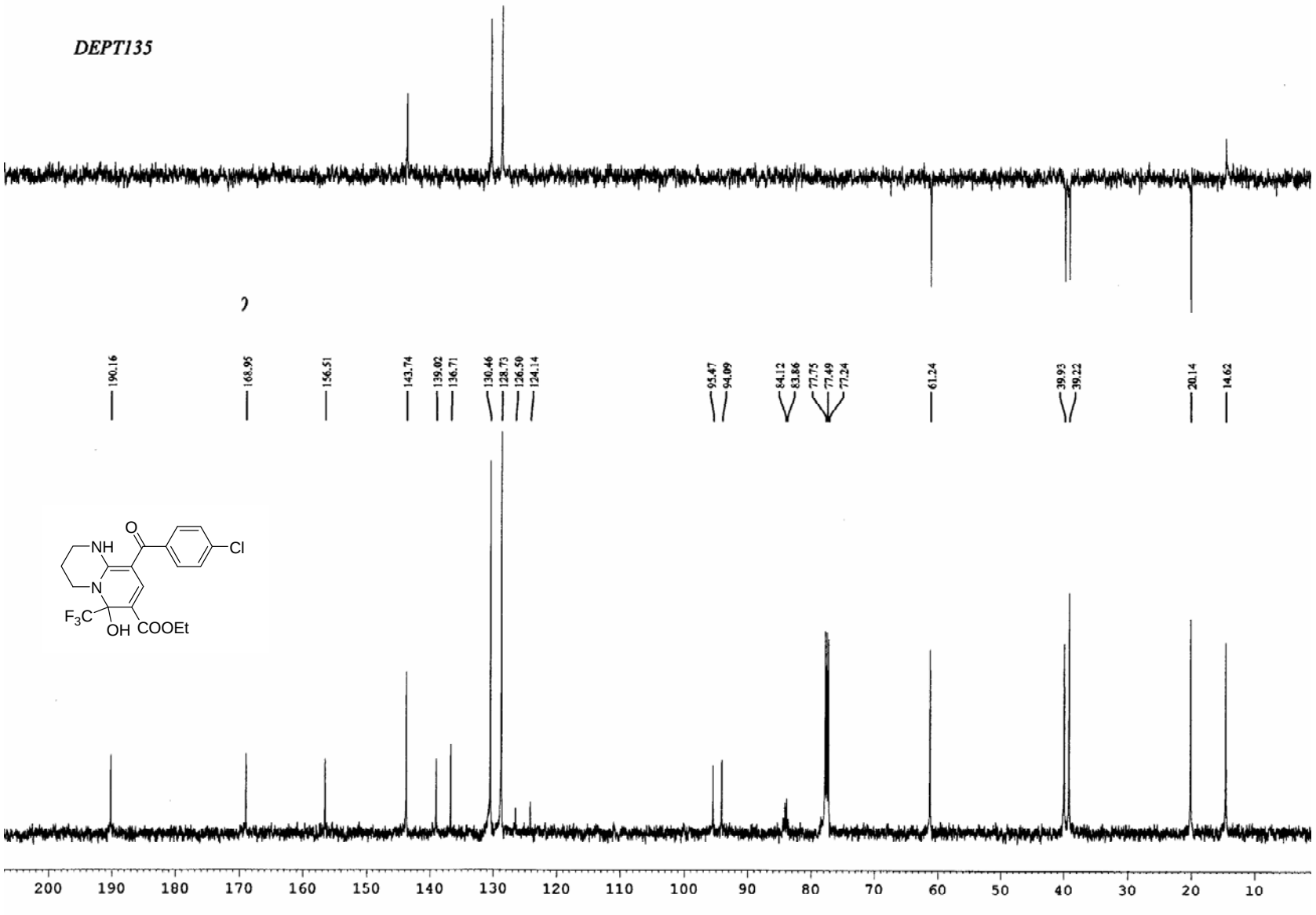


Figure 16. ^{13}C NMR (125 MHz, $CDCl_3$) spectra of compound **4h**

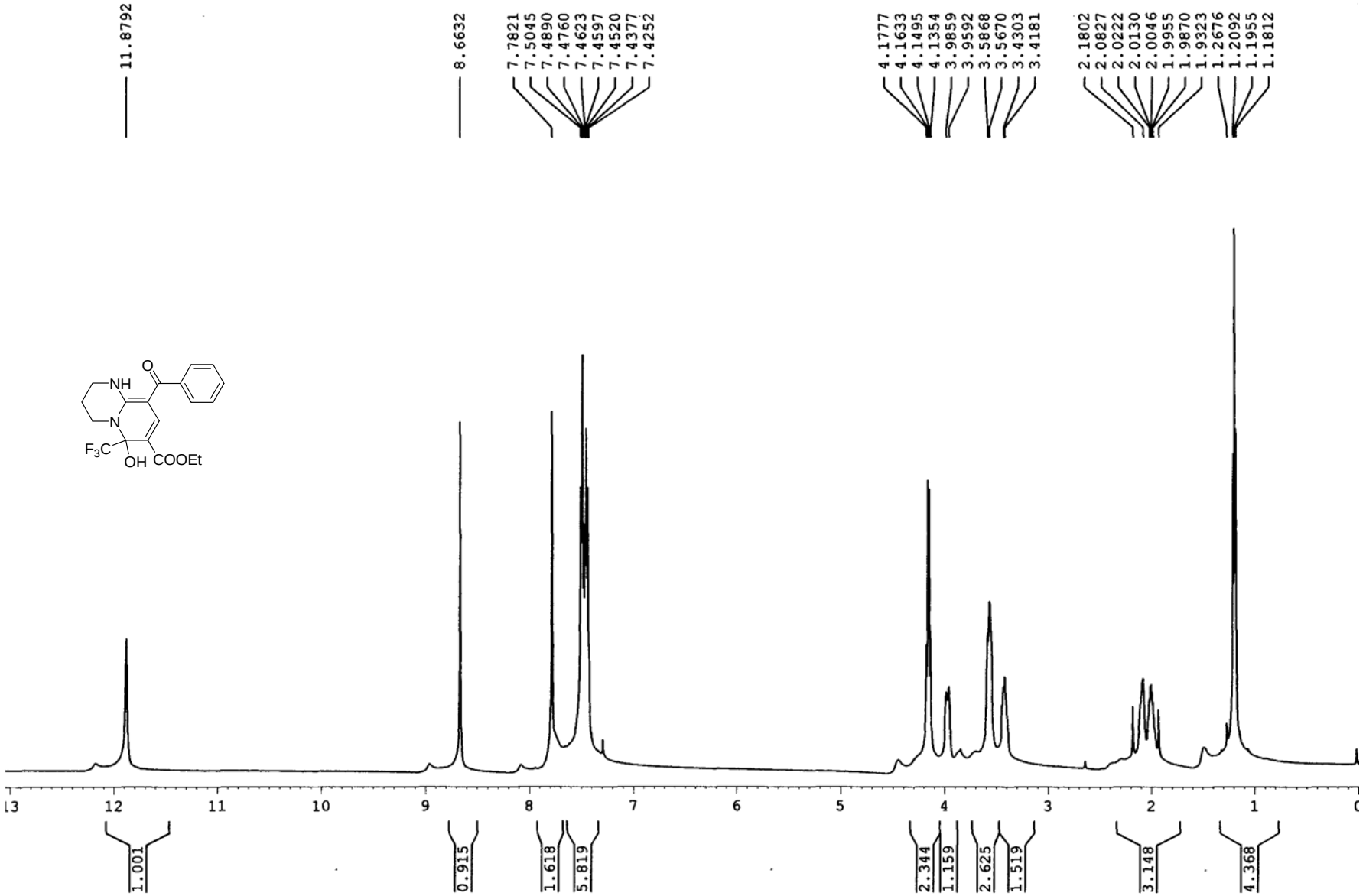


Figure 17. ^{1}H NMR (500 MHz, $CDCl_3$) spectra of compound **4i**

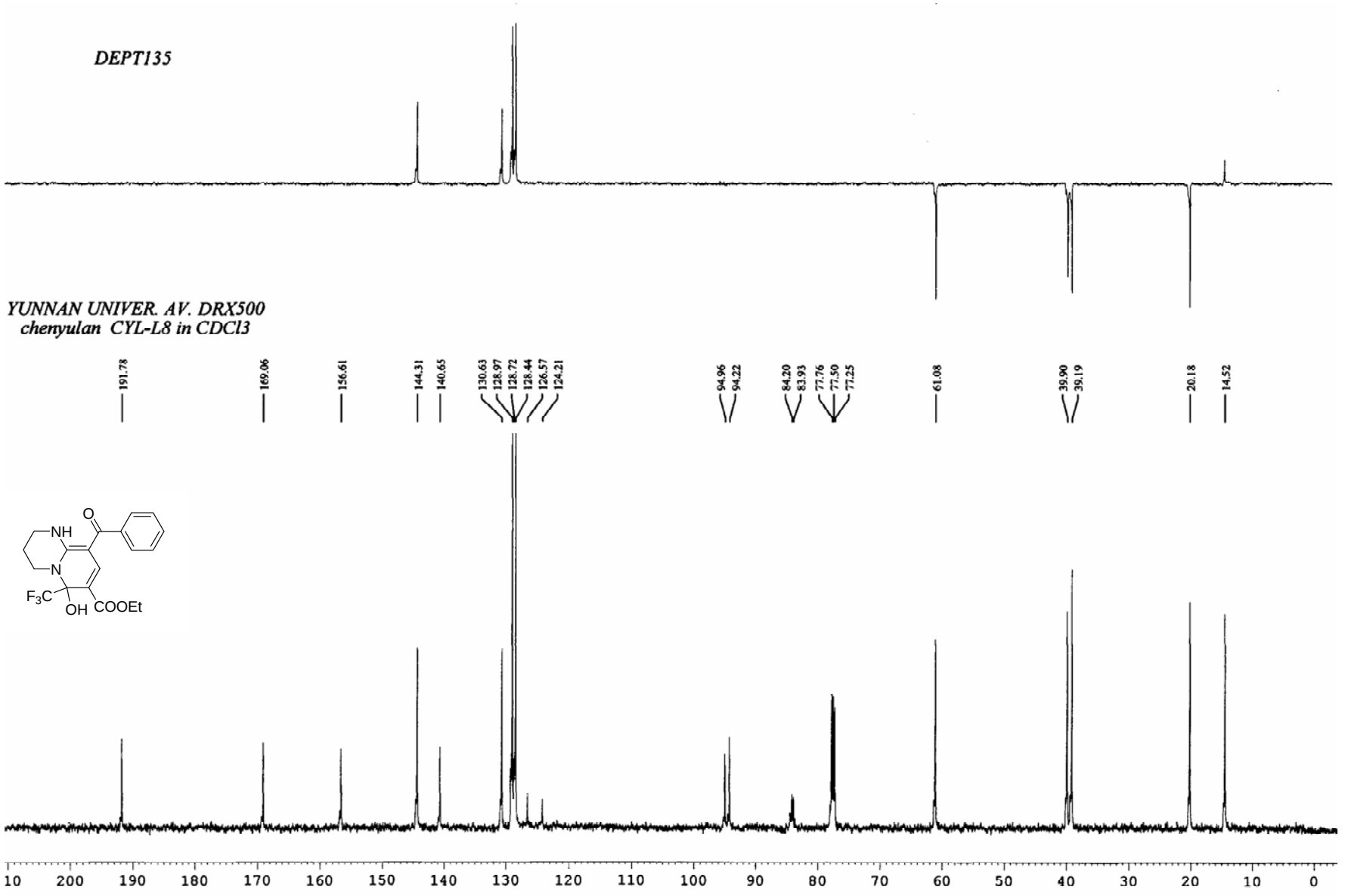


Figure 18. ^{13}C NMR (125 MHz, $CDCl_3$) spectra of compound **4i**

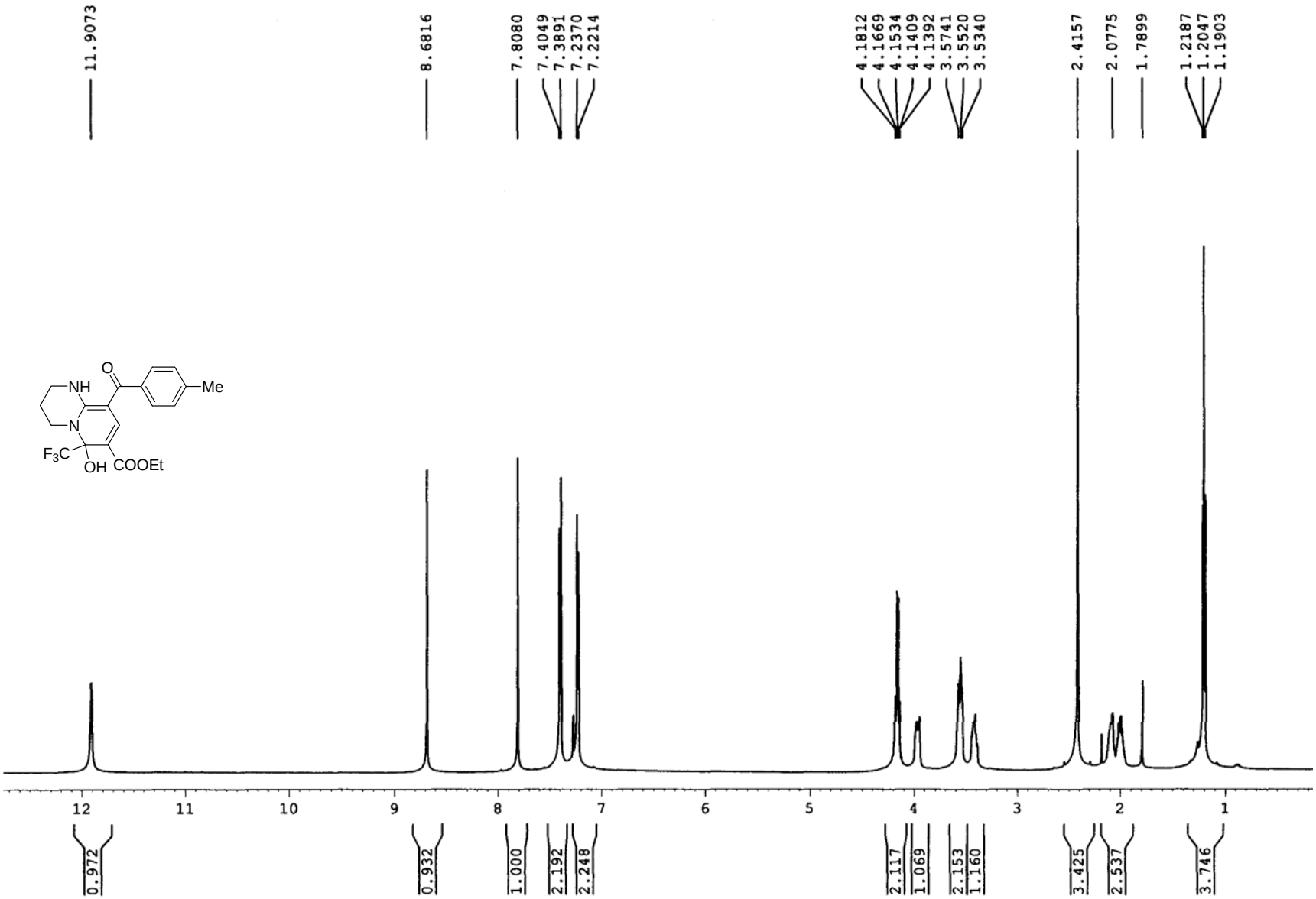


Figure 19. ^{1}H NMR (500 MHz, $CDCl_3$) spectra of compound **4j**

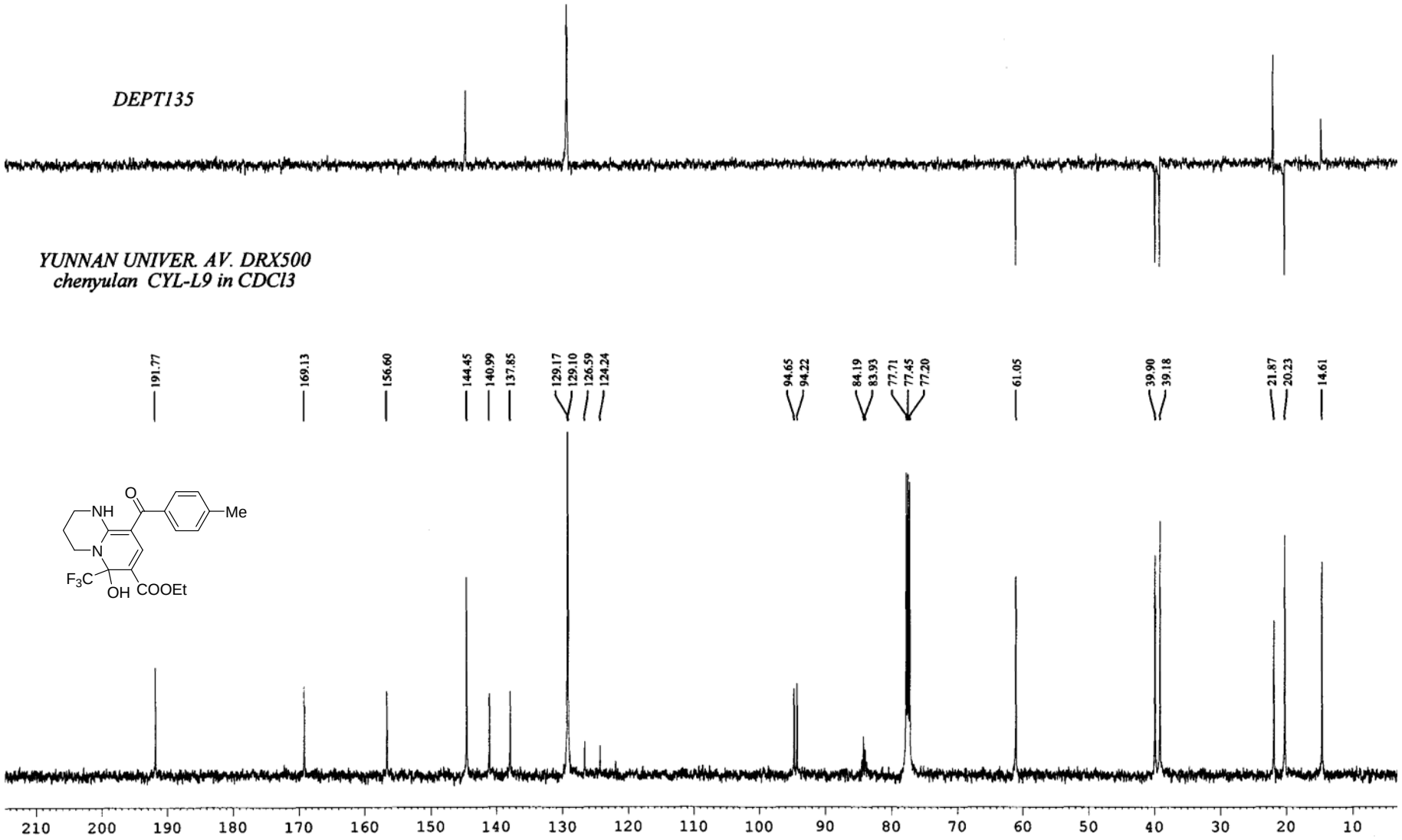


Figure 20. ^{13}C NMR (125 MHz, $CDCl_3$) spectra of compound **4j**

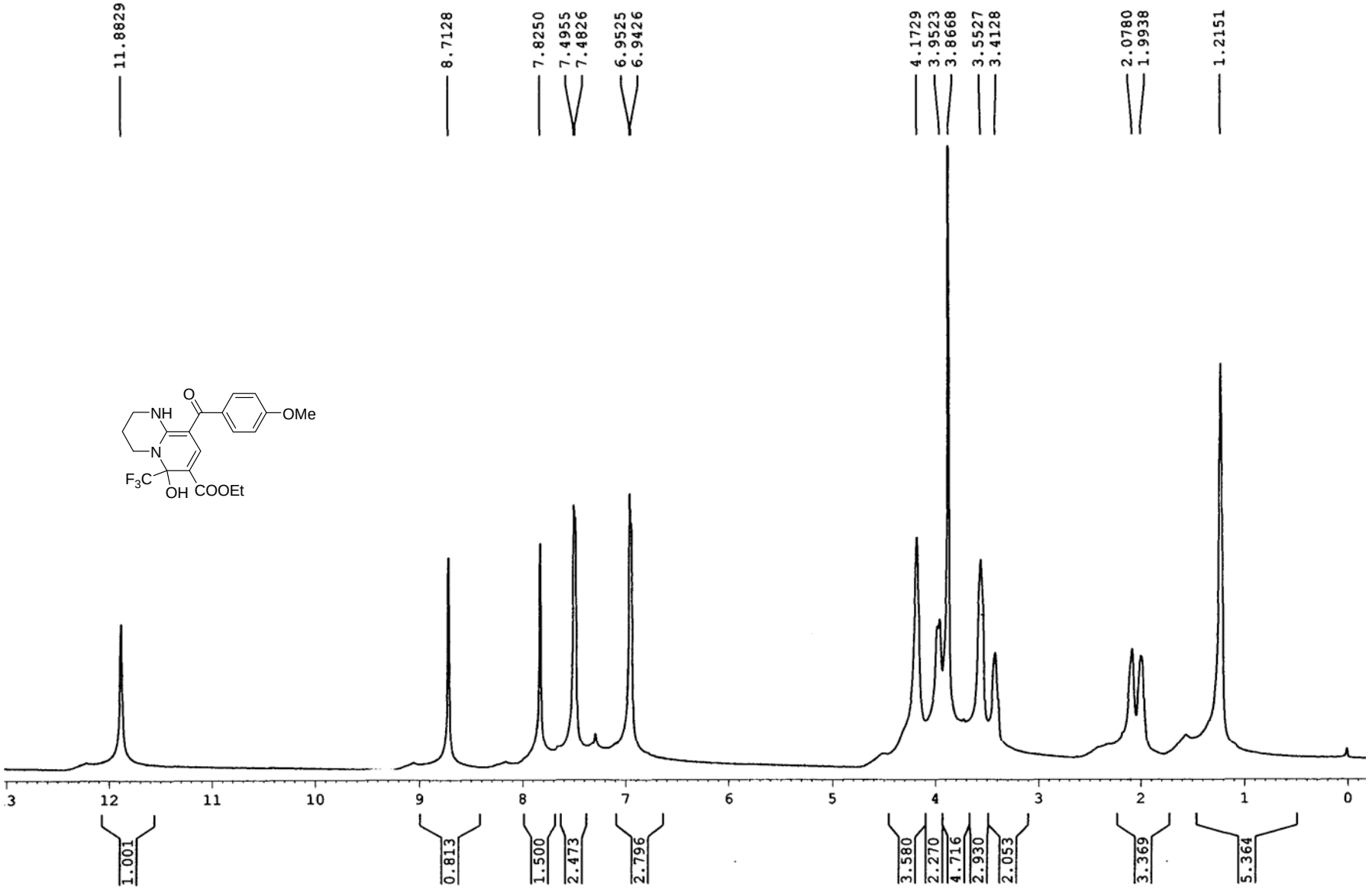


Figure 21. ^{1}H NMR (500 MHz, $CDCl_3$) spectra of compound **4k**

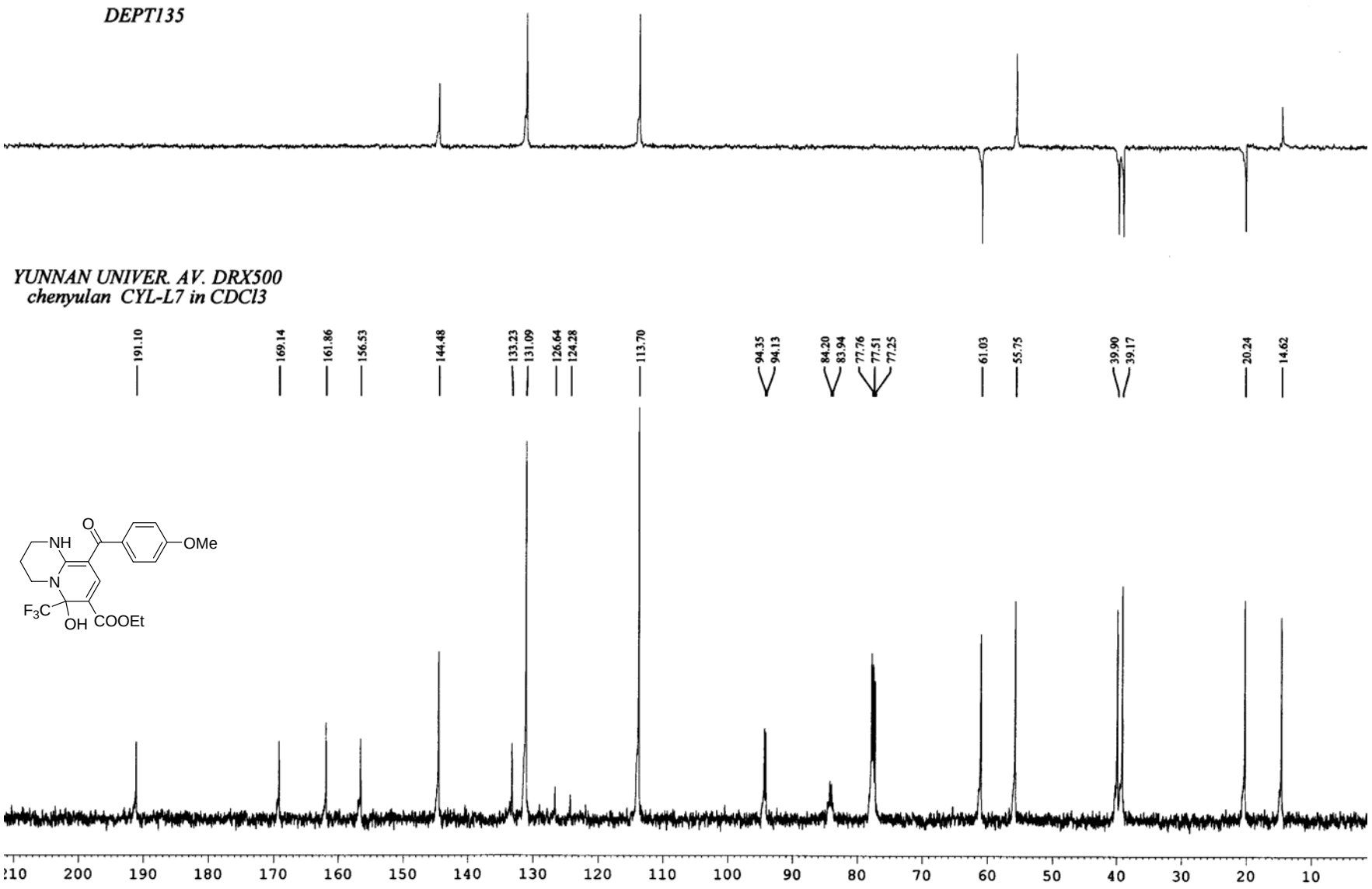


Figure 22. ^{13}C NMR (125 MHz, $CDCl_3$) spectra of compound **4k**

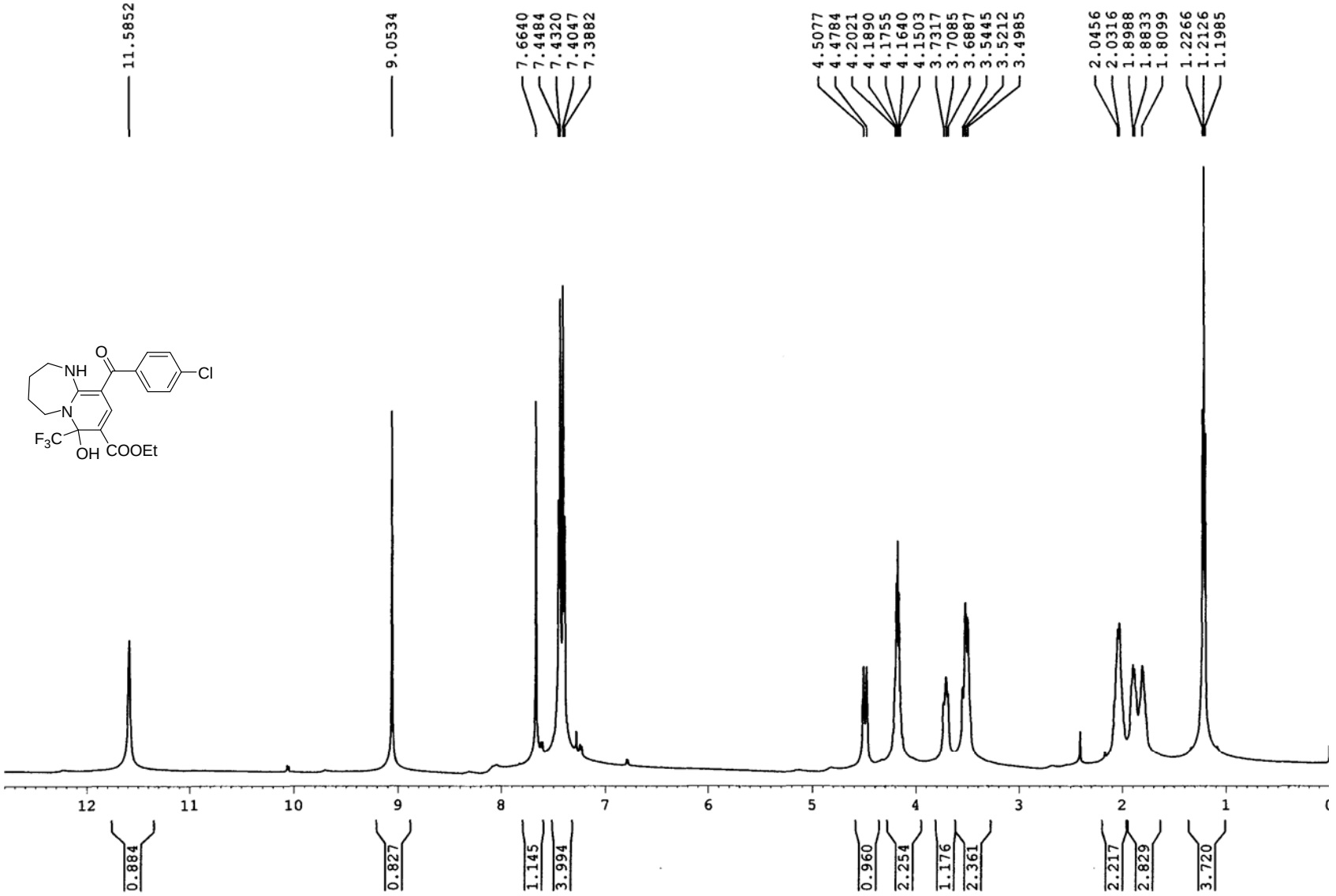


Figure 23. ^{1}H NMR (500 MHz, $CDCl_3$) spectra of compound **4l**

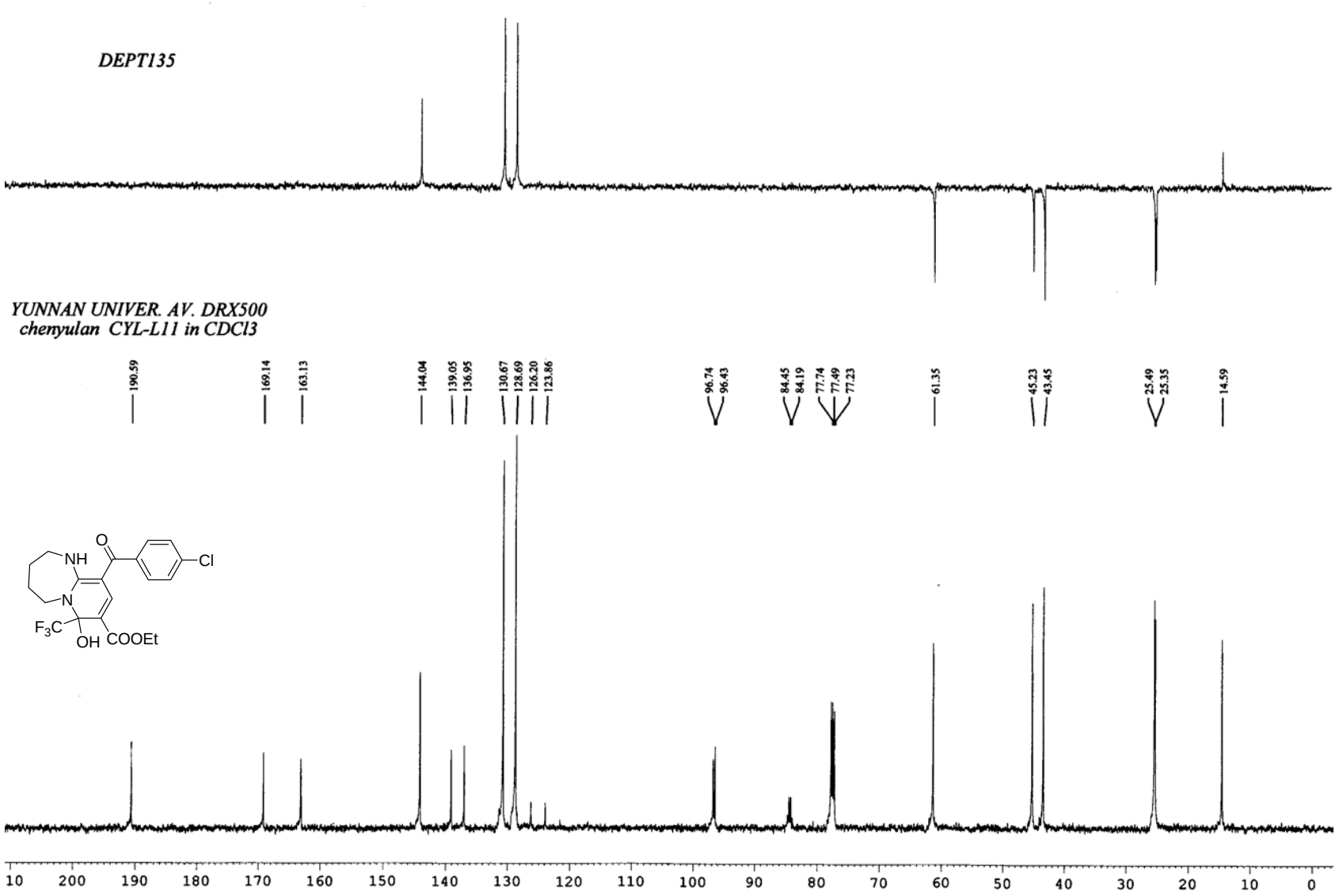


Figure 24. ^{13}C NMR (125 MHz, $CDCl_3$) spectra of compound **4l**

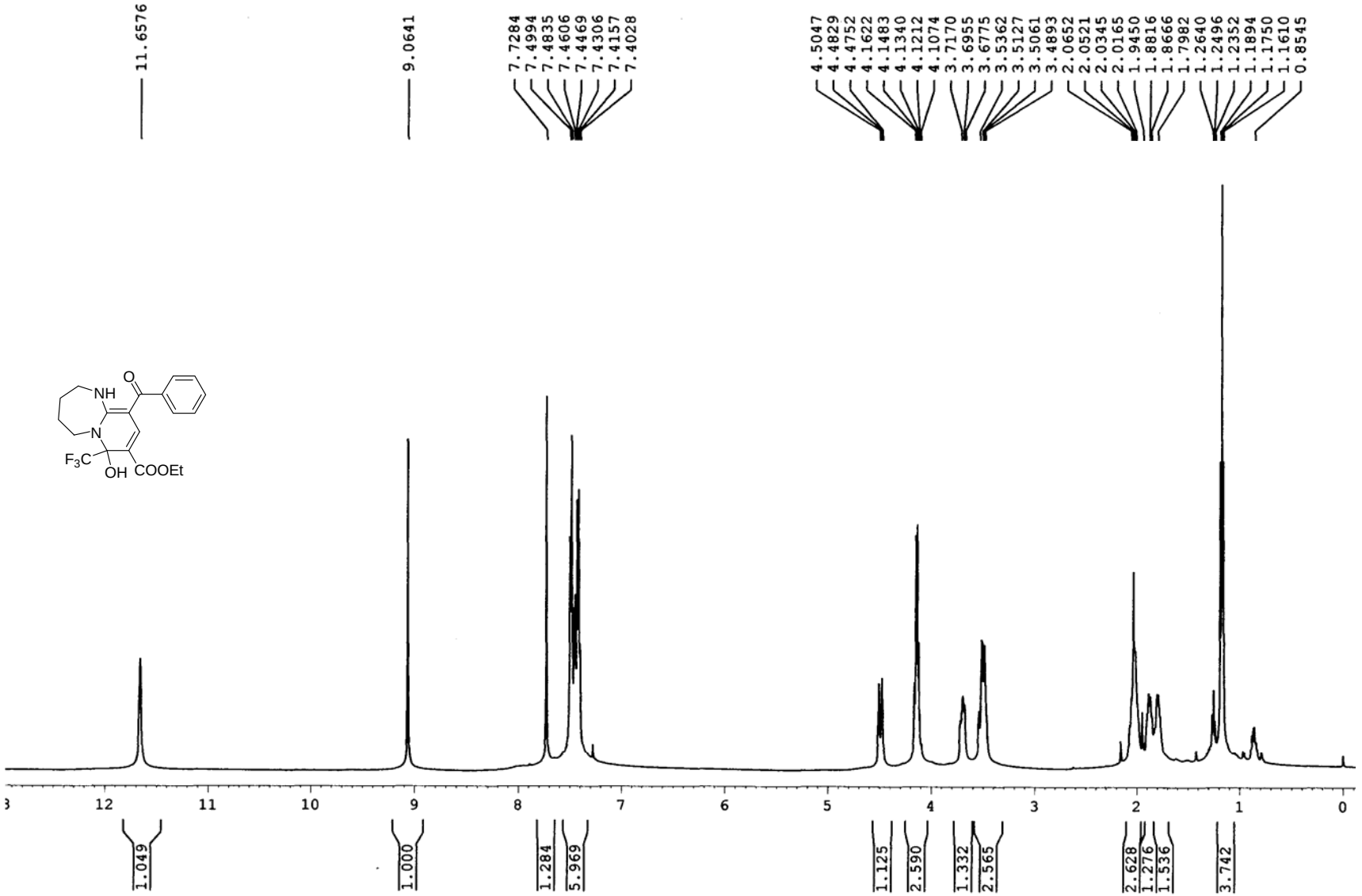


Figure 25. ^{1}H NMR (500 MHz, $CDCl_3$) spectra of compound **4m**

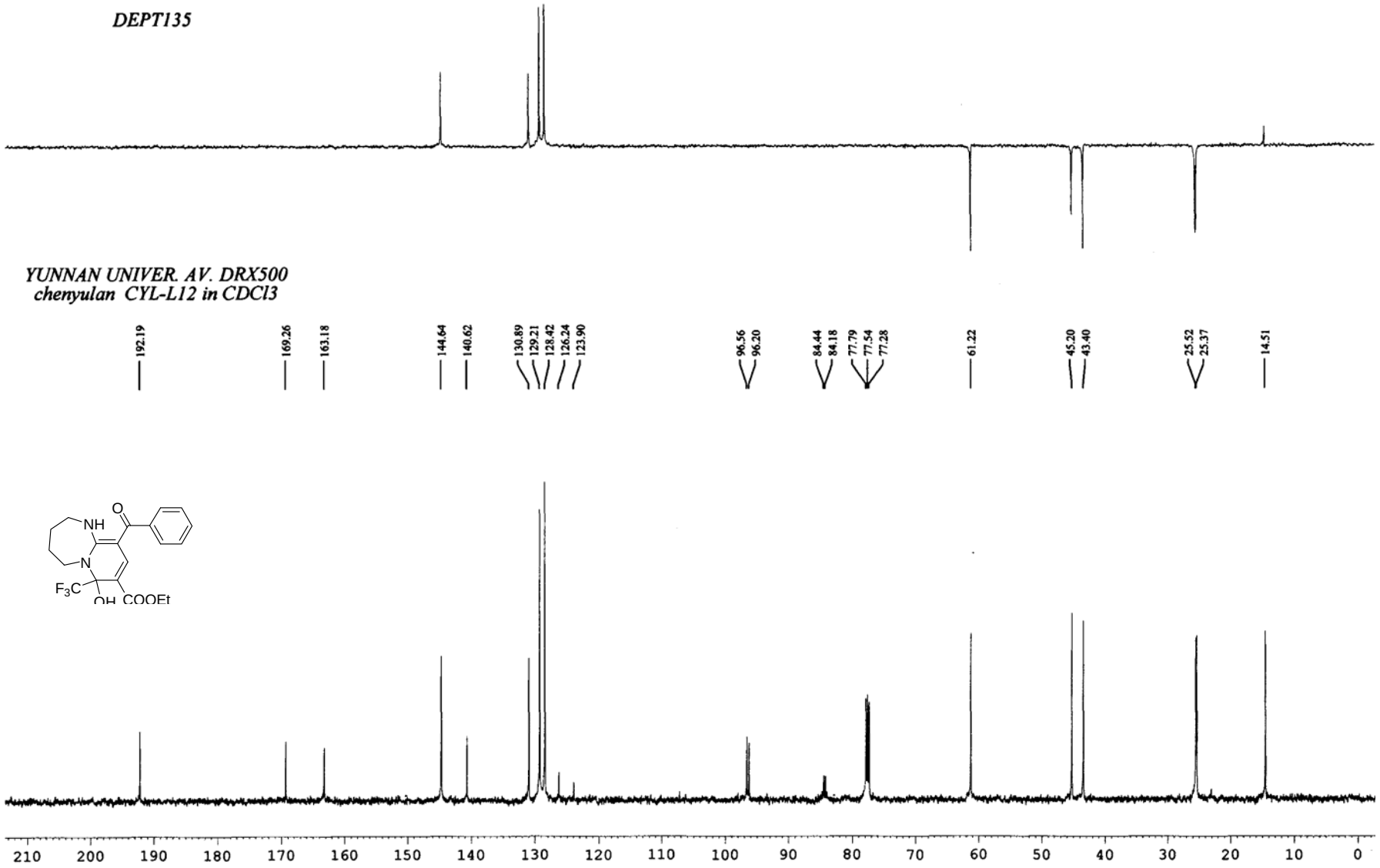


Figure 26. ^{13}C NMR (125 MHz, $CDCl_3$) spectra of compound **4m**

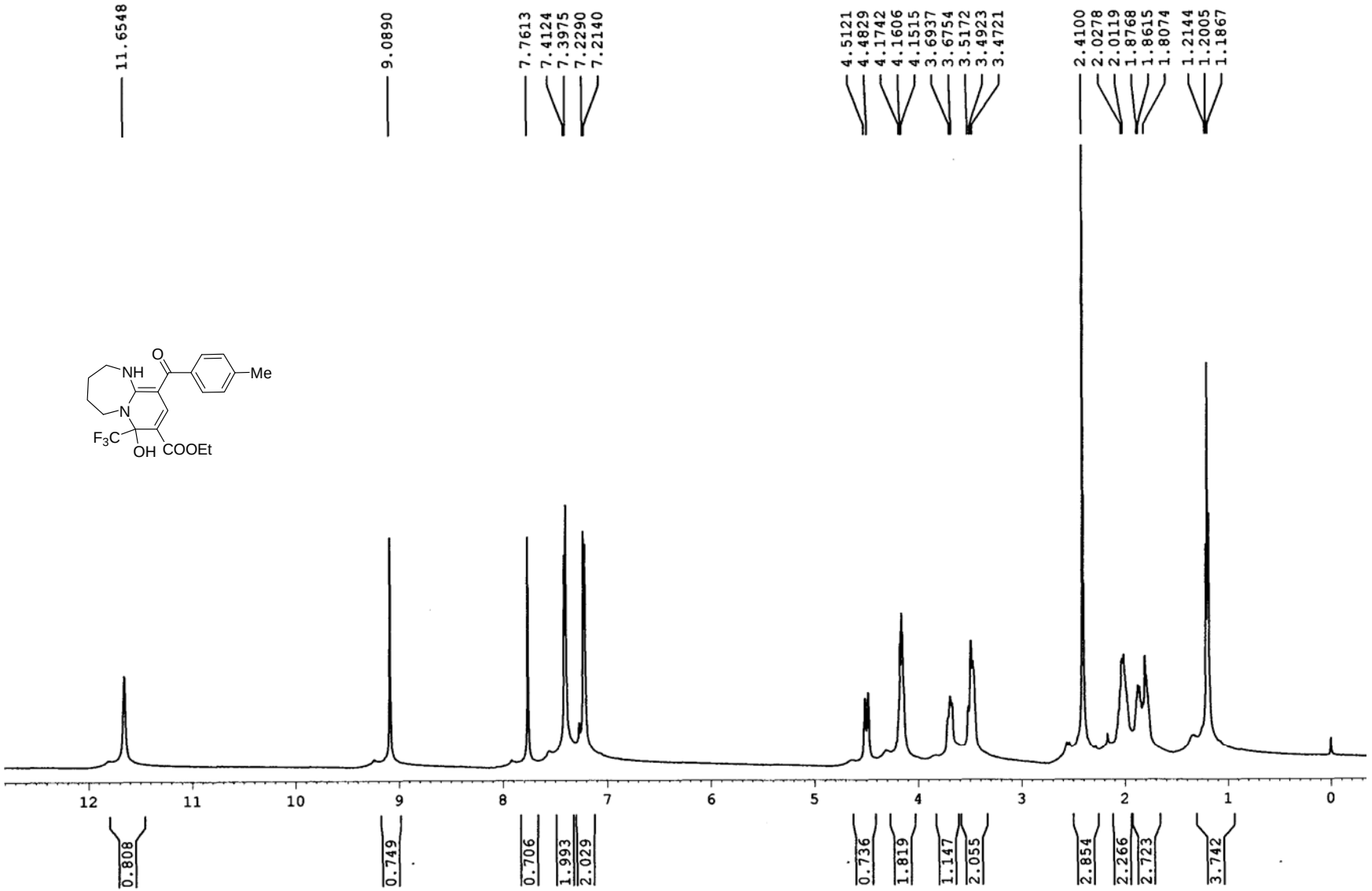


Figure 27. ^{1}H NMR (500 MHz, $CDCl_3$) spectra of compound **4n**

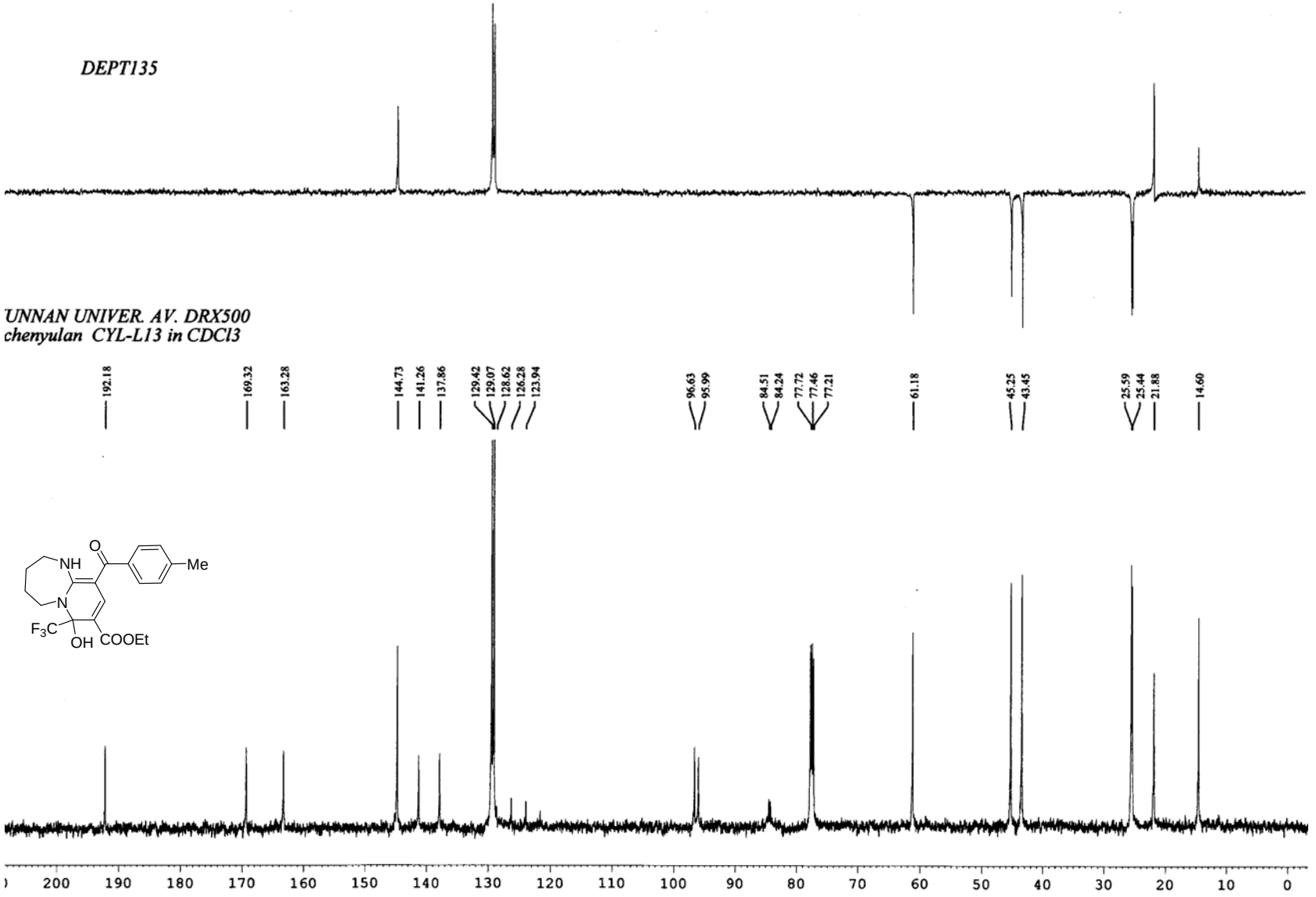


Figure 28. ^{13}C NMR (125 MHz, $CDCl_3$) spectra of compound **4n**

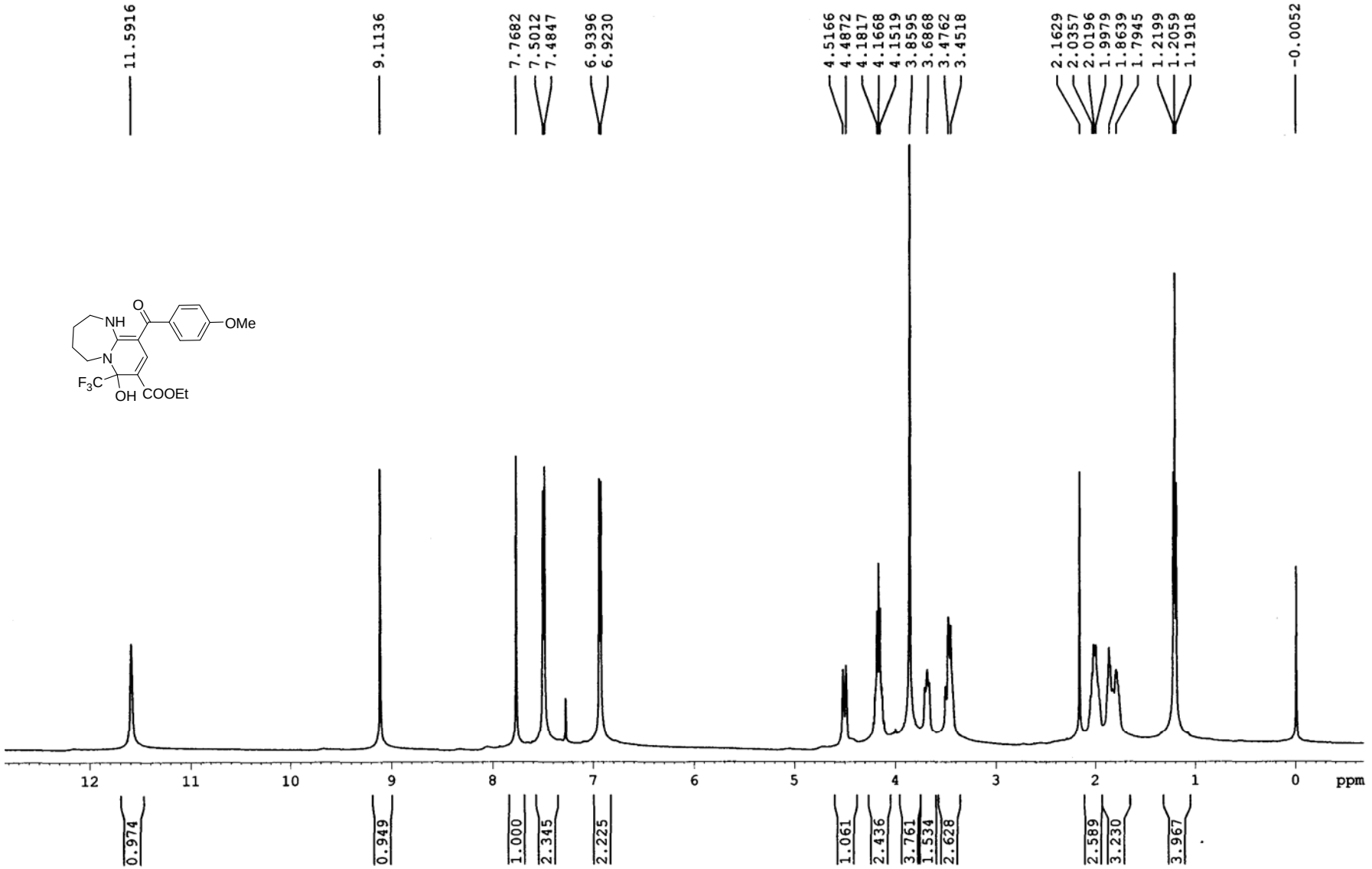


Figure 29. ^{1}H NMR (500 MHz, $CDCl_3$) spectra of compound **4o**

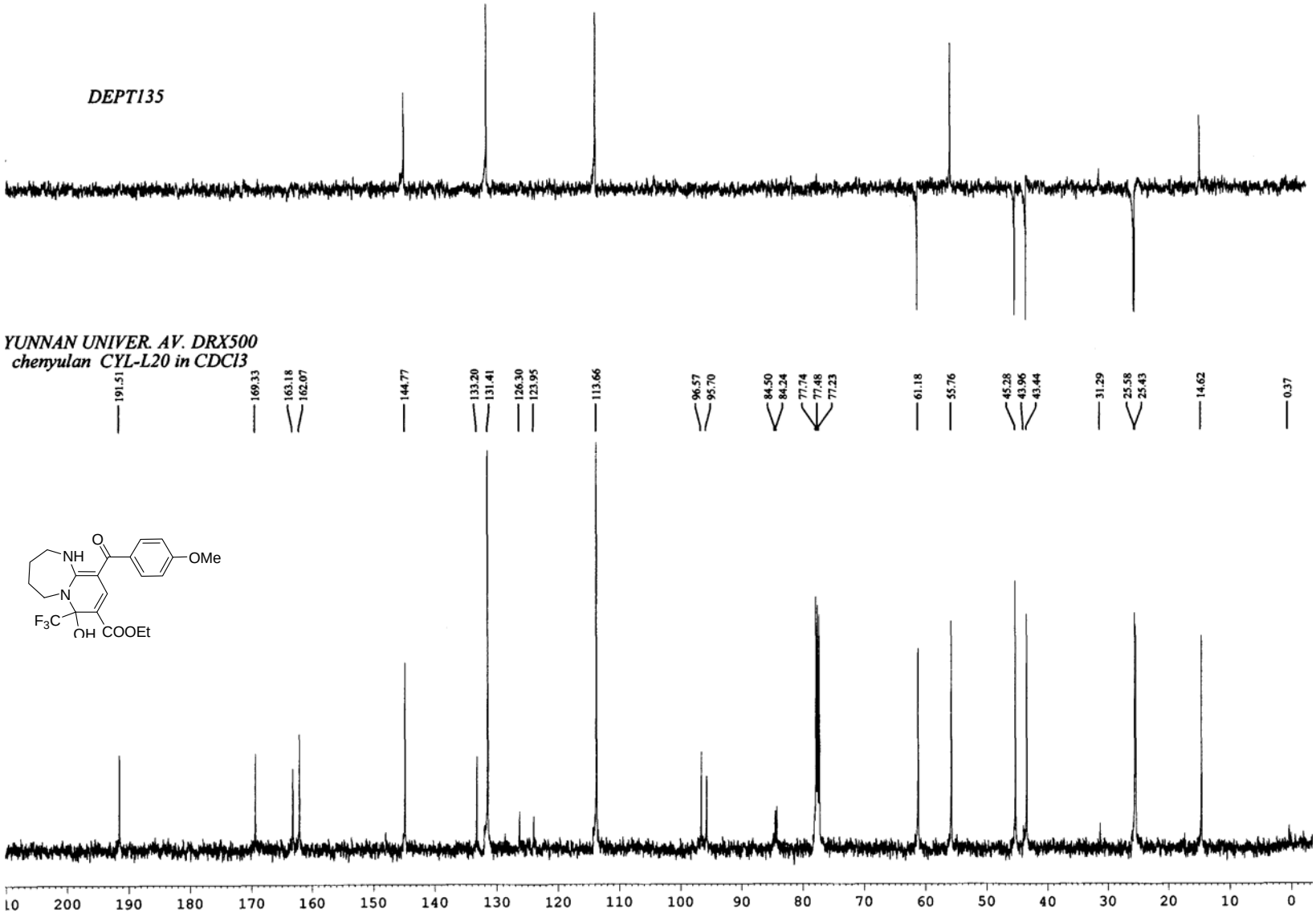


Figure 30. ^{13}C NMR (125 MHz, $CDCl_3$) spectra of compound **4o**

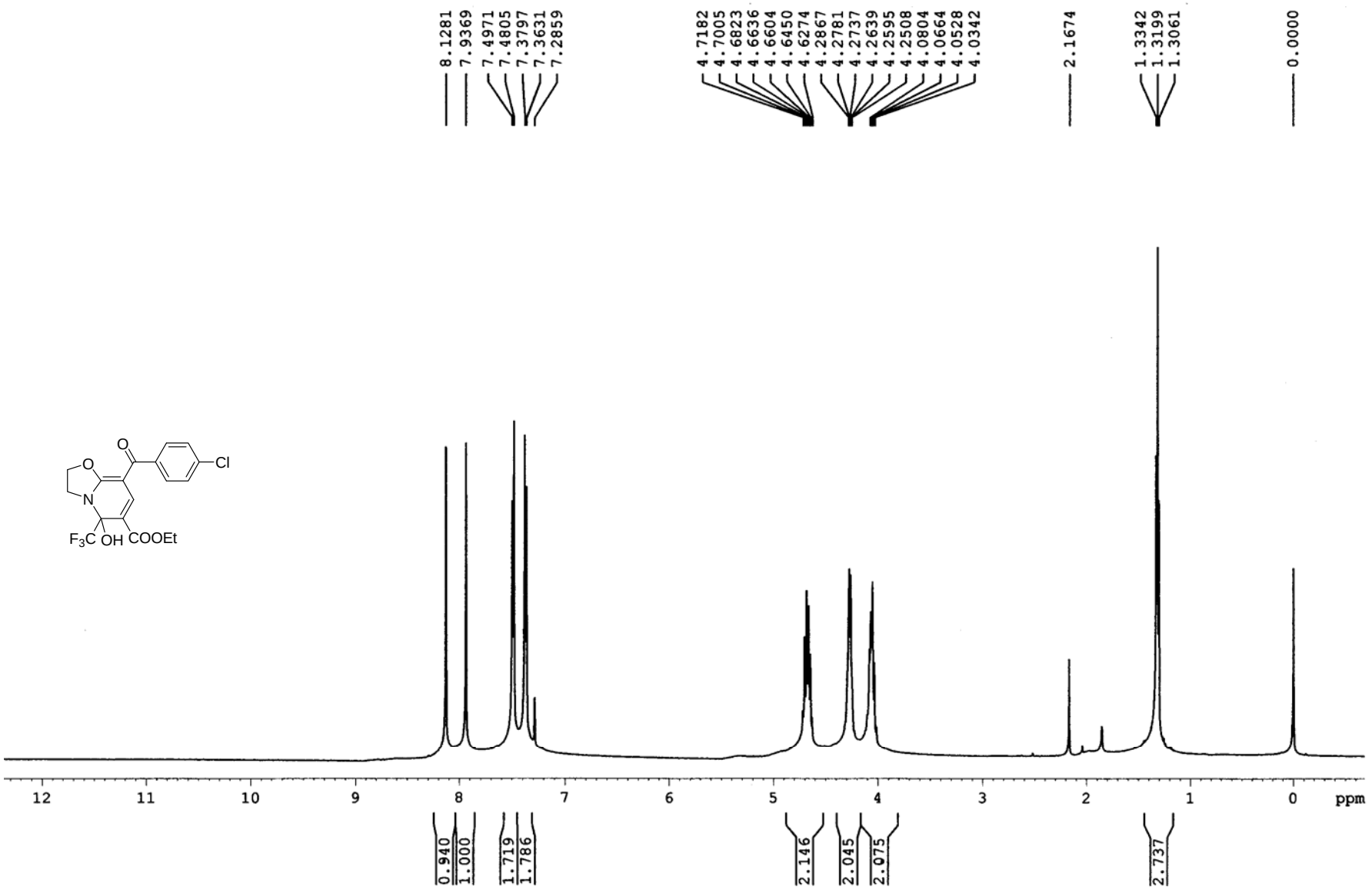


Figure 31. ^{1}H NMR (500 MHz, $CDCl_3$) spectra of compound **4p**

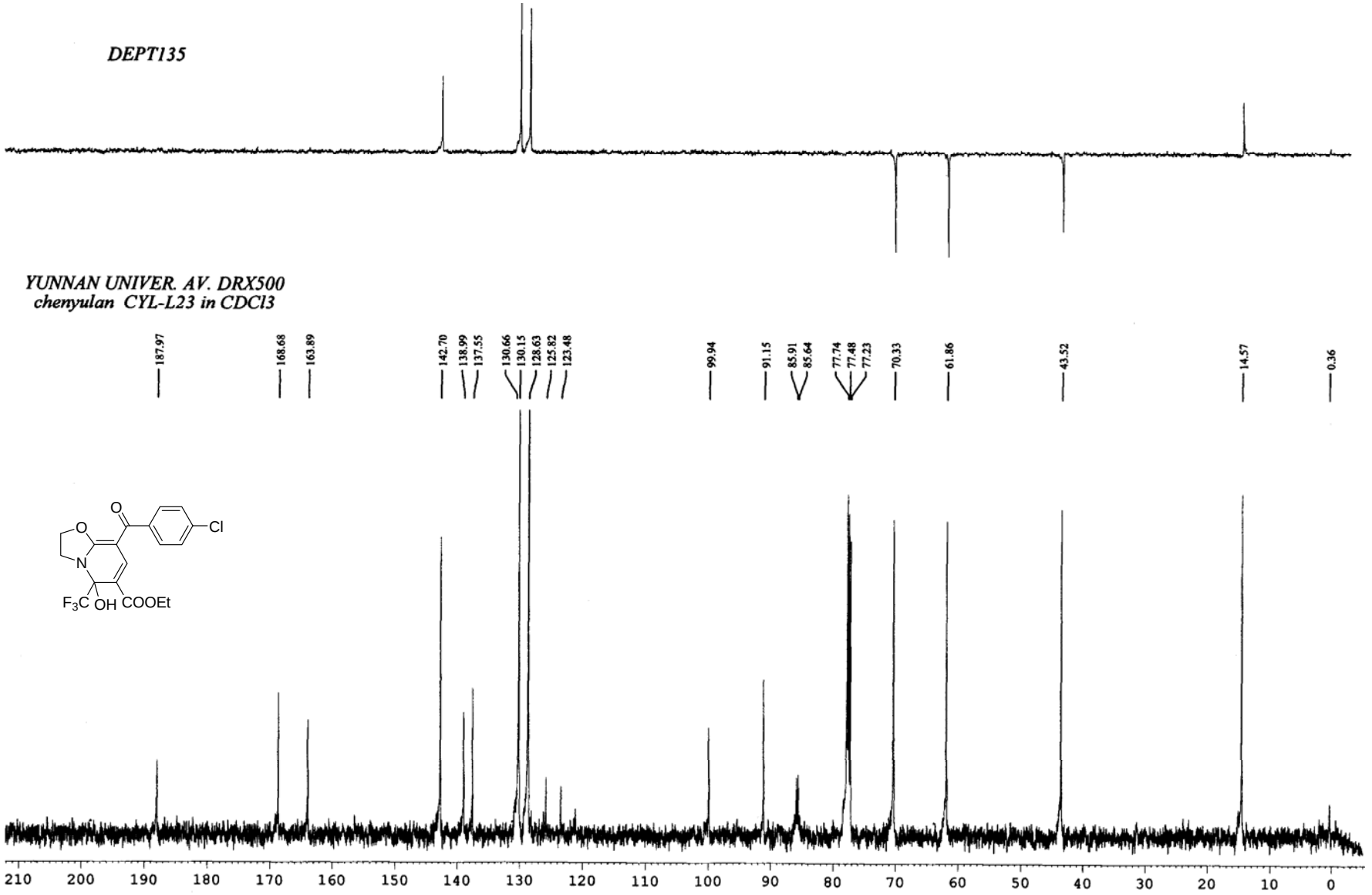


Figure 32. ^{13}C NMR (125 MHz, $CDCl_3$) spectra of compound **4p**

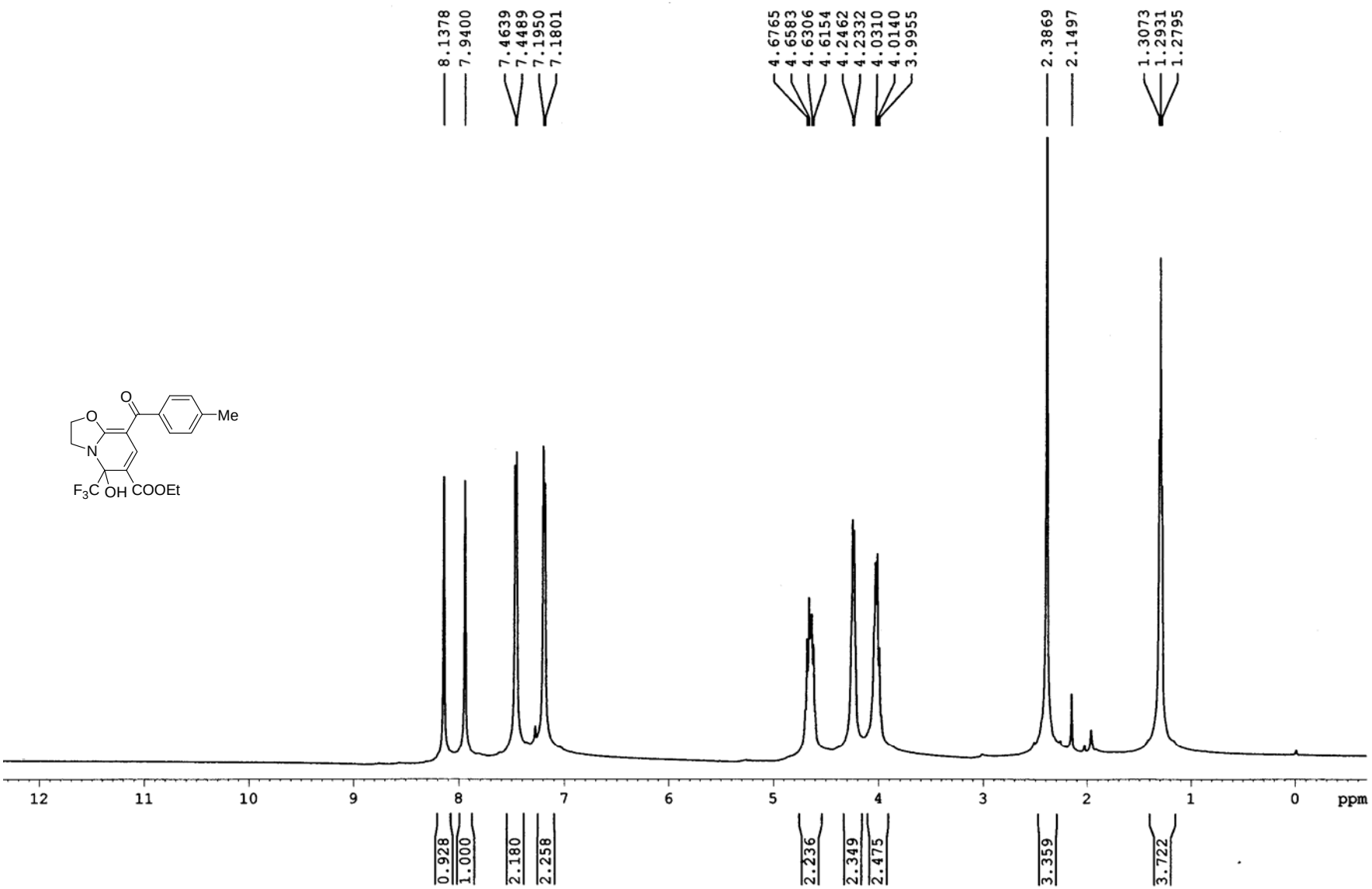


Figure 33. ^{1}H NMR (500 MHz, $CDCl_3$) spectra of compound **4q**

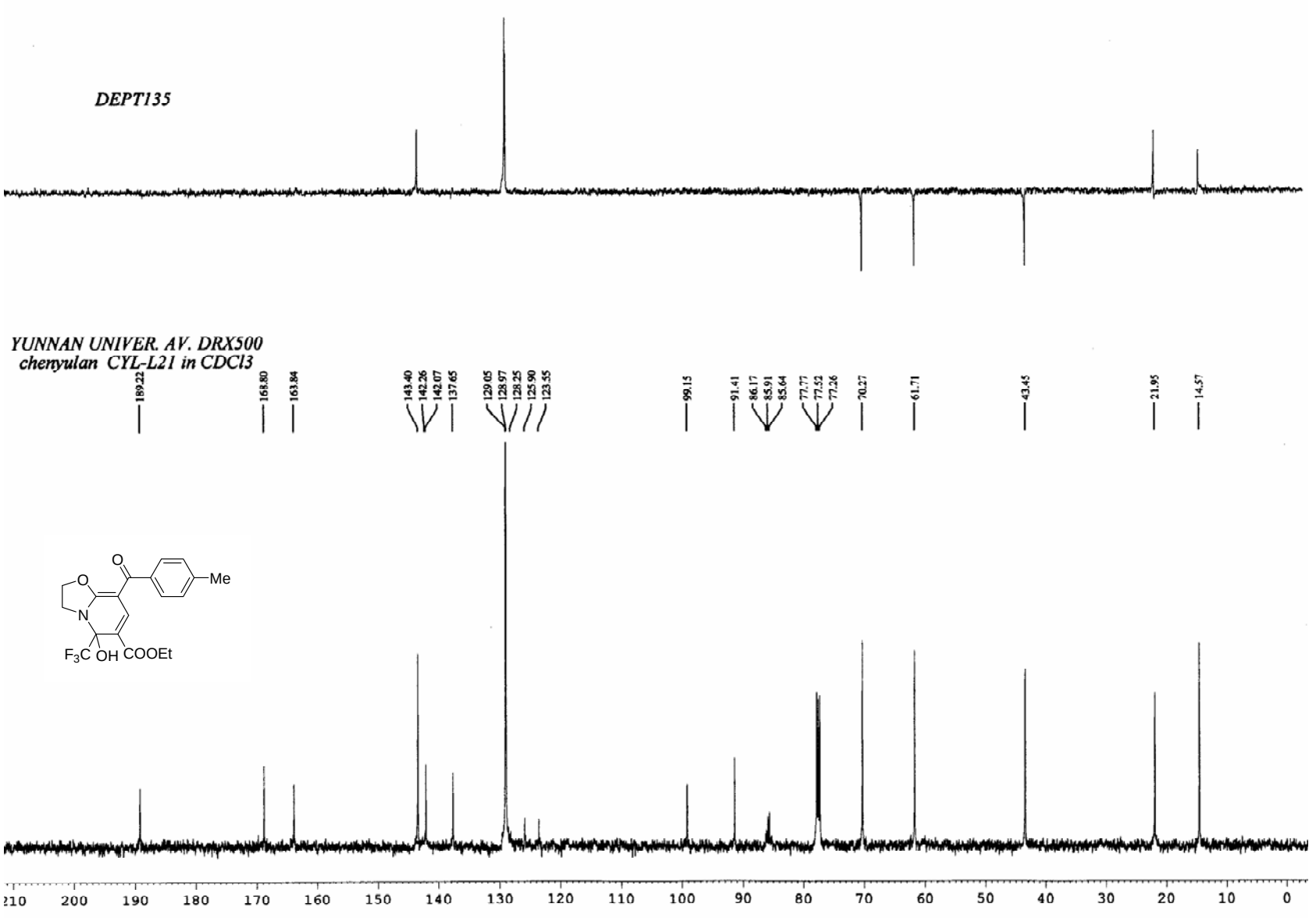


Figure 34. ^{13}C NMR (125 MHz, $CDCl_3$) spectra of compound **4q**

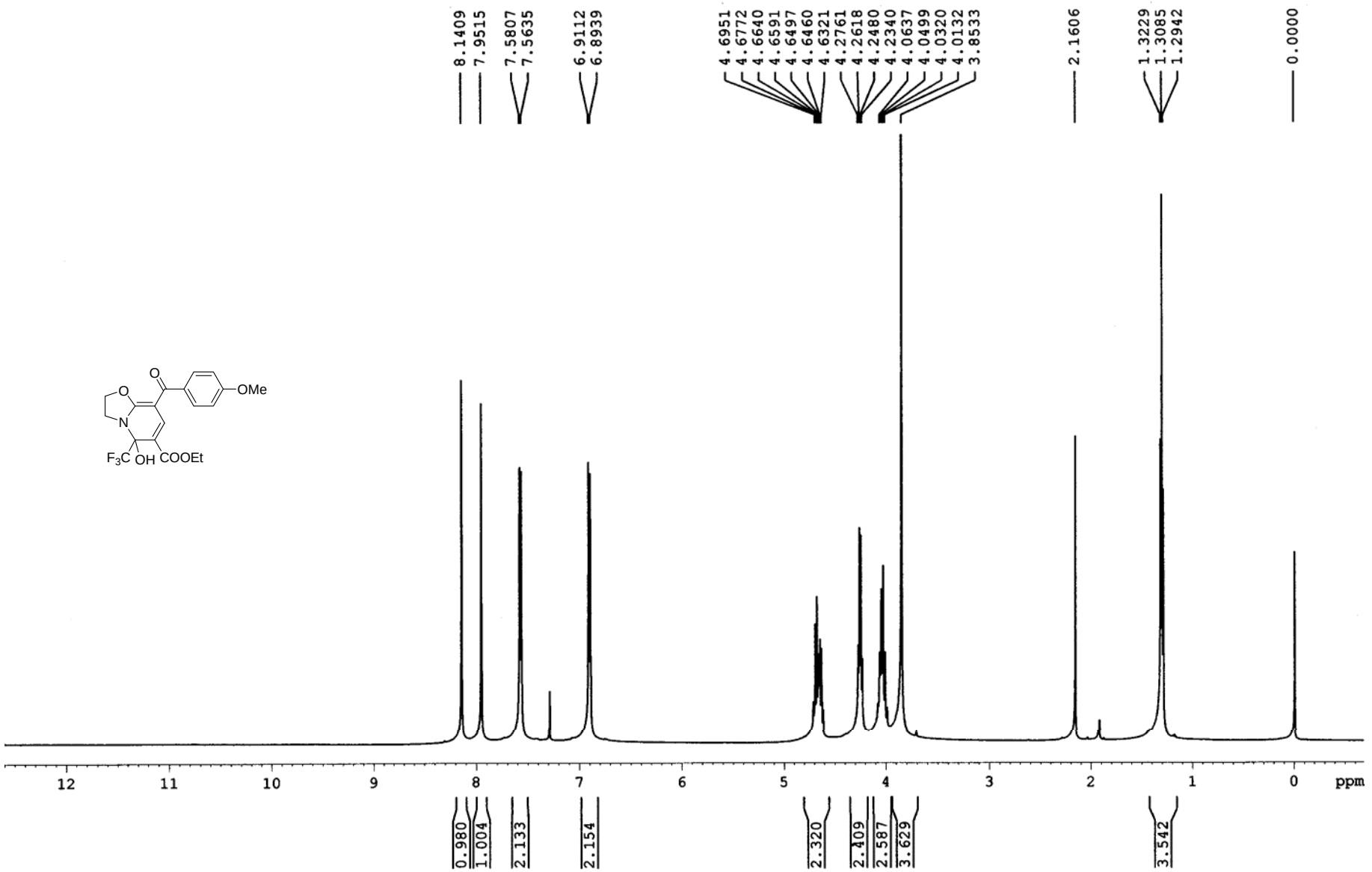


Figure 35. ^{1}H NMR (500 MHz, $CDCl_3$) spectra of compound **4r**

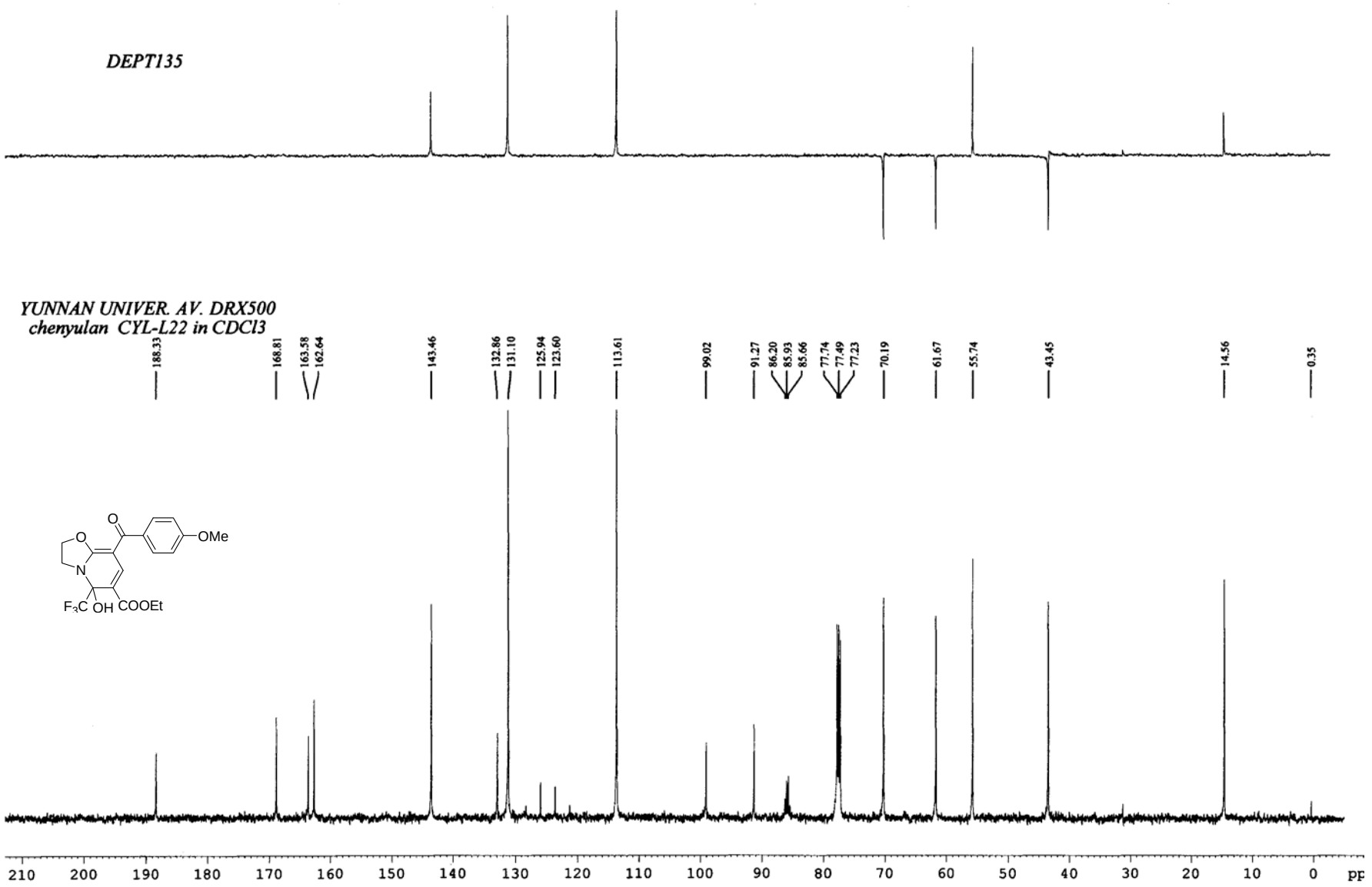


Figure 36. ^{13}C NMR (125 MHz, $CDCl_3$) spectra of compound **4r**

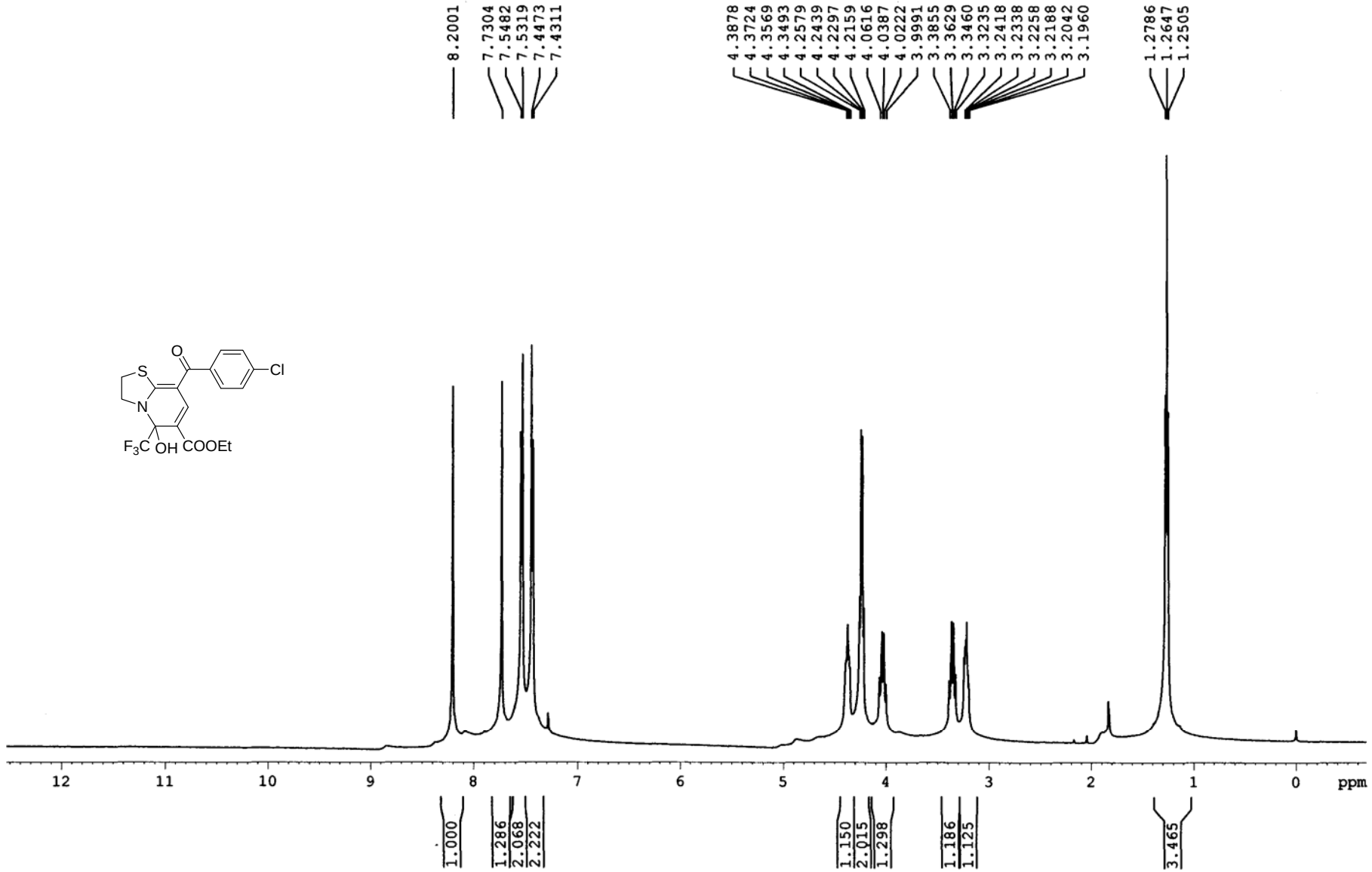


Figure 37. ^{1}H NMR (500 MHz, $CDCl_3$) spectra of compound **4s**

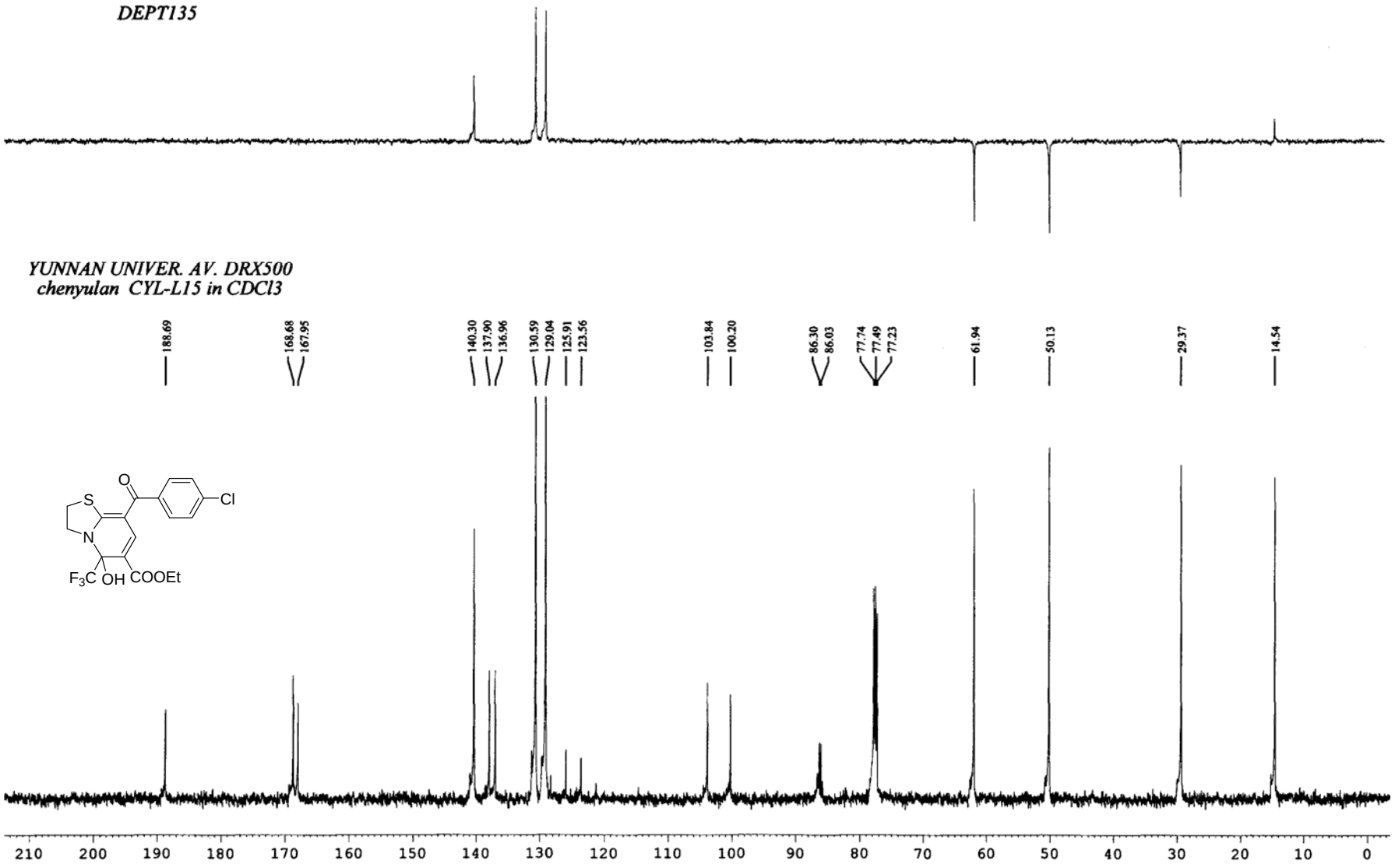


Figure 38. ^{13}C NMR (125 MHz, $CDCl_3$) spectra of compound **4s**

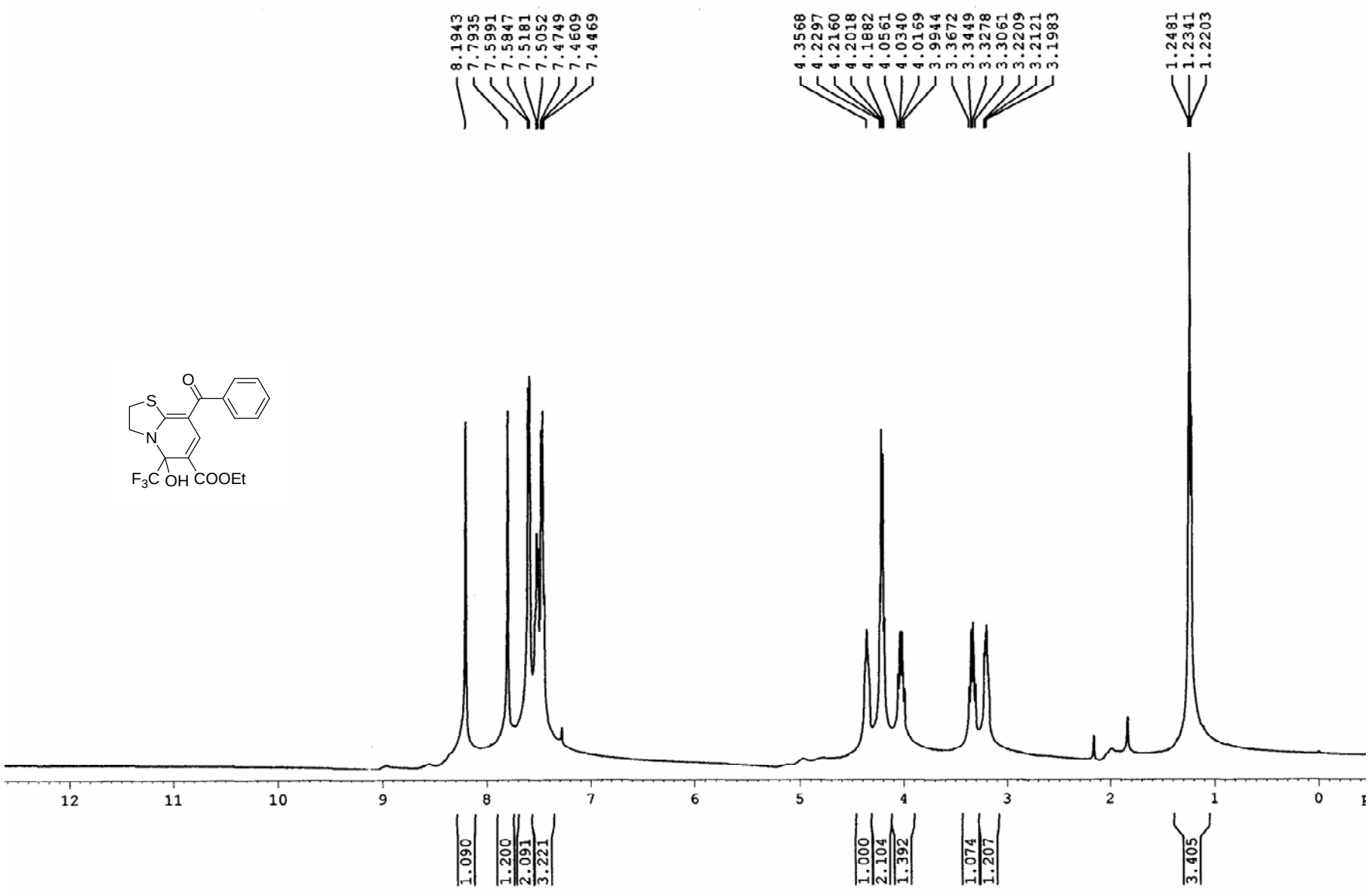


Figure 39. ^{1}H NMR (500 MHz, $CDCl_3$) spectra of compound **4t**

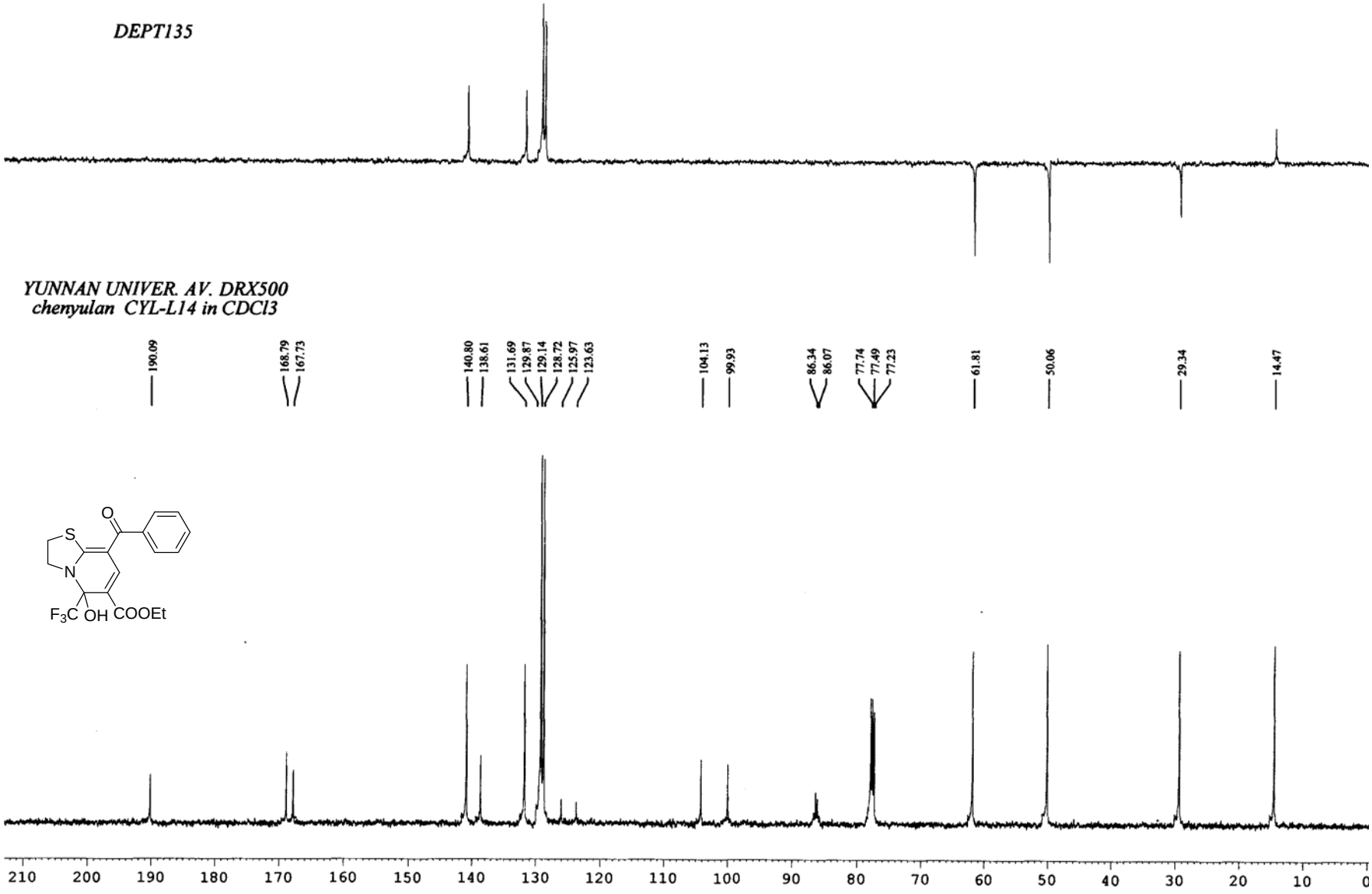


Figure 40. ^{13}C NMR (125 MHz, $CDCl_3$) spectra of compound **4t**

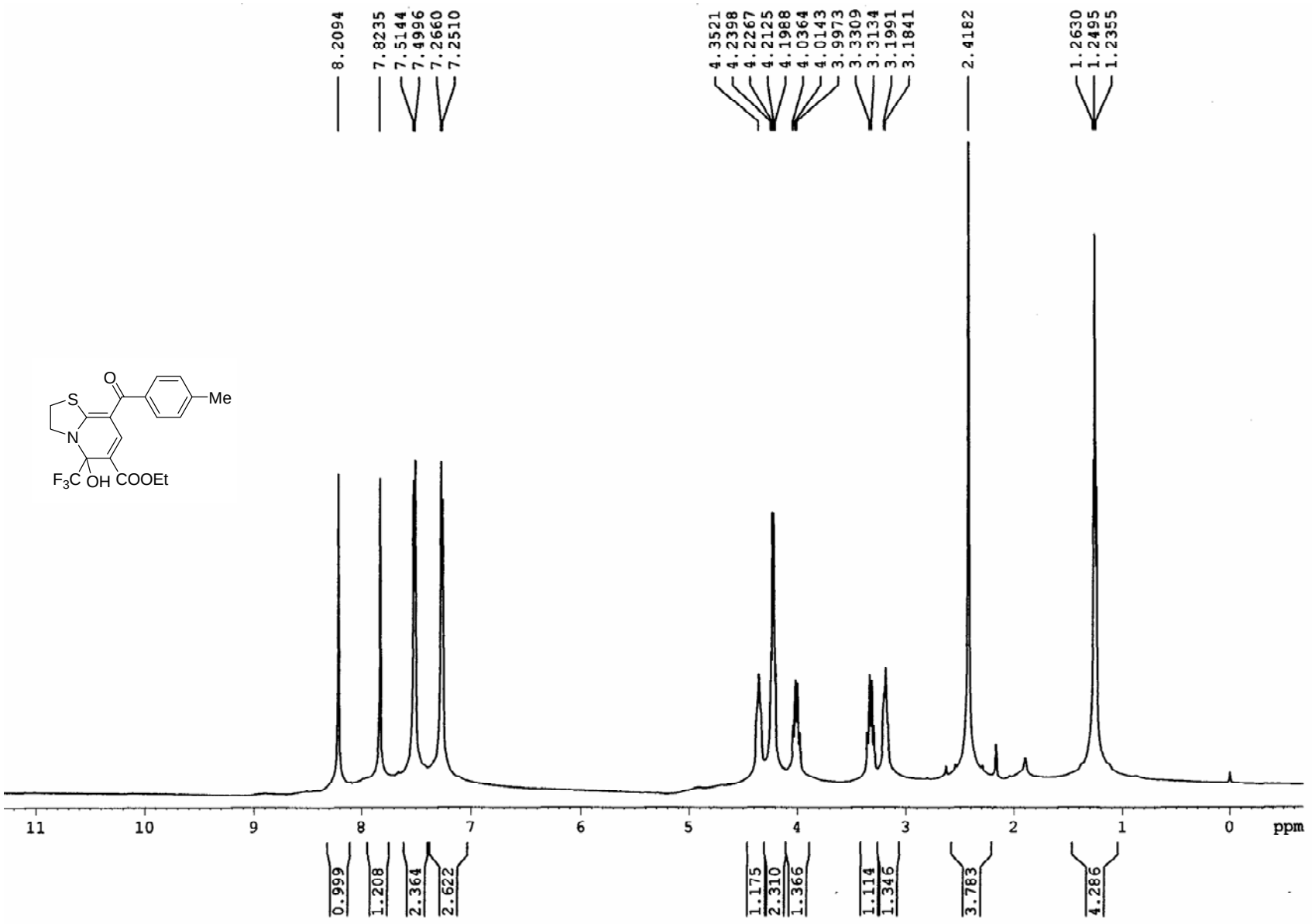


Figure 41. ^{1}H NMR (500 MHz, $CDCl_3$) spectra of compound **4u**

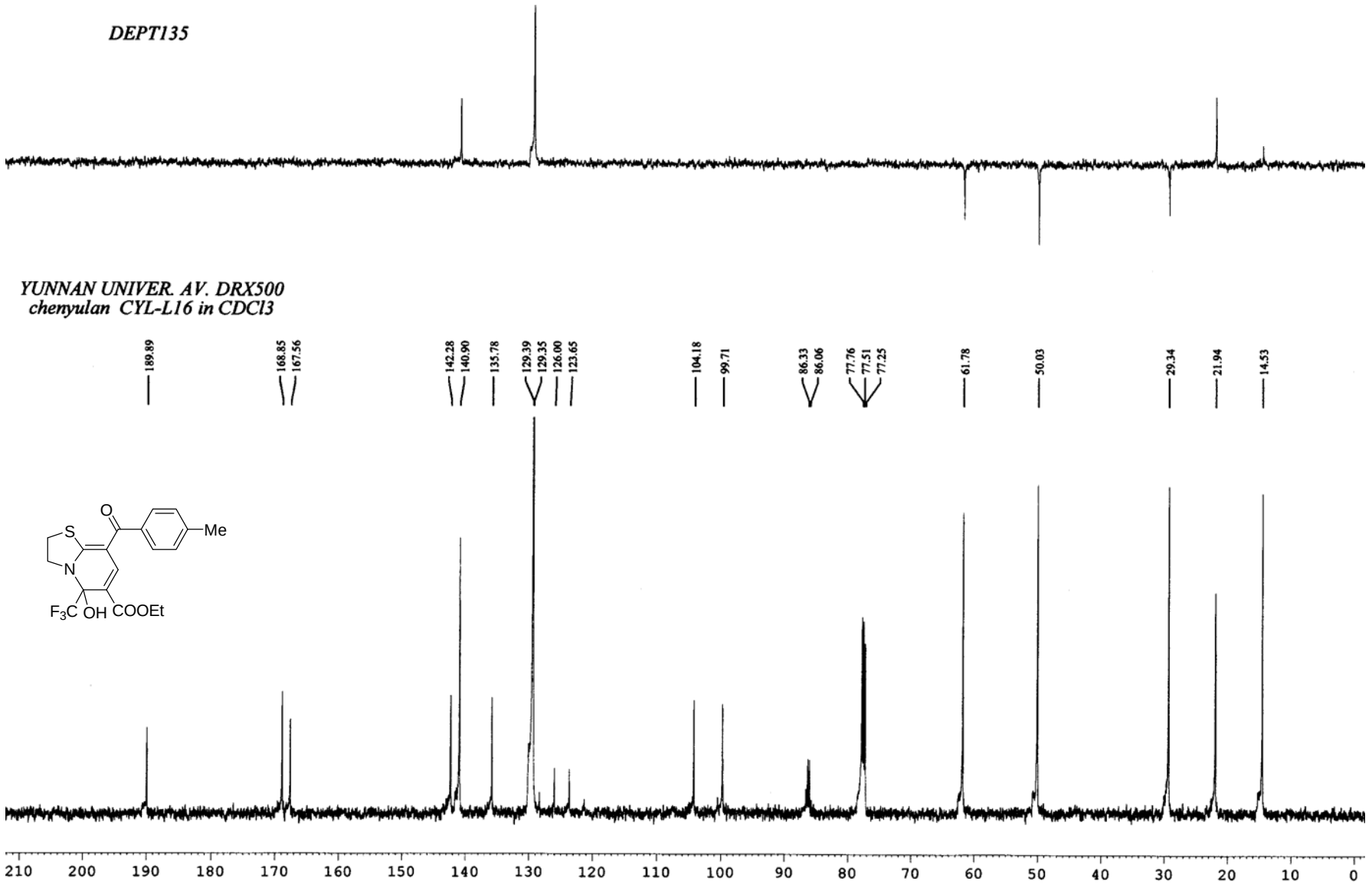


Figure 42. ^{13}C NMR (125 MHz, $CDCl_3$) spectra of compound **4u**

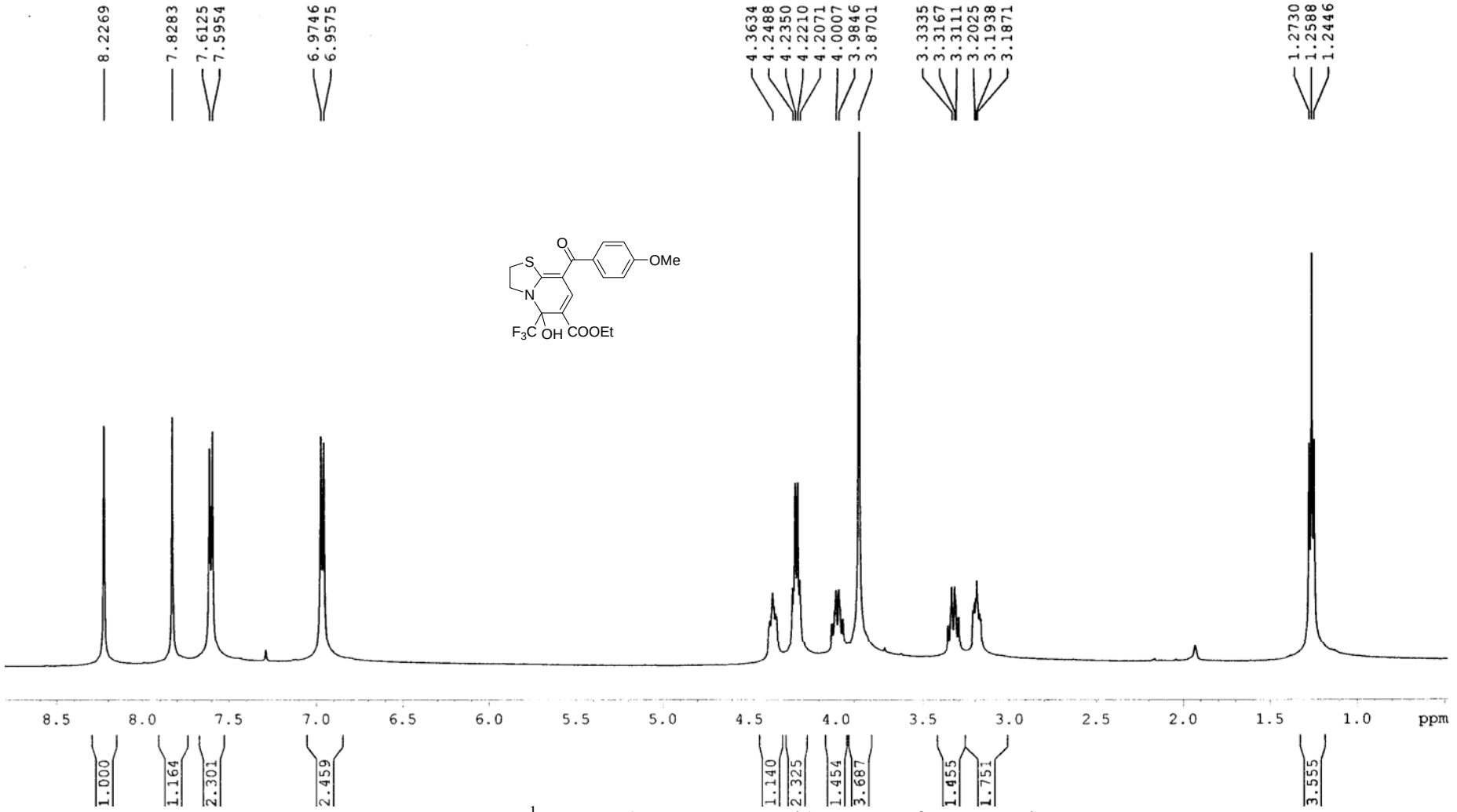


Figure 43. ^{1}H NMR (500 MHz, $CDCl_3$) spectra of compound **4v**

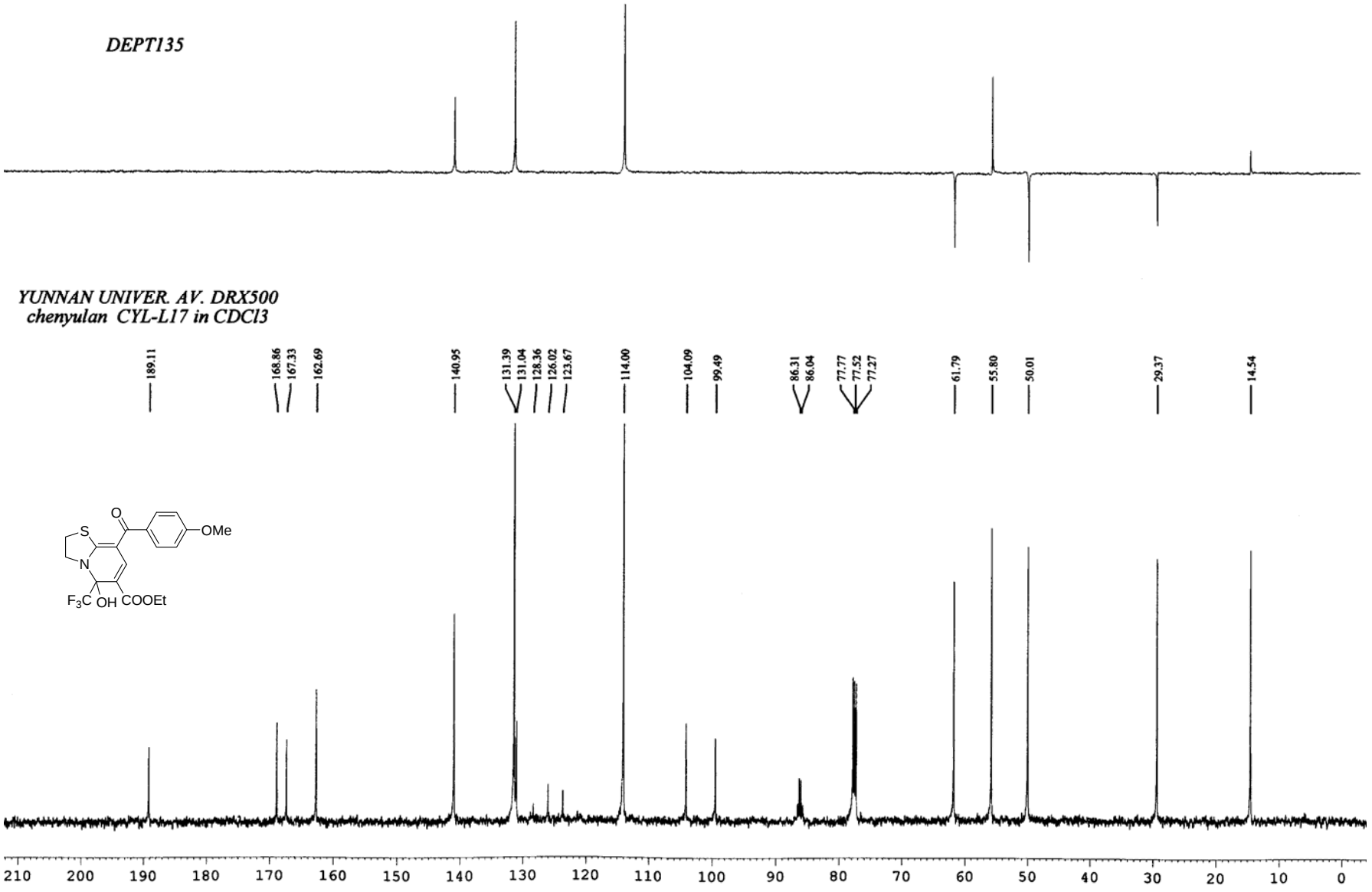


Figure 44. ^{13}C NMR (125 MHz, $CDCl_3$) spectra of compound **4v**

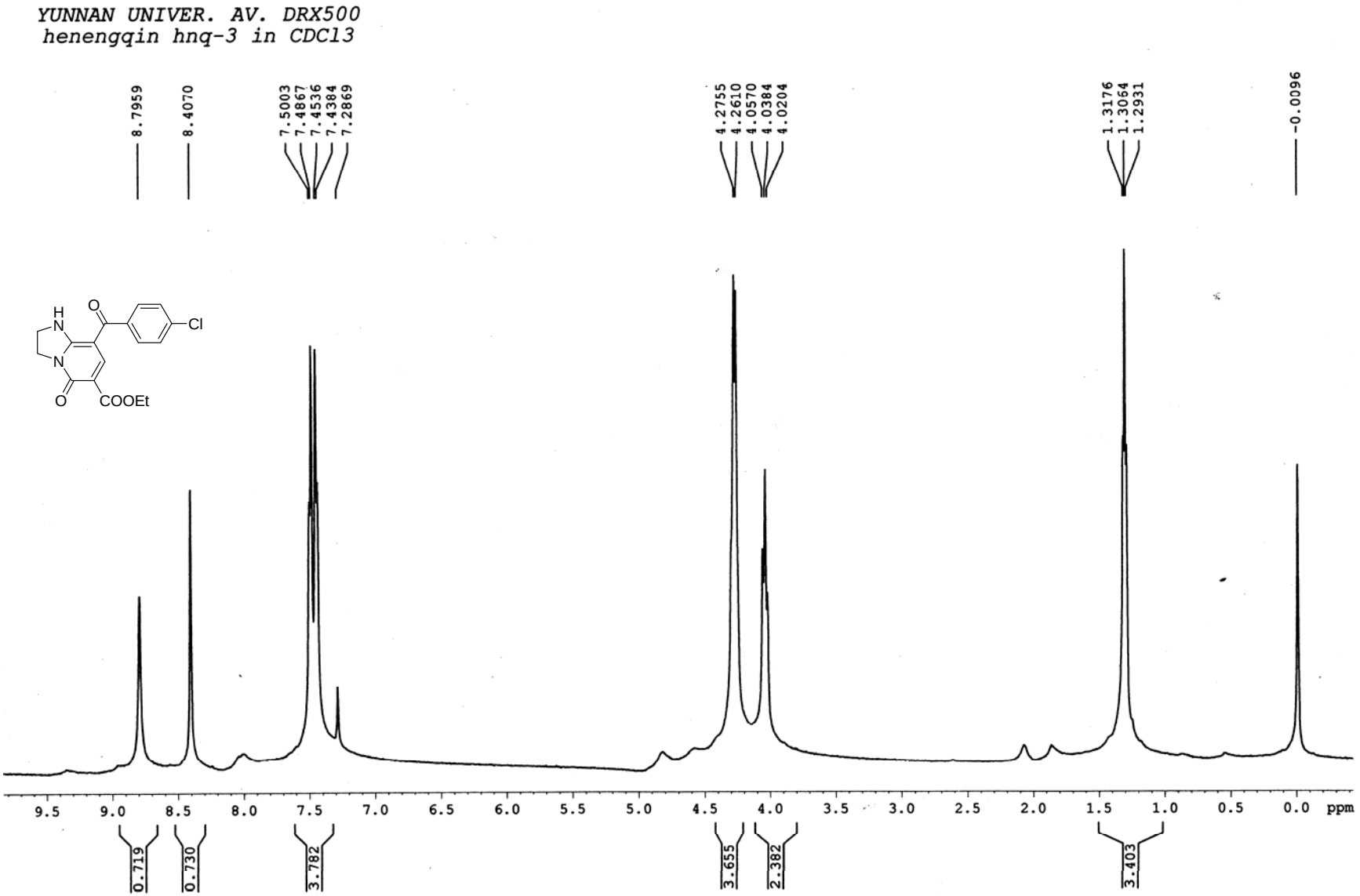


Figure 45. ^{1}H NMR (500 MHz, $CDCl_3$) spectra of compound **6a**

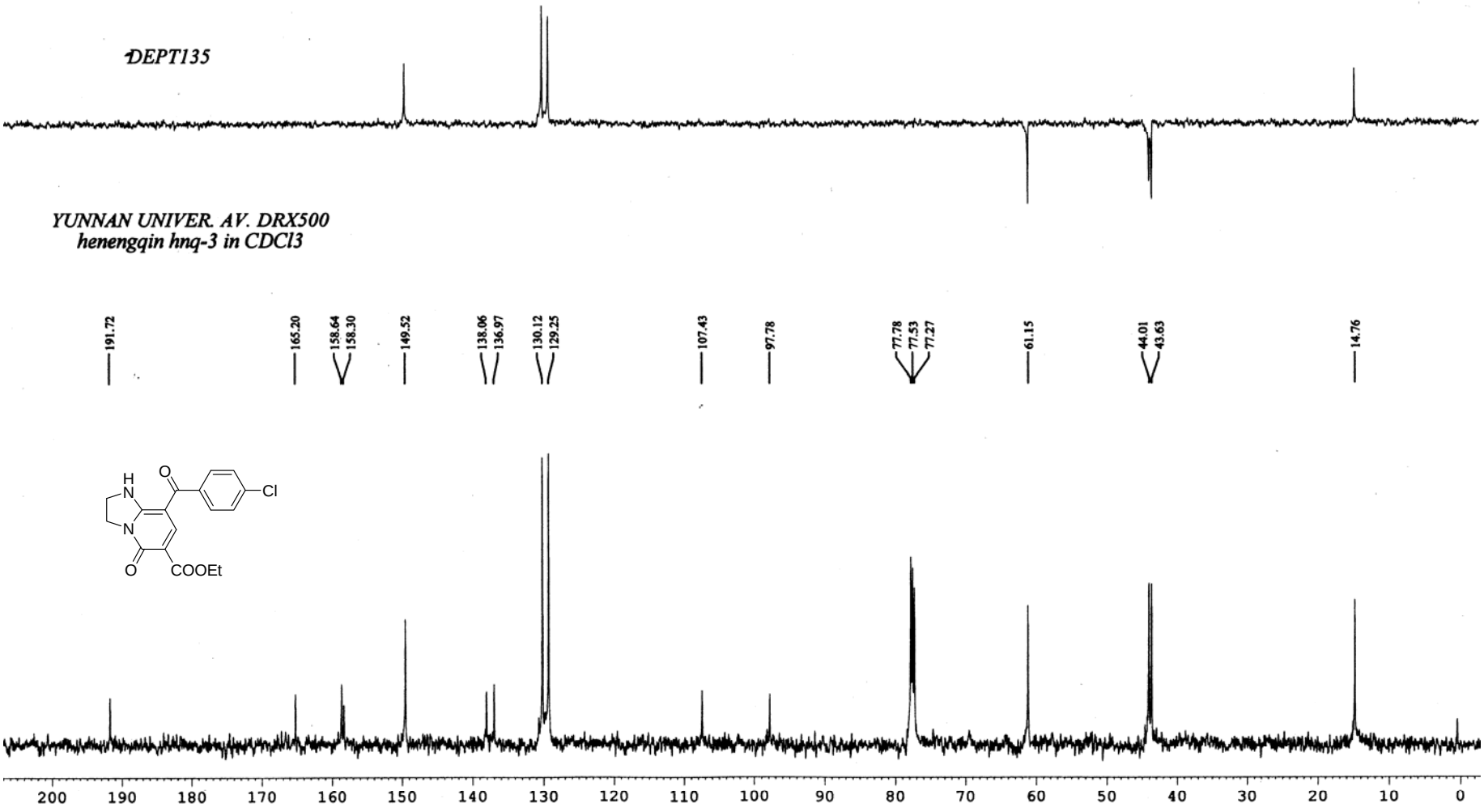


Figure 46. ^{13}C NMR (125 MHz, $CDCl_3$) spectra of compound **6a**

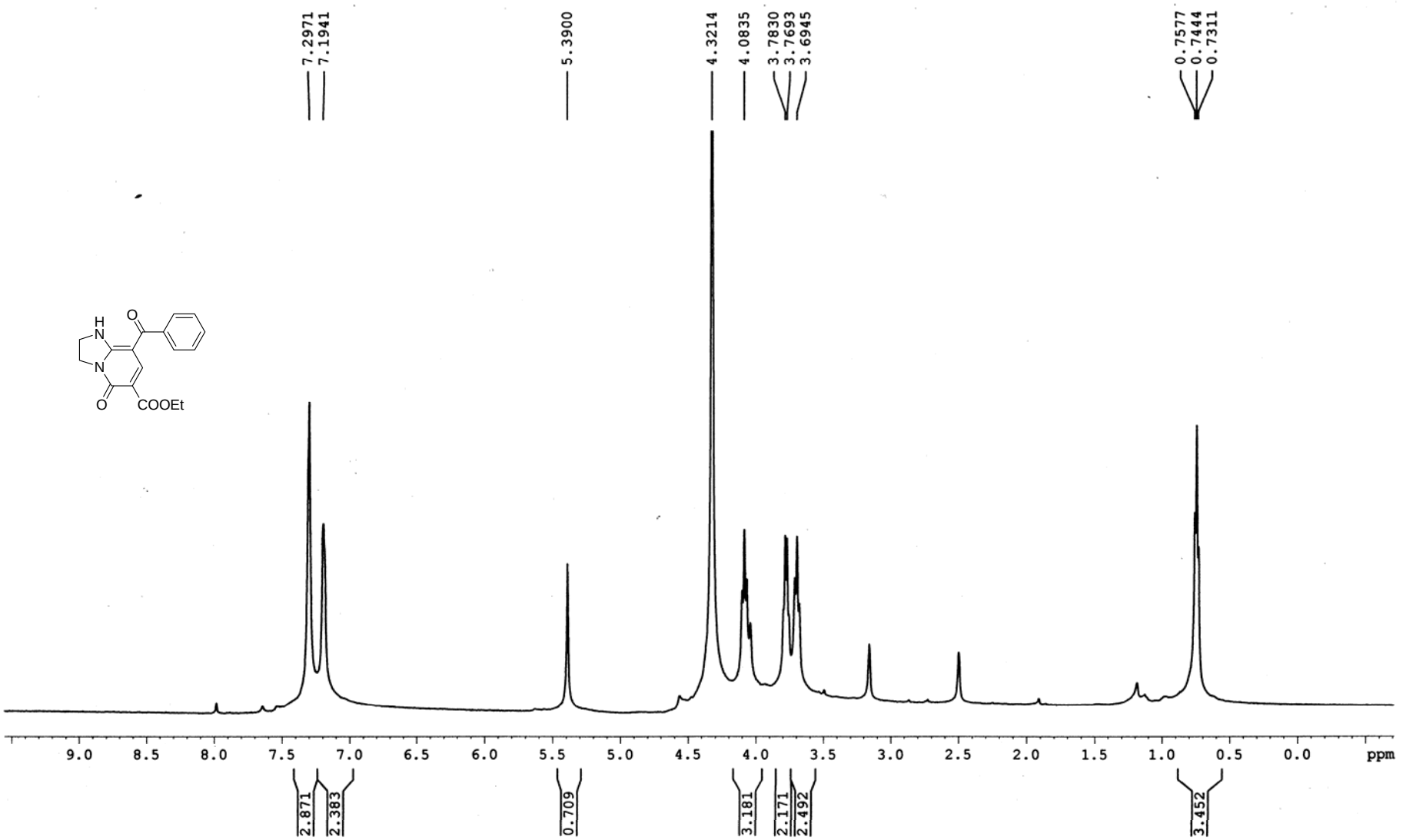


Figure 47. ^{1}H NMR (500 MHz, CH_3OD+DMSO-d_6) spectra of compound **6b**

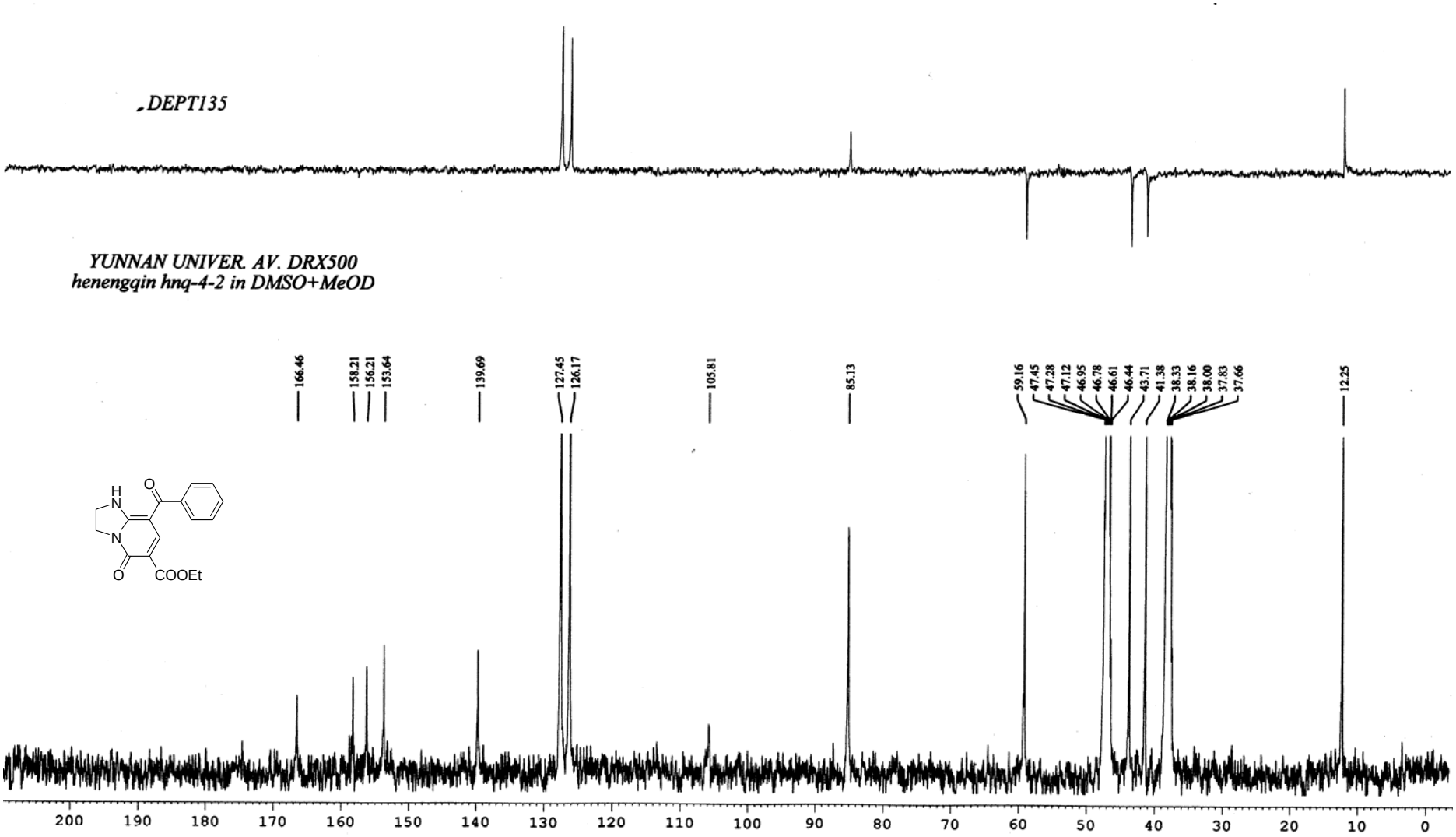


Figure 48. ^{13}C NMR (125 MHz, CH_3OD+DMSO-d_6) spectra of compound **6b**

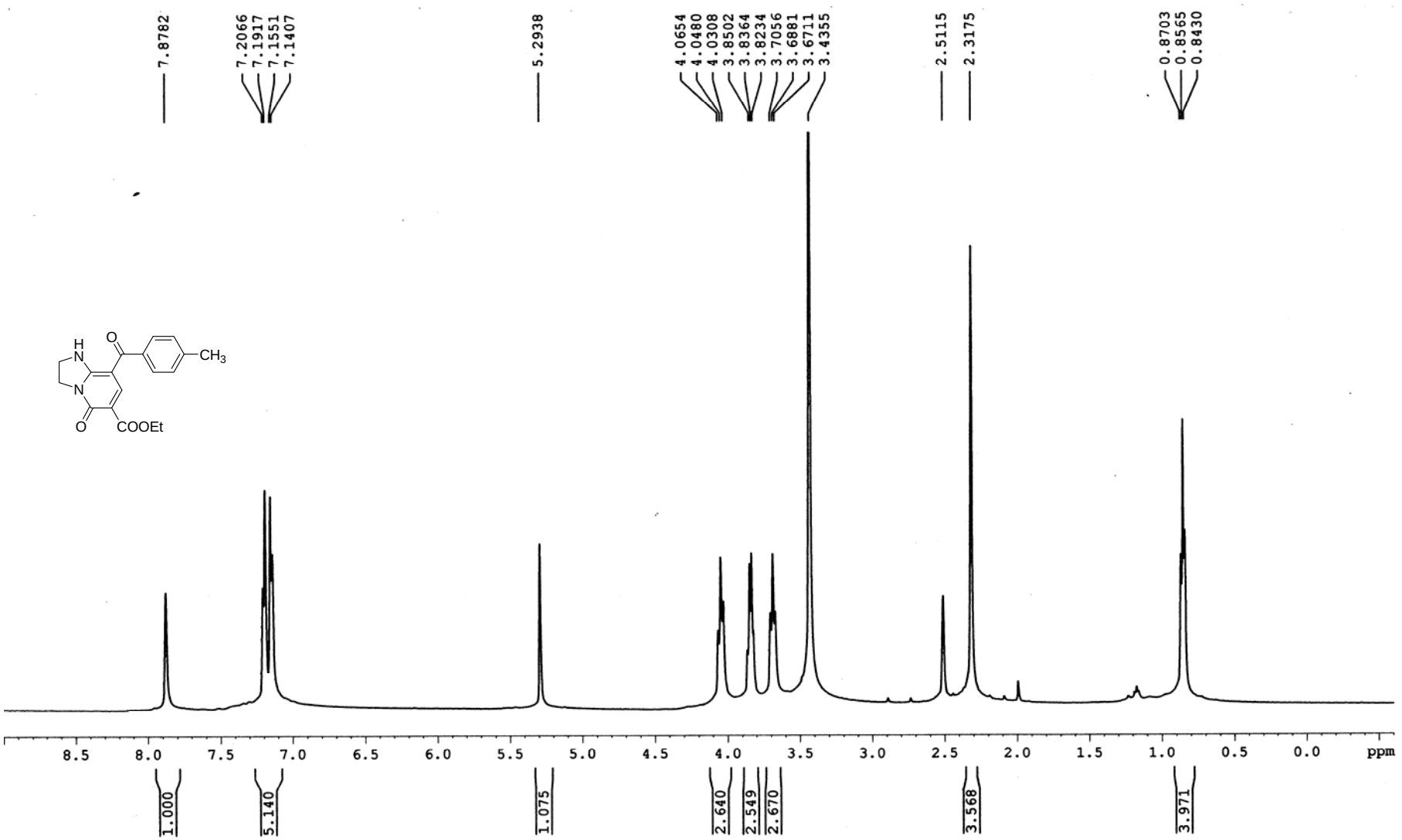


Figure 49. ^{1}H NMR (500 MHz, DMSO-d_6) spectra of compound **6c**

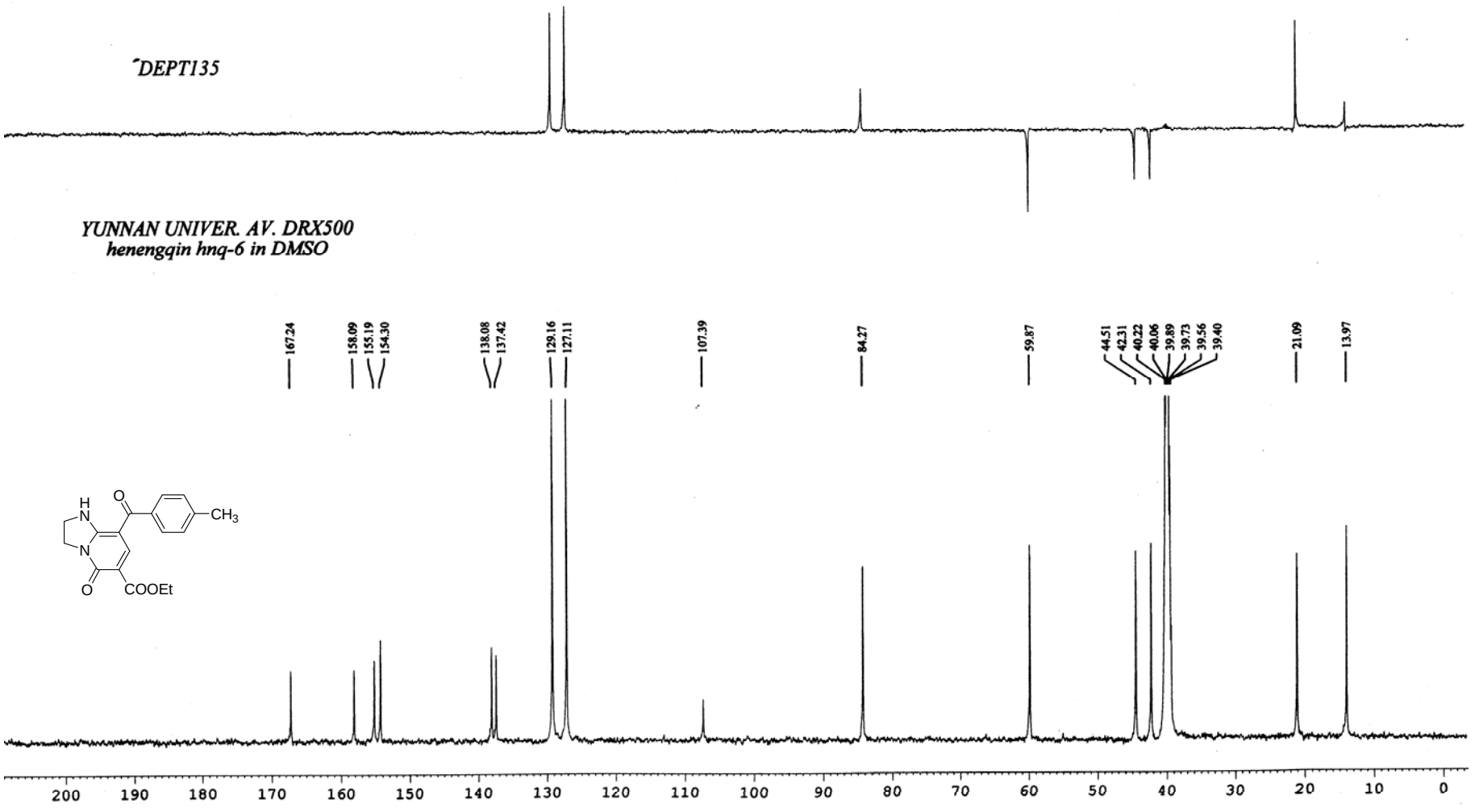


Figure 50. ^{13}C NMR (125 MHz, DMSO-d_6) spectra of compound **6c**

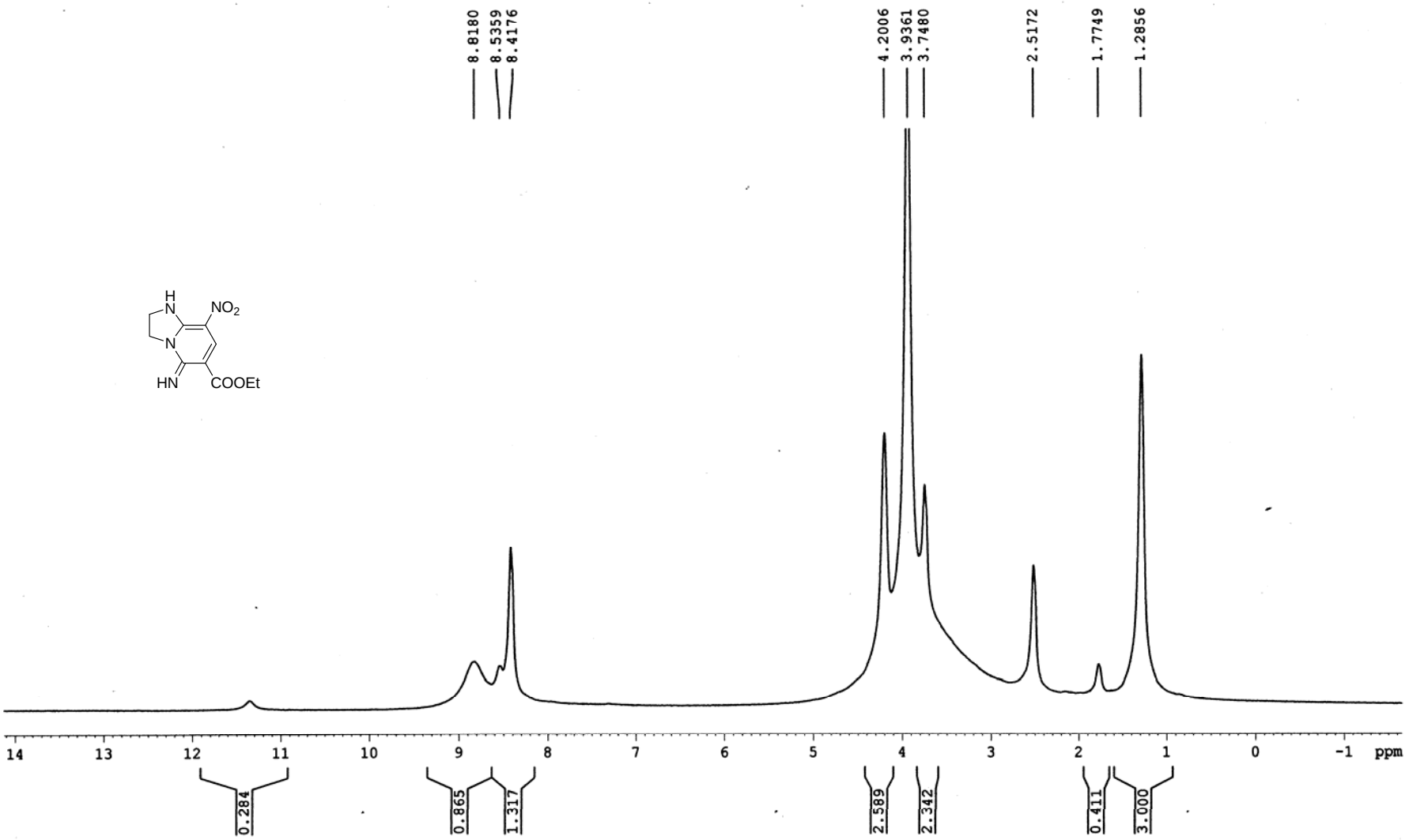


Figure 51. ^{1}H NMR (500 MHz, DMSO-d_6) spectra of compound **6d**

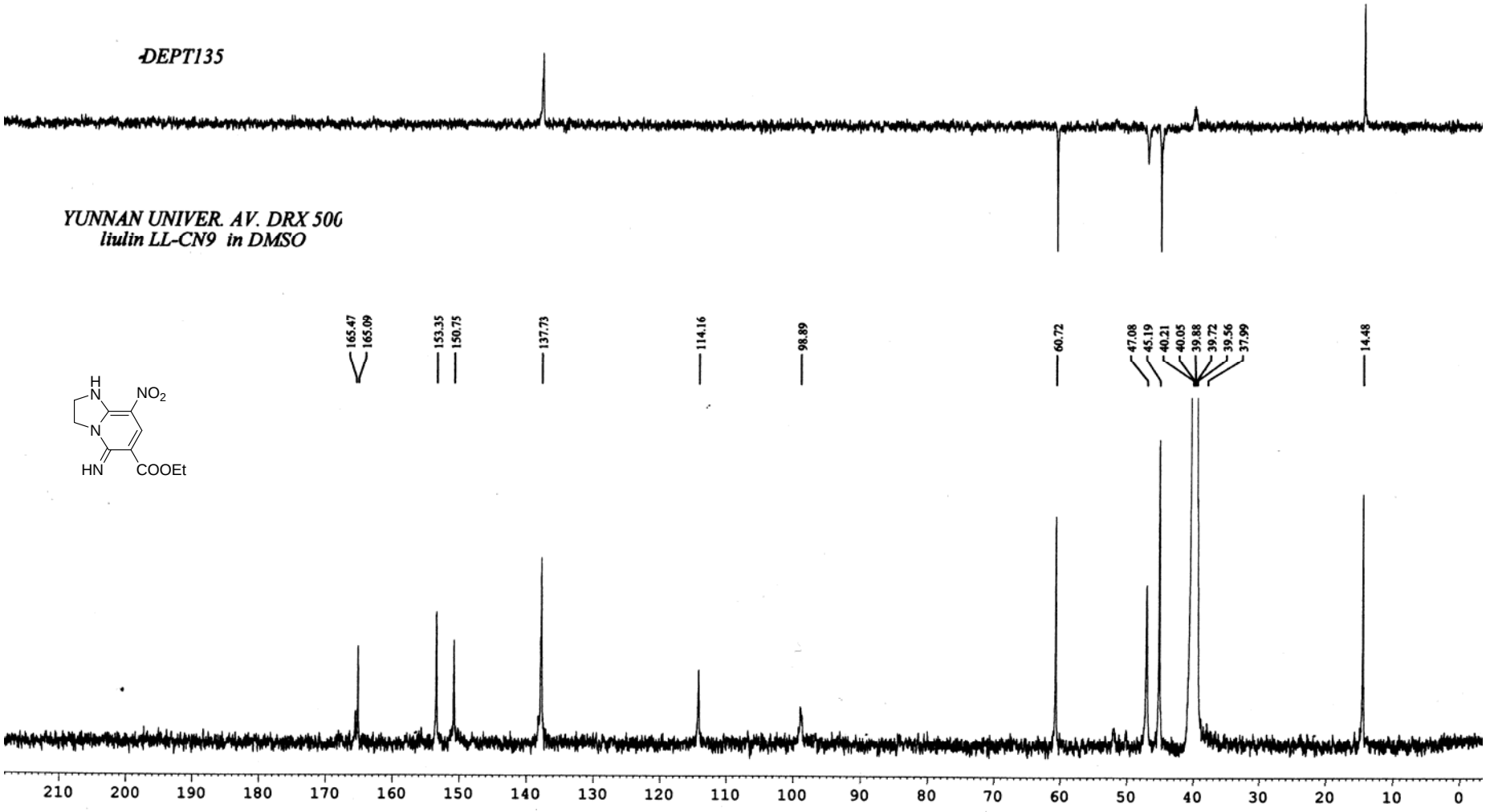


Figure 52. ^{13}C NMR (125 MHz, DMSO-d_6) spectra of compound **6d**

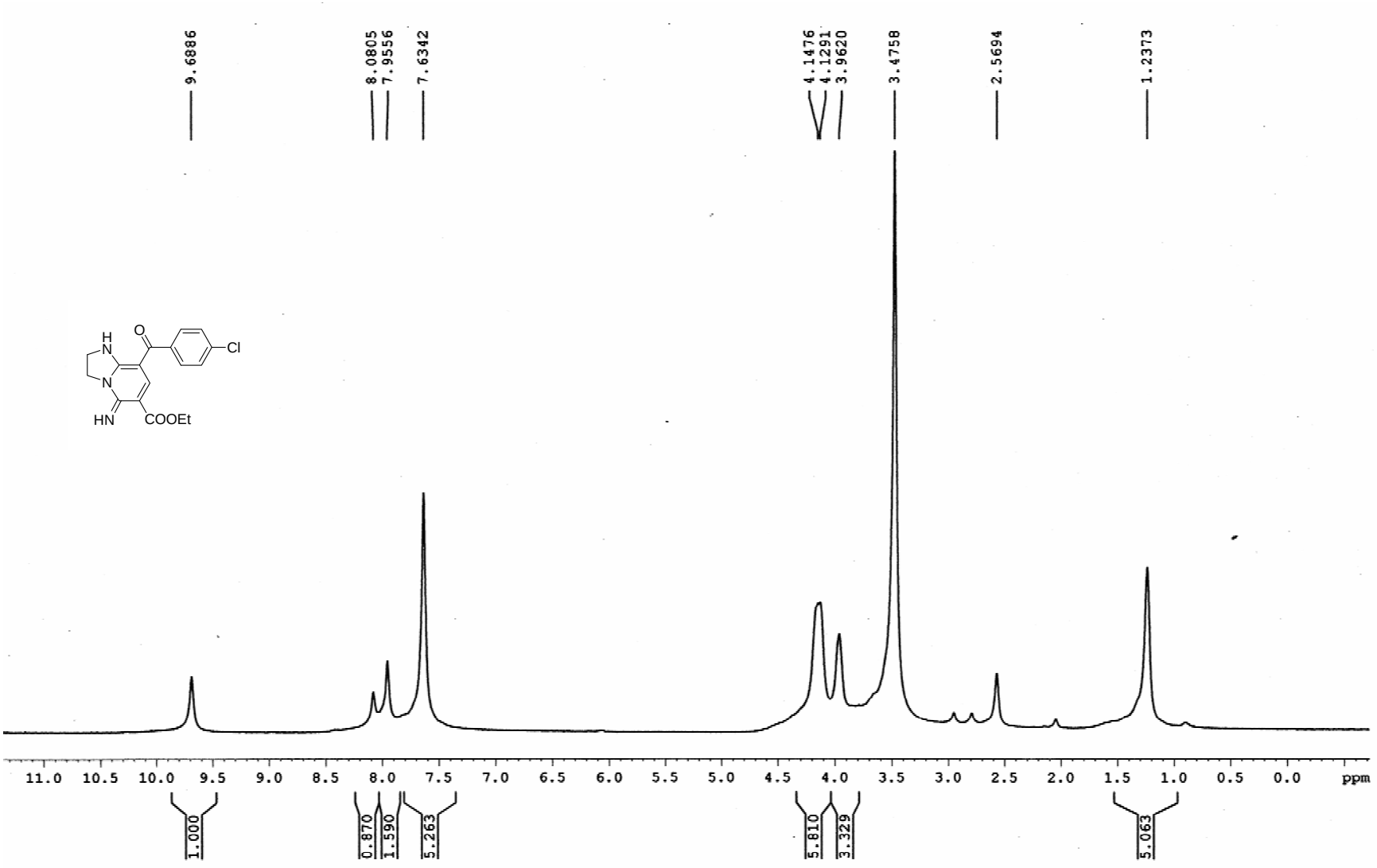


Figure 53. ^{1}H NMR (500 MHz, DMSO-d_6) spectra of compound **6e**

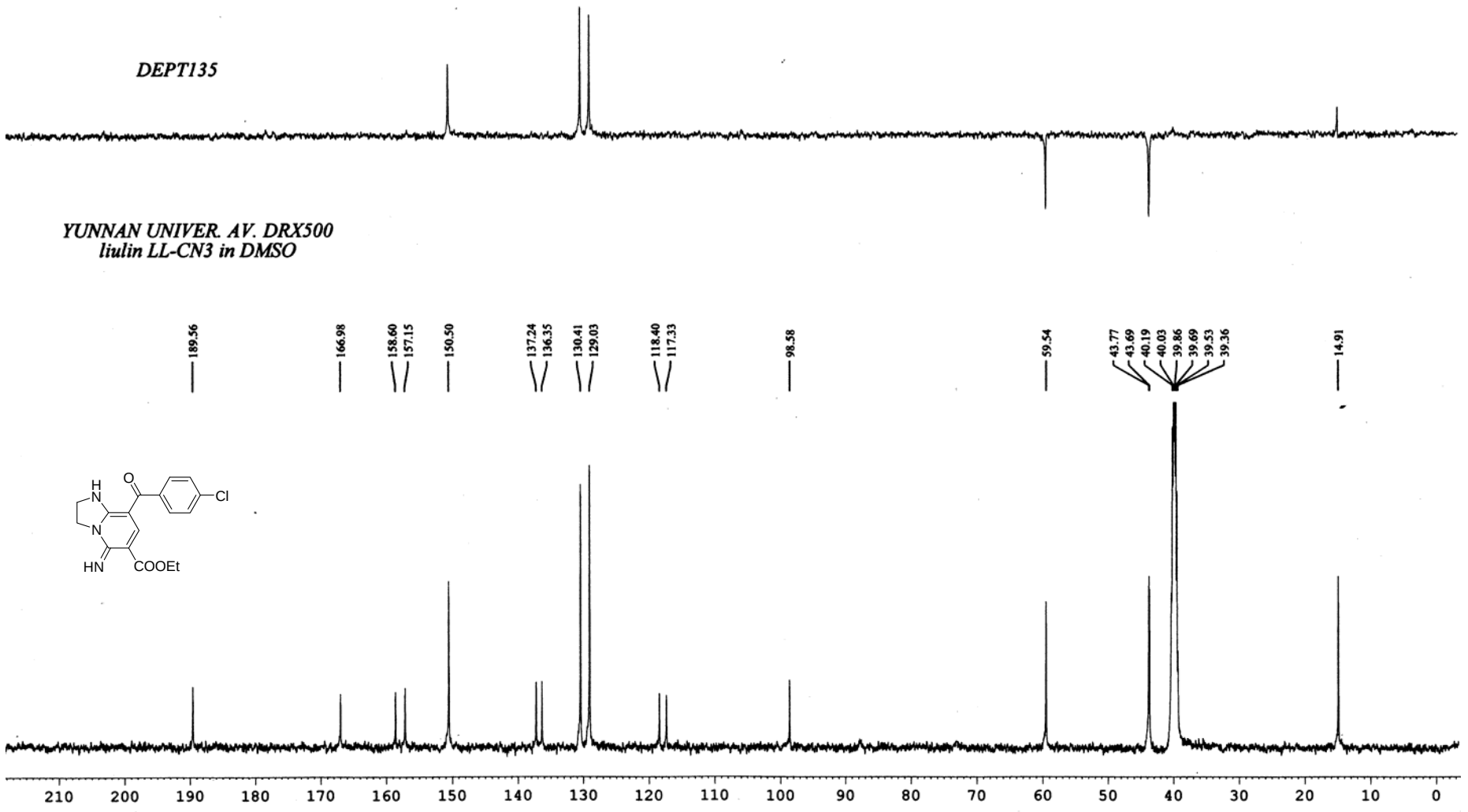


Figure 54. ^{13}C NMR (125 MHz, DMSO-d_6) spectra of compound **6e**

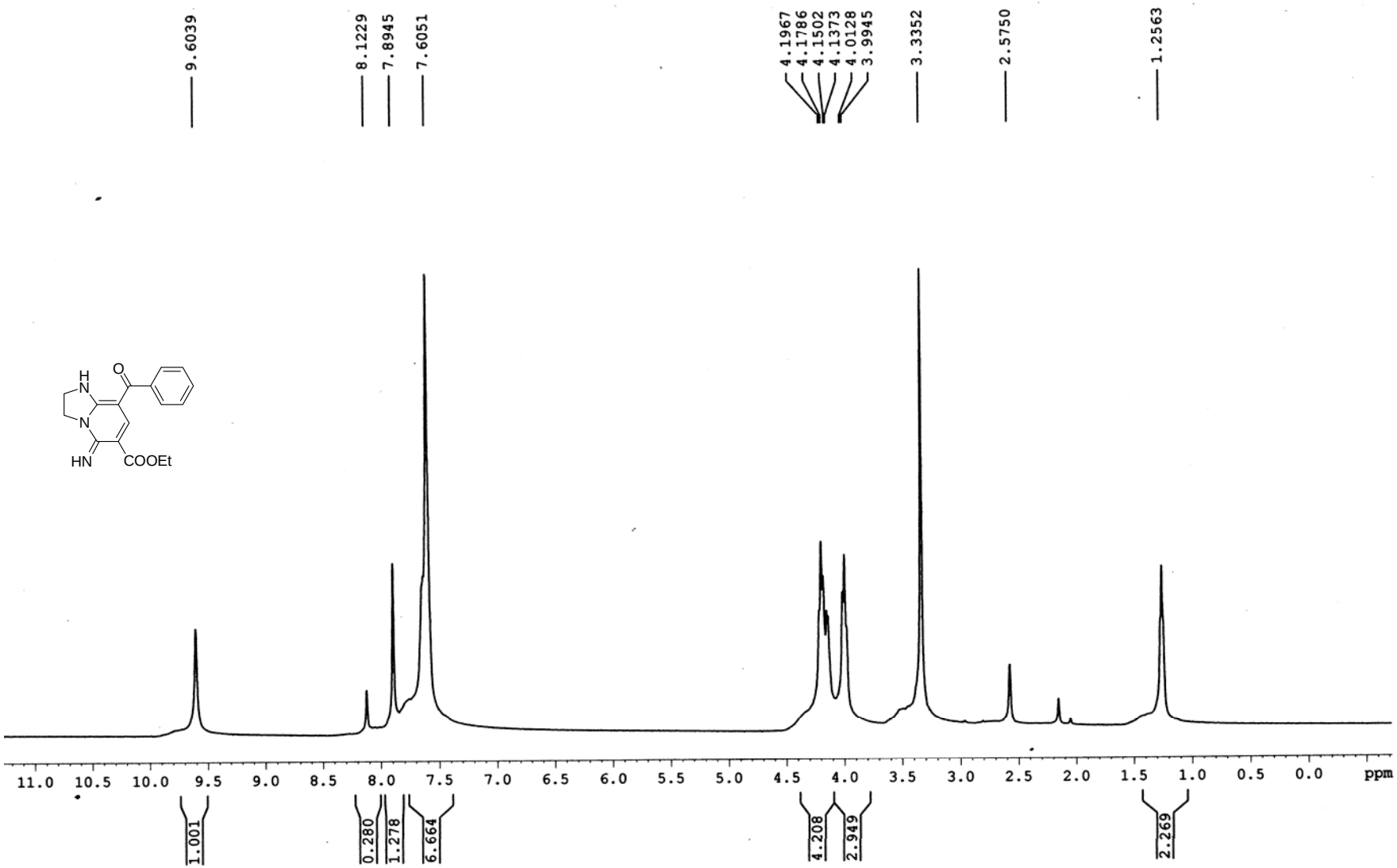


Figure 55. ^{1}H NMR (500 MHz, DMSO-d_6) spectra of compound **6f**

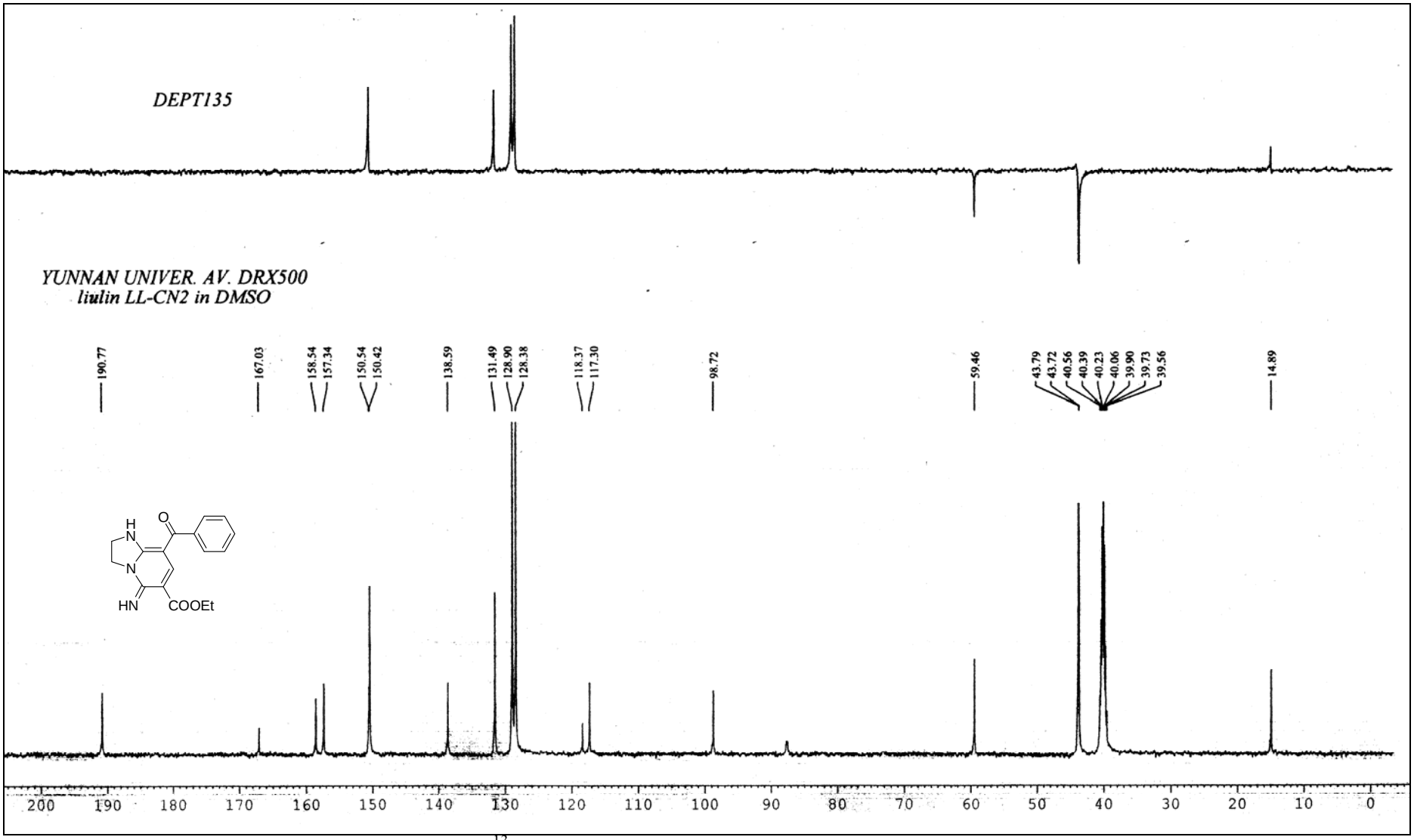


Figure 56. ^{13}C NMR (125 MHz, DMSO-d_6) spectra of compound **6f**

References and Notes

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7. CCDC 784140 contain the supplementary crystallographic data for compound **4m**. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.