Synthesis and Evaluation of the Antitumor Activity of Highly Functionalised Pyridin-2-ones and Pyrimidin-4-ones

Xuan-Xuan Du[a,‡], Rong Huang[a,‡], Chang-Long Yang[a], Jun Lin[a,*] and Sheng-Jiao Yan[a,*]

Key Laboratory of Medicinal Chemistry for Natural Resources (Yunnan University), Ministry of Education, School of Chemical Science and Technology, Yunnan University, Kunming, 650091, P. R. China

Supporting Information

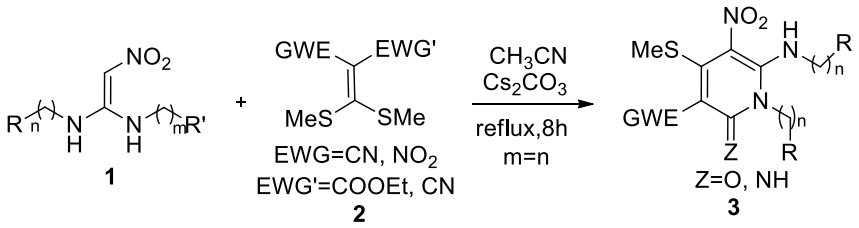
Table of Contents

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) or DRX600 (^{1}H: 600 MHz, ^{13}C: 150MHz), chemical shifts (δ) are expressed in ppm, and J values are given in Hz, deuterated DMSO-d_6 or $CDCl_3$ was 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 an Agilent LC/Msd TOF instrument.

All chemicals and solvents were used as received without further purification unless otherwise stated. Compounds **1** were prepared according to the literature[1] and compounds **2** were prepared according to the literature[2].

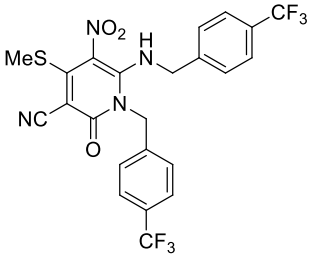
General Procedure for the Preparation Pyridin-2-ones 3



N,*N'*-disubstituted 1,1-ene diamines (DEDAMs) **1** (1.0 mmol), mercaptals **2** (1.0 mmol), Cs_2CO_3 (2.0 mmol), acetonitrile(15.0 mL) were added into a 25 mL round-bottom flask, mix at reflux for about 8 h and monitored by thin layer chromatography (TLC) until the DEDAMs **1** substrate was completely consumed. After the completion of the reaction, the reaction system was cooled to room temperature. The reaction mixture was poured into 25 mL of water and ethyl acetate for extraction and separation. Then the crude product was collected by filtering and enrichment, which was purified by column chromatography (petroleum ether/EtOAc =10: 1) or recrystallization and obtained a series of pyridin-2-one compounds **3** with 83–98% yield.

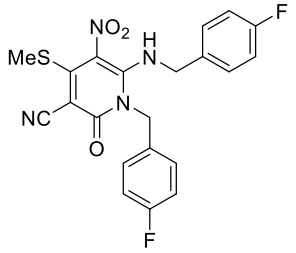
Spectroscopic Data of Pyridin-2-ones 3

4-(Methylthio)-5-nitro-2-oxo-1-(4-(trifluoromethyl)benzyl)-6-((4-(trifluoromethyl) -benzyl)amino)-1,2-dihydropyridine-3-carb-onitrile (3a).



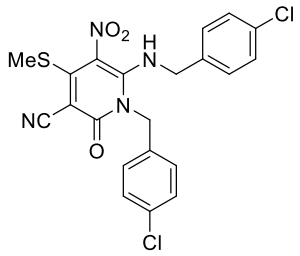
Yellow solid, mp 159.1–160.2 °C; IR (KBr): 3413, 2316, 1638, 1618, 1328, 1165, 1124, 1069 cm^{-1}; ^{1}H NMR (600 MHz, DMSO-d_6): δ = 2.74 (s, 3H, CH_3), 4.17 (m, 2H, CH_2), 5.47 (m, 2H, CH_2), 7.14−7.16 (m, 2H, ArH), 7.35−7.37 (m, 2H, ArH), 7.44−7.45 (m, 2H, ArH), 7.66−7.68 (m, 2H, ArH), 8.37 (br, 1H, NH); ^{13}C NMR (150 MHz, DMSO-d_6): δ = 19.4, 45.3, 49.2, 89.2, 116.8, 122.0, 122.7, 123.6, 123.8, 125.2, 125.3, 125.7, 125.9, 127.2, 127.4, 128.7, 128.7, 129.2, 139.5, 140.9, 149.9, 156.2, 159.2; HRMS (ESI-TOF): *m/z* calcd for $C_{23}H_{15}F_6N_4O_3S$ $[M-H]^-$, 541.0775; found, 541.0773.

1-(4-Fluorobenzyl)-6-((4-fluorobenzyl)amino)-4-(methylthio)-5-nitro-2-oxo-1,2-di -hydropyridine-3-carbonitrile (3b).



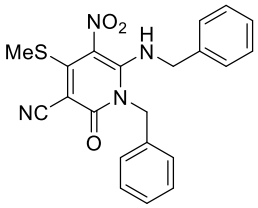
Yellow solid, mp 177.8−178.0 °C; IR (KBr): 3334, 1639, 1554, 1512, 1494, 1466, 1328, 1235 cm^{-1}; ^{1}H NMR (600 MHz, DMSO-d_6): δ = 2.72 (s, 3H, CH_3), 4.10 (m, 2H, CH_2), 5.36 (m, 2H, CH_2), 6.97–7.02 (m, 4H, ArH), 7.14–7.21 (m, 4H, ArH), 8.31 (br, 1H, NH); ^{13}C NMR (150 MHz, DMSO-d_6): δ = 19.4, 44.9, 49.0, 89.0, 115.3, 115.5, 115.8, 115.9, 116.9, 122.6, 128.9, 129.0, 130.6, 130.7, 132.3, 132.3, 149.8, 156.0, 159.2, 162.1, 162.1; HRMS (ESI-TOF): *m/z* calcd for $C_{21}H_{15}F_2N_4O_3S$ $[M-H]^-$, 441.0838; found, 441.0836.

1-(4-Chlorobenzyl)-6-((4-chlorobenzyl)amino)-4-(methylthio)-5-nitro-2-oxo-1,2-dihydropyridine-3-carbonitrile (3c).



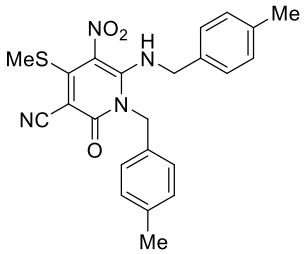
Yellow solid, mp 187.8–188.8 °C; IR (KBr): 3346, 2217, 1639, 1581, 1550, 1492, 1439, 1324 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ = 2.72 (s, 3H, CH_3), 4.09 (m, 2H, CH_2), 5.36 (m, 2H, CH_2), 6.94−6.96 (m, 2H, ArH), 7.15−7.21 (m, 4H, ArH), 7.37−7.39 (m, 2H, ArH), 8.30 (br, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 19.5, 45.0, 49.1, 89.0, 116.8, 122.6, 128.5, 128.5, 128.7, 128.7, 129.0, 129.0, 130.3, 130.3, 132.6, 132.9, 133.6, 135.1, 149.8, 156.0, 159.2; HRMS (ESI-TOF): *m/z* calcd for $C_{21}H_{15}Cl_2N_4O_3S$ $[M-H]^-$, 473.0247; found, 473.0247.

1-Benzyl-6-(benzylamino)-4-(methylthio)-5-nitro-2-oxo-1,2-di-hydropyridine-3-carbonitrile (3d).



Red solid, mp 134–135 °C; IR (KBr): 3442, 2193, 1603, 1566, 1444, 1345, 1287, 1187 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6): δ = 2.60 (s, 3H, CH_3), 4.14 (m, 2H, CH_2), 5.18 (m, 2H, CH_2), 7.12–7.25 (m, 10H, ArH), 7.27 (br, 1H, NH); ^{13}C NMR (150 MHz, DMSO-d_6): δ = 19.4, 44.6, 53.8, 82.6, 116.7, 119.2, 126.3, 126.3, 126.7, 126.7, 127.6, 127.6, 127.6, 128.3, 128.4, 128.4, 139.4, 142.6, 146.8, 157.4, 161.6; HRMS (ESI-TOF): *m/z* calcd for $C_{21}H_{17}N_4O_3S$ $[M-H]^-$ 405.1027; found, 405.1030.

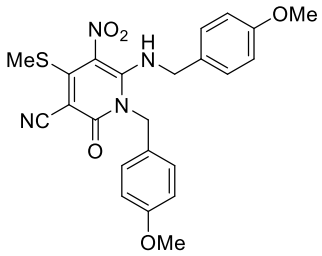
1-(4-Methylbenzyl)-6-((4-methylbenzyl)amino)-4-(methylthio)-5-nitro-2-oxo-1,2-dihydropyridine-3-carbonitrile (3e).



Yellow solid, mp 182.7–183.6 °C; IR (KBr): 3400, 2215, 1647, 1552, 1501, 1460, 1327 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ = 2.24 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 2.69 (s, 3H, CH_3), 4.08 (m, 2H, CH_2), 5.37 (m, 2H, CH_2), 6.73−6.74 (m, 2H, ArH), 6.94−6.95 (m, 2H, ArH), 7.03−7.04 (m, 2H, ArH), 7.14−7.15 (m, 2H, ArH), 8.28 (br, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 19.5, 21.1, 21.2, 45.2, 49.4, 88.9,

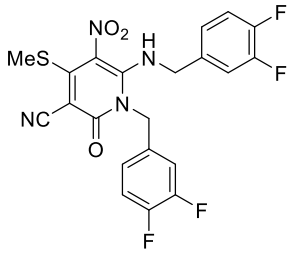
116.9, 122.4, 126.8, 126. 8, 128.3, 128.3, 129.2, 129.2, 129.6, 129.6, 131.5, 133.1, 137.2, 137.5, 149.7, 155.8, 159.2; HRMS (ESI-TOF): *m/z* calcd for $C_{23}H_{21}N_4O_3S$ $[M-H]^-$, 433.1340; found, 433.1340.

1-(4-Methoxybenzyl)-6-((4-methoxybenzyl)amino)-4-(methyl-thio)-5-nitro-2-oxo-1,2-dihydropyridine-3-carbonitrile (3f).



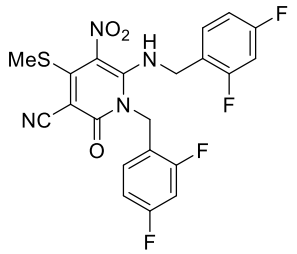
Yellow solid, mp 178.4–179.2 °C; IR (KBr): 3358, 2217, 1640, 1552, 1255, 1181, 1035, 812 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ = 2.70 (s, 3H, CH_3), 3.71 (s, 3H, CH_3), 3.76 (s, 3H, CH_3), 4.06 (m, 2H, CH_2), 5.33 (m, 2H, CH_2), 6.69−6.71 (m, 2H, ArH), 6.81−6.83 (m, 2H, ArH), 6.87−6.89 (m, 2H, ArH), 7.06−7.08 (m, 2H, ArH), 8.21 (br, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 19.5, 44.8, 49.2, 55.5, 55.6, 88.9, 114.1, 114.1, 114.6, 114.6, 116.9, 122.3, 126.3, 127.9, 128.3, 128.3, 129.9, 129.9, 149.6, 155.8, 159.2, 159.3, 159.3; HRMS (ESI-TOF): *m/z* calcd for $C_{23}H_{21}N_4O_5S$ $[M-H]^-$, 465.1238; found, 465.1240.

1-(3,4-Difluorobenzyl)-6-((3,4-difluorobenzyl)amino)-4-(meth-ylthio)-5-nitro-2-oxo-1,2-dihydropyridine-3-carbonitrile (3g).



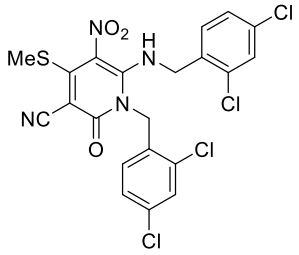
Yellow solid, mp 186.9–187.8 °C; IR (KBr): 3321, 2215, 1632, 1546, 1465, 1397, 1291, 1214 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6): δ = 2.74 (s, 3H, CH_3), 4.05 (m, 2H, CH_2), 5.33 (m, 2H, CH_2), 6.92−6.95 (m, 1H, ArH), 6.97−6.99 (m, 2H, ArH), 7.20−7.27 (m, 2H, ArH), 7.35−7.37 (m, 1H, ArH), 8.21 (br, 1H, NH); ^{13}C NMR (150 MHz, DMSO-d_6): δ = 19.4, 44.5, 48.9, 89.1, 116.4, 116.9, 117.4, 117.9, 118.0, 122.8, 123.6, 125.8, 132.2, 133.7, 149.3, 149.4, 149.5, 149.8, 149.8, 156.2, 159.2; HRMS (ESI-TOF): *m/z* calcd for $C_{21}H_{13}F_4N_4O_3S$ $[M-H]^-$, 477.0650; found, 477.0652.

1-(2,4-Difluorobenzyl)-6-((2,4-difluorobenzyl)amino)-4-(meth-ylthio)-5-nitro-2-oxo-1,2-dihydropyridine-3-carbonitrile (3h).



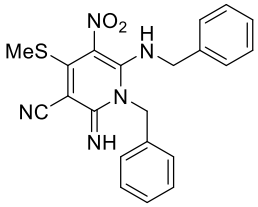
Yellow solid, mp 153.1–154.3 °C; IR (KBr): 3374, 2216, 1641, 1550, 1504, 1321, 1277, 1099 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ = 2.73 (s, 3H, CH_3), 4.17 (m, 2H, CH_2), 5.29 (m, 2H, CH_2), 6.96−7.02 (m, 2H, ArH), 7.08−7.18 (m, 2H, ArH), 7.22−7.31 (m, 2H, ArH), 8.39 (br, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 19.5, 41.3, 43.1, 89.3, 104.1, 104.4, 104.6, 111.8, 116.7, 118.3, 119.5, 122.6, 128.9, 132.3, 150.3, 156.4, 158.9, 160.2, 160.2, 162.4, 162.4; HRMS (ESI-TOF): *m/z* calcd for $C_{21}H_{13}F_4N_4O_3S$ $[M-H]^-$, 477.0650; found, 477.0651.

1-(2,4-Dichlorobenzyl)-6-((2,4-dichlorobenzyl)amino)-4-(meth-ylthio)-5-nitro-2-oxo-1,2-dihydropyridine-3-carbonitrile (3i).



Yellow solid, mp 164.4–165.6 °C; IR (KBr): 3417, 2216, 1666, 1555, 1476, 1384, 1330, 1106 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ = 2.74 (s, 3H, CH_3), 4.24 (m, 2H, CH_2), 5.21 (m, 2H, CH_2), 7.10−7.12 (m, 2H, ArH), 7.37−7.43 (m, 3H, ArH), 7.57−7.58 (m, 1H, ArH), 7.65−7.66 (m, 1H, ArH), 8.48 (br, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 19.5, 45.8, 47.3, 89.9, 116.6, 123.0, 127.7, 127.9, 128.1, 129.1, 129.3, 131.7, 132.9, 132.9, 133.1, 133.2, 133.8, 133.8, 151.0, 156.4, 159.0; HRMS (ESI-TOF): *m/z* calcd for $C_{21}H_{13}Cl_4N_4O_3S$, $[M-H]^-$, 540.9468; found, 540.9467.

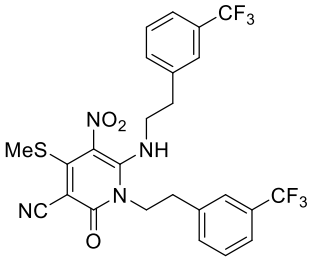
1-Benzyl-6-(benzylamino)-2-imino-4-(methylthio)-5-nitro-1,2-dihydropyridine-3-carbonitrile (3j).



Yellow solid, mp 175.9–176.0 °C; IR (KBr): 3345, 3033, 2923, 2215, 1638, 1590, 1492, 1466, 1351, 1054, 1031, 777, 693, 543, 465 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6): δ = 2.71 (s, 3H, CH_3), 4.13 (m, 2H, CH_2), 5.43 (m, 2H, CH_2), 6.86−6.87 (m, 2H, ArH), 7.13−7.17 (m, 4H, ArH), 7.20−7.22 (m, 1H, ArH), 7.33−7.37 (m, 3H,

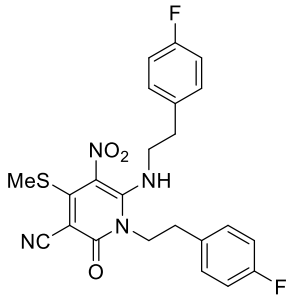
ArH), 8.41 (br, 1H, NH); ^{13}C NMR (150 MHz, DMSO-d_6): δ = 19.5, 29.5, 45.5, 49.7, 89.0, 116.9, 122.4, 126.7, 126.7, 127.9, 127.9, 128.2, 128.3, 128.8, 129.0, 129.1, 134.6, 136.1, 149.9, 155.9, 159.2; HRMS (ESI-TOF): *m/z* calcd for $C_{21}H_{19}N_5O_2S$ [M], 405.1259; found 405.1009.

4-(Methylthio)-5-nitro-2-oxo-1-(3-(trifluoromethyl)phenethyl)-6-((3-(trifluoro-methyl)phenethyl)amino)-1,2-dihydropyridine-3-carbonitrile (3k).



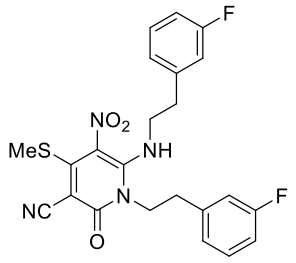
Yellow solid, mp 73.3–73.9 °C; IR (KBr): 3414, 2217, 1664, 1550, 1494, 1330, 1122, 1073 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 2.68 (s, 3H, CH_3), 2.76−2.79 (m, 2H, CH_2), 3.07−3.10 (m, 2H, CH_2), 4.25−4.28 (m, 2H, CH_2), 4.26(m, 2H, CH_2), 7.51−7.61 (m, 8H, ArH), 8.20 (br, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 19.2, 31.6, 34.7, 43.4, 47.0, 89.0, 116.6, 121.3, 121.4, 123.5, 123.6, 123.9, 125.7, 125.8, 127.9, 129.2, 129.6, 129.9, 133.4, 133.4, 139.4, 139.8, 149.7, 155.1, 158.7; HRMS (ESI-TOF): *m/z* calcd for $C_{25}H_{19}F_6N_4O_3S$ [M-H]$^-$, 569.1088; found, 569.1089.

1-(4-Fluorophenethyl)-6-((4-fluorophenethyl)amino)-4-(meth-ylthio)-5-nitro-2-oxo-1,2-dihydropyridine-3-carbonitrile (3l).



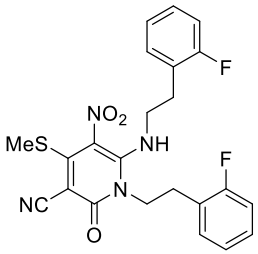
Yellow solid, mp 100.5–101.0 °C; IR (KBr): 3416, 2216, 1638, 1551, 1329, 1165, 1125, 1069 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 2.68 (s, 3H, CH_3), 2.70−2.71(m, 2H, CH_2), 2.93− 2.96 (m, 2H, CH_2), 3.25−3.26 (m, 2H, CH_2), 4.20−4.24 (m, 2H, CH_2), 7.10−7.17 (m, 4H, ArH), 7.23−7.26 (m, 4H, ArH), 8.11 (br, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 19.4, 31.2, 34.3, 43.8, 47.4, 89.0, 98.3, 115.5, 115.7, 115.7, 115.9, 116.8, 122.4, 131.0, 131.0, 131.0, 131.1, 134.3, 149.7, 155.1, 158.8, 161.6, 161.6; HRMS (ESI-TOF): *m/z* calcd for $C_{23}H_{19}F_2N_4O_3S$ [M-H]$^-$, 469.1151; found, 469.1152.

1-(3-Fluorophenethyl)-6-((3-fluorophenethyl)amino)-4-(methylthio)-5-nitro-2-oxo-1,2-dihydropyridine-3-carbonitrile (3m).



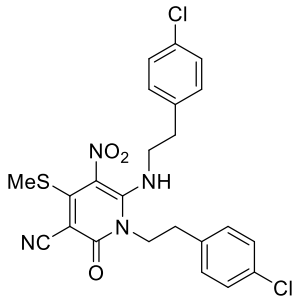
Yellow solid, mp 107.6–108.8 °C; IR (KBr): 3287, 2208, 1627, 1544, 1490, 1275, 1141 775 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 2.68 (s, 3H, CH_3), 2.69−2.72 (m, 2H, CH_2), 2.98−3.00 (m, 2H, CH_2), 3.30−3.31 (m, 2H, CH_2), 4.22−4.25 (m, 2H, CH_2), 7.05−7.09 (m, 6H, ArH), 7.33−7.35 (m, 2H, ArH), 8.13 (br, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 19.4, 31.6, 34.7, 43.5, 47.1, 89.1, 113.8, 114.0, 115.9, 116.0, 116.7, 122.4, 125.3, 125.3, 130.7, 130.9, 140.9, 141.2, 149.7, 155.2, 158.8, 161.7, 161.7; HRMS (ESI-TOF): *m/z* calcd for $C_{23}H_{19}F_2N_4O_3S$ $[M-H]^-$, 469.1151; found, 469.1153.

1-(2-Fluorophenethyl)-6-((2-fluorophenethyl)amino)-4-(meth-ylthio)-5-nitro-2-oxo-1,2-dihydropyridine-3-carbonitrile (3n).



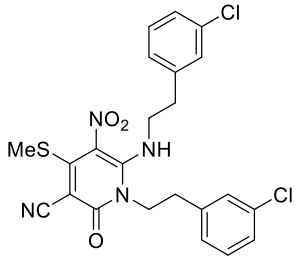
Yellow solid, mp 118.2–119.0 °C; IR (KBr): 3417, 2207, 1628, 1546, 1493, 1453, 1234, 757 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 2.66 (s, 3H, CH_3), 2.82−2.85 (m, 2H, CH_2), 2.98− 3.01 (m, 2H, CH_2), 3.24 (m, 2H, CH_2), 4.31−4.34 (m, 2H, CH_2), 7.12−7.17 (m, 4H, ArH), 7.26−7.29 (m, 4H, ArH), 8.17 (br, 1H, NH); ^{13}C NMR (125MHz, DMSO-d_6): δ = 19.4, 25.4, 28.7, 42.4, 46.1, 89.0, 115.5, 115.7, 116.7, 115.9, 116.7, 122.4, 124.7, 125.0, 129.3, 129.4, 131.6, 149.8, 155.1, 158.8, 160.1, 161.1, 161.1; HRMS (ESI-TOF): *m/z* calcd for $C_{23}H_{19}F_2N_4O_3S$ $[M-H]^-$, 469.1151; found, 469.1166.

1-(4-Chlorophenethyl)-6-((4-chlorophenethyl)amino)-4-(meth-ylthio)-5-nitro-2-oxo-1,2-dihydropyridine-3-carbonitrile (3o).



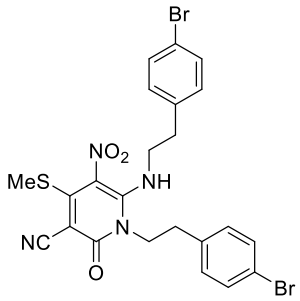
Yellow solid, mp 71.0–72.2 °C; IR (KBr): 3415, 2216, 1660, 1548, 1492, 1091, 1015, 816 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 2.68 (s, 3H, CH_3), 2.71 (m, 2H, CH_2), 2.94−2.97 (m, 2H, CH_2), 3.24−3.28 (m, 2H, CH_2), 4.21−4.24 (m, 2H, CH_2), 7.23−7.25 (m, 4H, ArH), 7.33−7.34 (m, 2H, ArH), 7.37−7.39 (m, 2H, ArH), 8.12 (br, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 19.4, 31.3, 34.4, 43.6, 47.2, 89.0, 116.7, 122.4, 128.8, 128.8, 129.0, 129.0, 131.0, 131.0, 131.1, 131.1, 131.8, 131.9, 137.0, 137.2, 149.6, 155.1, 158.8; HRMS (ESI-TOF): *m/z* calcd for $C_{23}H_{19}Cl_2N_4O_3S$ $[M-H]^-$, 501.0560; found, 501.0561.

1-(3-Chlorophenethyl)-6-((3-chlorophenethyl)amino)-4-(meth-ylthio)-5-nitro-2-oxo-1,2-dihydropyridine-3-carbonitrile (3p).



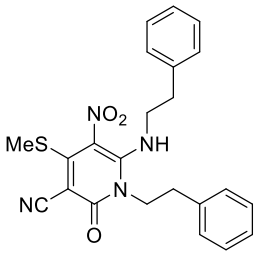
Yellow solid, mp 130.0–131.5 °C; IR (KBr): 3477, 3414, 1637, 1617, 1507, 1201, 767, 621 cm^{-1}; ^{1}H NMR (600 MHz, DMSO-d_6): δ = 2.68 (s, 3H, CH_3), 2.70 (m, 2H, CH_2), 2.96−2.99 (m, 2H, CH_2), 3.29−3.35 (m, 2H, CH_2), 4.21−4.24 (m, 2H, CH_2), 7.17−7.19 (m, 2H, ArH), 7.25−7.36 (m, 6H, ArH), 8.13 (br, 1H, NH); ^{13}C NMR (150 MHz, DMSO-d_6): δ = 19.4, 31.3, 34.7, 43.5, 47.0, 89.1, 116.7, 122.4, 127.1, 127.1, 127.9, 128.0, 129.1, 129.1, 130.7, 130.8, 133.5, 133.7, 140.5, 140.8, 149.7, 155.1, 158.7; HRMS (ESI-TOF): *m/z* calcd for $C_{23}H_{19}Cl_2N_4O_3S$ $[M-H]^-$, 501.0560; found, 501.0564.

1-(4-Bromophenethyl)-6-((4-bromophenethyl)amino)-4-(meth-ylthio)-5-nitro-2-oxo-1,2-dihydropyridine-3-carbonitrile (3q).



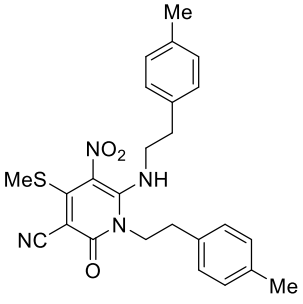
Yellow solid, mp 127.0–128.2 °C; IR (KBr): 3414, 2220, 1678, 1549, 1506, 1462, 1203, 767 cm^{-1}; ^{1}H NMR (600 MHz, DMSO-d_6): δ = 2.68 (s, 3H, CH_3), 2.65−2.67 (m, 2H, CH_2), 2.92−2.94 (m, 2H, CH_2), 3.23−3.26 (m, 2H, CH_2), 4.20−4.23 (m, 2H, CH_2), 7.17−7.18 (m, 4H, ArH), 7.46−7.48 (m, 2H, ArH), 7.51−7.52 (m, 2H, ArH), 8.12 (br, 1H, NH); ^{13}C NMR (150 MHz, DMSO-d_6): δ = 19.4, 31.4, 34.5, 43.5, 47.1, 89.0, 116.7, 120.2, 120.3, 122.4, 131.4, 131.4, 131.5, 131.5, 131.7, 131.7, 131.9, 131.9, 137.5, 137.7, 149.6, 155.1, 158.8; HRMS (ESI-TOF): *m/z* calcd for $C_{23}H_{19}Br_2N_4O_3S$, $[M-H]^-$, 588.9550; found, 588.9543.

4-(Methylthio)-5-nitro-2-oxo-1-phenethyl-6-(phenethylamino)-1,2-dihydropyridine-3-carbonitrile (3r).



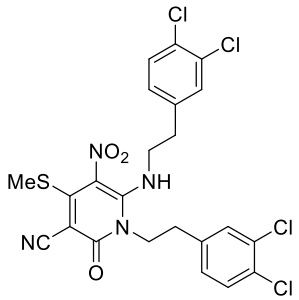
Yellow solid, mp 165.1–166.1 °C; IR (KBr): 3416, 3260, 2208, 1626, 1544, 1492, 1453, 1354 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 2.68 (s, 3H, CH_3), 2.71−2.72 (m, 2H, CH_2), 2.95−2.97 (m, 2H, CH_2), 3.26 (m, 2H, CH_2), 4.24−4.25 (m, 2H, CH_2), 7.22−7.34 (m, 10H, ArH), 8.13 (br, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 19.4, 31.6, 35.1, 43.8, 47.5, 89.0, 116.8, 122.4, 127.1, 127.1, 127.1, 127.1, 128.9, 128.9, 129.1, 129.1, 129.2, 129.2, 138.1, 138.2, 149.7, 155.1, 158.8; HRMS (ESI-TOF): *m/z* calcd for $C_{23}H_{21}N_4O_3S$ $[M-H]^-$, 433.1340; found, 433.1339.

1-(4-Methylphenethyl)-6-((4-methylphenethyl)amino)-4-(met-hylthio)-5-nitro-2-oxo-1,2-dihydropyridine-3-carbonitrile (3s).



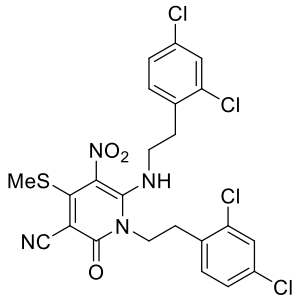
Yellow solid, mp 150.9–152.0 °C; IR (KBr):3475, 3415, 2210, 1617, 1540, 1494, 619, 478 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 2.23 (s, 3H, CH_3), 2.25 (s, 3H, CH_3), 2.65−2.67 (m, 2H, CH_2), 2.88−2.91 (m, 2H, CH_2), 3.22−3.24 (m, 2H, CH_2), 4.18−4.23 (m, 2H, CH_2), 7.02−7.12 (m, 8H, ArH), 8.09 (br, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 19.4, 21.1, 21.1, 31.6, 34.8, 43.9, 47.6, 88.9, 116.8, 122.4, 128.9, 129.1, 129.1, 129.2, 129.4, 129.5, 129.6, 129.8, 134.9, 135.2, 136.1 136.2, 149.7, 155.0, 158.8; HRMS (ESI-TOF): *m/z* calcd for $C_{25}H_{25}N_4O_3S$ $[M-H]^-$, 461.1653; found, 461.1652.

1-(3,4-Dichlorophenethyl)-6-((3,4-dichlorophenethyl)amino)-4-(methylthio)-5-nitro-2-oxo-1,2-dihydropyridine-3-carbonitrile (3t).



Yellow solid, m p. 162.2–163.1 °C; IR (KBr): 3417, 1638, 1618, 1561, 1220, 617, 479 cm^{-1}; ^{1}H NMR (600 MHz, DMSO-d_6): δ = 2.68 (m, 2H, CH_2), 2.68 (s, 3H, CH_3), 2.95−2.97 (m, 2H, CH_2), 3.30−3.31 (m, 2H, CH_2), 4.21−4.24 (m, 2H, CH_2), 7.19−7.22 (m, 2H, ArH), 7.44 (m, 1H, ArH), 7.51−7.58 (m, 3H, ArH), 8.11 (br, 1H, NH); ^{13}C NMR (150 MHz, DMSO-d_6): δ = 19.4, 31.0, 34.1, 43.3, 46.8, 89.0, 116.7, 122.5, 129.6, 129.6, 129.8, 129.9, 130.9, 131.0, 131.1, 131.3, 131.4, 131.6, 139.2, 139.5, 149.7, 155.2, 158.7; HRMS (ESI-TOF): *m/z* calcd for $C_{23}H_{17}Cl_4N_4O_3S$ $[M-H]^-$, 568.9781; found, 568.9764.

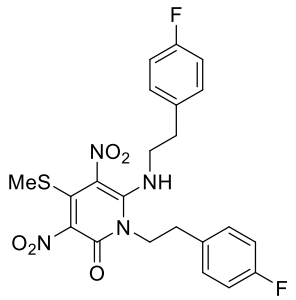
1-(2,4-Dichlorophenethyl)-6-((2,4-dichlorophenethyl)amino)-4-(methylthio)-5-nitro-2-oxo-1,2-dihydropyridine-3-carbonitrile (3u).



Yellow solid, mp 167.3–168.5 °C; IR (KBr): 3425, 3276, 2217, 1663, 1550, 1473, 1101, 867 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 2.67 (s, 3H, CH_3), 2.93 (m, 2H, CH_2), 3.06−3.09 (m, 2H, CH_2), 3.24 (m, 2H, CH_2), 4.37 (m, 2H, CH_2), 7.33−7.40 (m, 4H, ArH), 7.56−7.57 (m, 2H, ArH), 8.16 (br, 1H, NH); ^{13}C NMR (125 MHz,

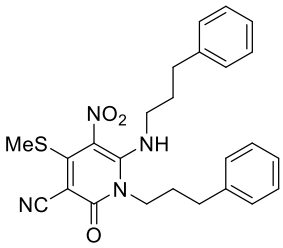
DMSO-d_6): δ = 19.4, 29.3, 32.4, 42.0, 45.5, 89.0, 116.6, 122.4, 127.8, 128.2, 129.1, 129.4, 132.7, 132.7, 132.8, 132.9, 134.5, 134.7, 134.9, 134.9. 149.8, 155.2, 158.8; HRMS (ESI-TOF): *m/z* calcd for $C_{23}H_{17}Cl_4N_4O_3S$ $[M-H]^-$, 568.9781; found, 568.9764.

1-(4-Fluorophenethyl)-6-((4-fluorophenethyl)amino)-4-(methylthio)-3,5-dinitropyridin-2(1*H*)-one (3v).



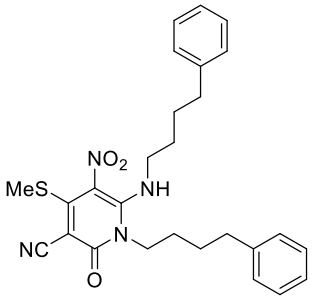
Yellow solid, mp 150.0–151.5 °C; IR (KBr): 3425, 2920, 1664, 1559, 1510, 1097, 802, 459 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.25 (s, 3H, CH_3), 2.79− 2.88(m, 4H, CH_2), 3.40−3.41 (m, 2H, CH_2), 4.13−4.16 (m, 2H, CH_2), 6.85−6.89 (m, 3H, ArH), 6.94−6.97 (m, 4H, ArH), 7.07−7.09 (m, 1H, ArH), 7.19 (br, 1H, NH); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 16.5, 31.5, 34.5, 47.0, 47.8, 114.7, 114.9, 115.0, 115.2, 119.7, 125.0, 129.1, 129.2, 129.2, 129.2, 130.9, 131.2, 144.3, 149.6, 152.6, 161.1, 161.1; HRMS (ESI-TOF): *m/z* calcd for $C_{22}H_{19}F_2N_4O_5S$ $[M-H]^-$, 489.1050; found, 489.1043.

4-(Methylthio)-5-nitro-2-oxo-1-(3-phenylpropyl)-6-((3-phenyl-propyl)amino)-1,2-dihydropyridine-3-carbonitrile (3w).



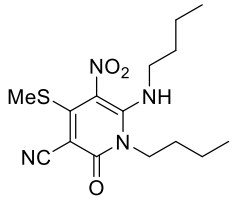
Yellow solid, mp 131.7–132.6 °C; IR (KBr): 3415, 2930, 2214, 1636, 1544, 1497, 1331, 700 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.84−1.90 (m, 2H, CH_2), 1.92−1.97 (m, 2H, CH_2), 2.55−2.58 (m, 2H, CH_2), 2.63 (s, 3H, CH_3), 2.65−2.66 (m, 2H, CH_2), 2.99−3.02 (m, 2H, CH_2), 4.07−4.10 (m, 2H, CH_2) 7.12−7.27 (m, 10H, ArH), 7.91 (br, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 19.3, 28.1, 30.8, 32.6, 32.7, 42.4, 46.1, 88.5, 117.0, 122.1, 126.4, 126.4, 126.4, 126.4, 126.4, 128.6, 128.6, 128.6, 128.8, 128.8, 141.3, 141.4, 149.8, 154.8, 158.9; HRMS (ESI-TOF): *m/z* calcd for $C_{25}H_{25}N_4O_3S$ $[M-H]^-$, 461.1653; found, 461.1653.

4-(Methylthio)-5-nitro-2-oxo-1-(4-phenylbutyl)-6-((4-phenyl-butyl)amino)-1,2-dihydropyridine-3-carbonitrile (3x).



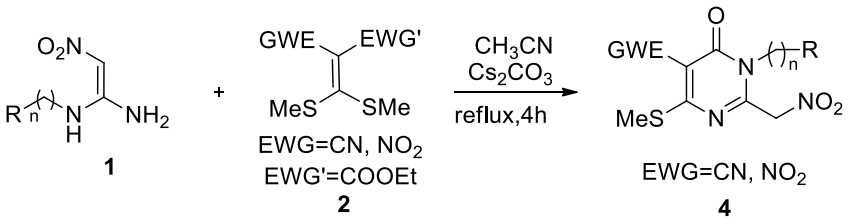
Yellow solid, mp 131.9–133.0 °C; IR (KBr): 3414, 3337, 2929, 2215, 1639, 1551, 1495, 1452 cm^{-1}; ^{1}H NMR (600 MHz, DMSO-d_6): δ = 1.54−1.60 (m, 8H, CH_2), 2.51−2.55 (m, 2H, CH_2), 2.57−2.60 (m, 2H, CH_2), 2.67 (s, 3H, CH_3), 2.96−2.98 (m, 2H, CH_2), 4.05−4.08 (m, 2H, CH_2), 7.15−7.18 (m, 6H, ArH), 7.24−7.29 (m, 4H, ArH) 7.81 (br, 1H, NH); ^{13}C NMR (150 MHz, DMSO-d_6): δ = 19.3, 26.4, 28.2, 28.4, 28.6, 35.0, 35.2, 42.3, 46.0, 88.4, 117.0, 122.2, 126.2, 126.2, 126.2, 126.2, 128.7, 128.7, 128.7, 128.7, 128.7, 128.7, 142.1, 142.2, 149.5, 154.7, 159.0; HRMS (ESI-TOF): *m/z* calcd for $C_{27}H_{29}N_4O_3S$ $[M-H]^-$, 489.1966; found, 489.1966.

1-Butyl-6-(butylamino)-4-(methylthio)-5-nitro-2-oxo-1,2-dihy-dropyridine-3-carb-onitrile (3y).



Yellow solid, mp 104.7–105.8 °C; IR (KBr): 3416, 3339, 2962, 2930, 2219, 1636, 1552, 1329 cm^{-1}; ^{1}H NMR (600 MHz, DMSO-d_6): δ = 0.83−0.86 (m, 3H, CH_3), 0.89−0.92 (m, 3H, CH_3), 1.23−1.27 (m, 2H, CH_2), 1.30−1.34 (m, 2H, CH_2), 1.49−1.56 (m, 2H, CH_2), 1.58−1.61 (m, 2H, CH_2), 2.68 (s, 3H, CH_3), 2.96−3.00 (m, 2H, CH_2), 4.04−4.06 (m, 2H, CH_2), 7.83 (br, 1H, NH); ^{13}C NMR (150 MHz, DMSO-d_6): δ = 13.9, 14.1, 19.3, 19.8, 19.9, 28.8, 31.2, 42.2, 45.9, 88.3, 117.0, 122.1, 149.5, 154.6, 158.9; HRMS (ESI-TOF): *m/z* calcd for $C_{15}H_{21}N_4O_3S$ $[M-H]^-$, 337.1340; found, 337.1341.

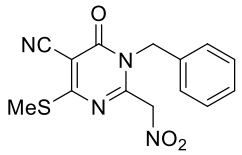
General Procedure for the Preparation pyrimidin-4-ones 4



N-monosubstituted 1,1-ene diamines (MEDAMs) **1** (1.0 mmol), mercaptals **2** (1.0 mmol), Cs_2CO_3 (2.0 mmol) and acetonitrile(15.0 mL) were added into a 25 mL round-bottom flask, mix at reflux for about 4 h and monitored by TLC until the MEDAMs **1** substrate was completely consumed. After the completion of the reaction, the reaction system was cooled to room temperature. The reaction mixture was poured into 25 mL of water and 25 mL ethyl acetate for extraction and separation. Then the crude product was collected by filtering and enrichment, which was purified by column chromatography (petroleum ether/EtOAc =3: 1) and obtained a series of pyrimidin-4-ones **4** with 92–98% yield.

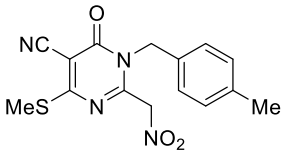
Spectroscopic Data of pyrimidin-4-ones 4

1-Benzyl-4-(methylthio)-2-(nitromethyl)-6-oxo-1,6-dihydropy-rimidine-5-carbo-nitrile (4a).



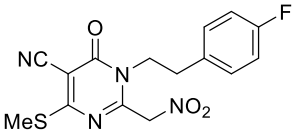
Orange solid, mp 115.0–116.2 °C; IR (KBr): 3291, 2926, 2206, 1506, 1439, 1291, 1215, 832 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ = 2.54 (s, 3H, CH_3), 5.25 (m, 2H, CH_2), 6.11 (s, 2H, CH_2), 7.27–7.32 (m, 2H, ArH), 7.32–7.39 (m, 3H, ArH); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 13.4, 47.2, 78.1, 94.1, 114.1, 127.3, 127.3, 128.4, 129.3, 129.3, 134.4, 154.8, 158.2, 174.3; HRMS (ESI-TOF): *m/z* calcd for $C_{14}H_{11}N_4O_3S$ $[M-H]^-$, 315.0557; found, 315.0546.

1-(4-Methylbenzyl)-4-(methylthio)-2-(nitromethyl)-6-oxo-1,6-dihydropyrimidine-5-carbonitrile (4b).



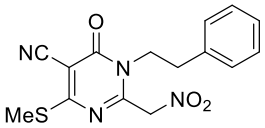
White solid, mp 158.0–158.5 °C; IR (KBr): 3441, 2930, 2222, 1684, 1572, 1506, 1379, 974 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ = 2.29 (s, 3H, CH_3), 2.53 (s, 3H, CH_3), 5.21 (m, 2H, CH_2), 6.10 (s, 2H, CH_2), 7.18 (m, 4H, ArH); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 13.4, 21.1, 46.9, 78.1, 94.0, 114.1, 126.9, 127.1, 129.9, 129.9, 131.4, 137.8, 154.8, 158.2, 174.2; HRMS (ESI-TOF): *m/z* calcd for $C_{15}H_{13}N_4O_3S$ $[M-H]^-$, 329.0714; found 329.0703.

1-(4-Fluorophenethyl)-4-(methylthio)-2-(nitromethyl)-6-oxo-1,6-dihydropyrimidine-5-carbonitrile (4c).



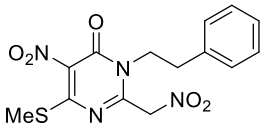
Yellow solid, mp 178.5–179.1°C; IR (KBr): 3415, 3015, 2223, 1671, 1553, 1508, 1161, 979 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ = 2.51 (s, 3H, CH_3), 2.91–2.94 (m, 2H, CH_2), 4.03–4.06 (m, 2H, CH_2), 6.24(s, 2H, CH_2), 7.16–7.19 (m, 2H, ArH), 7.33–7.36 (m, 2H, ArH); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 13.3, 32.4, 46.3, 78.1, 93.8, 114.1, 115.7, 115.9, 131.2, 131.3, 134.0, 154.6, 157.9, 161.7, 173.8; HRMS (ESI-TOF): *m/z* calcd for $C_{15}H_{12}FN_4O_3S$ $[M-H]^-$, 347.0620; found, 347.0610.

4-(Methylthio)-2-(nitromethyl)-6-oxo-1-phenethyl-1,6-dihydropyrimidine-5-carbonitrile (4d).



Yellow solid, mp 127.1–127.9°C; IR (KBr): 3439, 2952, 2222, 1670, 1574, 1502, 1374, 1187 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ = 2.50 (s, 3H, CH_3), 2.91–2.94 (m, 2H, CH_2), 4.04–4.07 (m, 2H, CH_2), 6.19 (s, 2H, CH_2), 7.26–7.36 (m, 5H, ArH); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 13.3, 33.2, 46.4, 78.1, 93.8, 114.1, 127.3, 129.1, 129.1, 129.4, 129.4, 137.8, 154.6, 157.9, 173.8; HRMS (ESI-TOF): *m/z* calcd for $C_{15}H_{13}N_4O_3S$ $[M-H]^-$, 329.0714; found, 329.0708.

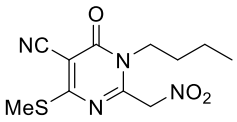
6-(Methylthio)-5-nitro-2-(nitromethyl)-3-phenethylpyrimidin-4(3*H*)-one (4e).



Yellow solid, mp 118.2–119.0 °C; IR (KBr): 3420, 1696, 1576, 1509, 1345, 1314,

969, 756 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 2.42 (s, 3H, CH_3), 2.94−2.98 (m, 2H, CH_2), 4.07−4.10 (m, 2H, CH_2), 6.22 (s, 2H, CH_2), 7.22−7.37 (m, 5H, ArH); ^{13}C NMR (125MHz, DMSO-d_6): δ = 14.4, 33.2, 46.6, 78.1, 127.2, 128.9, 129.1, 129.2, 129.4, 131.4, 137.9, 138.9, 153.1, 166.8; HRMS (ESI-TOF): *m/z* calcd for $C_{14}H_{13}N_4O_5S$ $[M-H]^-$, 349.0612; found, 349.0609.

1-Butyl-4-(methylthio)-2-(nitromethyl)-6-oxo-1,6-dihydropyrimidine-5-carbonitrile (4f).



Yellow solid, mp 175.0–176.5 °C; IR (KBr): 3422, 2962, 2222, 1690, 1505, 1342, 1135, 779 cm^{-1}; ^{1}H NMR (600 MHz, DMSO-d_6): δ = 0.90−0.92 (m, 3H, CH_3), 1.32−1.36(m, 3H, CH_2), 1.56−1.59 (m, 2H, CH_2), 3.87−3.89 (m, 3H, CH_3), 6.28 (s, 2H, CH_2); ^{13}C NMR (150 MHz, DMSO-d_6): δ = 13.2, 13.9, 19.9, 29.7, 44.8, 78.1, 93.7, 114.1, 154.6, 158.0, 173.7; HRMS (ESI-TOF): *m/z* calcd for $C_{11}H_{14}N_4O_3S$ $[M-H]^-$, 281.0714; found, 281.0704.

X-ray Structure and Data[3] of 3f

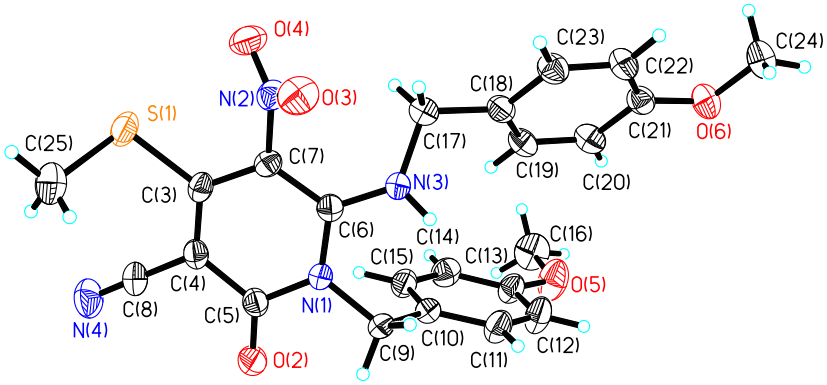


Figure S1 X-Ray crystal structure of **3f**

Table S1 Crystal data and structure refinement for **3f**

Empirical formula	$C_{25}H_{28}N_4O_6S_2$
Formula weight	544.63
Temperature	293(2) K
Wavelength	0.71073 A
Crystal system, space group	Triclinic, P-1
Unit cell dimensions	a = 10.2637(11) A alpha = 97.1560(10) deg. b = 12.3231(14) A beta = 107.7330(10) deg. c = 12.7383(14) A gamma = 112.9910(10) deg.
Volume	1357.1(3) A^3
Z, Calculated density	2, 1.333 Mg/m^3
Absorption coefficient	0.242 mm^-1
F(000)	572
Crystal size	0.30 x 0.24 x 0.16 mm
Theta range for data collection	1.75 to 25.15 deg.
Limiting indices	-12<=h<=12, -14<=k<=14, -15<=l<=15
Reflections collected / unique	10855 / 4829 [R(int) = 0.0309]
Completeness to theta = 25.15	99.4 %
Max. and min. transmission	0.9623 and 0.9309
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4829 / 0 / 339
Goodness-of-fit on F^2	1.052
Final R indices [I>2sigma(I)]	R1 = 0.0516, wR2 = 0.1439
R indices (all data)	R1 = 0.0834, wR2 = 0.1688
Largest diff. peak and hole	0.345 and -0.308 e.A^-3

Table S2 Bond lengths [A] and angles [deg] for **3f**

N(1)-C(6)	1.372(3)
N(1)-C(5)	1.408(3)
N(1)-C(9)	1.477(3)
N(2)-O(4)	1.216(3)
N(2)-O(3)	1.233(3)
N(2)-C(7)	1.452(4)
N(3)-C(6)	1.340(3)
N(3)-C(17)	1.459(3)
N(3)-H(3)	0.8600
N(4)-C(8)	1.141(4)
O(1)-S(2)	1.474(2)
O(2)-C(5)	1.222(3)
O(5)-C(13)	1.375(4)
O(5)-C(16)	1.400(4)
O(6)-C(21)	1.369(4)
O(6)-C(24)	1.427(4)
S(1)-C(3)	1.771(3)
S(1)-C(25)	1.776(4)
S(2)-C(2)	1.759(5)
S(2)-C(1)	1.774(5)
C(1)-H(1A)	0.9600
C(1)-H(1B)	0.9600
C(1)-H(1C)	0.9600
C(2)-H(2A)	0.9600
C(2)-H(2B)	0.9600
C(2)-H(2C)	0.9600
C(3)-C(4)	1.373(4)
C(3)-C(7)	1.400(4)
C(4)-C(8)	1.426(4)
C(4)-C(5)	1.447(4)
C(6)-C(7)	1.410(4)
C(9)-C(10)	1.501(4)
C(9)-H(9A)	0.9700
C(9)-H(9B)	0.9700
C(10)-C(15)	1.372(4)
C(10)-C(11)	1.394(4)
C(11)-C(12)	1.367(5)
C(11)-H(11)	0.9300
C(12)-C(13)	1.373(5)
C(12)-H(12)	0.9300
C(13)-C(14)	1.384(4)
C(14)-C(15)	1.405(4)
C(14)-H(14)	0.9300
C(15)-H(15)	0.9300
C(16)-H(16A)	0.9600
C(16)-H(16B)	0.9600
C(16)-H(16C)	0.9600
C(17)-C(18)	1.506(4)

C(17)-H(17A)	0.9700
C(17)-H(17B)	0.9700
C(18)-C(19)	1.385(4)
C(18)-C(23)	1.388(4)
C(19)-C(20)	1.377(4)
C(19)-H(19)	0.9300
C(20)-C(21)	1.393(4)
C(20)-H(20)	0.9300
C(21)-C(22)	1.375(4)
C(22)-C(23)	1.379(4)
C(22)-H(22)	0.9300
C(23)-H(23)	0.9300
C(24)-H(24A)	0.9600
C(24)-H(24B)	0.9600
C(24)-H(24C)	0.9600
C(25)-H(25A)	0.9600
C(25)-H(25B)	0.9600
C(25)-H(25C)	0.9600
C(6)-N(1)-C(5)	123.5(2)
C(6)-N(1)-C(9)	120.3(2)
C(5)-N(1)-C(9)	116.1(2)
O(4)-N(2)-O(3)	123.2(3)
O(4)-N(2)-C(7)	118.7(3)
O(3)-N(2)-C(7)	118.0(3)
C(6)-N(3)-C(17)	126.1(2)
C(6)-N(3)-H(3)	117.0
C(17)-N(3)-H(3)	117.0
C(13)-O(5)-C(16)	120.1(3)
C(21)-O(6)-C(24)	117.2(2)
C(3)-S(1)-C(25)	104.50(17)
O(1)-S(2)-C(2)	105.8(2)
O(1)-S(2)-C(1)	106.0(2)
C(2)-S(2)-C(1)	97.9(3)
S(2)-C(1)-H(1A)	109.5
S(2)-C(1)-H(1B)	109.5
H(1A)-C(1)-H(1B)	109.5
S(2)-C(1)-H(1C)	109.5
H(1A)-C(1)-H(1C)	109.5
H(1B)-C(1)-H(1C)	109.5
S(2)-C(2)-H(2A)	109.5
S(2)-C(2)-H(2B)	109.5
H(2A)-C(2)-H(2B)	109.5
S(2)-C(2)-H(2C)	109.5
H(2A)-C(2)-H(2C)	109.5
H(2B)-C(2)-H(2C)	109.5
C(4)-C(3)-C(7)	118.6(3)
C(4)-C(3)-S(1)	122.2(2)
C(7)-C(3)-S(1)	119.1(2)
C(3)-C(4)-C(8)	123.3(3)
C(3)-C(4)-C(5)	121.8(3)

C(8)-C(4)-C(5)	114.8(3)
O(2)-C(5)-N(1)	120.2(3)
O(2)-C(5)-C(4)	123.7(3)
N(1)-C(5)-C(4)	116.0(2)
N(3)-C(6)-N(1)	117.8(2)
N(3)-C(6)-C(7)	124.6(2)
N(1)-C(6)-C(7)	117.6(2)
C(3)-C(7)-C(6)	122.1(2)
C(3)-C(7)-N(2)	118.4(2)
C(6)-C(7)-N(2)	118.5(2)
N(4)-C(8)-C(4)	178.5(4)
N(1)-C(9)-C(10)	114.6(2)
N(1)-C(9)-H(9A)	108.6
C(10)-C(9)-H(9A)	108.6
N(1)-C(9)-H(9B)	108.6
C(10)-C(9)-H(9B)	108.6
H(9A)-C(9)-H(9B)	107.6
C(15)-C(10)-C(11)	118.3(3)
C(15)-C(10)-C(9)	122.7(3)
C(11)-C(10)-C(9)	119.1(3)
C(12)-C(11)-C(10)	121.2(3)
C(12)-C(11)-H(11)	119.4
C(10)-C(11)-H(11)	119.4
C(11)-C(12)-C(13)	120.4(3)
C(11)-C(12)-H(12)	119.8
C(13)-C(12)-H(12)	119.8
C(12)-C(13)-O(5)	115.8(3)
C(12)-C(13)-C(14)	120.0(3)
O(5)-C(13)-C(14)	124.2(3)
C(13)-C(14)-C(15)	119.0(3)
C(13)-C(14)-H(14)	120.5
C(15)-C(14)-H(14)	120.5
C(10)-C(15)-C(14)	121.1(3)
C(10)-C(15)-H(15)	119.4
C(14)-C(15)-H(15)	119.4
O(5)-C(16)-H(16A)	109.5
O(5)-C(16)-H(16B)	109.5
H(16A)-C(16)-H(16B)	109.5
O(5)-C(16)-H(16C)	109.5
H(16A)-C(16)-H(16C)	109.5
H(16B)-C(16)-H(16C)	109.5
N(3)-C(17)-C(18)	110.9(2)
N(3)-C(17)-H(17A)	109.5
C(18)-C(17)-H(17A)	109.5
N(3)-C(17)-H(17B)	109.5
C(18)-C(17)-H(17B)	109.5
H(17A)-C(17)-H(17B)	108.0
C(19)-C(18)-C(23)	117.0(3)
C(19)-C(18)-C(17)	123.1(3)
C(23)-C(18)-C(17)	119.9(3)

C(20)-C(19)-C(18)	121.7(3)
C(20)-C(19)-H(19)	119.2
C(18)-C(19)-H(19)	119.2
C(19)-C(20)-C(21)	120.1(3)
C(19)-C(20)-H(20)	119.9
C(21)-C(20)-H(20)	119.9
O(6)-C(21)-C(22)	124.7(3)
O(6)-C(21)-C(20)	116.2(3)
C(22)-C(21)-C(20)	119.1(3)
C(21)-C(22)-C(23)	119.9(3)
C(21)-C(22)-H(22)	120.1
C(23)-C(22)-H(22)	120.1
C(22)-C(23)-C(18)	122.2(3)
C(22)-C(23)-H(23)	118.9
C(18)-C(23)-H(23)	118.9
O(6)-C(24)-H(24A)	109.5
O(6)-C(24)-H(24B)	109.5
H(24A)-C(24)-H(24B)	109.5
O(6)-C(24)-H(24C)	109.5
H(24A)-C(24)-H(24C)	109.5
H(24B)-C(24)-H(24C)	109.5
S(1)-C(25)-H(25A)	109.5
S(1)-C(25)-H(25B)	109.5
H(25A)-C(25)-H(25B)	109.5
S(1)-C(25)-H(25C)	109.5
H(25A)-C(25)-H(25C)	109.5
H(25B)-C(25)-H(25C)	109.5

Symmetry transformations used to generate equivalent atoms:

X-ray Structure and Data[4] of 4f

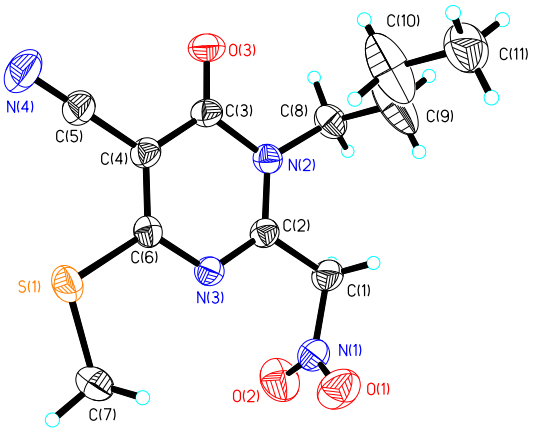


Figure S2 X-Ray crystal structure of **4f**

Table S3 Crystal data and structure refinement for **4f**

Identification code	1
Empirical formula	$C_{11}\ H_{14}\ N_4\ O_3\ S$
Formula weight	282.32
Temperature	293(2) K
Wavelength	0.71073 A
Crystal system, space group	Monoclinic, P 21/n
Unit cell dimensions	a = 5.033(4) A alpha = 90 deg b = 14.483(12) A beta =96.932(10) deg c = 19.140(16) A gamma = 90 deg.
Volume	1385(2) A^3
Z, Calculated density	4, 1.354 Mg/m^3
Absorption coefficient	0.244 mm^-1
F(000)	592
Crystal size	0.360 x 0.220 x 0.190 mm
Theta range for data collection	1.768 to 27.885 deg.
Limiting indices	-6<=h<=6, -18<=k<=19, -24<=l<=24
Reflections collected / unique	12559 / 3203 [R(int) = 0.0346]
Completeness to theta = 25.242	100.0 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.955 and 0.918
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3203 / 0 / 174
Goodness-of-fit on F^2	1.063
Final R indices [I>2sigma(I)]	R1 = 0.0669, wR2 = 0.2032
R indices (all data)	R1 = 0.0980, wR2 = 0.228
Extinction coefficient	n/a
Largest diff. peak and hole	0.657 and -0.688 e.A^-3

Table S4. Bond lengths [A] and angles [deg] for **4f**.

N(1)-O(1)	1.205(4)
N(1)-O(2)	1.208(4)
N(1)-C(1)	1.489(4)
N(2)-C(2)	1.359(4)
N(2)-C(3)	1.425(4)
N(2)-C(8)	1.488(4)
N(3)-C(2)	1.312(4)
N(3)-C(6)	1.362(4)
N(4)-C(5)	1.152(5)
O(3)-C(3)	1.214(4)
S(1)-C(6)	1.742(3)
S(1)-C(7)	1.799(4)
C(1)-C(2)	1.512(5)
C(1)-H(1A)	0.9700
C(1)-H(1B)	0.9700
C(3)-C(4)	1.446(4)
C(4)-C(6)	1.381(4)
C(4)-C(5)	1.436(4)
C(7)-H(7A)	0.9600
C(7)-H(7B)	0.9600
C(7)-H(7C)	0.9600
C(8)-C(9)	1.525(7)
C(8)-H(8A)	0.9700
C(8)-H(8B)	0.9700
C(9)-C(10)	1.283(8)
C(9)-H(9A)	0.9700
C(9)-H(9B)	0.9700
C(10)-C(11)	1.529(7)
C(10)-H(10A)	0.9700
C(10)-H(10B)	0.9700
C(11)-H(11A)	0.9600
C(11)-H(11B)	0.9600
C(11)-H(11C)	0.9600
O(1)-N(1)-O(2)	126.1(4)
O(1)-N(1)-C(1)	117.1(3)
O(2)-N(1)-C(1)	116.8(3)
C(2)-N(2)-C(3)	120.2(2)
C(2)-N(2)-C(8)	123.3(3)
C(3)-N(2)-C(8)	116.5(3)
C(2)-N(3)-C(6)	117.8(3)
C(6)-S(1)-C(7)	103.33(17)
N(1)-C(1)-C(2)	109.3(3)
N(1)-C(1)-H(1A)	109.8
C(2)-C(1)-H(1A)	109.8
N(1)-C(1)-H(1B)	109.8
C(2)-C(1)-H(1B)	109.8
H(1A)-C(1)-H(1B)	108.3
N(3)-C(2)-N(2)	125.5(3)
N(3)-C(2)-C(1)	117.5(3)

N(2)-C(2)-C(1)	117.0(3)
O(3)-C(3)-N(2)	120.6(3)
O(3)-C(3)-C(4)	125.9(3)
N(2)-C(3)-C(4)	113.5(3)
C(6)-C(4)-C(5)	121.3(3)
C(6)-C(4)-C(3)	121.2(3)
C(5)-C(4)-C(3)	117.4(3)
N(4)-C(5)-C(4)	178.7(4)
N(3)-C(6)-C(4)	121.5(3)
N(3)-C(6)-S(1)	118.3(2)
C(4)-C(6)-S(1)	120.2(2)
S(1)-C(7)-H(7A)	109.5
S(1)-C(7)-H(7B)	109.5
H(7A)-C(7)-H(7B)	109.5
S(1)-C(7)-H(7C)	109.5
H(7A)-C(7)-H(7C)	109.5
H(7B)-C(7)-H(7C)	109.5
N(2)-C(8)-C(9)	112.9(3)
N(2)-C(8)-H(8A)	109.0
C(9)-C(8)-H(8A)	109.0
N(2)-C(8)-H(8B)	109.0
C(9)-C(8)-H(8B)	109.0
H(8A)-C(8)-H(8B)	107.8
C(10)-C(9)-C(8)	124.6(7)
C(10)-C(9)-H(9A)	106.2
C(8)-C(9)-H(9A)	106.2
C(10)-C(9)-H(9B)	106.2
C(8)-C(9)-H(9B)	106.2
H(9A)-C(9)-H(9B)	106.4
C(9)-C(10)-C(11)	121.3(7)
C(9)-C(10)-H(10A)	107.0
C(11)-C(10)-H(10A)	107.0
C(9)-C(10)-H(10B)	107.0
C(11)-C(10)-H(10B)	107.0
H(10A)-C(10)-H(10B)	106.7
C(10)-C(11)-H(11A)	109.5
C(10)-C(11)-H(11B)	109.5
H(11A)-C(11)-H(11B)	109.5
C(10)-C(11)-H(11C)	109.5
H(11A)-C(11)-H(11C)	109.5
H(11B)-C(11)-H(11C)	109.5

Symmetry transformations used to generate equivalent atoms:

^{1}H NMR and ^{13}C NMR Spectra of compounds 3~4

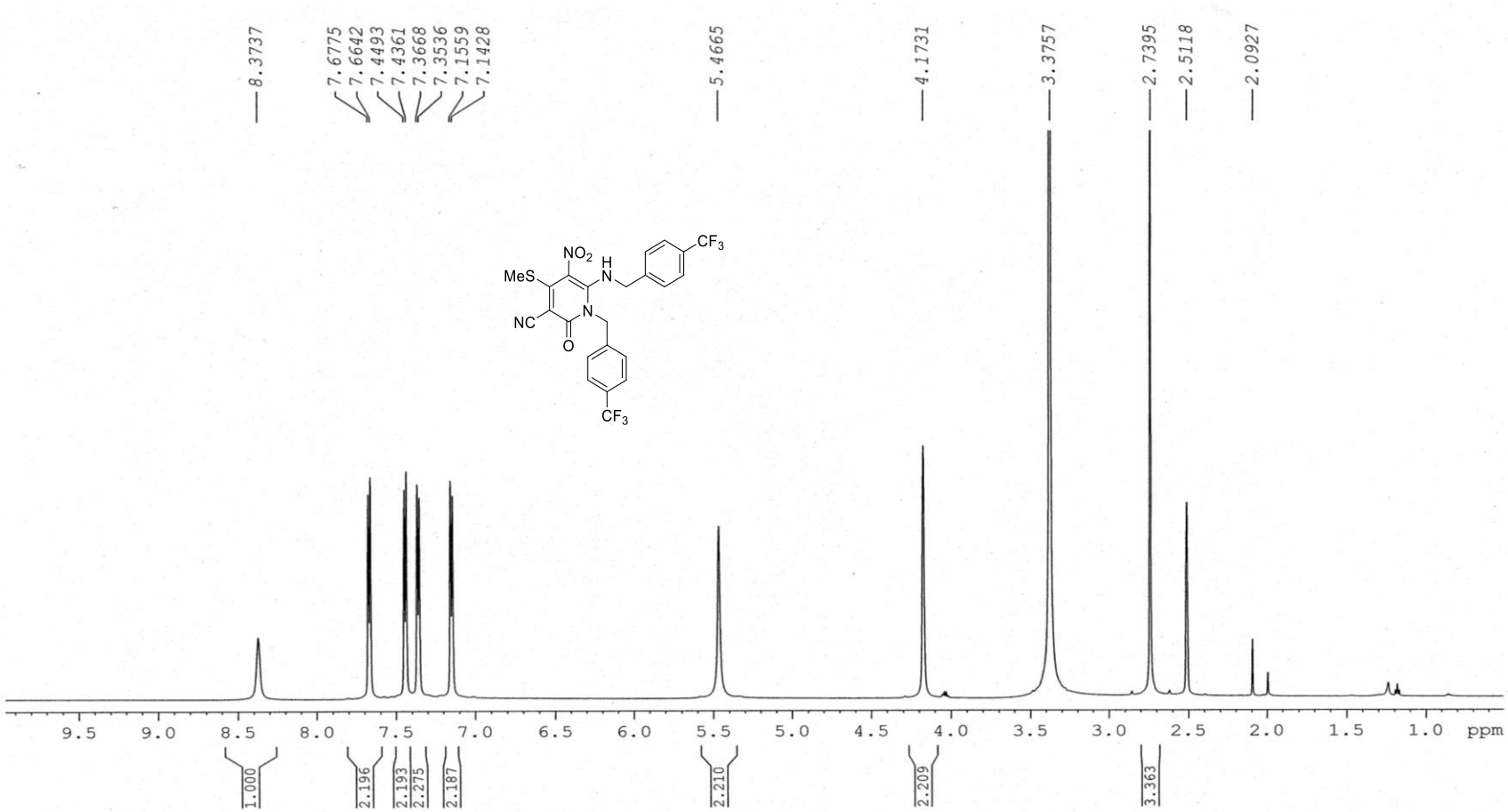


Figure 1. ^{1}H NMR (600 MHz, DMSO-d_6) spectra of compound **3a**

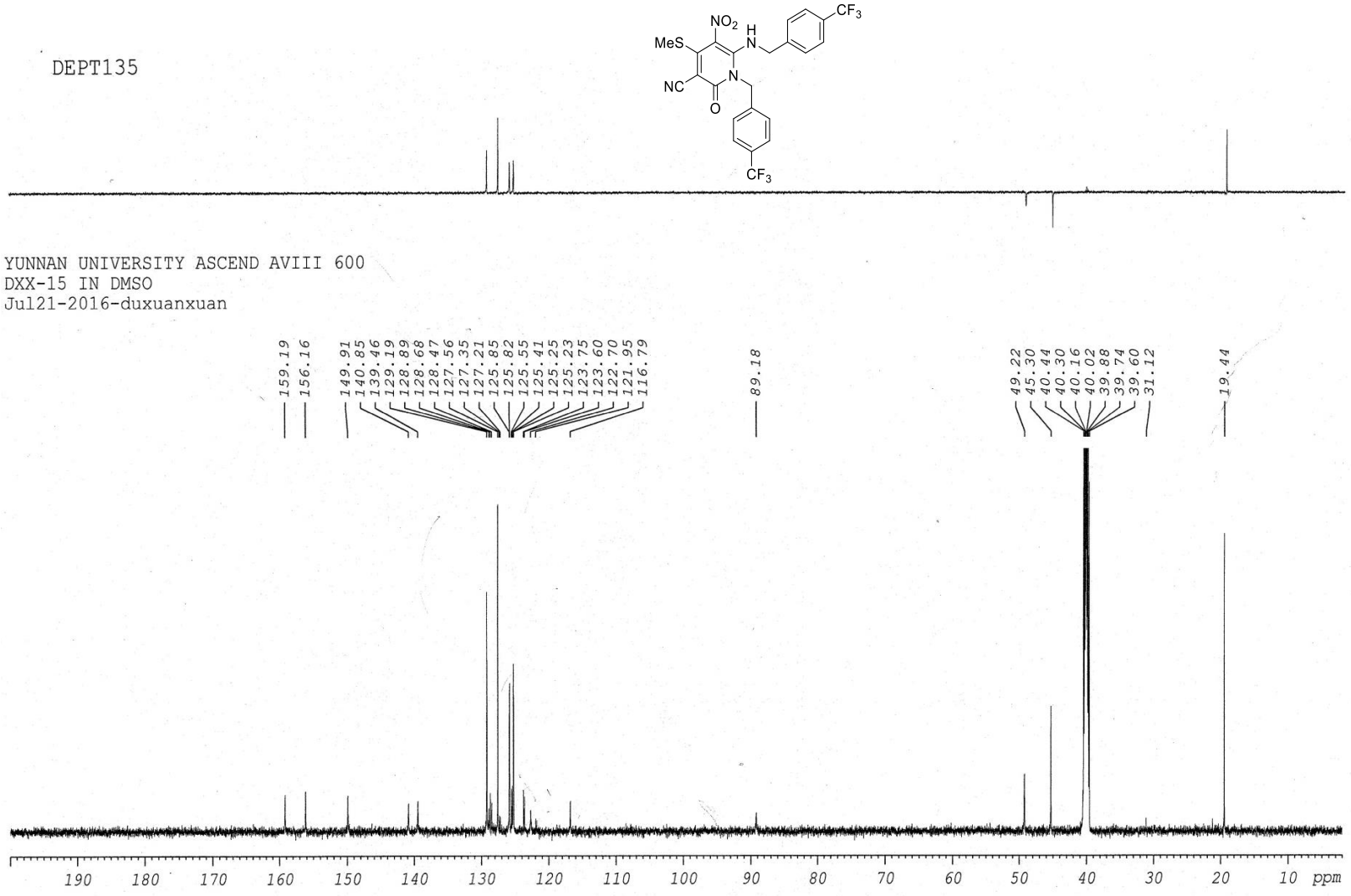


Figure 2. ^{13}C NMR (150MHz, DMSO-d_6) spectra of compound **3a**

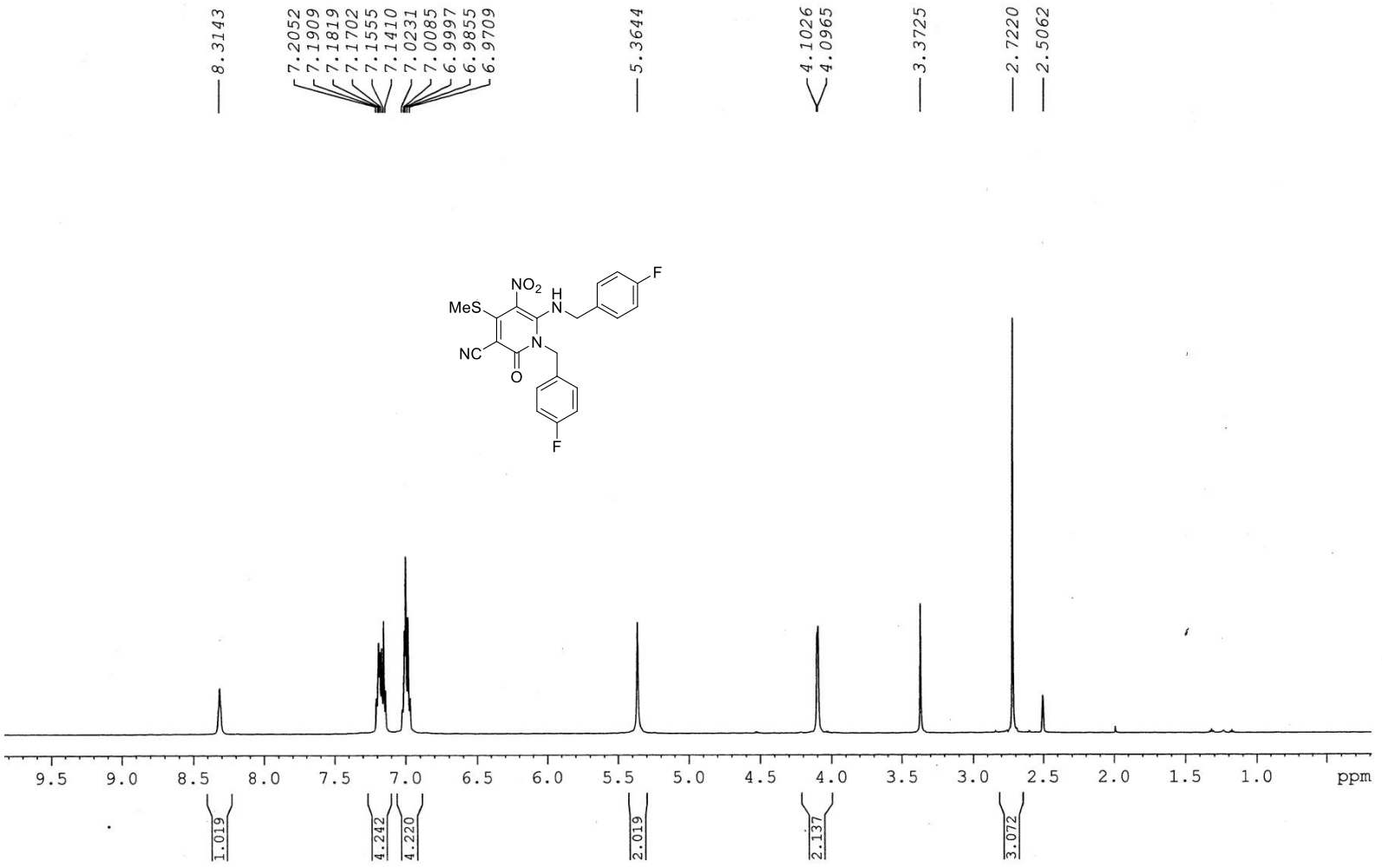


Figure 3. ^{1}HNMR (600 MHz, DMSO-d_6) spectra of compound **3b**

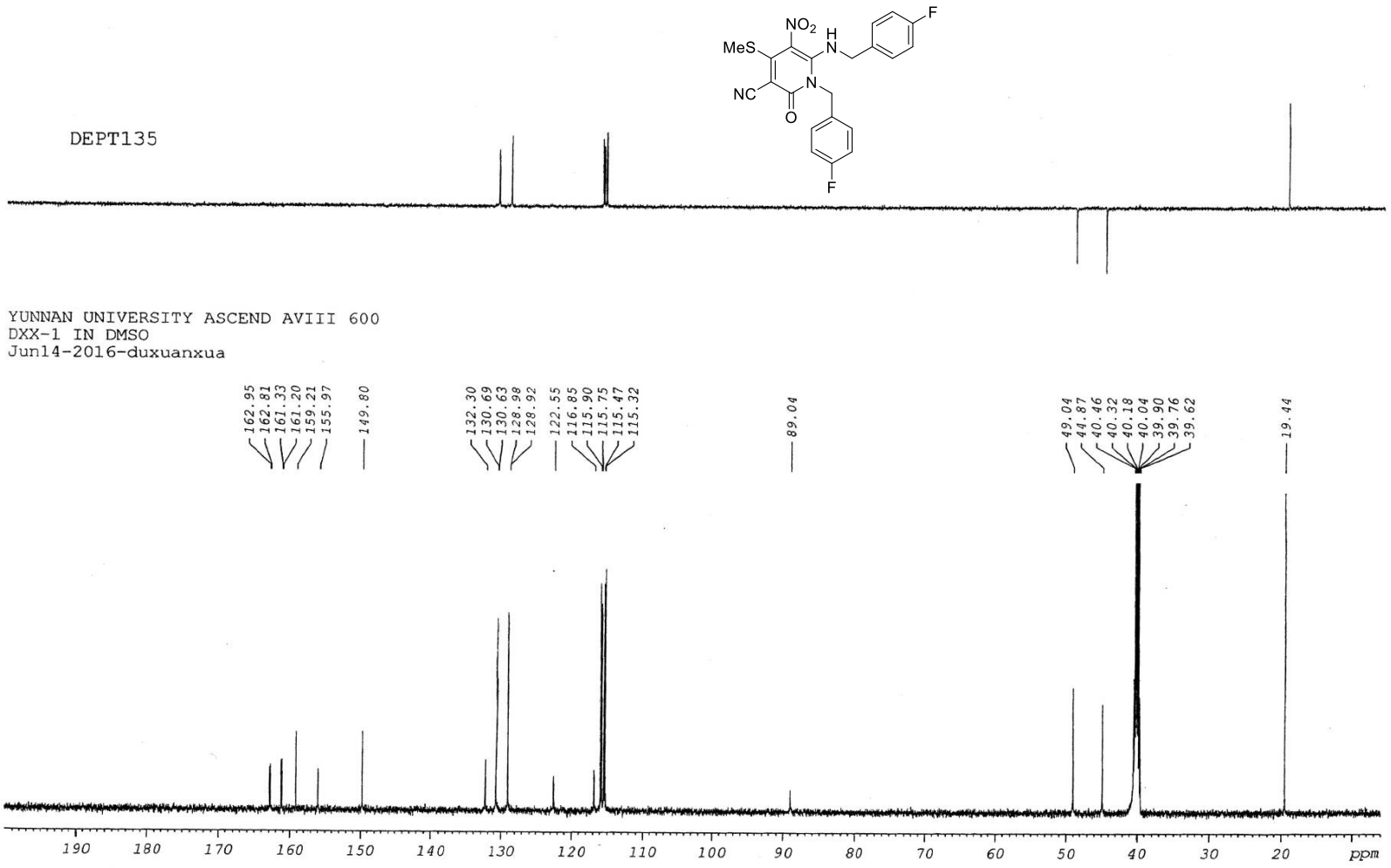


Figure 4. ^{13}CNMR (150 MHz, DMSO-d_6) spectra of compound **3b**

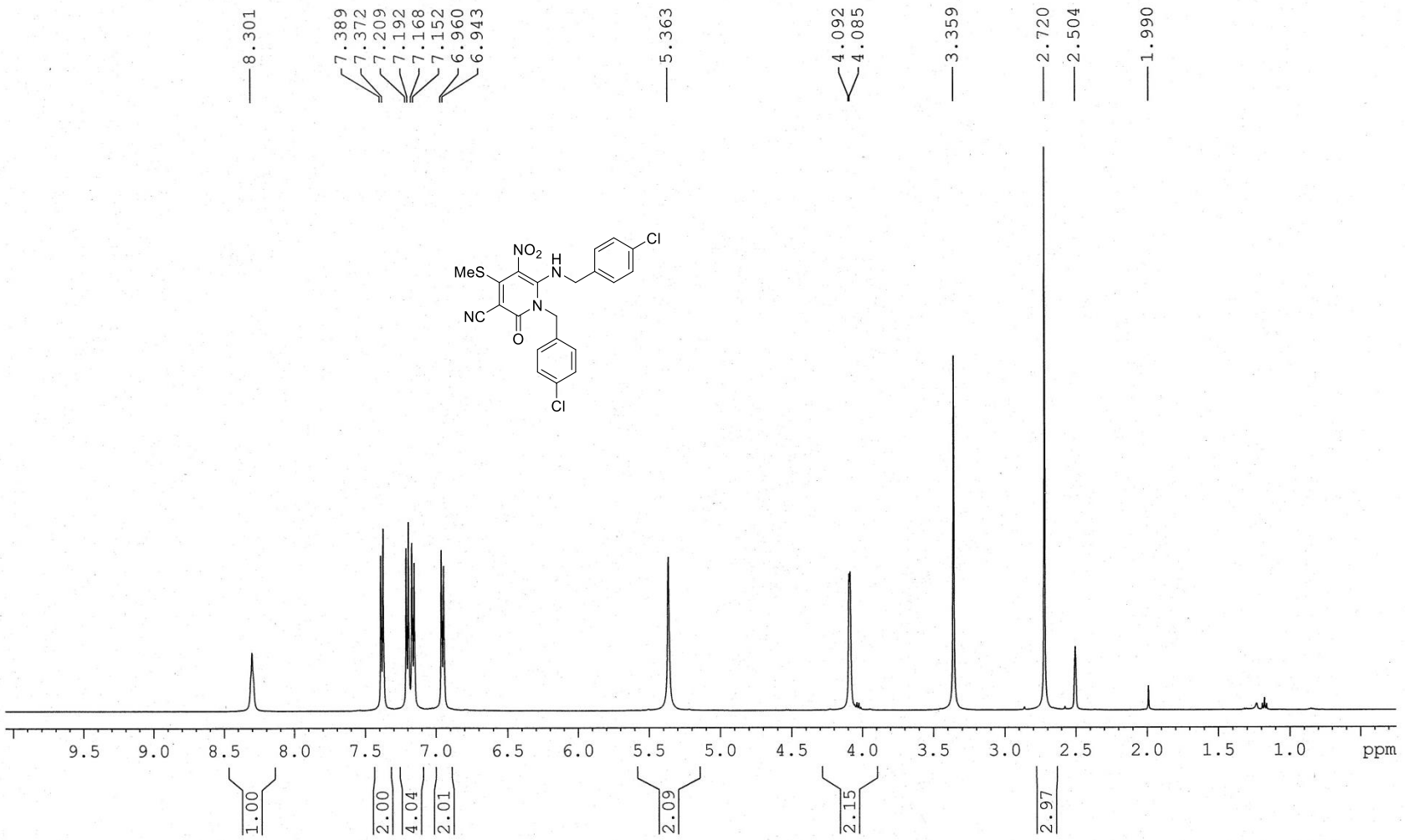


Figure 5. ^{1}HNMR (500 MHz, DMSO-d_6) spectra of compound **3c**

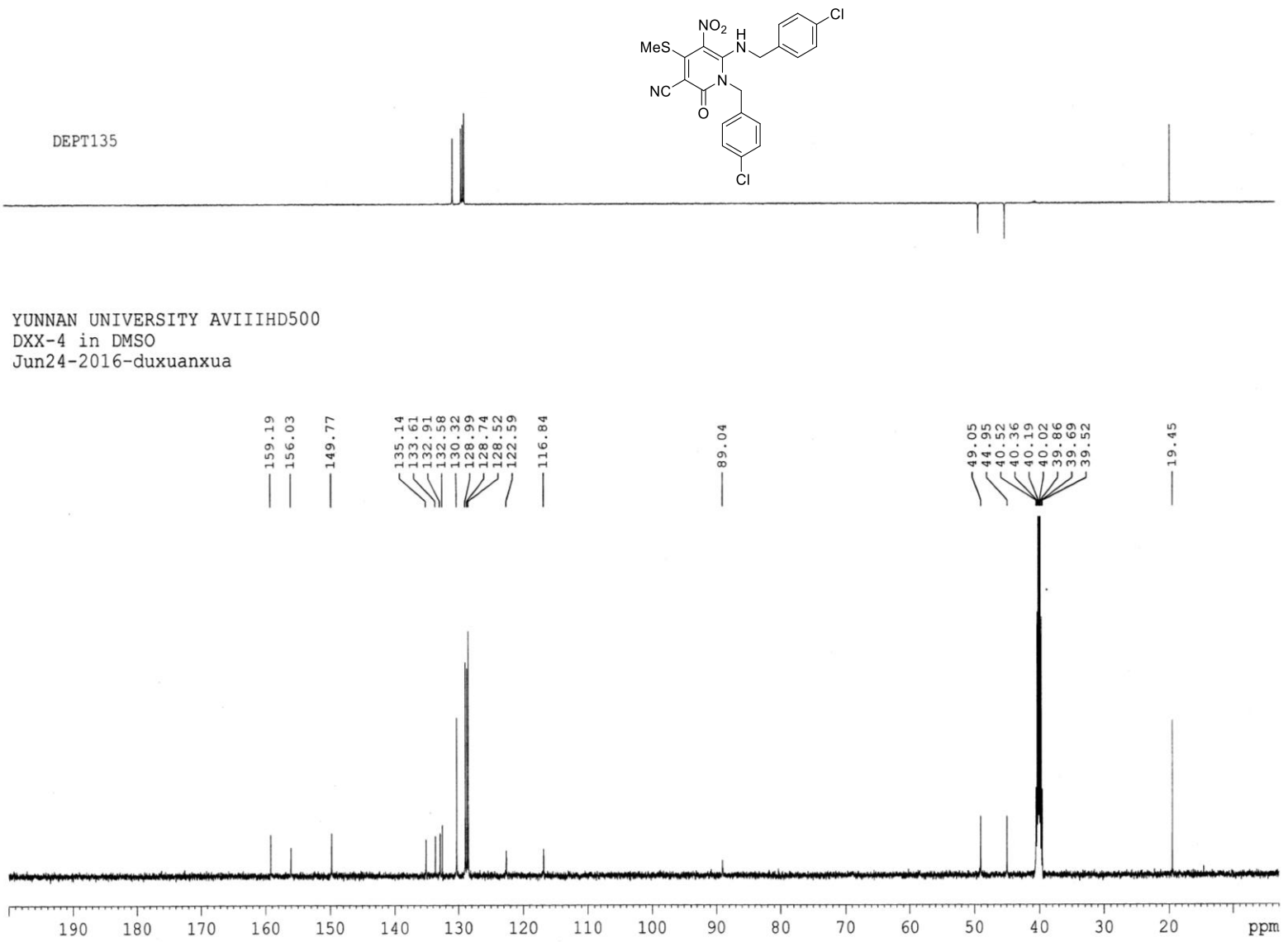


Figure 6. ^{13}CNMR (125 MHz, DMSO-d_6) spectra of compound **3c**

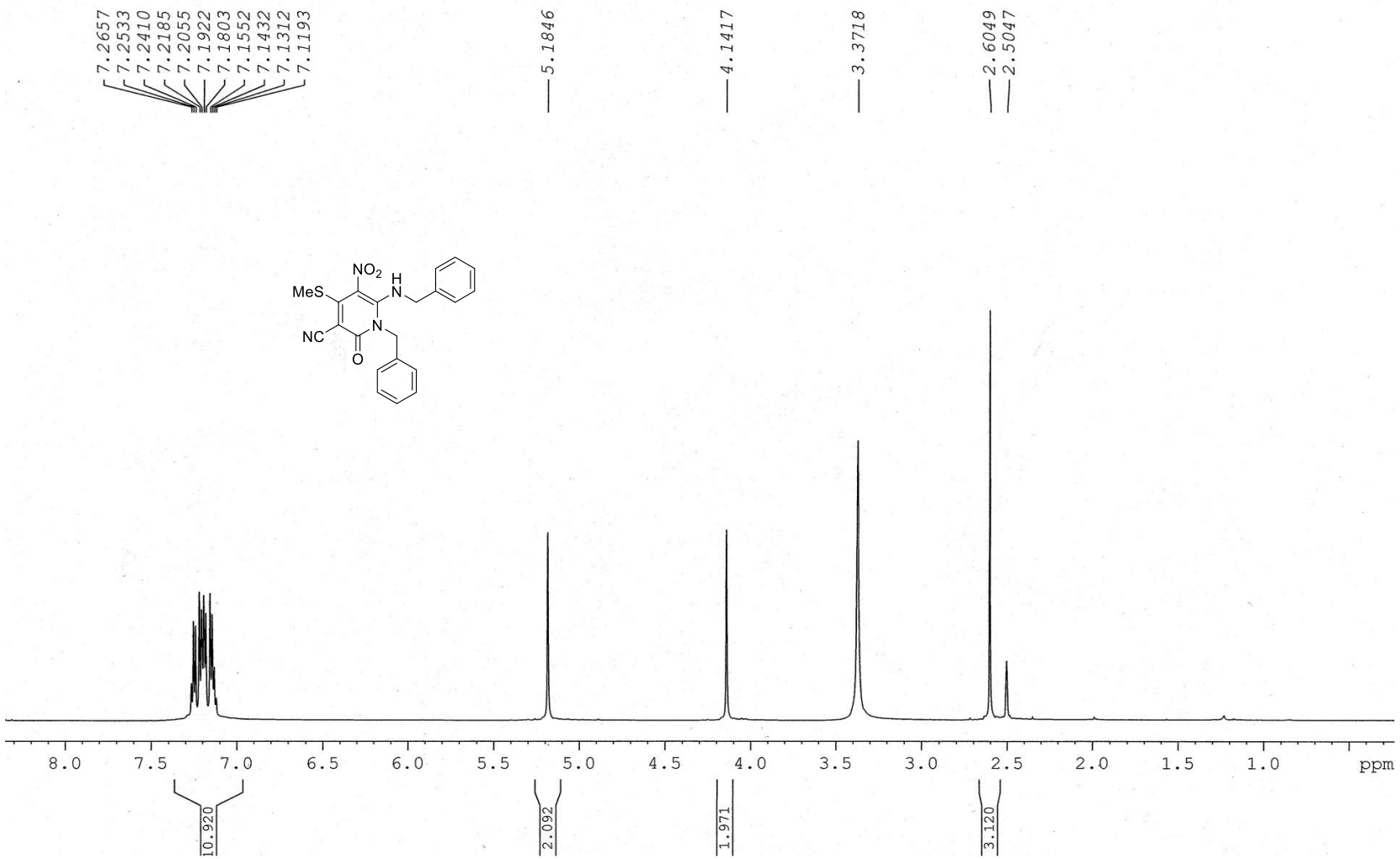


Figure 7. ^{1}HNMR (600 MHz, DMSO-d_6) spectra of compound **3d**

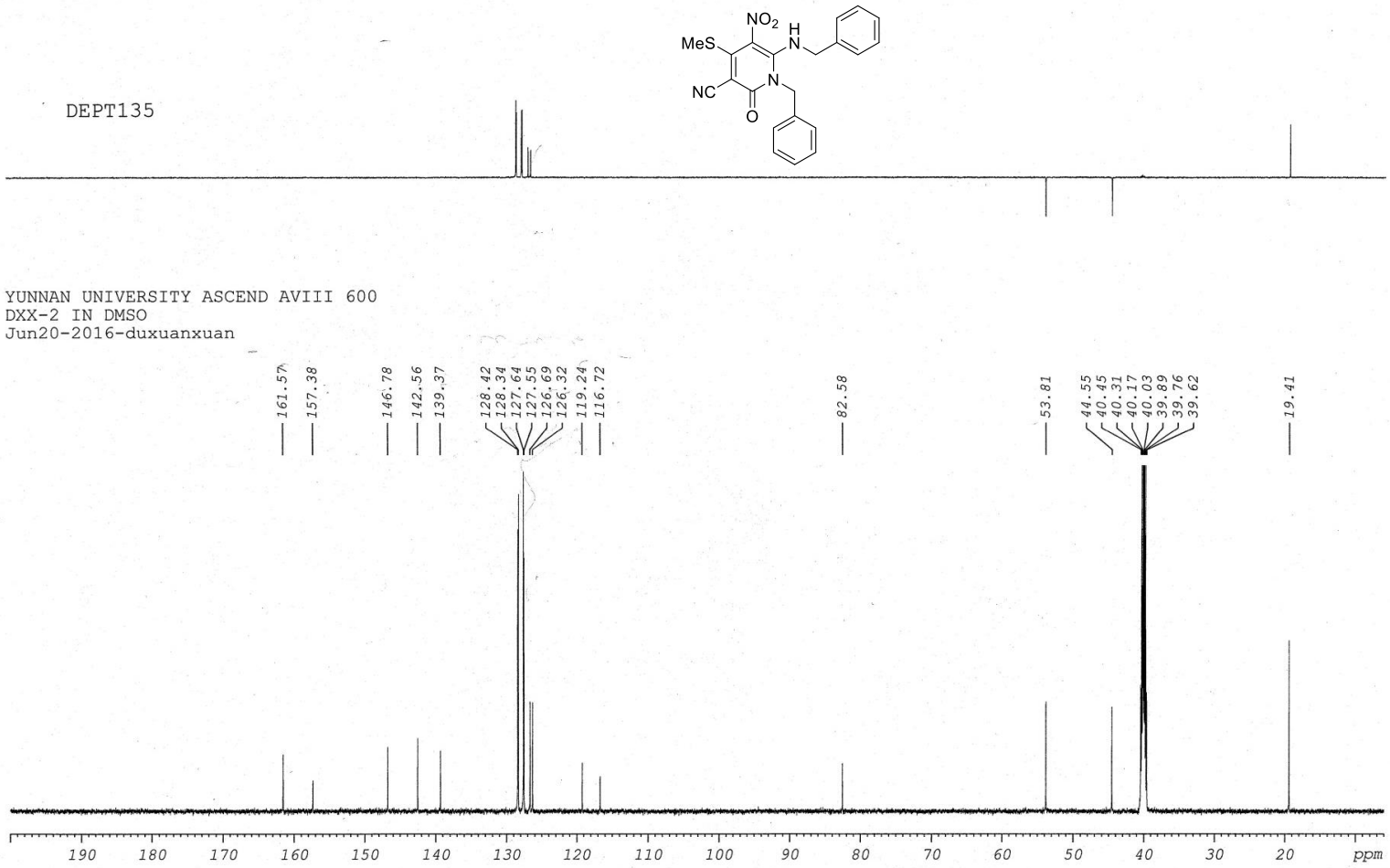


Figure 8. ^{13}CNMR (150 MHz, DMSO-d_6) spectra of compound **3d**

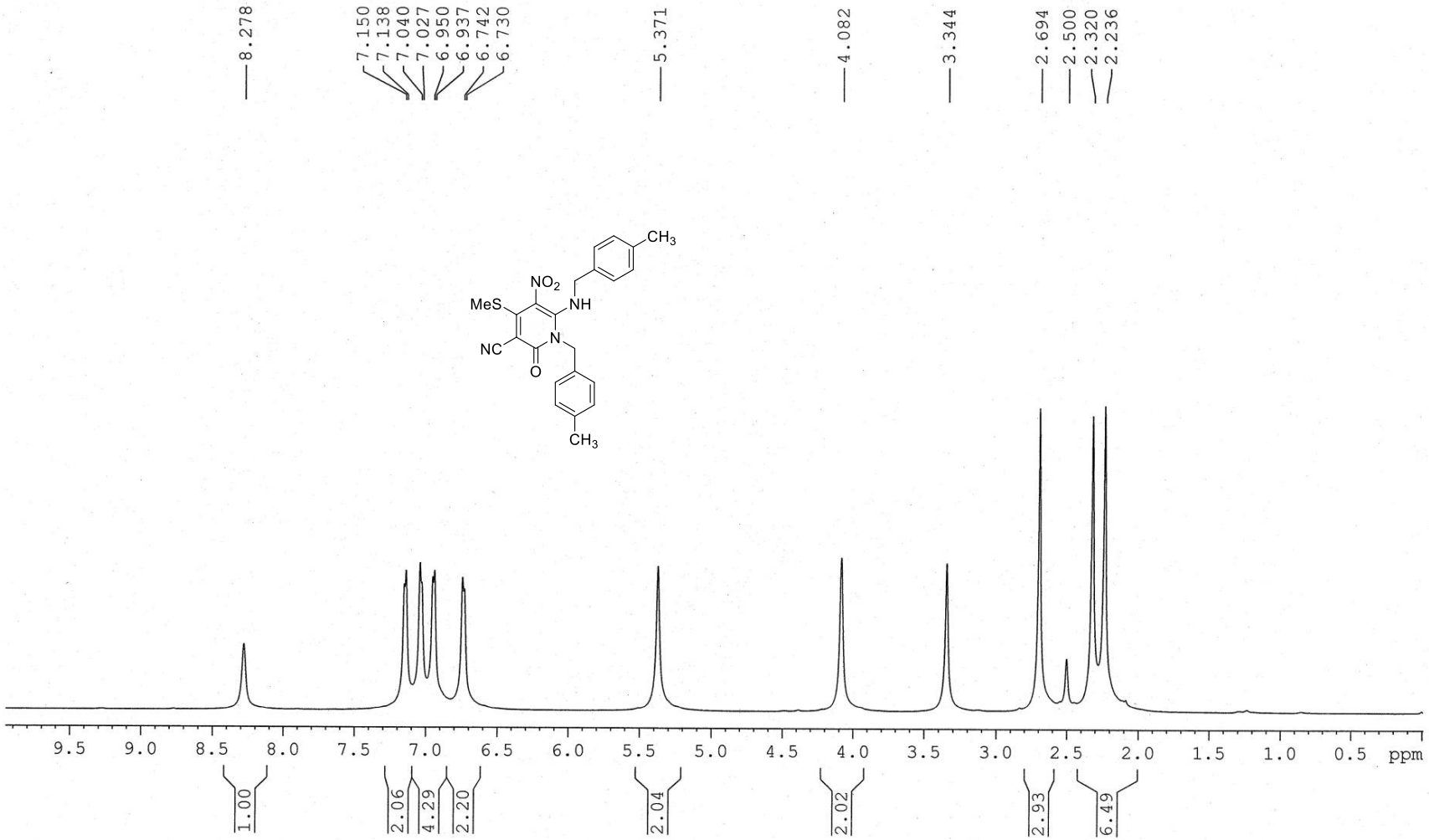


Figure 9. ^{1}H NMR (500 MHz, DMSO-d_6) spectra of compound **3e**

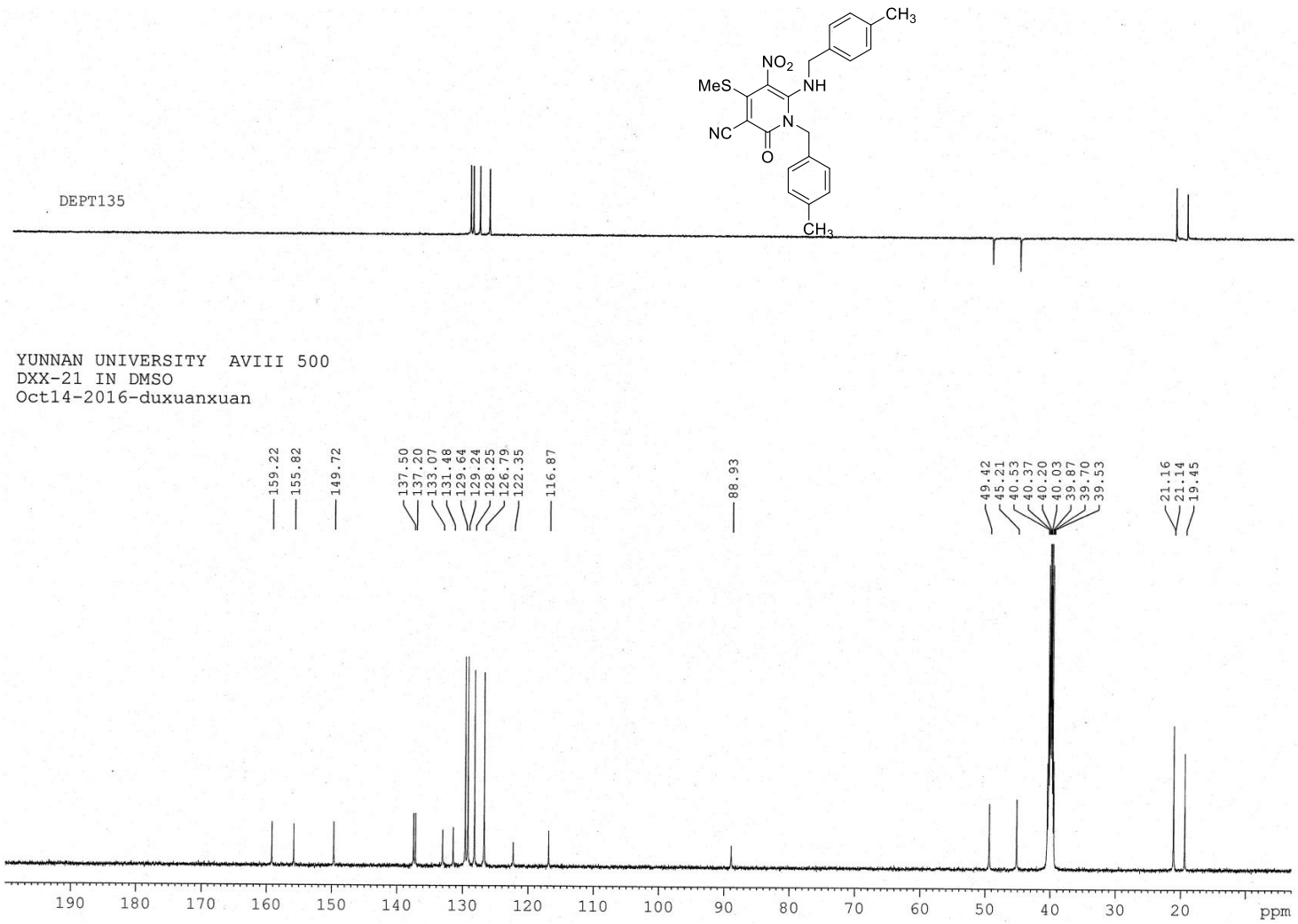


Figure 10. ^{13}C NMR (125 MHz, DMSO-d_6) spectra of compound **3e**

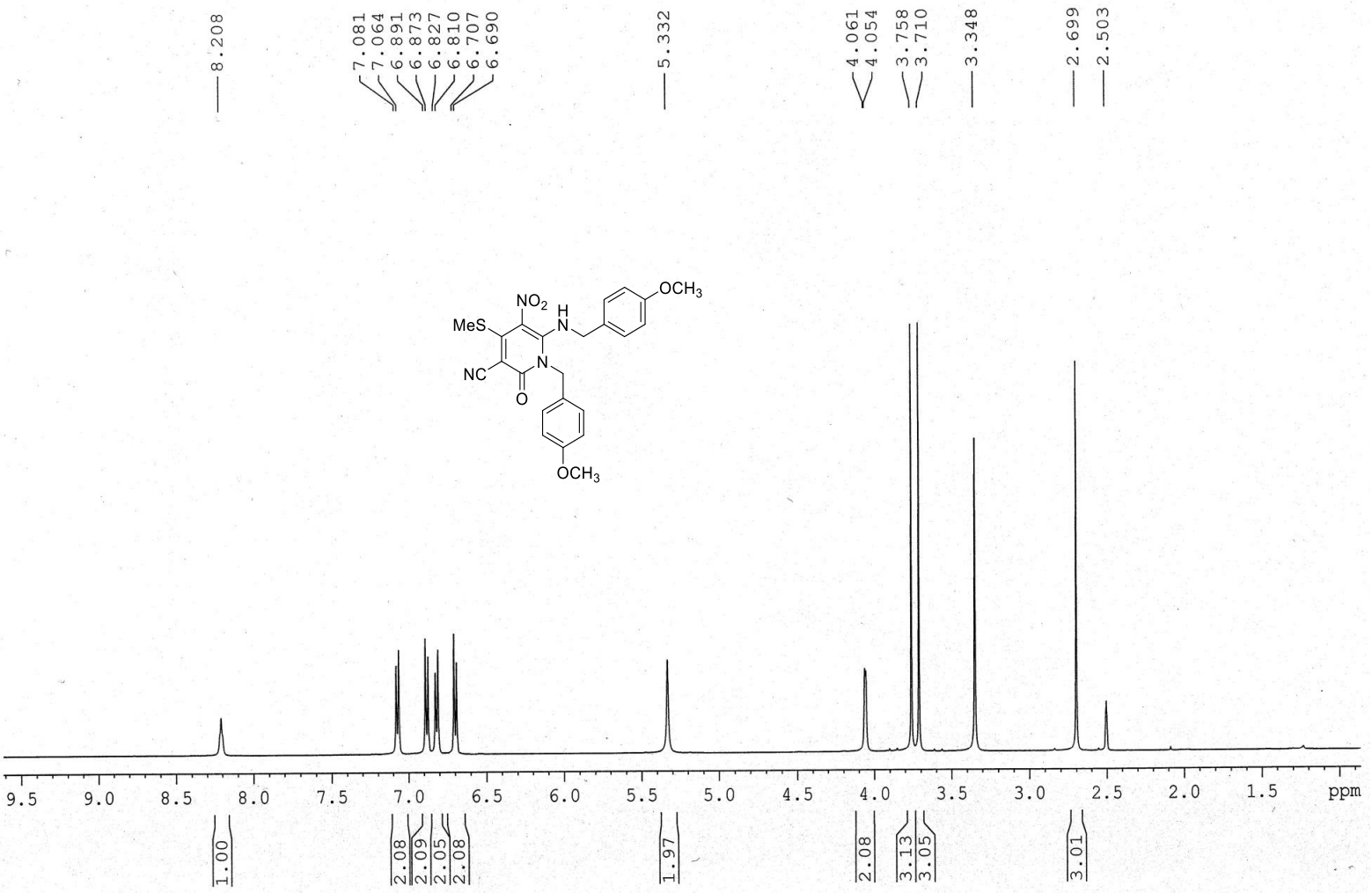


Figure 11. ^{1}H NMR (500 MHz, DMSO-d_6) spectra of compound **3f**

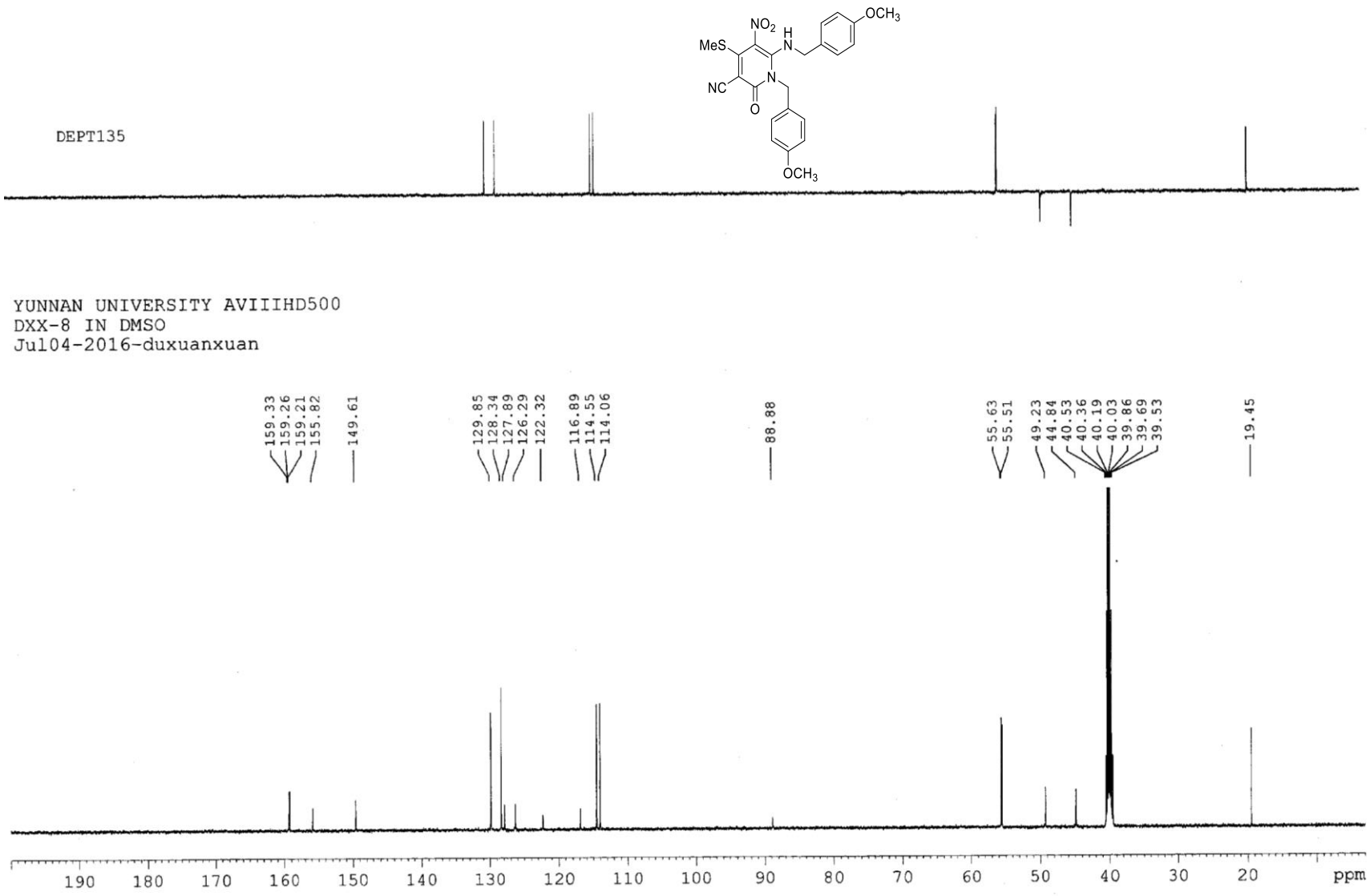


Figure 12. ^{13}C NMR (125MHz, DMSO-d_6) spectra of compound **3f**

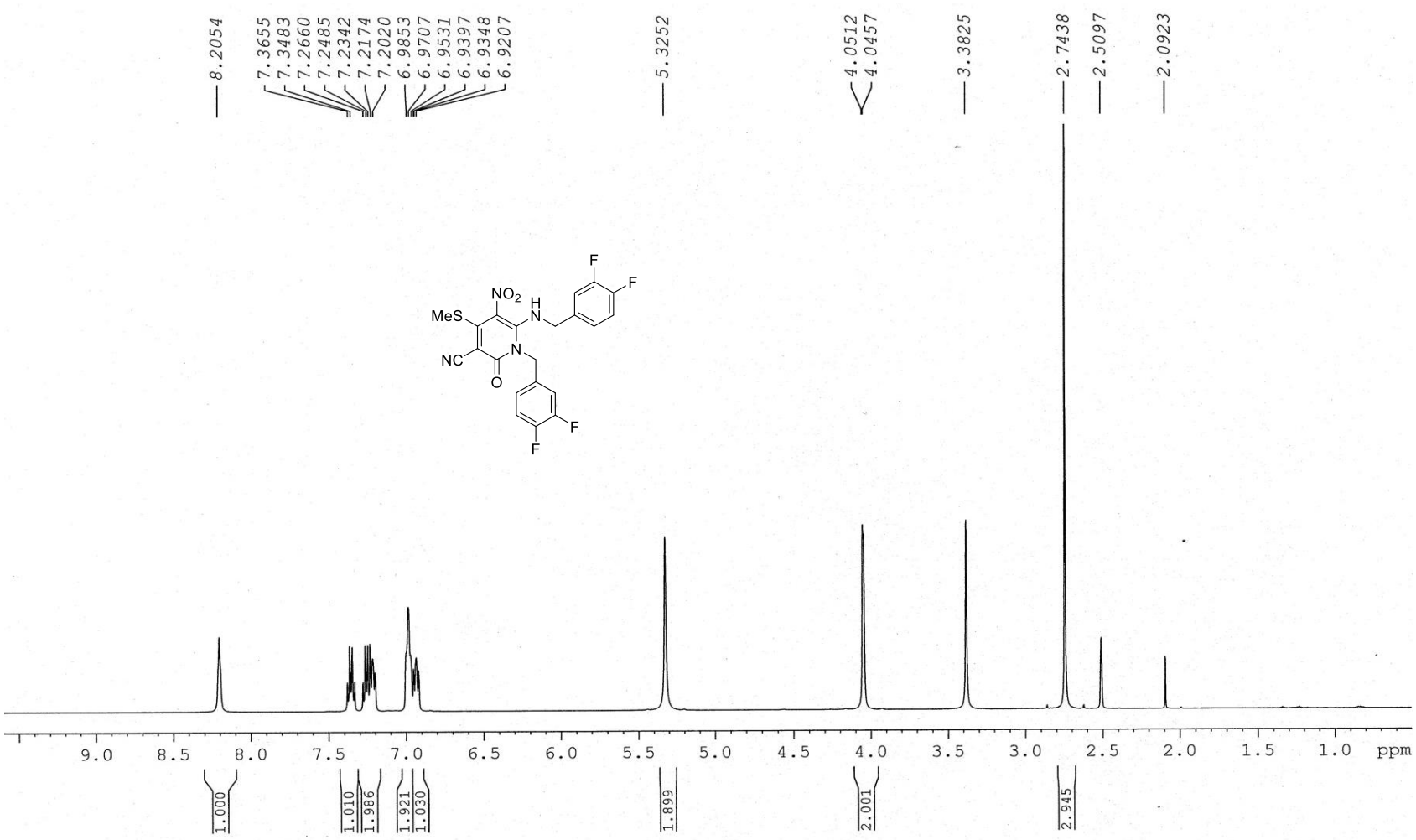


Figure 13. ^{1}H NMR (600 MHz, DMSO-d_6) spectra of compound **3g**

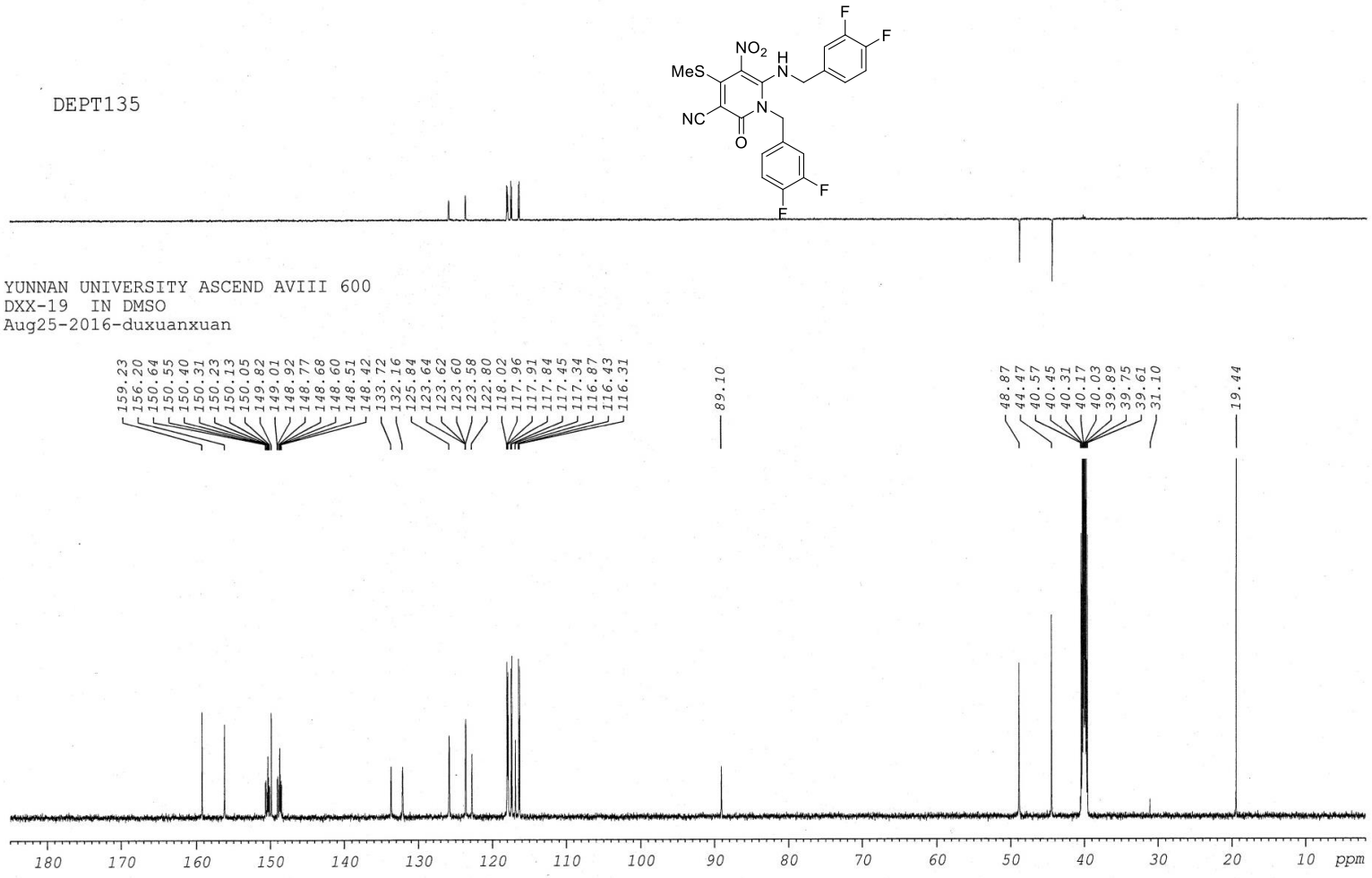


Figure 14. ^{13}C NMR (150 MHz, DMSO-d_6) spectra of compound **3g**

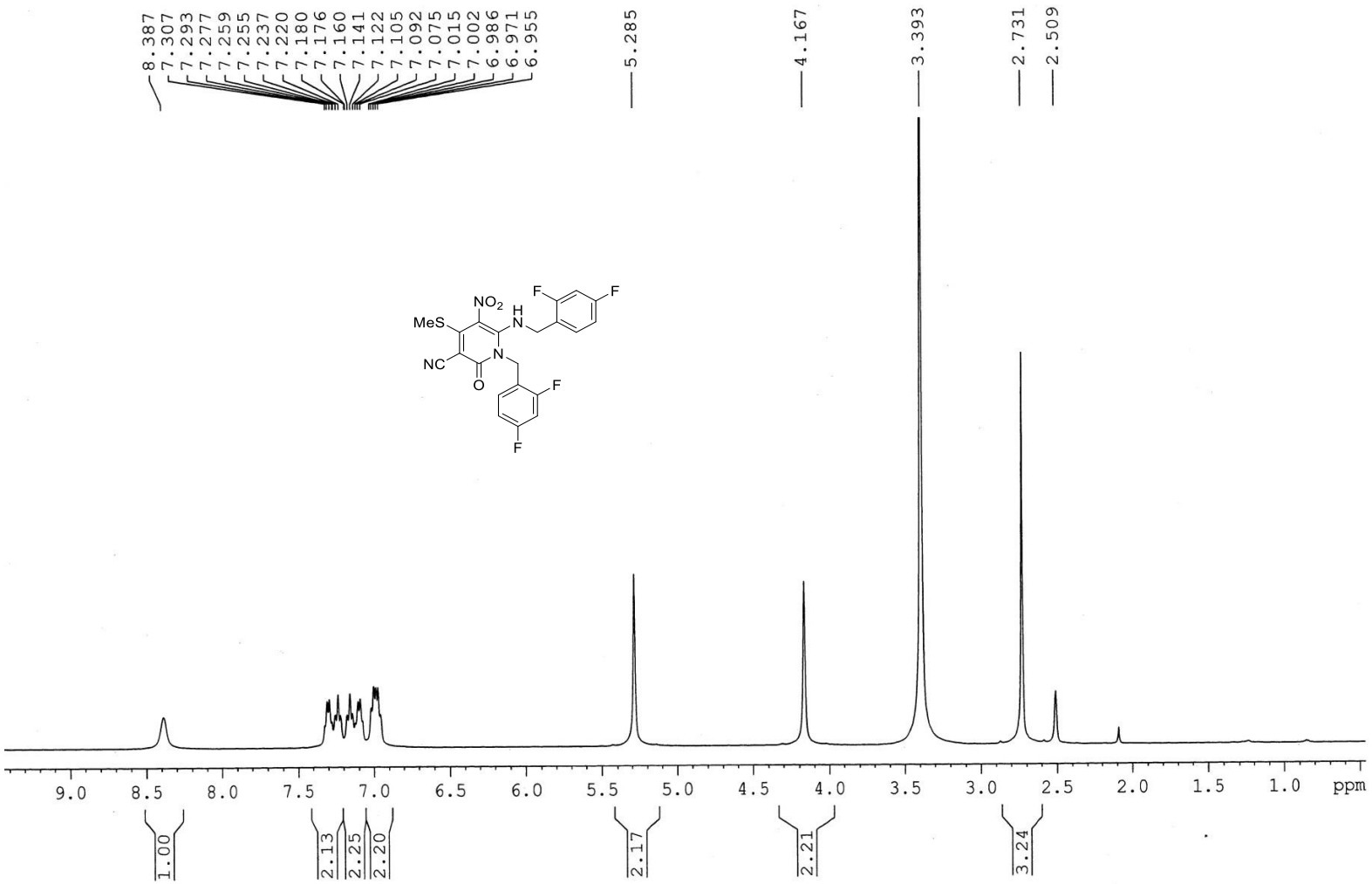


Figure 15. ^{1}H NMR (500 MHz, DMSO-d_6) spectra of compound **3h**

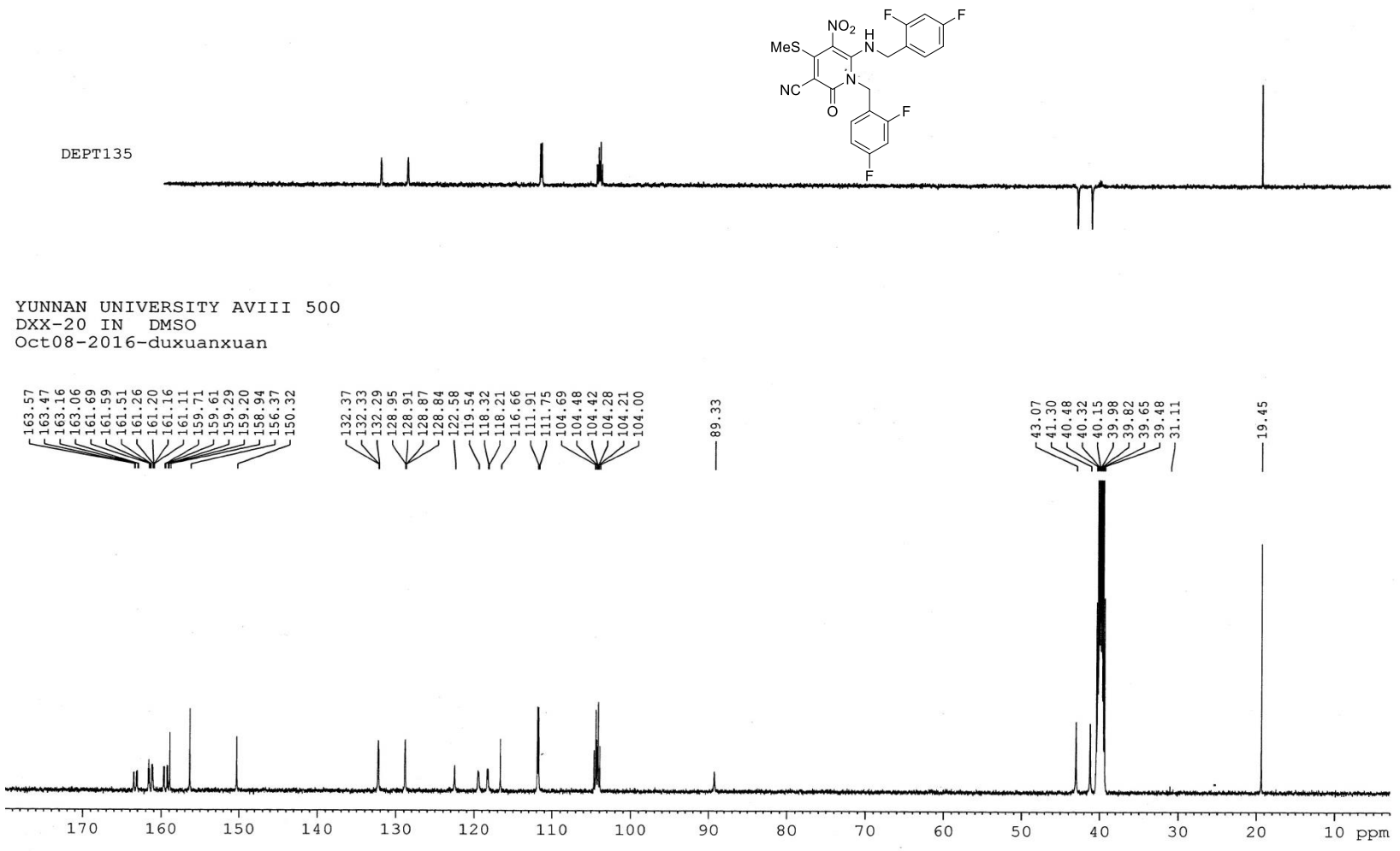


Figure 16. ^{13}C NMR (125 MHz, DMSO-d_6) spectra of compound **3h**

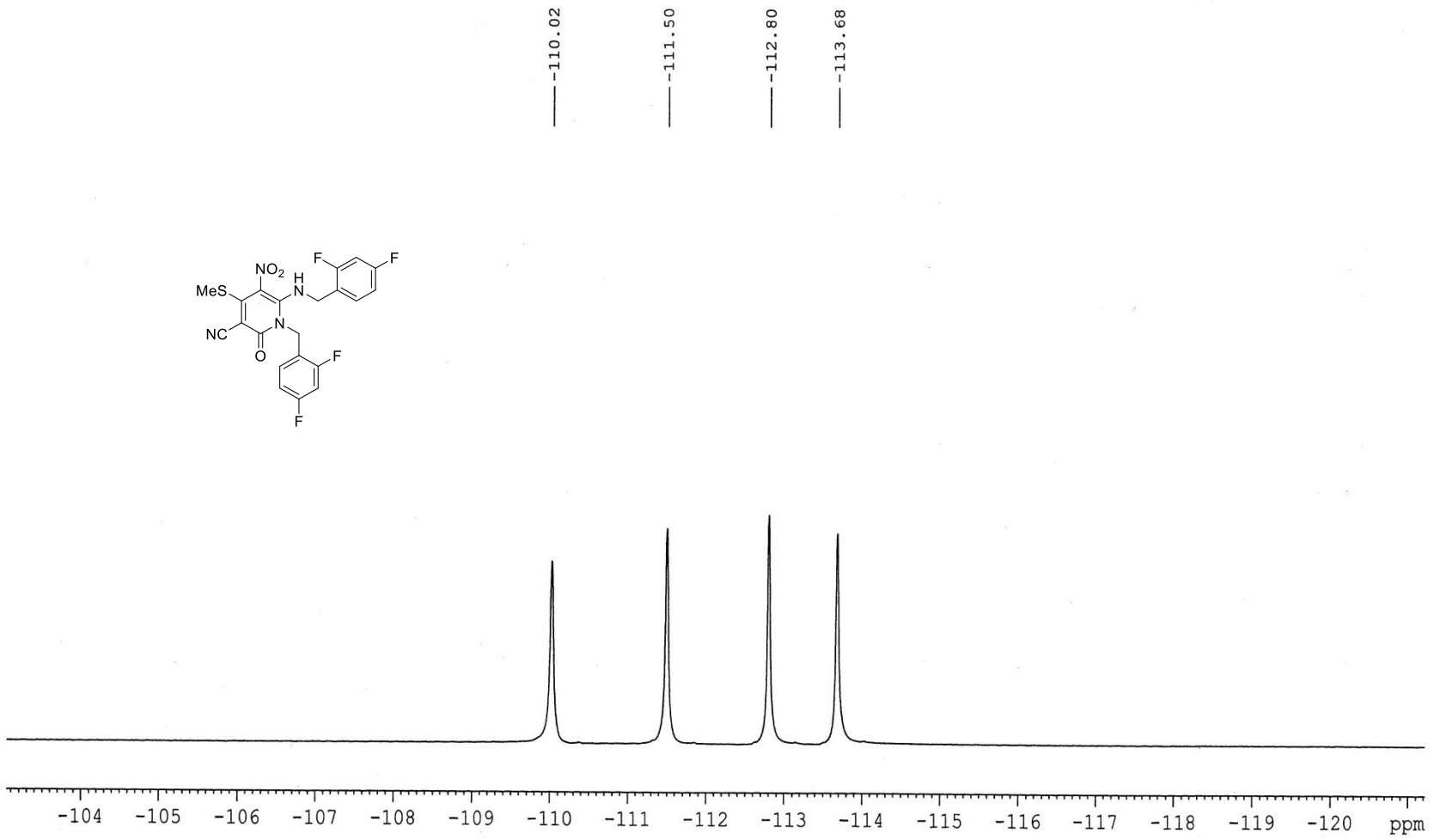


Figure 17. ^{19}F (467 MHz, DMSO-d_6) spectra of compound **3h**

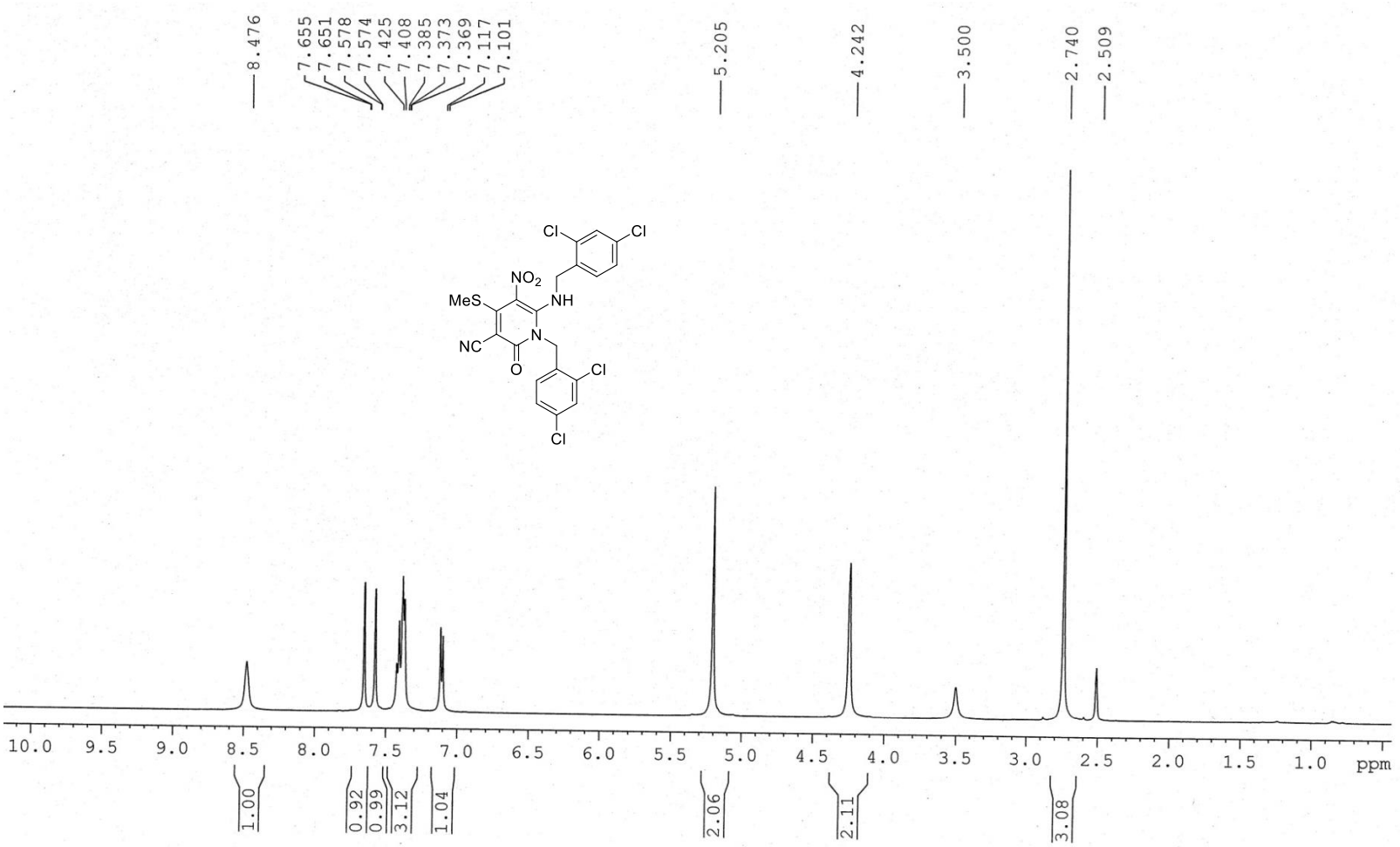


Figure 18. ^{1}H NMR (500 MHz, DMSO-d_6) spectra of compound **3i**

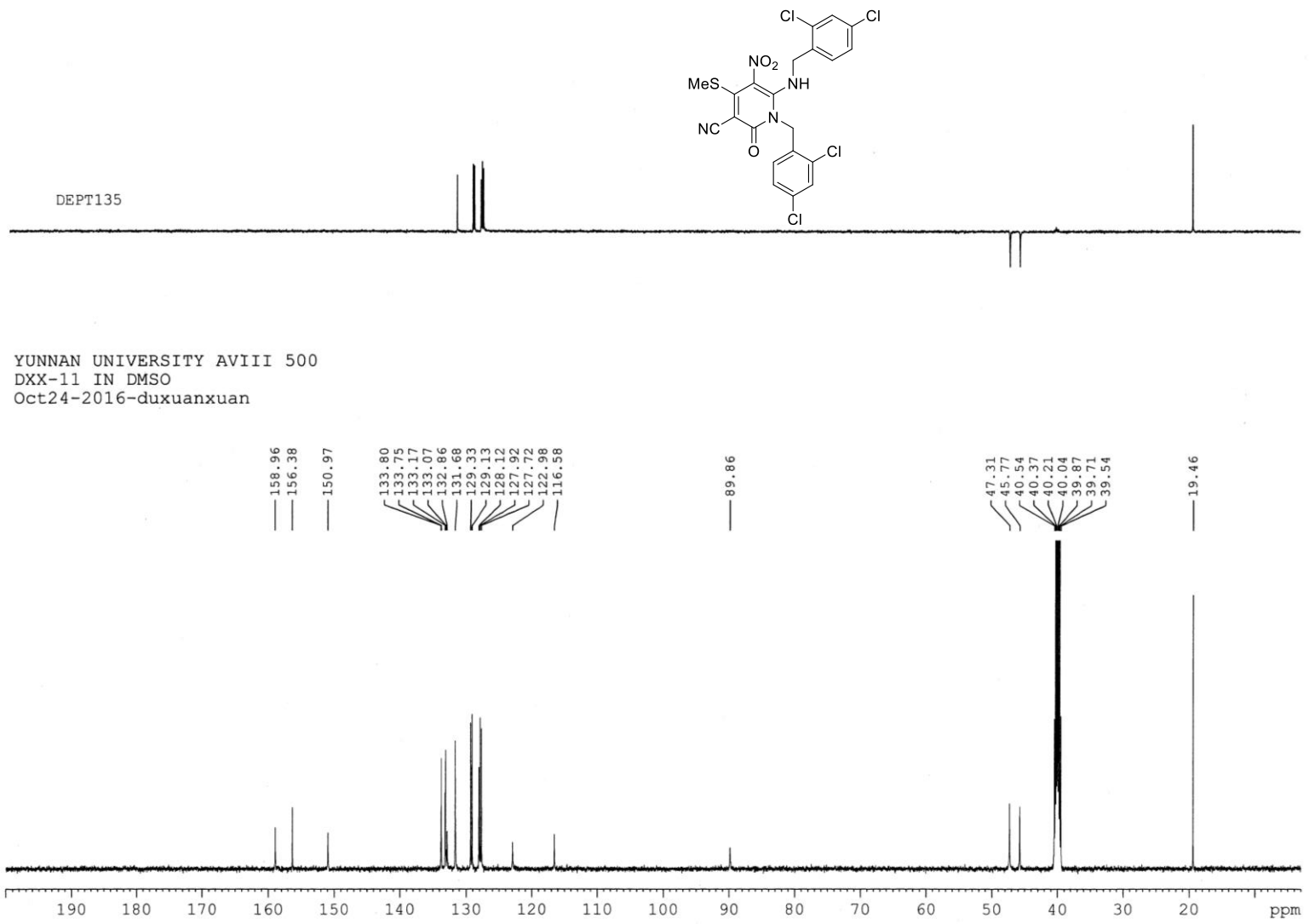


Figure 19. ^{13}C NMR (125MHz, DMSO-d_6) spectra of compound **3i**

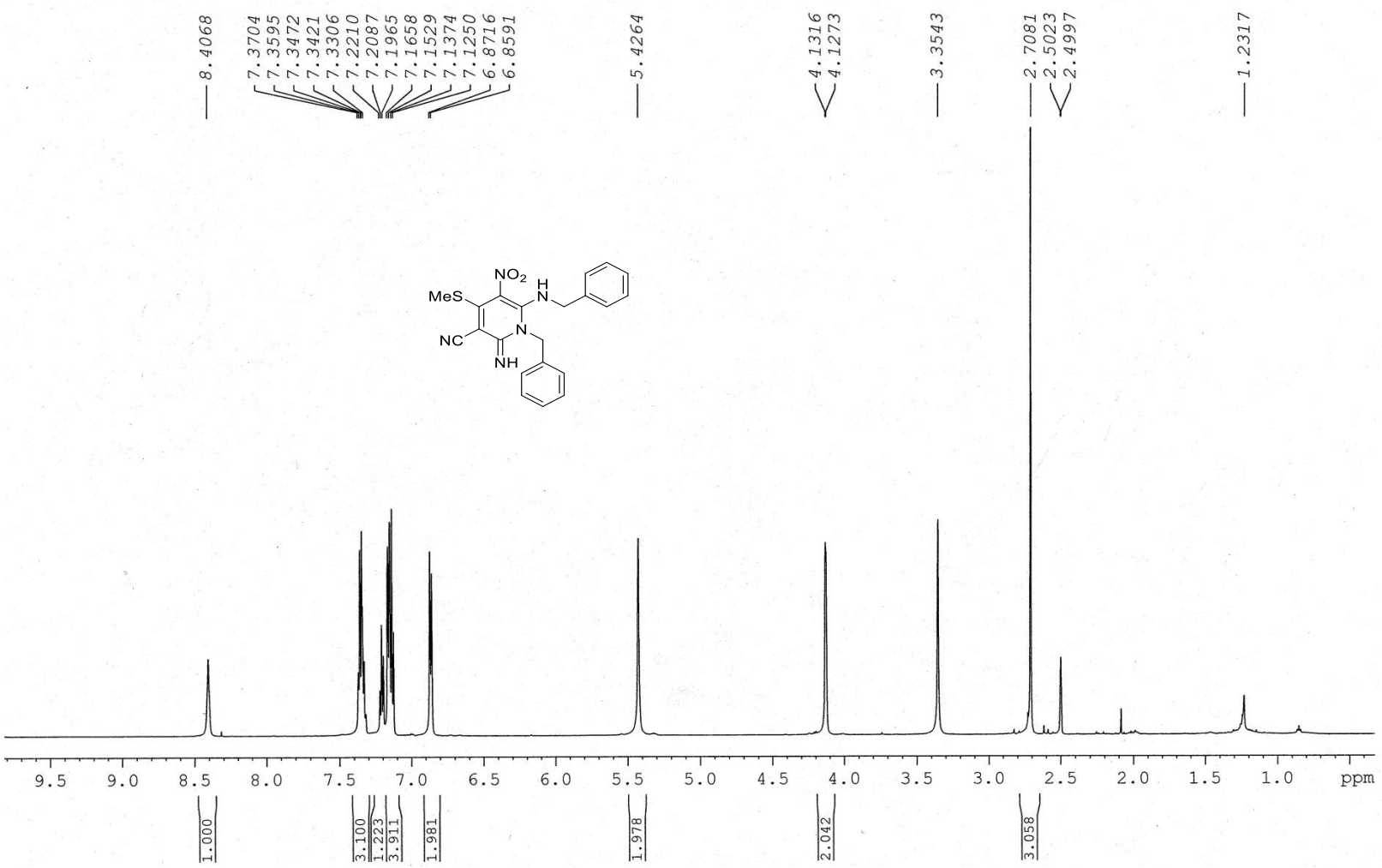


Figure 20. [1]HNMR (600 MHz, DMSO-d_6) spectra of compound **3j**

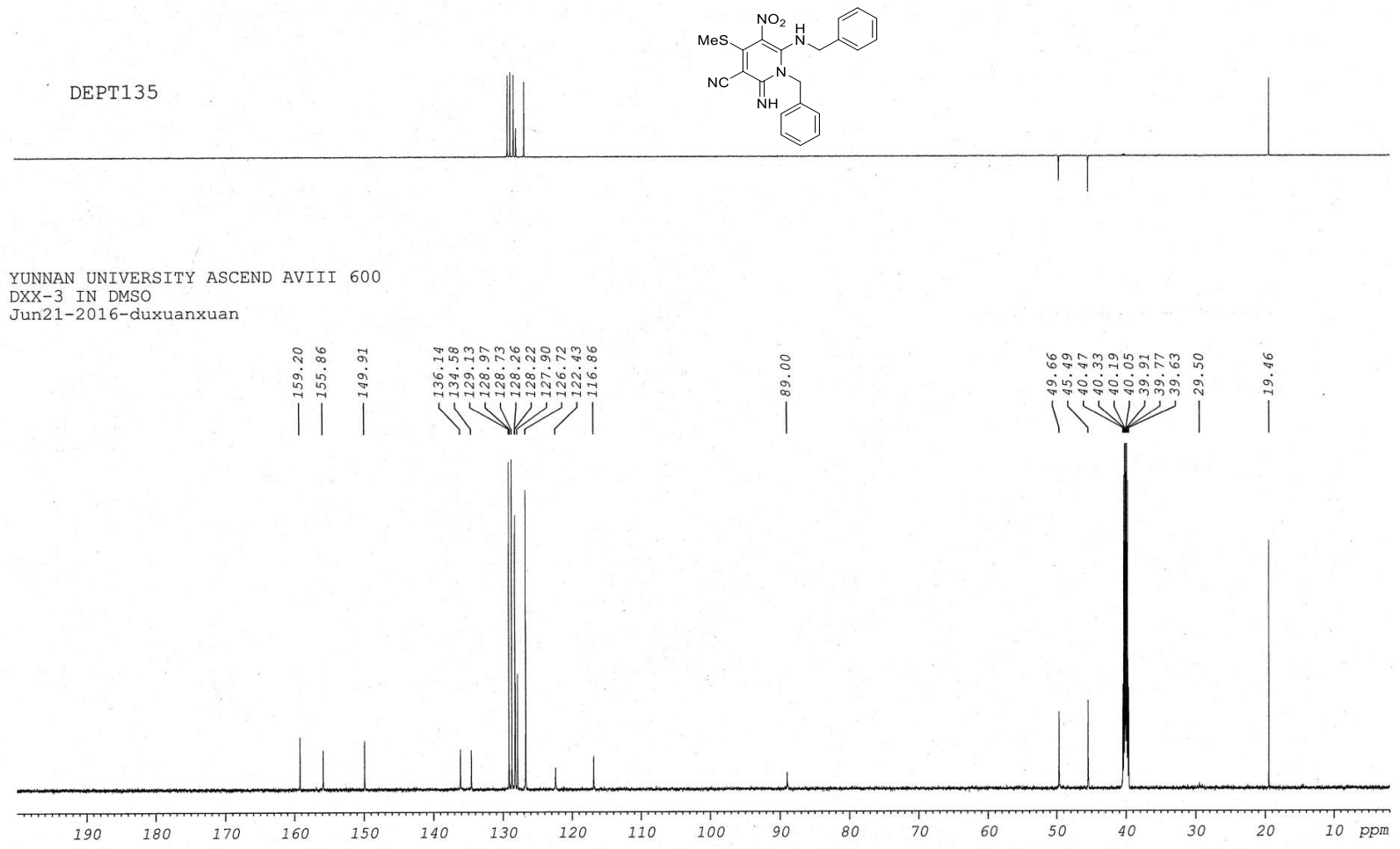


Figure 21. ^{13}CNMR (150 MHz, DMSO-d_6) spectra of compound **3j**

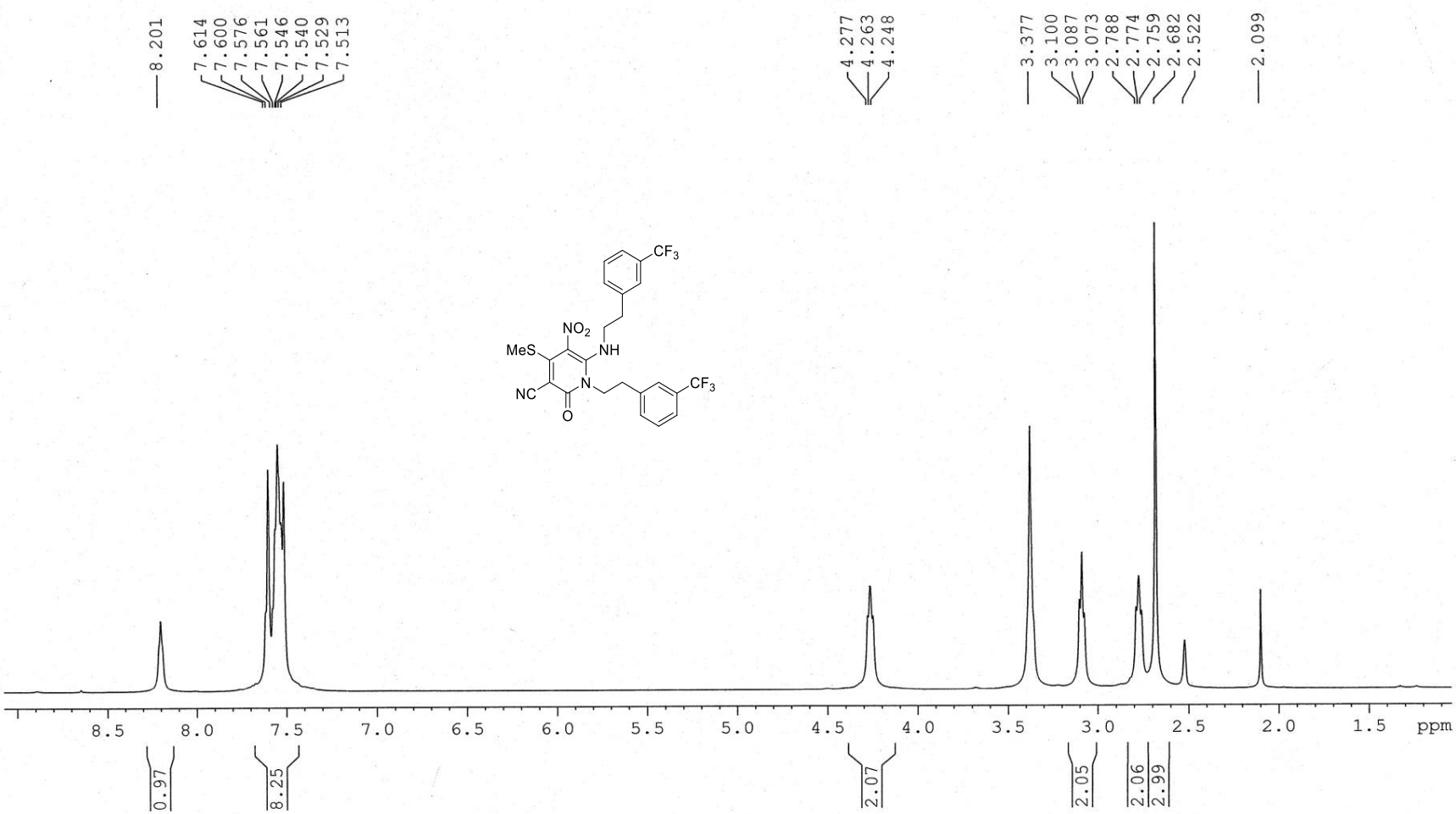


Figure 22. ^{1}H NMR (500 MHz, DMSO-d_6) spectra of compound **3k**

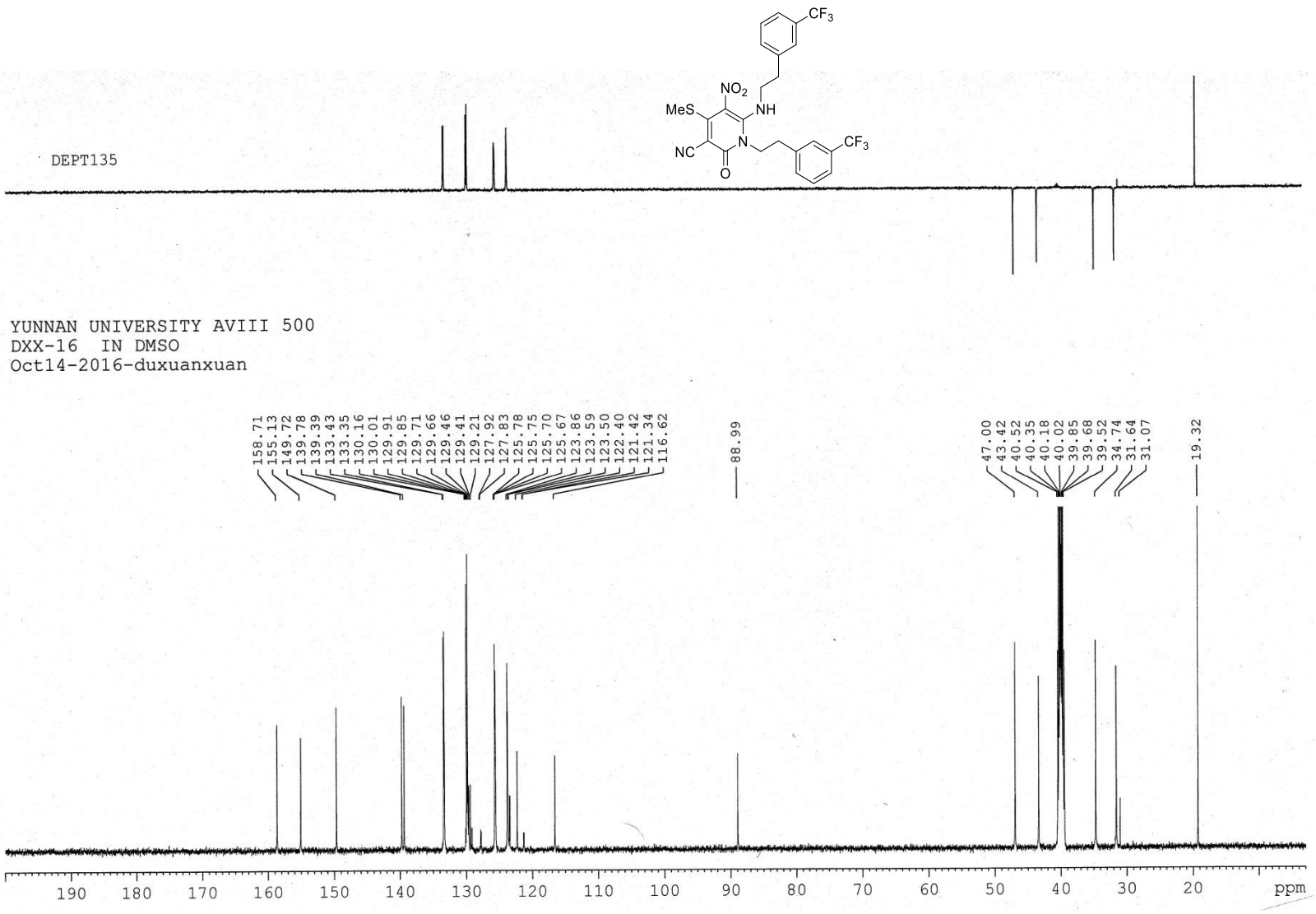


Figure 23. ^{13}C NMR (125 MHz, DMSO-d_6) spectra of compound **3k**

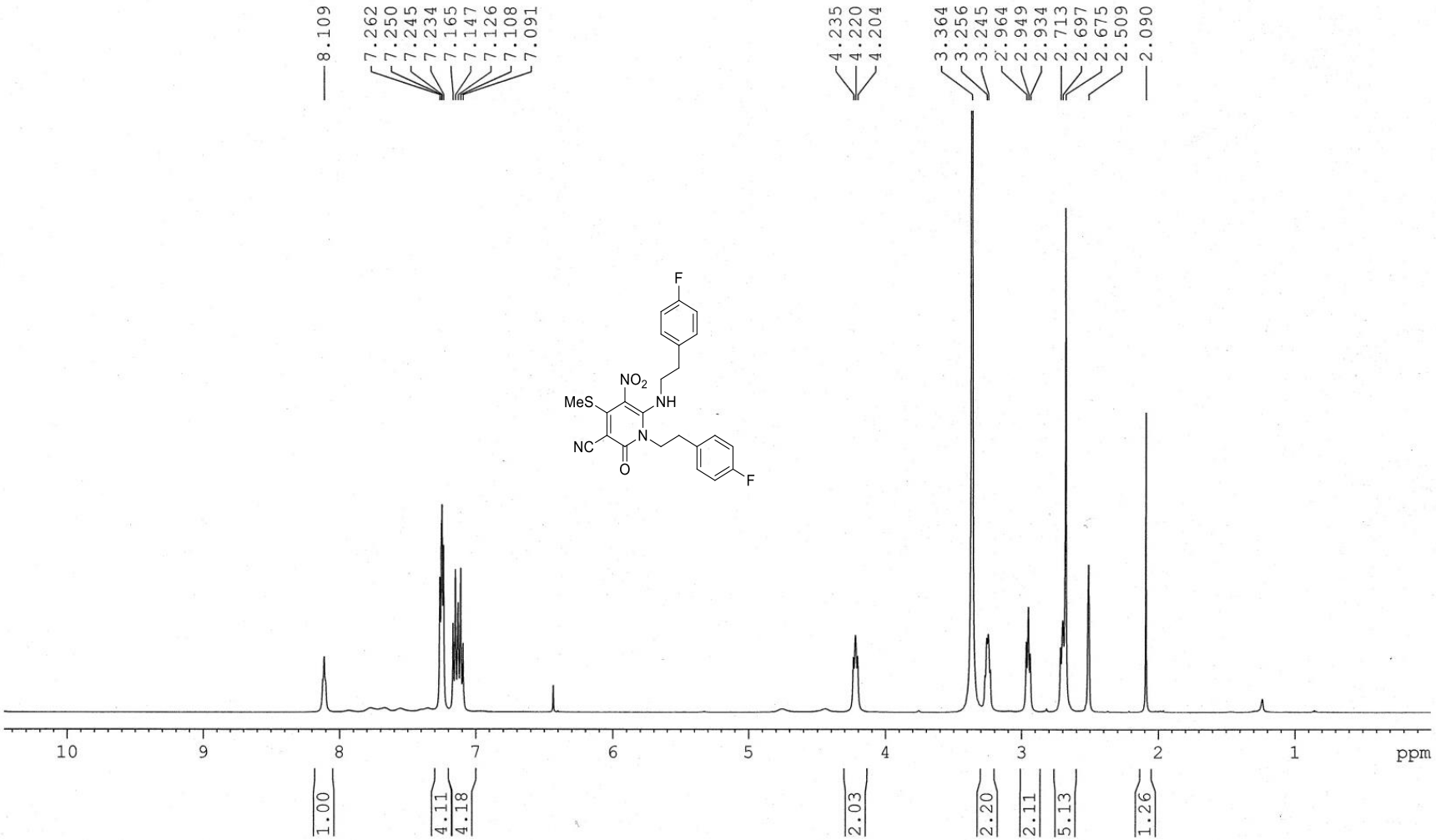


Figure 24. ^{1}H NMR (500 MHz, DMSO-d_6) spectra of compound **3l**

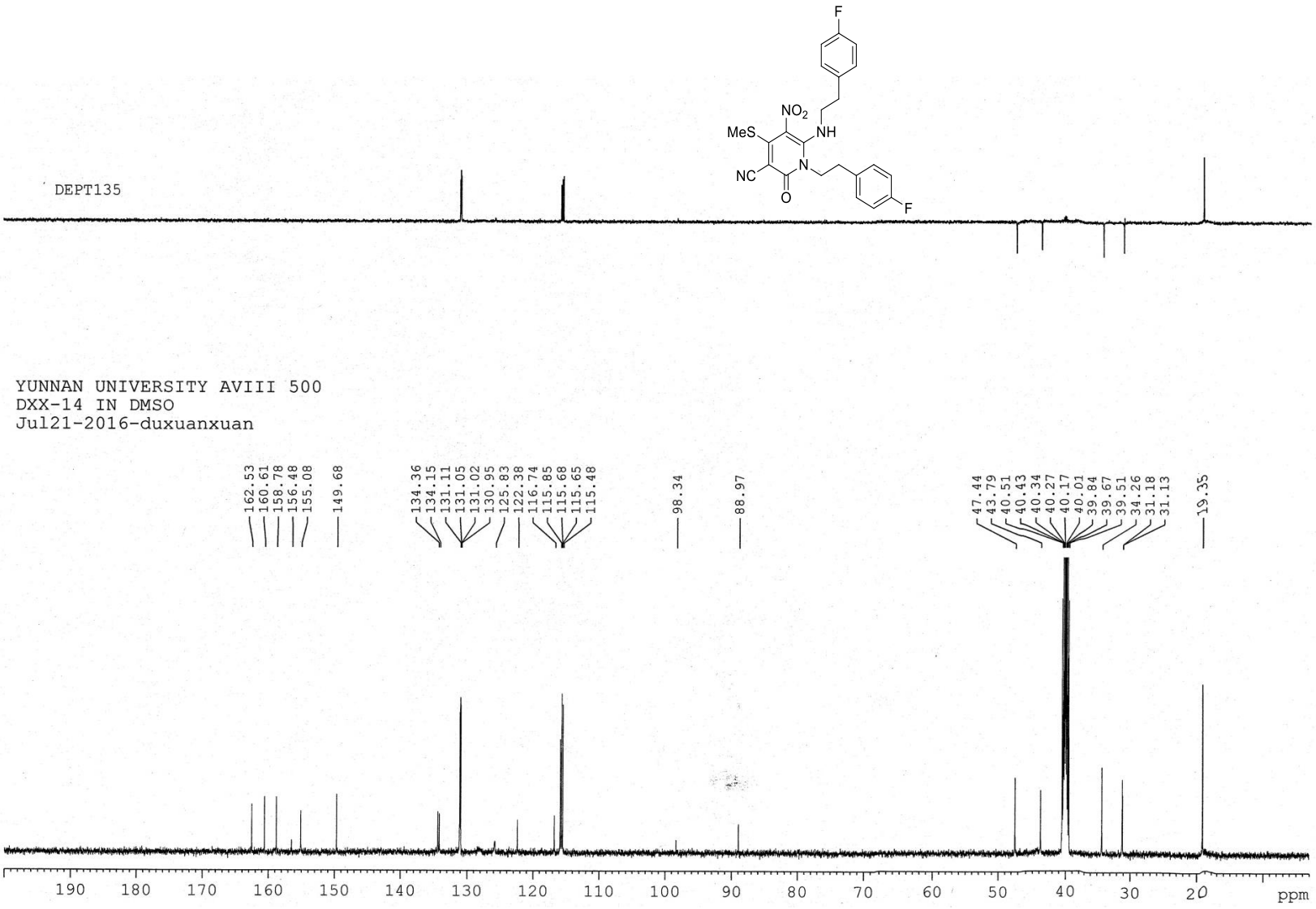


Figure 25. ^{13}C NMR (125 MHz, DMSO-d_6) spectra of compound **3l**

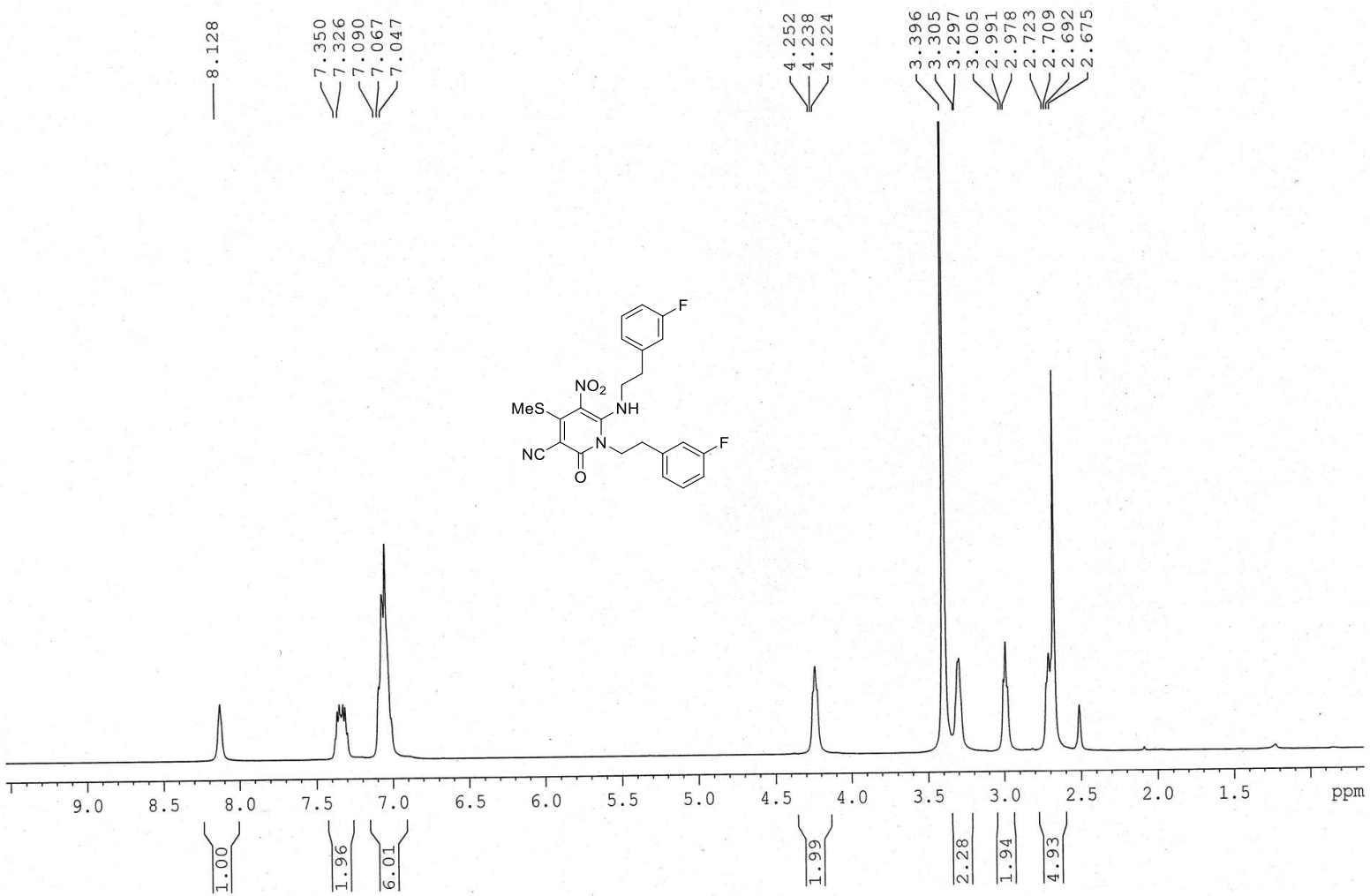


Figure 26. ^{1}H NMR (500 MHz, DMSO-d_6) spectra of compound **3m**

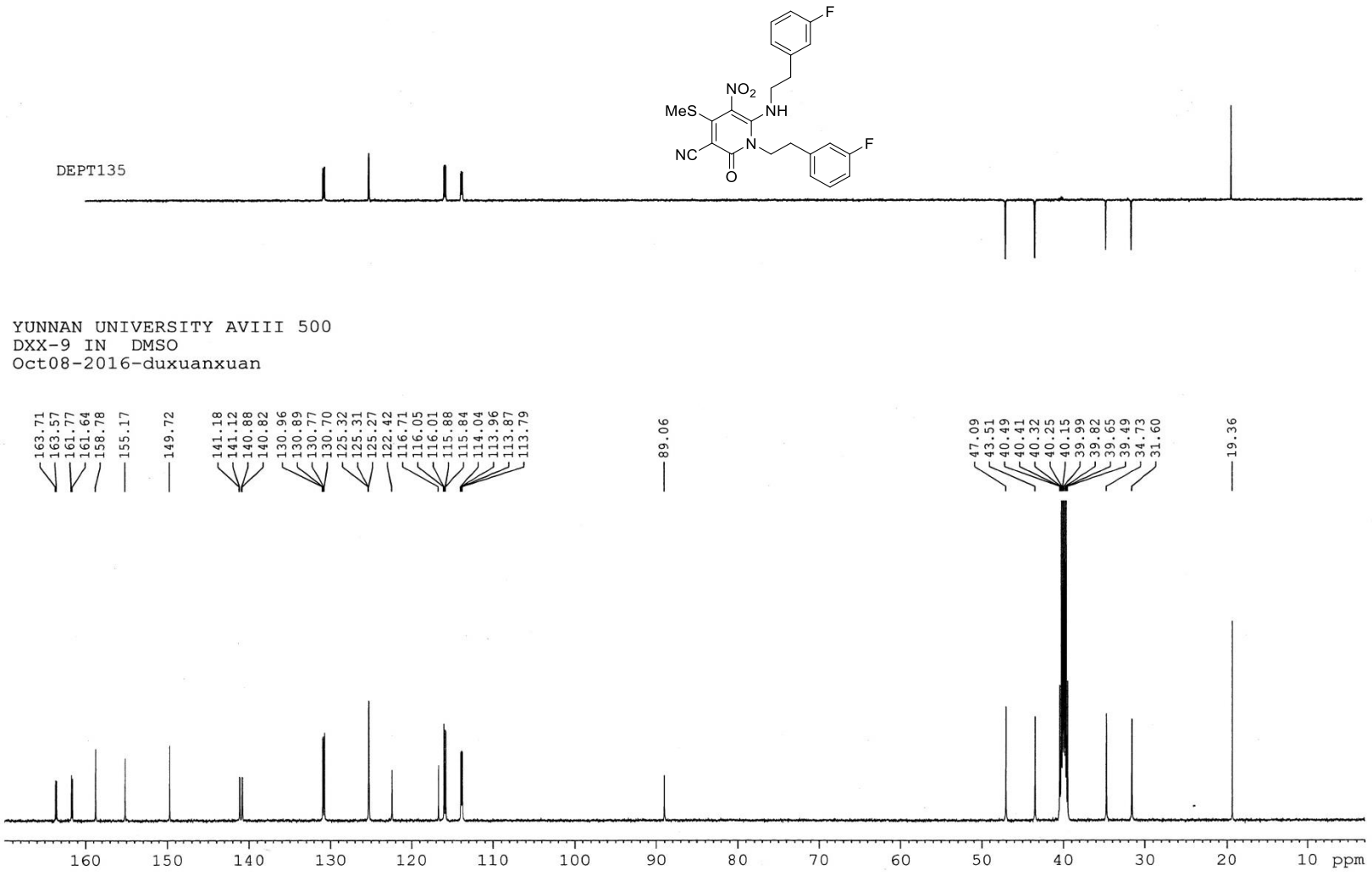


Figure 27. ^{13}C NMR (125 MHz, DMSO-d_6) spectra of compound **3m**

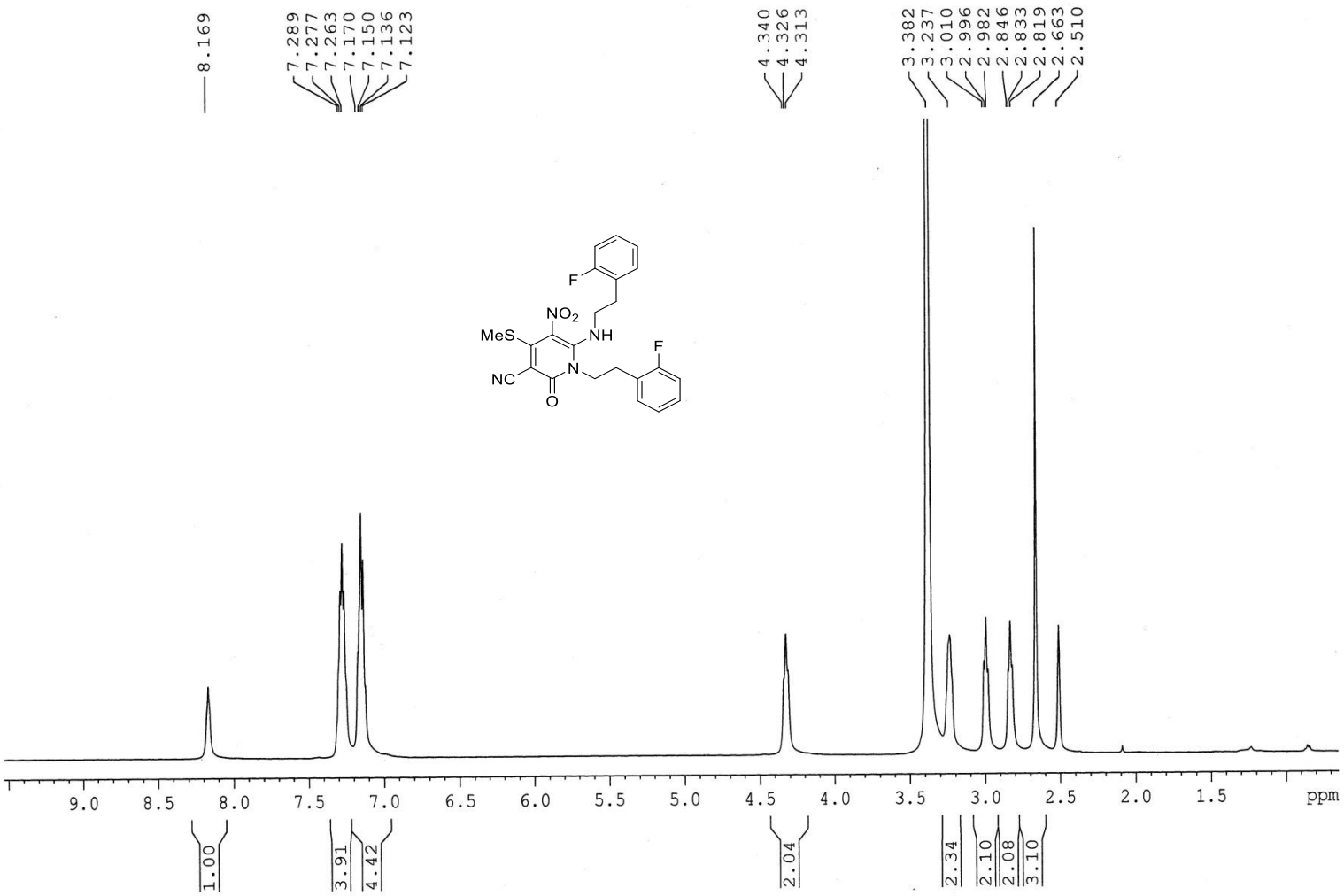


Figure 28. ^{1}H NMR (500 MHz, DMSO-d_6) spectra of compound **3n**

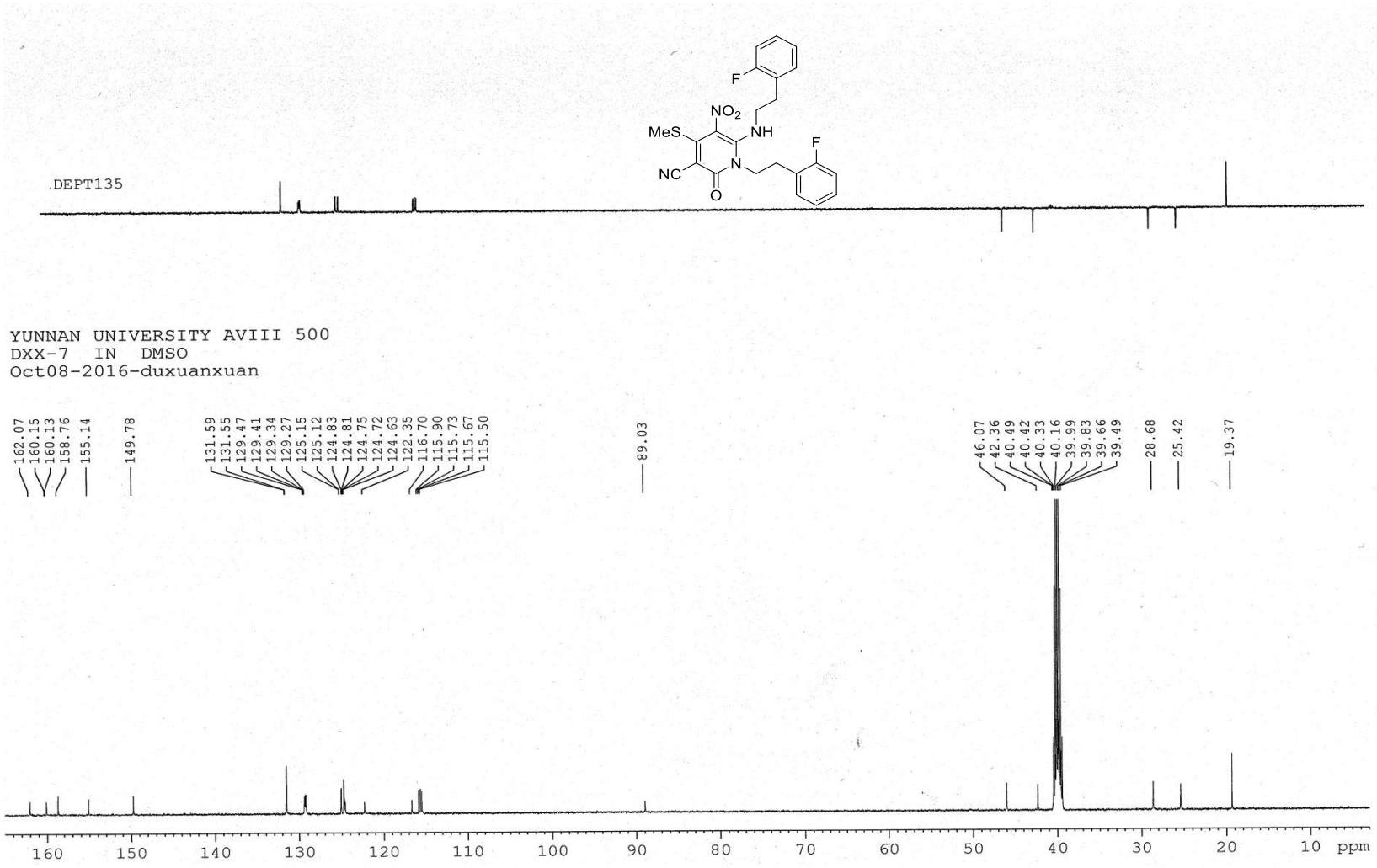


Figure 29. ^{13}C NMR (125 MHz, DMSO-d_6) spectra of compound **3n**

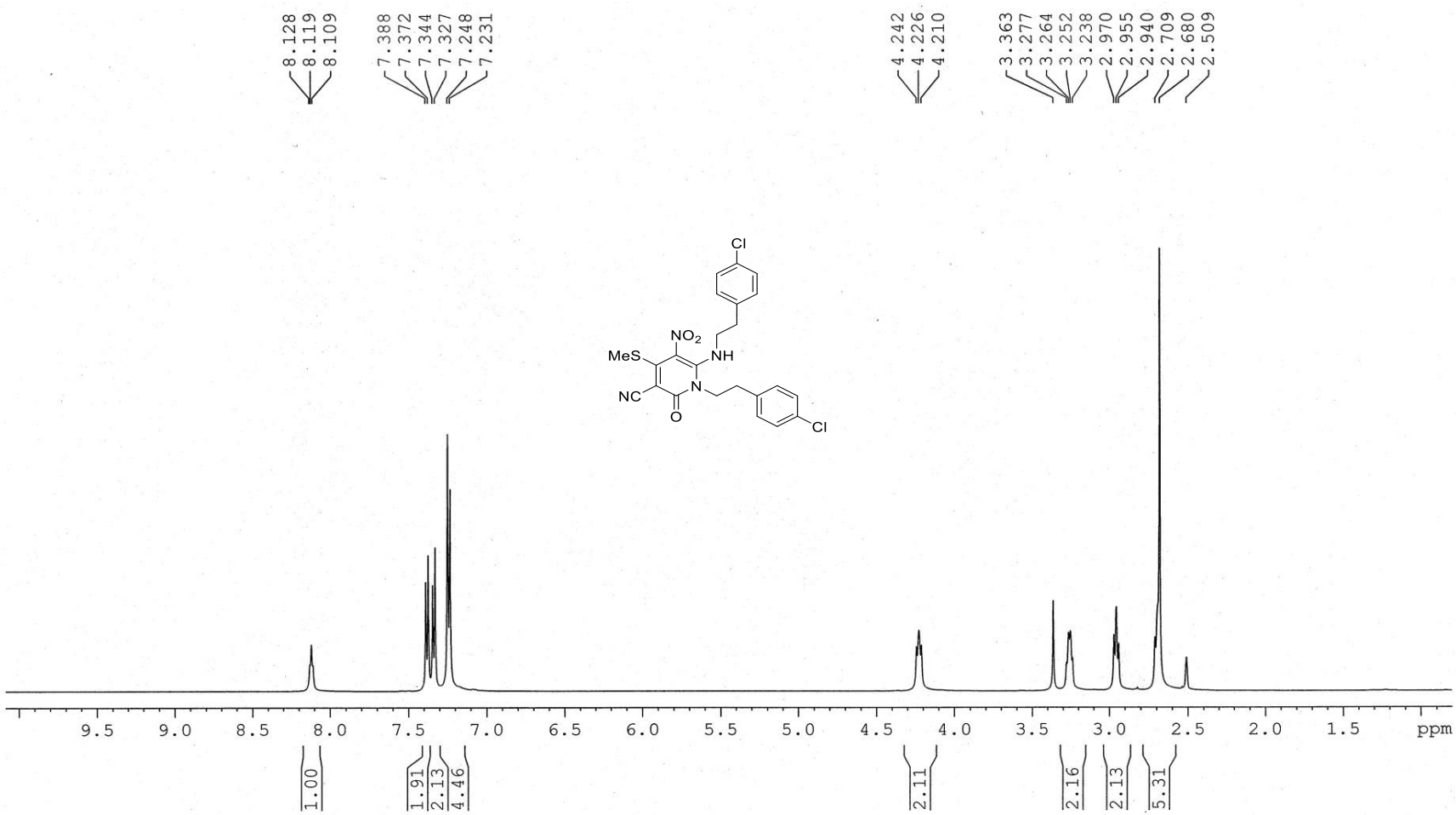


Figure 30. ^{1}H NMR (500 MHz, DMSO-d_6) spectra of compound **3o**

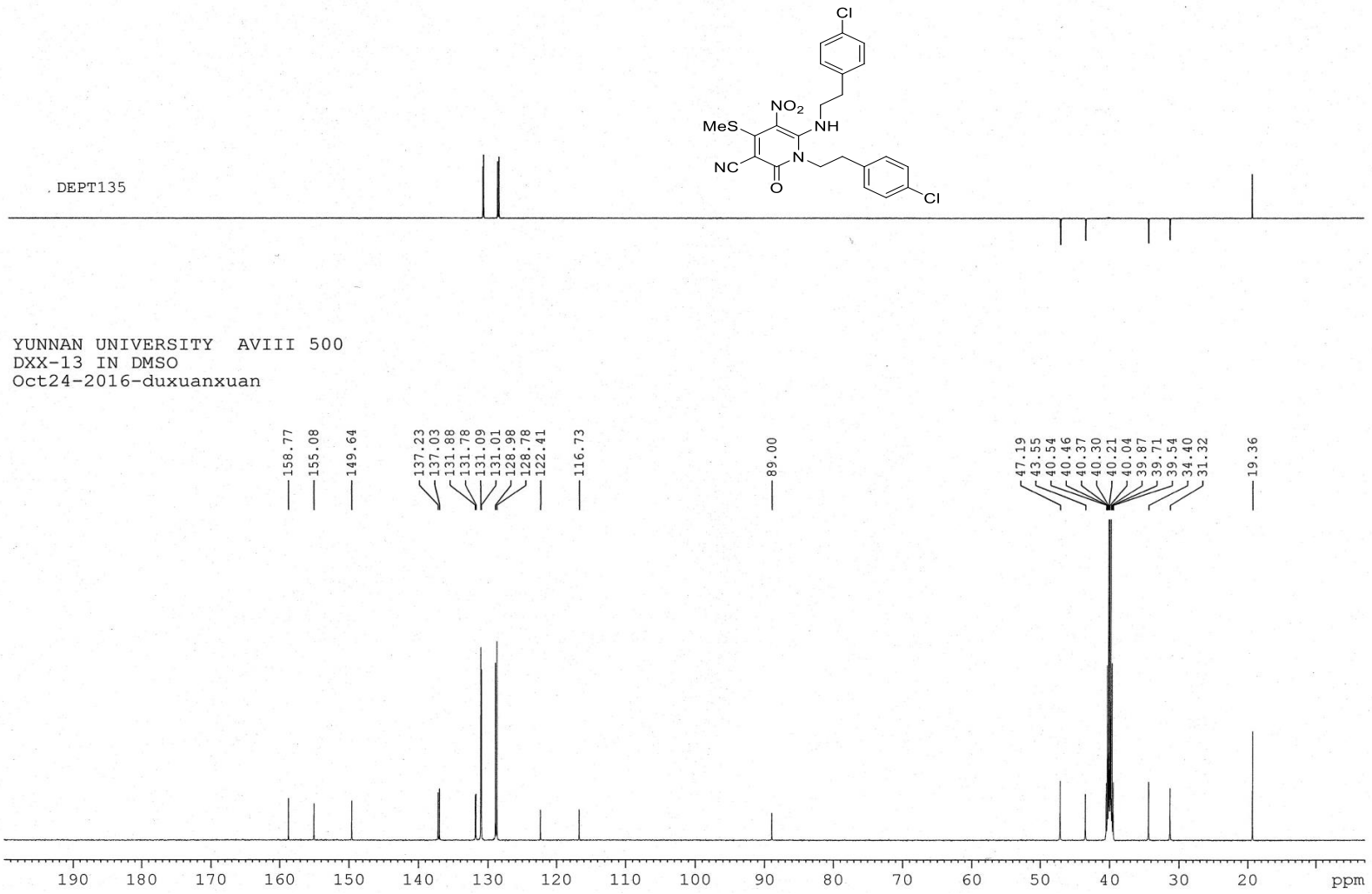


Figure 31. ^{13}C NMR (125 MHz, DMSO-d_6) spectra of compound **3o**

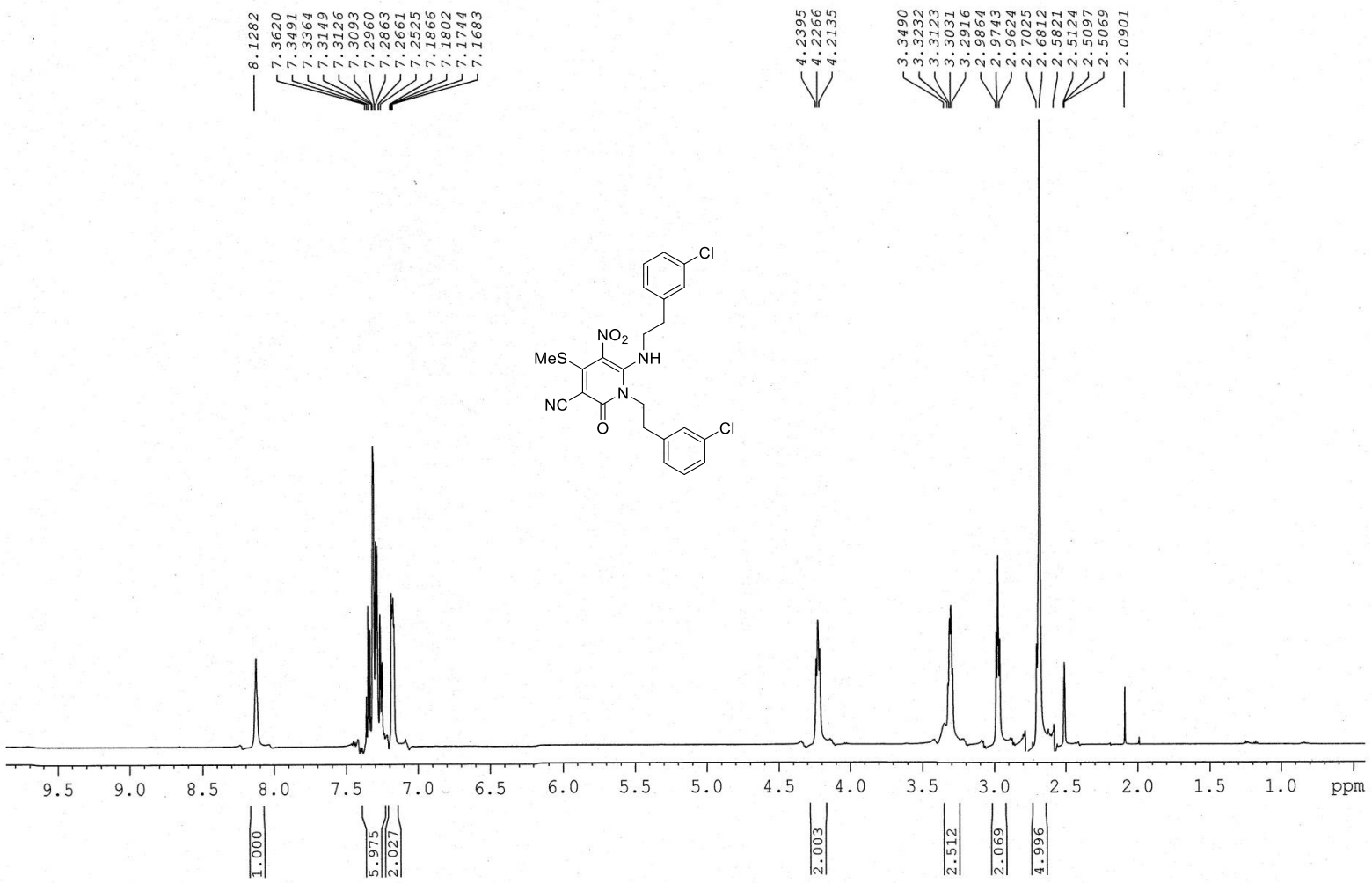


Figure 32. ^{1}H NMR (600 MHz, DMSO-d_6) spectra of compound **3p**

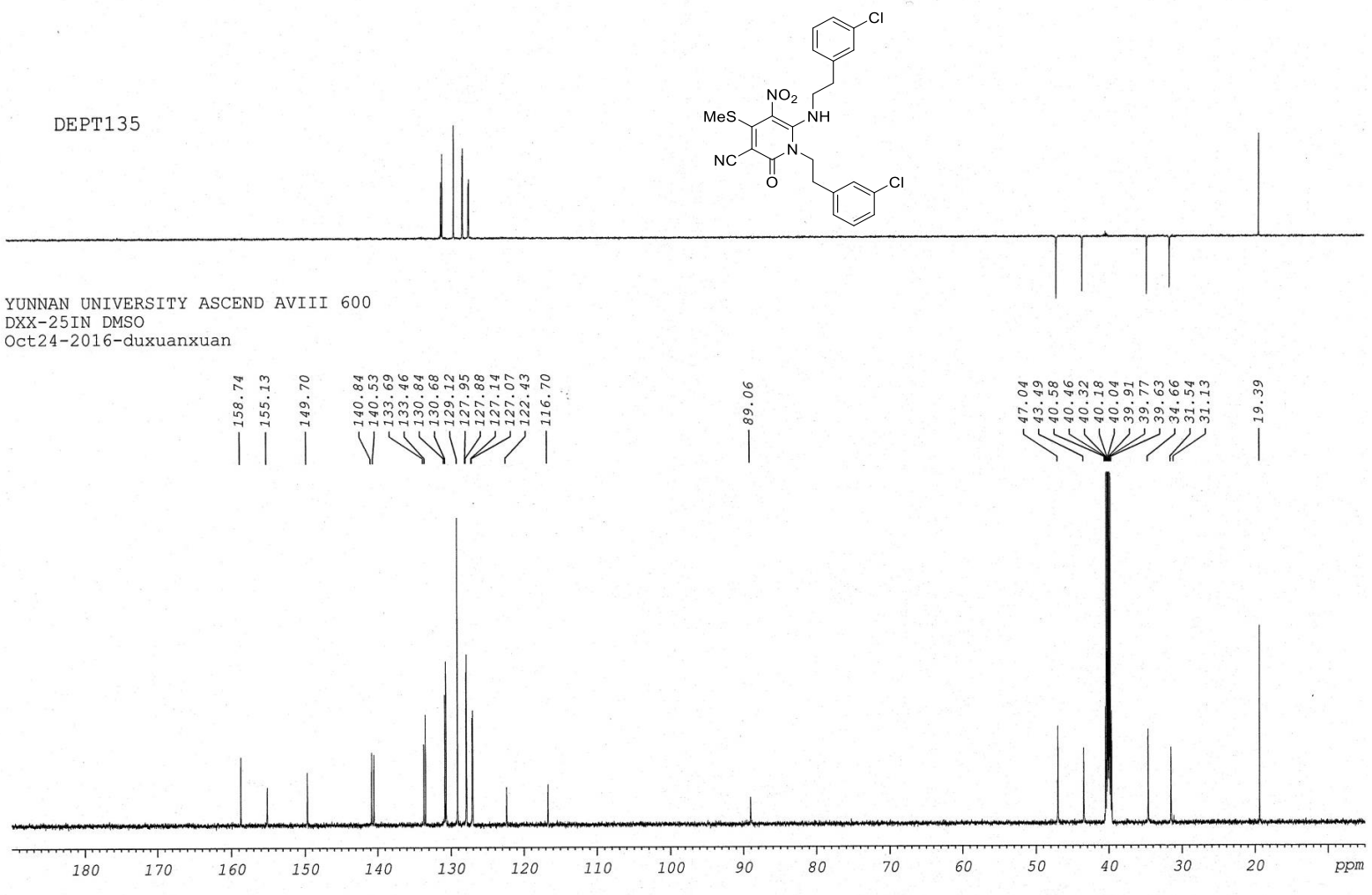


Figure 33. ^{13}C NMR (150 MHz, DMSO-d_6) spectra of compound **3p**

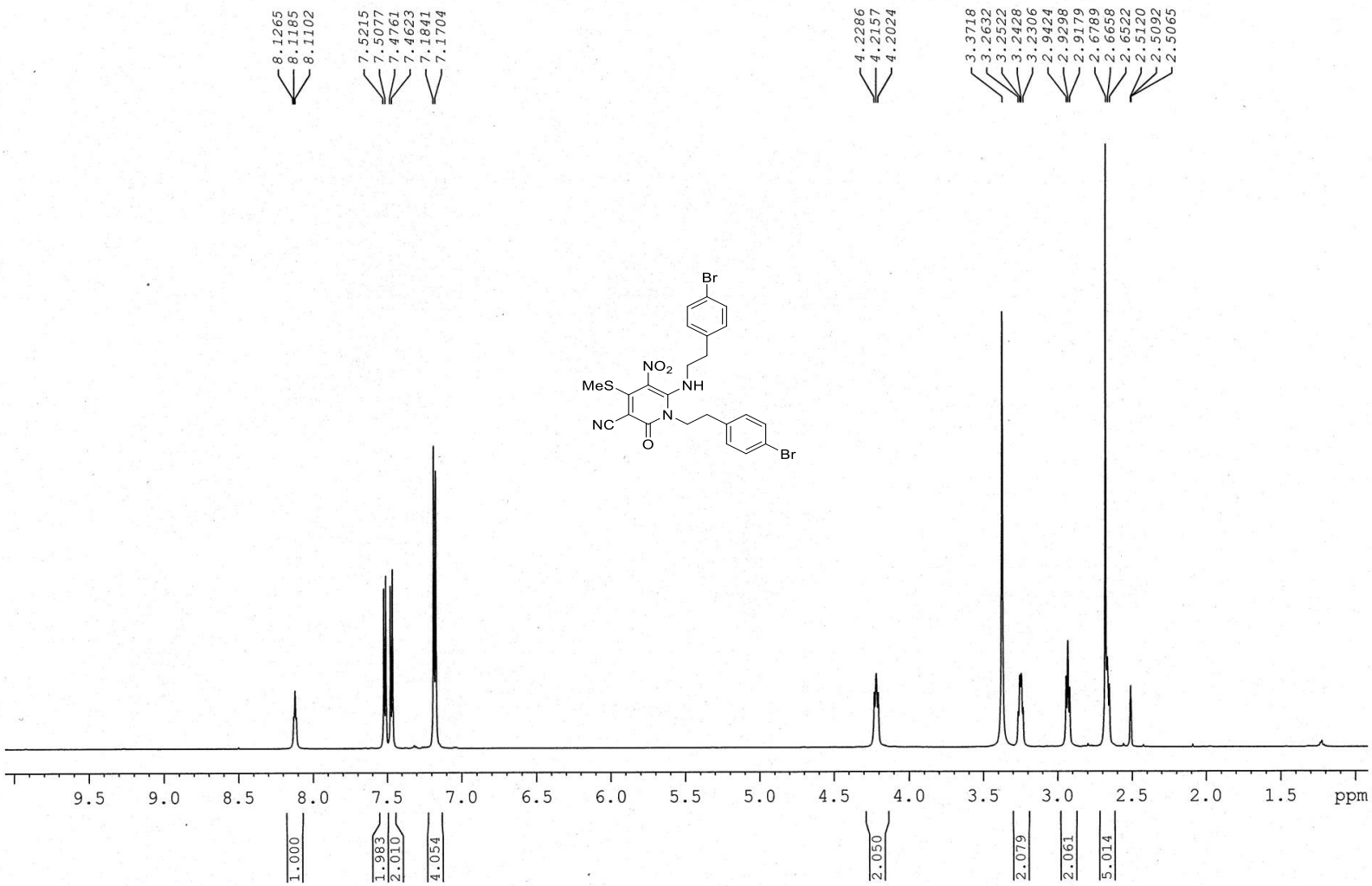


Figure 34. ^{1}H NMR (600 MHz, DMSO-d_6) spectra of compound **3q**

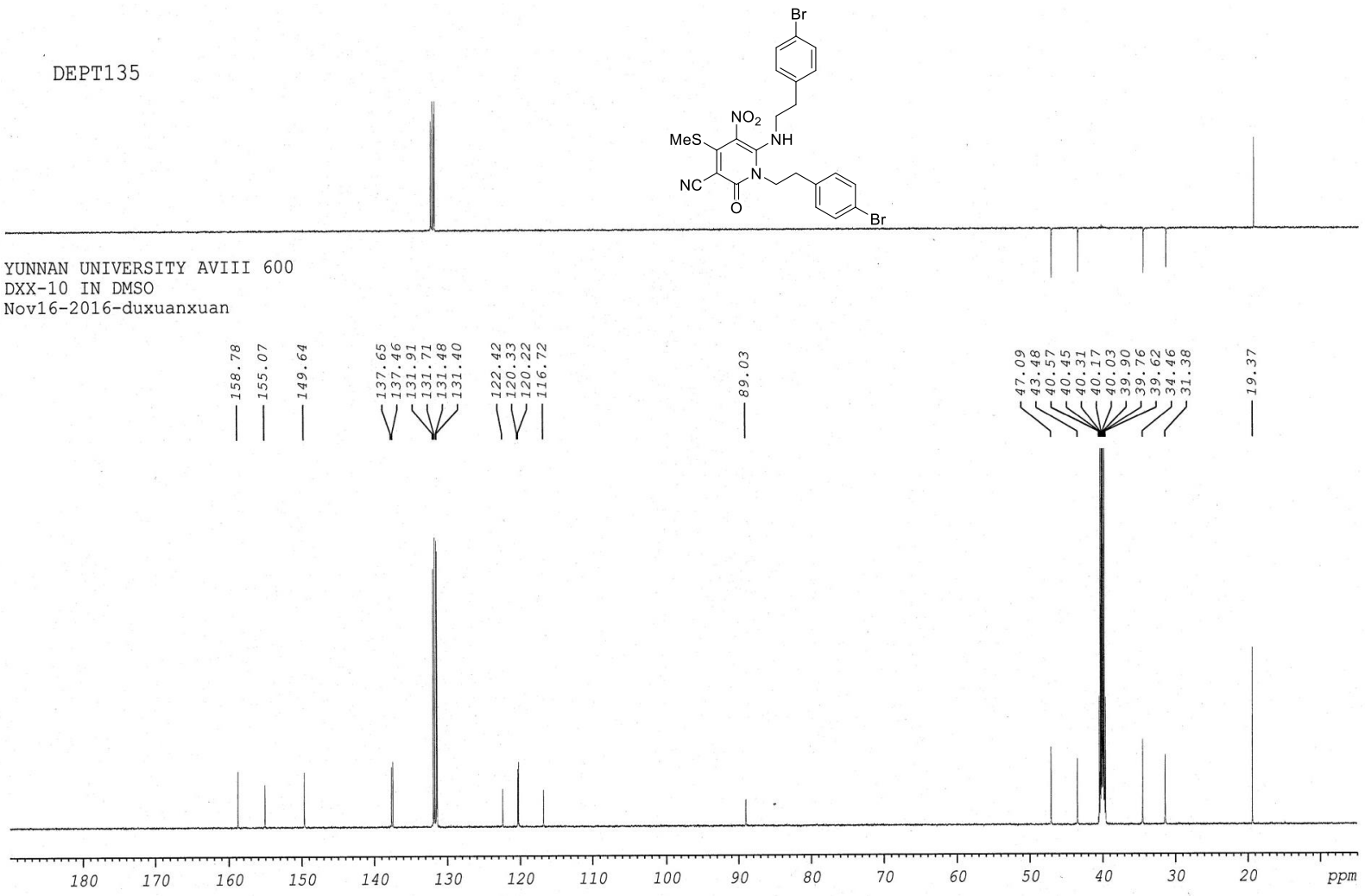


Figure 35. ^{13}C NMR (150 MHz, DMSO-d_6) spectra of compound **3q**

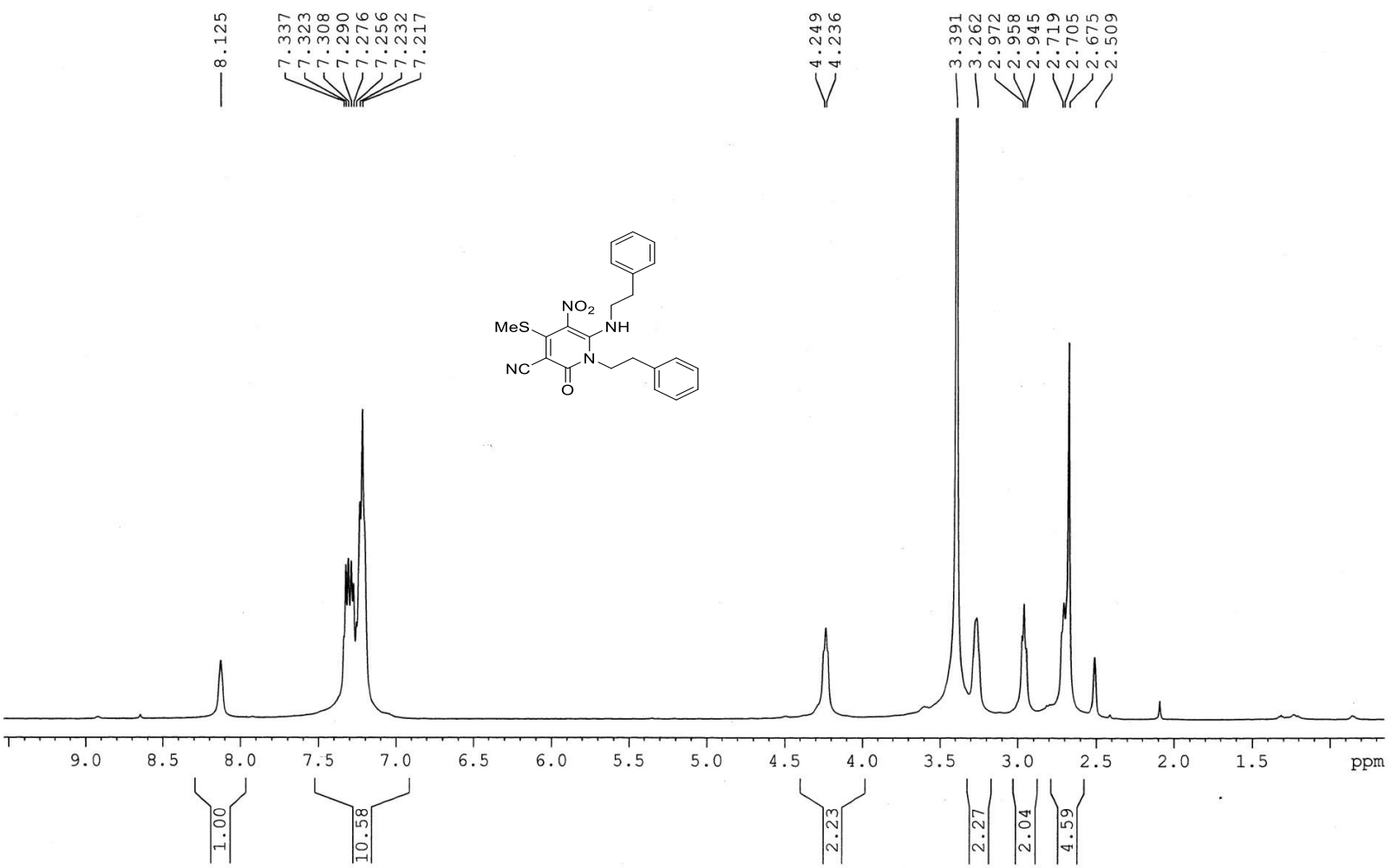


Figure 36. ^{1}H NMR (500 MHz, DMSO-d_6) spectra of compound **3r**

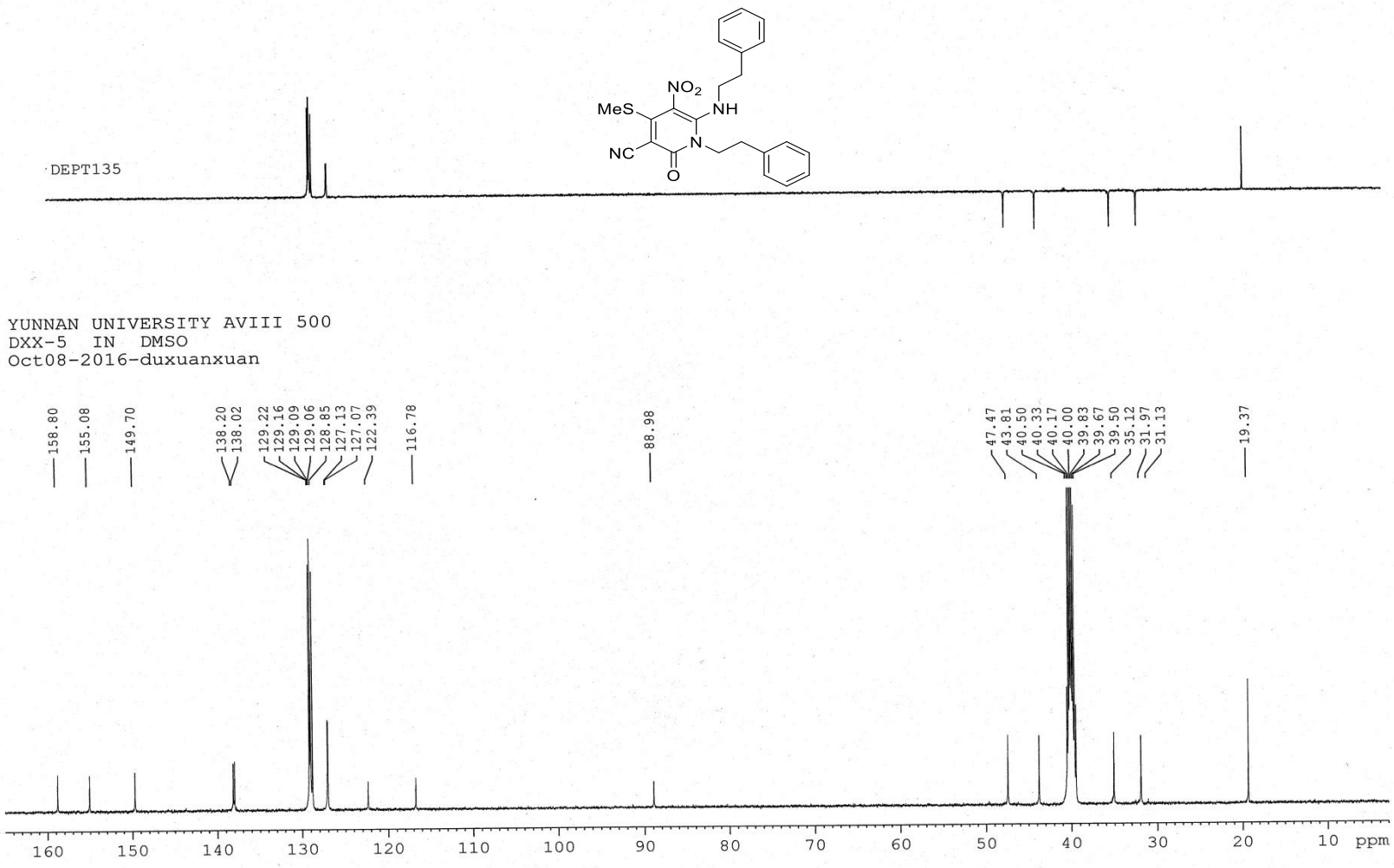


Figure 37. ^{13}CNMR (125 MHz, DMSO-d_6) spectra of compound **3r**

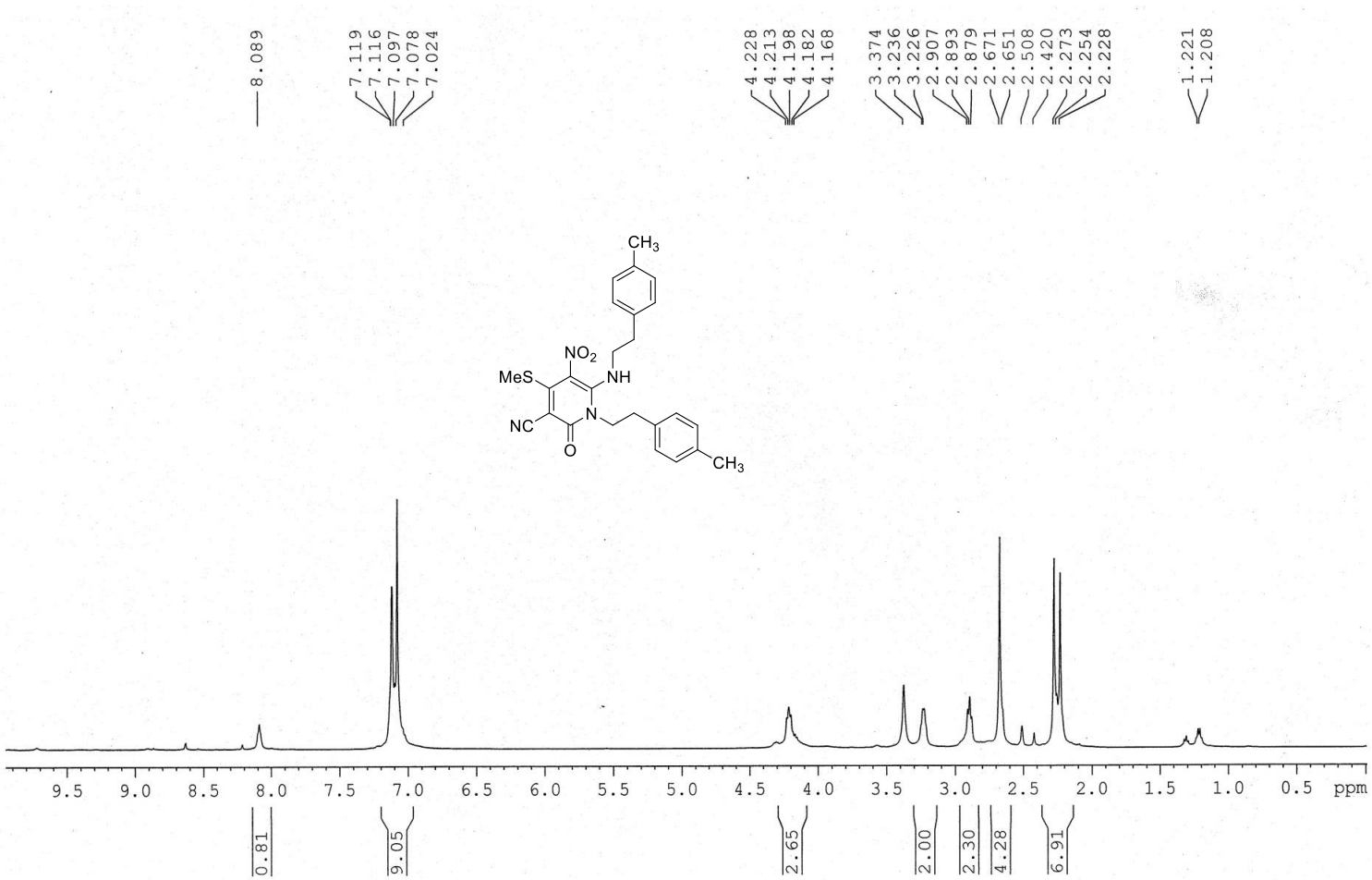


Figure 38. ^{1}H NMR (500 MHz, DMSO-d_6) spectra of compound **3s**

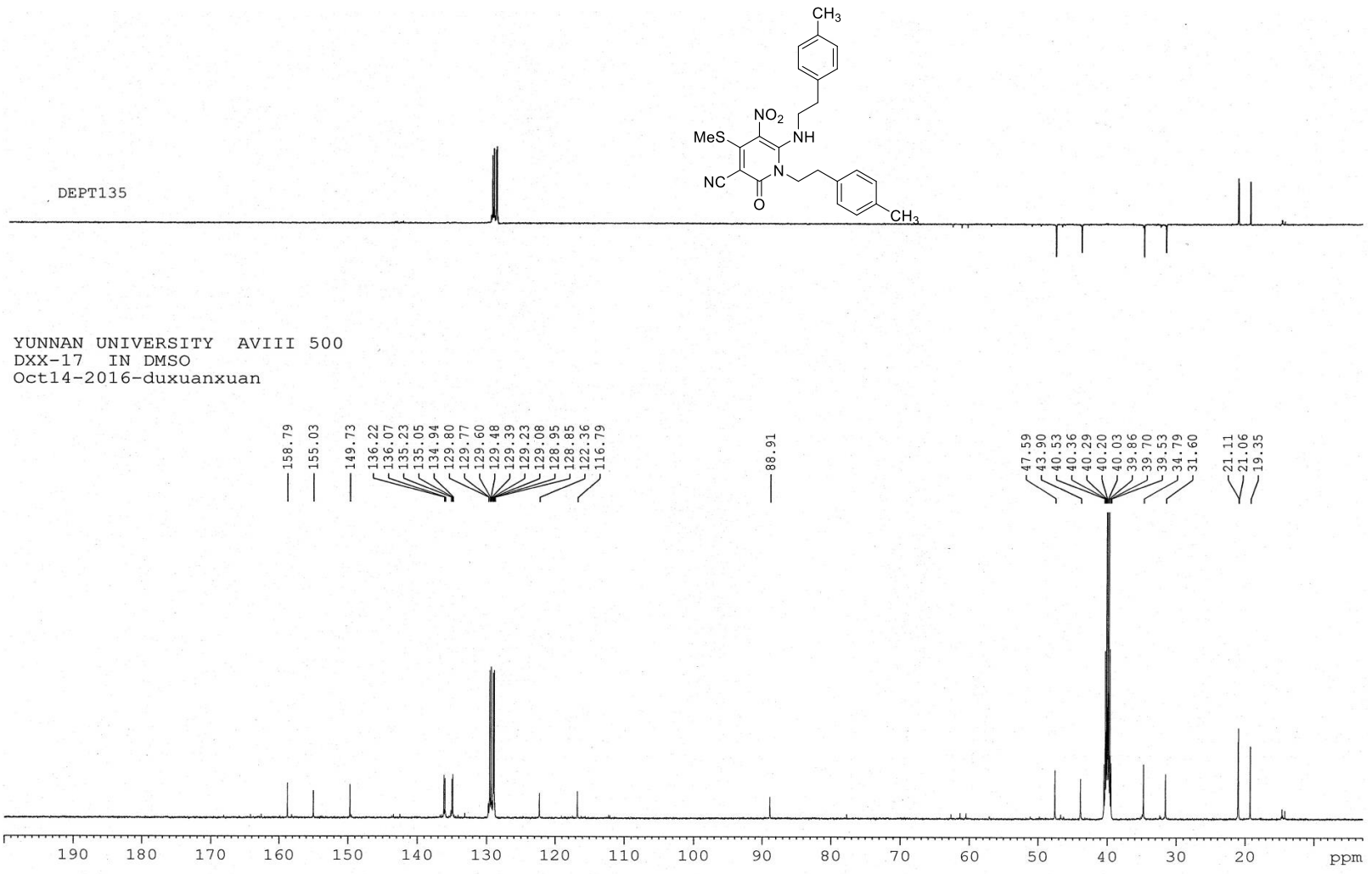


Figure 39. ^{13}C NMR (125 MHz, DMSO-d_6) spectra of compound **3s**

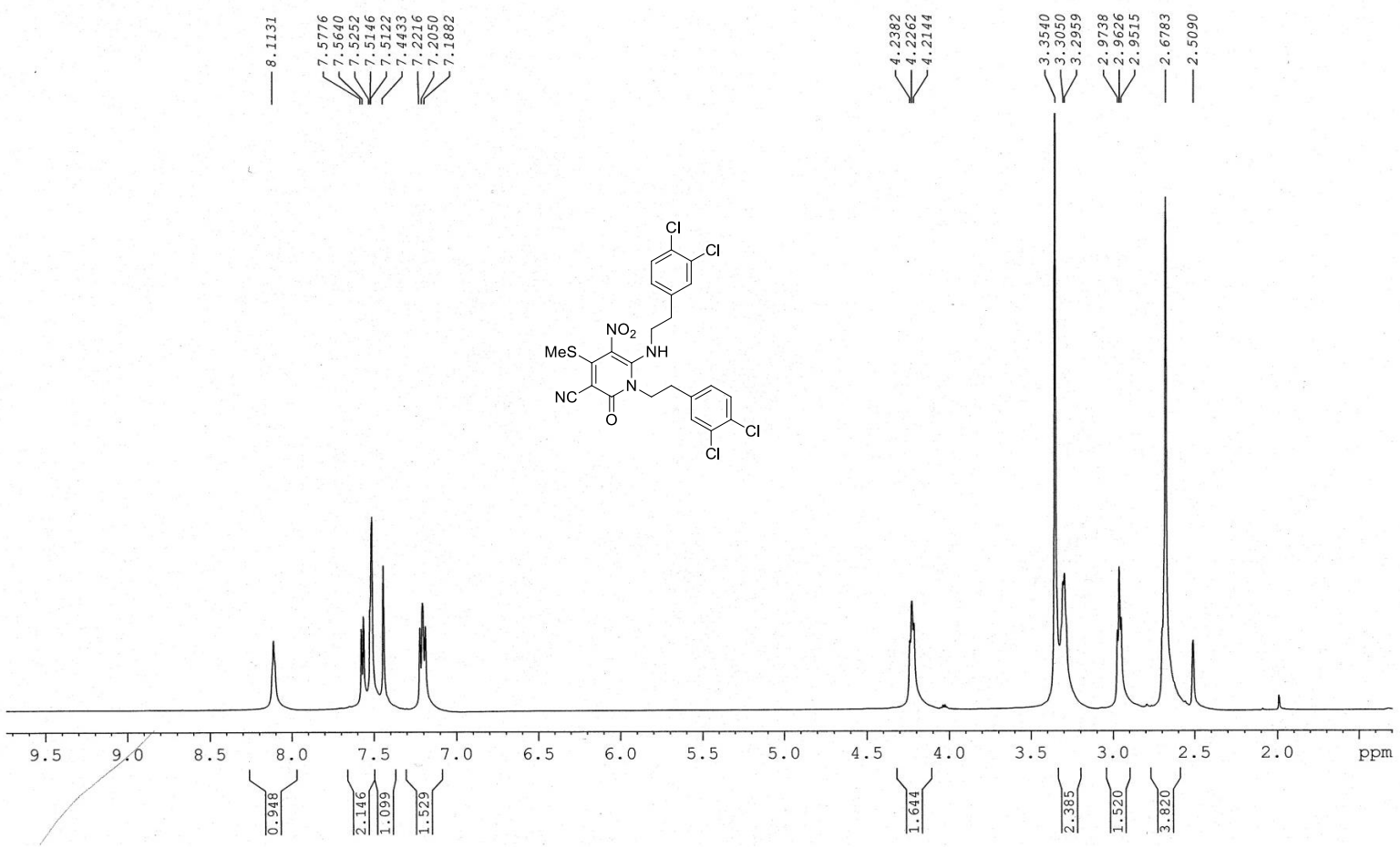


Figure 40. ^{1}H NMR (600 MHz, DMSO-d_6) spectra of compound **3t**

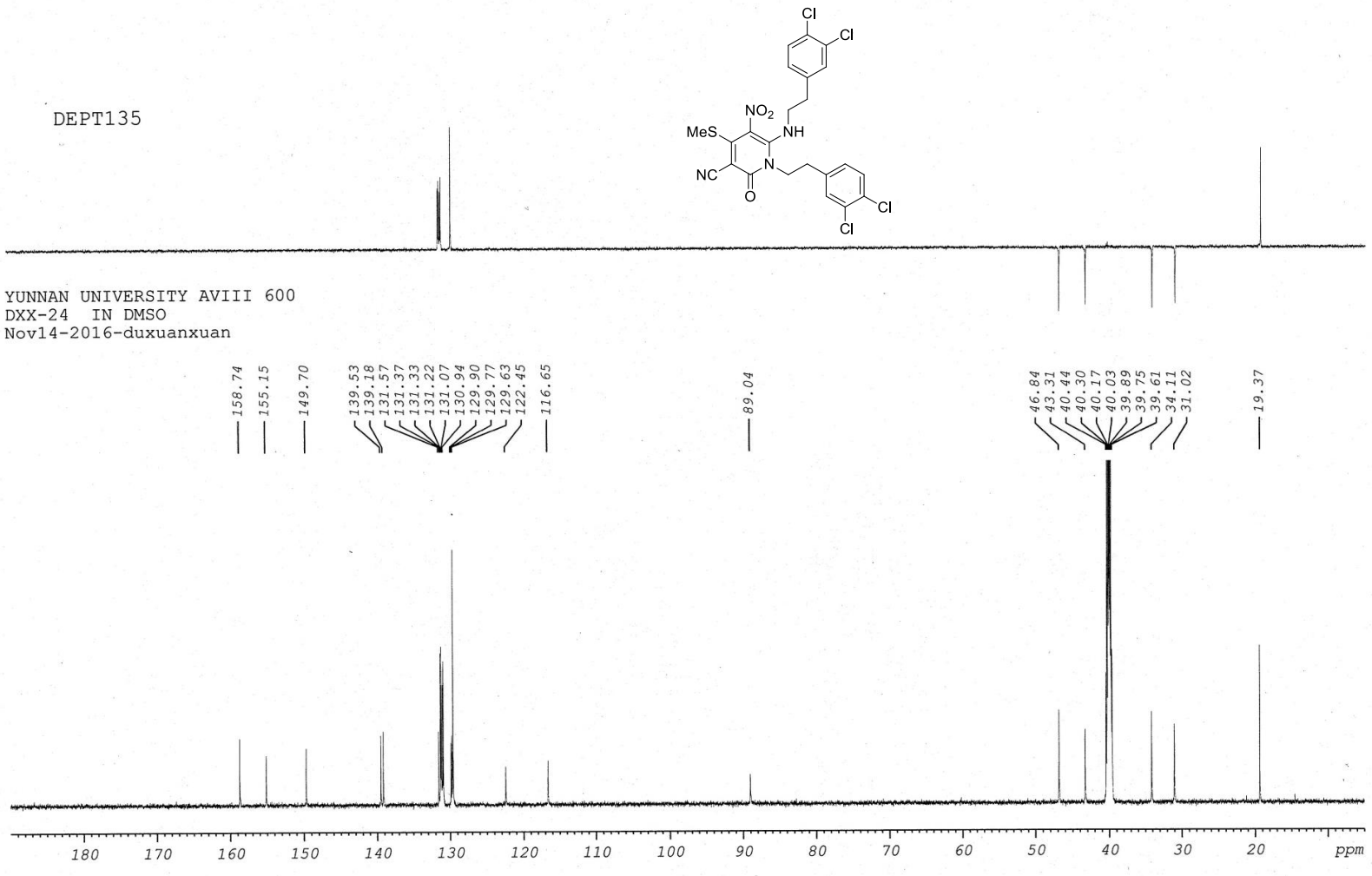


Figure 41. ^{13}C NMR (150 MHz, DMSO-d_6) spectra of compound **3t**

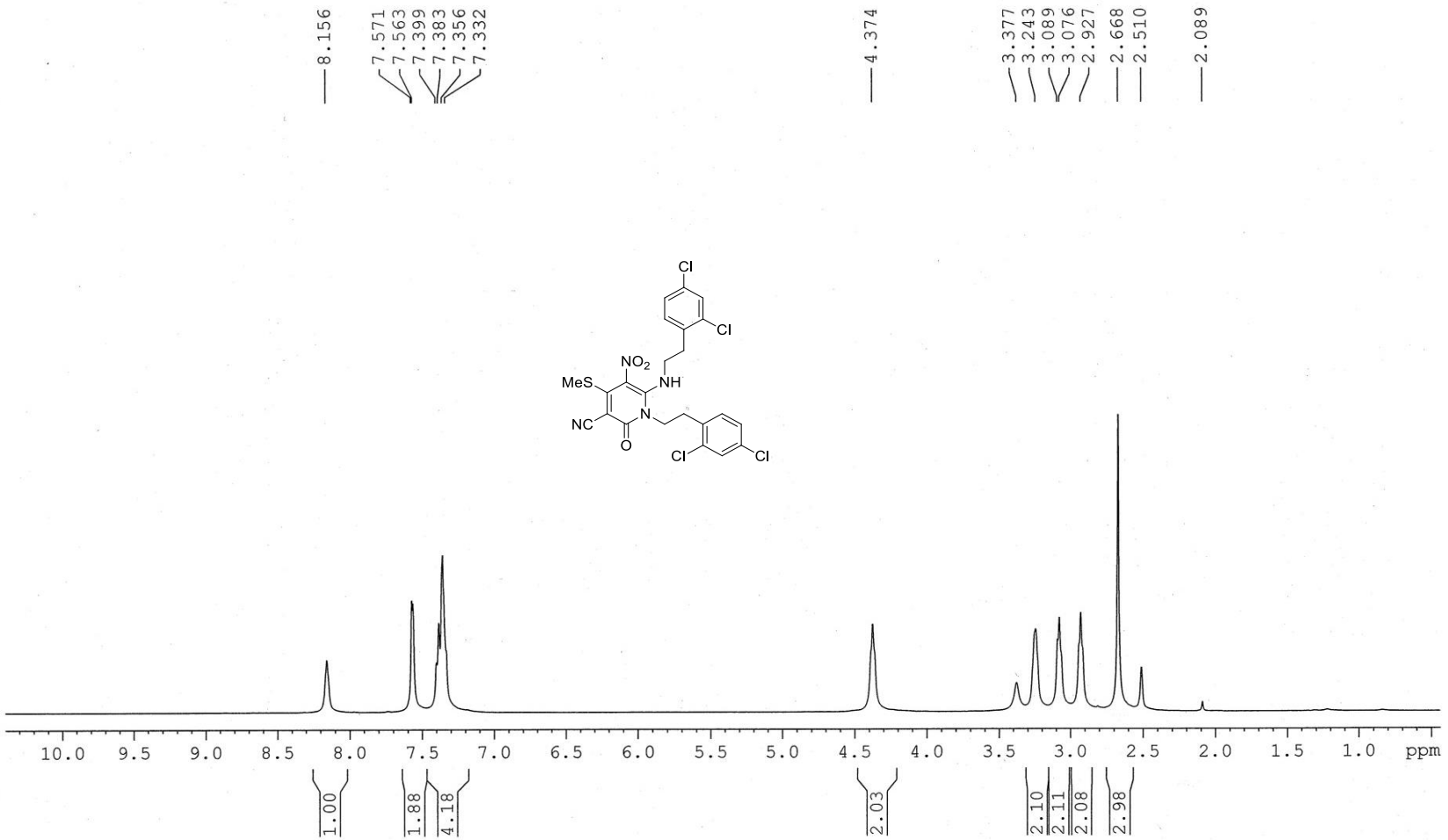


Figure 42. ^{1}H NMR (500 MHz, DMSO-d_6) spectra of compound **3u**

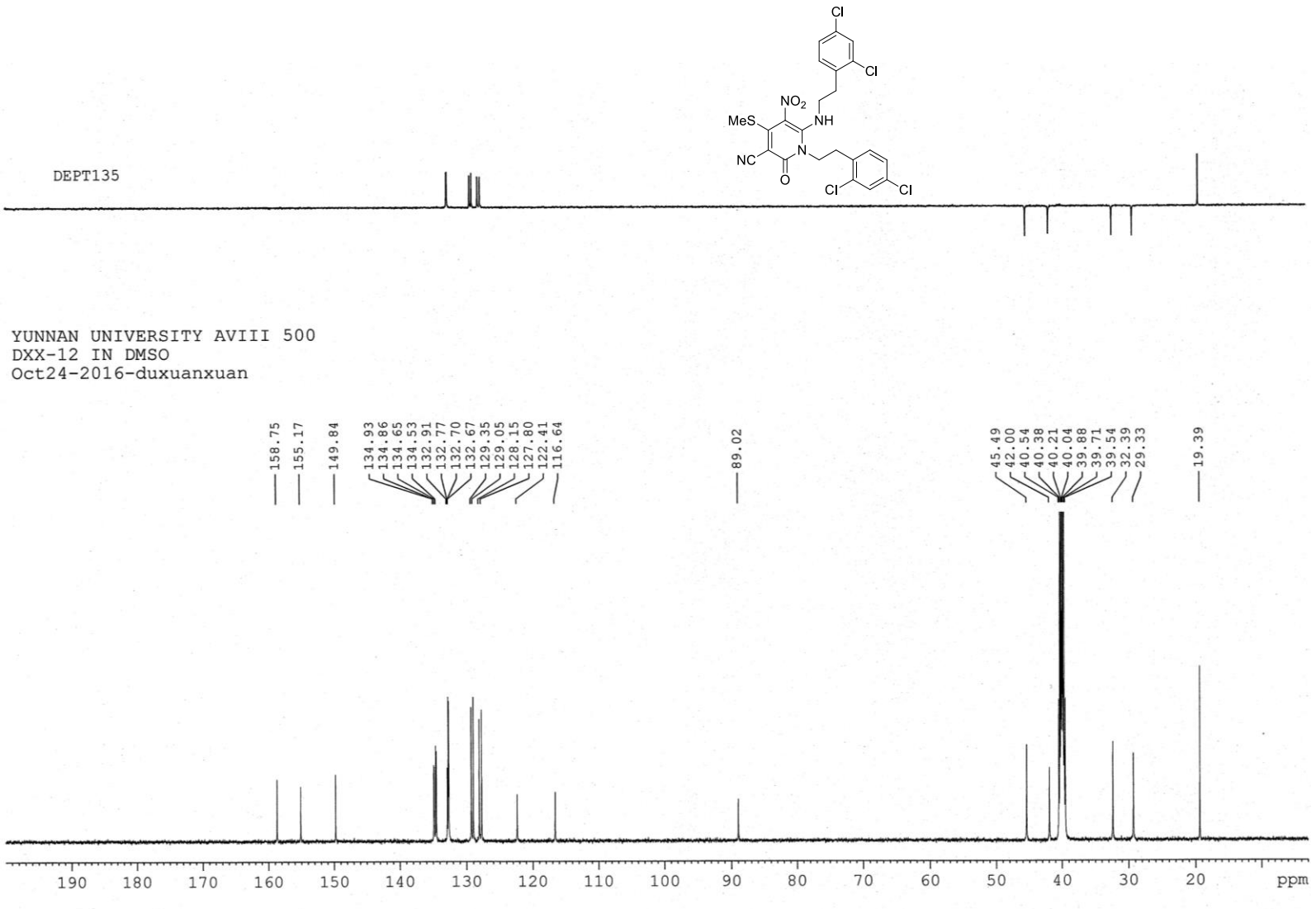


Figure 43. ^{13}C NMR (125 MHz, DMSO-d_6) spectra of compound **3u**

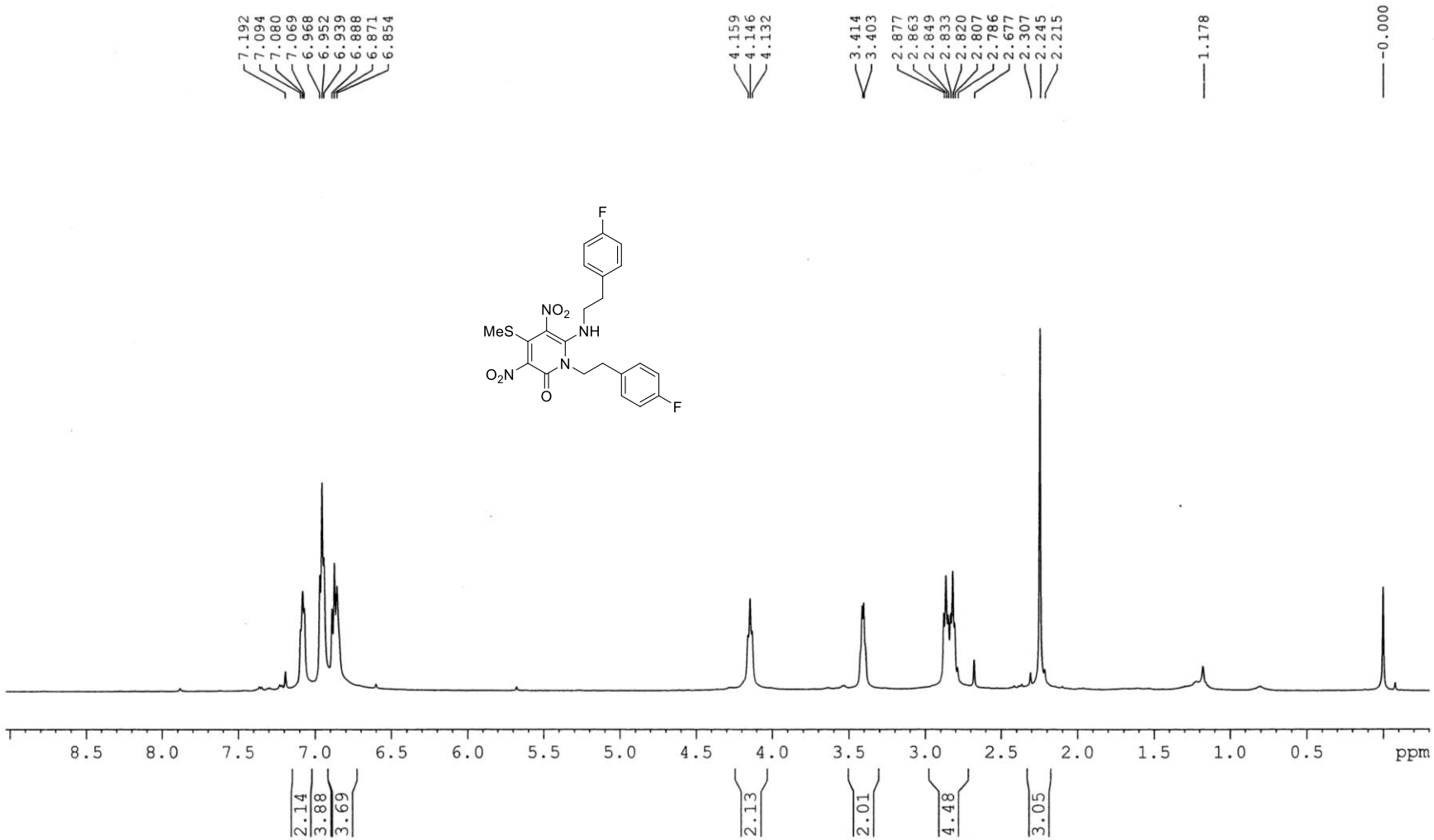


Figure 44. ^{1}H NMR (500 MHz, $CDCl_3$) spectra of compound **3v**

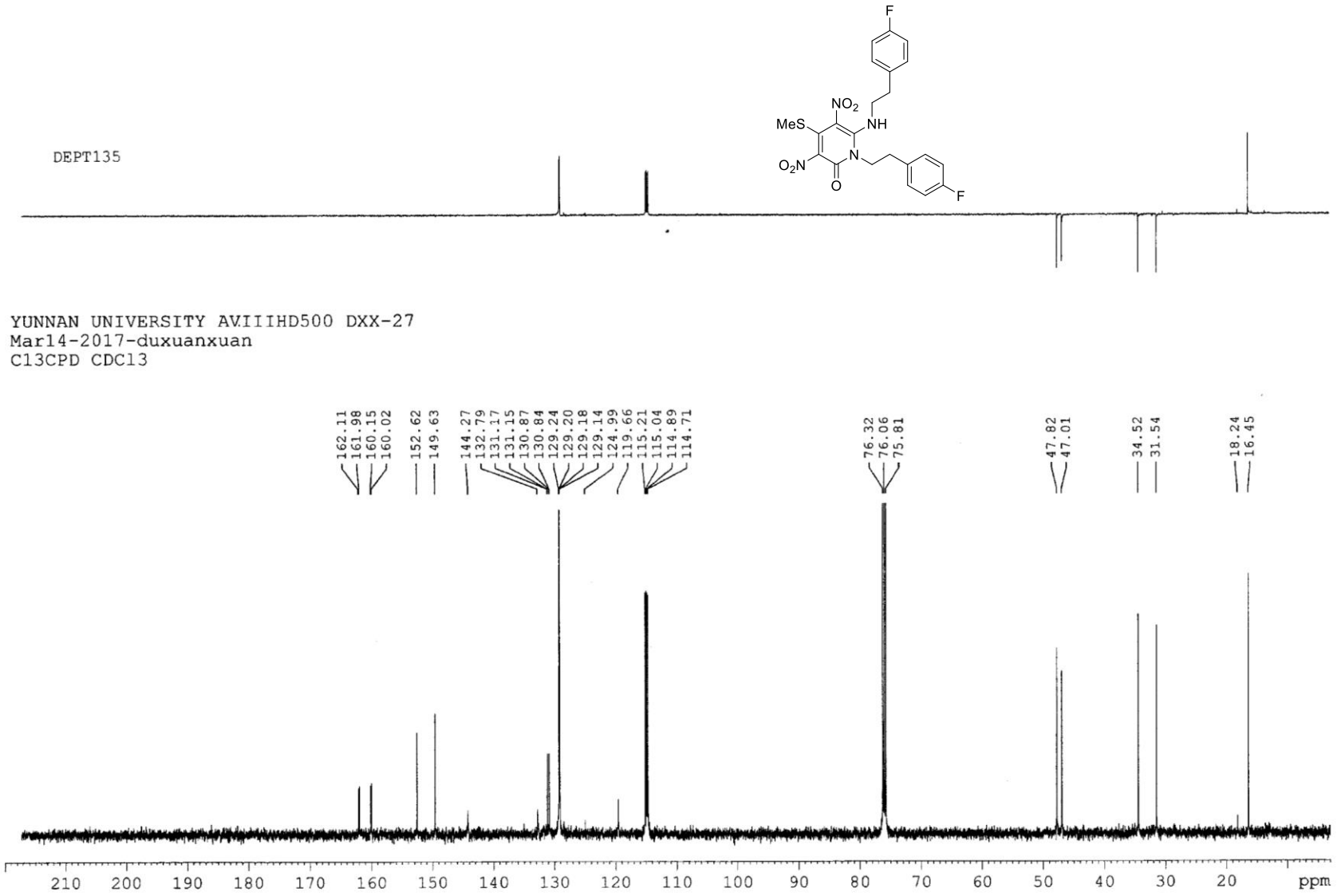


Figure 45. ^{13}C NMR (125 MHz, $CDCl_3$) spectra of compound **3v**

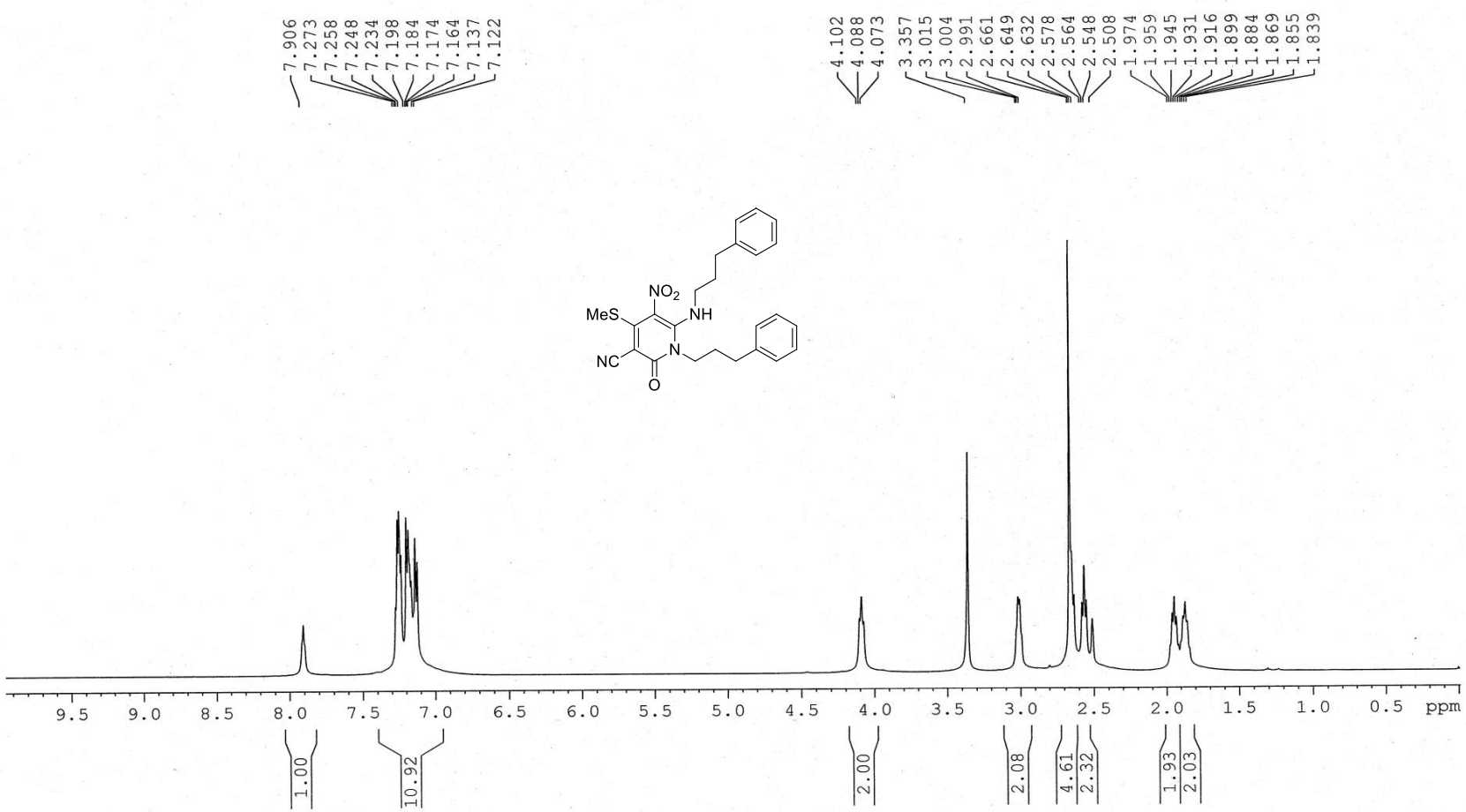


Figure 46. ^{1}H NMR (500 MHz, DMSO-d_6) spectra of compound **3w**

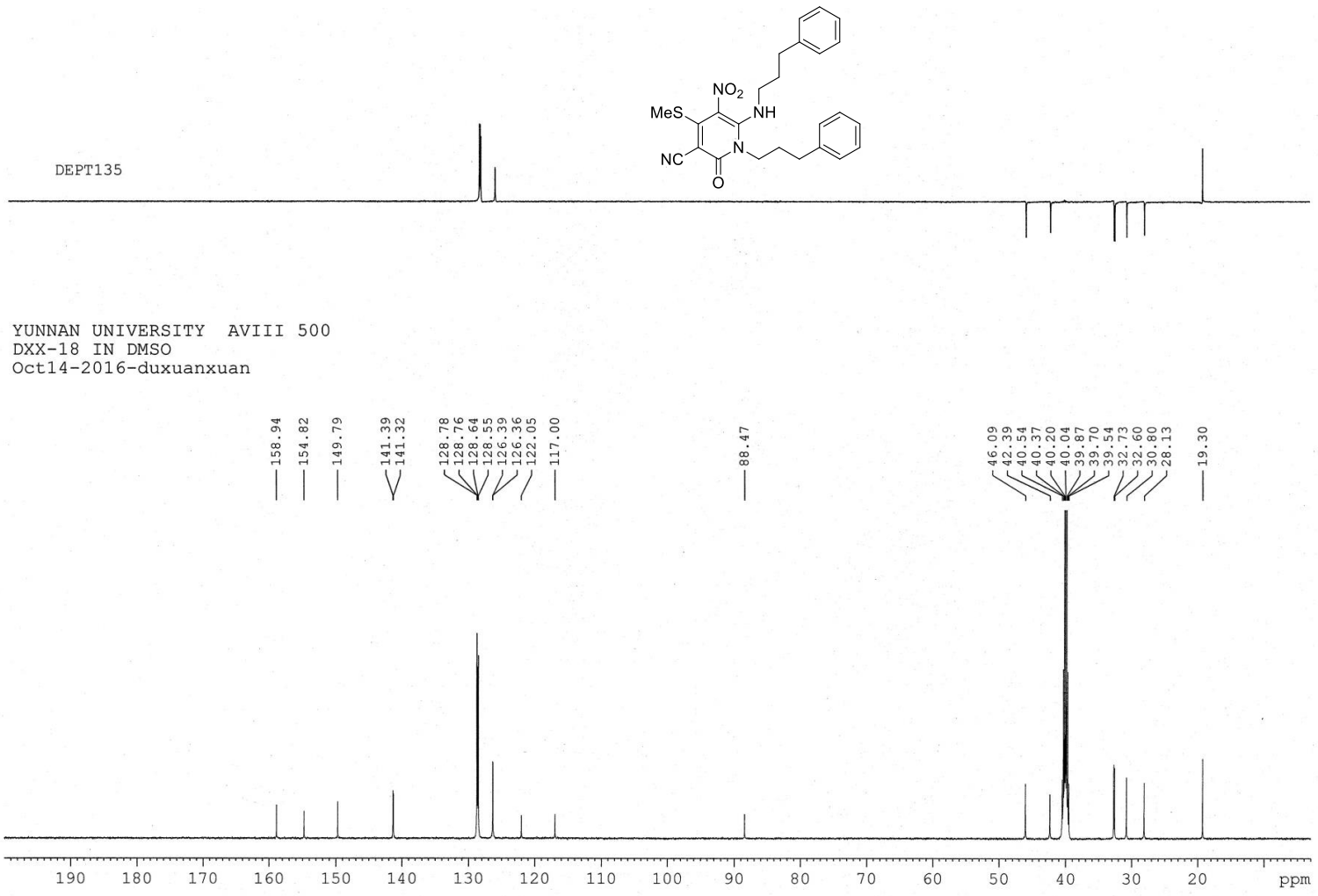


Figure 47. ^{13}C NMR (125 MHz, DMSO-d_6) spectra of compound **3w**

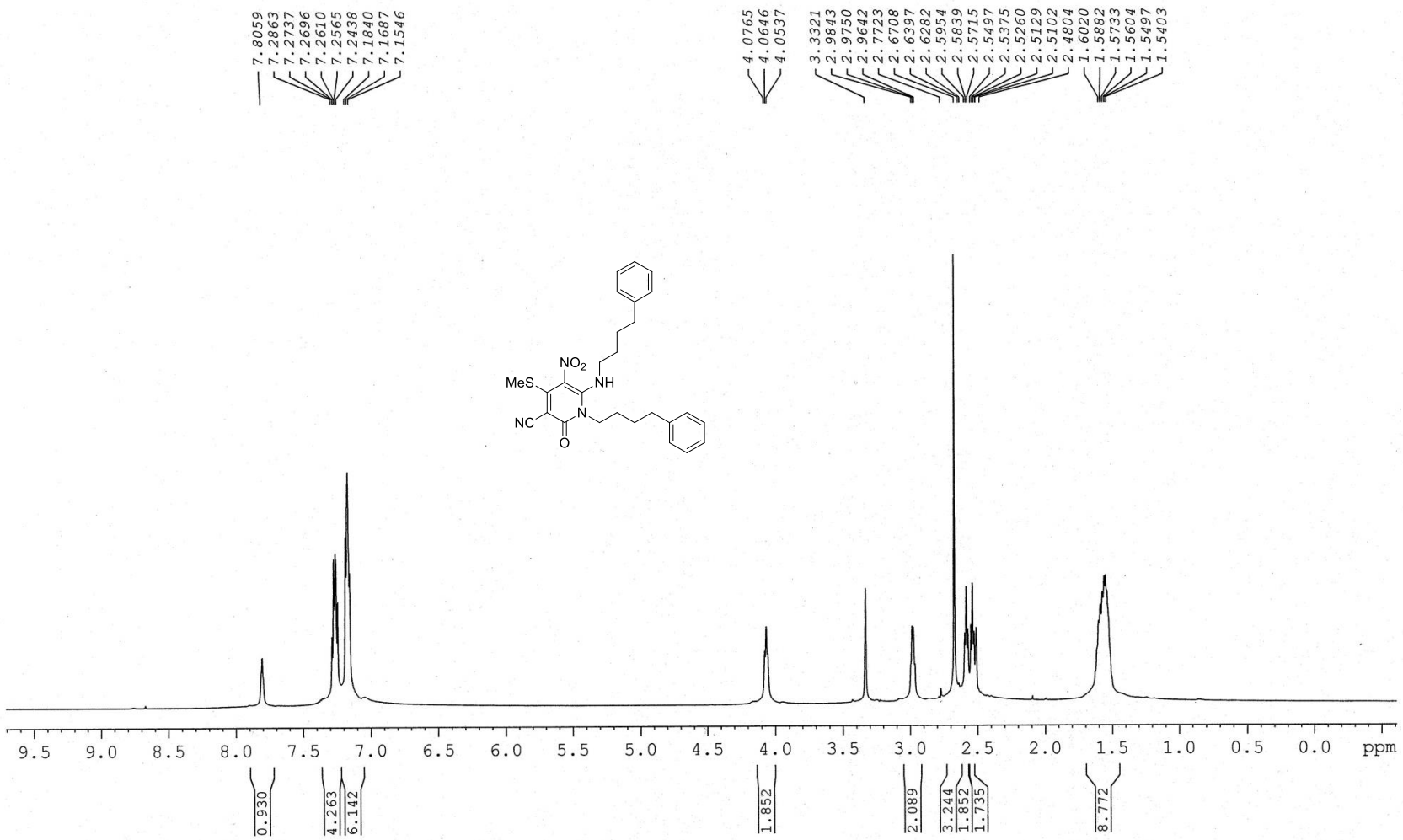


Figure 48. ^{1}H NMR (600 MHz, DMSO-d_6) spectra of compound **3x**

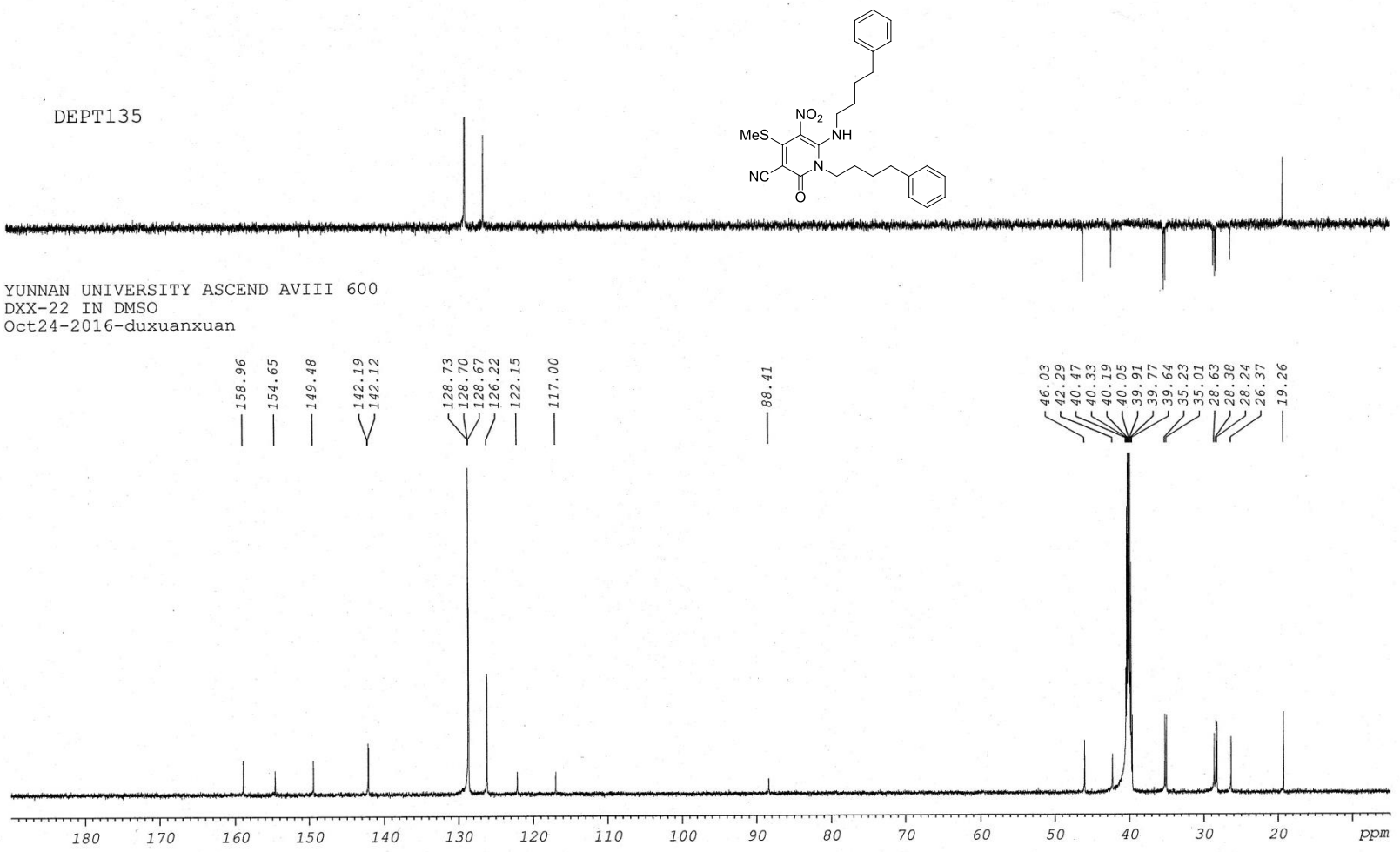


Figure 49. ^{13}C NMR (150 MHz, DMSO-d_6) spectra of compound **3x**

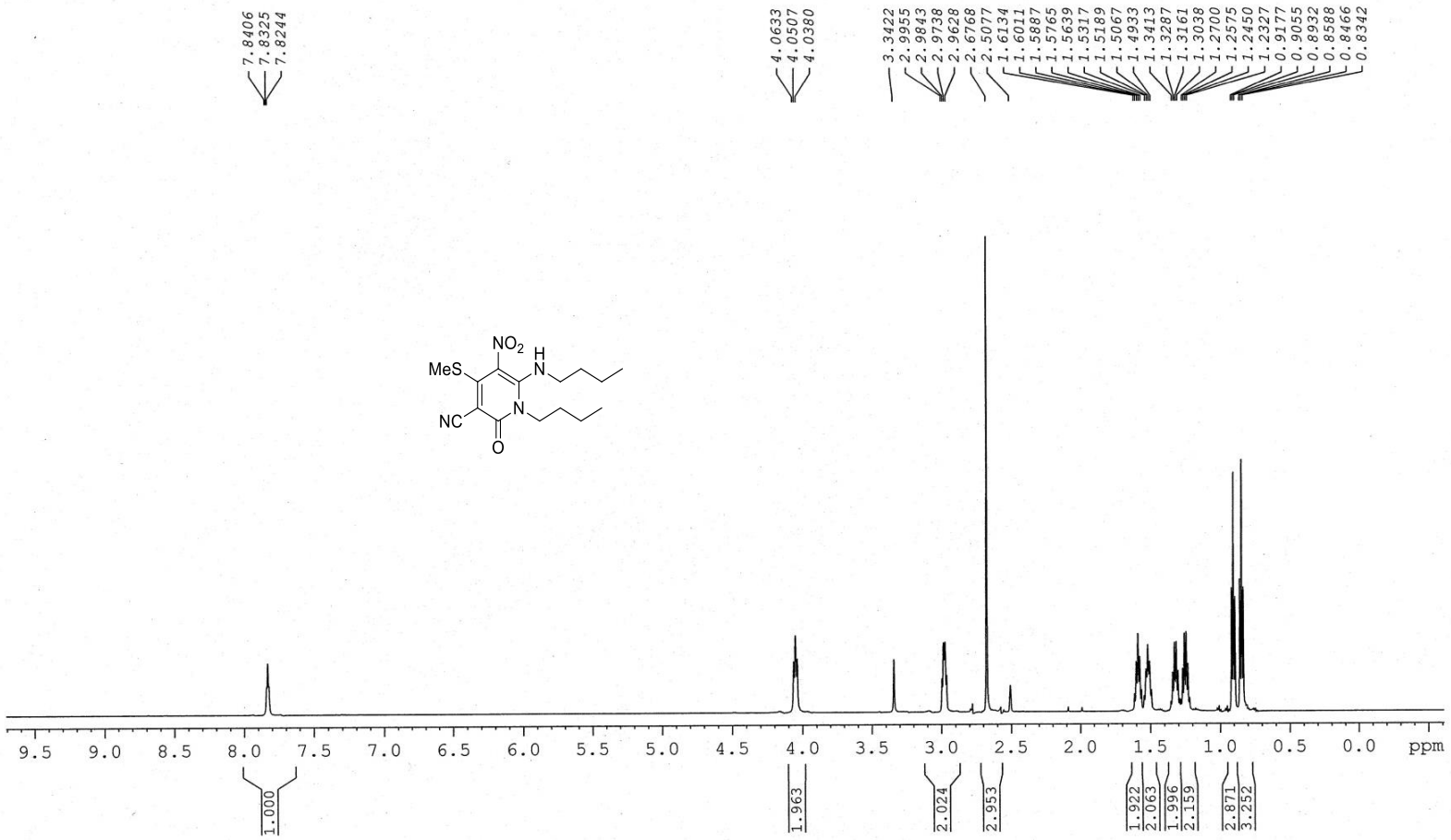


Figure 50. ^{1}H NMR (600 MHz, DMSO-d_6) spectra of compound **3y**

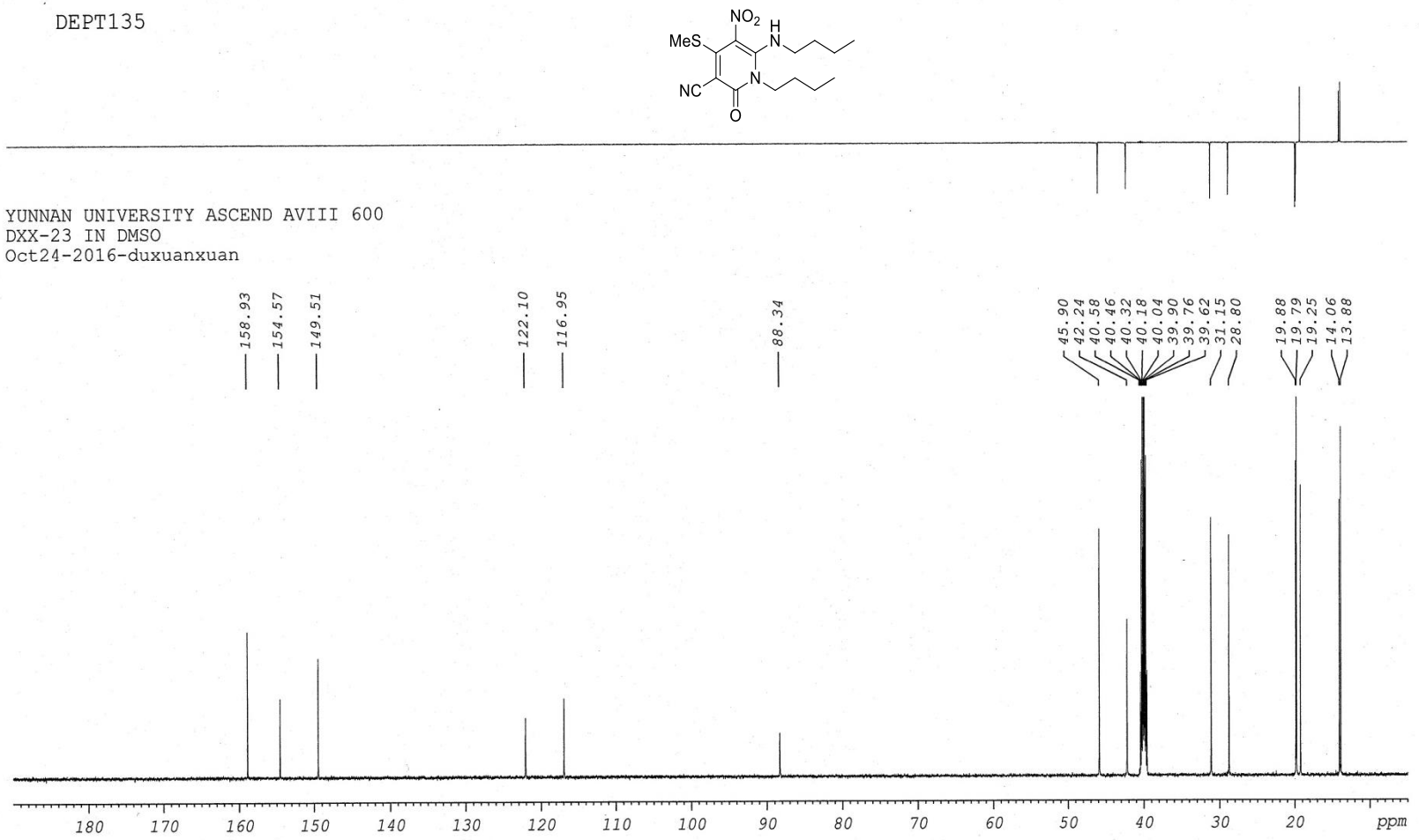


Figure 51. ^{13}C NMR (150 MHz, DMSO-d_6) spectra of compound **3y**

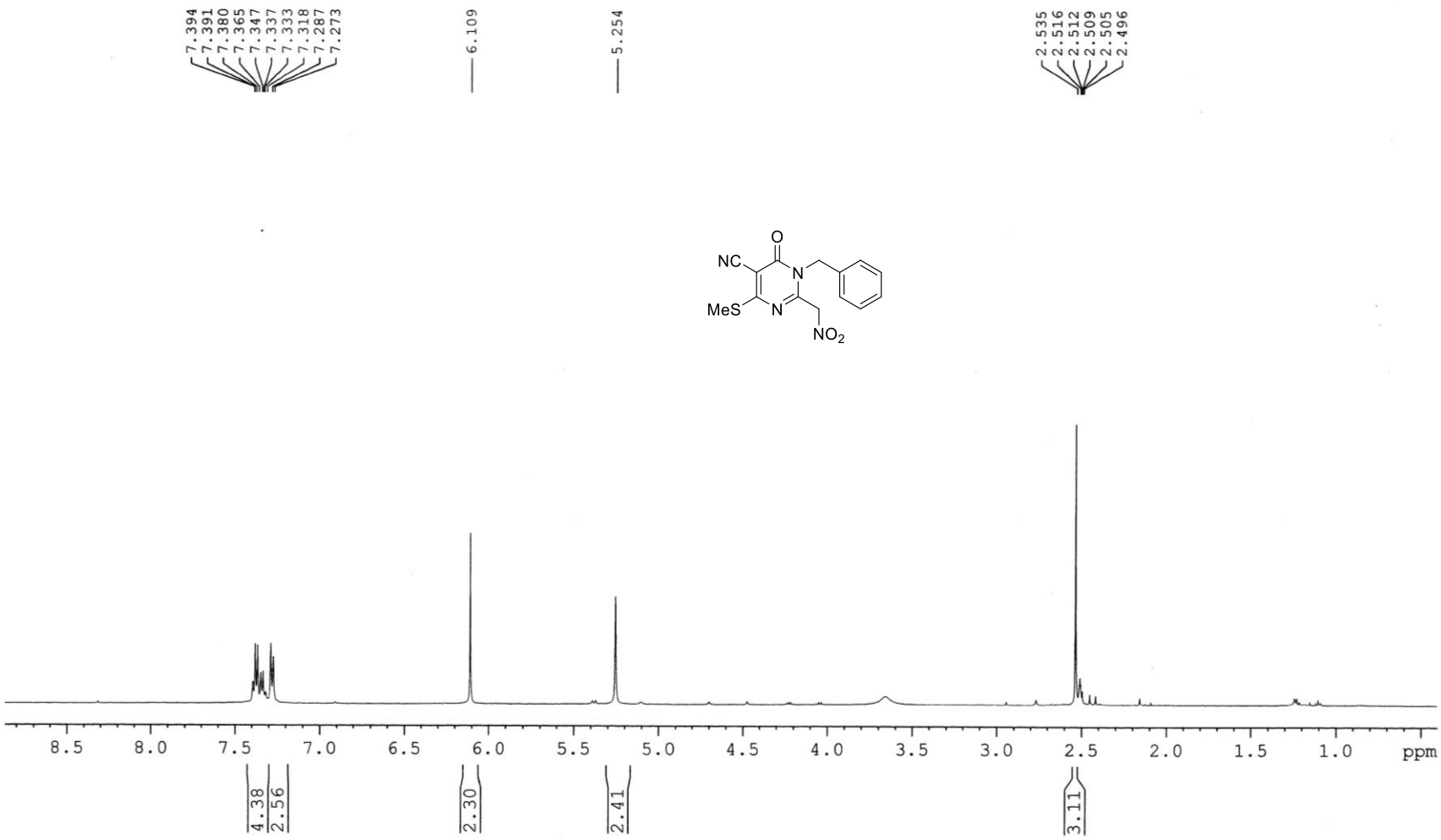


Figure 52. ^{1}H NMR (500 MHz, DMSO-d_6) spectra of compound **4a**

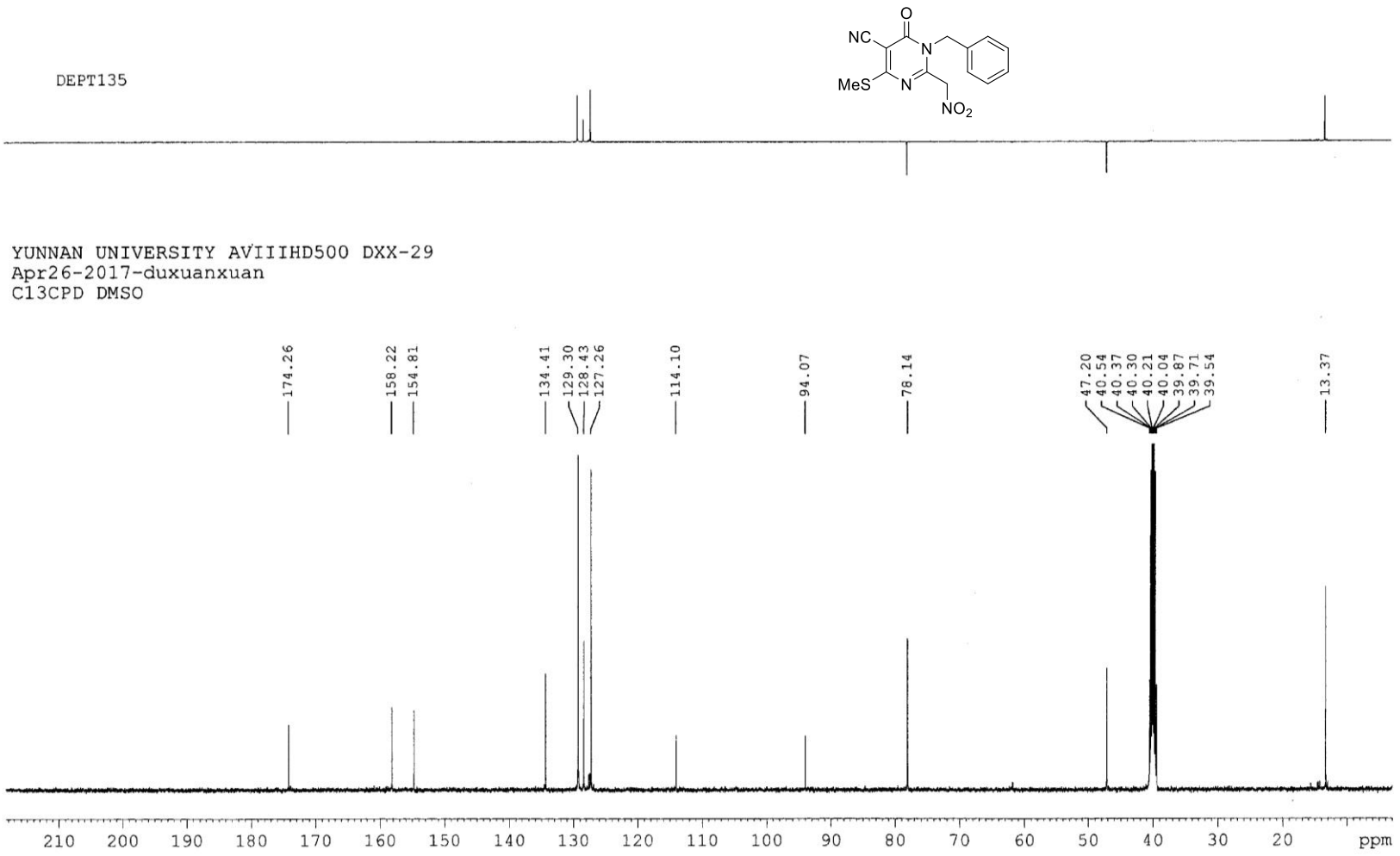


Figure 53. ^{13}C NMR (125 MHz, DMSO-d_6) spectra of compound **4a**

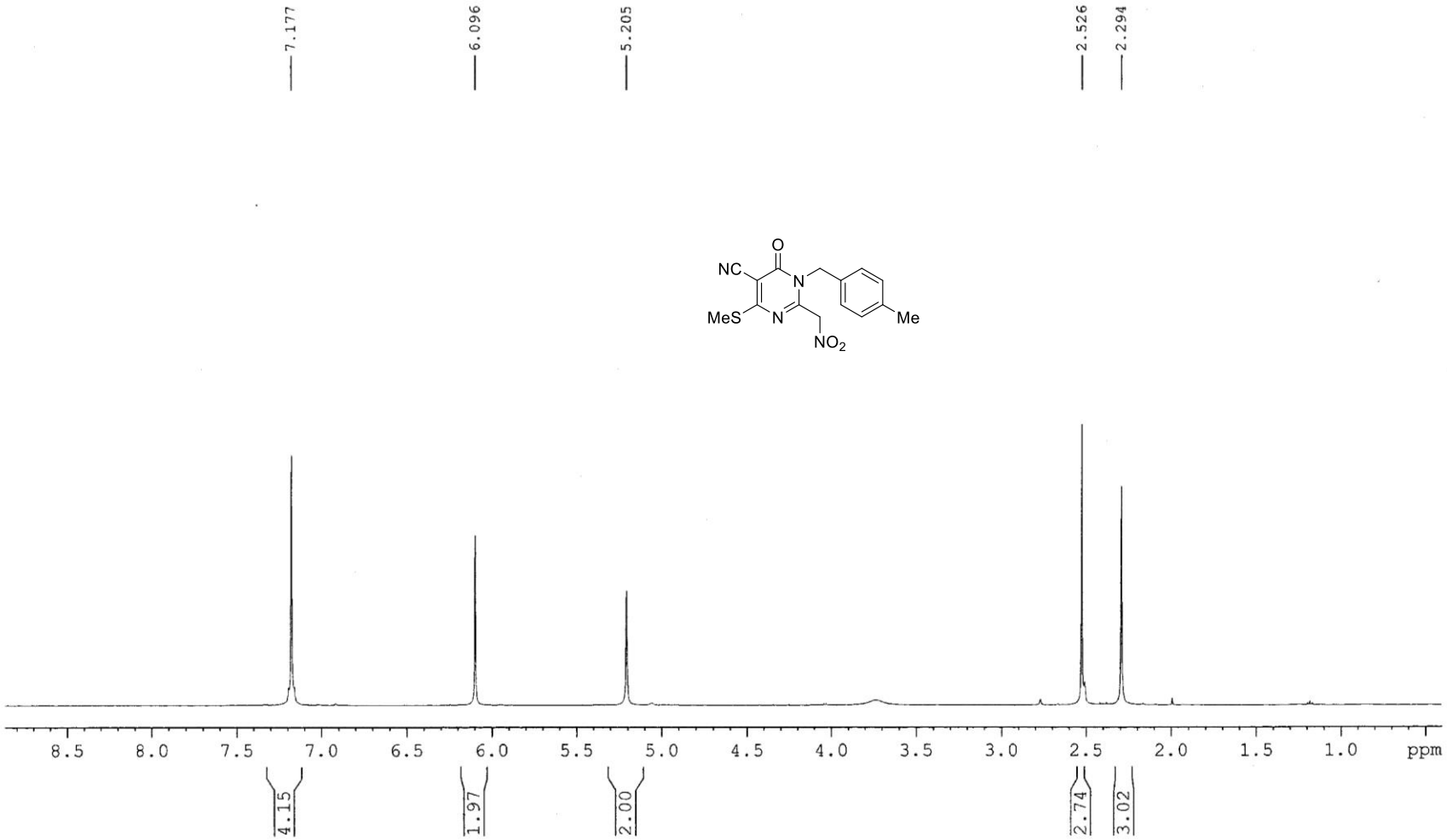


Figure 54. ^{1}H NMR (500 MHz, DMSO-d_6) spectra of compound **4b**

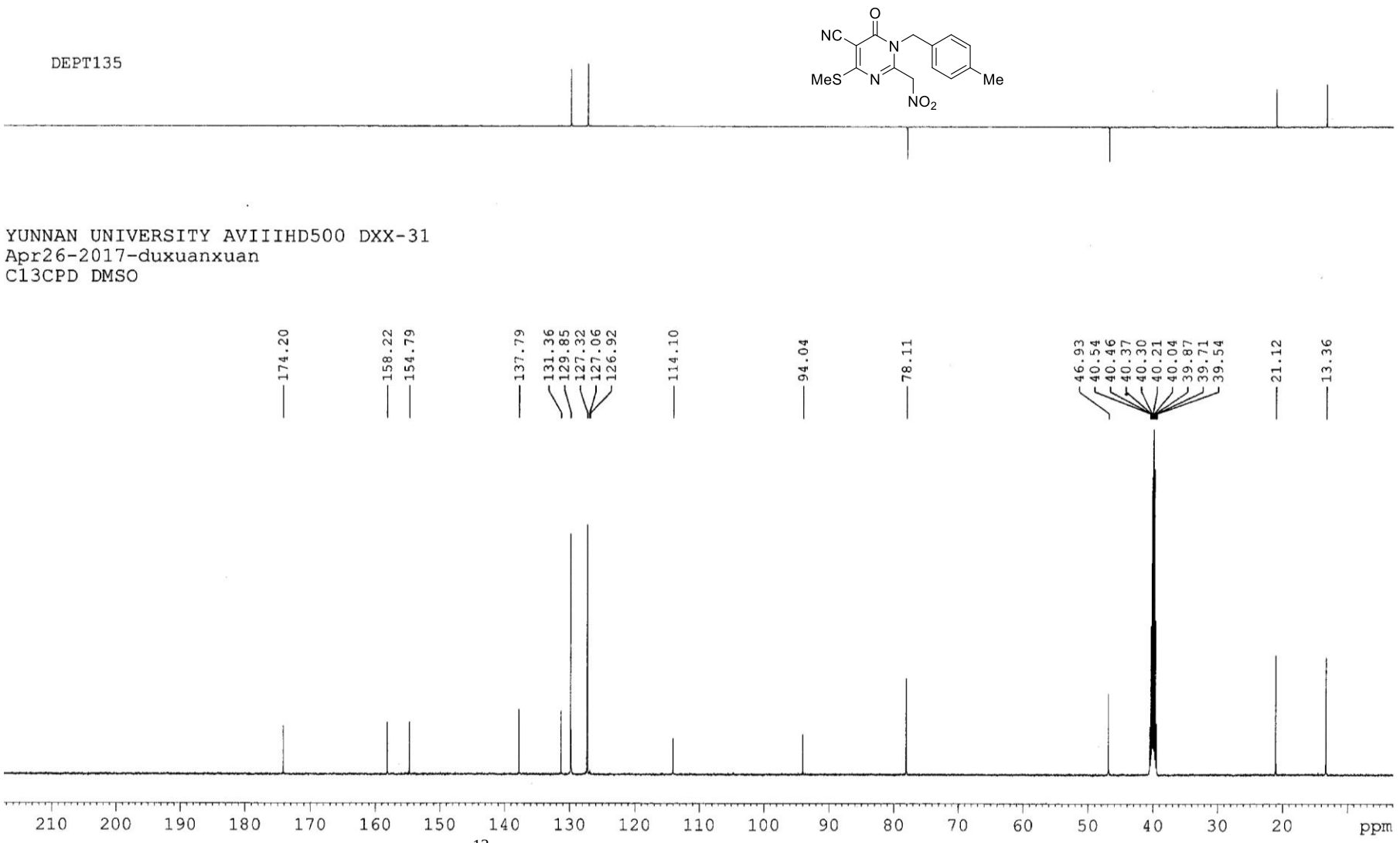


Figure 55. ^{13}C NMR (125 MHz, DMSO-d_6) spectra of compound **4b**

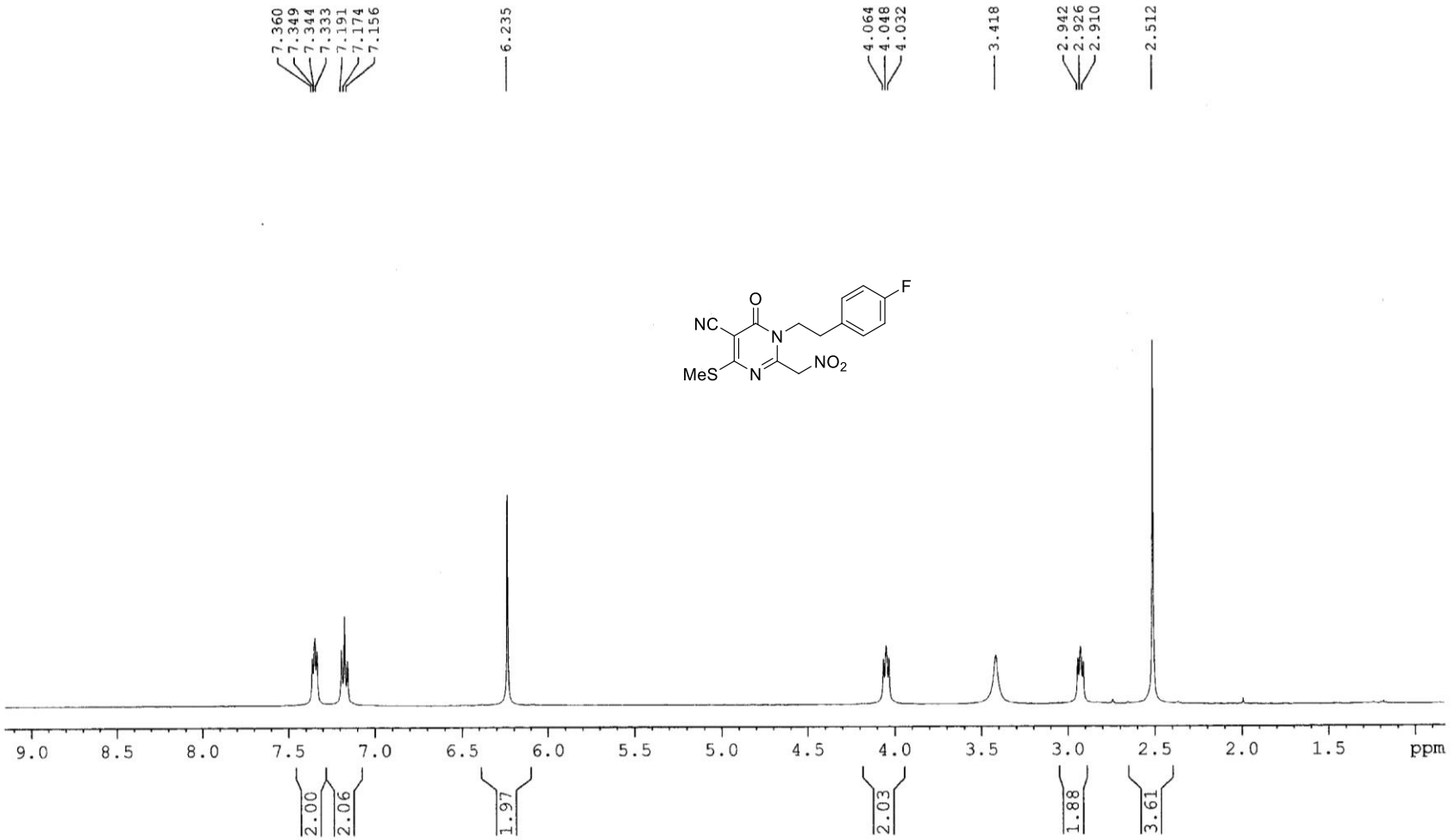


Figure 56. ^{1}H NMR (500 MHz, DMSO-d_6) spectra of compound **4c**

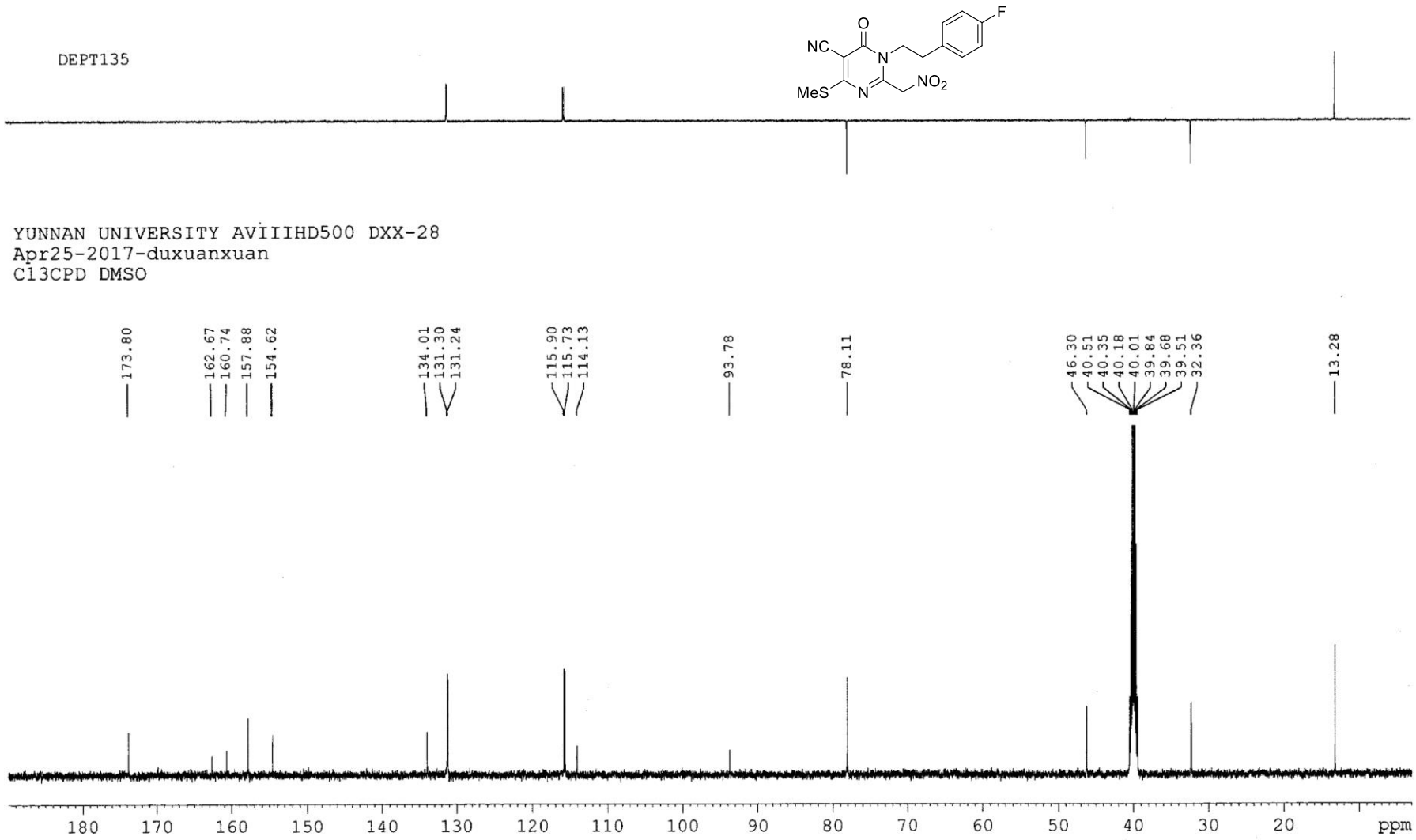


Figure 57. ^{13}C NMR (125 MHz, DMSO-d_6) spectra of compound **4c**

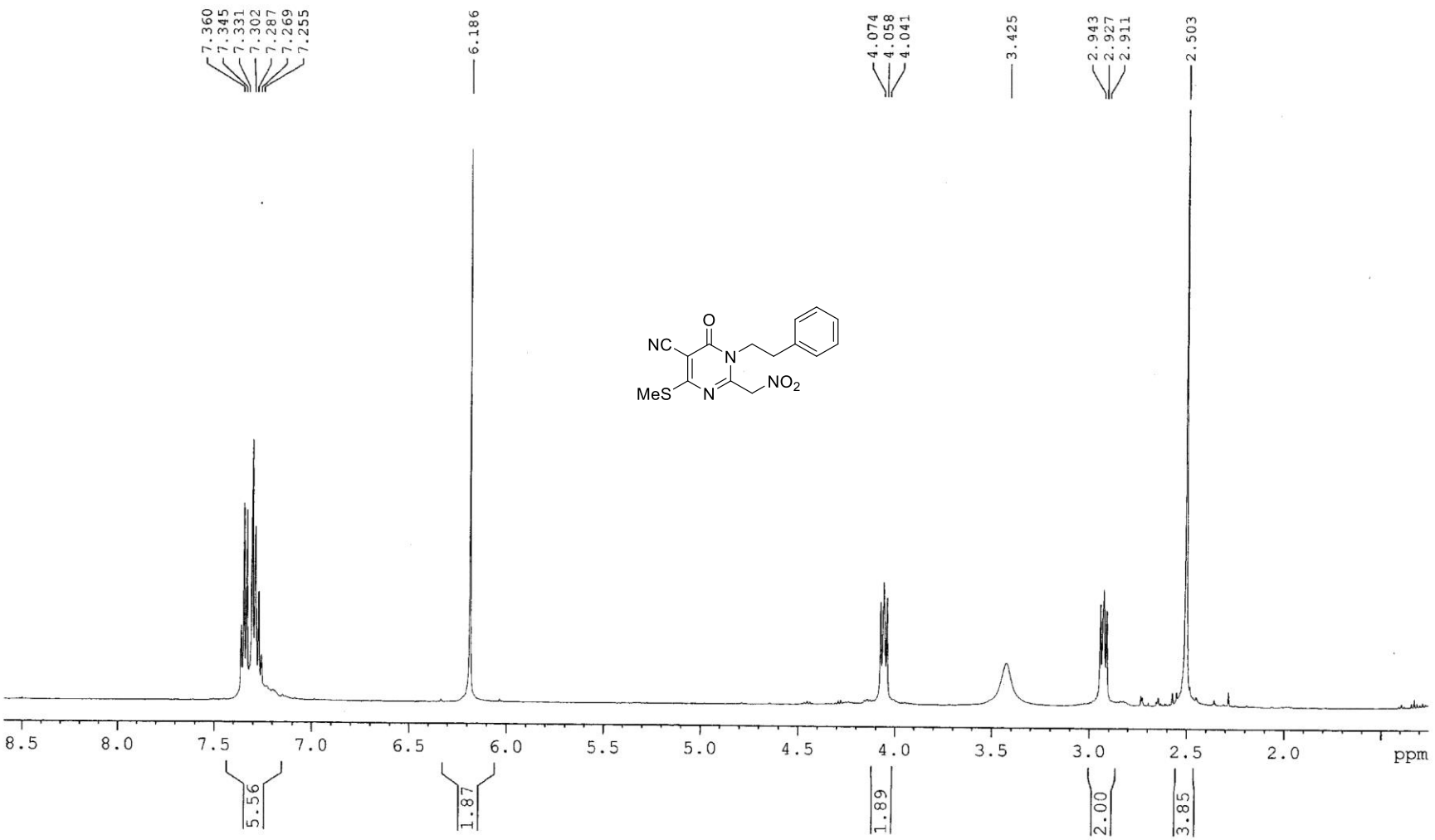


Figure 58. ^{1}H NMR (500 MHz, DMSO-d_6) spectra of compound **4d**

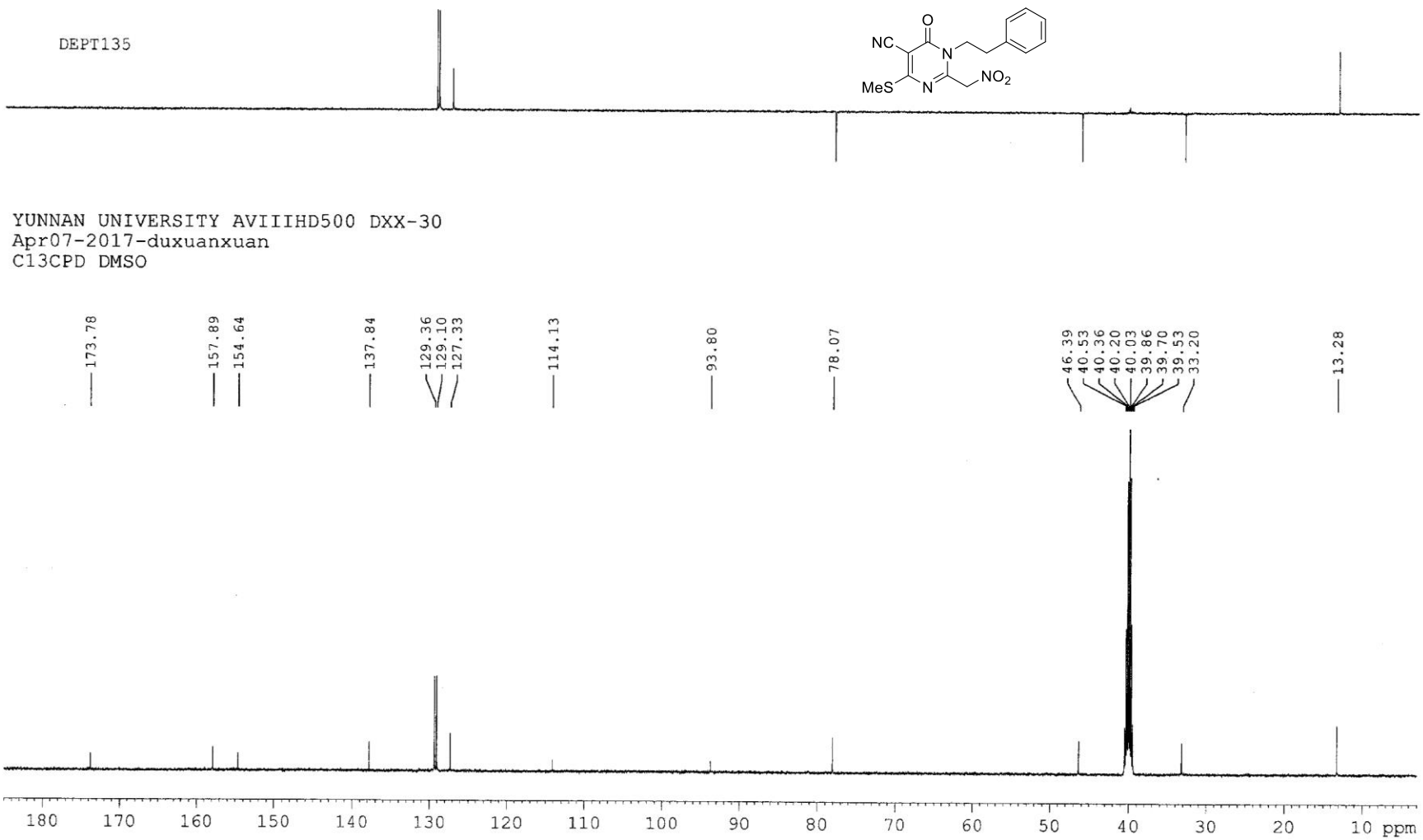


Figure 59. ^{13}C NMR (125 MHz, DMSO-d_6) spectra of compound **4d**

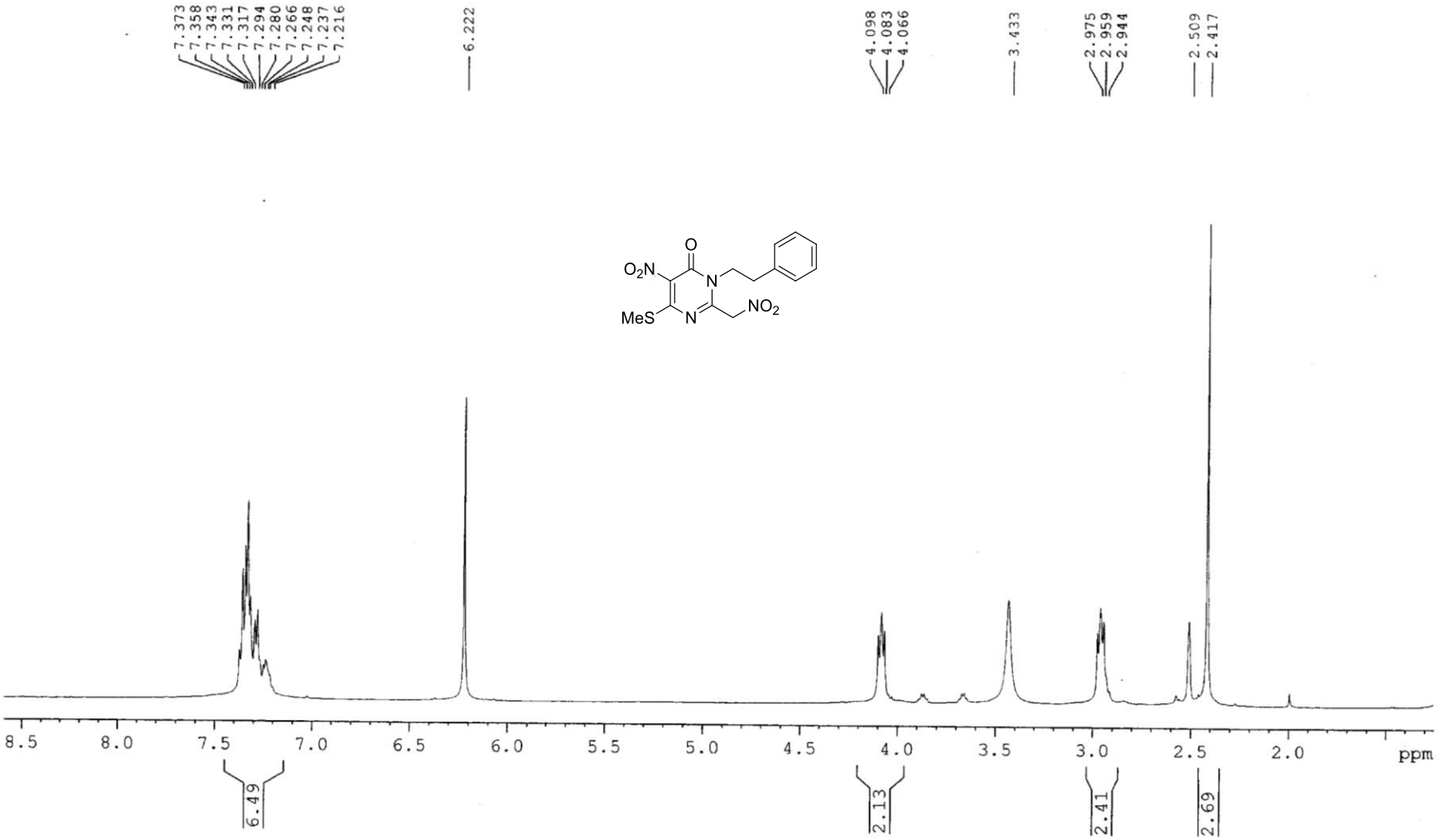


Figure 60. ^{1}H NMR (500 MHz, DMSO-d_6) spectra of compound **4e**

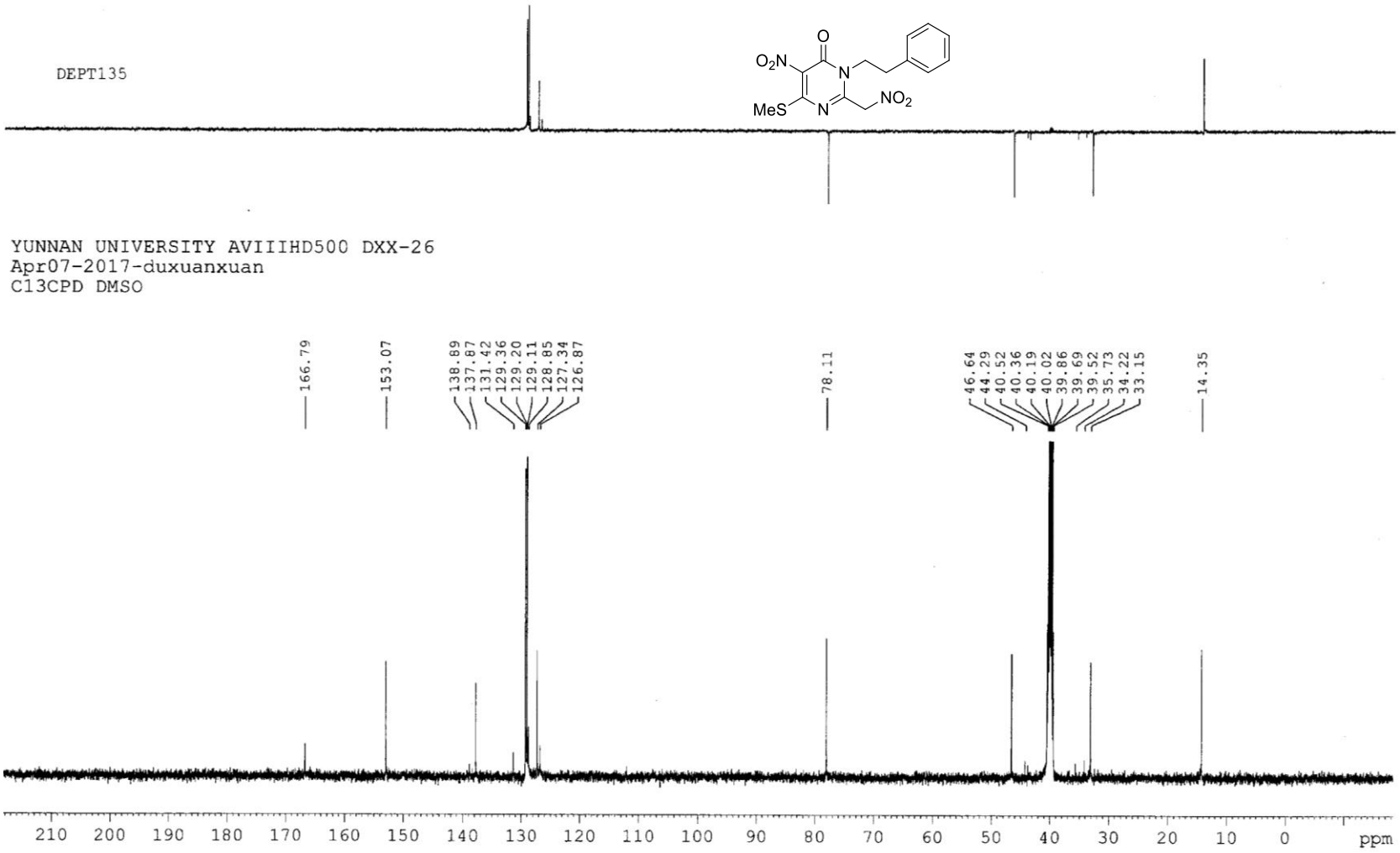


Figure 61. ^{13}C NMR (125 MHz, DMSO-d_6) spectra of compound **4e**

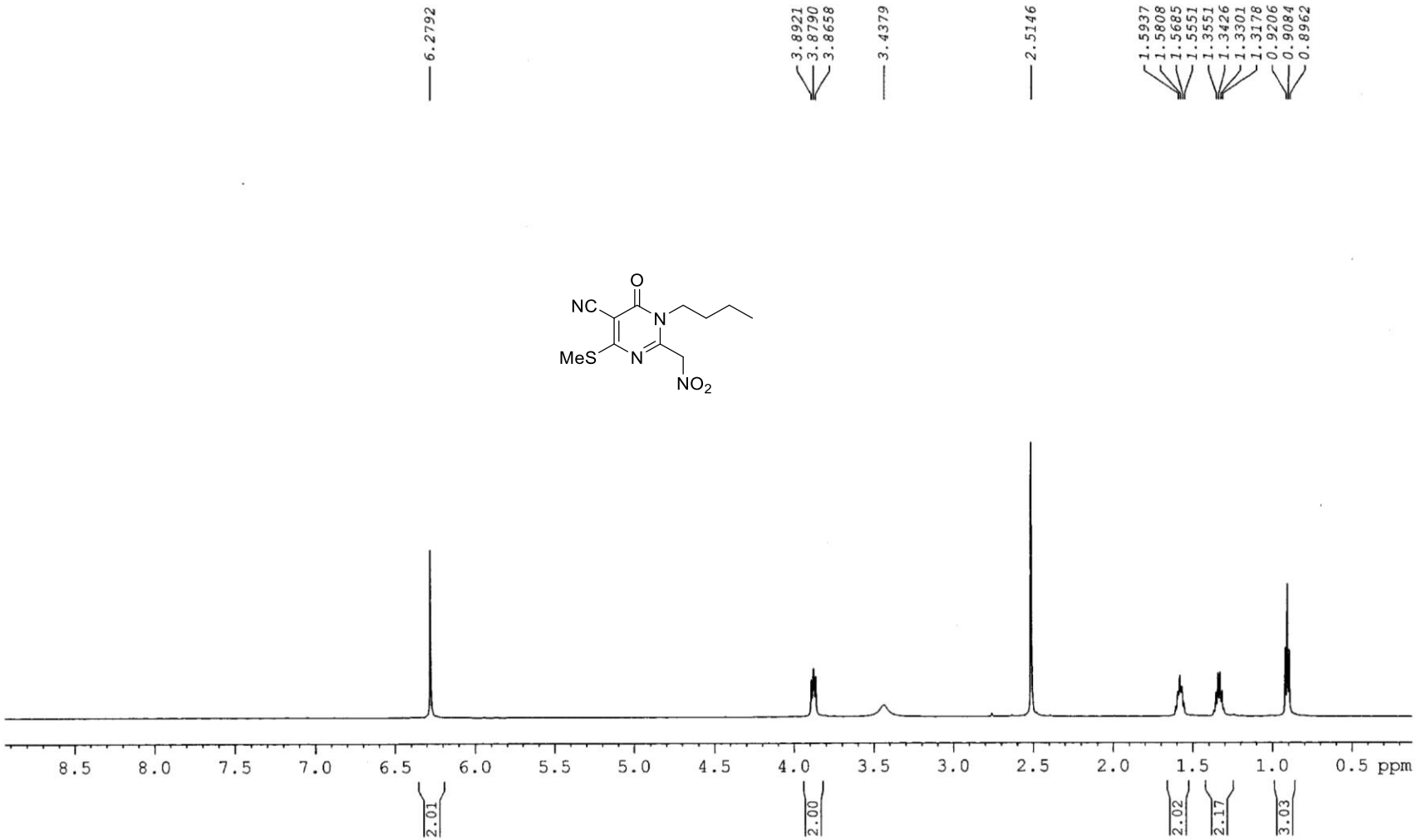


Figure 62. ^{1}H NMR (600 MHz, DMSO-d_6) spectra of compound **4f**

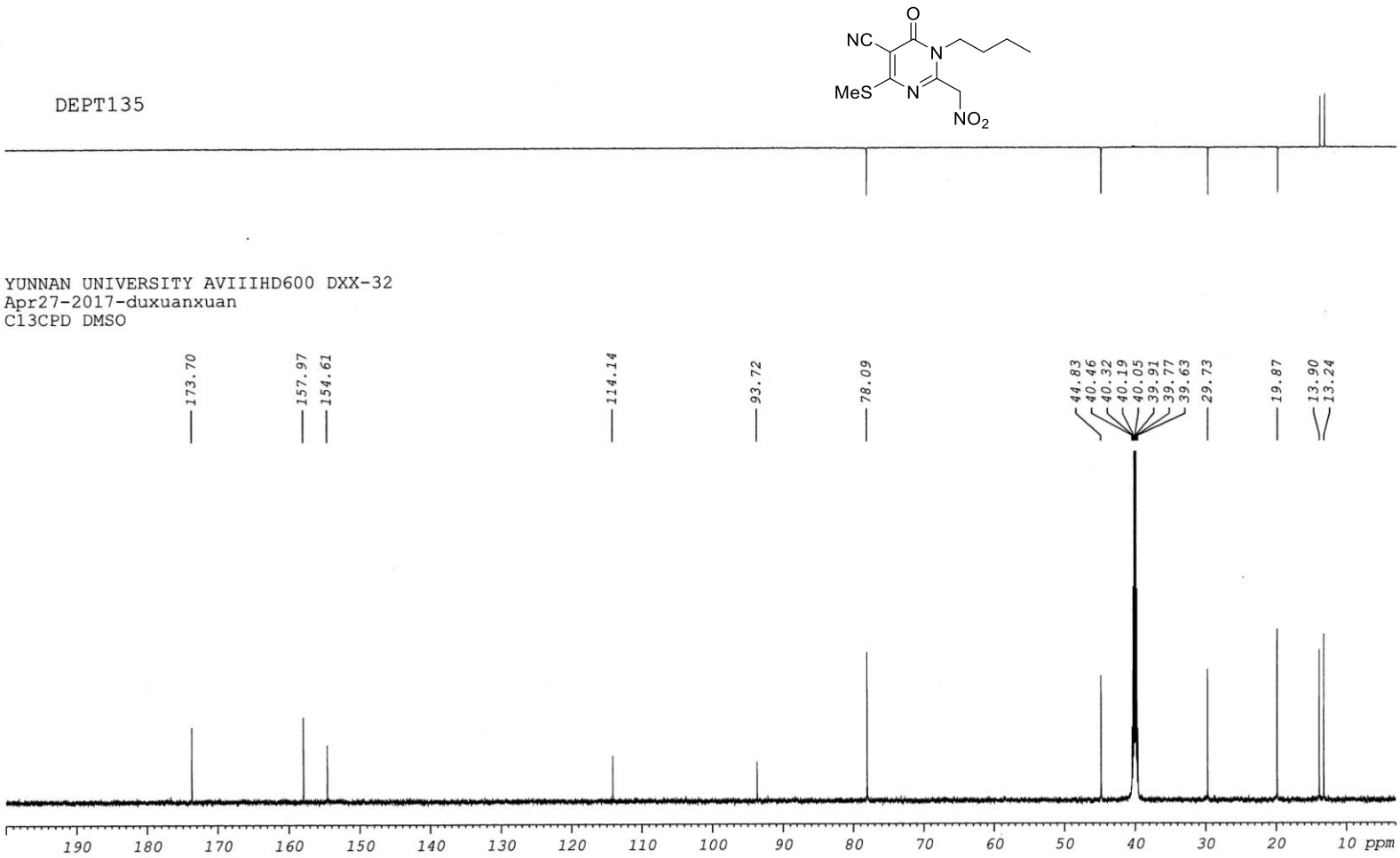


Figure 63. ^{13}C NMR (150 MHz, DMSO-d_6) spectra of compound **4f**

1. R. C. da Silva, G. P. da Silva, D. P. Sangi, J. G. de M. Pontes, A. G. Ferreira, A. G. Corrêa and M. W. Paixão, *Tetrahedron*, 2013, **69**, 9007.

2. (*a*) W. M. Al-Adiwish, M. I. M. Tahir and W. A. Yaacob, *Synthetic. Commun*., 2013, **43**, 3203; (*b*) Y.-C. Wu, H.-J. Li and H.-Z. Yang, *Org. Biomol. Chem*., 2010, **8**, 3394.

3. CCDC 1549520 contain the supplementary crystallographic data for compound **3f**. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk /data_request/cif.

4. CCDC 1553238 contain the supplementary crystallographic data for compound **4f**. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk /data_request/cif.