

Synthesis and antitumor-evaluation of polyhalo acridone derivatives

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General Method

All compounds were fully characterized by spectroscopic techniques. The NMR spectra were recorded on a Bruker-Avance 500 MHz spectrometer (^1H : 500 MHz, ^{13}C : 125 MHz) with tetramethylsilane (TMS) as the internal standard (δ 0.0 ppm), chemical shifts (δ) are expressed in ppm, and J values are given in Hz. Deuterated DMSO and DMF were used as the solvent. IR spectra were recorded on a FT-IR Thermo Nicolet Avatar 360 using a KBr pellet. The reactions were monitored by thin layer chromatography (TLC) using neutral alumina. The melting points were determined on an XT-4A melting point apparatus and are uncorrected. HRMS was performed on an Agilent LC-MSD TOF instrument.

1a, **1c** and **2** were purchased from Adrich Corporation Limited. All chemicals and solvents were used as received without further purification unless otherwise stated. Column chromatography was performed on silica gel (200–300 mesh).

General procedure for the synthesis of polyhalo isophthalonitrile 3

A 50 mL round-bottom flask was charged with polyhaloisophthalonitrile **1** (5 mmol), DMF (30 mL), aniline derivatives **2** (6.0 mmol), and potassium carbonate 1.4 g (10 mmol), and the solution was stirred for 0.5–18 h at room temperature until the polyhaloisophthalonitrile **1** was completely consumed. The mixture was dumped at beaker (100 mL) and quenched by the addition of water (30 mL). The mixture was filtered off and the residue was washed with water to give a crude product that was purified by flash column chromatography. The desired compounds **3** were formed in excellent yields: 84–96 %.

General procedure for the synthesis of polyhalo acridone with side chains containing amide group 4

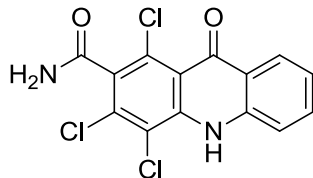
Polyhalo isophthalonitrile **3** (2 mmol) were dissolved in 6 mL 95–98 % sulfuric acid, and the solution was stirred for 1 h at 90 °C. The mixture was cooled to room temperature, and then was poured into 100 mL beaker, added 50 mL water under stirring. The pH of mixture was adjusted to 9–10 by solid potassium carbonate. The mixture was filtered off and the residue was washed with water to give a crude product that was purified by flash column chromatography. The desired compounds **4** were formed in good yields: 76–86 %.

General procedure for the synthesis of polyhalo acridone with side chains containing cyano group 5

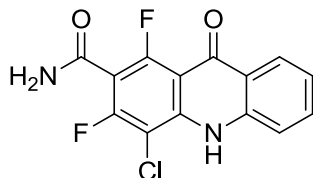
Polyhalo acridone with side chains containing amide group **4** (2 mmol) were dissolved in 8 mL dry pyridine, phosphorus oxychloride (0.5 mL) was added under the ice bath, and the solution was stirred for 1 h until the Polyhalo acridone with side chains containing amide group **4** was completely consumed. The reaction mixture was added to a beaker filled with crushed ice, and neutralized by Na₂CO₃ under stirring. The mixture was filtered off and the residue was washed with water to give a crude product that was purified by flash column chromatography. The desired compounds **5** were formed in good yields: 70–83 %.

The Data of the Polyhalo Isophthalonitrile 4 and 5

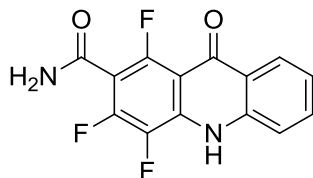
The Data of the Polyhalo Isophthalonitrile 4



1,3,4-Trichloro-9-oxo-9,10-dihydroacridine-2-carboxamide (4a) ^[1]: yellow solid; mp: 251–252 °C; IR (KBr) (ν_{\max} , cm^{-1}) 3478, 3416, 1665, 1568, 1398, 1326, 1164, 755, 612; ¹H NMR (500 MHz, DMSO-*d*₆): δ 8.48–8.18 (m, 3H, PhH), 7.95–7.80 (m, 3H, NH₂, PhH), 7.48 (br, 1H, NH); ¹³C NMR (125 MHz, DMSO-*d*₆): δ 162.7, 152.5, 148.5, 145.5, 132.2, 131.9, 130.7, 130.0, 129.2, 125.4, 124.4, 123.4, 115.1, 108.4; HRMS (TOF ES⁺): *m/z* calcd for C₁₄H₈Cl₃N₂O₂⁺ [(M+H)⁺], 340.9646; found, 340.9644.

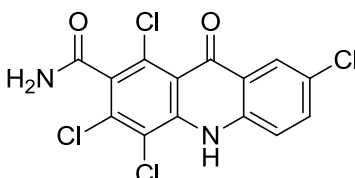


4-Chloro-1,3-difluoro-9-oxo-9,10-dihydroacridine-2-carboxamide (4b) ^[1]: yellow solid; mp: >300 °C; IR (KBr) (ν_{\max} , cm^{-1}) 3486, 3371, 3246, 1679, 1559, 1382, 1260, 834, 759, 601 cm^{-1} ; ¹H NMR (500 MHz, DMSO-*d*₆): δ 8.52–7.77 (m, 6H, PhH, NH₂), 7.46–7.43 (br, 1H, NH); ¹³C NMR (125 MHz, DMSO-*d*₆): δ 161.3, 156.2 (d, *J* = 267.5 Hz), 154.8 (d, *J* = 258.8 Hz), 151.8, 149.5, 145.2, 132.5, 129.1, 123.8, 123.4, 114.1, 111.6, 109.1 (t, *J* = 27.5 Hz), 101.2 (d, *J* = 32.5 Hz); ¹⁹F NMR (470 MHz, DMSO-*d*₆): δ -111.3 (d, *J* = 4.7 Hz, 1F), -111.7 (d, *J* = 4.7 Hz, 1F); HRMS (TOF ES⁺): *m/z* calcd for C₁₄H₈ClF₂N₂O₂⁺ [(M+H)⁺], 309.0237; found, 309.0233.

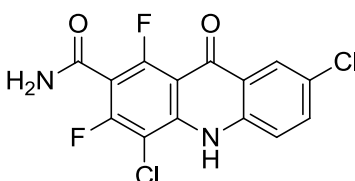


1,3,4-Trifluoro-9-oxo-9,10-dihydroacridine-2-carboxamide (4c) ^[1]: yellow solid; mp: >300 °C; IR (KBr) (ν_{\max} , cm^{-1}) 3526, 3421, 3151, 1685, 1557, 1388, 1265, 967, 758,

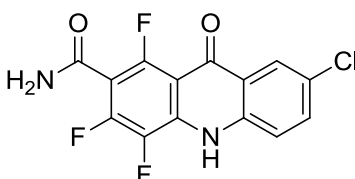
602 cm^{-1} ; ^1H NMR (500 MHz, $\text{DMSO-}d_6$): δ 8.53–7.78 (m, 6H, PhH, NH_2), 7.44 (br, 1H, NH); ^{13}C NMR (125 MHz, $\text{DMSO-}d_6$): δ 161.0, 152.6 (d, $J = 261.3$ Hz), 151.2, 149.4, 145.3 (d, $J = 252.5$ Hz), 140.5 (d, $J = 248.8$ Hz), 140.4, 132.4, 129.1, 123.7, 123.5, 114.1, 108.4 (t, $J = 25.0$ Hz), 101.2; HRMS (TOF ES^+): m/z calcd for $\text{C}_{14}\text{H}_8\text{F}_3\text{N}_2\text{O}_2^+$ [(M+H) $^+$], 293.0532; found, 293.0529.



1,3,4,7-Tetrachloro-9-oxo-9,10-dihydroacridine-2-carboxamide (4d) ^[1]: yellow solid; mp: >300 $^\circ\text{C}$; IR (KBr) (ν_{max} , cm^{-1}) 3297, 1637, 1553, 1437, 1234, 1094, 824, 637, 508 cm^{-1} ; HRMS (TOF ES^-) m/z calcd for $\text{C}_{14}\text{H}_4\text{Cl}_4\text{N}_2\text{O}_2^{2-}$ [(M-2H) $^{2-}$], 371.9038; found, 371.9045.

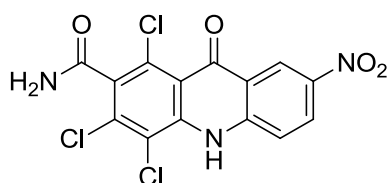


4,7-dichloro-1,3-difluoro-9-oxo-9,10-dihydroacridine-2-carboxamide (4e) ^[1]: yellow solid; mp: >300 $^\circ\text{C}$; IR (KBr) (ν_{max} , cm^{-1}) 3433, 3353, 3245, 1650, 1554, 1376, 1251, 1102, 834, 630 cm^{-1} ; ^1H NMR (500 MHz, $\text{DMSO-}d_6$): δ 8.67 (br, 1H, NH), 8.28–7.74 (m, 5H, PhH, NH_2); ^{13}C NMR (125 MHz, $\text{DMSO-}d_6$): δ 161.0, 156.0 (d, $J = 255.0$ Hz), 155.0 (d, $J = 247.5$ Hz), 151.2, 147.9, 145.4, 132.9, 131.3, 128.2, 122.4, 114.6, 111.8, 109.9 (t, $J = 26.3$ Hz), 101.2; HRMS (TOF ES^+): m/z calcd for $\text{C}_{14}\text{H}_7\text{Cl}_2\text{F}_2\text{N}_2\text{O}_2$ [(M+H) $^+$], 342.9847; found, 342.9845.

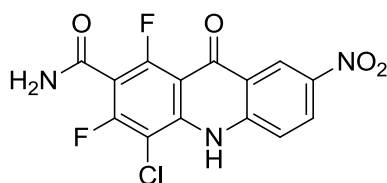


7-Chloro-1,3,4-trifluoro-9-oxo-9,10-dihydroacridine-2-carboxamide (4f): yellow solid; mp: 181–185 $^\circ\text{C}$; IR (KBr) (ν_{max} , cm^{-1}) 3494, 3347, 3181, 1661, 1558, 1376, 1117, 976, 829, 654 cm^{-1} ; ^1H NMR (500 MHz, $\text{DMSO-}d_6$): δ 8.64 (br, 1H, NH), 8.29–7.73 (m,

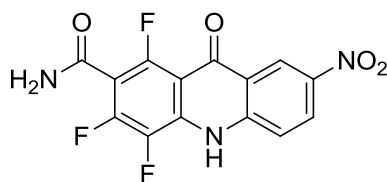
5H, PhH, NH₂); ¹³C NMR (125 MHz, DMSO-*d*₆): δ 160.8, 152.5 (d, *J* = 257.5 Hz), 150.7, 147.6, 145.6 (d, *J* = 247.5 Hz), 140.4 (d, *J* = 247.5 Hz), 140.3, 132.9, 131.0, 128.2, 122.4, 114.5, 109.1 (t, *J* = 25.0 Hz), 101.4; ¹⁹F NMR (467 MHz, DMSO-*d*₆): δ -115.4 (d, *J* = 14.1 Hz, 1F), -139.3 (s, 1F), -155.9 (d, *J* = 14.1 Hz, 1F); HRMS (TOF ES⁺): *m/z* calcd for C₁₄H₇ClF₃N₂O₂⁺ [(M+H)⁺], 327.0143; found, 327.0140.



1,3,4-Trichloro-7-nitro-9-oxo-9,10-dihydroacridine-2-carboxamide (4g): yellow solid; mp: >300 °C; IR (KBr) (*v*_{max}, cm⁻¹) 3369, 1567, 1498, 1329, 1182, 849, 748 cm⁻¹; ¹H NMR (500 MHz, DMF-*d*₆): δ 9.21 (br, 1H, NH), 8.48–7.84 (m, 5H, PhH, NH₂); HRMS (TOF ES⁻) *m/z* calcd for C₁₄H₄Cl₃N₃O₄²⁻ [(M-2H)²⁻], 382.9278; found, 382.9278.

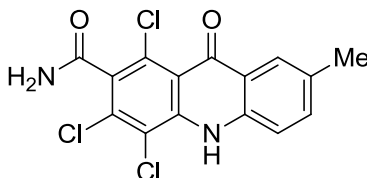


4-Chloro-1,3-difluoro-7-nitro-9-oxo-9,10-dihydroacridine-2-carboxamide (4h): yellow solid; mp: 219–221 °C; IR (KBr) (*v*_{max}, cm⁻¹) 3375, 1676, 1541, 1500, 1331, 1244, 1128, 914, 837, 745 cm⁻¹; ¹H NMR (500 MHz, DMSO-*d*₆): δ 9.60 (br, 1H, NH), 8.36–7.86 (m, 5H, PhH, NH₂); ¹³C NMR (125 MHz, DMSO-*d*₆): δ 160.8, 157.0, 155.1, 154.5, 151.5, 147.0, 142.4, 130.5, 125.3, 122.5, 112.4, 112.1, 110.3 (t, *J* = 27.5 Hz), 101.7; HRMS (TOF ES⁻) *m/z* calcd for C₁₄H₄ClF₂N₃O₄²⁻ [(M-2H)²⁻], 350.9869; found, 350.9878.

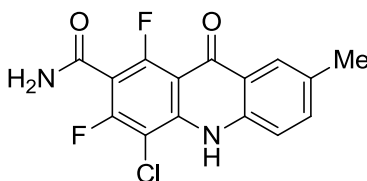


1,3,4-Trifluoro-7-nitro-9-oxo-9,10-dihydroacridine-2-carboxamide (4i): yellow solid; mp: >300 °C; IR (KBr) (*v*_{max}, cm⁻¹) 3409, 3233, 1656, 1501, 1332, 1252, 1127, 978, 616 cm⁻¹; ¹H NMR (500 MHz, DMF-*d*₆): δ 10.15 (br, 1H, NH), 9.74–8.17 (m, 5H, PhH, NH₂); ¹³C NMR (125 MHz, DMF-*d*₆): δ 159.8, 159.0, 154.3 (d, *J* = 252.5 Hz), 150.1 (d, *J* =

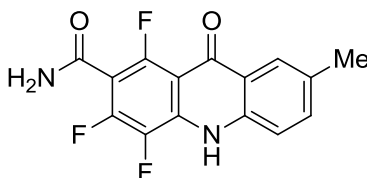
251.3 Hz), 144.1, 143.1, 136.8 (d, $J = 250.0$ Hz), 132.6, 130.3, 122.8, 121.3, 112.7, 111.8 (d, $J = 20.0$ Hz), 101.5; ^{19}F NMR (467 MHz, DMF- d_6): δ -116.8 (s, 1F), -131.5 (d, $J = 14.0$ Hz, 1F), -159.4 (s, 1F); HRMS (TOF ES $^-$) m/z calcd for $\text{C}_{14}\text{H}_4\text{F}_3\text{N}_3\text{O}_4^{2-}$ [(M-2H) $^{2-}$], 335.0165; found, 335.0176.



1,3,4-Trichloro-7-methyl-9-oxo-9,10-dihydroacridine-2-carboxamide (4j): yellow solid; mp: >300 °C; IR (KBr) (ν_{max} , cm^{-1}) 3389, 1682, 1631, 1456, 1329, 1258, 826, 648 cm^{-1} ; ^1H NMR (500 MHz, DMSO- d_6): δ 10.48 (br, 1H, NH), 8.30–7.65 (m, 5H, PhH, NH $_2$), 2.51–2.48 (m, 3H, CH $_3$); HRMS (TOF ES $^-$) m/z calcd for $\text{C}_{15}\text{H}_7\text{Cl}_3\text{N}_2\text{O}_2^{2-}$ [(M-2H) $^{2-}$], 351.9584; found, 351.9596.

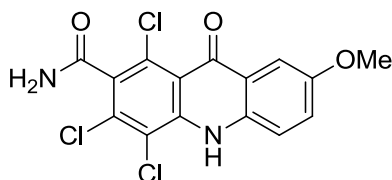


4-Chloro-1,3-difluoro-7-methyl-9-oxo-9,10-dihydroacridine-2-carboxamide (4k): yellow solid; mp: >300 °C; IR (KBr) (ν_{max} , cm^{-1}) 3358, 1634, 1556, 1372, 1258, 1047, 828, 630 cm^{-1} ; ^1H NMR (500 MHz, DMF- d_6): 7.65–6.88 (m, 6H, PhH, NH, NH $_2$), 2.33–2.12 (m, 3H, CH $_3$). ^{13}C NMR (125 MHz, DMF- d_6): δ 160.8, 155.9 (d, $J = 267.5$ Hz), 154.3 (d, $J = 260.0$ Hz), 150.5, 147.6, 144.3, 133.9, 133.0, 128.3, 120.8, 113.5, 111.3, 108.7 (t, $J = 26.3$ Hz), 100.6, 20.5; ^{19}F NMR (467 MHz, DMF- d_6): δ -112.9 (s, 1F), -113.4 (s, 1F); HRMS (TOF ES $^-$) m/z calcd for $\text{C}_{15}\text{H}_7\text{ClF}_2\text{N}_2\text{O}_2^{2-}$ [(M-2H) $^{2-}$], 320.0175; found, 320.0183.

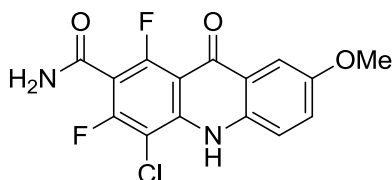


1,3,4-Trifluoro-7-methyl-9-oxo-9,10-dihydroacridine-2-carboxamide (4l): yellow solid; mp: 177–178 °C; IR (KBr) (ν_{max} , cm^{-1}) 3394, 1658, 1562, 1467, 1375, 1268, 1134,

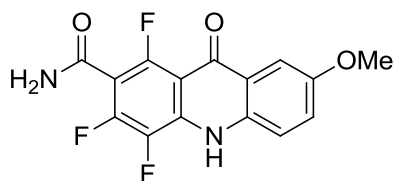
972, 628 cm^{-1} ; ^1H NMR (500 MHz, DMF- d_6): δ 8.39–7.65 (m, 6H, PhH, NH, NH₂), 2.95–2.74 (m, 3H, CH₃); ^{13}C NMR (125 MHz, DMF- d_6): δ 161.7, 153.4 (d, $J = 252.5$ Hz), 150.9, 148.9, 145.8 (d, $J = 247.5$ Hz), 141.4 (d, $J = 248.8$ Hz), 140.7, 134.9, 134.0, 129.5, 121.9, 114.6, 109.2 (t, $J = 26.3$ Hz), 101.9 (d, $J = 10.0$ Hz), 21.5; ^{19}F NMR (467 MHz, DMF- d_6): δ -117.5 (d, $J = 18.7$ Hz, 1F), -142.5 (d, $J = 18.7$ Hz, 1F), -157.7 (t, $J = 14.0$ Hz, 1F); HRMS (TOF ES⁻) m/z calcd for C₁₅H₇F₃N₂O₂²⁻ [(M-2H)²⁻], 304.0471; found, 304.0480.



1,3,4-Trichloro-7-hydroxy-9-oxo-9,10-dihydroacridine-2-carboxamide (4m): yellow solid; mp: >300 °C; IR (KBr) (ν_{max} , cm^{-1}) 3399, 1634, 1502, 1455, 1407, 1332, 1244, 837, 602; ^1H NMR (500 MHz, DMF- d_6): δ 10.29 (br, 1H, NH), 8.43–7.55 (m, 5H, PhH, NH₂), 3.08–2.74 (m, 1H, OH); ^{13}C NMR (125 MHz, DMF- d_6): δ 166.1, 155.2, 150.3, 144.3, 143.8, 132.2, 131.1, 128.7, 125.5, 125.2, 116.6, 108.2, 103.2, 88.9; HRMS (TOF ES⁻) m/z calcd for C₁₄H₅Cl₃N₂O₃²⁻ [(M-2H)²⁻], 353.9377; found, 353.9385.

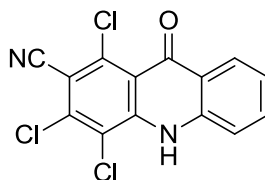


4-Chloro-1,3-difluoro-7-hydroxy-9-oxo-9,10-dihydroacridine-2-carboxamide (4n): yellow solid; mp: >300 °C; IR (KBr) (ν_{max} , cm^{-1}) 3398, 1641, 1463, 1366, 1243, 1067, 835, 630; ^1H NMR (500 MHz, DMF- d_6): 10.34 (br, 1H, NH), 8.36–6.82 (m, 5H, PhH, NH₂), 2.99–2.73 (m, 1H, OH); ^{13}C NMR (125 MHz, DMF- d_6): δ 161.3, 156.3 (d, $J = 250.0$ Hz), 154.8, 152.3 (d, $J = 317.5$ Hz), 150.0, 147.0, 144.6, 143.1, 125.8, 115.4, 114.7, 109.7, 103.4, 101.0; ^{19}F NMR (467 MHz, DMF- d_6): δ -112.5 (s, 1F), -113.2 (s, 1F); HRMS (TOF ES⁻) m/z calcd for C₁₄H₅ClF₂N₂O₃²⁻ [(M-2H)²⁻], 321.9968; found, 321.9975.

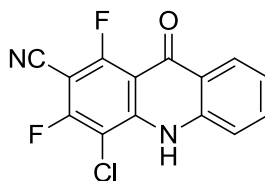


1,3,4-Trifluoro-7-hydroxy-9-oxo-9,10-dihydroacridine-2-carboxamide (4o): yellow solid; mp: 197–198 °C; IR (KBr) (ν_{\max} , cm^{-1}) 3379, 1657, 1465, 1369, 1259, 1129, 977; ^1H NMR (500 MHz, $\text{DMF-}d_6$): δ 10.19 (br, 1H, NH), 8.36–7.54 (m, 5H, PhH, NH_2), 3.09–2.57 (m, 1H, OH); ^{13}C NMR (125 MHz, $\text{DMF-}d_6$): δ 161.7, 155.1, 154.0, 152.0, 149.5, 145.6, 144.1, 139.2, 131.3, 126.1, 115.9, 109.2, 103.7, 101.6; ^{19}F NMR (467 MHz, $\text{DMF-}d_6$): δ -117.9 (d, $J = 14.1$ Hz, 1F), -143.7 (d, $J = 14.0$ Hz, 1F), -157.7 (t, $J = 14.0$ Hz, 1F); HRMS (TOF ES^-) m/z calcd for $\text{C}_{14}\text{H}_5\text{F}_3\text{N}_2\text{O}_3^{2-}$ [(M-2H) $^{2-}$], 306.0263; found, 320.0272.

The Data of the Polyhalo Isophthalonitrile 5

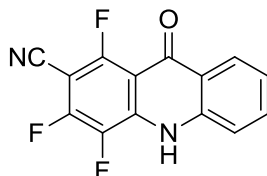


1,3,4-Trichloro-9-oxo-9,10-dihydroacridine-2-carbonitrile (5a): yellow solid; mp: 242–243 °C; IR (KBr) (ν_{\max} , cm^{-1}) 3394, 2229, 1633, 1563, 1335, 1167, 756, 599 cm^{-1} ; ^1H NMR (500 MHz, $\text{DMSO-}d_6$): δ 8.60–7.49 (m, 5H, PhH, NH); ^{13}C NMR (125 MHz, $\text{DMSO-}d_6$): δ 154.3, 149.2, 146.6, 137.4, 133.9, 131.4, 131.2, 129.6, 125.5, 124.2, 115.8, 115.6, 108.8, 106.6; HRMS (TOF ES^-) m/z calcd for $\text{C}_{14}\text{H}_3\text{Cl}_3\text{N}_2\text{O}^{2-}$ [(M-2H) $^{2-}$], 319.9322; found, 321.9456.

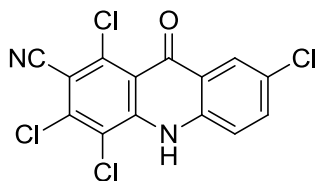


4-Chloro-1,3-difluoro-9-oxo-9,10-dihydroacridine-2-carbonitrile (5b): yellow solid; mp: >300 °C; IR (KBr) (ν_{\max} , cm^{-1}) 3394, 2237, 1634, 1559, 1382, 1262, 1078, 760 cm^{-1} ; ^1H NMR (500 MHz, $\text{DMF-}d_6$): δ 8.60–7.50 (m, 5H, PhH, NH); ^{13}C NMR (125 MHz,

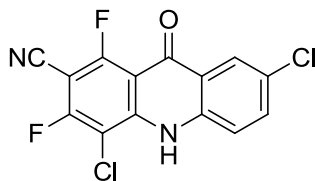
DMF-*d*₆): δ 161.6, 154.8 (d, $J = 260.0$ Hz), 153.0, 150.1, 146.6, 133.5, 129.3, 124.7, 123.3, 114.6, 112.4, 110.1, 100.5, 83.4 (t, $J = 21.3$ Hz); ¹⁹F NMR (467 MHz, DMF-*d*₆): δ -100.5 (s, 1F), -110.3 (s, 1F); HRMS (TOF ES⁻) m/z calcd for C₁₄H₄ClF₂N₂O⁻ [(M-H)⁻], 288.9986; found, 288.9998.



1,3,4-Trifluoro-9-oxo-9,10-dihydroacridine-2-carbonitrile (5c): yellow solid; mp: 196–197 °C; IR (KBr) (ν_{\max} , cm⁻¹) 3369, 3232, 2237, 1660, 1563, 1499, 1273, 1144, 981, 763, 598 cm⁻¹; ¹H NMR (500 MHz, DMSO-*d*₆): δ 8.57–7.51 (m, 5H, PhH, NH); ¹³C NMR (125 MHz, DMSO-*d*₆): δ 162.0, 159.9, 152.2, 149.8, 146.3, 142.1, 133.7, 129.1, 124.7, 123.8, 114.5, 110.5, 100.9, 82.4 (d, $J = 32.5$ Hz); ¹⁹F NMR (467 MHz, DMSO-*d*₆): δ -102.6 (d, $J = 14.0$ Hz, 1F), -138.1 (s, 1F), -154.5 (t, $J = 18.7$ Hz, 1F); HRMS (TOF ES⁻) m/z calcd for C₁₄H₃F₃N₂O²⁻ [(M-2H)²⁻], 272.0208; found, 272.0216.

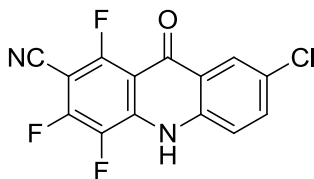


1,3,4,7-Tetrachloro-9-oxo-9,10-dihydroacridine-2-carbonitrile (5d): yellow solid; mp: 240–241 °C; IR (KBr) (ν_{\max} , cm⁻¹) 3403, 2235, 1636, 1555, 1312, 1253, 1085, 870, 610 cm⁻¹; ¹H NMR (500 MHz, DMF-*d*₆): δ 8.77–7.97 (m, 4H, PhH, NH); ¹³C NMR (125 MHz, DMF-*d*₆): δ 162.8, 159.5, 142.6, 138.4, 137.7, 135.0, 128.9, 125.2, 124.4, 122.2, 121.4, 116.6, 114.1, 109.5; HRMS (TOF ES⁻) m/z calcd for C₁₄H₅Cl₃N₂O⁻ [(M-Cl)⁻], 321.9473; found, 321.9483.

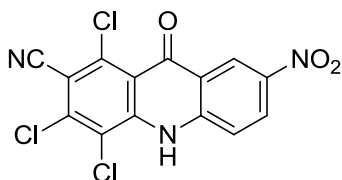


4,7-Dichloro-1,3-difluoro-9-oxo-9,10-dihydroacridine-2-carbonitrile (5e): yellow solid; mp: >300 °C; IR (KBr) (ν_{\max} , cm⁻¹) 3446, 2239, 1622, 1543, 1333, 1245, 1140, 841,

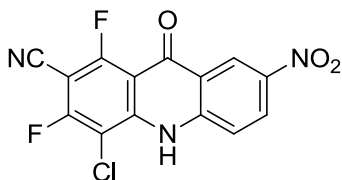
596 cm^{-1} ; ^1H NMR (500 MHz, $\text{DMSO-}d_6$): δ 8.61–7.75 (m, 4H, PhH, NH); ^{13}C NMR (125 MHz, $\text{DMSO-}d_6$): δ 163.7 (dd, $J_1 = 270.0$ Hz, $J_2 = 8.8$ Hz), 154.7 (d, $J = 243.8$ Hz), 152.0, 148.2, 146.5, 133.9, 131.2, 129.2, 122.7, 114.9, 112.2 (d, $J = 13.8$ Hz), 110.3, 100.6 (d, $J = 6.3$ Hz), 83.9 (t, $J = 22.5$ Hz); ^{19}F NMR (467 MHz, $\text{DMSO-}d_6$): δ -98.7 (s, 1F), -108.7 (s, 1F); HRMS (TOF ES $^-$) m/z calcd for $\text{C}_{14}\text{H}_2\text{Cl}_2\text{F}_2\text{N}_2\text{O}^{2-}$ [(M-2H) $^{2-}$], 321.9523; found, 321.9532.



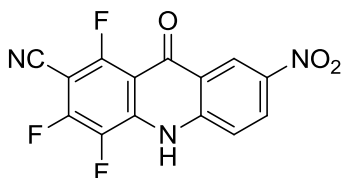
7-Chloro-1,3,4-trifluoro-9-oxo-9,10-dihydroacridine-2-carbonitrile (5f): yellow solid; mp: 240–241 $^{\circ}\text{C}$; IR (KBr) (ν_{max} , cm^{-1}) 3452, 3216, 2923, 2234, 1663, 1559, 1500, 1248, 985, 833, 594 cm^{-1} ; ^1H NMR (500 MHz, $\text{DMSO-}d_6$): δ 8.60–7.77 (m, 4H, PhH, NH); ^{13}C NMR (125 MHz, $\text{DMSO-}d_6$): δ 160.6 (d, $J = 267.5$ Hz), 151.4, 148.1, 145.2 (dt, $J_1 = 253.8$ Hz, $J_2 = 8.8$ Hz), 142.1, 140.1 (d, $J = 241.3$ Hz), 133.9, 131.2, 129.1, 122.7, 114.9, 110.3, 100.9 (d, $J = 6.3$ Hz), 83.0 (t, $J = 21.3$ Hz); ^{19}F NMR (467 MHz, $\text{DMSO-}d_6$): δ -102.6 (d, $J = 14.0$ Hz, 1F), -137.4 (d, $J = 18.7$ Hz, 1F), -154.0 (t, $J = 18.7$ Hz, 1F); HRMS (TOF ES $^-$) m/z calcd for $\text{C}_{14}\text{H}_2\text{ClF}_3\text{N}_2\text{O}^{2-}$ [(M-2H) $^{2-}$], 305.9819; found, 305.9830.



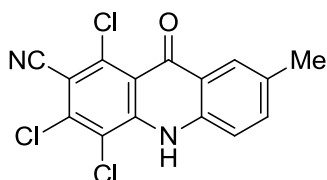
1,3,4-Trichloro-7-nitro-9-oxo-9,10-dihydroacridine-2-carbonitrile (5g): yellow solid; mp: 201–203 $^{\circ}\text{C}$; IR (KBr) (ν_{max} , cm^{-1}) 3426, 3175, 2238, 1681, 1608, 1555, 1335, 1251, 743, 614 cm^{-1} ; HRMS (TOF ES $^-$) m/z calcd for $\text{C}_{14}\text{H}_2\text{Cl}_3\text{N}_3\text{O}_3^{2-}$ [(M-2H) $^{2-}$], 364.9173; found, 364.9173.



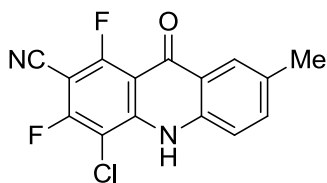
4-Chloro-1,3-difluoro-7-nitro-9-oxo-9,10-dihydroacridine-2-carbonitrile (5h): yellow solid; mp: 251–252 °C; IR (KBr) (ν_{\max} , cm^{-1}) 3445, 2925, 2243, 1625, 1334, 1245, 742, 610 cm^{-1} ; HRMS (TOF ES⁻) m/z calcd for $\text{C}_{14}\text{H}_2\text{ClF}_2\text{N}_3\text{O}_3^{2-}$ [(M-2H)²⁻], 332.9764; found, 332.9775.



1,3,4-Trifluoro-7-nitro-9-oxo-9,10-dihydroacridine-2-carbonitrile (5i): yellow solid; mp: 255–256 °C; IR (KBr) (ν_{\max} , cm^{-1}) 3443, 3369, 3268, 2241, 1655, 1500, 1335, 1254, 1142, 982, 609 cm^{-1} ; ¹H NMR (500 MHz, DMF-*d*₆): δ 9.78 (br, 1H, NH), 8.75–7.98 (m, 3H, PhH); ¹³C NMR (125 MHz, DMF-*d*₆): δ 159.2, 144.5 (d, J = 166.3 Hz), 144.4, 143.6, 136.3, 131.2, 129.2, 123.3, 122.8, 122.1, 120.7, 113.9, 108.7, 102.3; ¹⁹F NMR (467 MHz, DMF-*d*₆): δ -103.6 (s, 1F), -130.3 (s, 1F), -164.7 (s, 1F); HRMS (TOF ES⁻) m/z calcd for $\text{C}_{14}\text{H}_2\text{F}_3\text{N}_3\text{O}_3^{2-}$ [(M-2H)²⁻], 317.0059; found, 317.0068.

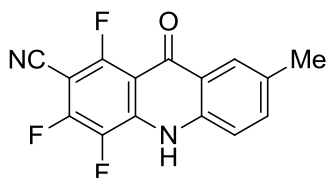


1,3,4-Trichloro-7-methyl-9-oxo-9,10-dihydroacridine-2-carbonitrile (5j): yellow solid; mp: 197–198 °C; IR (KBr) (ν_{\max} , cm^{-1}) 3391, 2925, 2230, 1640, 1563, 1496, 1085, 831, 723, 553 cm^{-1} ; ¹H NMR (500 MHz, DMF-*d*₆): δ 10.83–10.09 (m, 1H, NH), 8.35–7.43 (m, 3H, PhH), 2.48–2.32 (m, 3H, CH₃); ¹³C NMR (125 MHz, DMF-*d*₆): δ 159.1, 140.3, 139.4, 138.4, 137.7, 137.1, 134.5, 123.7, 122.1, 119.7, 114.6, 113.5, 110.5, 109.1, 20.8; HRMS (TOF ES⁻) m/z calcd for $\text{C}_{15}\text{H}_5\text{Cl}_3\text{N}_2\text{O}^{2-}$ [(M-2H)²⁻], 333.9478; found, 333.9486.



4-Chloro-1,3-difluoro-7-methyl-9-oxo-9,10-dihydroacridine-2-carbonitrile (5k): yellow solid; mp: 237–238 °C; IR (KBr) (ν_{\max} , cm^{-1}) 3344, 2924, 2235, 1639, 1548, 1391,

1296, 1083, 866, 619 cm^{-1} ; ^1H NMR (500 MHz, $\text{DMF-}d_6$): δ 8.29-7.65 (m, 4H, PhH, NH), 2.54-2.46 (m, 3H, CH_3); ^{13}C NMR (125 MHz, $\text{DMF-}d_6$): δ 155.7, 149.9, 142.7, 136.4, 136.2, 129.2, 125.7, 124.5, 122.6, 122.6, 119.3, 110.6, 108.6, 88.7, 21.6; ^{19}F NMR (467 MHz, $\text{DMF-}d_6$): δ -102.9 (s, 1F), -104.0 (s, 1F); HRMS (TOF ES $^-$) m/z calcd for $\text{C}_{15}\text{H}_6\text{ClF}_2\text{N}_2\text{O}^-$ [(M-H) $^-$], 303.0142; found, 303.0153.



1,3,4-Trifluoro-7-methyl-9-oxo-9,10-dihydroacridine-2-carbonitrile (51): yellow solid; mp: 213–214 $^\circ\text{C}$; IR (KBr) (ν_{max} , cm^{-1}) 3387, 2925, 2235, 1658, 1562, 1388, 1266, 1047, 609 cm^{-1} ; ^1H NMR (500 MHz, $\text{DMF-}d_6$): δ 9.02–7.72 (m, 4H, PhH, NH), 2.53 (s, 3H, CH_3); ^{13}C NMR (125 MHz, $\text{DMF-}d_6$): δ 160.6, 152.0, 149.2, 142.2, 142.1, 140.1, 136.1, 135.1, 129.6, 122.4, 114.9, 110.6, 101.5, 82.9, 21.5; ^{19}F NMR (467 MHz, $\text{DMF-}d_6$): δ -104.6 (d, $J = 14.0$ Hz, 1F), -140.3 (d, $J = 18.7$ Hz, 1F), -155.5 (t, $J = 14.0$ Hz, 1F); HRMS (TOF ES $^-$) m/z calcd for $\text{C}_{15}\text{H}_5\text{F}_3\text{N}_2\text{O}^{2-}$ [(M-2H) $^{2-}$], 286.0365; found, 286.0378.

^1H , ^{13}C and ^{19}F NMR Spectra of Compounds 4 and 5

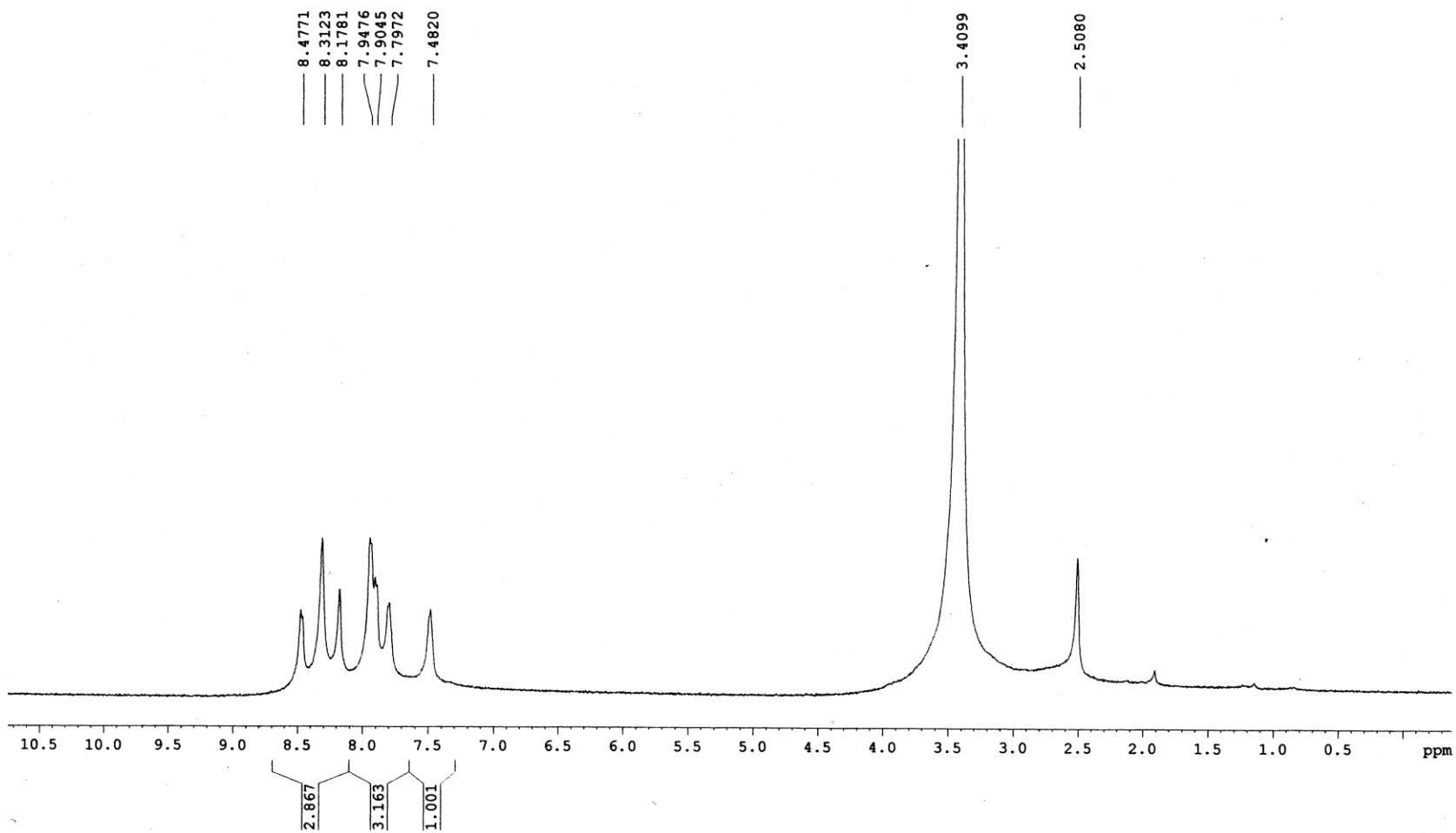


Figure 1. ^1H NMR (500 MHz, DMSO- d_6) spectra of compound 4a

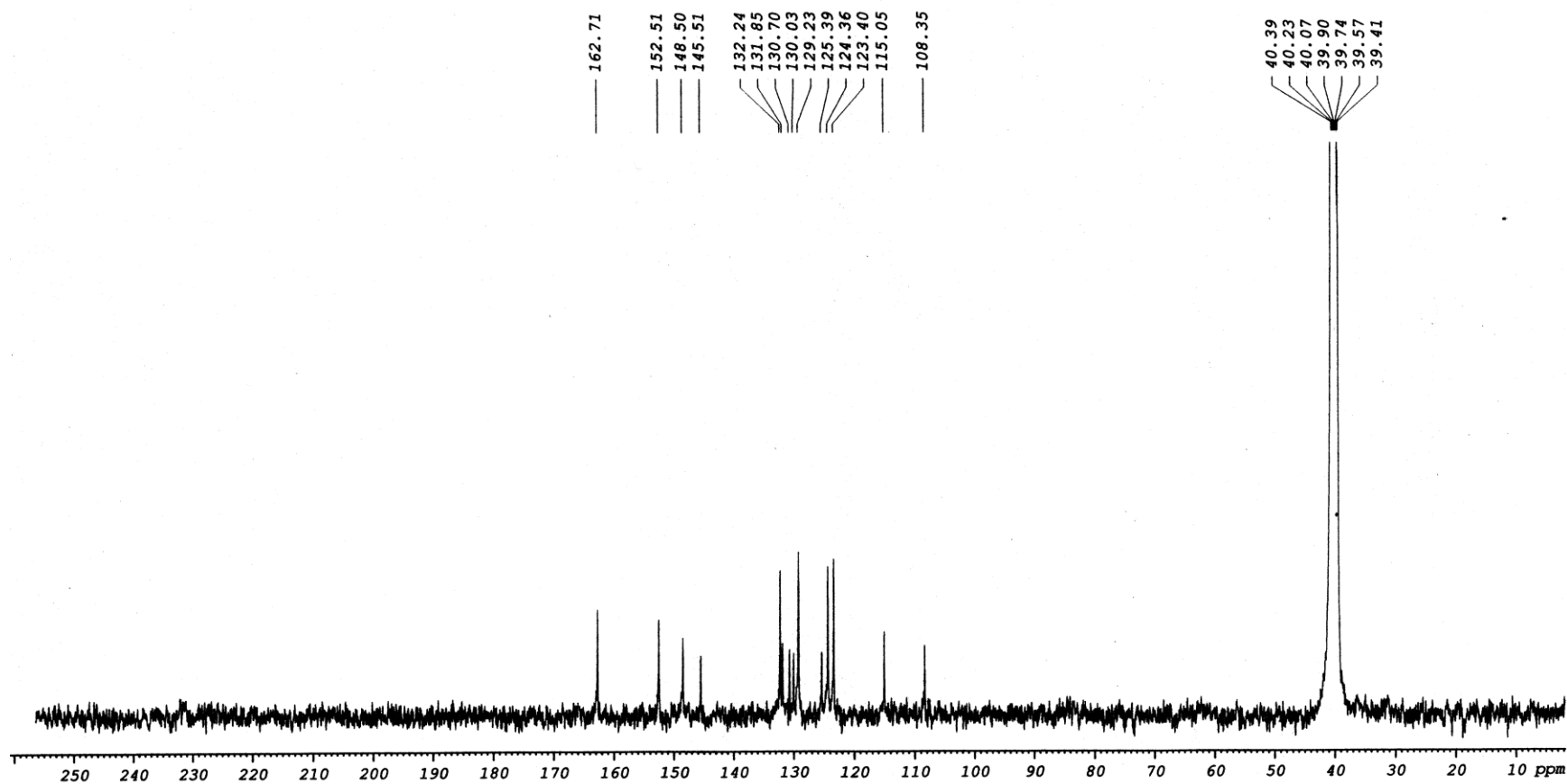


Figure 2. ^{13}C NMR (125 MHz, $\text{DMSO-}d_6$) spectra of compound 4a

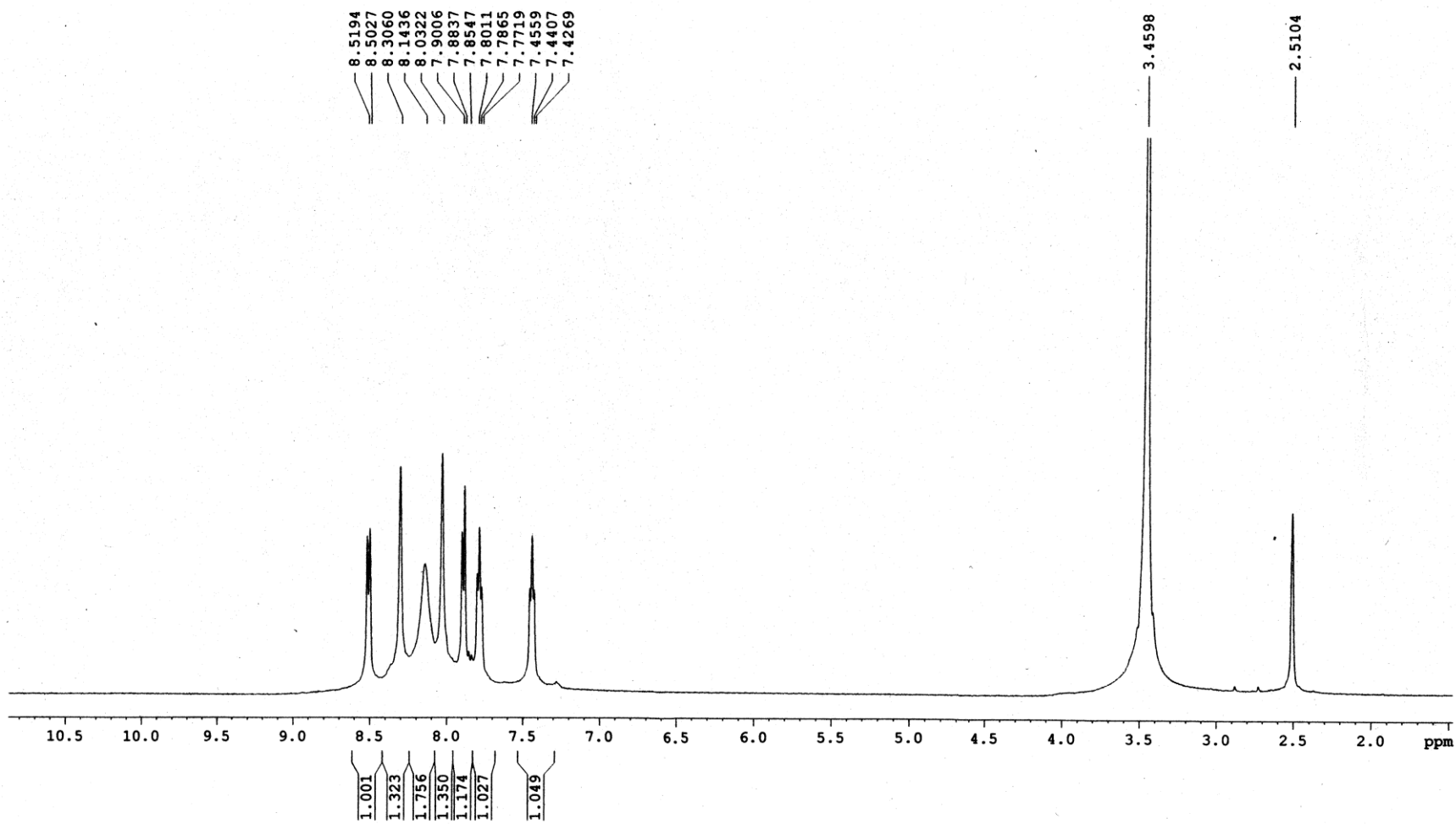


Figure 3. ^1H NMR (500 MHz, $\text{DMSO}-d_6$) spectra of compound **4b**

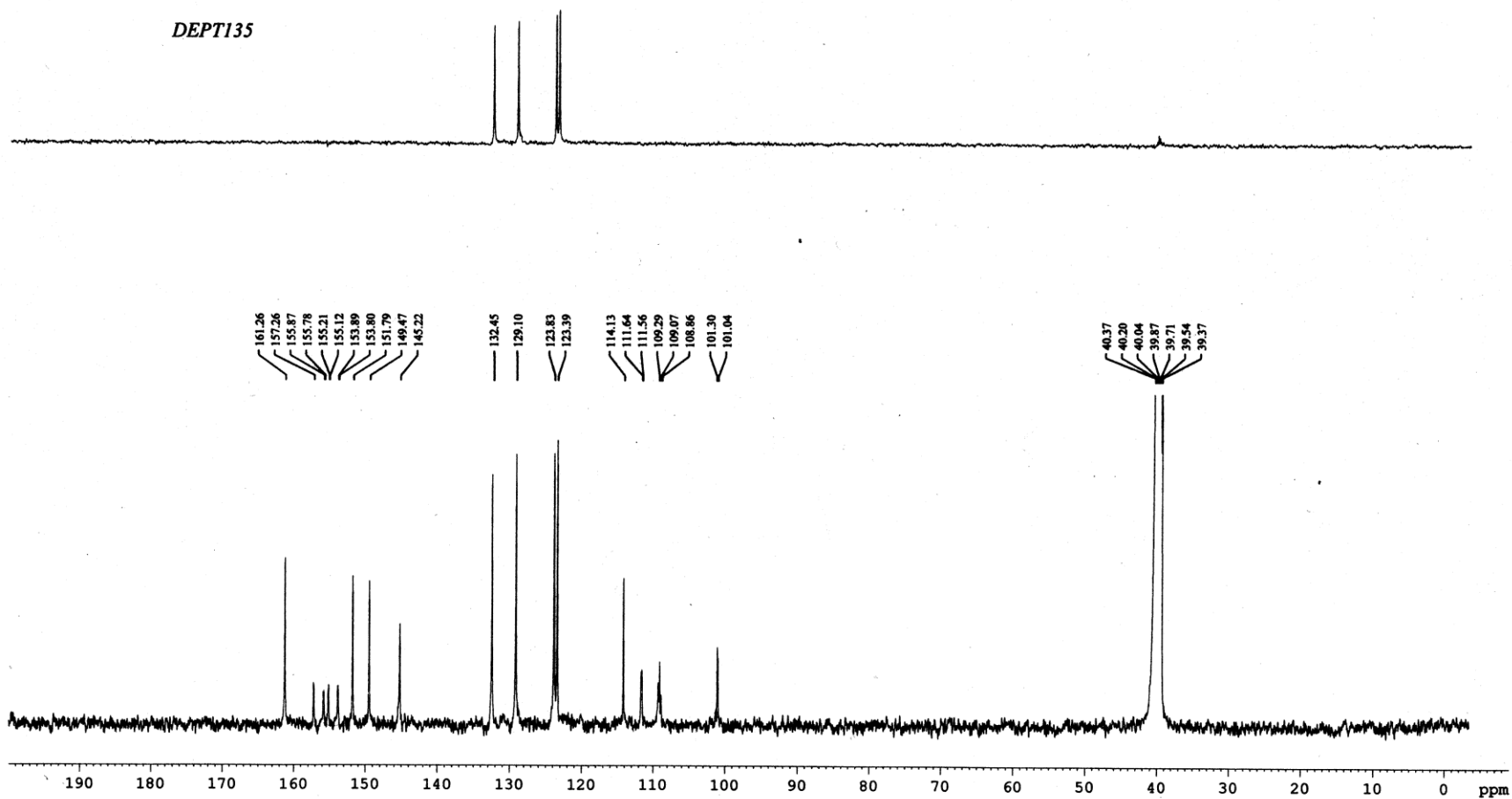


Figure 4. ^{13}C NMR (125 MHz, $\text{DMSO-}d_6$) spectra of compound **4b**

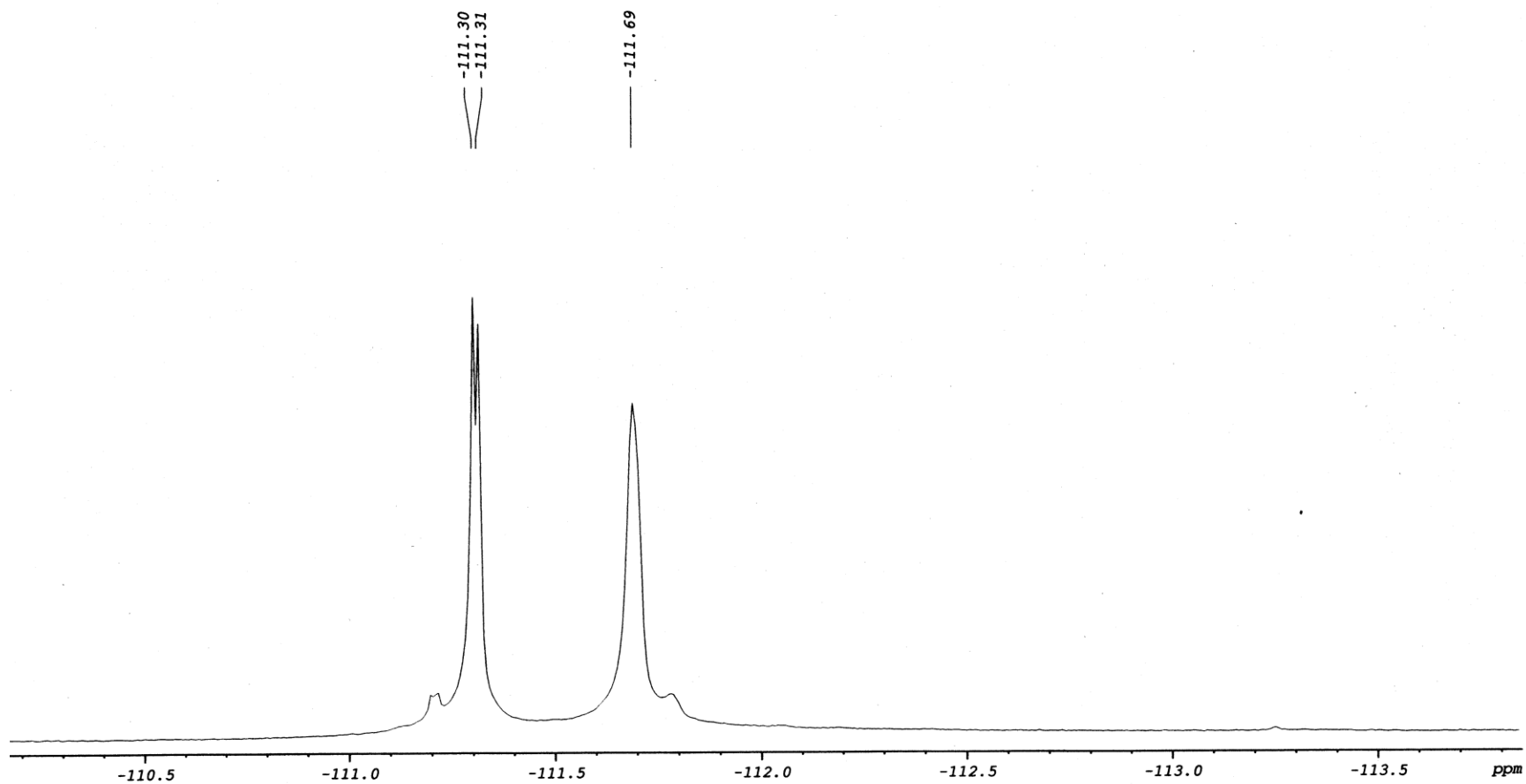


Figure 5. ^{19}F NMR (470 MHz, $\text{DMSO-}d_6$) spectra of compound **4b**

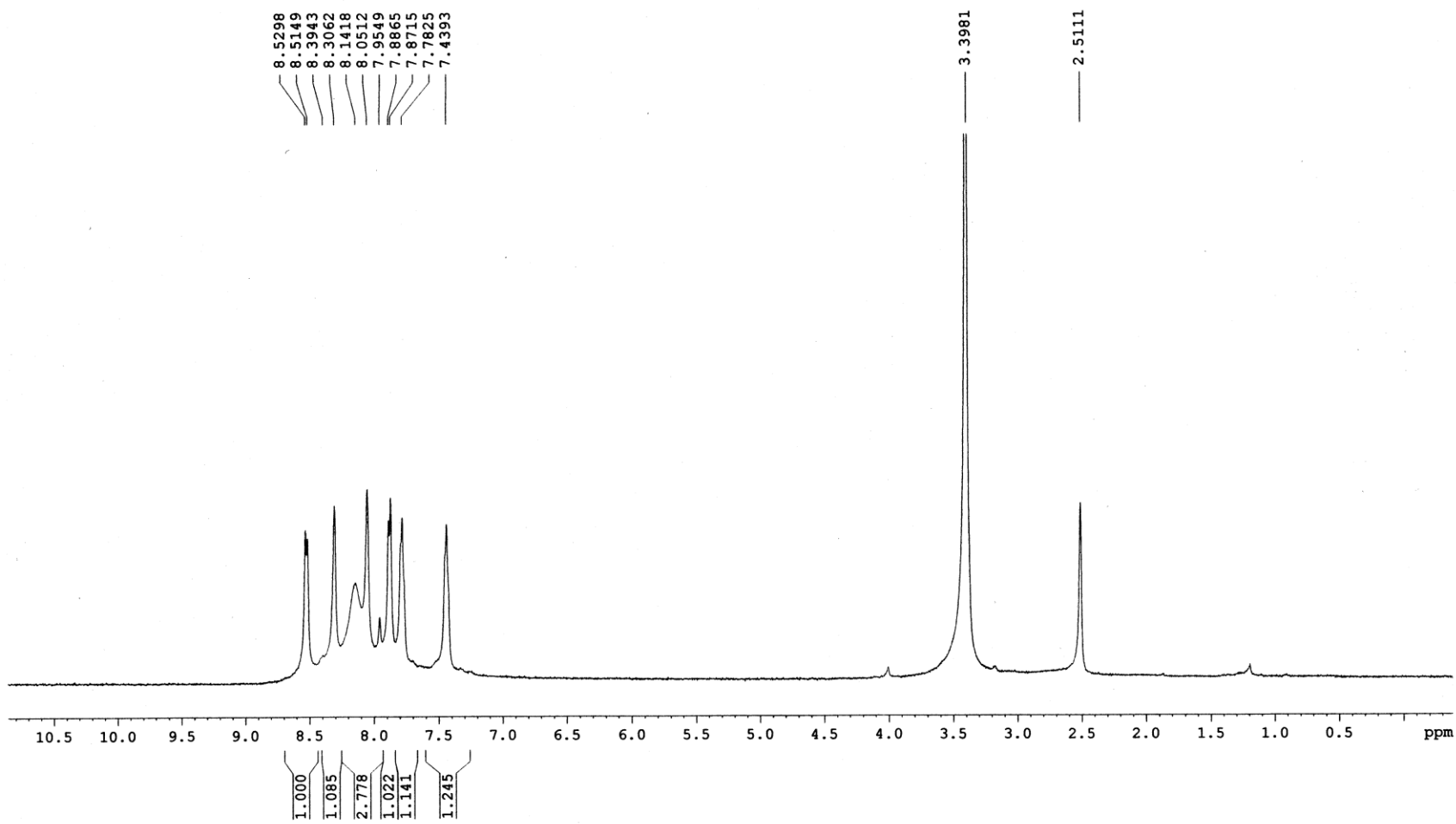


Figure 6. ^1H NMR (500 MHz, $\text{DMSO-}d_6$) spectra of compound **4c**

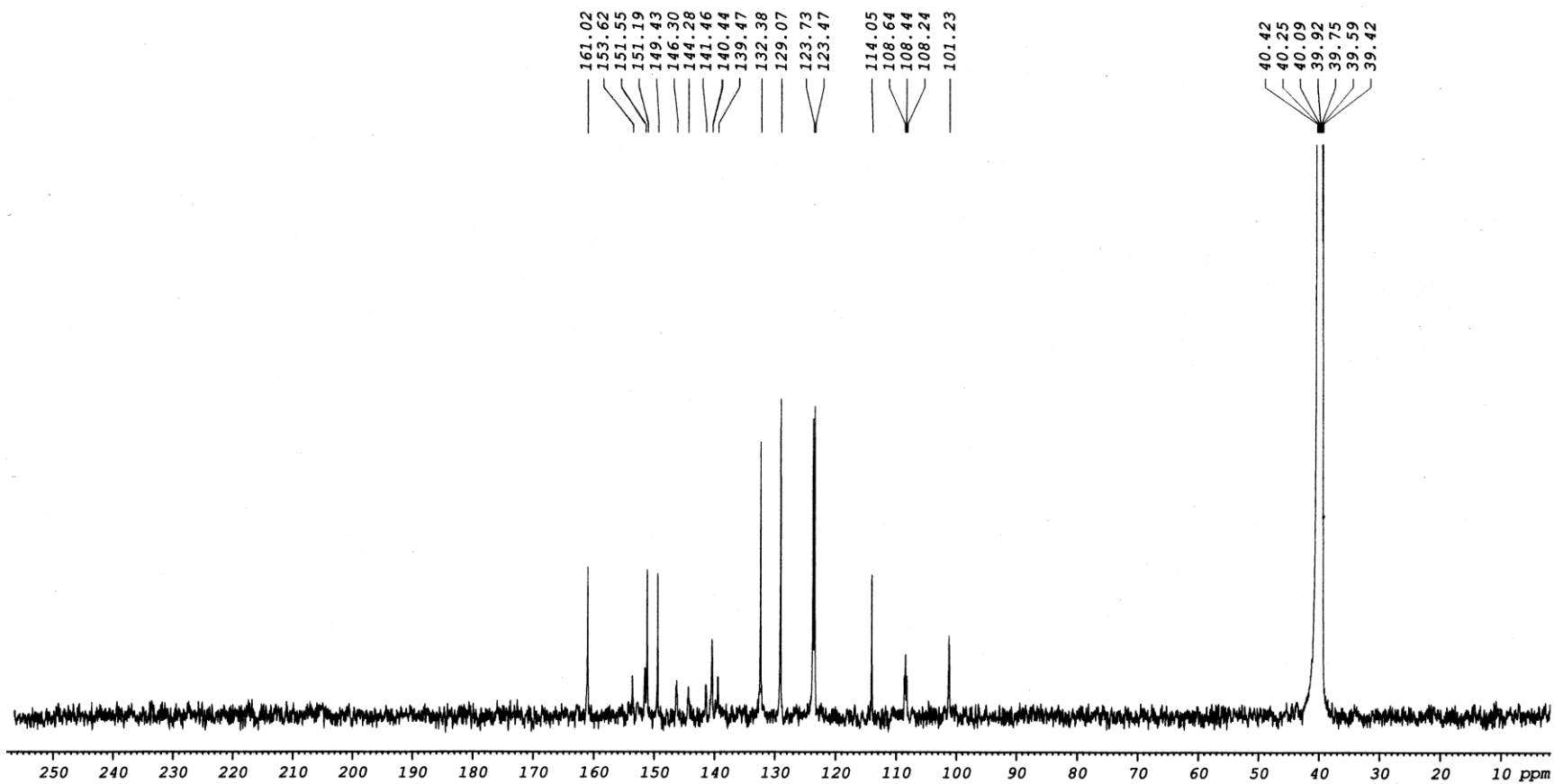


Figure 7. ^{13}C NMR (125 MHz, $\text{DMSO-}d_6$) spectra of compound **4c**

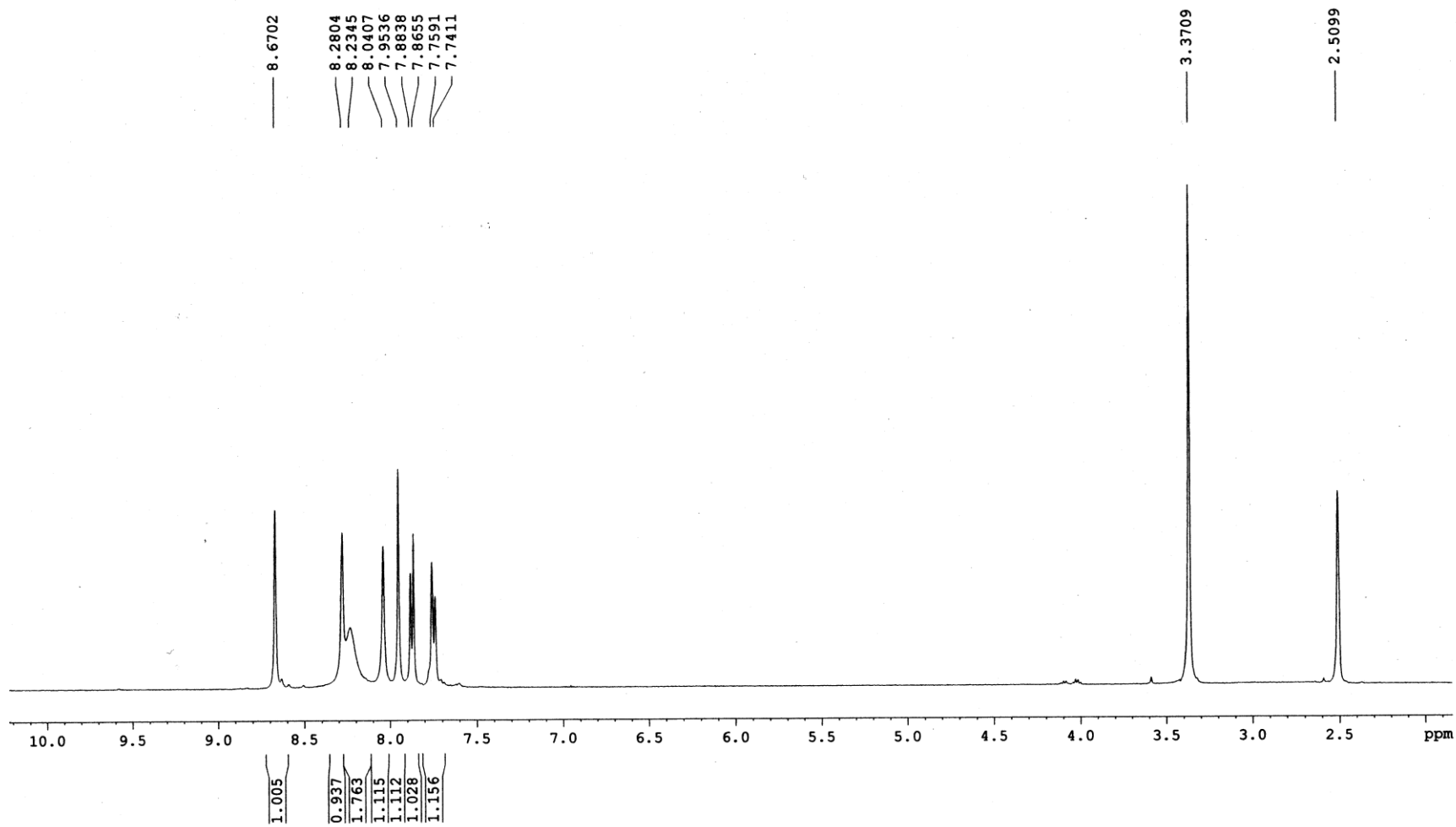


Figure 8. ^1H NMR (500 MHz, $\text{DMSO-}d_6$) spectra of compound 4e

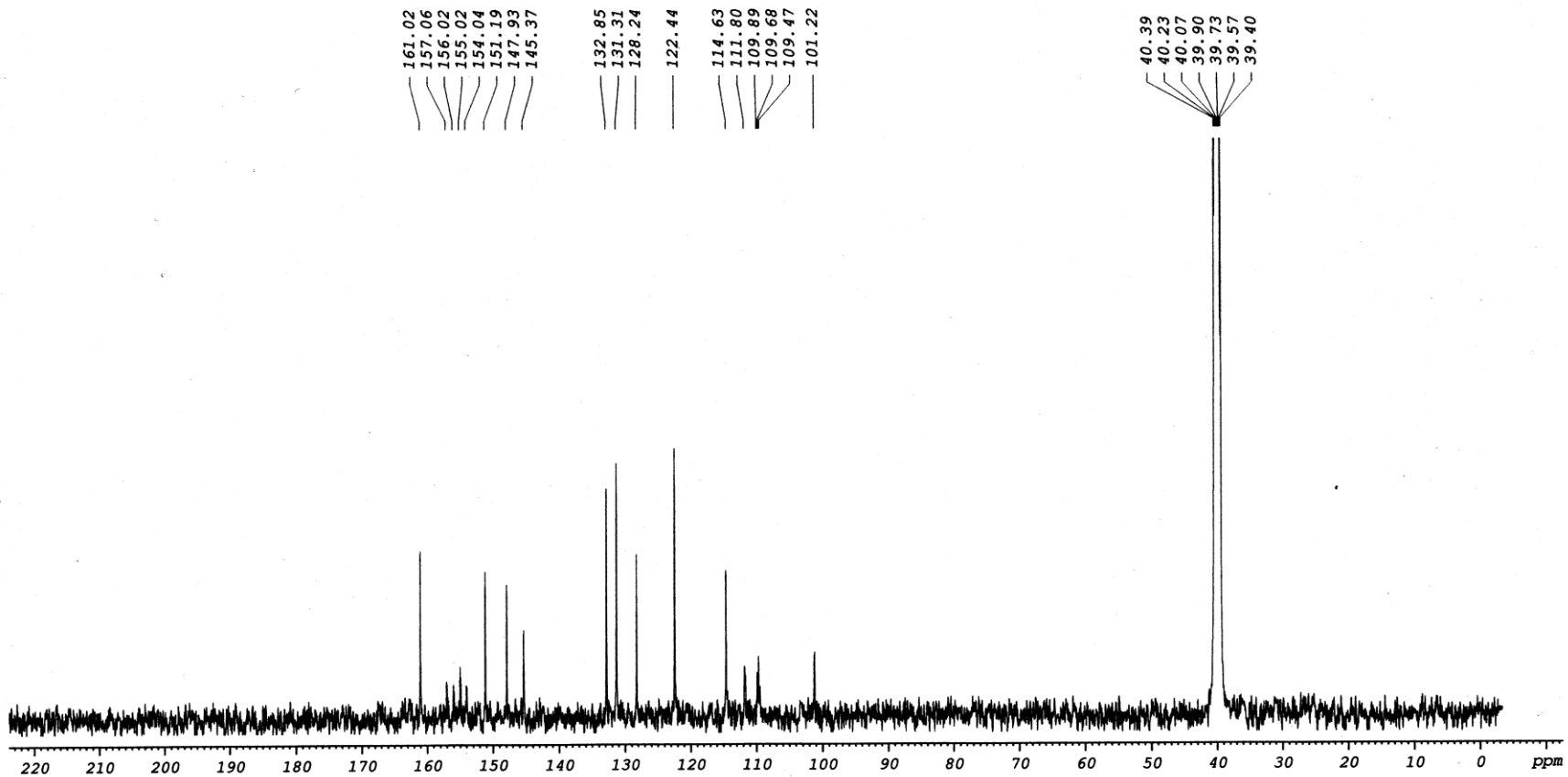


Figure 9. ^{13}C NMR (125 MHz, $\text{DMSO}-d_6$) spectra of compound 4e

YUNNAN UNIVER. AV. DRX500
huangchao hc6g in DMSO

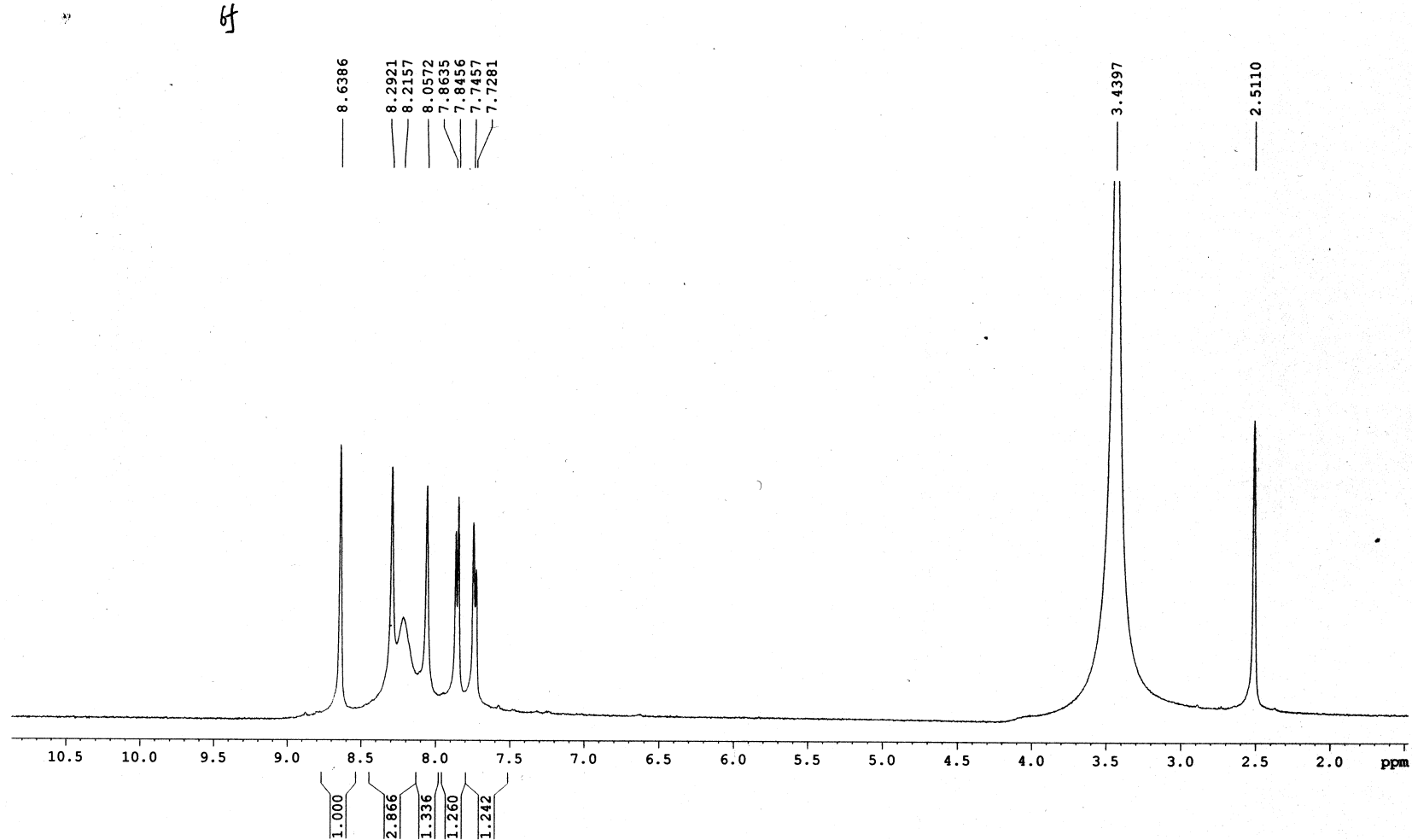


Figure 10. ^1H NMR (500 MHz, $\text{DMSO}-d_6$) spectra of compound **4f**

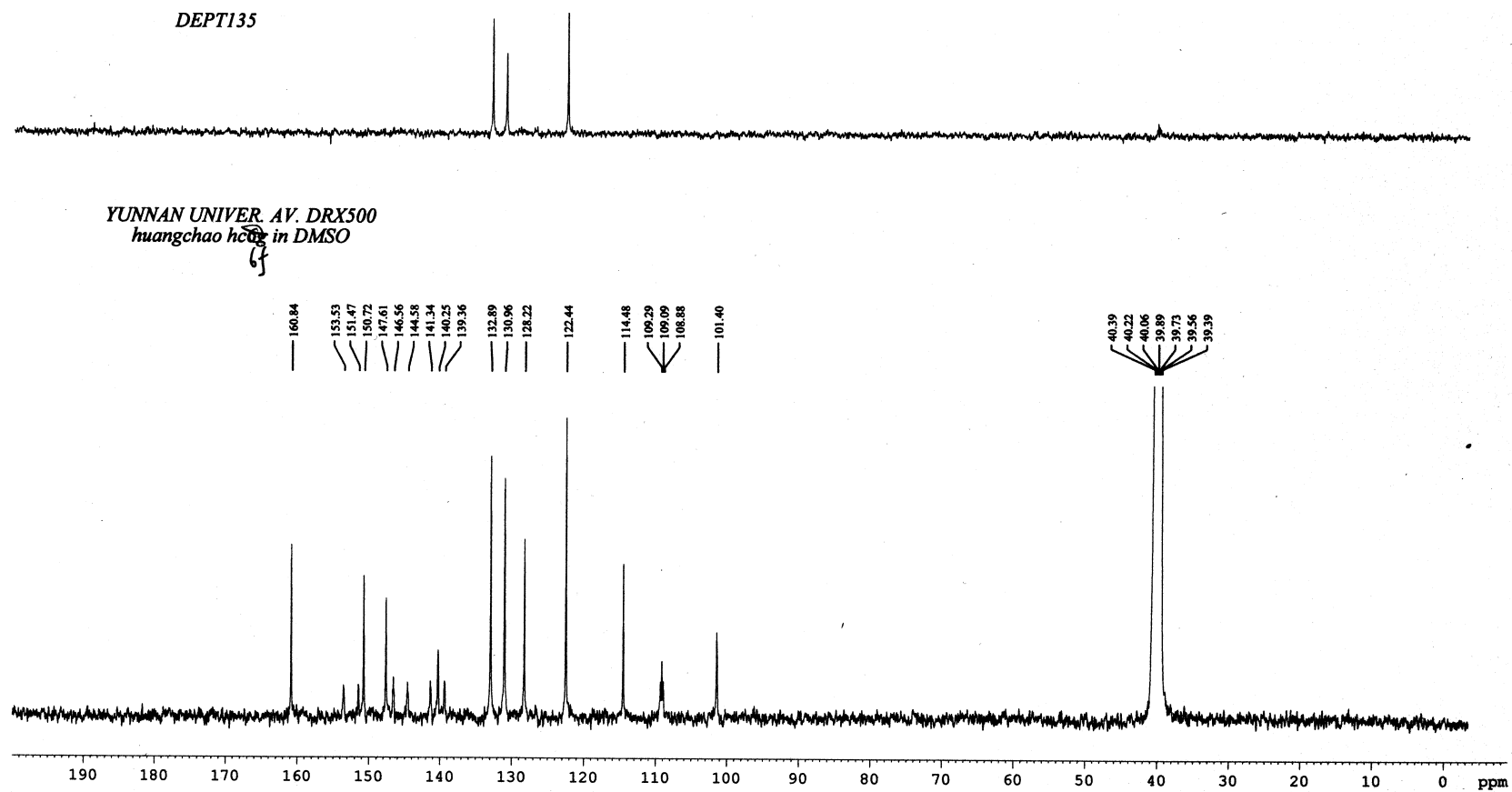


Figure 11. ^{13}C NMR (125 MHz, $\text{DMSO-}d_6$) spectra of compound 4f

YUNNAN UNIVER. AV. DRX500
Huangchao hcs in DMSO
19F decoupling 4f

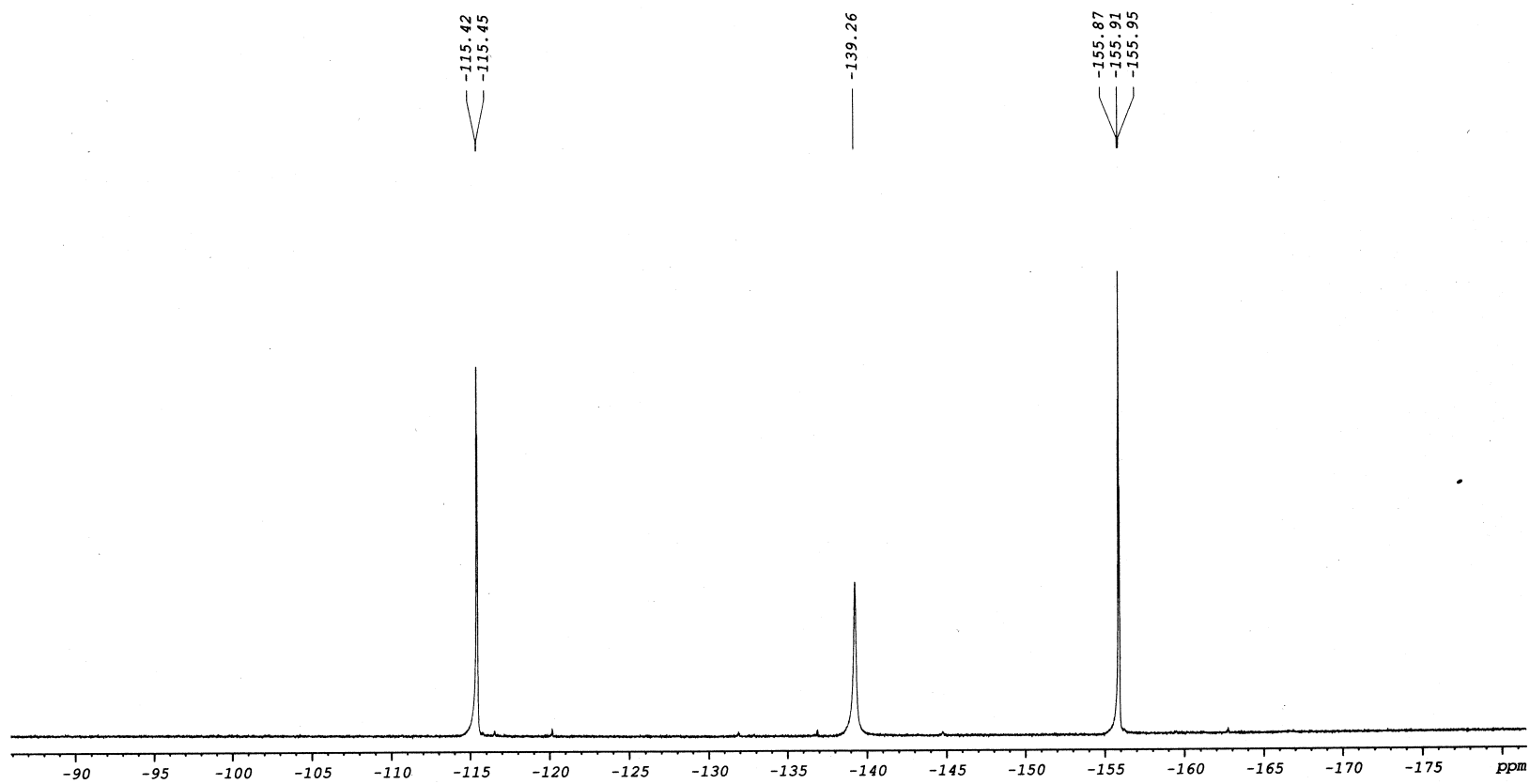


Figure 12. ^{19}F NMR (470 MHz, $\text{DMSO-}d_6$) spectra of compound 4f

YUNNAN UNIVER. AV. DRX500
huangchao hch6g in DMF
10121002

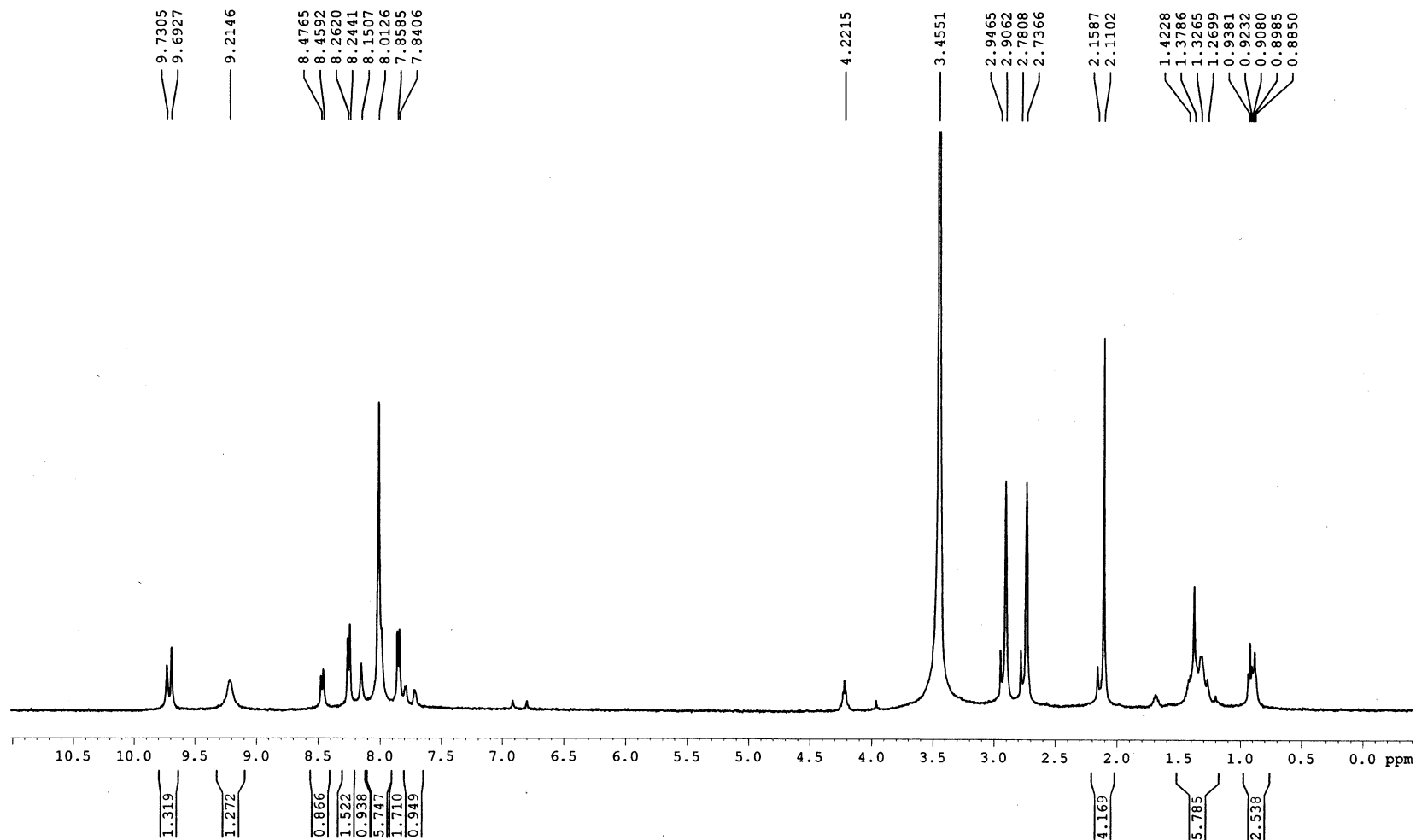


Figure 13. ^1H NMR (500 MHz, $\text{DMF-}d_6$) spectra of compound 4g

YUNNAN UNIVER. AV. DRX500
huangchao h₂c₂ in DMSO

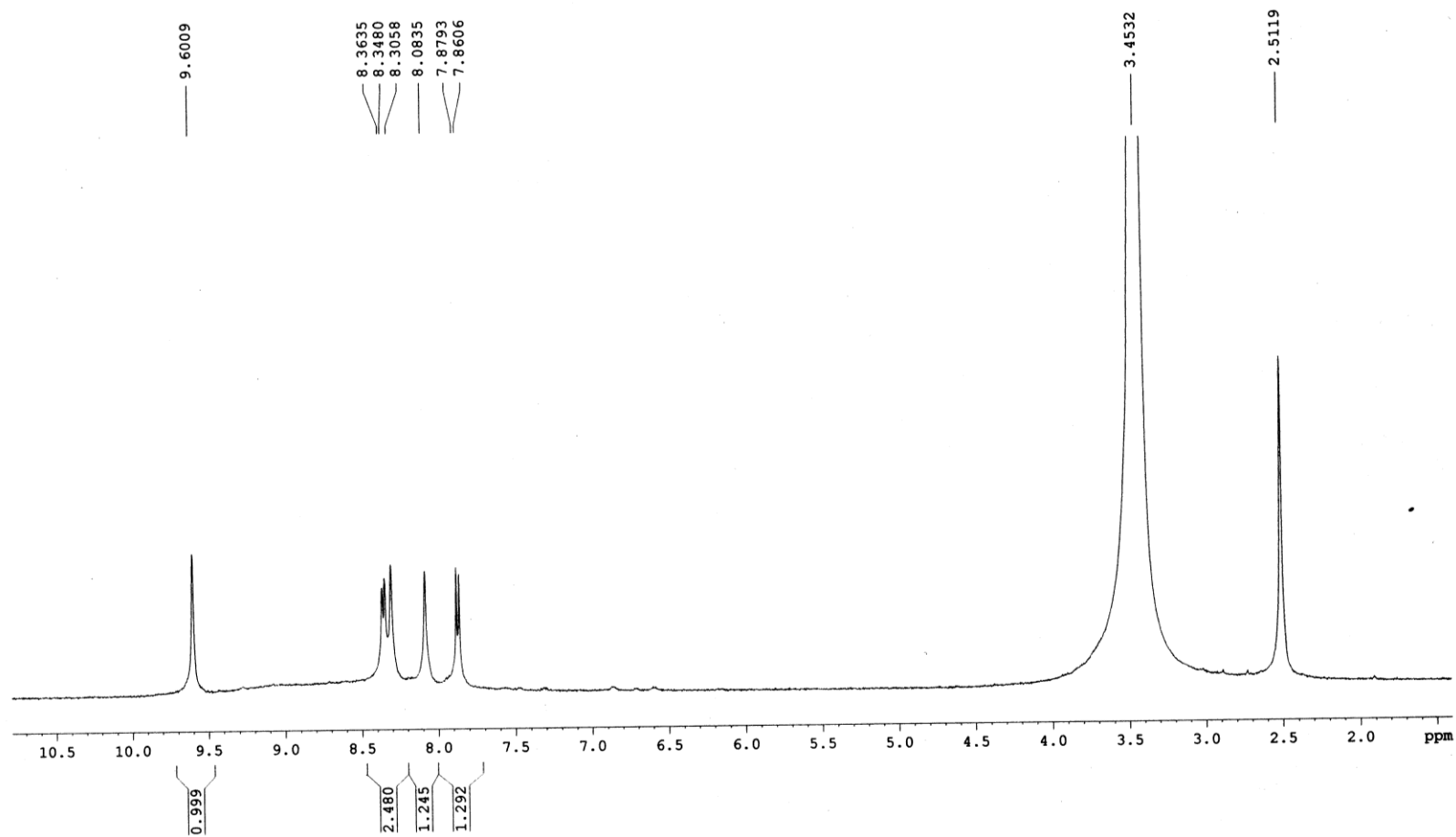


Figure 14. ¹H NMR (500 MHz, DMSO-*d*₆) spectra of compound 4h

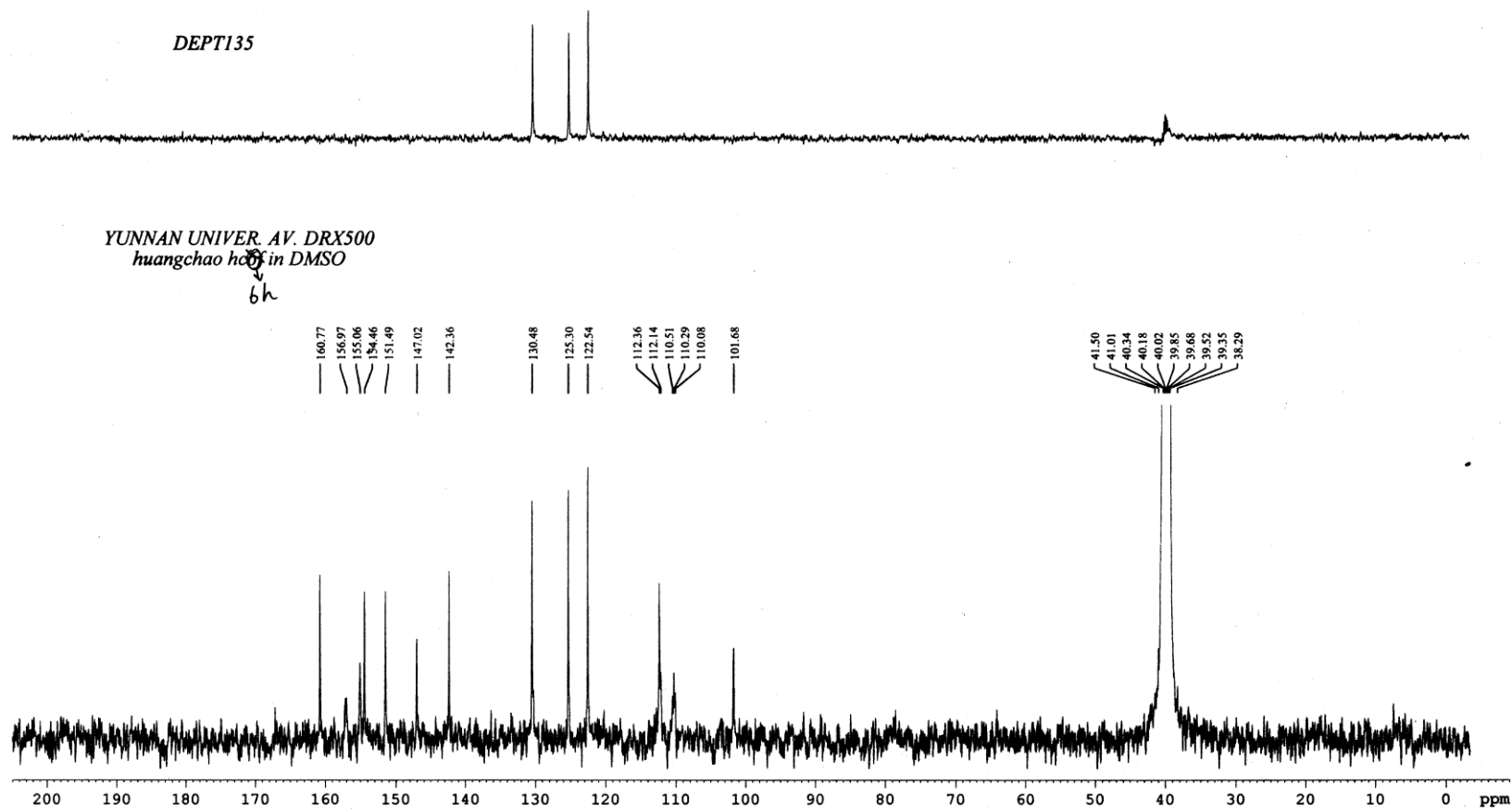


Figure 15. ^{13}C NMR (125 MHz, $\text{DMSO-}d_6$) spectra of compound 4h

YUNNAN UNIVER. AV. DRX500
huangchao hc6i in DMF
11011803

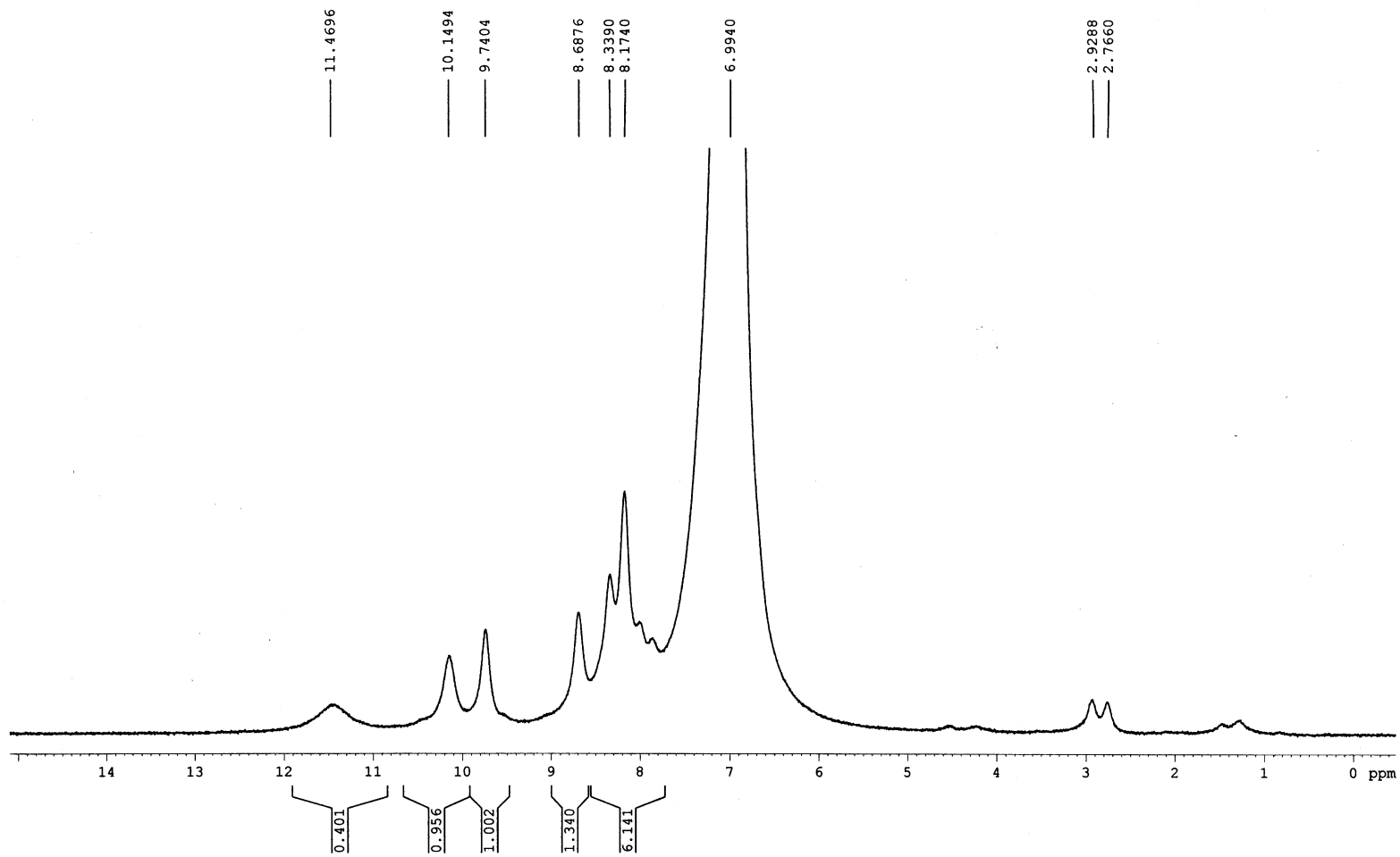


Figure 16. ^1H NMR (500 MHz, $\text{DMF-}d_6$) spectra of compound **4i**

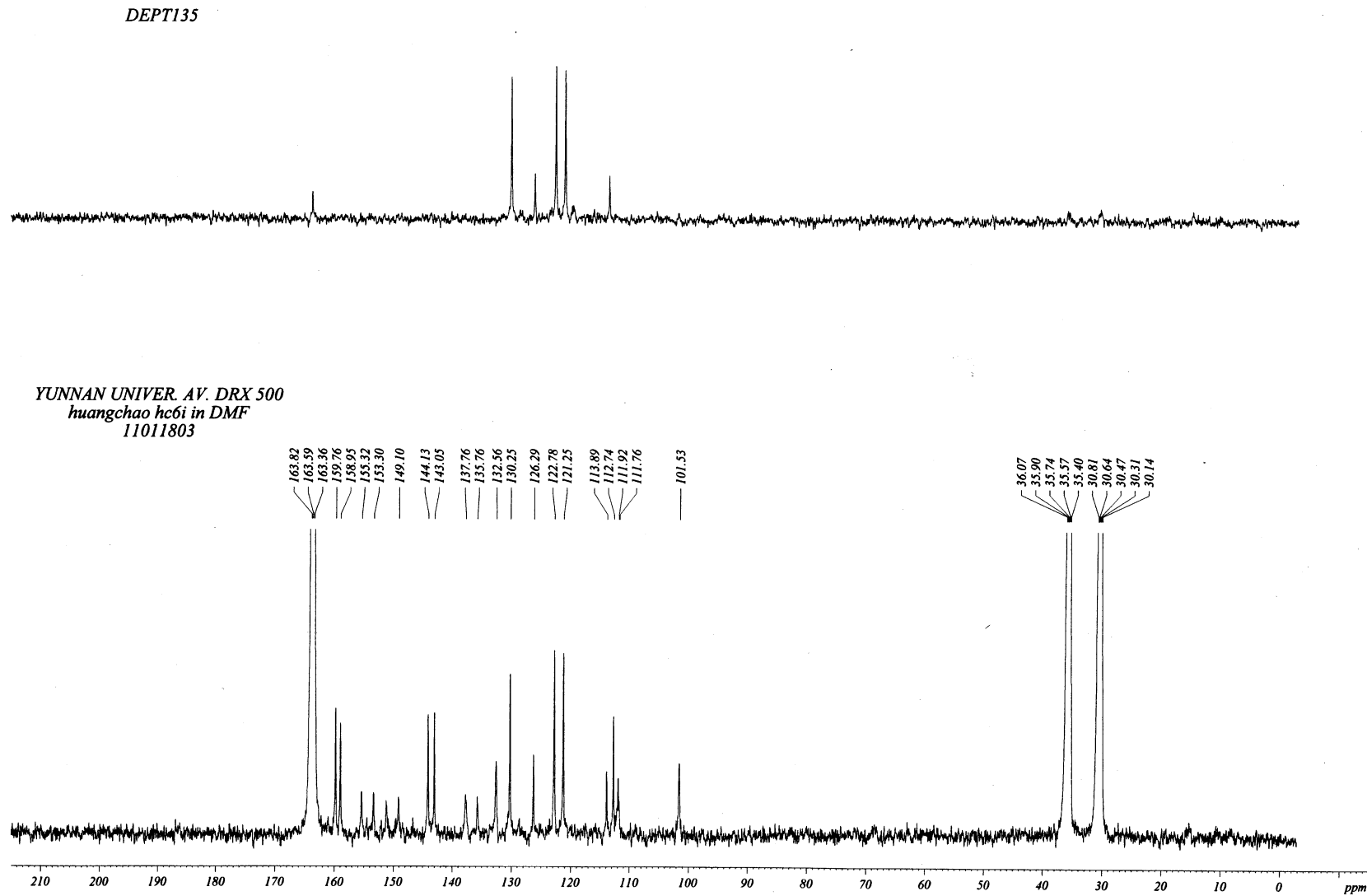


Figure 17. ^{13}C NMR (125 MHz, DMF-d_6) spectra of compound **4i**

YUNNAN UNIVER. AV. DRX500
huangchao hc6i in DMF
19F decoupling 11011803

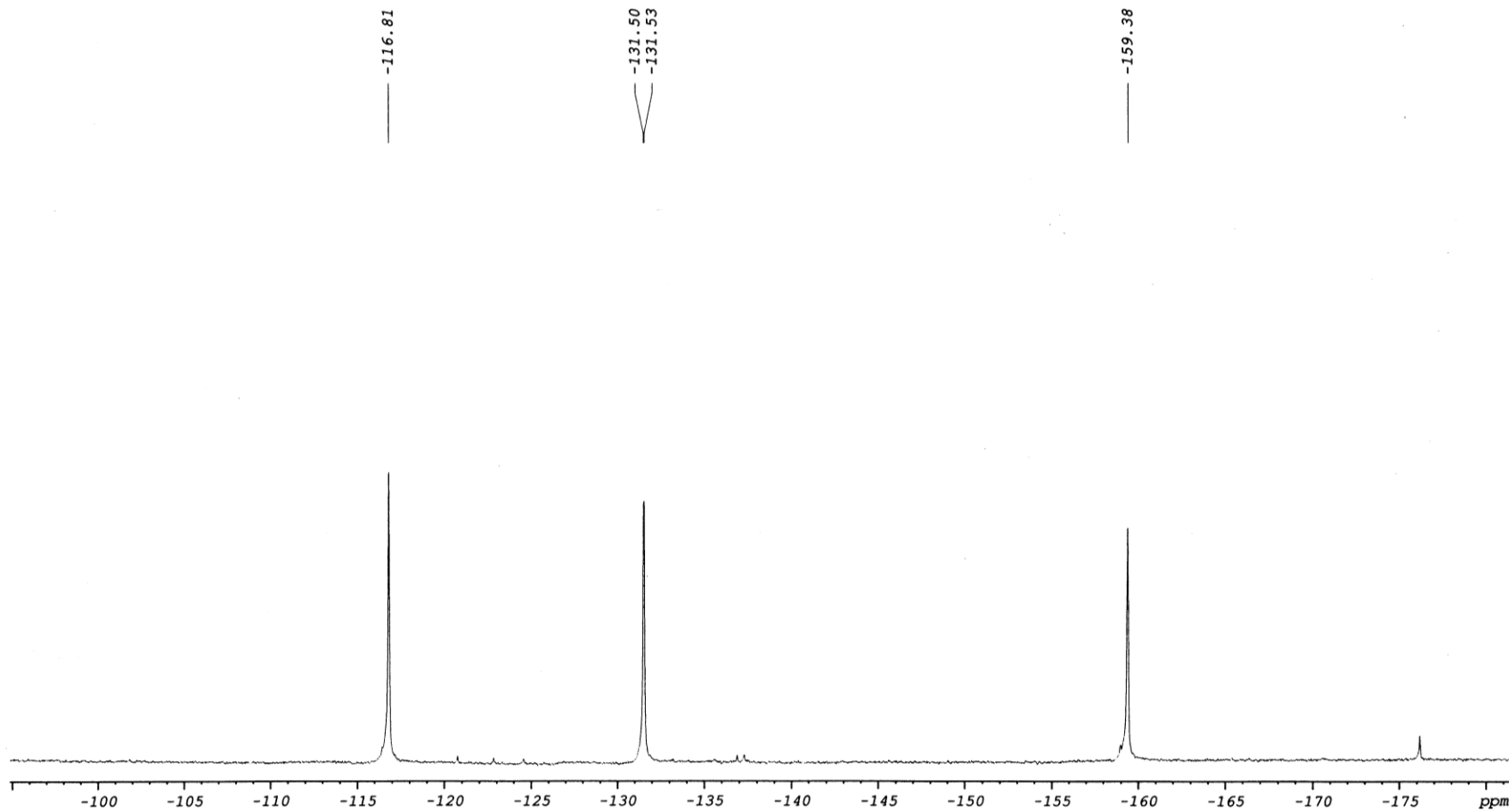


Figure 18. ^{19}F NMR (470 MHz, DMF-d_6) spectra of compound **4i**

YUNNAN UNIVER. AV. DRX500
huangchao hc6j in DMSO
10111601

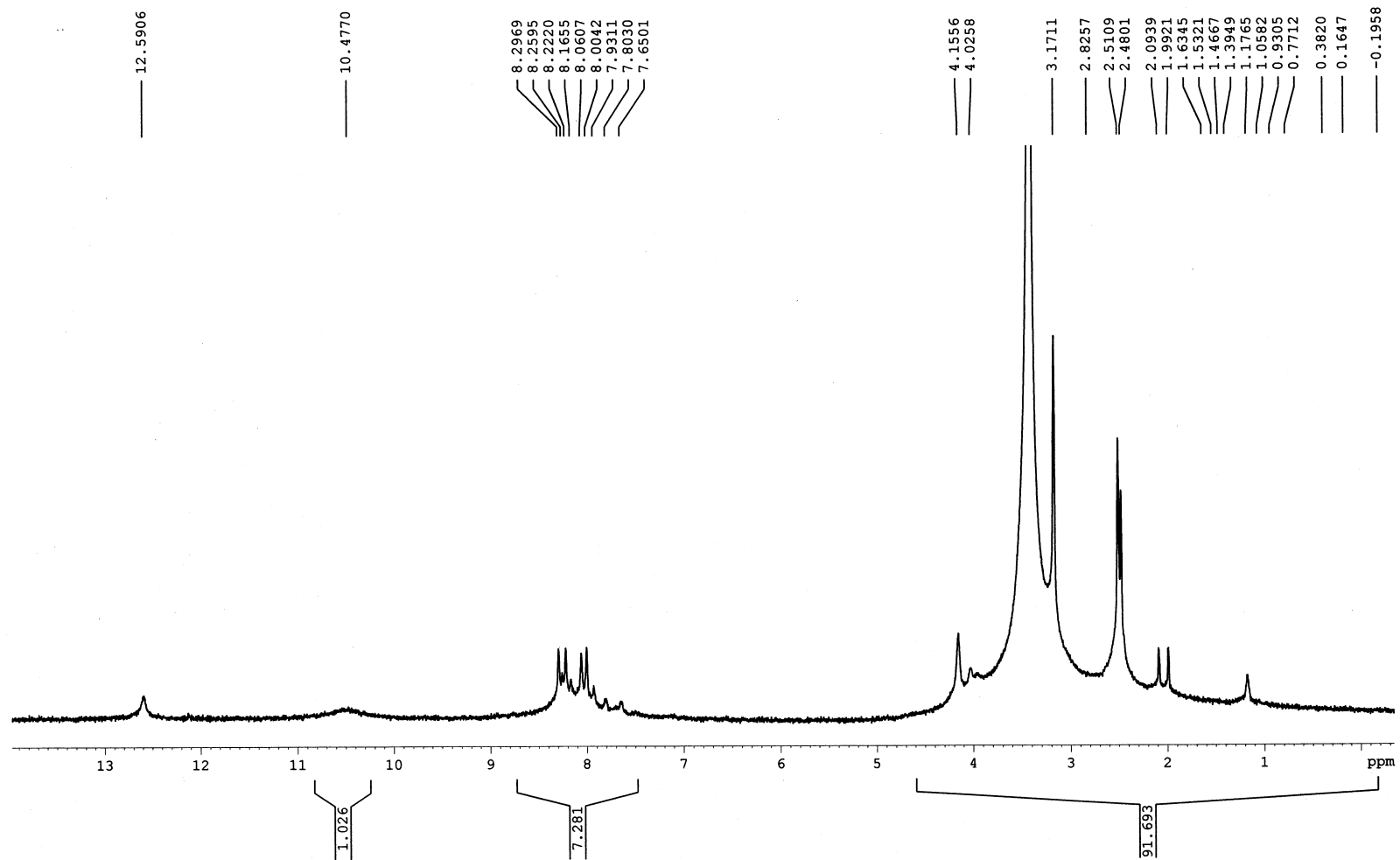


Figure 19. ^1H NMR (500 MHz, $\text{DMSO-}d_6$) spectra of compound **4j**

YUNNAN UNIVER. AV. DRX500 ?
huangchao hch6k in DMF
10112904

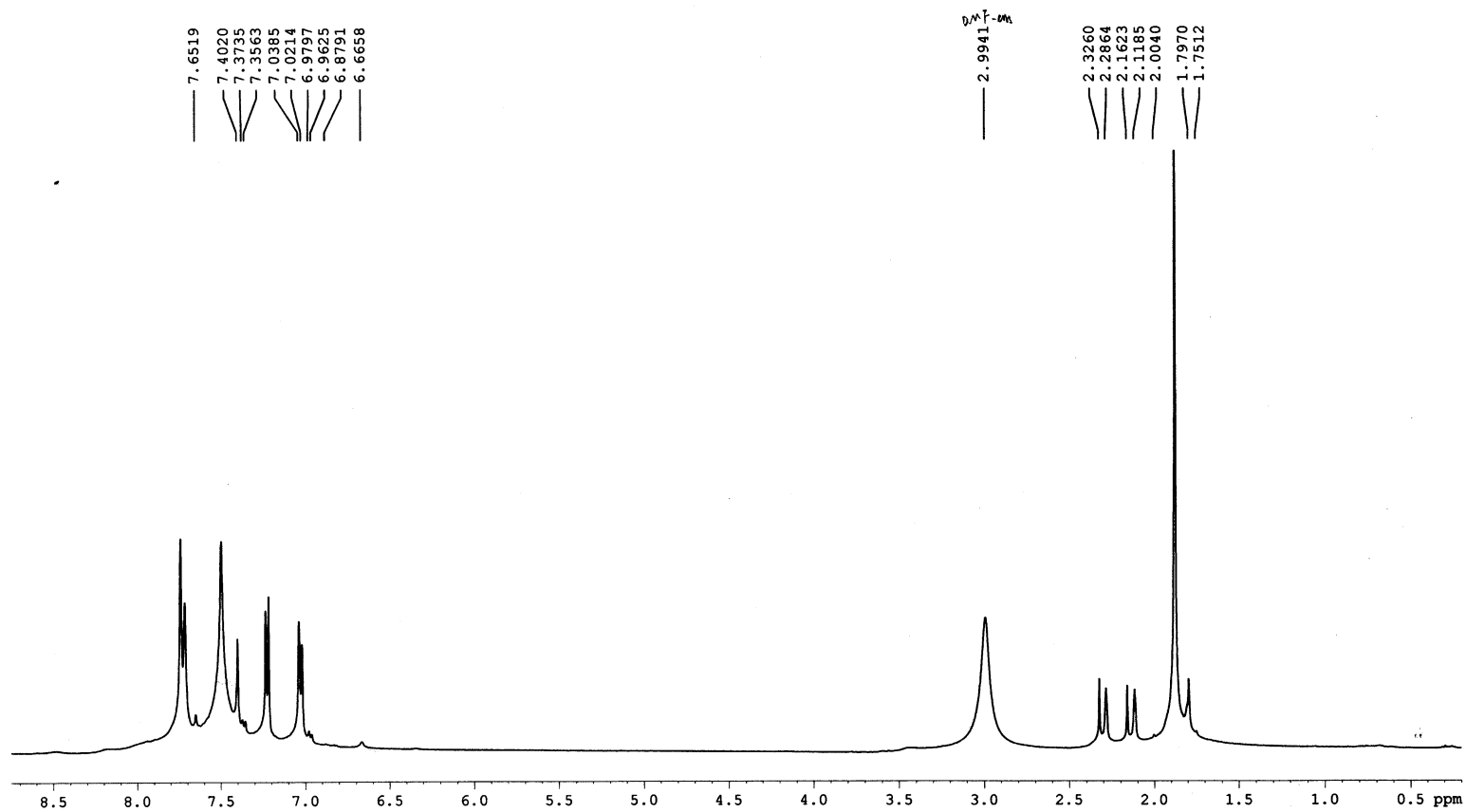


Figure 20. ^1H NMR (500 MHz, DMF- d_6) spectra of compound 4k

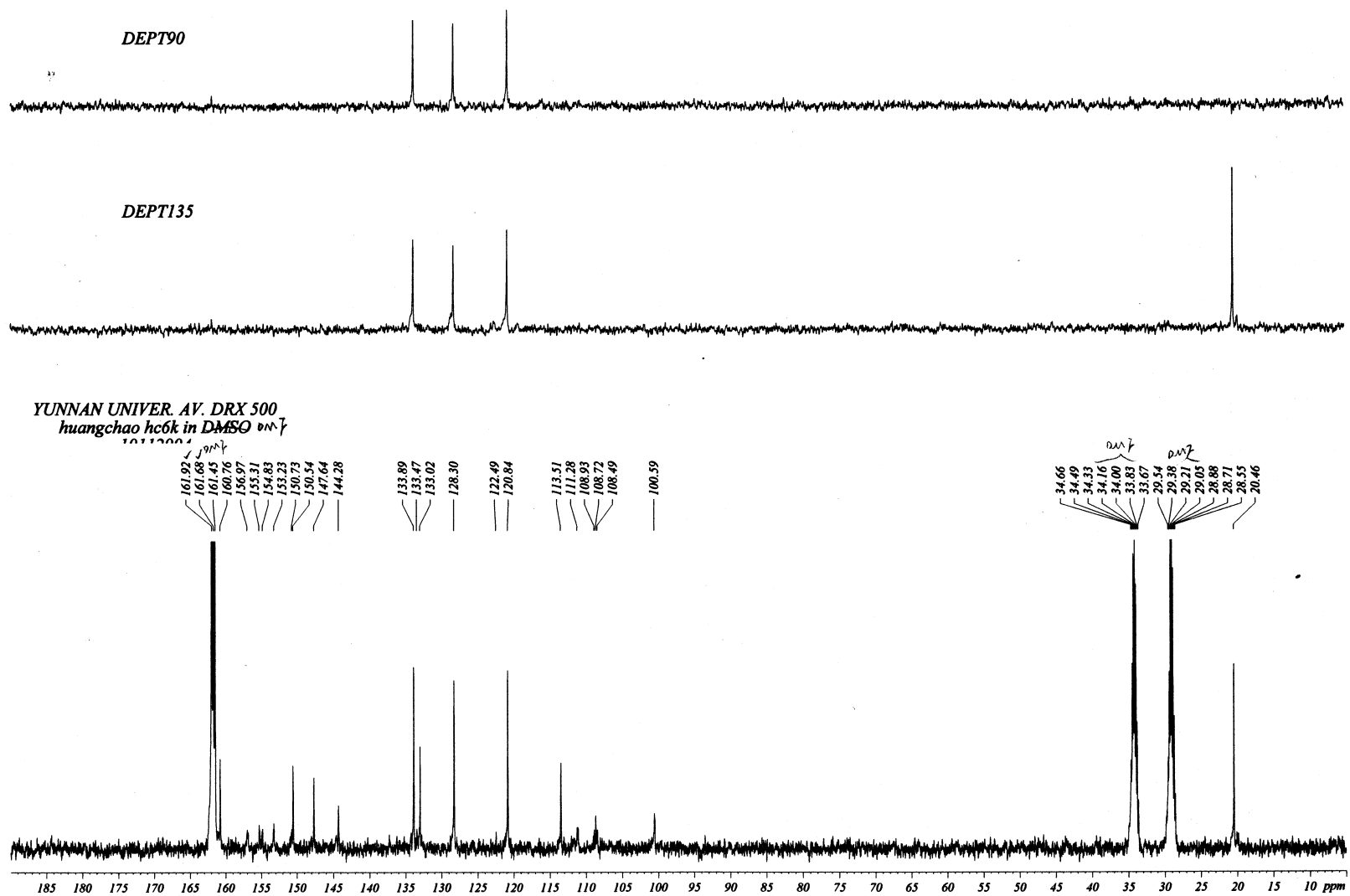


Figure 21. ^{13}C NMR (125 MHz, $\text{DMF}-d_6$) spectra of compound 4k

YUNNAN UNIVER. AV. DRX500
huangchao hc6k in DMF
19F decoupling

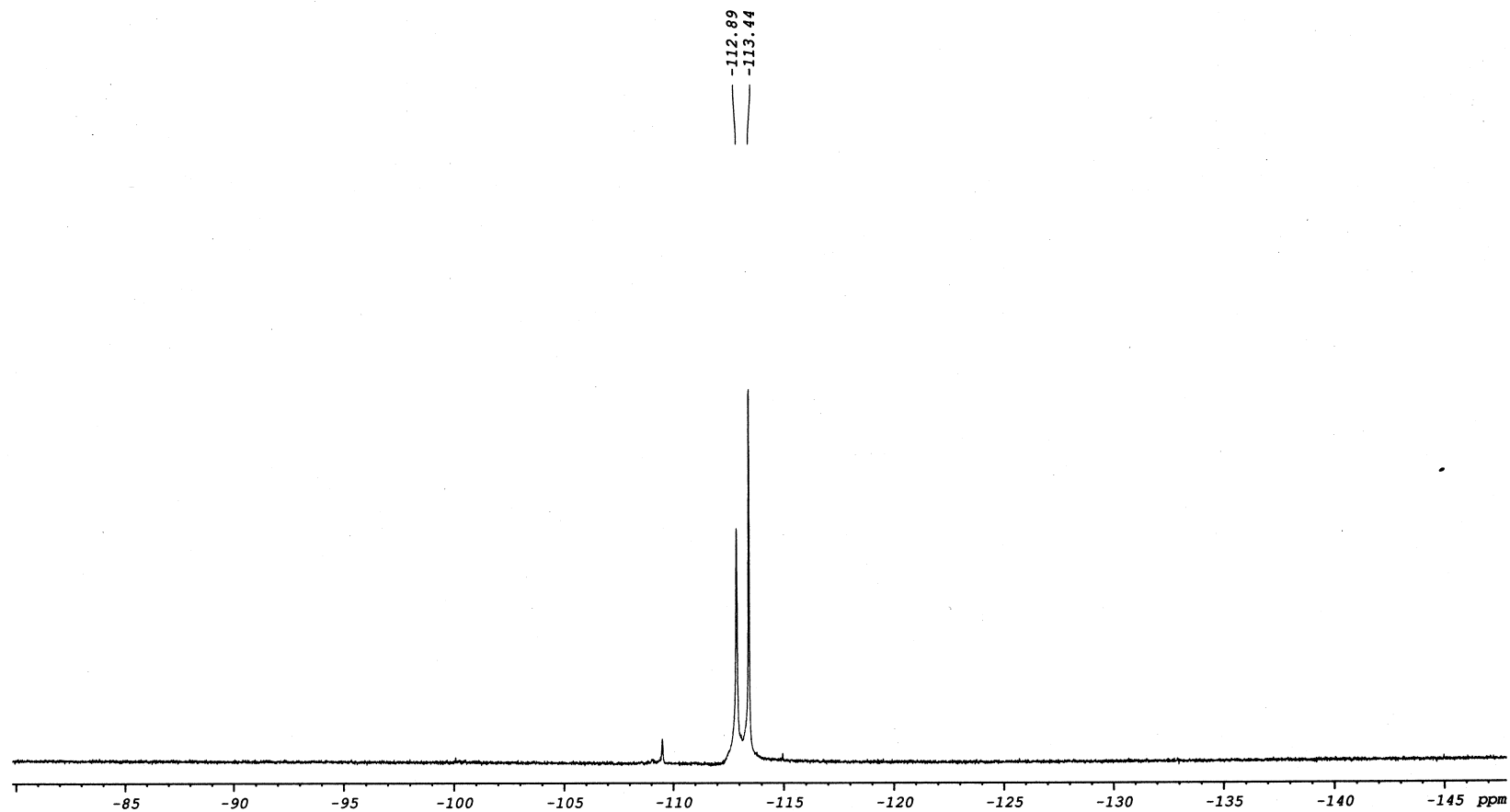


Figure 22. ^{19}F NMR (470 MHz, $\text{DMF-}d_6$) spectra of compound 4k

YUNNAN UNIVER. AV. DRX500
huangchao hch61 in DMF
10121001

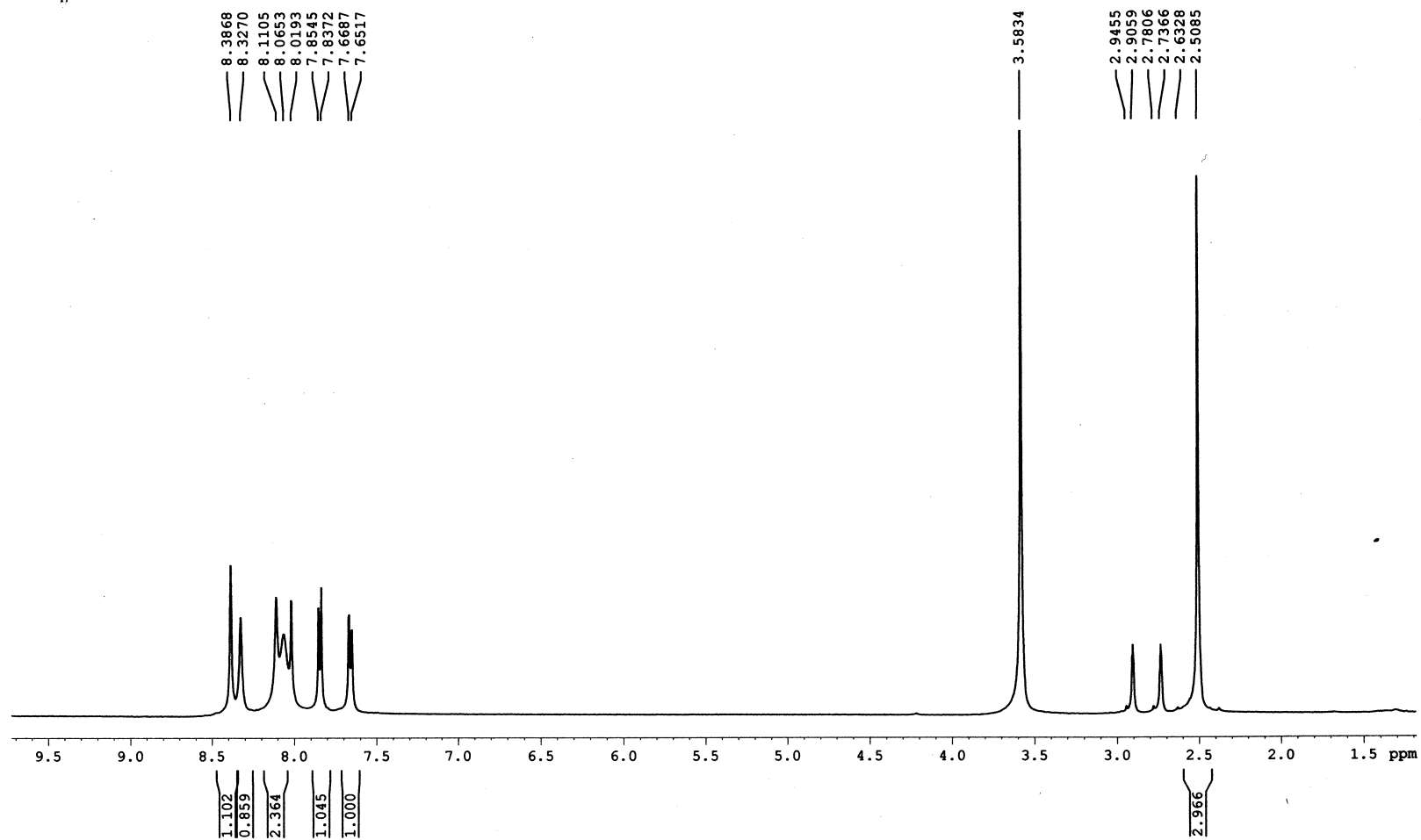


Figure 23. ^1H NMR (500 MHz, $\text{DMF-}d_6$) spectra of compound 4l

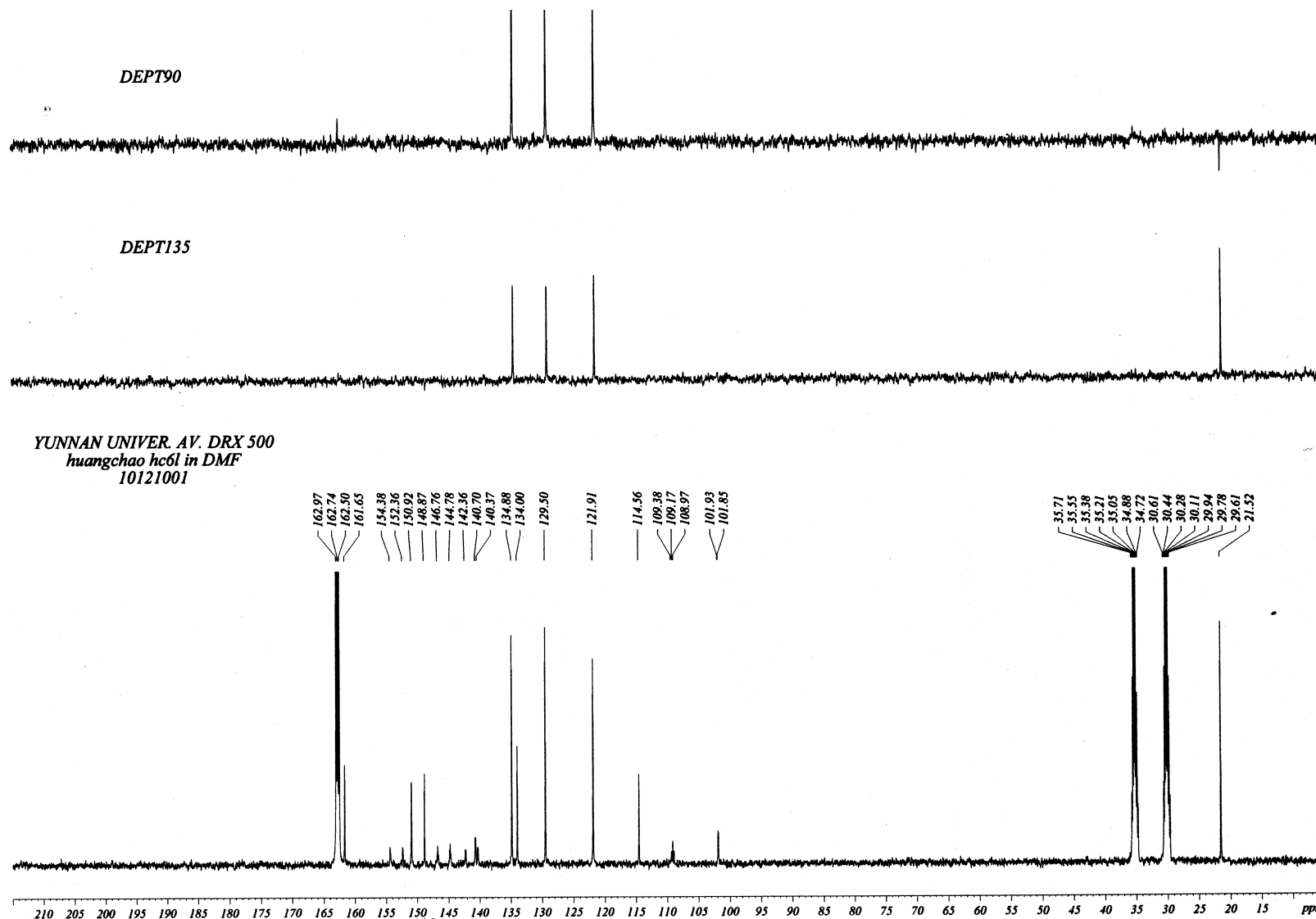


Figure 24. ^{13}C NMR (125 MHz, DMF-d_6) spectra of compound **4I**

YUNNAN UNIVER. AV. DRX500
huangchao hc61 in DMF
 ^{19}F decoupling

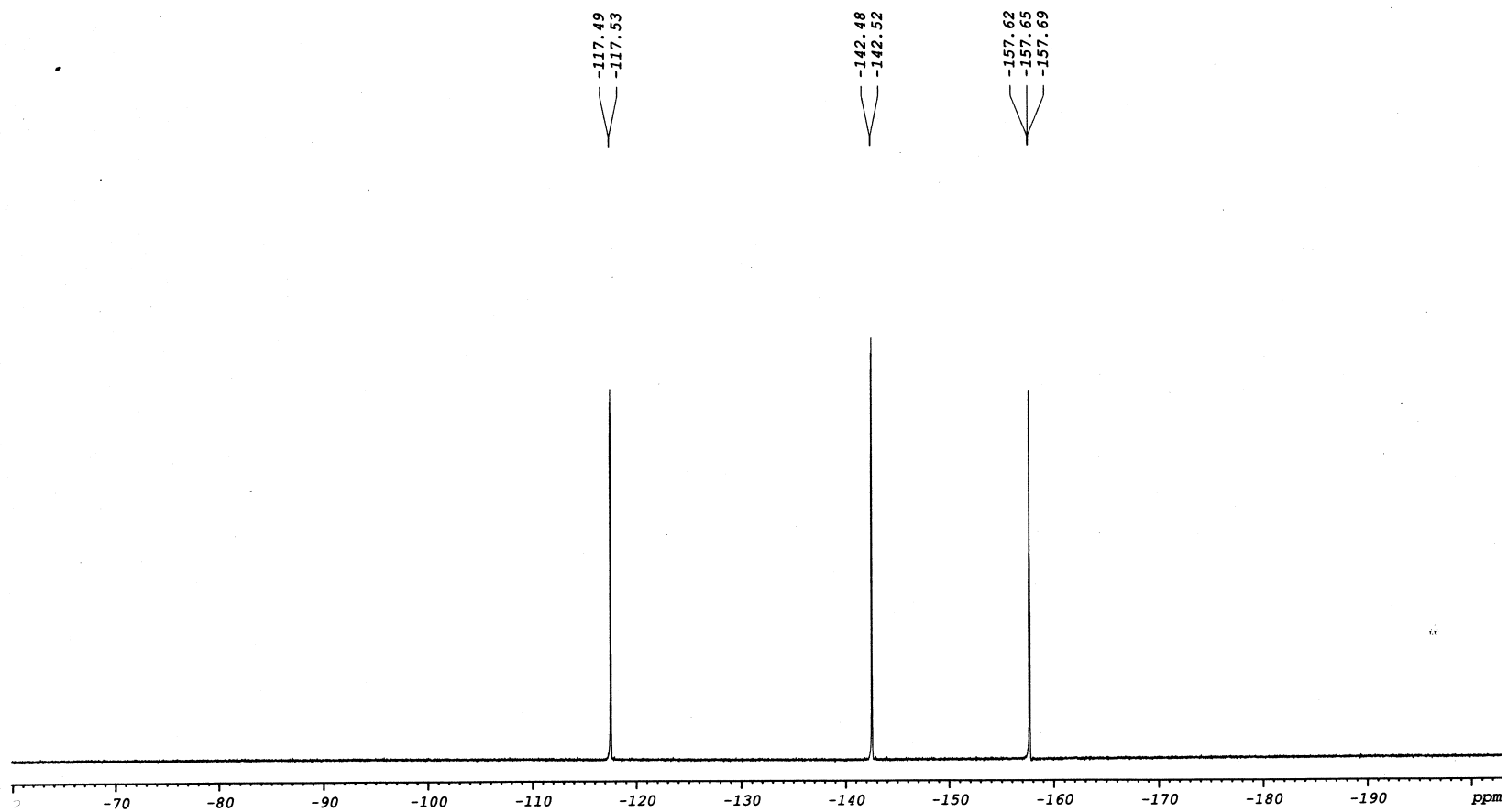


Figure 25. ^{19}F NMR (470 MHz, $\text{DMF-}d_6$) spectra of compound **41**

YUNNAN UNIVER. AV. DRX500
huangchao hc6m in DMF
11011804

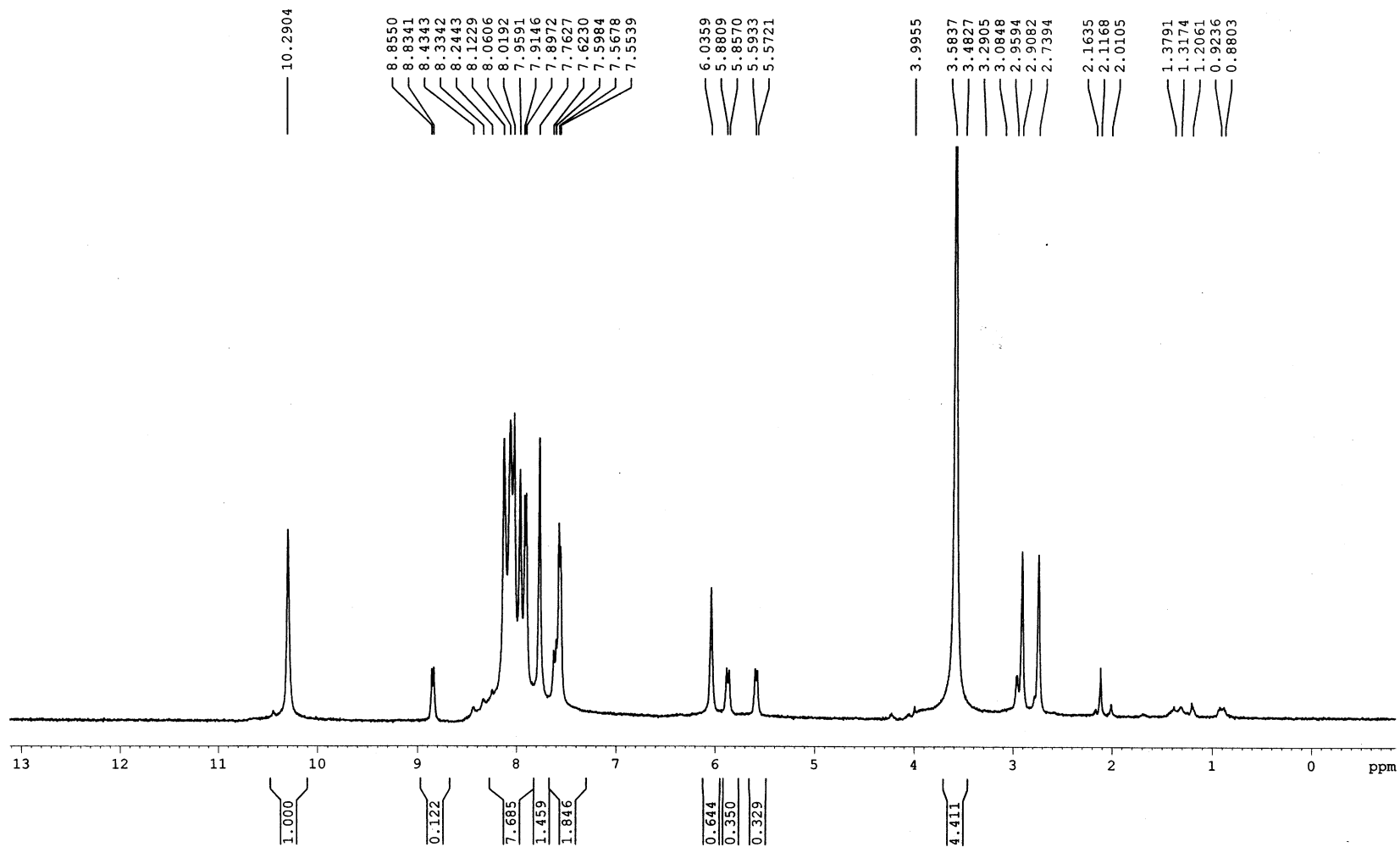
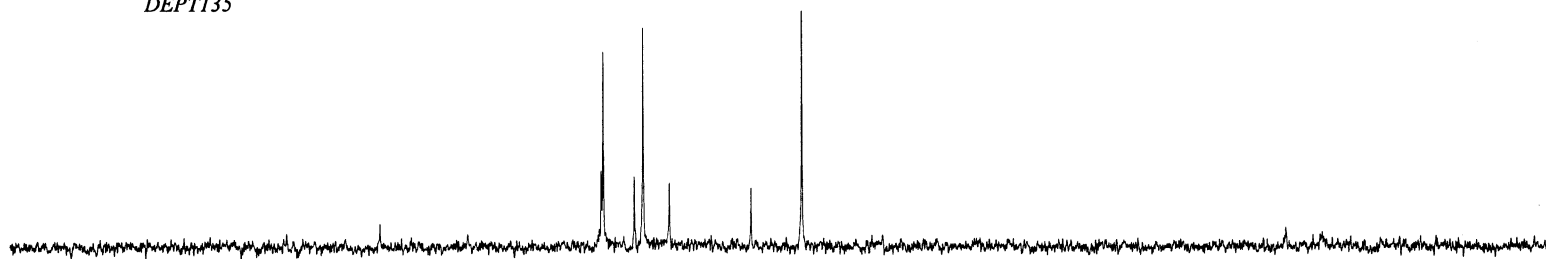


Figure 26. ^1H NMR (500 MHz, DMF-d_6) spectra of compound **4m**

DEPT135



YUNNAN UNIVER. AV. DRX 500
huangchao hc6m in DMF
11011804

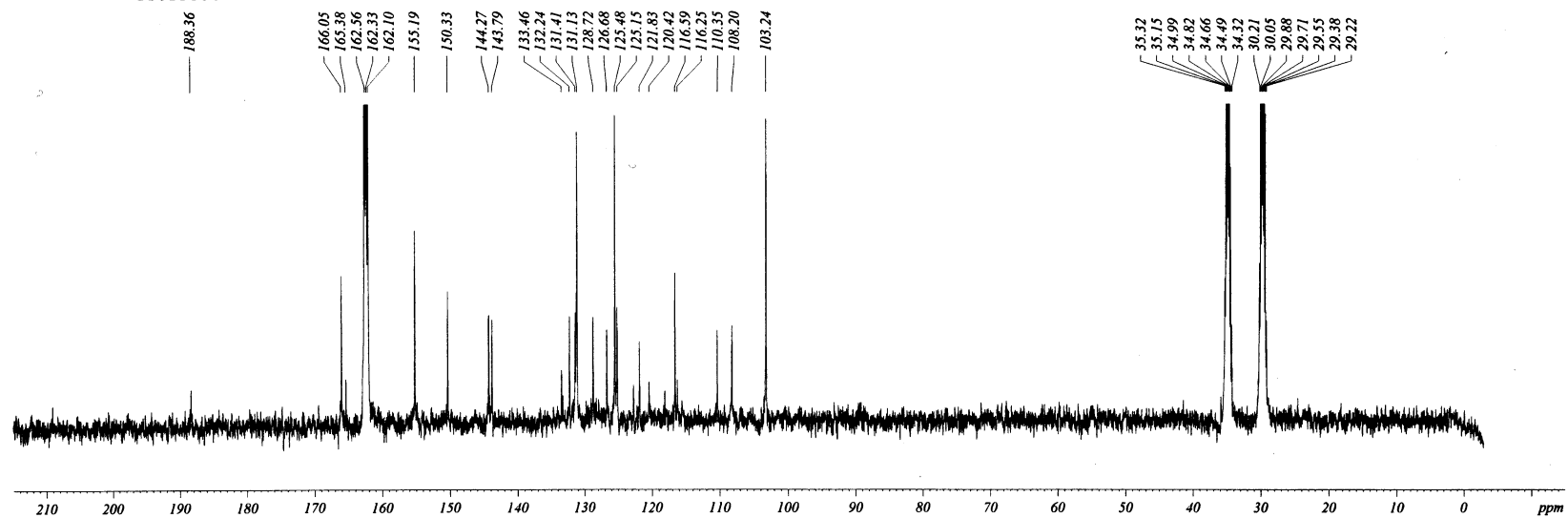


Figure 27. ^{13}C NMR (125 MHz, DMF-d_6) spectra of compound 4m

YUNNAN UNIVER. AV. DRX500
huangchao hc6n in DMF
10122801

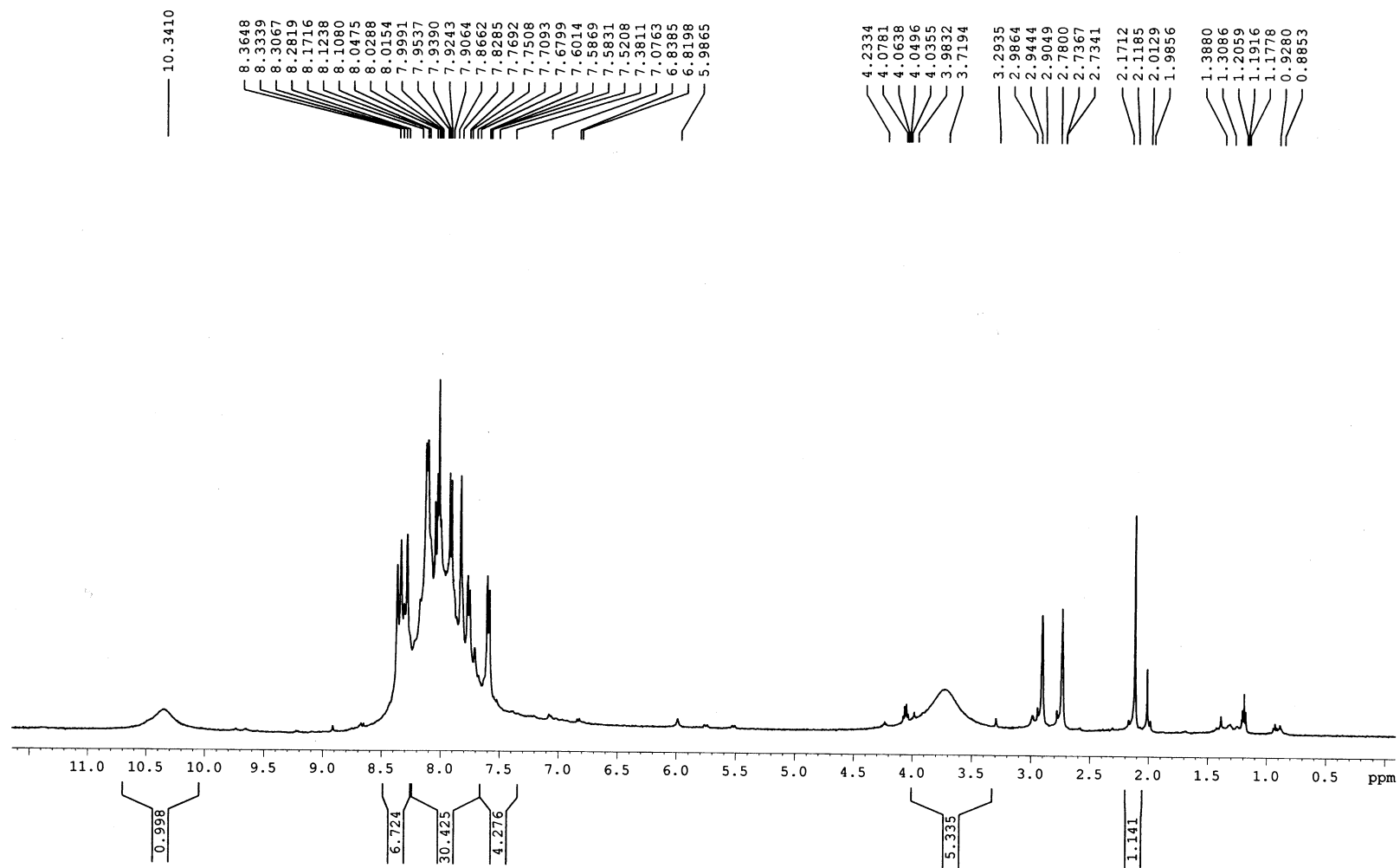


Figure 28. ^1H NMR (500 MHz, $\text{DMF-}d_6$) spectra of compound **4n**

DEPT135

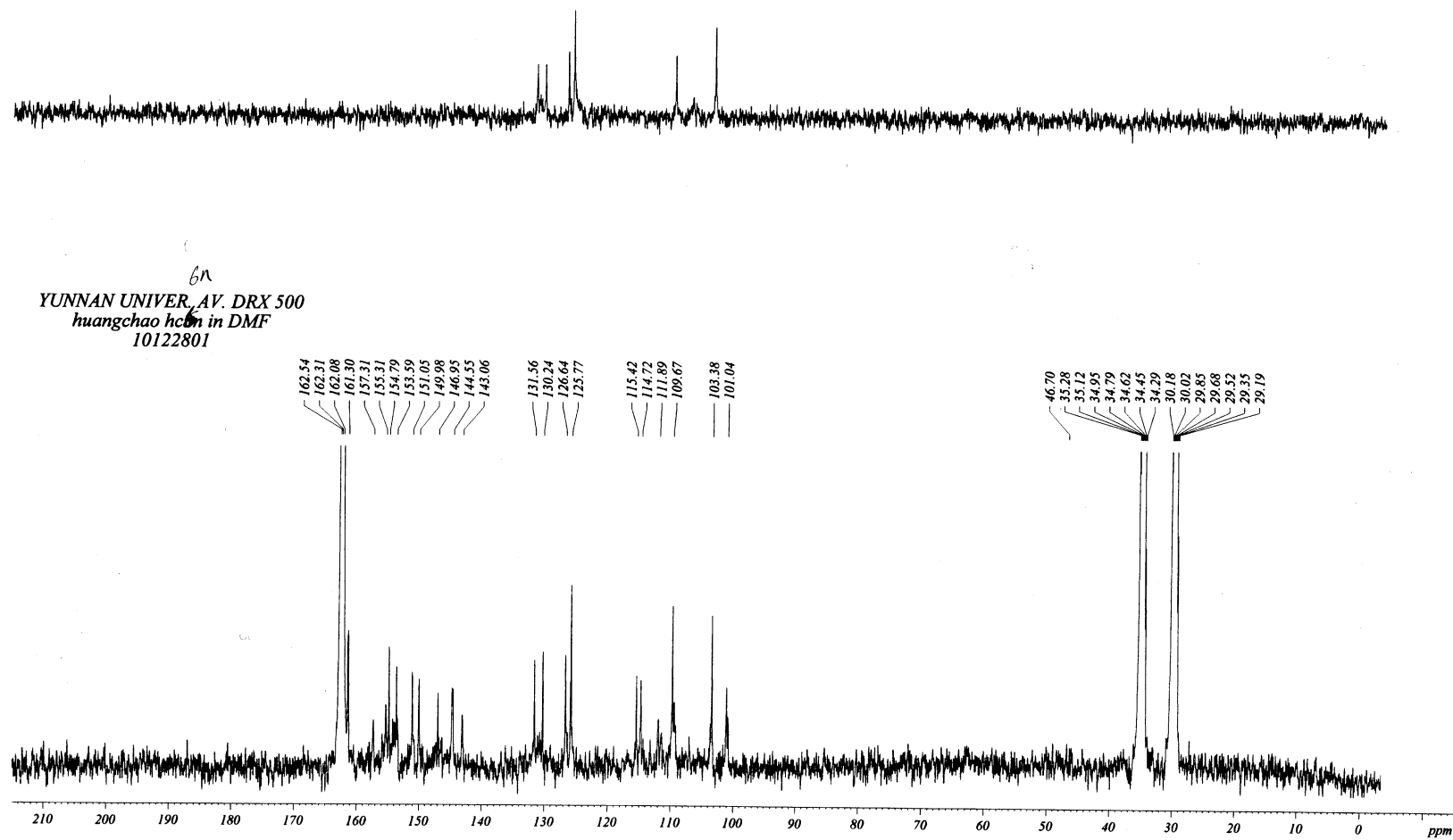


Figure 29. ^{13}C NMR (125 MHz, $\text{DMF-}d_6$) spectra of compound 4n

YUNNAN UNIVER. AV. DRX500
huangchao hc6n in DMF
19F decoupling
10122801

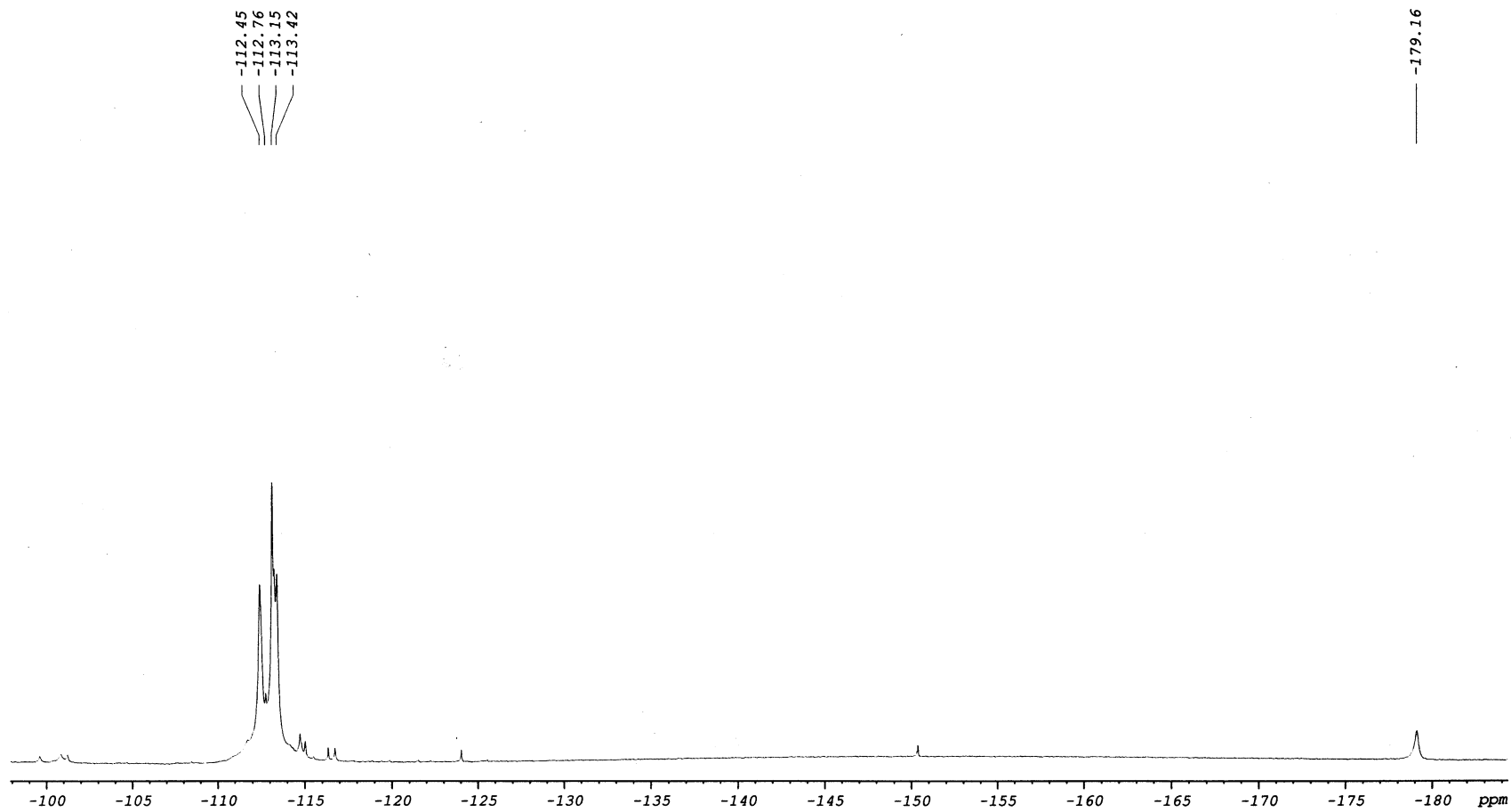


Figure 30. ^{19}F NMR (470 MHz, DMF-d_6) spectra of compound **4n**

YUNNAN UNIVER. AV. DRX500
huangchao hc6o in DMF
10122802

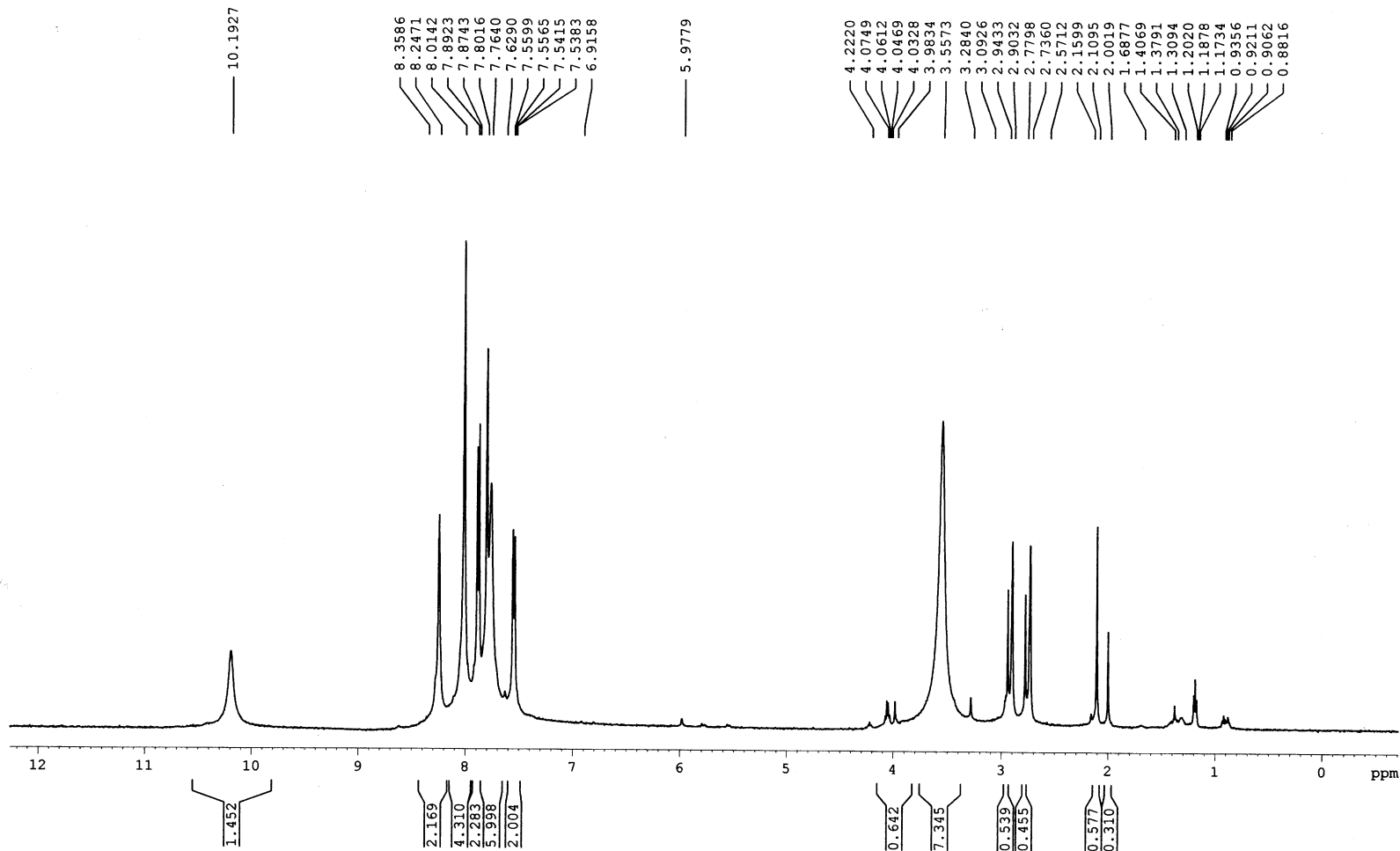
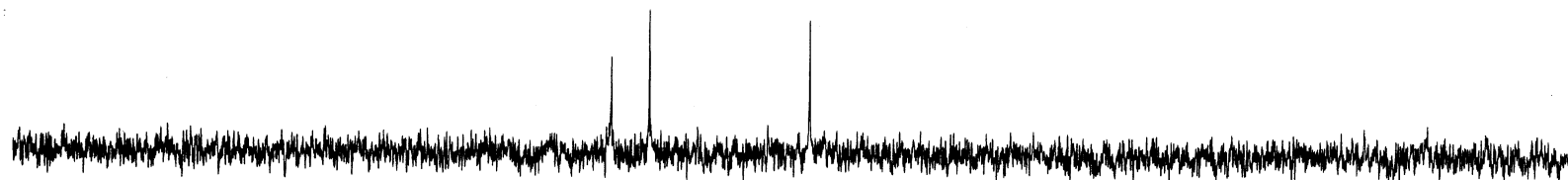


Figure 31. ^1H NMR (500 MHz, $\text{DMF-}d_6$) spectra of compound **4o**

DEPT135



YUNNAN UNIVER. AV. DRX 500
huangchao hc6o in DMF
10122802

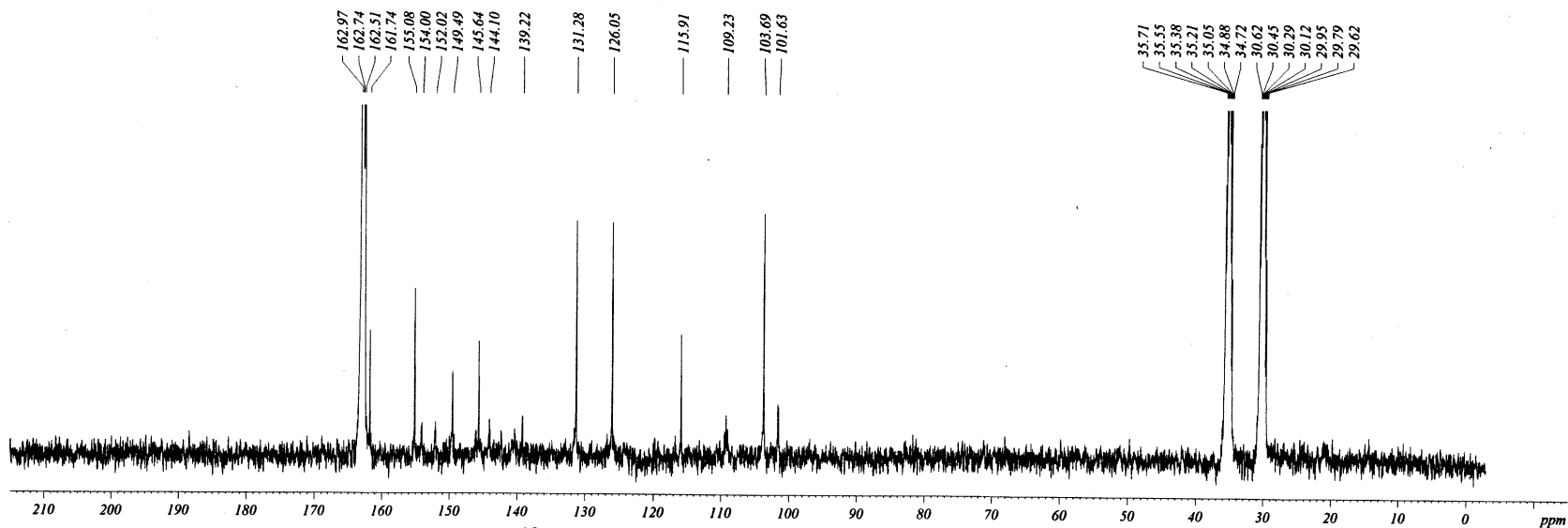


Figure 32. ^{13}C NMR (125 MHz, $\text{DMF-}d_6$) spectra of compound **4o**

YUNNAN UNIVER. AV. DRX500
huangchao hc60 in DMF
19F decoupling
10122802

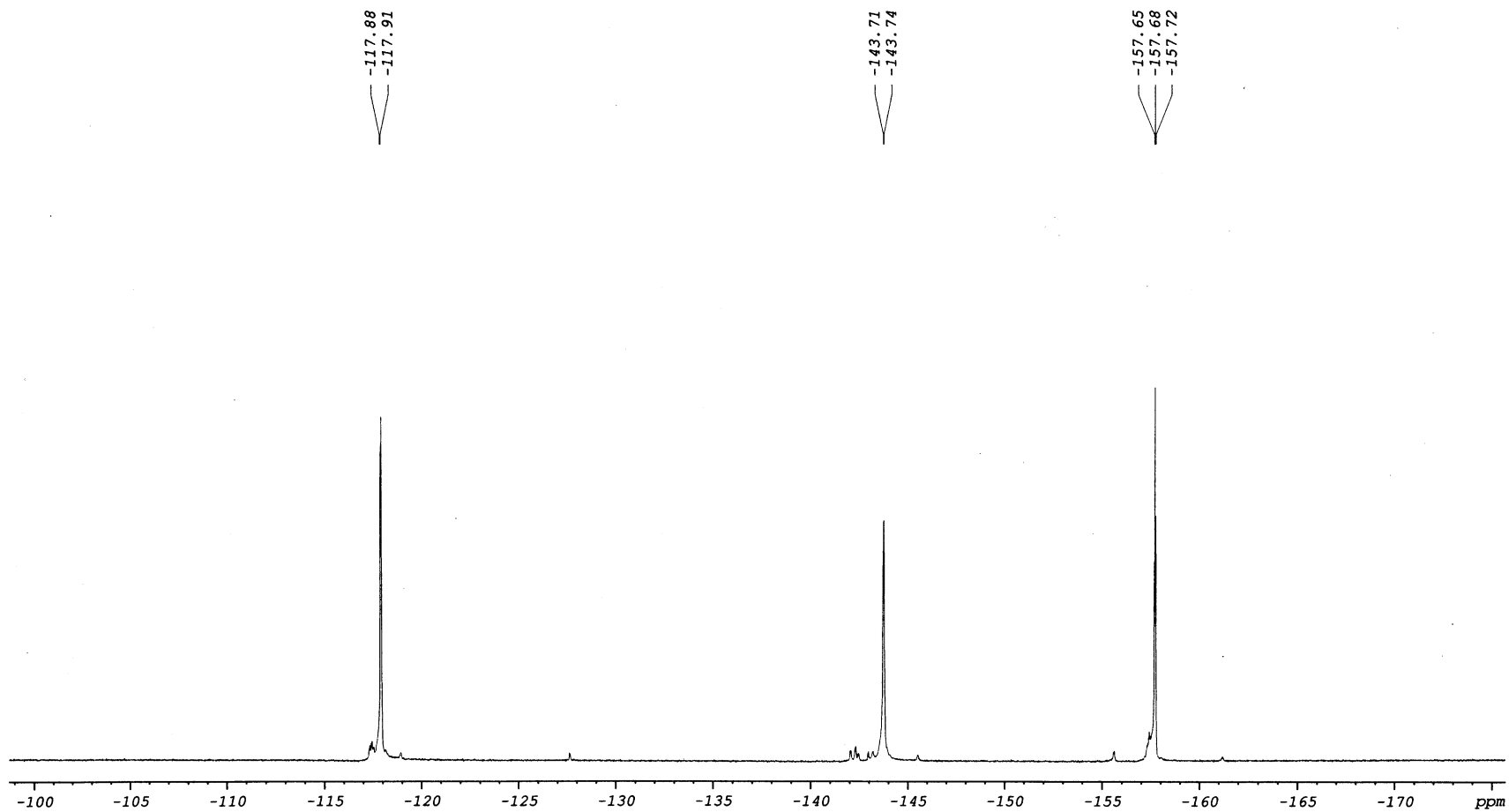


Figure 33. ^{19}F NMR (470 MHz, DMF-d_6) spectra of compound **4o**

YUNNAN UNIVER. AV. DRX500
yanglijuan YLJ-503-7a in DMSO

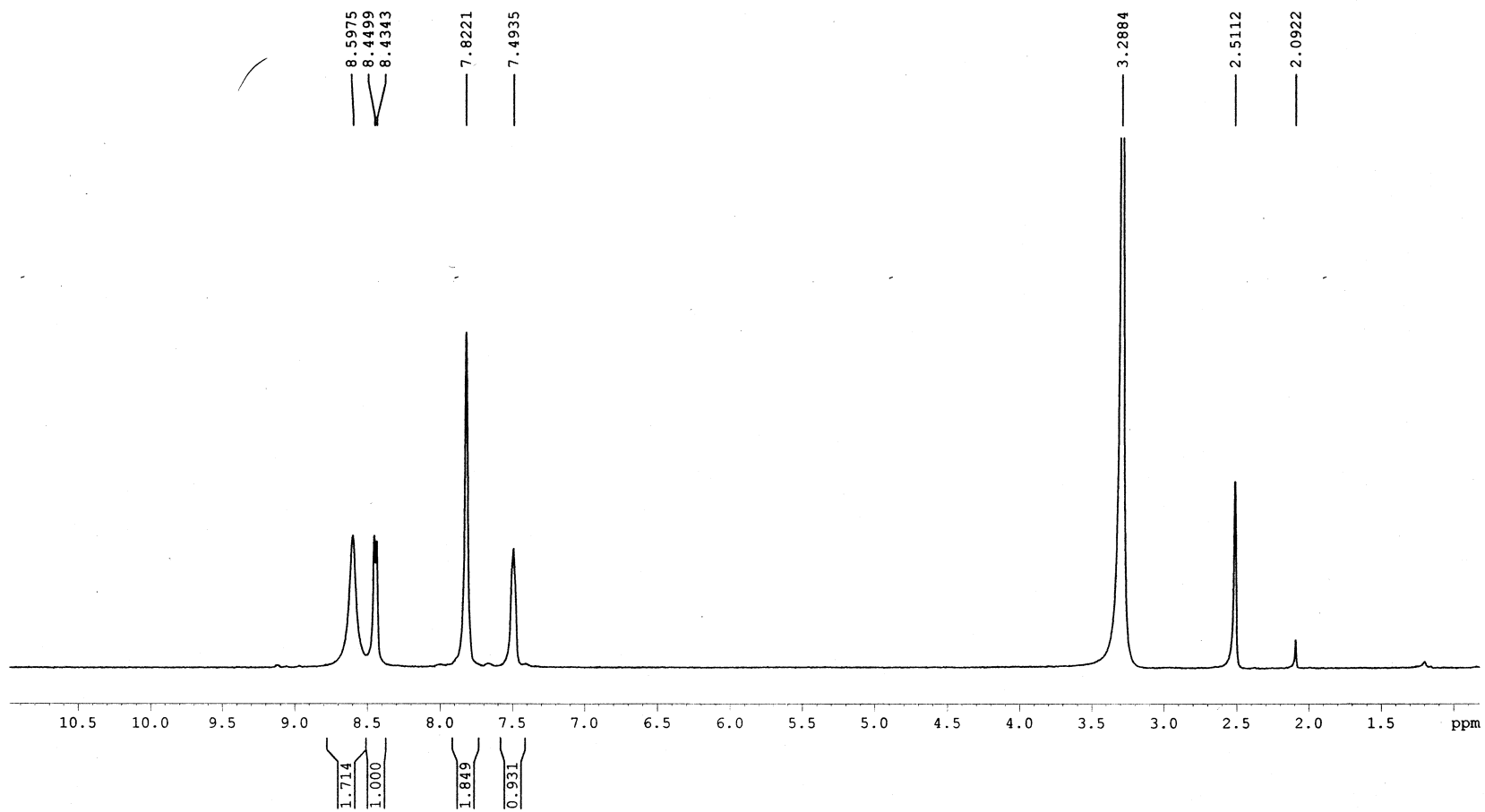


Figure 34. ^1H NMR (500 MHz, $\text{DMSO-}d_6$) spectra of compound 5a

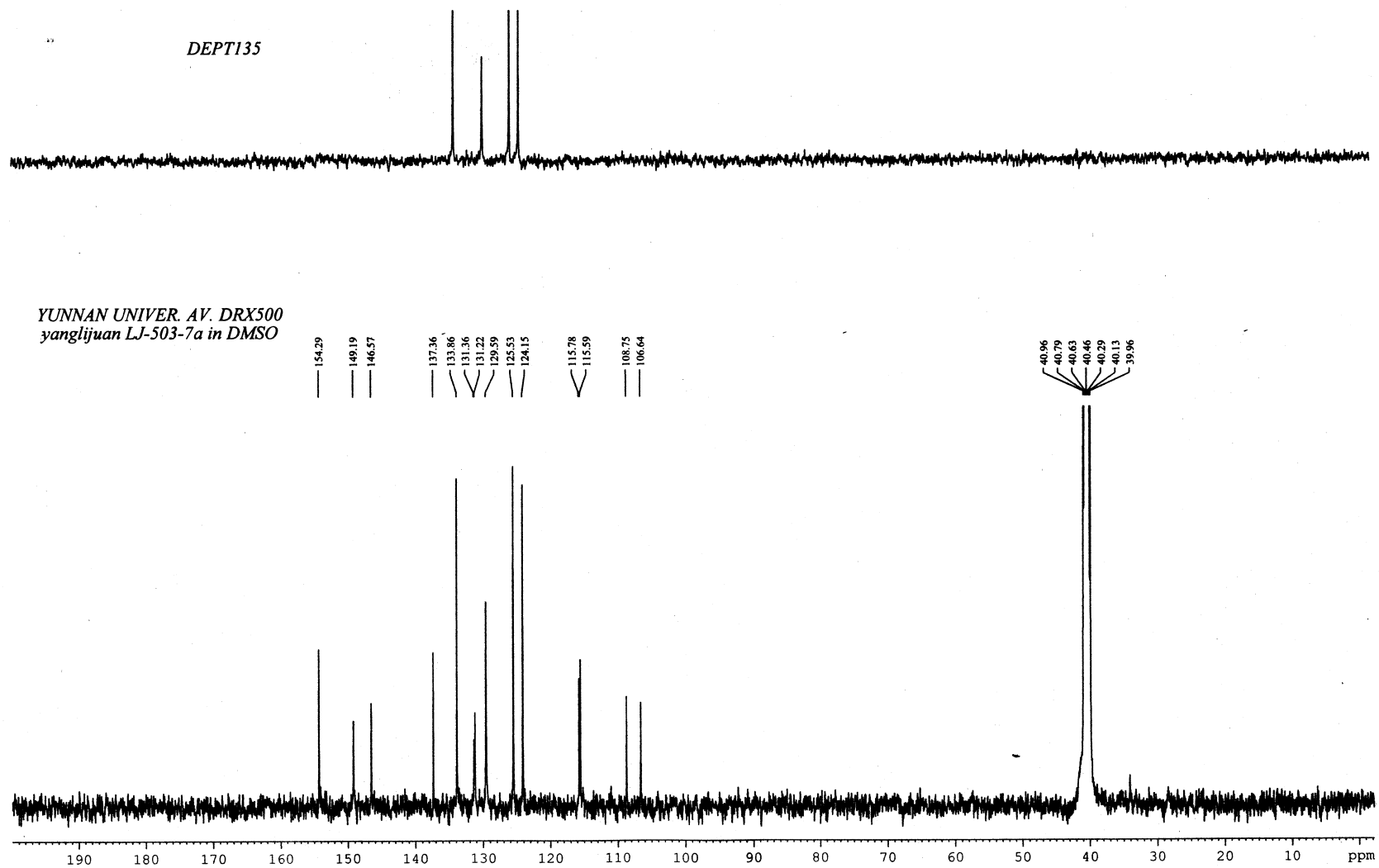


Figure 35. ^{13}C NMR (125 MHz, $\text{DMSO-}d_6$) spectra of compound 5a

YUNNAN UNIVER. AV. DRX500
huangchao hc7b in DMF
11011806

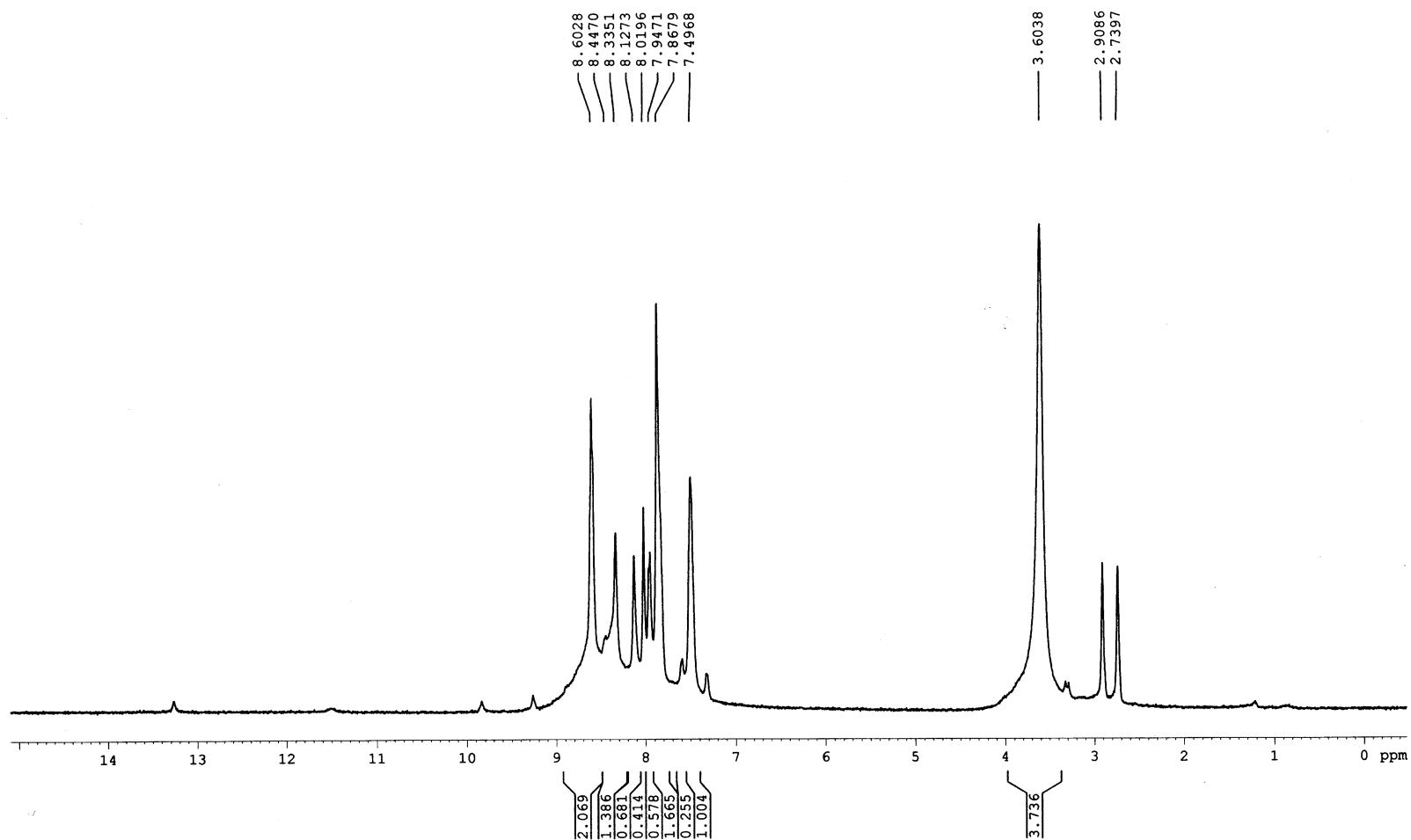
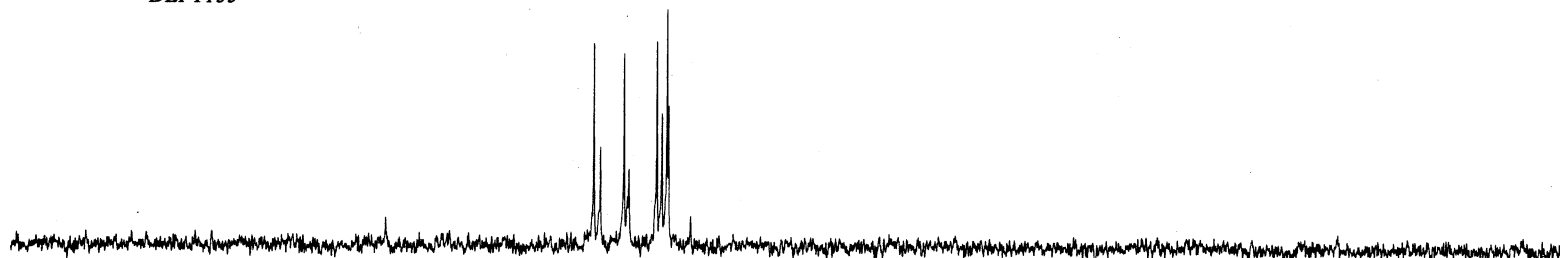


Figure 36. ^1H NMR (500 MHz, $\text{DMF-}d_6$) spectra of compound **5b**

DEPT135



YUNNAN UNIVER. AV. DRX 500
huangchao hc7b in DMF
11011806

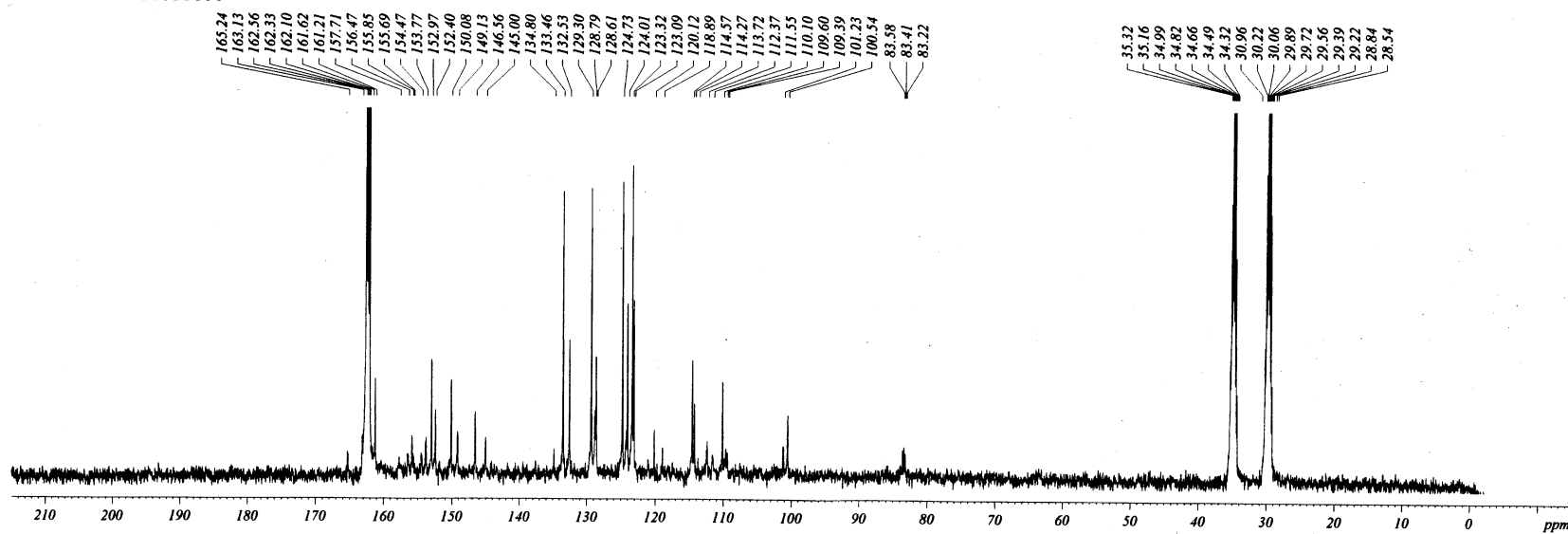


Figure 37. ^{13}C NMR (125 MHz, $\text{DMF-}d_6$) spectra of compound 5b

YUNNAN UNIVER. AV. DRX500
huangchao hc7b in DMF
19F decoupling 11011806

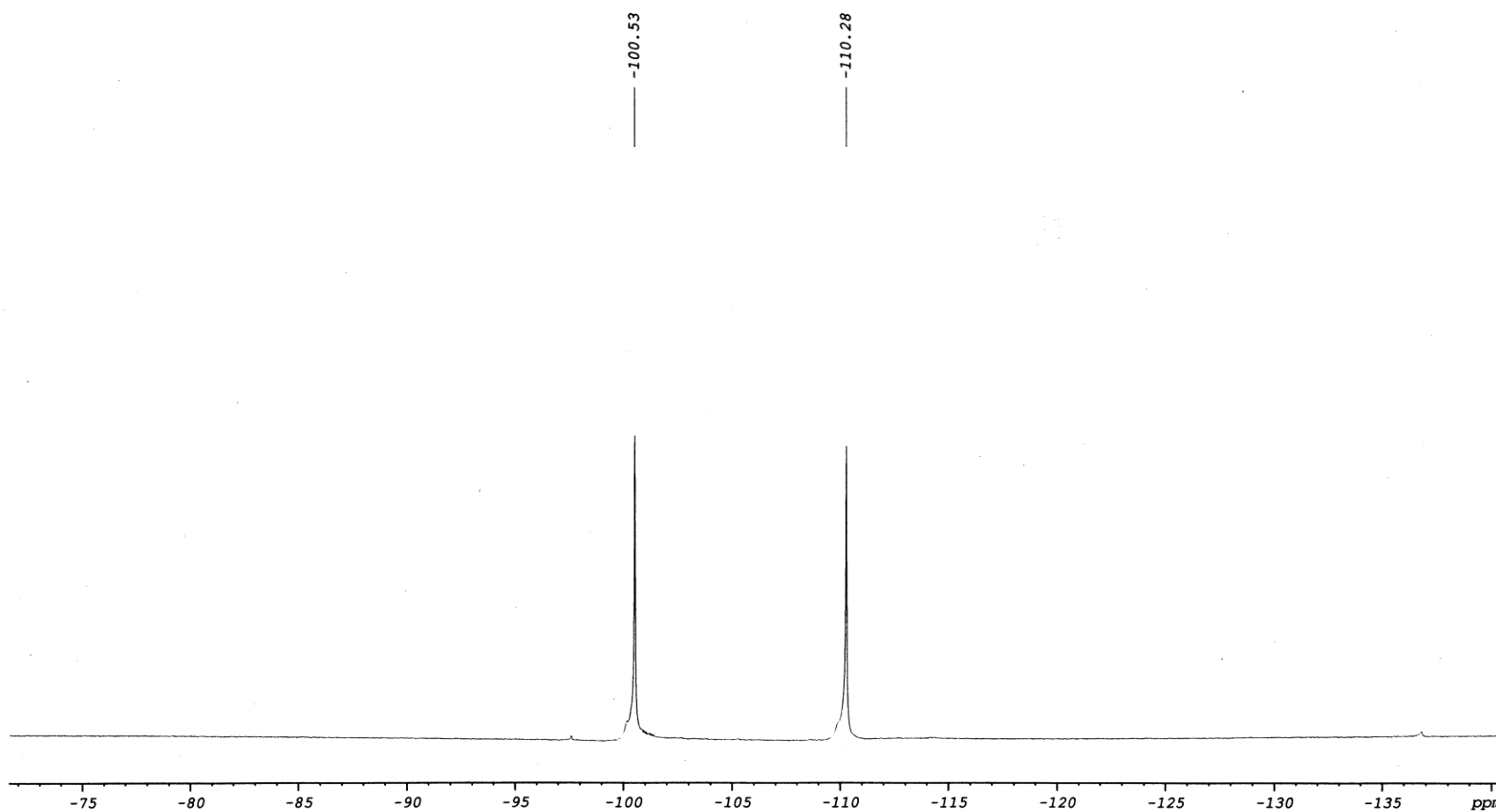


Figure 38. ^{19}F NMR (470 MHz, $\text{DMF-}d_6$) spectra of compound **5b**

YUNNAN UNIVER. AV. DRX500
yanglijuan YLJ-503-7c in DMSO

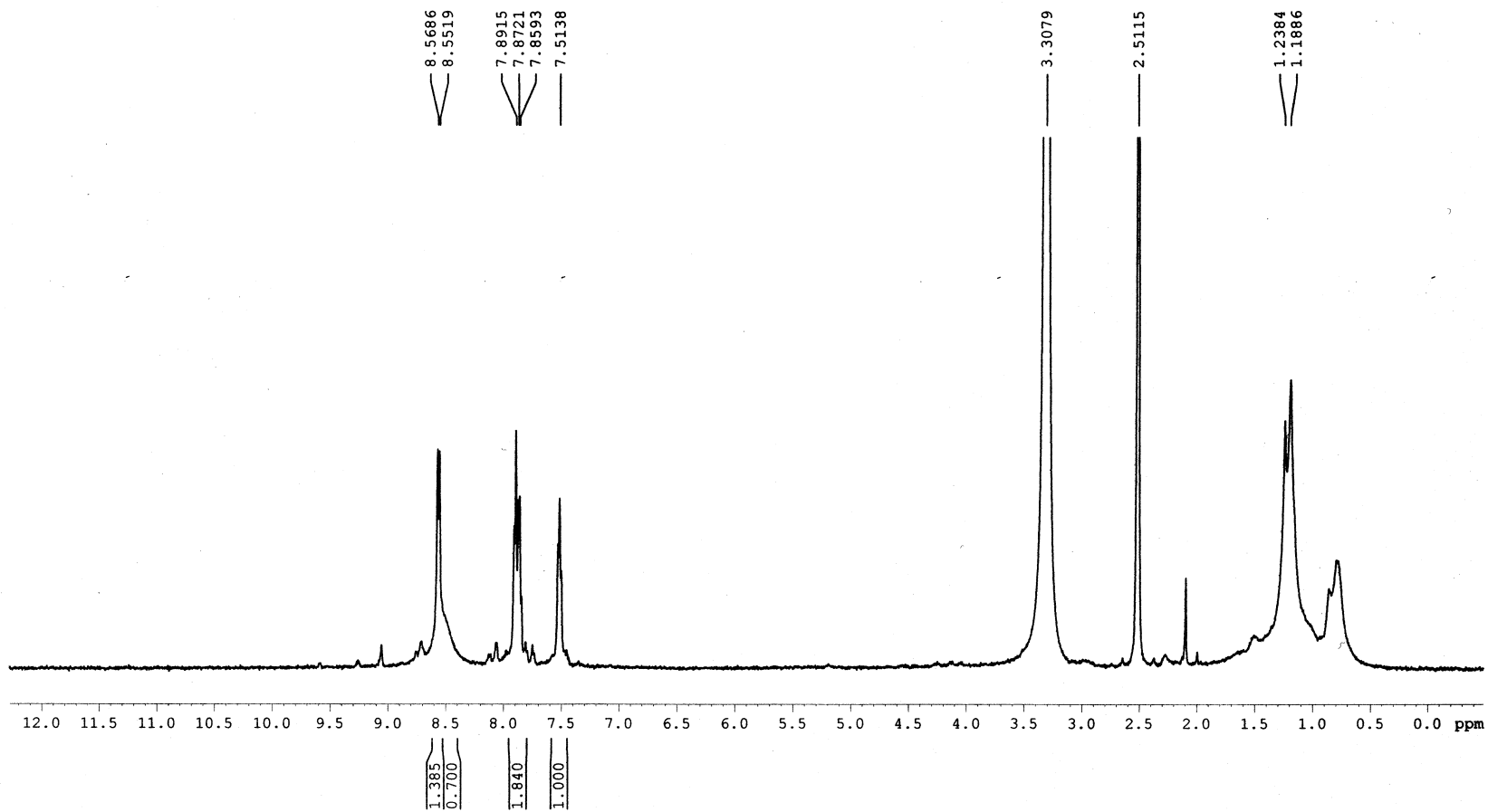


Figure 39. ^1H NMR (500 MHz, $\text{DMSO-}d_6$) spectra of compound **5c**

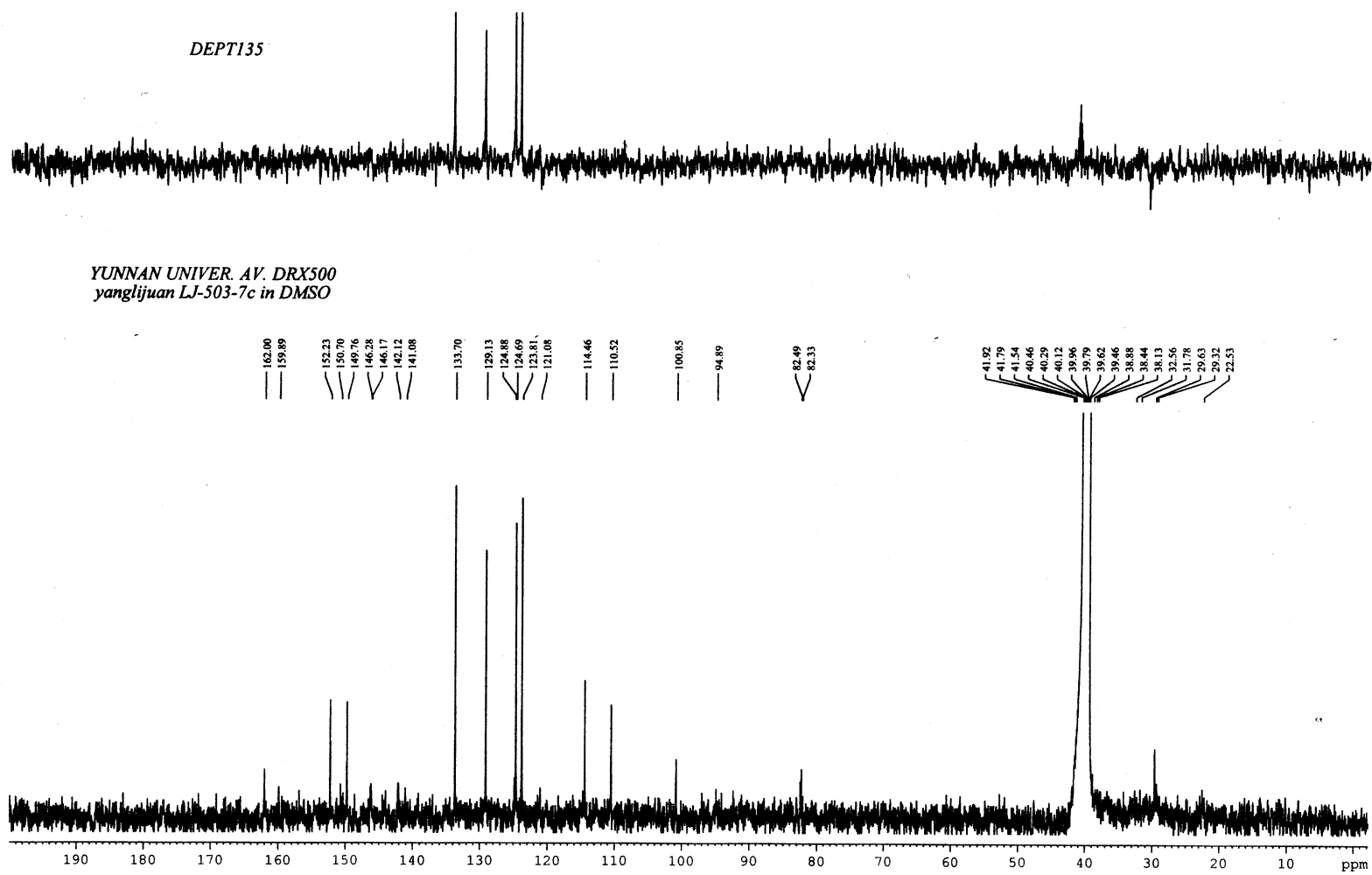


Figure 40. ^{13}C NMR (125 MHz, $\text{DMSO-}d_6$) spectra of compound **5c**

YUNNAN UNIVER. AV. DRX500
yanglijuan 503-7c in DMSO
 ^{19}F decoupling

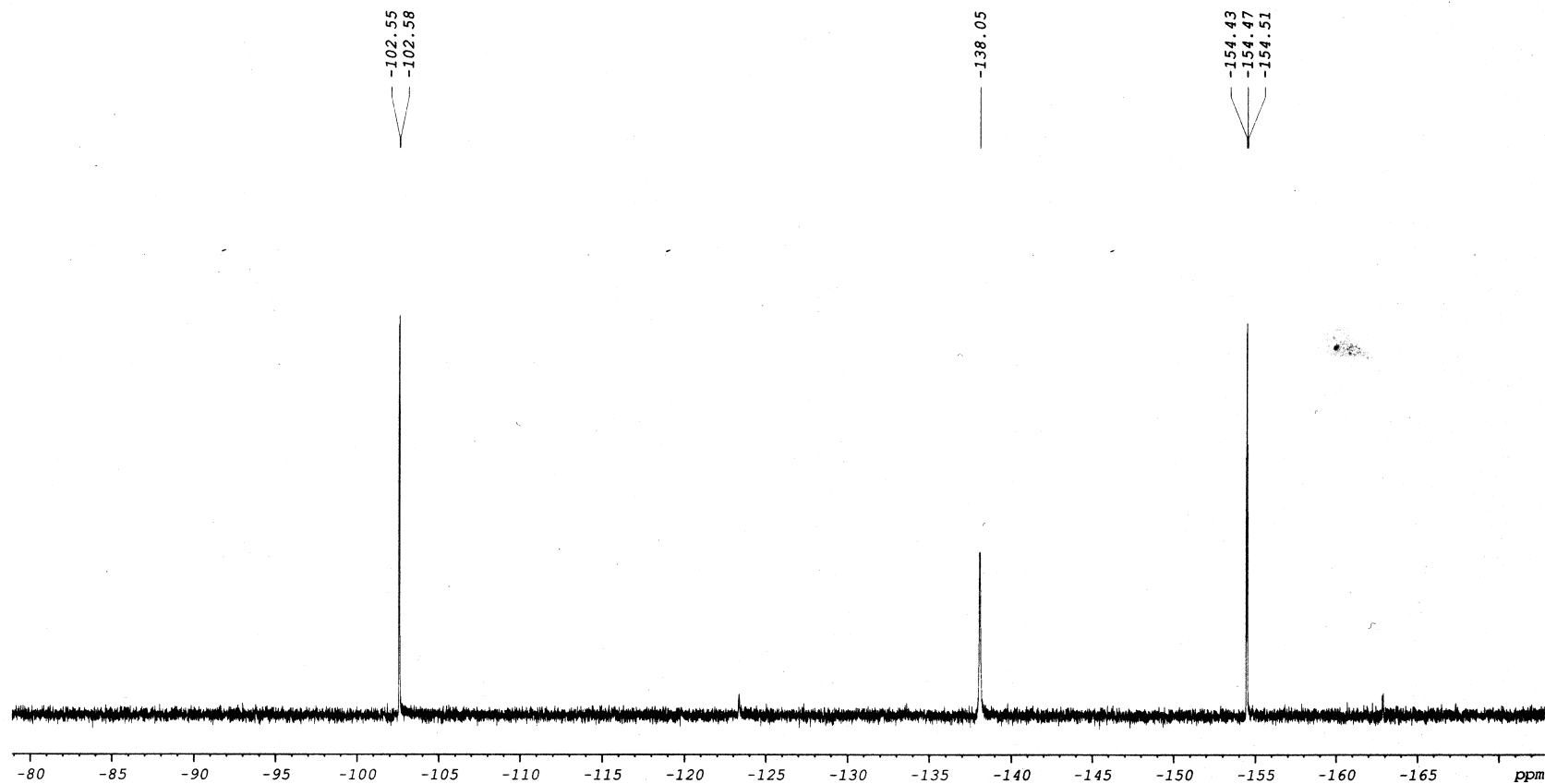


Figure 41. ^{19}F NMR (470 MHz, $\text{DMSO-}d_6$) spectra of compound 5c

YUNNAN UNIVER. AV. DRX500
huangchao hc7d in DMF
11011807

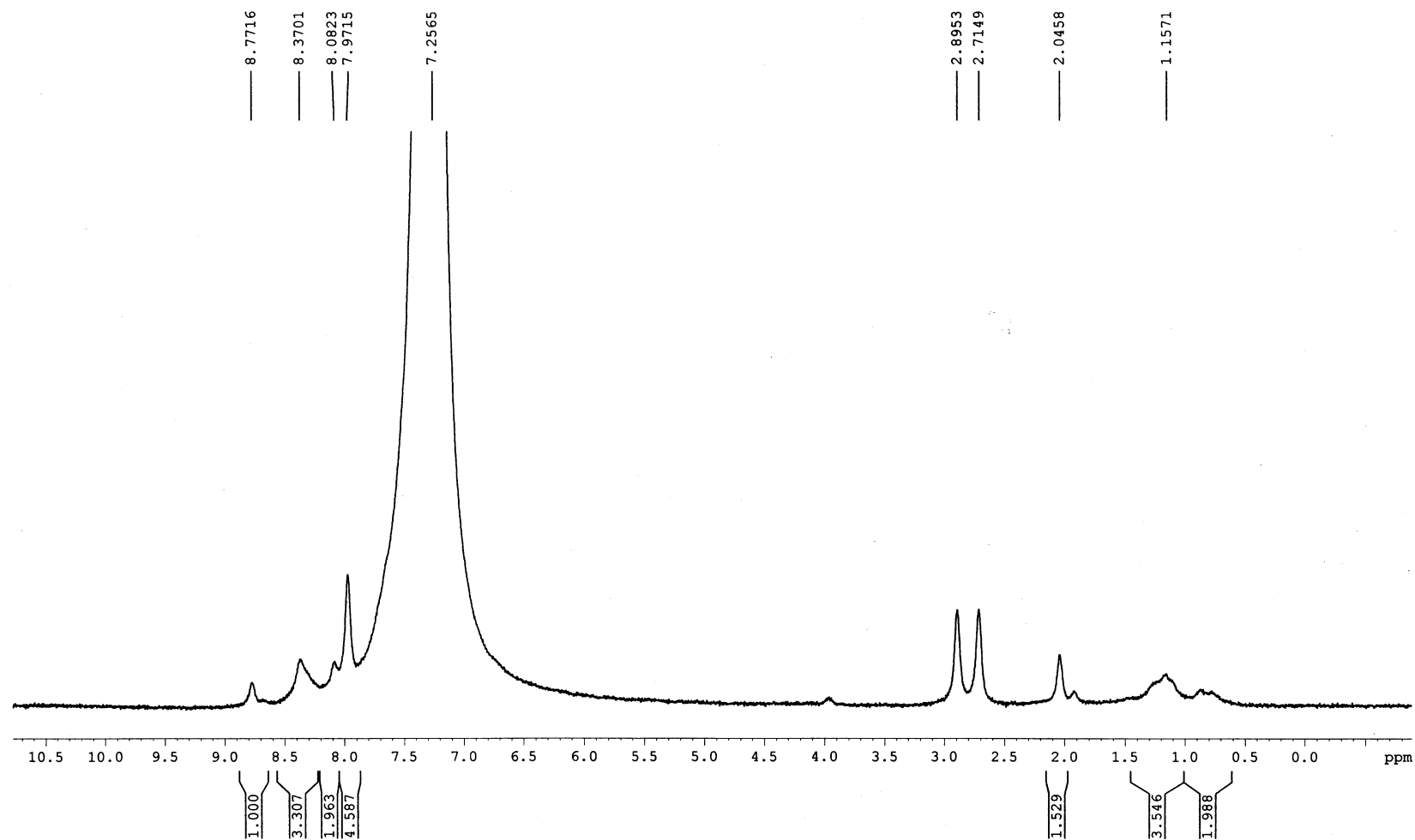
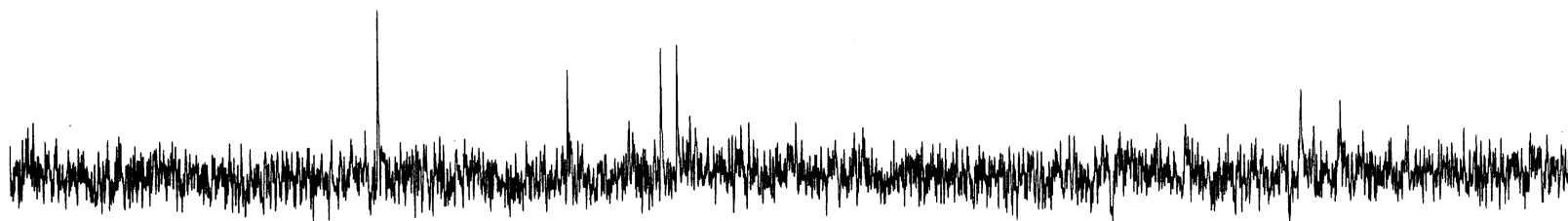


Figure 42. ^1H NMR (500 MHz, $\text{DMF-}d_6$) spectra of compound **5d**

DEPT135



YUNNAN UNIVER. AV. DRX 500
huangchao hc7d in DMF
11011807

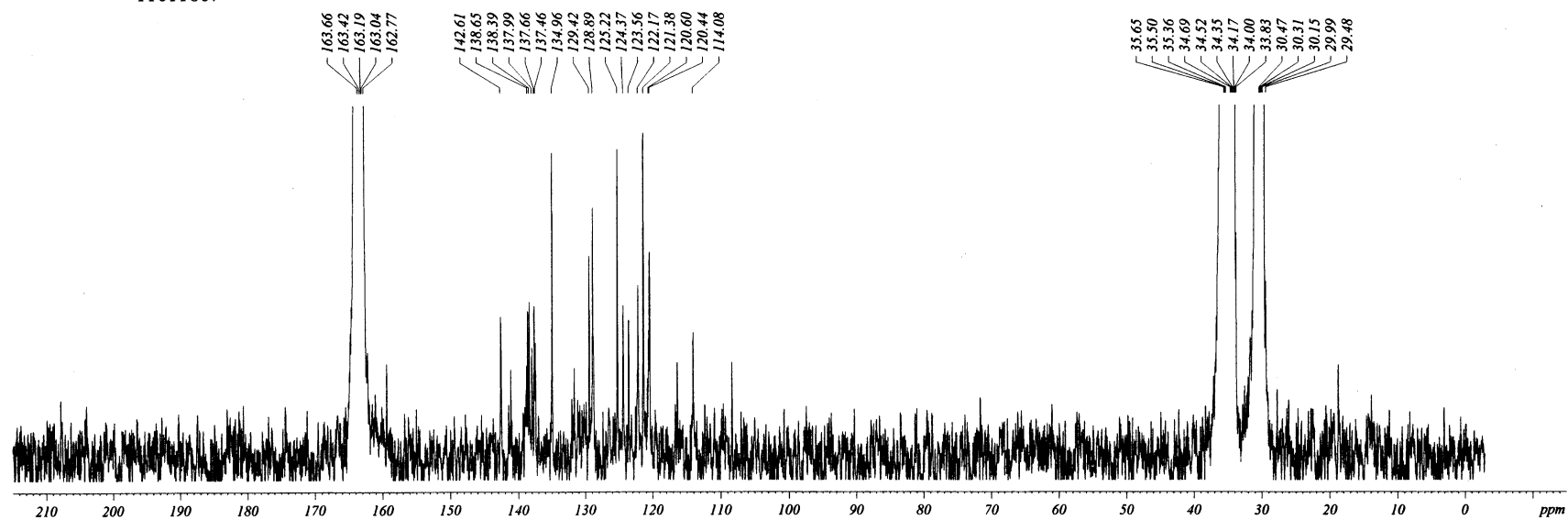


Figure 43. ¹³C NMR (125 MHz, DMF-*d*₆) spectra of compound 5d

YUNNAN UNIVER. AV. DRX500
yanglijuan YLJ-503-7a in DMSO
7e

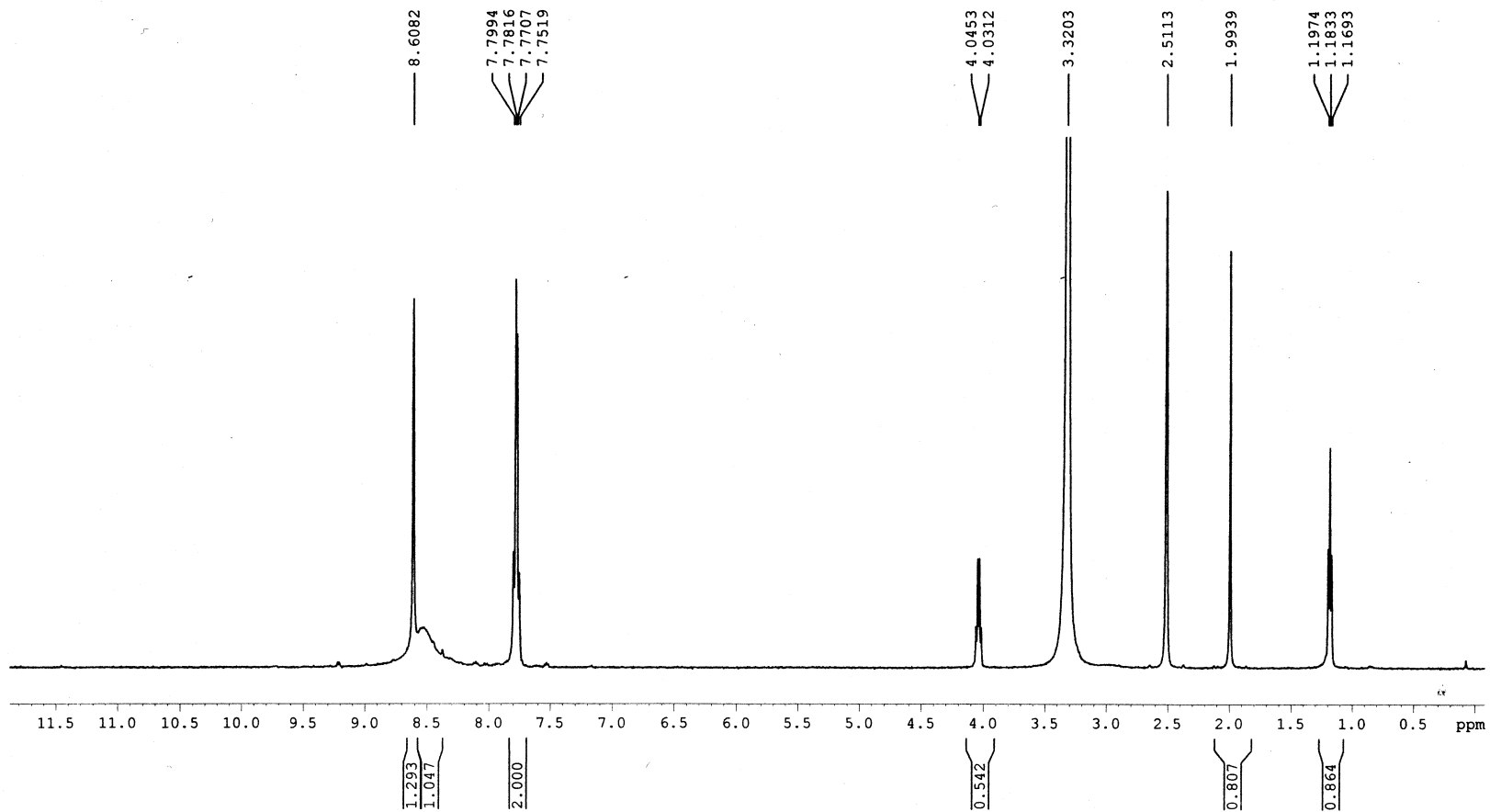


Figure 44. ^1H NMR (500 MHz, $\text{DMSO}-d_6$) spectra of compound **5e**

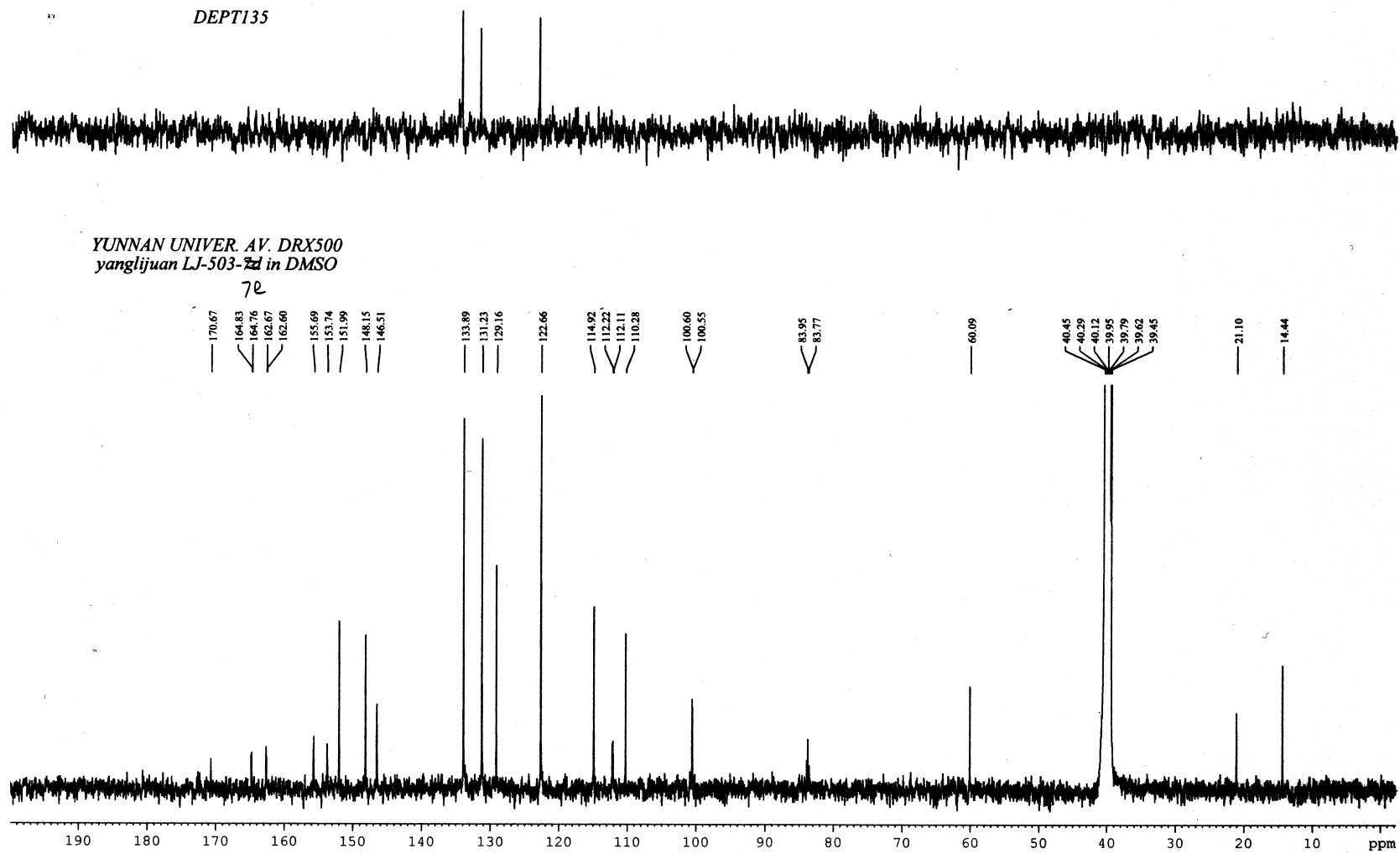


Figure 45. ^{13}C NMR (125 MHz, $\text{DMSO-}d_6$) spectra of compound **5e**

YUNNAN UNIVER. AV. DRX500
yanglijuan 503-7a in DMSO
19F decoupling 7e

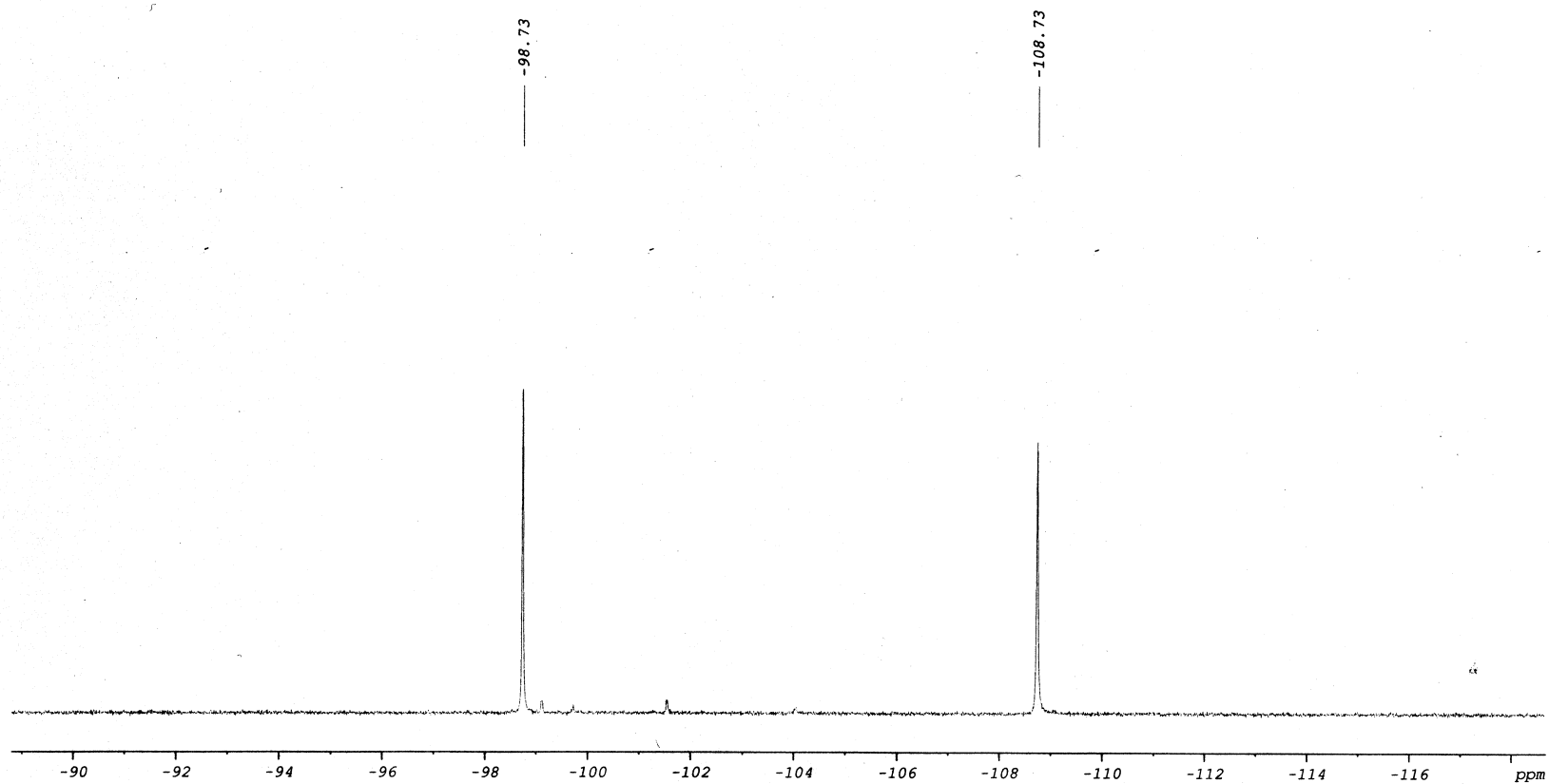


Figure 46. ^{19}F NMR (470 MHz, $\text{DMSO-}d_6$) spectra of compound **5e**

YUNNAN UNIVER. AV. DRX500
yanglijuan YLJ-503-7g in DMSO

7i

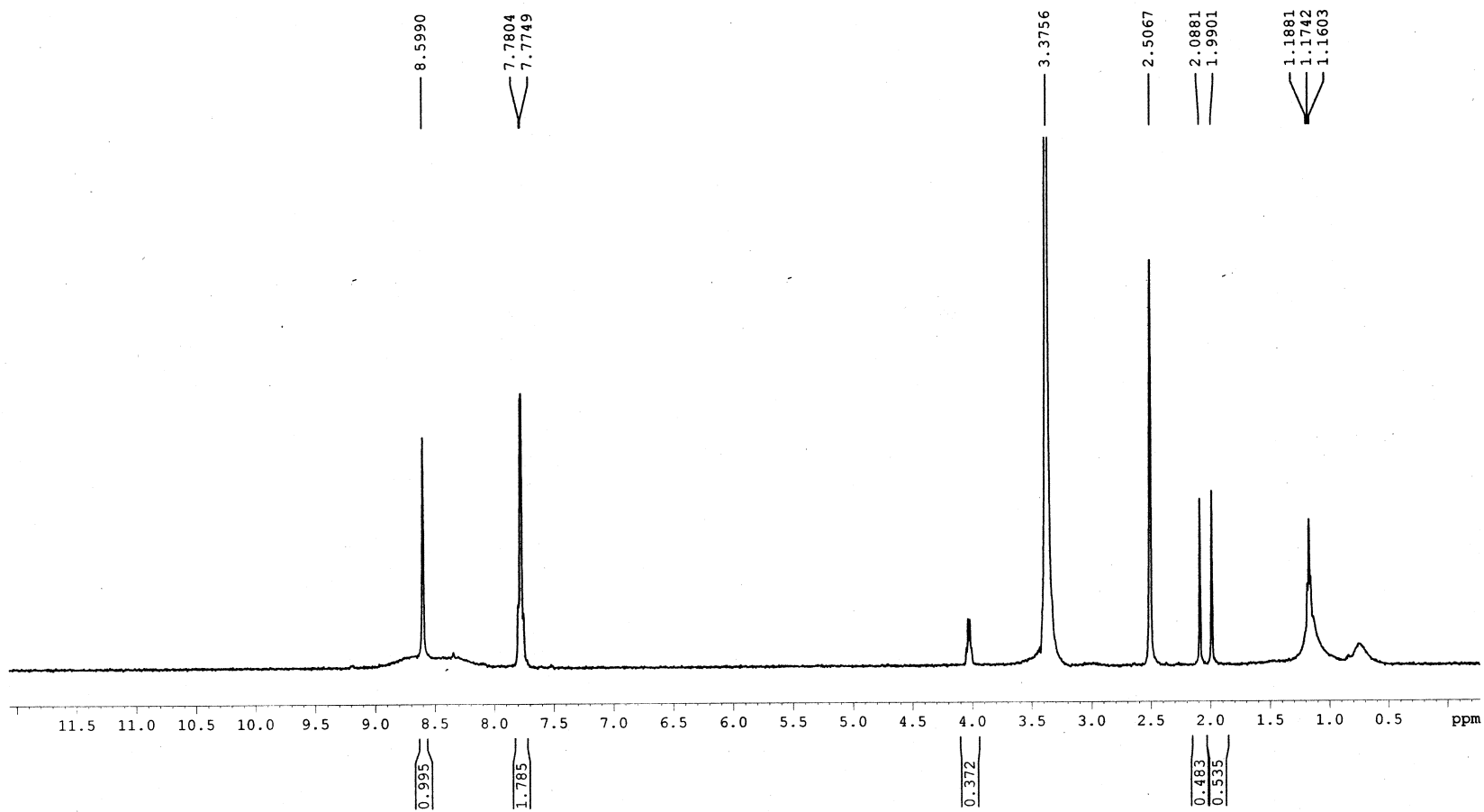


Figure 47. ^1H NMR (500 MHz, $\text{DMSO-}d_6$) spectra of compound **5f**

DEPT135



YUNNAN UNIVER. AV. DRX500
yanglijuan LJ-503-7g in DMSO
72

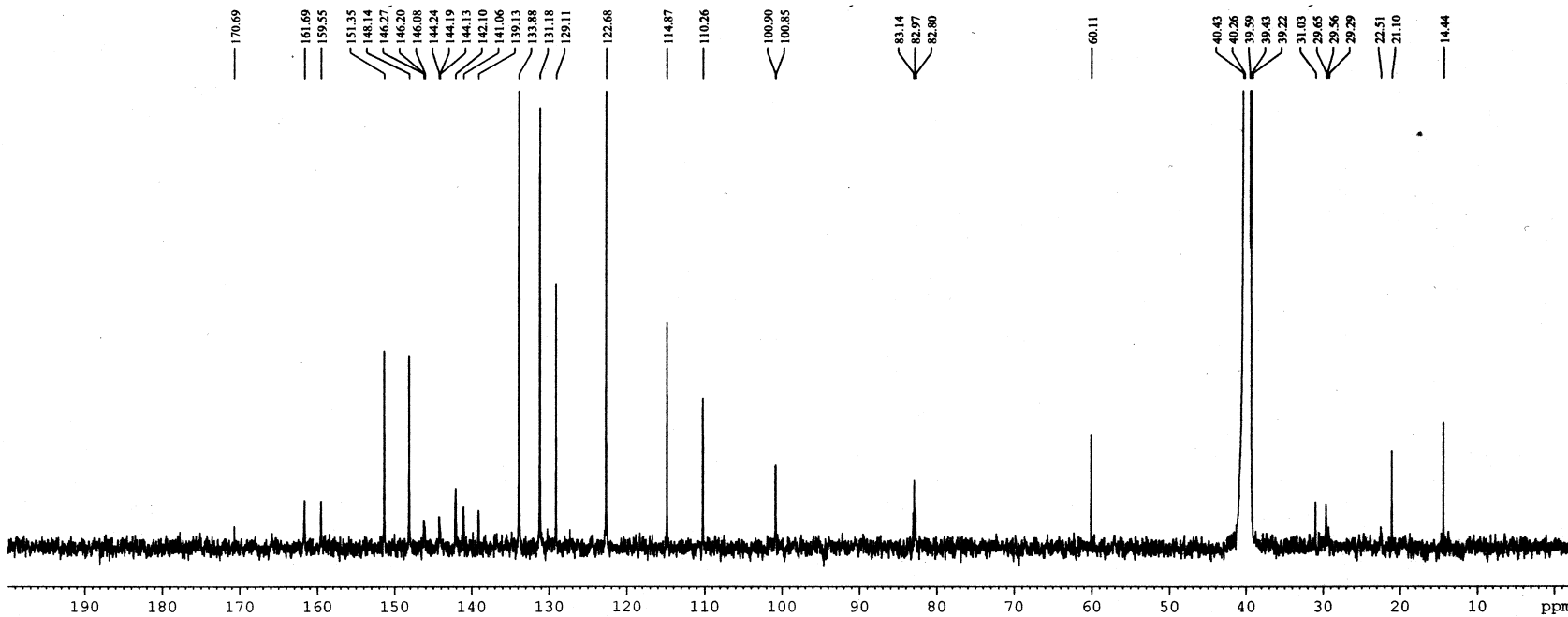


Figure 48. ¹³C NMR (125 MHz, DMSO-*d*₆) spectra of compound 5f

YUNNAN UNIVER. AV. DRX500
yanglijuan 503-7~~g~~ in DMSO
19F decoupling γ

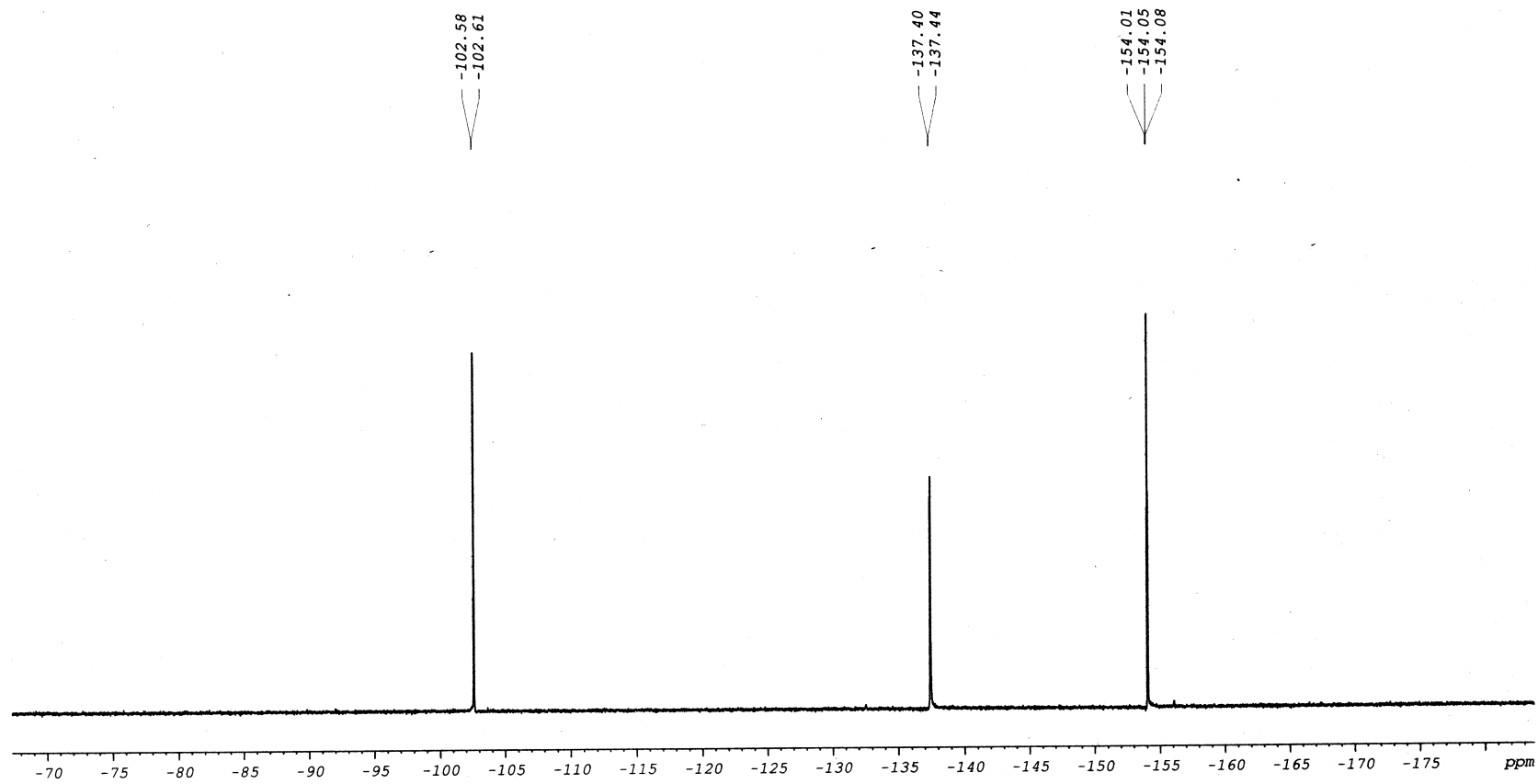


Figure 49. ^{19}F NMR (470 MHz, $\text{DMSO-}d_6$) spectra of compound 5f

YUNNAN UNIVER. AV. DRX500
huangchao hc7i in DMF
11011810

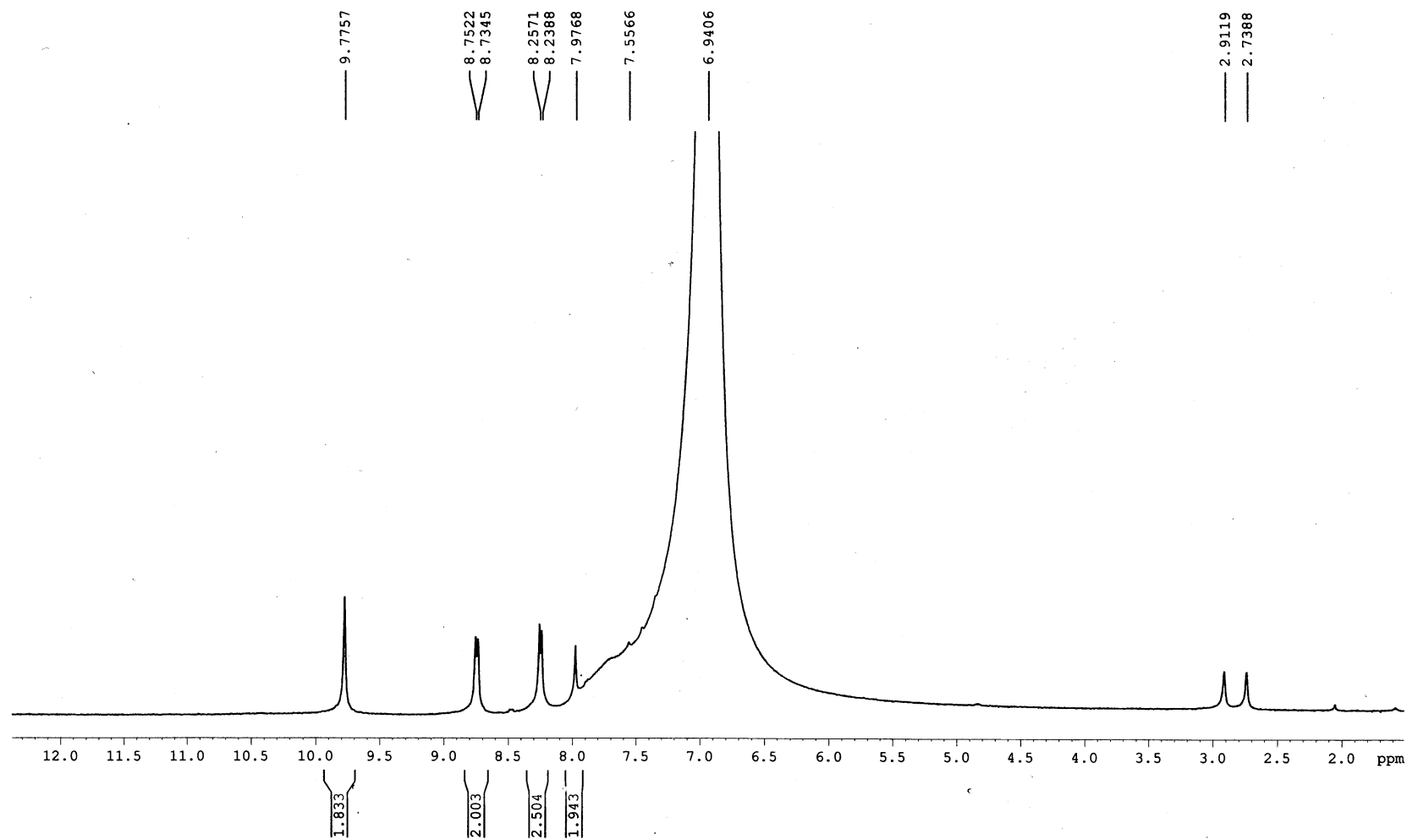


Figure 50. ¹H NMR (500 MHz, DMF-*d*₆) spectra of compound 5i

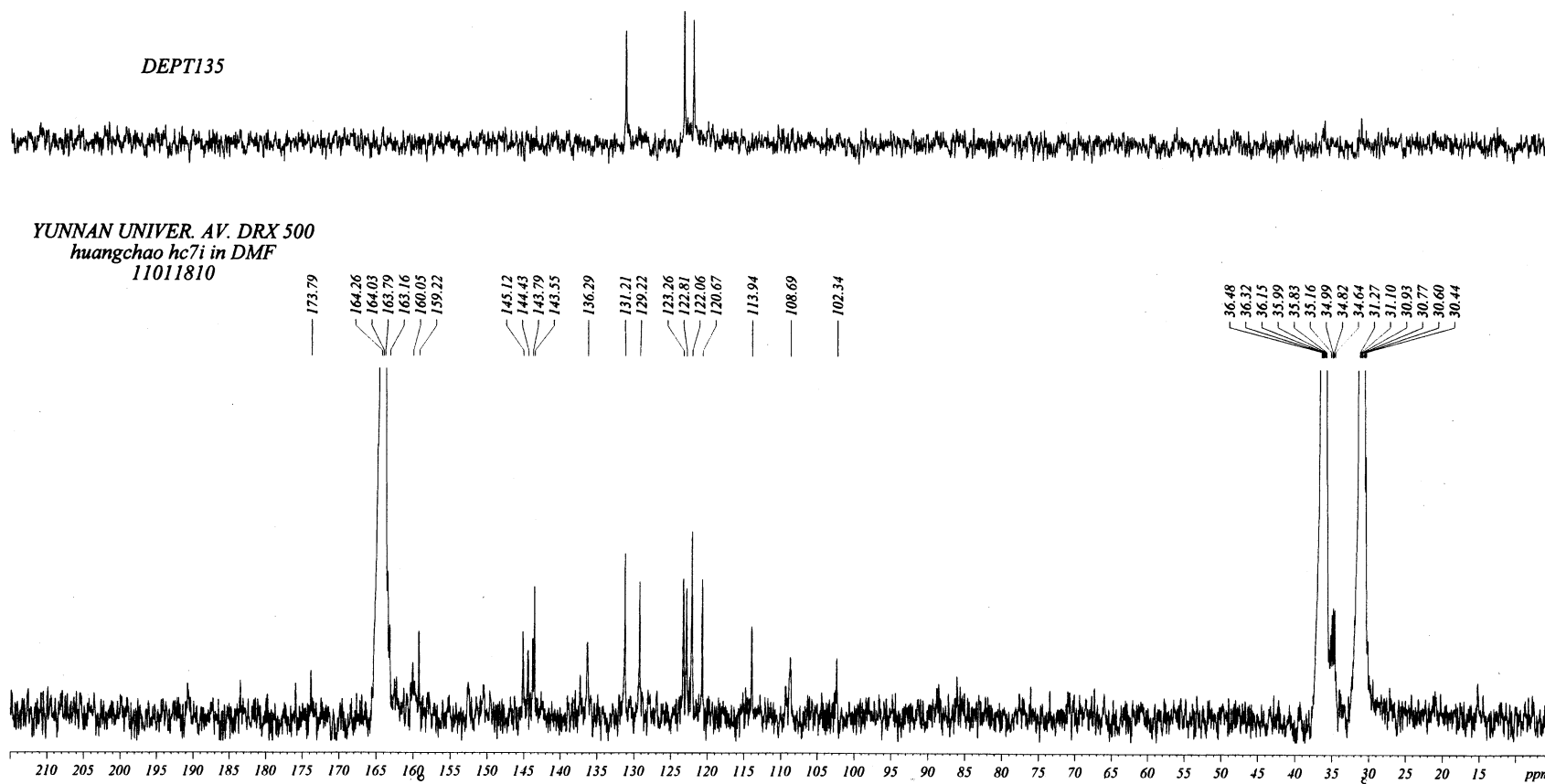


Figure 51. ^{13}C NMR (125 MHz, DMF-d_6) spectra of compound **5i**

YUNNAN UNIVER. AV. DRX500
huangchao hc7i in DMF
19F decoupling 11011810

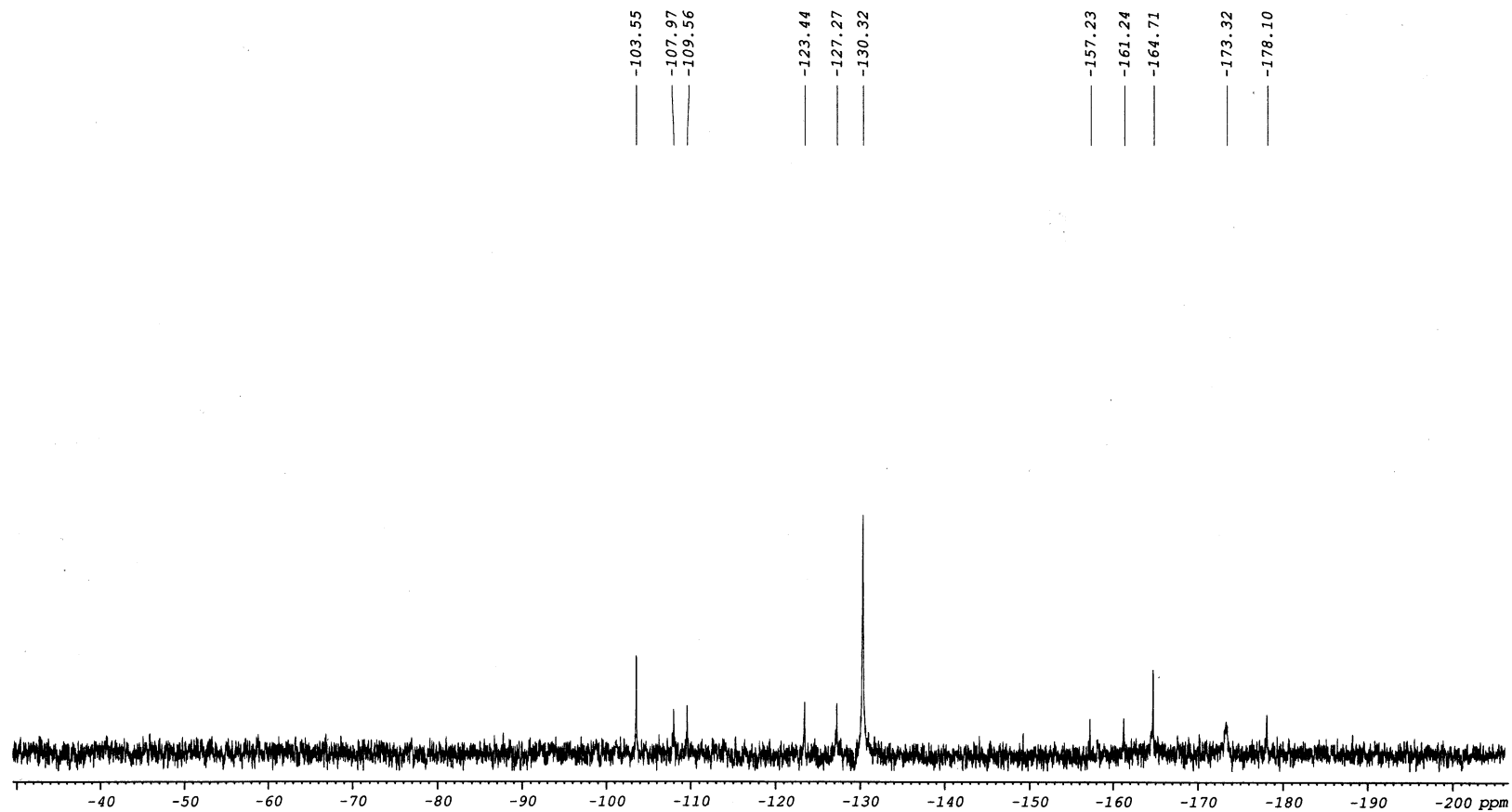


Figure 52. ^{19}F NMR (470 MHz, DMF-d_6) spectra of compound **5i**

YUNNAN UNIVER. AV. DRX500
huangchao hc7j in DMF
11011811

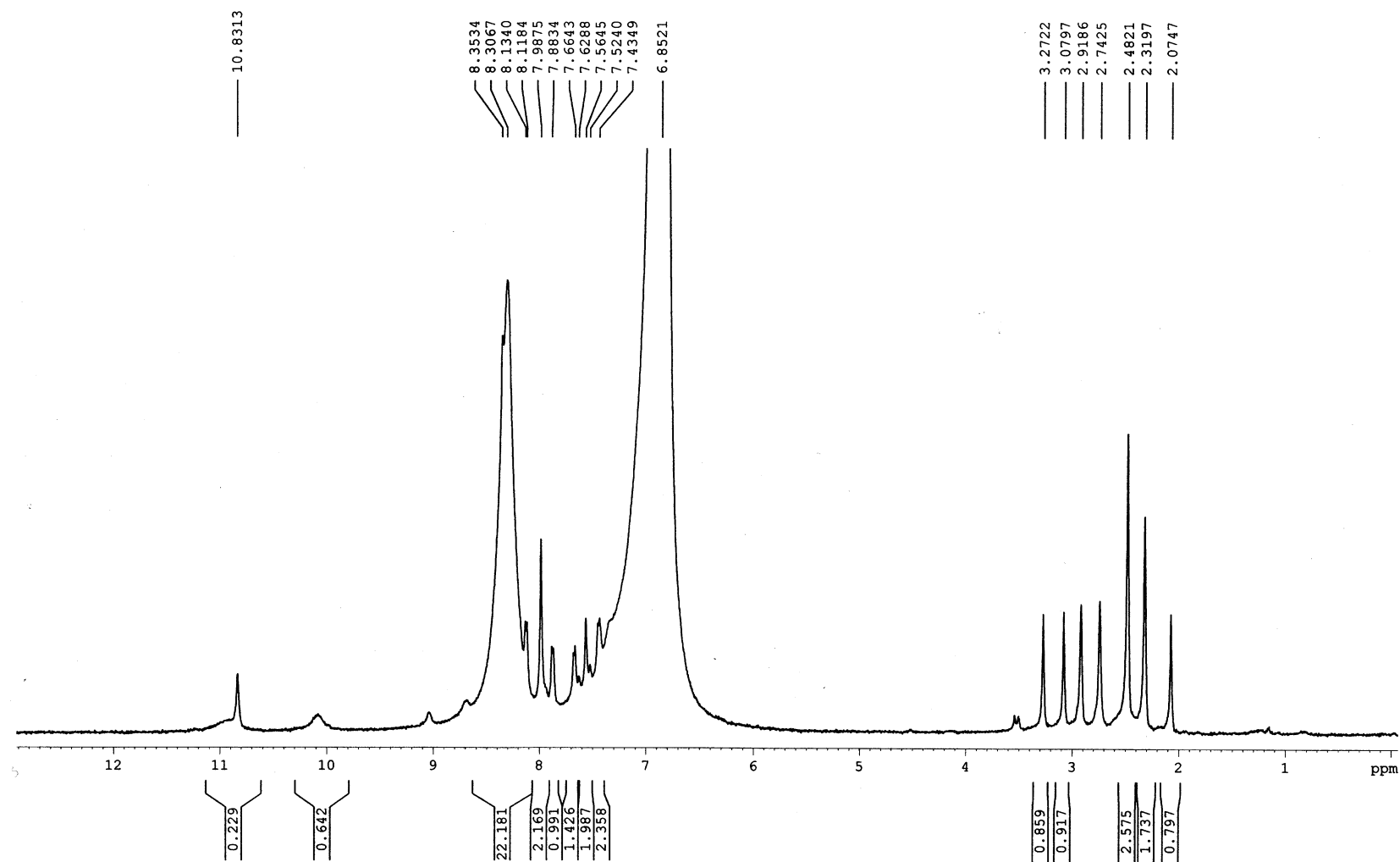
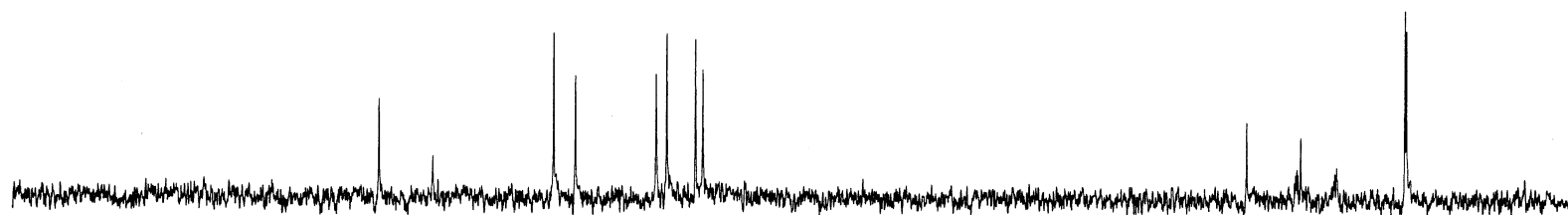


Figure 53. ^1H NMR (500 MHz, DMF-d_6) spectra of compound **5j**

DEPT135



YUNNAN UNIVER. AV. DRX 500
huangchao hc7j in DMF
11011811

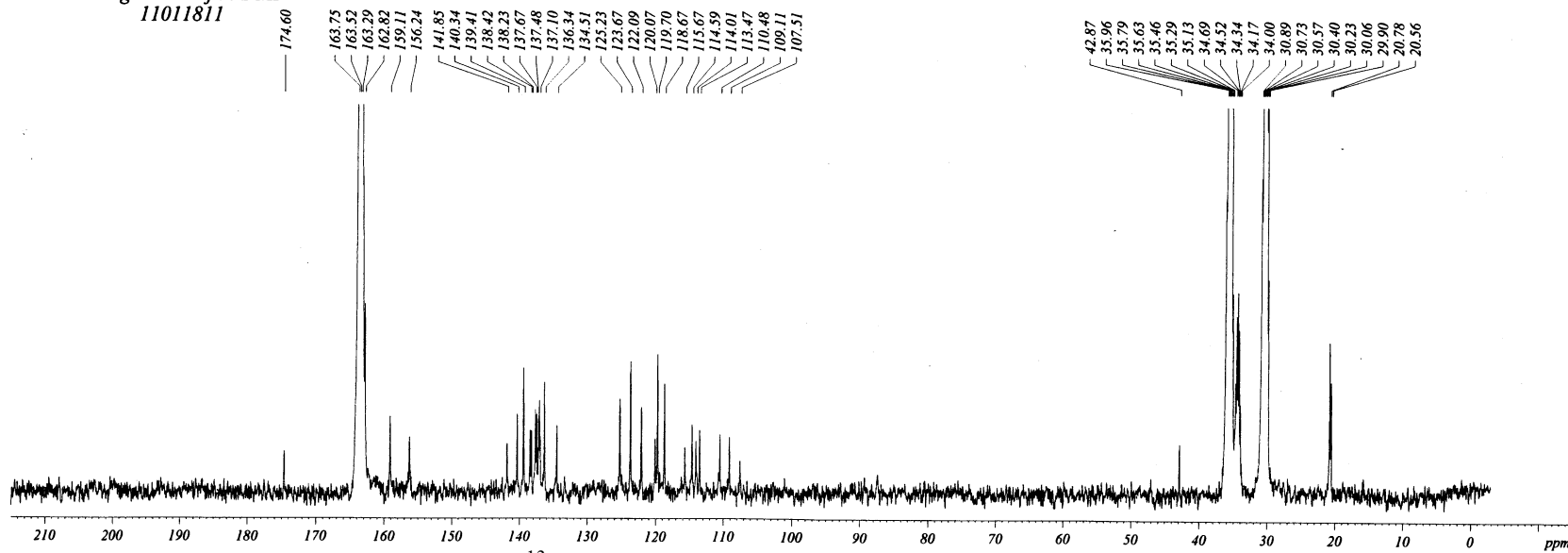


Figure 54. ^{13}C NMR (125 MHz, DMF-d_6) spectra of compound **5j**

YUNNAN UNIVER. AV. DRX500
huangchao hc7k in DMF
11011812

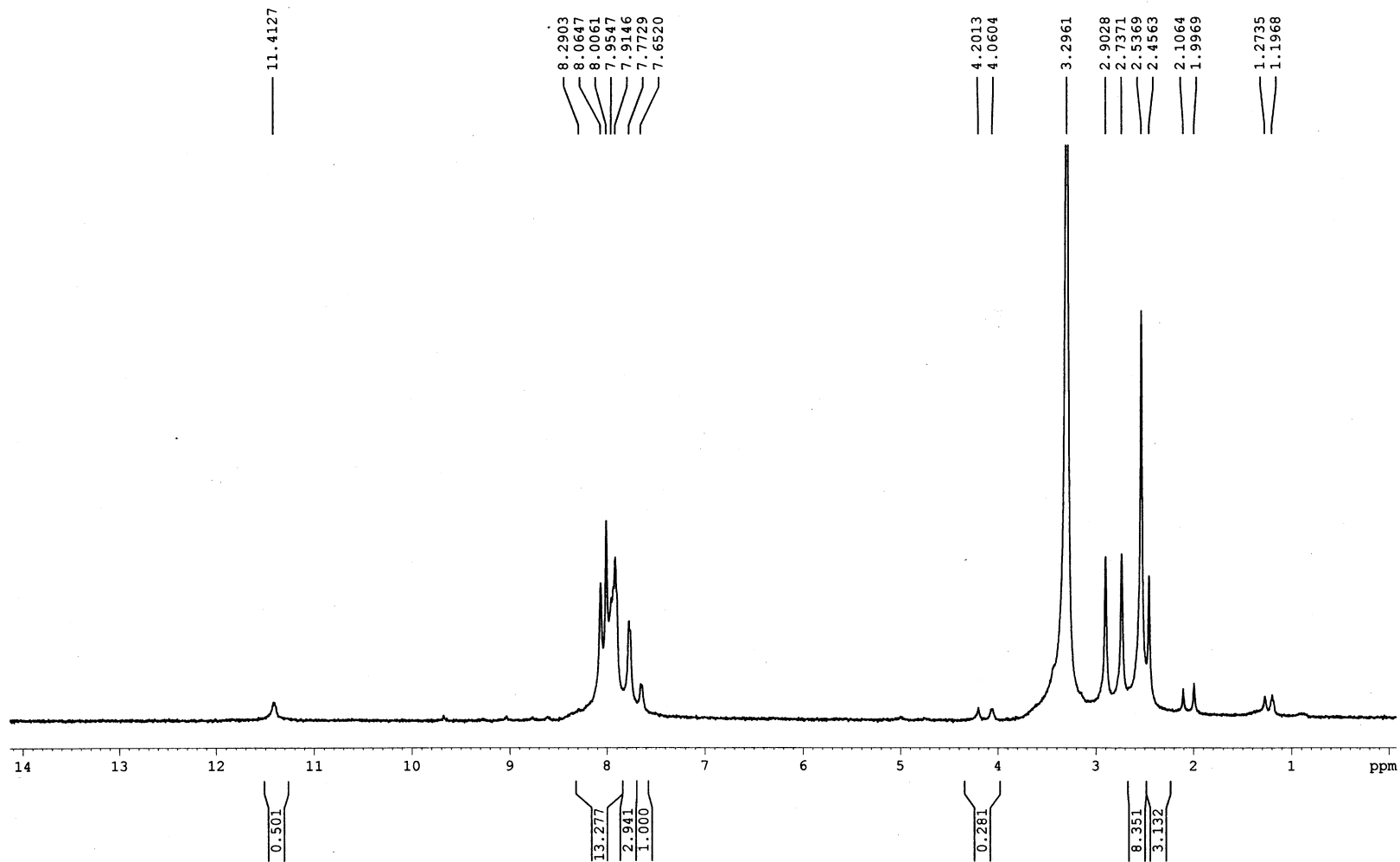


Figure 55. ^1H NMR (500 MHz, $\text{DMF}-d_6$) spectra of compound 5k

DEPT135

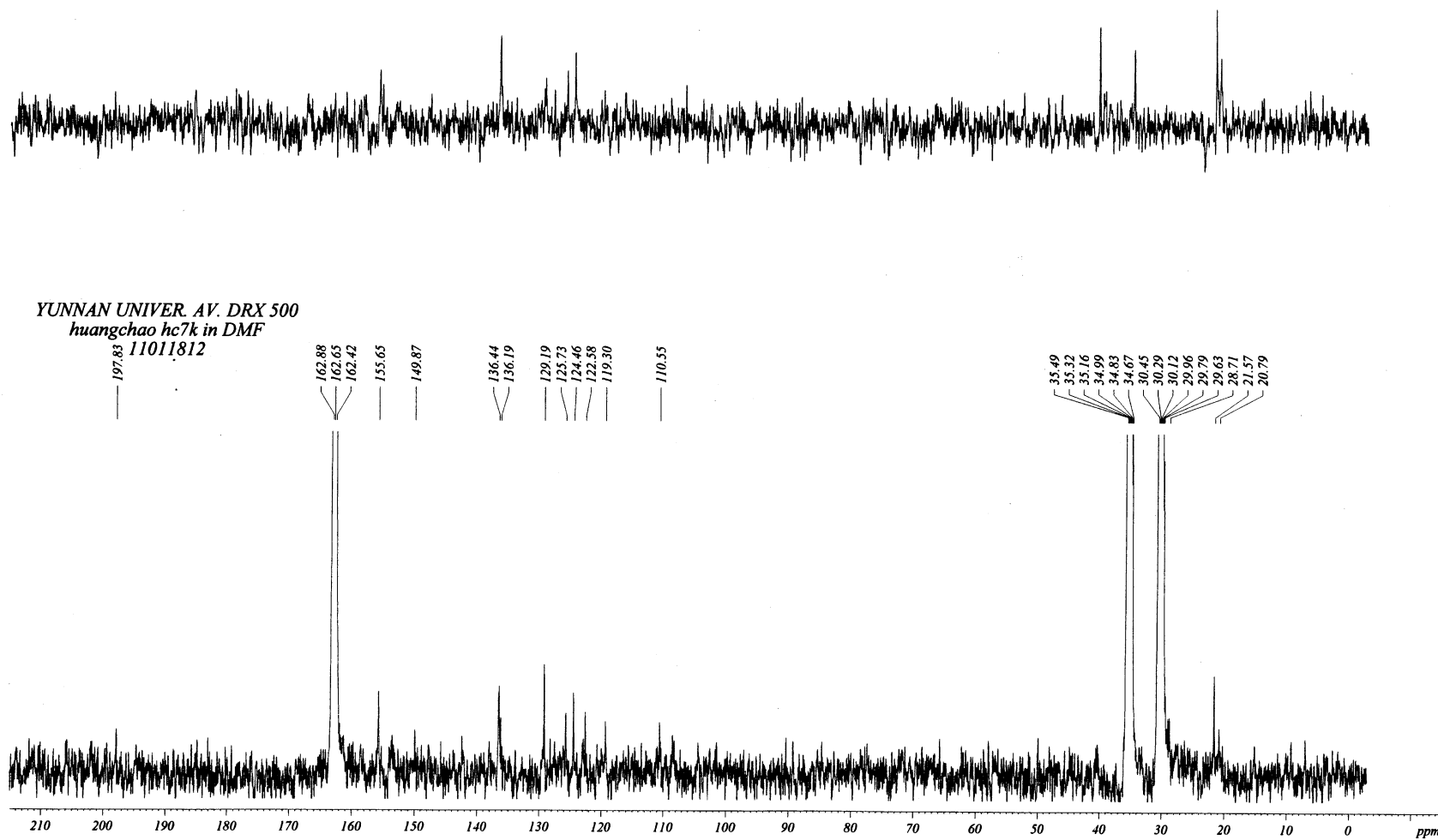


Figure 56. ^{13}C NMR (125 MHz, DMF-d_6) spectra of compound 5k

YUNNAN UNIVER. AV. DRX500
huangchao hc7k in DMF
19F decoupling 11011812

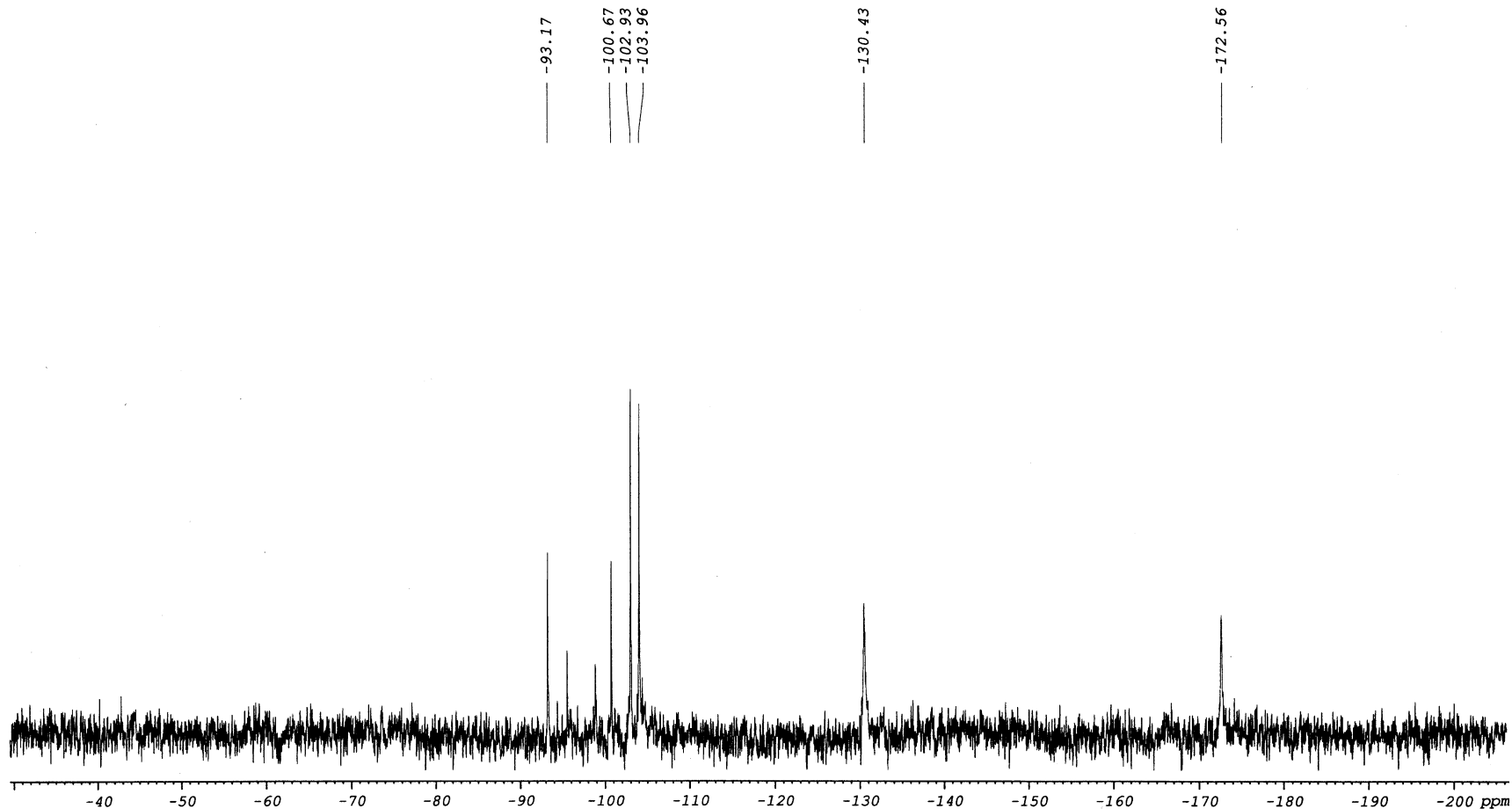


Figure 57. ^{19}F NMR (470 MHz, $\text{DMF-}d_6$) spectra of compound 5k

YUNNAN UNIVER. AV. DRX500
huangchao hch71 in DMF
10121003

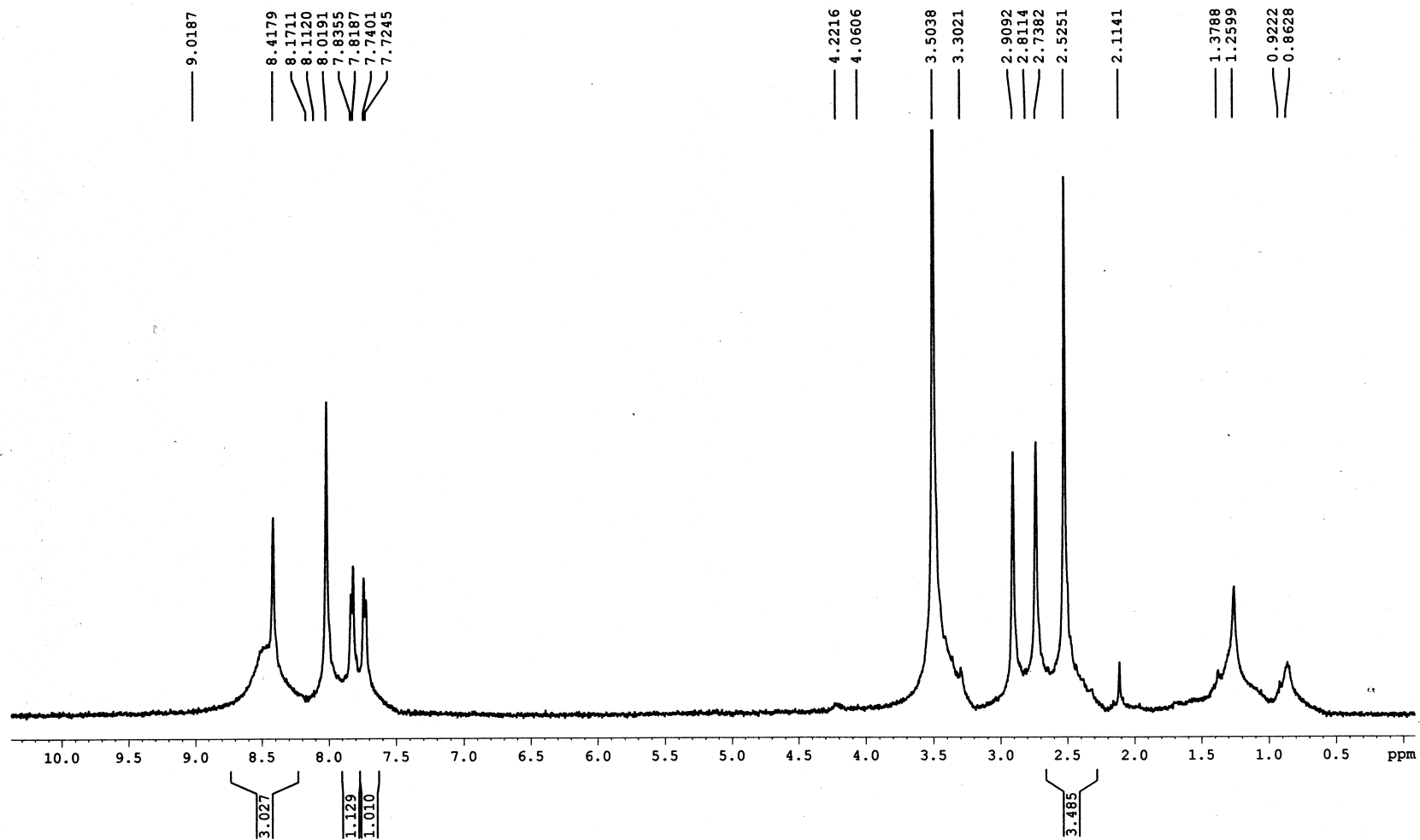


Figure 58. ^1H NMR (500 MHz, DMF-d_6) spectra of compound 51

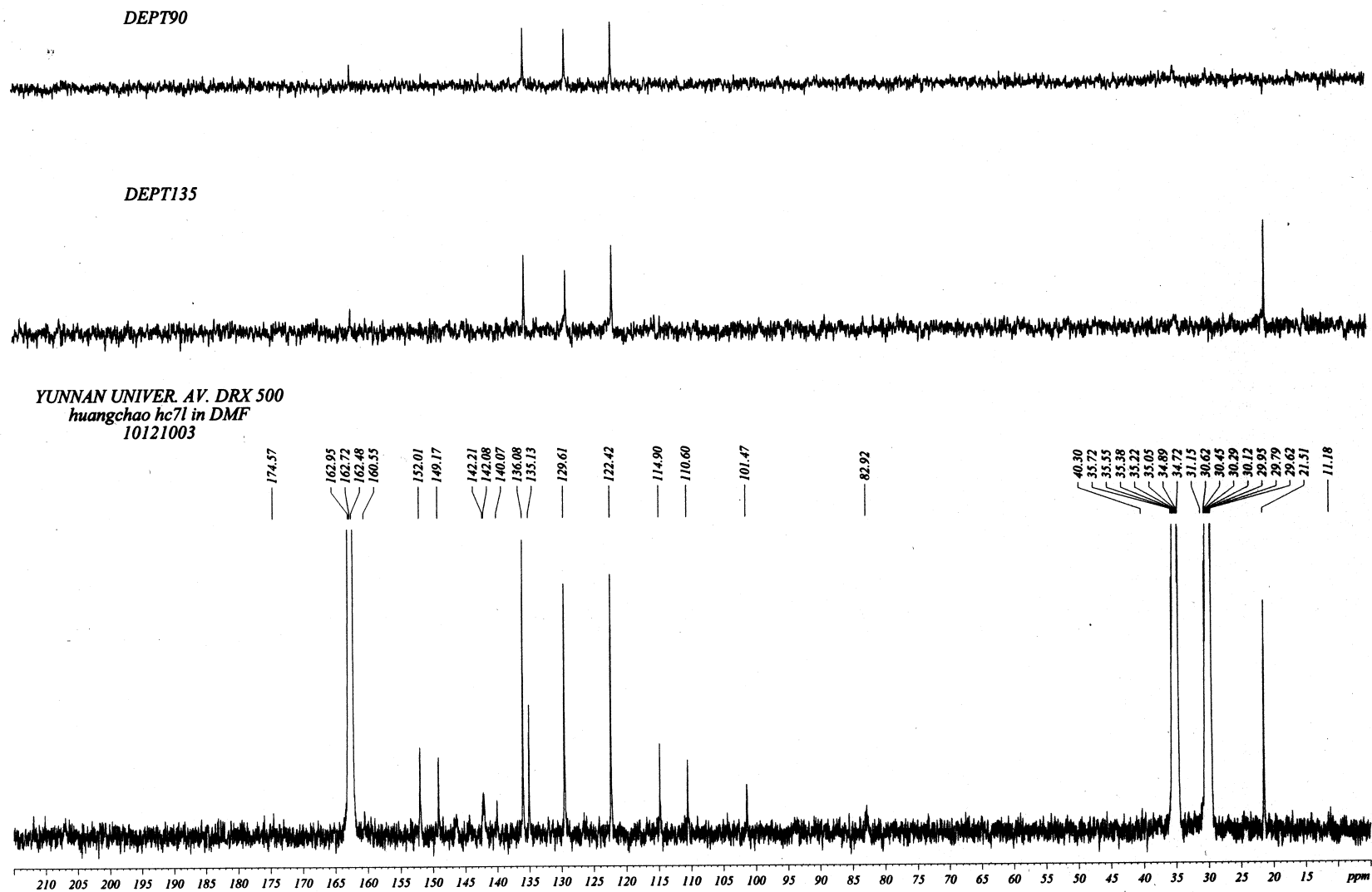


Figure 59. ^{13}C NMR (125 MHz, DMF-d_6) spectra of compound 51

YUNNAN UNIVER. AV. DRX500
huangchao hc71 in DMF
19F decoupling

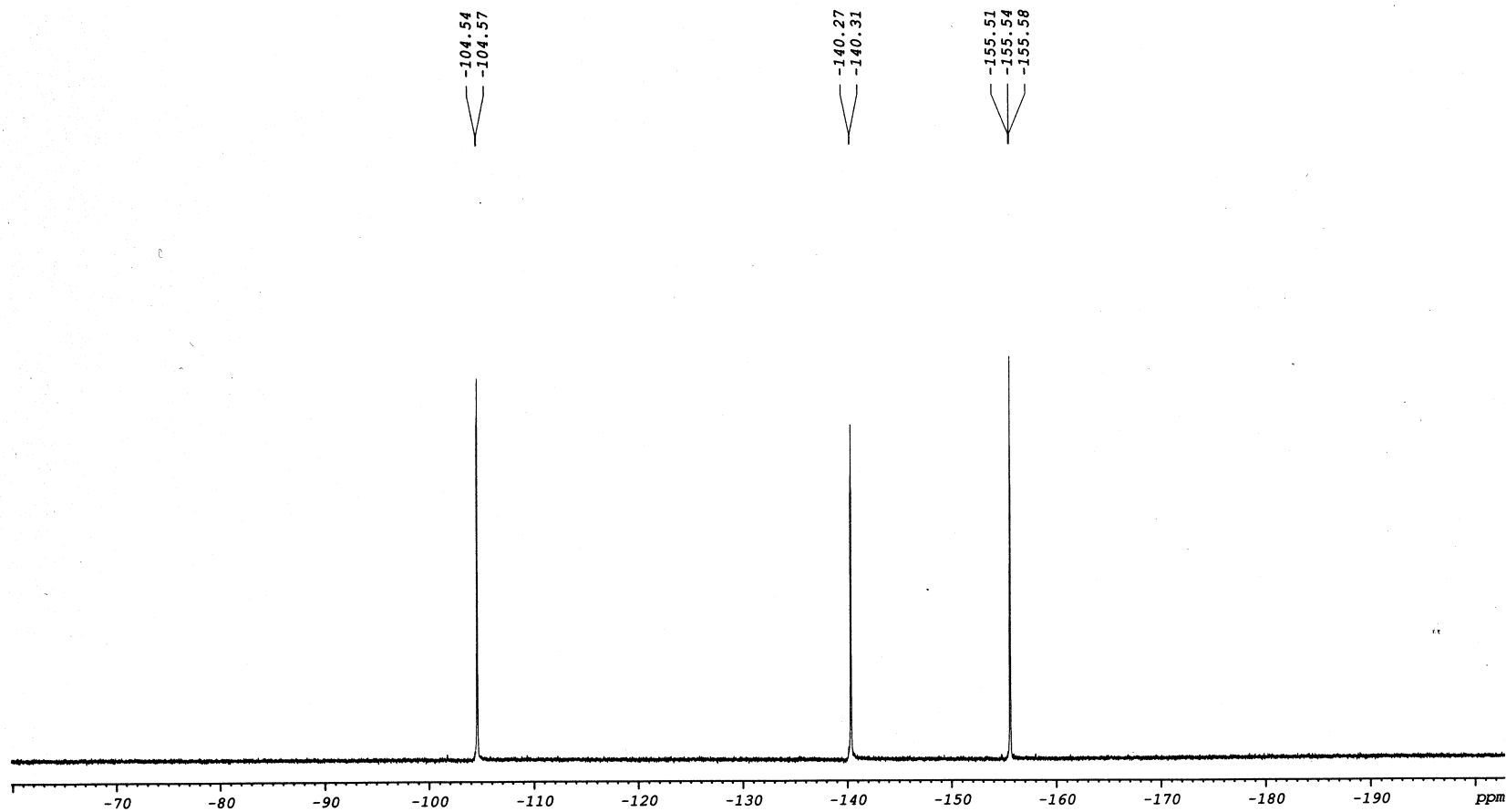


Figure 60. ^{19}F NMR (470 MHz, DMF-d_6) spectra of compound 51

References

- 1、 Huang, C.; Yan, S. J.; Li, Y. M.; Huang, R.; Lin, J. *Bioorg. Med. Chem. Lett.* **2010**, 20, 4665–4669.