Multicomponent synthesis of functionalized pyrrolo[3,4-*e*] isoindole-1,3,6,8-tetraones via [2+2+2] cycloaddition of maleimides with nitroenamines

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Supporting Information

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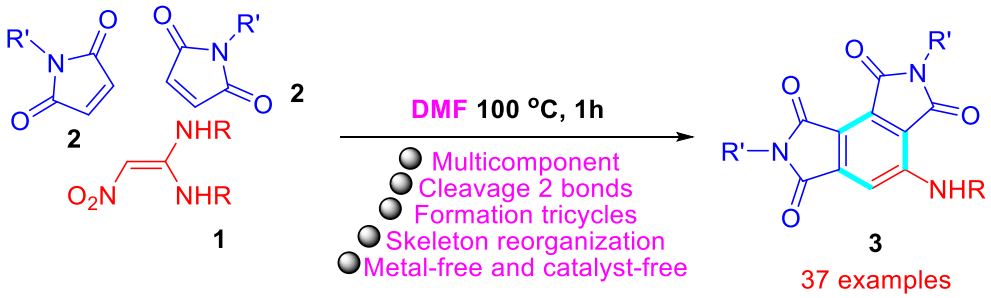
General Information

All compounds were fully characterised by spectroscopic data. The NMR spectra were recorded on a Bruker DRX600 or Bruker DRX500. Chemical shifts (δ) are expressed in ppm, J values are given in Hz, and deuterated $CDCl_3$ or DMSO-d_6 were used as 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 silica gel GF_{254}. The melting points were determined on a XT-4A melting point apparatus and are uncorrected. HRMs were performed on an Agilent LC/Msd TOF instrument.

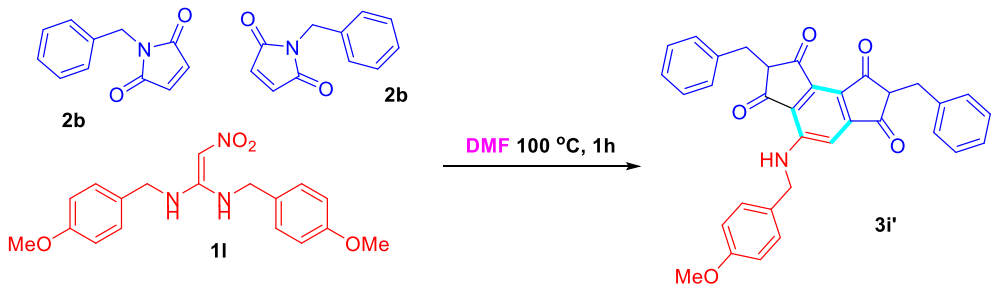
The nitro-enamines **1** were synthesized by known literature procedures.[1] Other materials were purchased from Adamas-beta Corporation Limited. All chemicals and solvents were used as received without further purification unless otherwise stated. Two kinds of reagents which were used in the experiment were commercially available reagents.

General Procedure for the Preparation of 3



A round-bottom flask was charged with 1,1-enediamine **1** (1 mmol, 1.0 equiv.) and maleimide **2** (2.4 mmol, 2.4 equiv.). Then, the flask was supplemented with DMF (6 mL), and the mixture was stirred on an oil bath at 100 °C for approximately 1 h while the reaction was monitored by TLC until the substrate was completely consumed. After the reaction was cooled to room temperature, the mixture was extracted with ethyl acetate (6 × 15 mL). The organic layer was washed with water and brine, and the combined organic phases were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford the crude product. Finally, the product **3** was purified from the crude mixture by flash column chromatography over silica gel using a mixture of petroleum ether/ethyl acetate (20:1–10:1, v/v) as the eluent.

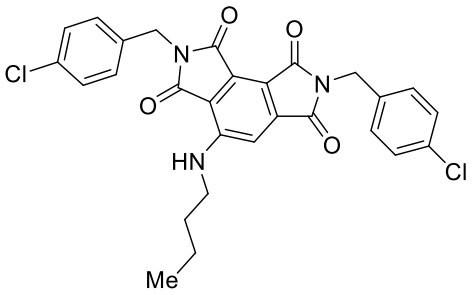
The gram-scale experiment



A 25 mL round-bottom flask was charged with *N*,*N'*-bis(4-methoxybenzyl)-2-nitroethene-1,1-diamine (**1a**) (4 mmol, 1.0 equiv.) and *N*-benzylmaleimide (**2a**) (9.6 mmol, 2.4 equiv.). The flask was then charged with 8 mL of DMF, and the mixture was stirred on an oil bath at 100 °C for 1 hour, monitoring the reaction progress via thin-layer chromatography (TLC) until complete substrate consumption was observed. After cooling the reaction mixture to room temperature, it was extracted with ethyl acetate (6 × 20 mL). The organic phase was washed with water and brine, after which the combined organic layers were dried over anhydrous sodium sulfate (Na_2SO_4), filtered, and concentrated under reduced pressure to obtain the crude product. The final product, **3i'**, was purified from the crude mixture using flash column chromatography over silica gel, employing a petroleum ether/ethyl acetate mixture (20:1 to 10:1, v/v) as the eluent. The resulting purified product weighed 998 mg, corresponding to a calculated yield of 47%.

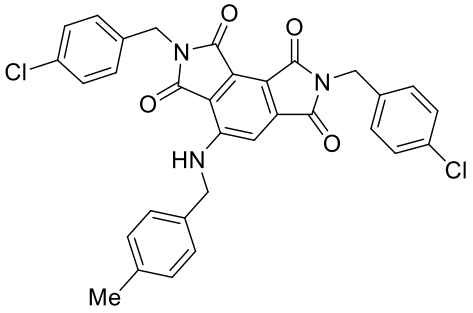
Spectroscopic Data of 3a-3k'

2,7-Dibenzyl-4-(butylamino)pyrrolo[3,4-*e*]isoindole-1,3,6,8(2*H*,7*H*)-tetraone(3a)



Yellow solid (58%); Mp: 210.4–215.1 °C; IR (KBr): 3495, 3446, 2989, 1745, 1726, 1620, 1510, cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.39–7.35 (m, 4H, ArH), 7.20 (m, 5H, ArH), 7.14 (t, 1H, J = 6.2 Hz, NH), 4.79 (s, 2H, CH_2), 4.75 (s, 2H, CH_2), 3.37–3.33 (m, 2H, CH_2), 1.71–1.65 (m, 2H, CH_2), 1.49–1.43 (m, 2H, CH_2)，0.98 (t, 3H, J = 5.6 Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.4, 166.7, 164.2, 164.0, 150.3, 140.1, 134.6, 134.4, 134.0, 133.9,130.4, 130.4, 130.3, 130.4,130.3, 128.9, 128.9, 128.8, 128.8, 113.5, 113.3, 110.1, 42.9, 41.2, 41.0, 31.0, 20.0, 13.7. HRMS KM P[BBB(TOF ES^+) m/z: $[M+Na]^+$ calcd for $C_{28}H_{23}N_3O_4Cl_2$ 558.0958; found, 558.0964.

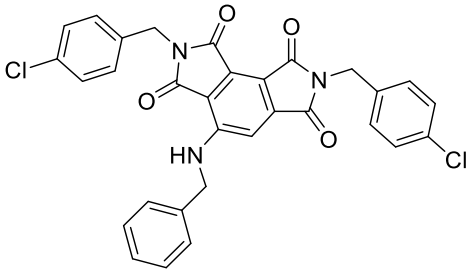
2,7-Bis(4-chlorobenzyl)-4-((4-methylbenzyl)amino)pyrrolo[3,4-*e*]isoindole-1,3,6,8(2*H*,7*H*)-tetraone (3b)



Yellow solid (52%); Mp: 206.1–207.6 °C; IR (KBr): 3475, 3440, 2982, 1745, 1715, 1662, 1515, 806cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.54 (t, J = 5.9 Hz, 1H, NH), 7.38–7.35 (m, 6H, ArH), 7.32–7.30 (m, 3H, ArH), 7.27–7.23 (m, 5H, ArH), 4.76 (s, 2H, CH_2), 4.76 (s, 2H, CH_2), 4.57 (d, J = 5.9 Hz, 2H, CH_2). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.3, 166.5, 164.1, 163.9, 150.1, 140.1, 136.0, 134.5, 134.3, 134.1, 134.0, 130.4, 130.4, 130.4, 130.4, 130.2, 129.2, 129.2, 128.9, 128.9, 128.8, 128.8, 128.3, 127.1, 127.1, 114.2, 114.1, 110.5, 47.1, 41.3, 41.1. HRMS (TOF ES^+) m/z: $[M+Na]^+$ calcd for $C_{32}H_{23}Cl_2N_3O_4$ 606.0958; found, 606.0965.

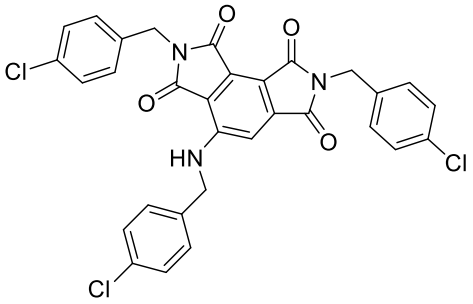
4-(Benzylamino)-2,7-bis(4-chlorobenzyl)pyrrolo[3,4-*e*]isoindole-1,3,6,8(2*H*,7*H*)-

tetraone (3c)



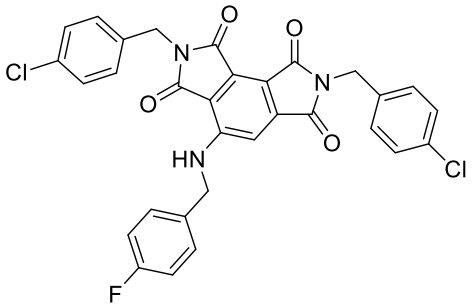
Yellow solid (46%); Mp: 165.3–166.5°C; IR (KBr): 3477, 3418, 2998, 1743, 1636, 1571, 1374, 831 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.54 (t, J = 5.9 Hz, 1H, NH), 7.38–7.35 (m, 6H, ArH), 7.32–7.30 (m, 3H, ArH), 7.27–7.23 (m, 5H, ArH), 4.76 (s, 2H, CH_2), 4.76 (s, 2H, CH_2), 4.57 (d, J = 5.9 Hz, 2H, CH_2). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.3, 166.5, 164.1, 163.9, 150.1, 140.1, 136.0, 134.5, 134.3, 134.1, 134.0, 130.4, 130.4, 130.4, 130.4, 130.2, 129.2, 129.2, 128.9, 128.9, 128.8, 128.8, 128.3, 127.1, 127.1, 114.2, 114.1, 110.5, 47.1, 41.3, 41.1. HRMS (TOF ES^+) m/z: $[M+Na]^+$ calcd for $C_{31}H_{21}Cl_2N_3O_4$ 592.0801; found, 592.0810.

2,7-Bis(4-chlorobenzyl)-4-((4-chlorobenzyl)amino)pyrrolo[3,4-*e*]isoindole-1,3, 6,8(2*H*,7*H)*-tetraone (3d)



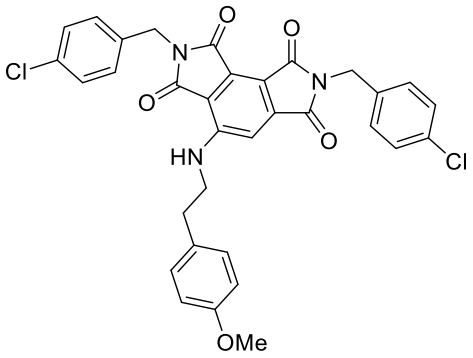
Yellow solid (44%); Mp: 135.1–136.7 °C; IR (KBr): 3484, 3365, 2944, 1712, 1634, 1525, 1494, 820 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.53 (t, J = 5.8 Hz, 1H, NH), 7.37–7.33 (m, 6H, NH), 7.28–7.24 (m, 6H, ArH), 7.19 (s, 1H, ArH), 4.77 (s, 2H, CH_2), 4.76 (s, 2H, CH_2), 2.55 (t, J = 5.8 Hz, 2H, CH_2). ^{13}C NMR (125 MHz, $CDCl_3$): δ =166.4, 163.9, 149.9, 140.1, 134.5, 134.4, 134.2, 134.1, 134.1, 134.0, 130.4, 130.4, 130.4, 129.4, 129.4, 128.9, 128.9, 128.9, 128.9, 128.9, 128.9, 128.4, 128.4, 128.4, 114.4, 114.4, 110.3, 46.4, 41.3, 41.1. HRMS (TOF ES^+) m/z: $[M+Na]^+$ calcd for $C_{31}H_{20}Cl_3N_3O_4$ 626.0412; found, 626.0421.

2,7-Bis(4-chlorobenzyl)-4-((4-fluorobenzyl)amino)pyrrolo[3,4-*e*]isoindole-1,3,6,8 (2*H*,7*H*)-tetraone (3e)



Yellow solid (43%); Mp: 184.9–187.8 °C; IR (KBr): 3541, 3430, 2983, 1742, 1714, 1643, 1624, 832 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ = 7.50 (t, J = 4.2 Hz, 1H, NH), 7.37 (s, 2H, ArH), 7.6 (s, 2H, ArH), 7.30–7.21 (m, 7H, ArH), 7.08–7.04 (m, 2H, ArH), 4.77 (s, 2H, CH_2), 4.76 (s, 2H, CH_2), 4.55 (d, J = 5.82 Hz, 2H, CH_2); ^{13}C NMR (150 MHz, $CDCl_3$): δ =169.3, 166.4, 164.1, 163.9, 162.5, 149.9, 140.2, 134.4, 134.3, 134.1, 134.0, 131.7, 131.7, 130.4, 130.4, 130.4, 130.2, 128.9, 128.9, 128.9, 128.9, 128.8, 128.8, 116.3, 116.1, 114.3, 114.3, 110.3, 46.4, 41.3, 41.1. ^{19}F NMR (564 MHz, DMSO-d_6): δ = –113.5 ppm.HRMS (TOF ES^+) m/z: $[M+H]^+$ calcd for $C_{31}H_{21}Cl_3N_3O_4$ 588.0888; found, 588.0885.

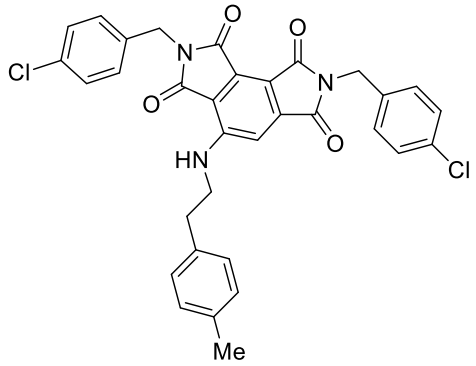
2,7-Bis(4-chlorobenzyl)-4-((4-methoxyphenethyl)amino)pyrrolo[3,4-*e*]isoindole-1,3,6,8(2*H*,7*H*)-tetraone (3f)



Yellow solid (58%); Mp: 176.1–179.7 °C; IR (KBr): 3476, 3397, 2926, 1745, 1709, 1636, 1518, 831 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ = 7.38–7.34 (m, 4H, ArH), 7.27–7.24 (m, 4H, ArH), 7.18 (s, 2H, ArH), 7.14 (s, 1H, NH), 7.13 (s, 1H, ArH), 6.85 (d, 2H, J = 8.4 Hz, ArH), 4.77 (s, 2H, CH_2), 4.73 (s, 2H, CH_2), 3.77 (s, 3H, CH_3), 3.57 (d, 2H, J = 6.18 Hz CH_2), 2.92 (t, 2H, J = 6.96 Hz CH_2). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 169.2, 166.6, 164.2, 163.9, 158.7, 150.1, 140.0, 134.5, 134.4, 134.0, 133.9, 130.4, 130.4, 130.3, 130.3, 130.2, 130.2, 129.7, 129.7, 129.4, 128.9, 128.9, 128.8, 128.8, 114.4, 113.7, 113.5, 110.1, 55.3, 44.7, 41.2, 41.0, 34.5. HRMS (TOF ES^+) m/z: $[M+H]^+$ calcd for $C_{33}H_{25}Cl_2N_3O_5$ 614.1244; found, 614.1249.

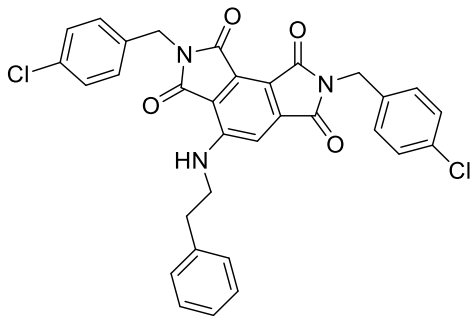
2,7-Bis(4-chlorobenzyl)-4-((4-methylphenethyl)amino)pyrrolo[3,4-*e*]isoindole-1,3,

6,8(2*H*,7*H*)-tetraone (3g)



Yellow solid (52%); Mp: 128.3–134.5°C; IR (KBr): 3477, 3418, 2998, 1743, 1636, 1571, 1374, 831 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.38 (s, 1H, NH), 7.36 (t, J = 5.6 Hz, 3H, ArH), 7.26 (t, J = 6.7 Hz, 4H, ArH), 7.19 (s, 2H, ArH), 7.12 (t, J = 8.3 Hz, 4H, ArH), 4.78 (s, 2H, CH_2), 4.74 (s, 2H, CH_2), 3.61–3.57 (m, 2H, CH_2), 2.94 (t, J = 7.0 Hz, 2H, CH_2), 2.32 (d, J = 8.4 Hz, 3H, CH_3),. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.2, 166.6, 164.2, 164.0, 150.1, 140.0, 136.7, 134.5, 134.4, 134.0, 133.9, 130.4, 130.4, 130.3, 130.3, 130.2, 130.2, 129.6, 129.6, 128.9, 128.9, 128.8, 128.8, 128.6, 128.6, 113.7, 113.6, 110.6, 44.6, 41.2, 41.0, 35.0, 21.0. HRMS (TOF ES^+) m/z: $[M+H]^+$ calcd for $C_{33}H_{25}Cl_2N_3O_4$ 598.1295; found, 598.1298.

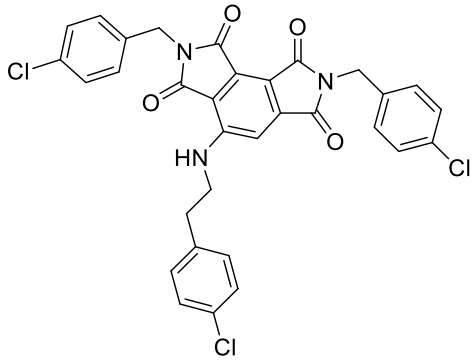
2,7-Bis(4-chlorobenzyl)-4-(phenethylamino)pyrrolo[3,4-e]isoindole-1,3,6,8(2*H*,7*H*) -tetraone (3h)



Yellow solid (44%); Mp: 116.1–119.7 °C; IR (KBr): 3496, 3372, 2944, 1712, 1634, 1525, 1494 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.38 (s, 1H, NH), 7.36–7.32 (m, 5H, NH), 7.27–7.24 (m, 7H, ArH), 4.78 (s, 2H, CH_2), 4.73 (s, 2H, CH_2), 3.64–3.60 (m, 2H, CH_2), 2.98 (t, J = 9.0 Hz, 2H, CH_2). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.2, 166.6, 164.2, 164.0, 150.1, 140.1, 137.5, 134.5, 134.4, 134.0, 133.9, 130.4, 130.4, 130.3, 130.3, 129.0, 120.9, 128.9, 128.9, 128.8, 128.8, 128.7, 128.7, 127.1, 113.8, 113.6, 110.0, 44.5, 41.3, 41.0, 35.4. HRMS (TOF ES^+) m/z: $[M+Na]^+$ calcd for $C_{32}H_{23}Cl_2N_3O_4$ 606.0958; found, 606.0966.

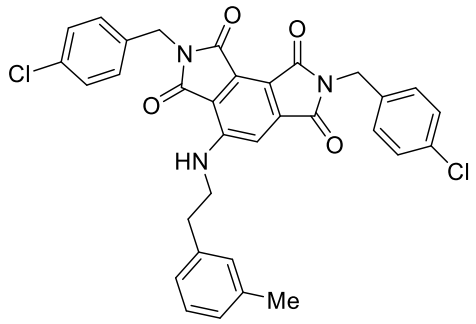
2,7-Bis(4-chlorobenzyl)-4-((4-chlorophenethyl)amino)pyrrolo[3,4-*e*]isoindole-1,3,

6,8(2*H*,7*H*)-tetraone (3i)



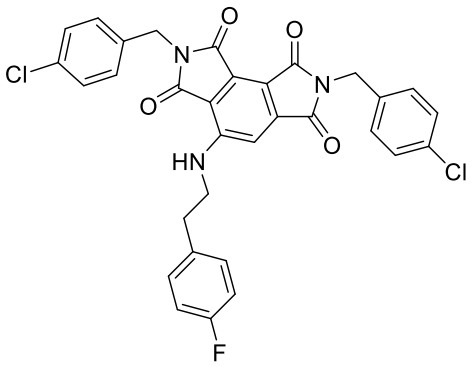
Yellow solid (41%); Mp: 184.9–187.8 °C; IR (KBr): 3541, 3410, 2993, 1742, 1704, 1636, 1624, 832 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.38 (s, 1H, NH), 7.36 (t, J = 5.8 Hz, 3H, ArH), 7.30–7.25 (m, 7H, ArH), 7.16 (d, J = 8.1 Hz, 3H, ArH), 4.78 (s,2H, CH_2), 4.74 (s,2H, CH_2), 3.62–3.58 (m, 2H, CH_2), 2.96 (t, J = 6.9 Hz, 2H, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.2, 166.5, 164.1, 163.9, 150.1, 140.1, 135.9, 134.5, 134.3, 134.0, 133.9, 133.0, 130.4, 130.4, 130.4, 130.4, 130.2, 130.1, 130.1, 129.1, 129.1, 128.9, 128.9, 128.8, 128.8, 113.9, 113.8, 109.9, 44.2, 41.3, 41.0, 34.7. HRMS (TOF ES^+) m/z: $[M+H]^+$ calcd for $C_{32}H_{22}Cl_3N_3O_4$ 618.0749; found, 618.0754.

2,7-dibenzyl-4-((3-methylphenethyl)amino)pyrrolo[3,4-*e*]isoindole-1,3,6,8(2H, 7H)-tetraone (3j)



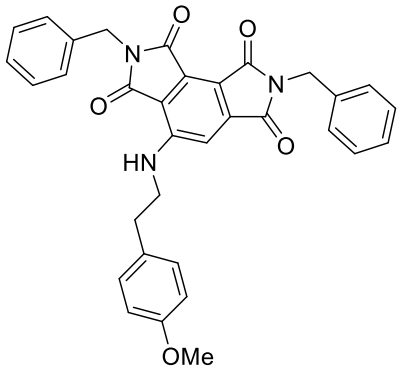
Yellow solid (53%); Mp: 206.1–207.6 °C; IR (KBr): 3482, 3437, 2989, 1745, 1713, 1663, 1518, 983, 806, 751 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.38 (s, 1H, NH), 7.36 (t, J = 5.9 Hz, 3H, ArH), 7.26 (m, 4H, ArH), 7.18 (s, 2H, ArH), 7.11 (d, J = 8.2 Hz, 4H, ArH), 4.77 (s, 2H, CH_2), 4.73 (s, 2H, CH_2), 3.60–3.56 (m, 2H, CH_2), 2.94 (t, J = 7.0 Hz, 2H, CH_2), 2.31 (s, 3H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.2, 166.6, 164.2, 164.0, 150.1, 140.0, 136.7, 134.5, 134.4, 134.0, 133.9, 130.4, 130.4, 130.3, 130.3, 130.2, 130.2, 129.6, 129.6, 128.9, 128.9, 128.8, 128.8, 128.6, 128.6, 113.7, 113.5, 110.1, 44.6, 41.2, 41.0, 35.0, 21.0. HRMS (TOF ES^+) m/z: $[M+H]^+$ calcd for $C_{33}H_{25}Cl_2N_3O_4$ 598.1295; found, 598.1298.

2,7-Bis(4-chlorobenzyl)-4-((4-fluorophenethyl)amino)pyrrolo[3,4-*e*]isoindole-1,3,6,8(2*H*,7*H*)-tetraone (3k)



Yellow solid (40%); Mp: 215.1–216.2 °C; IR (KBr): 3467, 3376, 2987, 1748, 1712, 1632, 1525, 848, 790, 741 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ = 7.54 (t, J = 6.1 Hz, 1H, ArH), 7.50 (s, 1H, NH), 7.39 (d, J = 8.4 Hz, 4H, ArH), 7.35–7.30 (m, 5H, ArH), 7.19 (d, J = 10.1 Hz, 1H, ArH), 7.13 (d, J = 7.6 Hz, 1H, ArH), 7.03 (t, J = 5.4 Hz, 1H, ArH), 4.74 (s, 2H, CH_2), 4.71 (s, 2H, CH_2), 3.77–3.73 (m, 2H, CH_2), 2.94 (t, J = 7.1 Hz, 2H, CH_2); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 169.2, 166.9, 164.4, 164.1, 162.7 (d, J_1 = 241.3 Hz), 150.2, 142.1, 142.0, 139.9, 136.1, 135.9, 132.6, 130.7, 130.7, 130.6, 129.9, 129.9, 129.9, 129.9, 129.0, 129.0, 125.5, 116.0 (d, J_2 = 21.3 Hz), 113.7, 113.5, 113.5, 113.0, 111.3, 43.6, 40.8, 40.6, 34.7. ^{19}F NMR (470 MHz, DMSO-d_6): δ = –113.5 ppm. HRMS (TOF ES^+) m/z: $[M+Na]^+$ calcd for $C_{32}H_{22}Cl_2N_3O_4$ 624.0864; found, 624.0867.

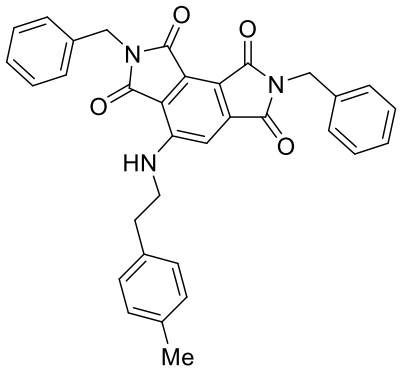
2,7-Dibenzyl-4-((4-methoxyphenethyl)amino)pyrrolo[3,4-*e*]isoindole-1,3,6,8(2*H*, 7*H*)-tetraone (3l)



Yellow solid (55%); Mp: 186.8–188.2 °C; IR (KBr): 3468, 3454, 2941, 1746, 1711, 1634, 1517, 830 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ = 7.44–7.41 (m, 4H, ArH), 7.31–7.24 (m, 4H, ArH), 7.19 (d, J = 6.7 Hz, 2H, ArH), 7.15 (s, 1H, ArH), 7.13 (s, 1H, NH), 6.86 (s, 1H, ArH) , 6.85 (s, 1H, ArH), 4.82 (s, 2H, CH_2), 4.78 (s, 2H, CH_2), 3.77 (s, 3H, CH_3), 3.58–3.55 (m, 2H, CH_2), 2.91 (t, J = 7.0 Hz, 2H, CH_2); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 169.4, 166.7, 164.3, 164.1, 158.7, 150.0, 140.1, 136.1, 136.0, 130.3, 129.7, 129.7, 129.5, 128.9, 128.9, 128.8, 128.8, 128.7, 128.7, 128.7, 128.7, 128.0, 127.9, 114.4,

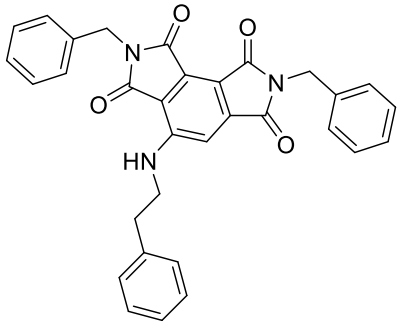
114.4, 113.8, 113.7, 110.0, 55.3, 44.7, 41.9, 41.7, 34.6; HRMS (TOF ES$^+$) m/z: [M+H]$^+$ calcd for $C_{33}H_{28}N_3O_5$ 546.2023; found, 546.2023.

2,7-Dibenzyl-4-((4-methylphenethyl)amino)pyrrolo[3,4-*e*]isoindole-1,3,6,8(2*H*, 7*H*)-tetraone (3m)



Yellow solid (49%); Mp: 203.3–206.1 °C; IR (KBr): 3500, 3468, 2991, 1745, 1718, 1634, 1519, 846 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.42 (t, J = 9.2 Hz, 4H, ArH), 7.30–7.18 (m, 11H, ArH), 7.11 (s, 1H, NH), 4.81 (s, 2H, CH_2), 4.77 (s, 2H, CH_2), 3.59–3.55 (m, 2H, CH_2), 2.92 (t, J = 7.0 Hz, 2H, CH_2), 2.30 (s, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.4, 166.7, 164.3, 164.1, 150.0, 140.1, 136.6, 136.2, 136.0, 134.5, 130.3, 129.6, 129.6, 128.9, 128.9, 128.8, 128.8, 128.7, 128.7, 128.6, 128.6, 128.6, 128.6, 128.0, 127.9, 113.9, 113.7, 109.9, 44.6, 41.9, 41.7, 35.0, 21.0. HRMS (TOF ES$^+$) m/z: [M+Na]$^+$ calcd for $C_{33}H_{27}N_3O_4$ 552.1894; found, 552.1902.

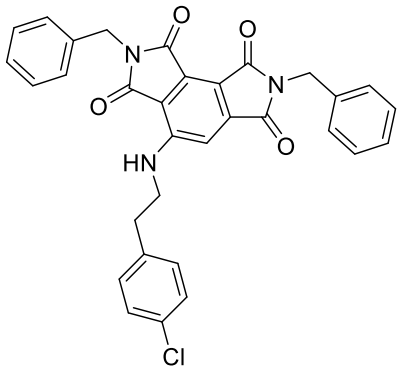
2,7-Dibenzyl-4-(phenethylamino)pyrrolo[3,4-*e*]isoindole-1,3,6,8(2*H*,7*H*)-tetraone (3n)



Yellow solid (45%); Mp: 199.3–202.5 °C; IR (KBr): 3348, 3376, 2927, 1753, 1712, 1635, 1525 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.43–7.40 (m, 4H, ArH), 7.33–7.21 (m, 12H, ArH), 7.20 (s, 1H, NH), 4.82 (s, 2H, CH_2), 4.77 (s, 2H, CH_2), 3.62–3.58 (m, 2H, CH_2), 2.97 (t, J = 7.1 Hz, 2H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.4, 166.7, 164.3, 164.0, 150.0, 140.2, 137.6, 136.1, 136.0, 130.3, 128.9, 128.9, 128.9, 128.8, 128.8, 128.7, 128.7, 128.7, 128.7, 128.0, 128.0, 127.9, 127.9, 127.1, 127.1, 114.0, 113.8, 109.9,

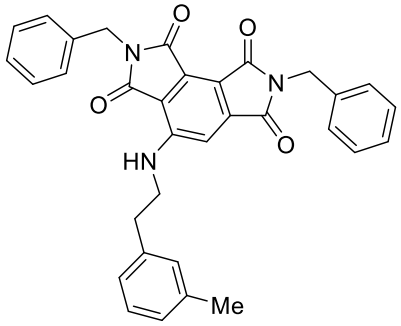
44.5, 41.9, 41.7, 35.4. HRMS (TOF ES$^+$) m/z: [M+H]$^+$ calcd for $C_{32}H_{25}N_3O_4$ 516.1918; found, 516.1909.

2,7-Dibenzyl-4-((4-chlorophenethyl)amino)pyrrolo[3,4-*e*]isoindole-1,3,6,8(2*H*, 7*H*)-tetraone (3o)



Yellow solid (42%); Mp: 208.3–212.8 °C; IR (KBr): 3460, 3372, 2940, 1754, 1709, 1634, 1524, 819 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.43–7.39 (m, 4H, ArH), 7.30–7.15 (m, 11H, ArH), 7.13 (s, 1H, NH), 4.86 (s, 2H, CH_2), 4.77 (s, 2H, CH_2), 3.56 (s, J = 6.2 Hz, 2H, CH_2), 2.93 (s, J = 6.8 Hz, 2H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.4, 166.7, 164.2, 164.0, 149.9, 140.2, 136.1, 136.1, 135.9, 133.0, 130.3, 130.1, 130.1, 129.1, 129.1, 128.9, 128.9, 128.8, 128.8, 128.7, 128.7, 128.7, 128.7, 128.0, 128.0, 114.0, 114.0, 109.8, 44.2, 42.0, 41.7, 34.7; HRMS (TOF ES$^+$) m/z: [M+H]$^+$ calcd for $C_{32}H_{24}ClN_3O_4$ 550.1528; found, 550.1534.

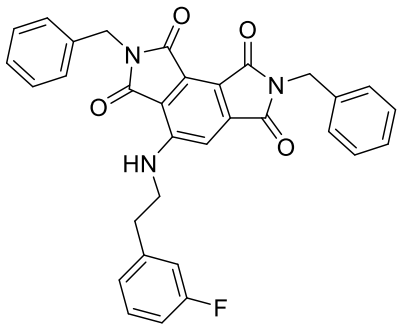
2,7-Dibenzyl-4-((3-methylphenethyl)amino)pyrrolo[3,4-*e*]isoindole-1,3,6,8(2*H*, 7*H*)-tetraone (3p)



Yellow solid (53%); Mp: 202.6–205.2°C; IR (KBr): 3449, 3366, 2938, 1757, 1710, 1635, 1522, 869, 807, 702 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.42 (t, J = 9.2 Hz, 4H, ArH), 7.31–7.24 (m, 5H, ArH), 7.22 (s, 2H, ArH), 7.13 (s, 1H, NH), 7.11 (s, 4H, ArH) , 4.82 (s, 2H, CH_2), 4.78 (s, 2H, CH_2), 3.59–3.55 (m, 2H, CH_2), 2.93 (t, J = 7.0 Hz, 2H, CH_2), 2.30 (s, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.4, 166.7, 164.3, 164.1, 150.0, 140.1, 136.7, 136.1, 136.0, 134.5, 130.3, 129.6, 129.6, 128.9, 128.9, 128.8,

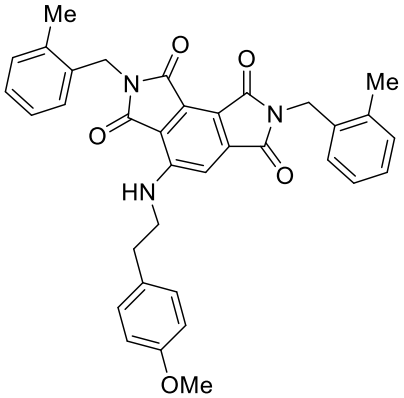
128.8, 128.7, 128.7, 128.7, 128.7, 128.6, 128.6, 128.0, 127.9, 113.8, 113.7, 109.9, 44.6, 41.9, 41.7, 35.0, 21.0; HRMS (TOF ES$^+$) m/z: [M+Na]$^+$ calcd for $C_{33}H_{27}N_3O_4$ 552.1894; found, 552.1902.

2,7-Dibenzyl-4-((3-fluorobenzyl)amino)pyrrolo[3,4-*e*]isoindole-1,3,6,8(2*H*,7*H*)-tetraone (3q)



Yellow solid (40%); Mp: 185.6–187.2 °C; IR (KBr): 3462, 3383, 2935, 1751, 1713, 1634, 1524, 864, 783, 691 cm^{-1}; ^{1}H NMR (600 MHz, DMSO-d_6): δ = 7.54–7.46 (m, 1H, ArH), 7.44 (s, 1H, NH), 7.34–7.25 (m, 11H, ArH), 7.19–7.12 (m, 2H, ArH), 7.03–7.00 (m, 1H, ArH), 4.75 (s, 2H, CH_2), 4.72 (s, 2H, CH_2), 3.75–3.72 (m, 2H, CH_2), 2.94 (t, J = 7.1 Hz, 2H , CH_2). ^{13}C NMR (150 MHz, DMSO-d_6): δ = 169.3, 166.9, 164.5, 164.1, 162.7 (d, J_1 = 241.5 Hz), 150.2, 142.1, 142.0, 139.9, 137.0, 136.9, 130.7, 130.7, 130.6, 129.0, 129.0, 127.9, 127.9, 127.9, 127.9, 125.5, 116.1, 116.0, 113.7, 113.5, 113.5, 113.0, 111.3, 43.6, 41.4, 41.3, 34.7. ^{19}F NMR (564 MHz, DMSO-d_6): δ = –113.51 ppm. HRMS (TOF ES$^+$) m/z: [M+H]$^+$ calcd for $C_{31}H_{22}FN_3O_4$ 534.1824; found, 534.1824.

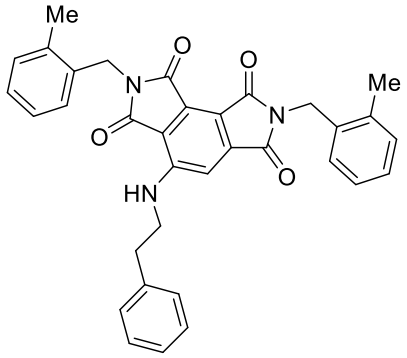
4-((4-Methoxyphenethyl)amino)-2,7-bis(2-methylbenzyl)pyrrolo[3,4-*e*]isoindole-1,3,6,8(2*H*,7*H*)-tetraone (3r)



Yellow solid (54%); Mp: 104.5–107.8 °C; IR (KBr): 3523, 3461, 2991, 1744, 1633, 1564, 1514, 835 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.29 (d, J = 4.1 Hz, 2H, ArH), 7.23–7.21 (m, 2H, ArH), 7.15 (s, 1H, NH), 7.13–7.10 (m, 6H, ArH), 6.85 (d, J = 8.4 Hz, 2H, ArH), 4.84 (s, 2H, CH_2), 4.81 (s, 2H, CH_2), 3.76 (s, 3H, CH_3), 3.59–3.56 (m, 2H,

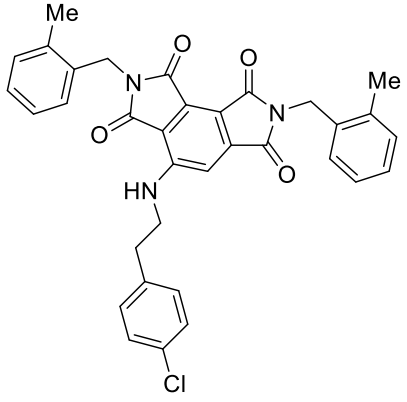
CH_2), 2.92 (t, J = 6.9 Hz, 2H, CH_2), 2.48 (d, J = 3.3 Hz, 6H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.7, 167.0, 164.4, 164.2,158.7, 150.1, 140.1, 136.3, 136.3, 134.1, 133.9, 130.5, 130.5, 130.3, 129.7, 129.7, 129.6, 128.9, 128.8, 127.9, 127.8, 126.2, 126.2, 114.3, 114.3, 113.9, 113.7, 109.9, 55.3, 44.7, 39.4, 39.2, 34.6, 19.5, 19.5. HRMS (TOF ES$^+$) m/z: $[M+H]^+$ calcd for $C_{35}H_{31}N_3O_5$ 574.2336; found, 574.2327.

2,7-Bis(2-methylbenzyl)-4-(phenethylamino)pyrrolo[3,4-*e*]isoindole-1,3,6,8(2*H*, 7*H*)-tetraone (3s)



Yellow solid (47%); Mp: 147.6–155.8 °C; IR (KBr): 3447, 3373, 2937, 1748, 1711, 1635, 1525, cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.33–7.28 (m, 4H, ArH), 7.26–7.22(m, 5H, ArH), 7.16 (s, 1H, NH), 7.14–7.09 (m, 5H, ArH), 4.85 (s, 2H, CH_2), 4.80 (s, 2H, CH_2), 3.64–3.60 (m, 2H, CH_2), 2.98 (t, J = 7.1 Hz, 2H, CH_2), 2.48 (t, J = 4.3 Hz, 6H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.7, 167.0, 164.4, 164.2, 150.0, 140.1, 137.4, 136.3, 136.3, 134.1, 133.9, 130.5, 130.5, 130.3, 128.9, 128.9, 128.9, 128.8, 128.8, 128.7, 127.9, 127.8, 127.1, 126.2, 126.2, 113.9, 113.7, 109.9, 44.5, 39.4, 39.2, 35.5, 19.5, 19.5. HRMS (TOF ES$^+$) m/z: $[M+H]^+$ calcd for $C_{34}H_{29}N_3O_4$ 544.2231; found, 544.2237.

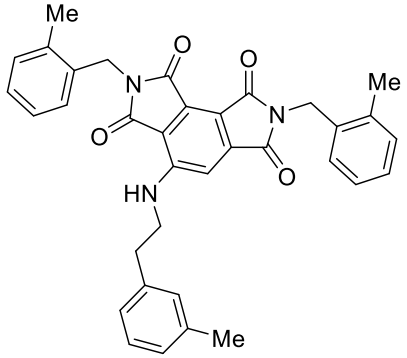
4-((4-Chlorophenethyl)amino)-2,7-bis(2-methylbenzyl)pyrrolo[3,4-*e*]Nisoindole-1,3,6,8(2*H*,7*H*)-tetraone (3t)



Yellow solid (41%); Mp: 214.2–214.8 °C; IR (KBr): 3449, 3426, 2935, 1750, 1712,

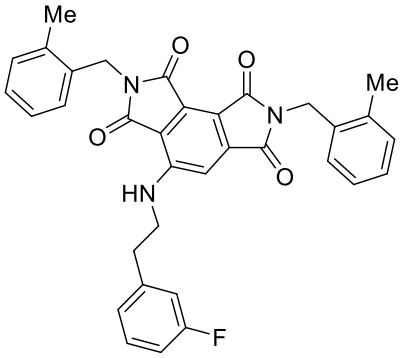
1635, 1525, 835 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.29–7.22 (m, 5H, ArH), 7.20–7.15(m, 2H, ArH), 7.14 (s, 1H, NH), 7.11 (d, J = 3.8 Hz, 2H, ArH), 4.85 (s, 2H, CH_2), 4.81 (s, 2H, CH_2), 3.62–3.58 (m, 2H, CH_2), 2.95 (t, J = 6.9 Hz, 2H, CH_2), 2.48 (t, J = 1.2 Hz, 6H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.7, 166.9, 164.4, 164.2, 149.9, 140.2, 136.3, 136.0, 134.0, 133.8, 133.0, 130.5, 130.3, 130.1, 130.1, 129.1,129.1, 128.9, 128.9, 128.8, 128.0, 127.8, 126.2, 126.2, 114.1, 113.9, 109.8, 44.3, 39.4, 39.2, 34.8, 19.5, 19.5. HRMS (TOF ES^+) m/z: $[M+H]^+$ calcd for $C_{34}H_{28}ClN_3O_4$ 578.1841; found, 578.1847.

2,7-Bis(2-methylbenzyl)-4-((3-methylphenethyl)amino)pyrrolo[3,4-*e*]isoindole-1,3,6,8(2*H*,7*H*)-tetraone (3u)



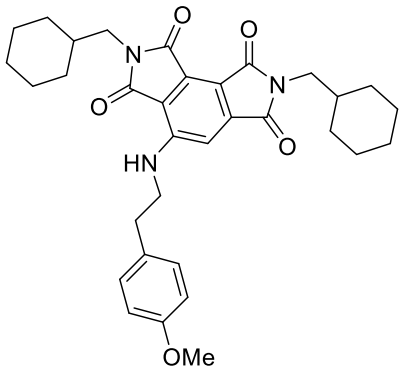
Yellow solid (49%); Mp: 194.4–197.1 °C; IR (KBr): 3451, 3373, 2932, 1751, 1712, 1635, 1521, 855, 791, 744 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.29 (d, J = 6.9 Hz, 2H, ArH), 7.23 (t, J = 8.3 Hz, 1H, ArH), 7.16 (s, 1H, NH), 7.13 (t, J = 7.0 Hz, 1H, ArH), 4.85 (s, 2H, CH_2), 4.81 (s, 2H, CH_2), 3.61–3.57 (m, 2H, CH_2), 2.94 (t, J = 7.0 Hz, 2H, CH_2), 2.48 (t, J = 6.6 Hz, 6H, CH_3), 2.31 (s, 3H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.7, 167.0, 164.4, 164.2, 150.1, 140.1, 136.7, 136.3, 136.3, 134.5, 134.1, 133.9, 130.5, 130.5, 130.3, 129.6, 129.6, 128.9, 128.8, 128.8, 128.6, 127.9, 127.8, 126.2, 126.2, 113.9, 113.7, 109.9, 44.6, 39.4, 39.2, 35.0, 21.1, 19.5, 19.5. HRMS (TOF ES^+) m/z: $[M+H]^+$ calcd for $C_{35}H_{31}N_3O_4$ 558.2387; found, 558.2390.

4-((3-Fluorophenethyl)amino)-2,7-bis(2-methylbenzyl)pyrrolo[3,4-*e*]isoindole-1,3,6,8(2*H*,7*H*)-tetraone (3v)



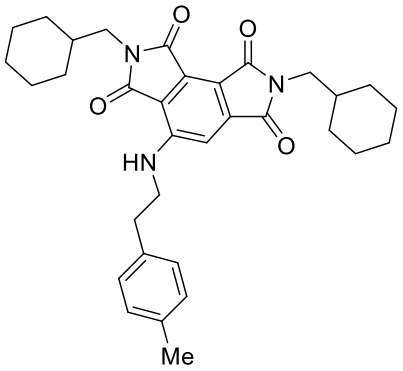
Yellow solid (38%); Mp: 213.0–216.3 °C; IR (KBr): 3448, 3417, 2934, 1745, 1709, 1634, 1526, 1050, 831, 747 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.31–7.21 (m, 6H, ArH), 7.16–7.09 (m, 5H, ArH), 7.01 (d, J = 8.8 Hz, 1H, NH), 6.95 (t, J = 8.6 Hz, 2H, ArH), 4.85 (s, 2H, CH_2), 4.81 (s, 2H, CH_2), 3.65–3.61 (m, 2H, CH_2), 2.98 (t, J = 7.0 Hz, 2H, CH_2), 2.98 (t, J = 4.8 Hz, 6H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.7, 166.9, 164.4, 164.2, 163.1 (d, J_1 = 245.1 Hz), 149.9, 140.2, 140.0 (d, J_3 = 7.5 Hz), 136.3, 133.9 (d, J_2 = 21.3 Hz),, 134.0, 133.8, 130.4, 130.3, 128.9, 128.8, 127.9, 127.8, 126.2, 126.2, 124.4, 124.4, 115.6 (d, J_2 = 21.3 Hz), 114.2, 114.1, 114.0, 113.9, 109.8, 44.1, 39.4, 39.2, 35.1, 19.5, 19.5. ^{19}F NMR (470 MHz, $CDCl_3$): δ = –112.5 ppm. HRMS (TOF ES^+) m/z: $[M+H]^+$ calcd for $C_{34}H_{28}FN_3O_4$ 562.2137; found, 562.2137.

2,7-Dicyclohexyl-4-((4-methoxyphenethyl)amino)pyrrolo[3,4-*e*]isoindole-1,3,6, 8(2*H*,7*H*)-tetraone (3w)



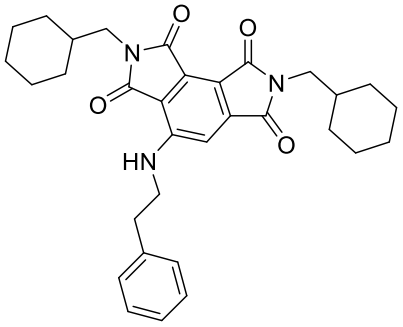
Yellow solid (49%); Mp: 260.5–262.3 °C; IR (KBr): 3471, 3453, 2935, 1745, 1710, 1636, 1517, 843 cm^{-1}; ^1H NMR (500 MHz, CDCl3): δ = 7.22 (t, J = 5.3 Hz, 1H, NH), 7.17 (d, J = 8.3 Hz, 3H, ArH), 6.88 (d, J = 8.5 Hz, 2H, ArH), 4.13–4.02 (m, 2H, CH), 3.80 (s, 3H, CH_3), 3.61–3.57 (m, 2H, CH_2), 2.95 (d, J = 7.0 Hz, 2H, CH_2), 2.22–2.14 (m, 4H, CH_2), 1.86 (d, J = 12.8 Hz, 4H, CH_2), 1.69 (d, J = 11.4 Hz, 6H, CH_2), 1.39–1.24 (m, 6H, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.1, 167.3, 164.8, 164.7, 158.6, 149.8, 140.0, 130.1, 129.7, 129.7, 114.3, 114.3, 114.3, 113.8, 113.7, 109.4, 55.3, 51.3, 51.0, 44.6, 34.6, 29.8, 29.8, 29.7, 29.7, 26.0, 26.0, 26.0, 26.025.1, 25.1. HRMS (TOF ES^+) m/z: $[M+Na]^+$ calcd for $C_{31}H_{35}N_3O_5$ 552.2469; found, 552.2469.

2,7-Dicyclohexyl-4-((4-methylphenethyl)amino)pyrrolo[3,4-*e*]isoindole-1,3,6,8(2*H*,7*H*)-tetraone (3x)



Yellow solid (44%); Mp: 267.4–268.3 °C; IR (KBr): 3462, 3441, 2941, 1746, 1710, 1627, 1518, 848 cm^{-1}; ^1H NMR (500 MHz, CDCl3): δ = 7.23 (t, J = 5.1 Hz, 1H, NH), 7.18 (s, 1H, ArH), 7.15 (s, 4H, ArH), 4.13–4.02 (m, 2H, CH), 3.62–3.59 (m, 2H, CH_2), 2.96 (t, J = 7.0 Hz, 2H, CH_2), 2.33 (s, 3H, CH_3), 2.25–2.14 (m, 4H, CH_2), 1.86 (d, J = 12.2 Hz, 4H, CH_2), 1.69 (d, J = 11.0 Hz, 6H, CH_2), 1.39–1.24 (m, 6H, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.1, 167.3, 164.8, 164.7, 149.8, 140.0, 136.6, 134.6, 130.1, 129.6, 129.6, 128.6, 128.6, 113.8, 113.7, 109.4, 51.2, 51.0, 44.6, 35.0, 29.8, 29.8, 29.7, 29.7, 26.0, 26.0, 26.0, 26.0, 25.1, 25.1, 21.1. HRMS (TOF ES^+) m/z: $[M+H]^+$ calcd for $C_{31}H_{35}N_3O_4$ 514.2700; found,514.2704.

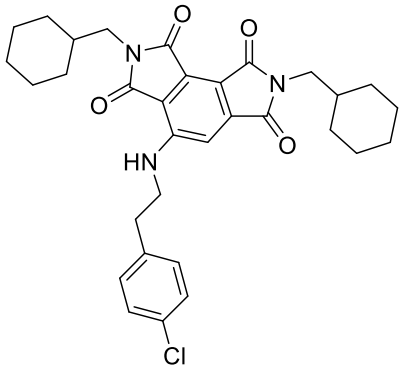
2,7-Dicyclohexyl-4-(phenethylamino)pyrrolo[3,4-*e*]isoindole-1,3,6,8(2*H*,7*H*)-tetraone (3y)



Yellow solid (43%); Mp: 285.6–288.4 °C; IR (KBr): 3498, 3468, 2934, 1746, 1704, 1634, 1520 cm^{-1}; ^1H NMR (500 MHz, CDCl3): δ = 7.35 (t, J = 7.4 Hz, 2H, ArH), 7.28–7.20 (m, 4H, ArH), 4.13–4.02 (m, 2H, CH), 3.01 (m, J = 7.0 Hz, 2H, CH_2), 2.25–2.14 (m, 4H, CH_2), 1.86 (d, J = 12.7 Hz, 4H, CH_2), 1.69 (d, J = 11.6 Hz, 6H, CH_2), 1.39–1.18 (m, 6H, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.1, 167.3, 164.8, 164.7, 149.8, 140.0, 137.7, 130.1, 128.9, 128.9, 128.7, 128.7, 127.0, 113.9, 113.8, 109.3, 51.3, 51.0, 44.4, 35.5, 29.8, 29.8, 29.7, 29.7, 26.0, 26.0, 26.0, 26.0, 25.1, 25.1. HRMS (TOF ES^+)

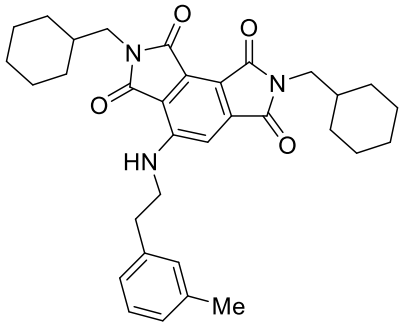
m/z: $[M+H]^+$ calcd for $C_{30}H_{33}N_3O_4$ 500.2544; found, 500.2545.

4-((4-Chlorophenethyl)amino)-2,7-dicyclohexylpyrrolo[3,4-*e*]isoindole-1,3,6,8 (2*H*,7*H*)-tetraone (3z)



Yellow solid (40%); Mp: 260.5–262.3 °C; IR (KBr): 3430, 3397, 2987, 1745, 1711, 1635, 1520, 834 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.32 (d, J = 8.1 Hz, 3H, ArH), 7.19 (d, J = 8.1 Hz, 2H, ArH), 7.01 (s, 1H, NH), 4.14–4.02 (m, 2H, CH), 3.64–3.60 (m, 2H, CH_2), 2.98 (t, J = 6.8 Hz, 2H, CH_2), 2.22–2.04 (m, 4H, CH_2), 1.86 (d, J = 12.4 Hz, 4H, CH_2), 1.69 (d, J = 11.3 Hz, 6H, CH_2), 1.50–0.86 (m, 6H, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.1, 167.2, 164.7, 164.7, 149.7, 140.0, 136.2, 133.0, 130.1, 130.1, 130.1, 130.1, 129.1, 114.0, 114.0, 109.2, 51.3, 51.1, 44.2, 34.8, 29.8, 29.8, 29.7, 29.7, 26.0, 26.0, 26.0, 26.0, 25.1, 25.1. HRMS (TOF ES^+) m/z: $[M+Na]^+$ calcd for $C_{30}H_{32}N_3O_4$ 556.1974; found, 556.1976.

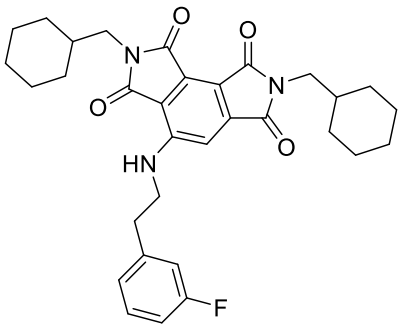
2,7-Dicyclohexyl-4-((3-methylphenethyl)amino)pyrrolo[3,4-*e*]isoindole-1,3,6,8(2*H*, 7*H*)-tetraone (3a')



Yellow solid (47%); Mp: 269.5–270.4 °C; IR (KBr): 3465, 3439, 2939, 1744, 1714, 1630, 1515, 892, 780, 685 cm^{-1}; ^1H NMR (500 MHz, CDCl3): δ = 7.23 (t, J = 5.3 Hz, 1H, NH), 7.18 (s, 1H, ArH), 7.15 (s, 4H, ArH), 4.13–4.02 (m, 2H, CH), 3.63–3.57 (m, 2H, CH_2), 2.96 (t, J = 7.0 Hz, 2H, CH_2), 2.33 (s, 3H, CH_3), 2.25–2.14 (m, 4H, CH_2), 1.86 (d, J = 12.1 Hz, 4H, CH_2), 1.69 (d, J = 10.8 Hz, 6H, CH_2), 1.39–1.24 (m, 6H, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.1, 167.3, 164.8, 164.7, 149.8, 140.0, 136.6, 134.6,

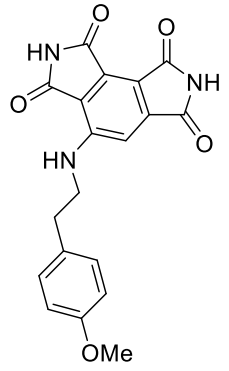
130.1, 129.6, 129.6, 128.6, 128.6, 113.8, 113.7, 109.4, 51.2, 51.0, 44.6, 35.0, 29.8, 29.8, 29.7, 29.7, 26.0, 26.0, 26.0, 26.0, 25.1, 25.1, 21.1. HRMS (TOF ES$^+$) m/z: [M+H]$^+$ calcd for $C_{31}H_{35}N_3O_4$ 514.2700; found,514.2704.

2,7-Dicyclohexyl-4-((3-fluorophenethyl)amino)pyrrolo[3,4-*e*]isoindole-1,3,6,8(2*H*, 7*H*)-tetraone (3b')



Yellow solid (37%); Mp: 281.6–288.4 °C; IR (KBr): 3495, 3481, 2940, 1745, 1708, 1635, 1520, 834, 866, 781, 679 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.34–7.30 (m, 1H, ArH), 7.21 (t, J = 5.0 Hz, 2H, ArH), 7.04 (d, J = 3.8 Hz, 1H, NH), 7.97 (t, J = 8.3 Hz, 2H, ArH), 4.14–4.02 (m, 2H, CH), 3.66–3.62 (m, 2H, CH_2), 3.01 (t, J = 7.0 Hz, 2H, CH_2), 2.25–2.13 (m, 4H, CH_2), 1.86 (d, J = 14.8 Hz, 4H, CH_2), 1.69 (d, J = 11.4 Hz, 6H, CH_2), 1.40–1.24 (m, 6H, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.1, 167.2, 164.7, 164.7, 163.1 (d, J_1 = 246.3 Hz), 149.7, 140.2,130.4 (d, J_3 = 7.5 Hz), 130.1, 124.4 (d, J_4 = 2.5 Hz), 115.6 (d, J_2 = 21.3 Hz), 114.0 (d, J_2 = 21.3 Hz), 114.1, 114.0, 109.2, 51.3, 51.1, 44.1, 35.1, 29.8, 29.8, 29.7, 29.7, 26.0, 26.0, 26.0, 26.0, 25.1, 25.1. ^{19}F NMR (470 MHz, $CDCl_3$): δ = –112.6 ppm. HRMS (TOF ES$^+$) m/z: [M+H]$^+$ calcd for $C_{30}H_{32}FN_3O_4$ 518.2450; found, 518.2440.

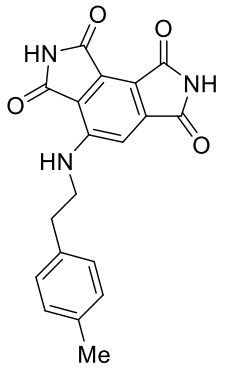
4-((4-Methoxyphenethyl)amino)pyrrolo[3,4-*e*]isoindole-1,3,6,8(2*H*,7*H*)-tetraone (3c')



Yellow solid (52%); Mp: 293.1–301.5 °C; IR (KBr): 3515, 3430, 2996, 1743, 1635, 1529, 1448, 835 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 11.32 (s, 1H, NH), 11.30 (s, 1H, NH), 7.41 (s, 1H, NH), 7.27 (s, 1H, ArH), 7.21 (s, 1H, ArH), 7.21 (d, J = 8.4 Hz,

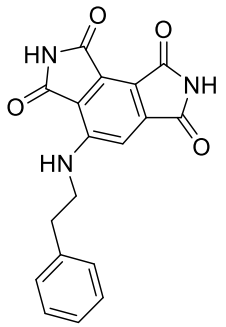
2H, ArH), 6.86 (d, J = 8.5 Hz, 2H, ArH), 3.71 (s, 3H, CH_3), 3.65 (d, J = 6.6 Hz, 2H, CH_2), 2.85 (t, J = 7.0 Hz, 2H, CH_2); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 171.3, 168.5, 166.1, 165.8, 158.4, 150.3, 141.3, 131.6, 130.9, 130.3, 130.3, 114.9, 114.4, 114.4, 114.1, 110.1, 55.5, 44.2, 34.3. HRMS (TOF ES$^+$) m/z: $[M+H]^+$ calcd for $C_{19}H_{15}N_3O_5$ 366.1084; found, 366.1075.

4-((4-Methylphenethyl)amino)pyrrolo[3,4-*e*]isoindole-1,3,6,8(2*H*,7*H*)-tetraone (3d')



Yellow solid (48%); Mp: 339.0–340.0 °C; IR (KBr): 3457, 3434, 2994, 1742, 1701, 1638, 1529, 832 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 11.33 (s, 1H, NH), 11.31 (s, 1H, NH), 7.41 (t, J = 6.0 Hz, 1H, NH), 7.29 (s, 1H, ArH), 7.18 (t, J = 7.9 Hz, 1H, ArH), 7.11 (t, J = 7.8 Hz, 2H, ArH), 3.68–3.64 (m, 2H, CH_2), 2.86 (t, J = 7.1 Hz, 2H, CH_2), 2.26 (s, 3H, CH_3); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 171.3, 168.5, 166.1, 165.8, 150.2, 141.3, 136.0, 135.8, 131.5, 129.5, 129.5, 129.2, 129.2, 114.9, 114.1, 110.1, 44.0, 34.7, 21.1. HRMS (TOF ES$^+$) m/z: $[M+H]^+$ calcd for $C_{19}H_{15}N_3O_4$ 350.1135; found, 350.1127.

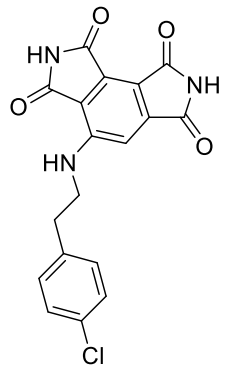
4-(Phenethylamino)pyrrolo[3,4-*e*]isoindole-1,3,6,8(2*H*,7*H*)-tetraone (3e')



Yellow solid (44%); Mp: 325.8–332.6 °C; IR (KBr): 3517, 3442, 2994, 1744, 1631, 1532, 1455 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 11.31 (s, 2H, NH), 7.43 (t, J = 5.9 Hz, 1H, NH), 7.30 (m, J = 4.1 Hz, 5H, ArH), 7.23–7.19 (m, 1H, ArH), 3.71–3.67 (m, 2H, CH_2), 2.91 (t, J = 7.1 Hz, 2H, CH_2); ^{13}C NMR (125 MHz, DMSO-d_6): δ =

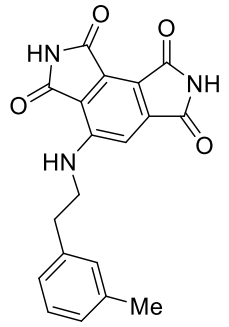
171.3, 168.5, 166.1, 165.8, 150.2, 141.3, 139.1, 131.5, 129.3, 129.3, 128.9, 128.9, 126.8, 114.9, 114.1, 110.1, 43.9, 35.1. HRMS (TOF ES$^+$) m/z: [M+Na]$^+$ calcd for $C_{18}H_{13}N_3O_4$ 358.0798; found, 358.0792.

4-((4-Chlorophenethyl)amino)pyrrolo[3,4-*e*]isoindole-1,3,6,8(2*H*,7*H*)-tetraone (3f')



Yellow solid (41%); Mp: 315.6–320.6 °C; IR (KBr): 3452, 3427, 2927, 1713, 1630, 1527, 1374, 836 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 11.23 (s, 1H, NH), 11.31 (s, 1H, NH), 7.41 (t, J = 6.0 Hz, 1H, NH), 7.35–7.31 (m, 4H, ArH), 7.29 (s, 1H, ArH), 3.70–3.66 (m, 2H, CH_2), 2.91 (t, J = 7.1 Hz, 2H, CH_2); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 171.2, 168.5, 166.0, 165.8, 150.2, 141.3, 138.2, 131.5, 131.2, 131.2, 128.8, 128.8, 128.8, 115.0, 114.2, 110.1, 43.7, 34.0. HRMS (TOF ES$^+$) m/z: [M+H]$^+$ calcd for $C_{18}H_{12}ClN_3O_4$ 370.0589; found, 370.0593.

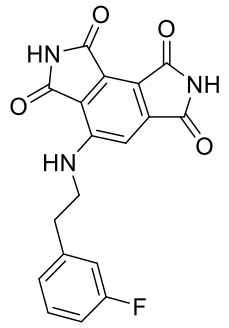
4-((3-Methylphenethyl)amino)pyrrolo[3,4-*e*]isoindole-1,3,6,8(2*H*,7*H*)-tetraone (3g')



Yellow solid (50%); Mp: 302.5–308.6 °C; IR (KBr): 3348, 3309, 2996, 1743, 1635, 1530, 1452, 831, 781, 725 cm^{-1}; ^{1}H NMR (600 MHz, DMSO-d_6): δ = 11.32 (s, 1H, NH), 11.30 (s, 1H, NH), 7.40 (t, J = 4.9 Hz, 1H, NH), 7.28 (s, 1H, ArH), 7.18 (d, J = 6.5 Hz, 2H, ArH), 7.10 (d, J = 6.5 Hz, 2H, ArH), 3.67–3.64 (m, 2H, CH_2), 2.86 (t, J = 5.8 Hz, 2H, CH_2), 2.26 (s, 3H, CH_3); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 171.3, 168.5, 166.0, 165.8, 150.3, 141.3, 136.0, 135.8, 131.5, 129.5, 129.5, 129.2, 129.2, 115.0, 114.1, 110.1, 44.0, 34.7, 21.1. HRMS (TOF ES$^+$) m/z: [M+H]$^+$ calcd for $C_{19}H_{15}N_3O_4$ 350.1135; found,

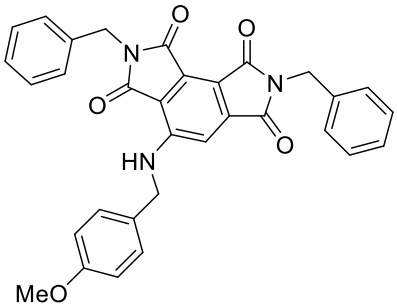
350.1127.

4-((3-fluorophenethyl)amino)pyrrolo[3,4-*e*]isoindole-1,3,6,8(2*H*,7*H*)-tetraone (3h')



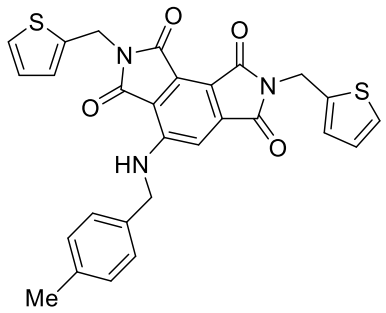
Yellow solid (40%); Mp: 328.6–335.9 °C; IR (KBr): 3347, 3308, 2995, 1742, 1634, 1529, 1452, 831, 780, 724 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6): δ = 11.25 (s, 1H, NH), 11.22 (s, 1H, NH), 7.37 (s, 1H, NH), 7.30 (d, J = 6.3Hz, 2H, ArH), 7.01–7.05 (m, 2H, ArH), 6.95 (s, 1H, ArH), 3.73–3.69 (m, 2H, CH_2), 3.99 (t, J = 7.0 Hz, 2H, CH_2). ^{13}C NMR (150 MHz, DMSO-d_6): δ = 171.1, 168.2, 166.1, 165.9, 162.8 (d, J_1 = 243.8 Hz), 150.2, 141.4, 141.2 (d, J_3 = 8.8 Hz), 131.4, 130.4 (d, J_3 = 8.8 Hz), 124.9 (d, J_4 = 2.5 Hz), 115.8 (d, J_2 = 21.3 Hz), 115.2, 114.4, 113.5 (d, J_2 = 21.3 Hz), 109.6, 43.7, 34.9. ^{19}F NMR (564 MHz, DMSO-d_6): δ = –113.1 ppm. HRMS (TOF ES$^+$) m/z: $[M+H]^+$ calcd for $C_{18}H_{12}FN_3O_4$ 354.0885; found, 354.0876.

2,7-dibenzyl-4-((4-methoxybenzyl)amino)pyrrolo[3,4-e]isoindole-1,3,6,8(2H,7H)-tetraone (3i')



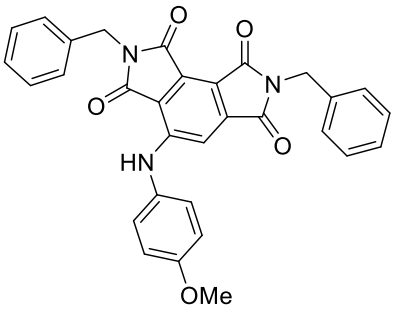
Yellow solid (53%); Mp: 213.5–214.8 °C; IR (KBr): 3449, 3376, 2984, 1746, 1711, 1634, 1517, 830 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6): δ = 8.10 (t, 1H, J = 6.2 Hz, NH), 7.35–7.24 (m, 13H, ArH), 6.90 (d, J = 8.6 Hz, 2H, ArH), 4.78 (s, 2H, CH_2), 4.72 (s, 2H, CH), 4.64 (d, J = 6.2 Hz, 2H, CH_2), 3.71 (s, 3H, CH_3); ^{13}C NMR (150 MHz, DMSO-d_6): δ =169.2, 167.0, 164.5, 164.1, 159.0, 150.1, 139.8, 137.0, 137.0, 130.7, 130.2, 129.0, 129.0, 129.0, 129.0, 128.9, 128.9, 128.0, 128.0, 127.9, 127.9, 127.9, 127.9, 114.6, 114.6, 114.0, 113.3, 111.2, 55.5, 45.6, 41.5, 41.3. HRMS (TOF ES$^+$) m/z: $[M+Na]^+$ calcd for $C_{32}H_{25}N_3O_5$ 554.1686; found, 554.1694.

4-((4-methylbenzyl)amino)-2,7-bis(thiophen-2-ylmethyl)pyrrolo[3,4-e]isoindole-1,3,6,8(2*H*,7*H*)-tetraone (3j')



Yellow solid (43%); Mp: 204.6–208.2 °C; IR (KBr): 3447, 3358, 2965, 1748, 1644, 1526, 1432, 851, 782, 683 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6): δ = 8.18 (t, J = 6.3 Hz, 1H, NH), 7.42 (ddd, J = 19.2, 5.1, 1.3 Hz, 2H, ArH), 7.25 (d, J = 8.6 Hz, 3H, ArH), 7.15 – 7.10 (m, 3H, ArH), 7.05 (d, J = 3.5 Hz, 1H, ArH), 6.95 (ddd, J = 16.8, 5.1, 3.4 Hz, 2H, ArH), 4.88 (d, J = 18.4 Hz, 4H, CH_2), 4.67 (d, J = 6.3 Hz, 2H, CH_2), 2.24 (s, 3H, CH_3). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 168.67, 166.43, 164.01, 163.59, 150.13, 139.63, 138.84, 138.80, 136.87, 135.33, 130.60, 129.71, 127.71, 127.58, 127.43, 127.37, 126.67, 113.85, 113.03, 111.39, 45.82, 36.16, 35.96, 21.12. HRMS (TOF ES^+) m/z: $[M+H]^+$ calcd for $C_{28}H_{21}N_3O_4S_2$ 528.1047; found, 528.1046.

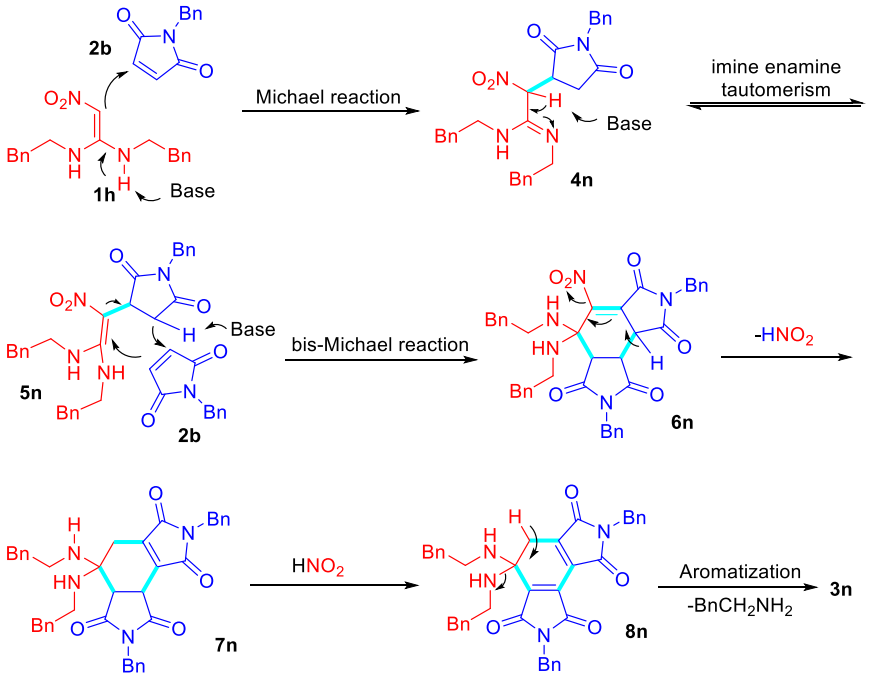
2,7-Dibenzyl-4-((4-methoxyphenyl)amino)pyrrolo[3,4-*e*]isoindole-1,3,6,8(2*H*,7*H*)-tetraone (3k')



Yellow solid (55%); Mp: 220.4–222.1 °C; IR (KBr): 3483, 3445, 2989, 1745, 1714, 1636, 1517, 831 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6): δ = 9.13 (s, 1H, NH), 7.35–7.24 (m, 12H, ArH), 7.20 (s, 1H, ArH), 7.06–7.03 (m, 2H, ArH), 4.78 (s, 2H, CH_2), 4.73 (s, 2H, CH_2), 3.80 (s, 3H, CH_3); ^{13}C NMR (150 MHz, DMSO-d_6): δ = 168.8, 166.8, 164.4, 164.0, 158.2, 148.8, 139.6, 136.9, 131.0, 130.8, 129.1, 129.1, 129.1, 129.0, 129.0, 129.0, 128.0, 128.0, 128.0, 127.9, 127.9, 127.9, 127.1, 127.1, 115.4, 114.7, 114.7, 111.6, 55.8, 41.5, 41.4. HRMS (TOF ES^+) m/z: $[M+H]^+$ calcd for $C_{31}H_{23}N_3O_5$ 518.1710; found, 518.1700.

The proposed mechanism of the cascade reaction

The proposed mechanism is shown in Scheme 2. First, the *α*-C of the substrate **1h** attacks the double bond of the maleimide derivative **2b** promoted by the base *via* Michael addition to form the intermediate **4n**, which undergoes an imine–enamine tautomerism to obtain the intermediate **5n**. Then, the intermediate **5n** with substrate **2b** enters a bis-Michael addition promoted by the base **2b** to form the intermediate **6n**. The key intermediate **6n** loses HNO_2 to generate the intermediate **7n**, followed by dehydrogenation and then the loss of an alkyl amine to generate the final product **3n**.



Scheme S1. The proposed mechanism of the cascade reaction.

Verification of reaction mechanisms

To verify the rationality of the mechanism, we packed 1,1-enediamine (**1h**) (0.1 mmol) and maleimide (**2b**) (0.2 mmol) into a round bottom flask. The reaction was carried out in DMF solvent at 100 ℃ for 20 minutes, with continuous sampling. After the reaction, the obtained intermediate samples were detected by the high-pressure liquid chromatography-high-resolution mass spectrometry (HPLC-HRMS) system. HRMS (TOF ES^+): *m/z* calcd. for

$C_{18}H_{22}N_3O_2$ [M+H]$^+$, 312.1707; found, 312.1701, which is the HRMS spectrum of substrate **1h** (SI, Figure S82); HRMS (TOF ES$^+$): *m/z* calcd. for $C_{11}H_9NO_2$ [M+H]$^+$, 210.0525; found, 210.0522, which is the HRMS spectra of substrate **2b** (SI, Figure S83); HRMS (TOF ES$^+$): *m/z* calcd. for $C_{29}H_{31}N_4O_4$ [M+H]$^+$, 499.2340; found, 499.2346. HRMS (TOF ES$^+$): *m/z* calcd. for $C_{29}H_{31}N_4O_4$ [M+H]$^+$, 499.2340; found, 499.2344. There are the HRMS spectra of intermediates **4n**–**5n** (SI, Figure S84–S85). HRMS (TOF ES$^+$): *m/z* calcd. for $C_{40}H_{38}N_5O_6$ [M+H]$^+$, 684.2817; found, 684.2809. Which is the HRMS spectra of intermediates **6n** (SI, Figure S86); HRMS (TOF ES$^+$): *m/z* calcd. for $C_{40}H_{39}N_4O_4$ [M+H]$^+$, 639.2966; found, 639.2969. That is the HRMS spectra of intermediates **7n** (SI, Figure S87); HRMS (TOF ES$^+$): *m/z* calcd. for $C_{40}H_{37}N_4O_4$ [M+H]$^+$, 637.2809; found, 637.2812. Which is the HRMS spectra of intermediates **8n** (SI, Figure S88); HRMS (TOF ES$^+$): *m/z* calcd. for $C_{32}H_{26}N_3O_4$ [M+H]$^+$, 516.1918; found, 516.1914. Which is the HRMS spectra of target compound **3n** (SI, Figure S89). In high-resolution mass spectrometry, the molecular ion peaks of intermediates **4n**–**8n**, and the target compound were detected. Based on the experimental results, we believe that the proposed reaction mechanism is reasonable.

X-ray Structure and Data of 3n.

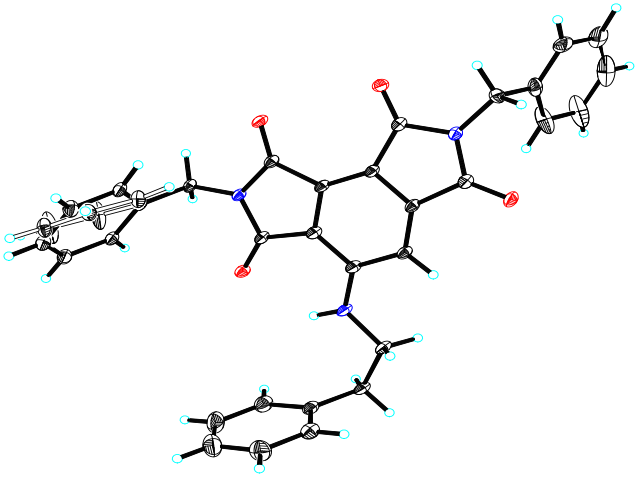


Figure S1. X-Ray crystal structure of **3n**

Table S1. Crystal data and structure refinement for **3n**

Identification code	mo_230801B_0m
Empirical formula	$C_{32}H_{25}N_3O_4$
Formula weight	515.55
Temperature	100.00 K
Wavelength	0.71073 Å
Crystal system, space group	monoclinic, P 1 21/n 1
Space group	P 1 21/n 1
Unit cell dimensions	a = 10.1041 (6) Å α = 90°. b = 16.5967 (12) Å β = 95.114 (2)°. c = 30.366 (16) Å γ = 90°.
Volume	5071.9(6) $Å^3$
Z, Calculated density	8, 1.350 Mg/m^3
Density (calculated)	1.350 g/cm^3
Absorption coefficient	0.090 mm^{-1}
F(000)	2160
Theta range for data collection	2.08 to 28.36°.
Index ranges	-10<=h<=13, -22<=k<=22, -40<=l<=40
Reflections collected / unique	147402 / 12653 [R(int) = 0.0852]
Max. and min. transmission	0.7457 and 0.0.6851
Independent reflections	12653 [R(int) = 0.0852]
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	12653 / 166 / 795
Goodness-of-fit on F^2	1.159
Final R indexes [I>=2sigma(I)]	R_1 = 0.0928, wR_2 = 0.1804
Final R indexes (all data)	R_1 = 0.1241, wR_2 = 0.1931
Extinction coefficient	n/a
Largest diff. peak and hole	0.607 /-0.567e.$Å^{-3}$

Table S2. Bond Lengths for **3n**

Atom	Atom	Length/Å	Atom	Atom	Length/Å
O1	C11	1.209(4)	O2	C64	1.210(4)
O3	C63	1.219(4)	O4	C8	1.212(4)
N1	C7	1.461(4)	N1	C8	1.381(4)
N1	C11	1.408(4)	N2	C24	1.463(4)
N2	C63	1.399(4)	N2	C64	1.399(4)
N3	H3	0.88	N3	C14	1.349(4)
N3	C16	1.465(4)	C1	H1	0.95
C1	C2	1.405(7)	C1	C6	1.375(6)
C2	H2	0.95	C2	C3	1.383(9)
C3	H3A	0.95	C3	C4	1.385(9)
C4	H4	0.95	C4	C5	1.382(6)
C5	H5	0.95	C5	C6	1.392(6)
C6	C7	1.513(5)	C7	H7A	0.99
C7	H7B	0.99	C8	C9	1.490(4)
C9	C10	1.412(4)	C9	C15	1.368(4)
C10	C11	1.489(5)	C10	C12	1.377(4)
C12	C13	1.394(4)	C12	C64	1.504(4)
C13	C14	1.408(4)	C13	C63	1.467(4)
C14	C15	1.423(4)	C15	H15	0.95
C16	H16A	0.99	C16	H16B	0.99
C16	C17	1.522(5)	C17	H17A	0.99
C17	H17B	0.99	C17	C18	1.504(5)
C18	C19	1.400(5)	C18	C23	1.390(5)
C19	H19	0.95	C19	C20	1.381(6)
C20	H20	0.95	C20	C21	1.385(7)
C21	H21	0.95	C21	C22	1.382(7)
C22	H22	0.95	C22	C23	1.388(6)
C23	H23	0.95	C24	H24A	0.99
C24	H24B	0.99	C24	C25	1.509(5)
C25	C26	1.457(6)	C25	C26A	1.303(10)
C25	C30	1.348(6)	C25	C30A	1.462(10)
C26	H26	0.95	C26	C27	1.396(7)
C26A	H26A	0.95	C26A	C27A	1.400(12)
C27	H27	0.95	C27	C28	1.382(8)
C27A	H27A	0.95	C27A	C28A	1.391(13)
C28	H28	0.95	C28	C29	1.372(9)
C28A	H28A	0.95	C28A	C29A	1.356(12)
C29	H29	0.95	C29	C30	1.396(7)
C29A	H29A	0.95	C29A	C30A	1.392(11)
C30	H30	0.95	C30A	H30A	0.95
O5	C41	1.217(4)	O6	C38	1.206(4)

O7	C46	1.211(4)	O8	C47	1.210(4)
N4	C37	1.451(4)	N4	C38	1.413(4)
N4	C41	1.381(4)	N5	C46	1.394(4)
N5	C47	1.402(4)	N5	C48	1.459(4)
N6	H6	0.88	N6	C43	1.347(4)
N6	C55	1.464(4)	C31	H31	0.95
C31	C32	1.386(6)	C31	C36	1.377(5)
C32	H32	0.95	C32	C33	1.371(7)
C33	H33	0.95	C33	C34	1.360(7)
C34	H34	0.95	C34	C35	1.392(6)
C35	H35	0.95	C35	C36	1.385(5)
C36	C37	1.515(5)	C37	H37A	0.99
C37	H37B	0.99	C38	C39	1.479(5)
C39	C40	1.403(4)	C39	C45	1.385(4)
C40	C41	1.494(4)	C40	C42	1.362(4)
C42	H42	0.95	C42	C43	1.428(4)
C43	C44	1.414(4)	C44	C45	1.388(4)
C44	C47	1.478(4)	C45	C46	1.504(4)
C48	H48A	0.99	C48	H48B	0.99
C48	C49	1.507(5)	C49	C50	1.397(6)
C49	C50A	1.357(11)	C49	C54	1.362(6)
C49	C54A	1.498(11)	C50	H50	0.95
C50	C51	1.388(7)	C50A	H50A	0.95
C50A	C51A	1.394(13)	C51	H51	0.95
C51	C52	1.362(7)	C51A	H51A	0.95
C52	C53	1.409(8)	C52A	H52A	0.95
C52A	C53A	1.377(14)	C53	H53	0.95
C53	C54	1.391(7)	C53A	H53A	0.95
C53A	C54A	1.392(14)	C54	H54	0.95
C54A	H54A	0.95	C55	H55A	0.99
C55	H55B	0.99	C55	C56	1.521(5)
C56	H56A	0.99	C56	H56B	0.99
C56	C57	1.509(5)	C57	C58	1.389(5)
C57	C62	1.399(5)	C58	H58	0.95
C58	C59	1.389(5)	C59	H59	0.95
C59	C61	1.387(5)	C60	H60	0.95
C60	C61	1.381(6)	C60	C62	1.384(5)
C61	H61	0.95	C62	H62	0.95

Table S3. Bond Angles for **3n**

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
C8	N1	C7	123.6(3)	C8	N1	C11	112.5(3)
C11	N1	C7	123.3(3)	C63	N2	C24	123.7(3)
C64	N2	C24	124.6(3)	C64	N2	C63	111.6(2)
C14	N3	H3	118.2	C14	N3	C16	123.5(3)
C16	N3	H3	118.2	C2	C1	H1	119.8
C6	C1	H1	119.8	C6	C1	C2	120.4(5)
C1	C2	H2	119.6	C3	C2	C1	120.7(5)
C3	C2	H2	119.6	C2	C3	H3A	120.7
C2	C3	C4	118.6(5)	C4	C3	H3A	120.7
C3	C4	H4	119.7	C5	C4	C3	120.6(6)
C5	C4	H4	119.7	C4	C5	H5	119.4
C4	C5	C6	121.2(5)	C6	C5	H5	119.4
C1	C6	C5	118.4(4)	C1	C6	C7	118.4(4)
C5	C6	C7	123.1(4)	N1	C7	C6	114.5(3)
N1	C7	H7A	108.6	N1	C7	H7B	108.6
C6	C7	H7A	108.6	C6	C7	H7B	108.6
H7A	C7	H7B	107.6	O4	C8	N1	125.6(3)
O4	C8	C9	128.2(3)	N1	C8	C9	106.2(3)
C10	C9	C8	107.8(3)	C15	C9	C8	127.1(3)
C15	C9	C10	124.9(3)	C9	C10	C11	107.6(3)
C12	C10	C9	116.9(3)	C12	C10	C11	135.1(3)
O1	C11	N1	124.3(3)	O1	C11	C10	130.1(3)
N1	C11	C10	105.7(3)	C10	C12	C13	119.6(3)
C10	C12	C64	132.9(3)	C13	C12	C64	107.5(3)
C12	C13	C14	123.6(3)	C12	C13	C63	108.6(3)
C14	C13	C63	127.7(3)	N3	C14	C13	120.9(3)
N3	C14	C15	122.3(3)	C13	C14	C15	116.7(3)
C9	C15	C14	118.2(3)	C9	C15	H15	120.9
C14	C15	H15	120.9	N3	C16	H16A	109.8
N3	C16	H16B	109.8	N3	C16	C17	109.4(3)
H16A	C16	H16B	108.2	C17	C16	H16A	109.8
C17	C16	H16B	109.8	C16	C17	H17A	109
C16	C17	H17B	109	H17A	C17	H17B	107.8
C18	C17	C16	112.9(3)	C18	C17	H17A	109
C18	C17	H17B	109	C19	C18	C17	119.4(3)
C23	C18	C17	122.1(3)	C23	C18	C19	118.4(4)
C18	C19	H19	119.6	C20	C19	C18	120.8(4)
C20	C19	H19	119.6	C19	C20	H20	119.9
C19	C20	C21	120.2(4)	C21	C20	H20	119.9
C20	C21	H21	120.1	C22	C21	C20	119.7(4)
C22	C21	H21	120.1	C21	C22	H22	119.9

C21	C22	C23	120.3(4)	C23	C22	H22	119.9
C18	C23	H23	119.7	C22	C23	C18	120.6(4)
C22	C23	H23	119.7	N2	C24	H24A	109
N2	C24	H24B	109	N2	C24	C25	113.0(3)
H24A	C24	H24B	107.8	C25	C24	H24A	109
C25	C24	H24B	109	C26	C25	C24	117.9(3)
C26A	C25	C24	124.4(6)	C26A	C25	C30A	119.1(7)
C30	C25	C24	124.9(4)	C30	C25	C26	117.2(4)
C30A	C25	C24	115.1(5)	C25	C26	H26	120.2
C27	C26	C25	119.6(5)	C27	C26	H26	120.2
C25	C26A	H26A	119.3	C25	C26A	C27A	121.4(10)
C27A	C26A	H26A	119.3	C26	C27	H27	119.9
C28	C27	C26	120.2(5)	C28	C27	H27	119.9
C26A	C27A	H27A	119.8	C28A	C27A	C26A	120.4(10)
C28A	C27A	H27A	119.8	C27	C28	H28	119.9
C29	C28	C27	120.2(5)	C29	C28	H28	119.9
C27A	C28A	H28A	120.2	C29A	C28A	C27A	119.5(10)
C29A	C28A	H28A	120.2	C28	C29	H29	120
C28	C29	C30	119.9(6)	C30	C29	H29	120
C28A	C29A	H29A	119.8	C28A	C29A	C30A	120.4(9)
C30A	C29A	H29A	119.8	C25	C30	C29	122.8(5)
C25	C30	H30	118.6	C29	C30	H30	118.6
C25	C30A	H30A	120.6	C29A	C30A	C25	118.7(8)
C29A	C30A	H30A	120.6	O3	C63	N2	124.6(3)
O3	C63	C13	128.7(3)	N2	C63	C13	106.6(3)
O2	C64	N2	124.9(3)	O2	C64	C12	129.5(3)
N2	C64	C12	105.6(3)	C38	N4	C37	123.6(3)
C41	N4	C37	123.5(3)	C41	N4	C38	112.1(3)
C46	N5	C47	111.9(2)	C46	N5	C48	124.7(3)
C47	N5	C48	123.2(3)	C43	N6	H6	118.4
C43	N6	C55	123.2(3)	C55	N6	H6	118.4
C32	C31	H31	120.1	C36	C31	H31	120.1
C36	C31	C32	119.7(4)	C31	C32	H32	119.3
C33	C32	C31	121.5(4)	C33	C32	H32	119.3
C32	C33	H33	120.4	C34	C33	C32	119.3(4)
C34	C33	H33	120.4	C33	C34	H34	120
C33	C34	C35	119.9(4)	C35	C34	H34	120
C34	C35	H35	119.5	C36	C35	C34	121.0(4)
C36	C35	H35	119.5	C31	C36	C35	118.5(4)
C31	C36	C37	123.2(3)	C35	C36	C37	118.2(3)
N4	C37	C36	115.1(3)	N4	C37	H37A	108.5
N4	C37	H37B	108.5	C36	C37	H37A	108.5
C36	C37	H37B	108.5	H37A	C37	H37B	107.5

O6	C38	N4	123.5(3)	O6	C38	C39	130.8(3)
N4	C38	C39	105.6(3)	C40	C39	C38	108.3(3)
C45	C39	C38	134.9(3)	C45	C39	C40	116.5(3)
C39	C40	C41	107.5(3)	C42	C40	C39	125.8(3)
C42	C40	C41	126.6(3)	O5	C41	N4	125.6(3)
O5	C41	C40	128.1(3)	N4	C41	C40	106.3(3)
C40	C42	H42	121	C40	C42	C43	118.0(3)
C43	C42	H42	121	N6	C43	C42	122.4(3)
N6	C43	C44	121.4(3)	C44	C43	C42	116.2(3)
C43	C44	C47	127.2(3)	C45	C44	C43	123.8(3)
C45	C44	C47	108.9(3)	C39	C45	C44	119.5(3)
C39	C45	C46	133.1(3)	C44	C45	C46	107.4(3)
O7	C46	N5	125.0(3)	O7	C46	C45	129.2(3)
N5	C46	C45	105.8(3)	O8	C47	N5	125.4(3)
O8	C47	C44	128.7(3)	N5	C47	C44	105.9(3)
N5	C48	H48A	108.7	N5	C48	H48B	108.7
N5	C48	C49	114.2(3)	H48A	C48	H48B	107.6
C49	C48	H48A	108.7	C49	C48	H48B	108.7
C50	C49	C48	120.2(4)	C50A	C49	C48	130.7(6)
C50A	C49	C54A	111.6(8)	C54	C49	C48	118.2(4)
C54	C49	C50	120.9(4)	C54A	C49	C48	117.0(5)
C49	C50	H50	120.6	C51	C50	C49	118.8(5)
C51	C50	H50	120.6	C49	C50A	H50A	117.9
C49	C50A	C51A	124.2(11)	C51A	C50A	H50A	117.9
C50	C51	H51	119.5	C52	C51	C50	121.0(5)
C52	C51	H51	119.5	C50A	C51A	H51A	118.7
C52A	C51A	C50A	122.6(12)	C52A	C51A	H51A	118.7
C51	C52	H52	120.1	C51	C52	C53	119.7(5)
C53	C52	H52	120.1	C51A	C52A	H52A	120.9
C51A	C52A	C53A	118.2(12)	C53A	C52A	H52A	120.9
C52	C53	H53	120.3	C54	C53	C52	119.4(5)
C54	C53	H53	120.3	C52A	C53A	H53A	120.3
C52A	C53A	C54A	119.5(12)	C54A	C53A	H53A	120.3
C49	C54	C53	119.9(5)	C49	C54	H54	120
C53	C54	H54	120	C49	C54A	H54A	118.5
C53A	C54A	C49	122.9(10)	C53A	C54A	H54A	118.5
N6	C55	H55A	109.8	N6	C55	H55B	109.8
N6	C55	C56	109.4(3)	H55A	C55	H55B	108.2
C56	C55	H55A	109.8	C56	C55	H55B	109.8
C55	C56	H56A	109.1	C55	C56	H56B	109.1
H56A	C56	H56B	107.8	C57	C56	C55	112.6(3)
C57	C56	H56A	109.1	C57	C56	H56B	109.1
C58	C57	C56	121.1(3)	C58	C57	C62	118.6(3)

C62	C57	C56	120.3(3)	C57	C58	H58	119.8
C57	C58	C59	120.4(3)	C59	C58	H58	119.8
C58	C59	H59	120	C61	C59	C58	120.0(4)
C61	C59	H59	120	C61	C60	H60	120.3
C61	C60	C62	119.4(4)	C62	C60	H60	120.3
C59	C61	H61	119.8	C60	C61	C59	120.4(4)
C60	C61	H61	119.8	C57	C62	H62	119.4
C60	C62	C57	121.1(3)	C60	C62	H62	119.4

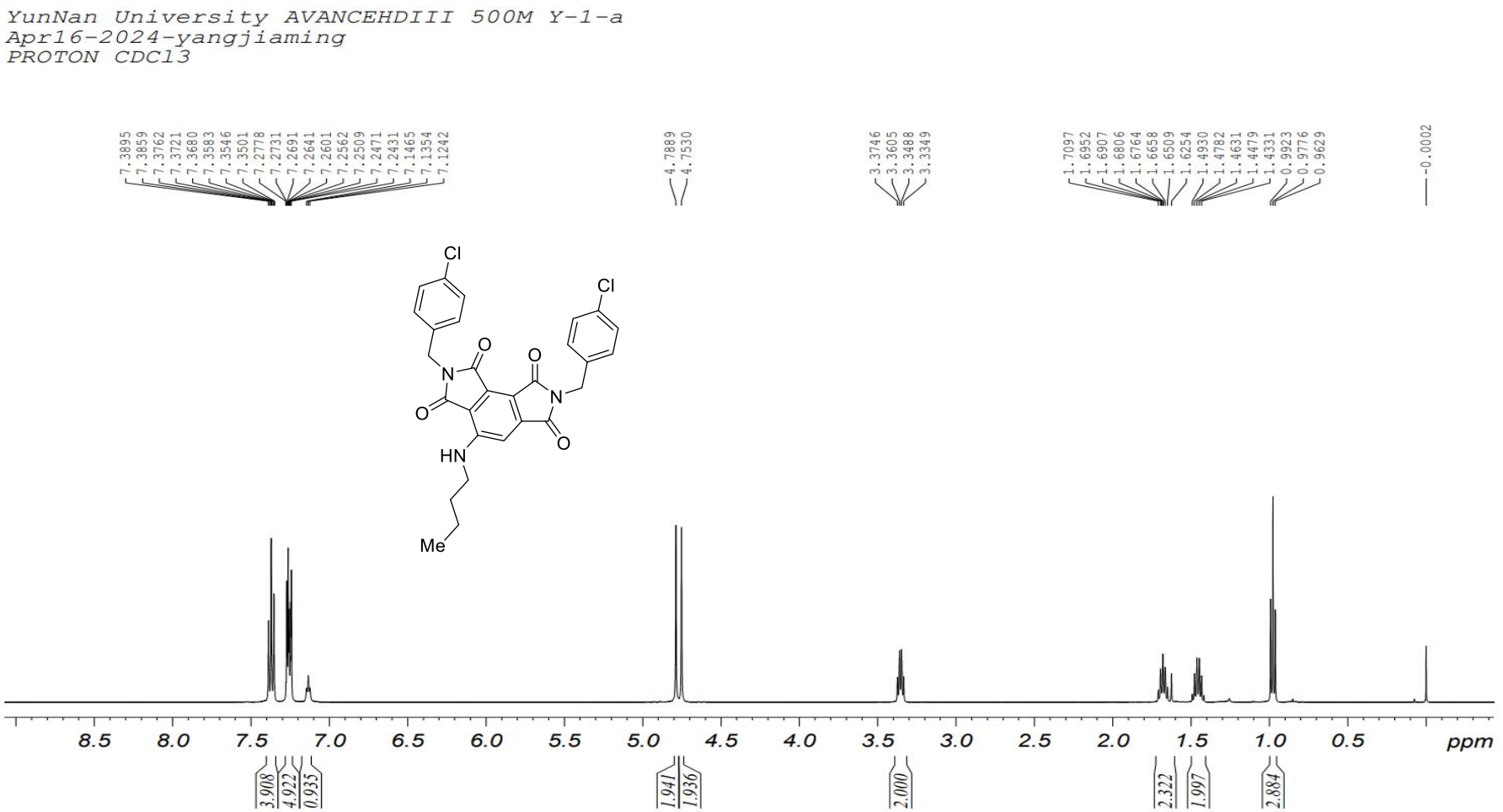


Figure S2. ^{1}H NMR (500 MHz, $CDCl_3$) spectra of compound **3a**

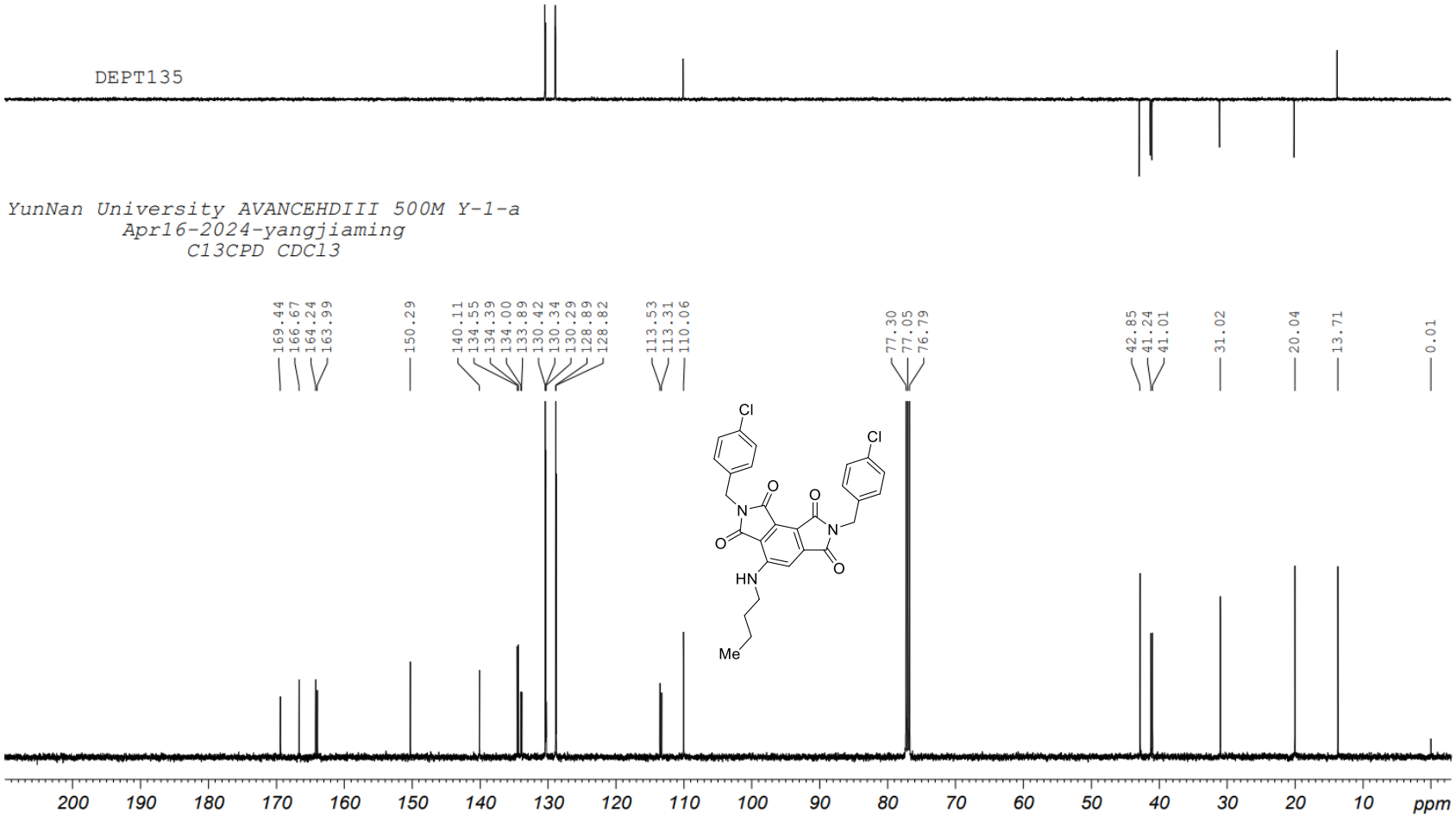


Figure S3. ^{13}C NMR (125 MHz, $CDCl_3$) spectra of compound **3a**

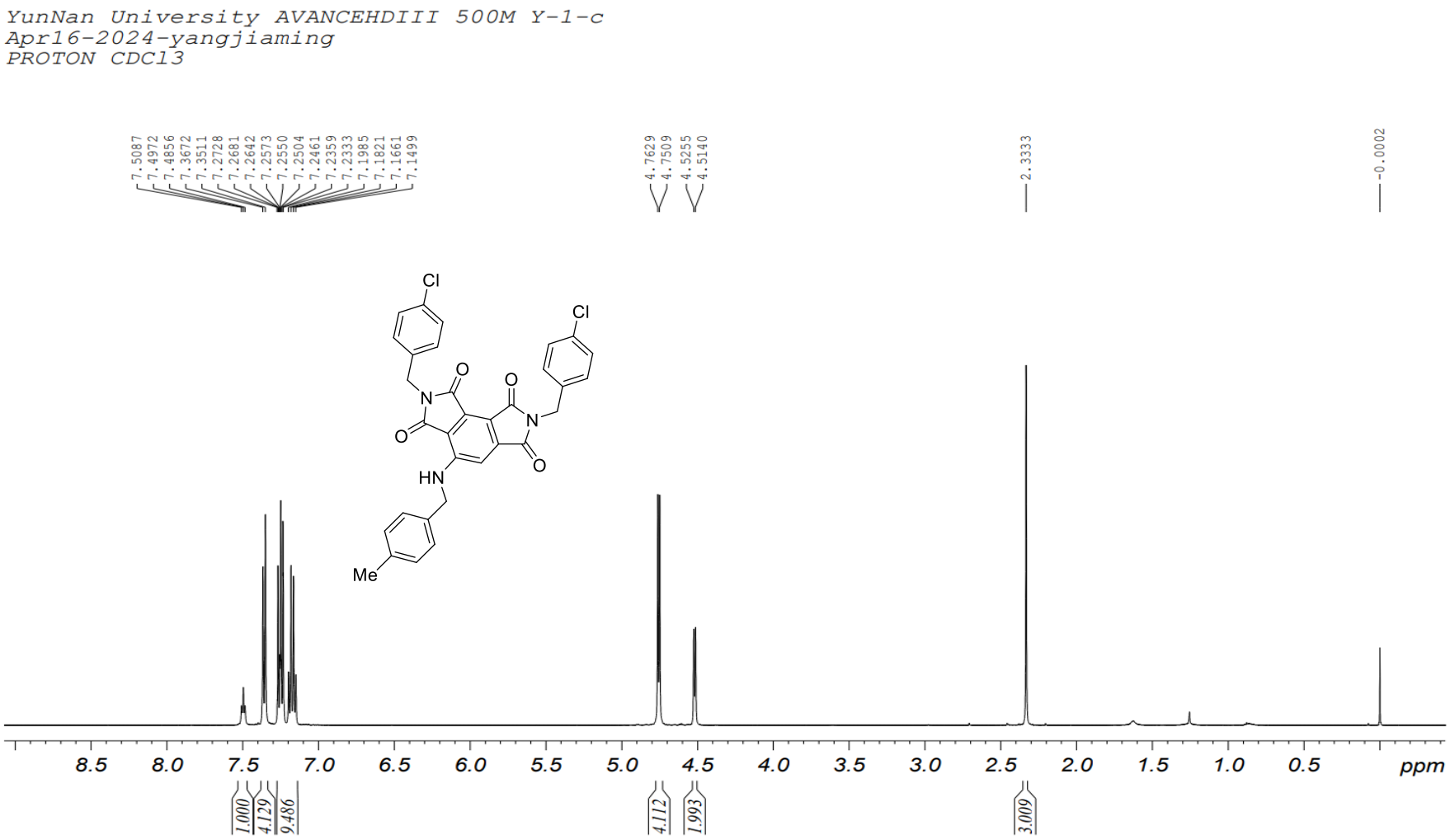


Figure S4. ^{1}H NMR (500 MHz, $CDCl_3$) spectra of compound **3b**

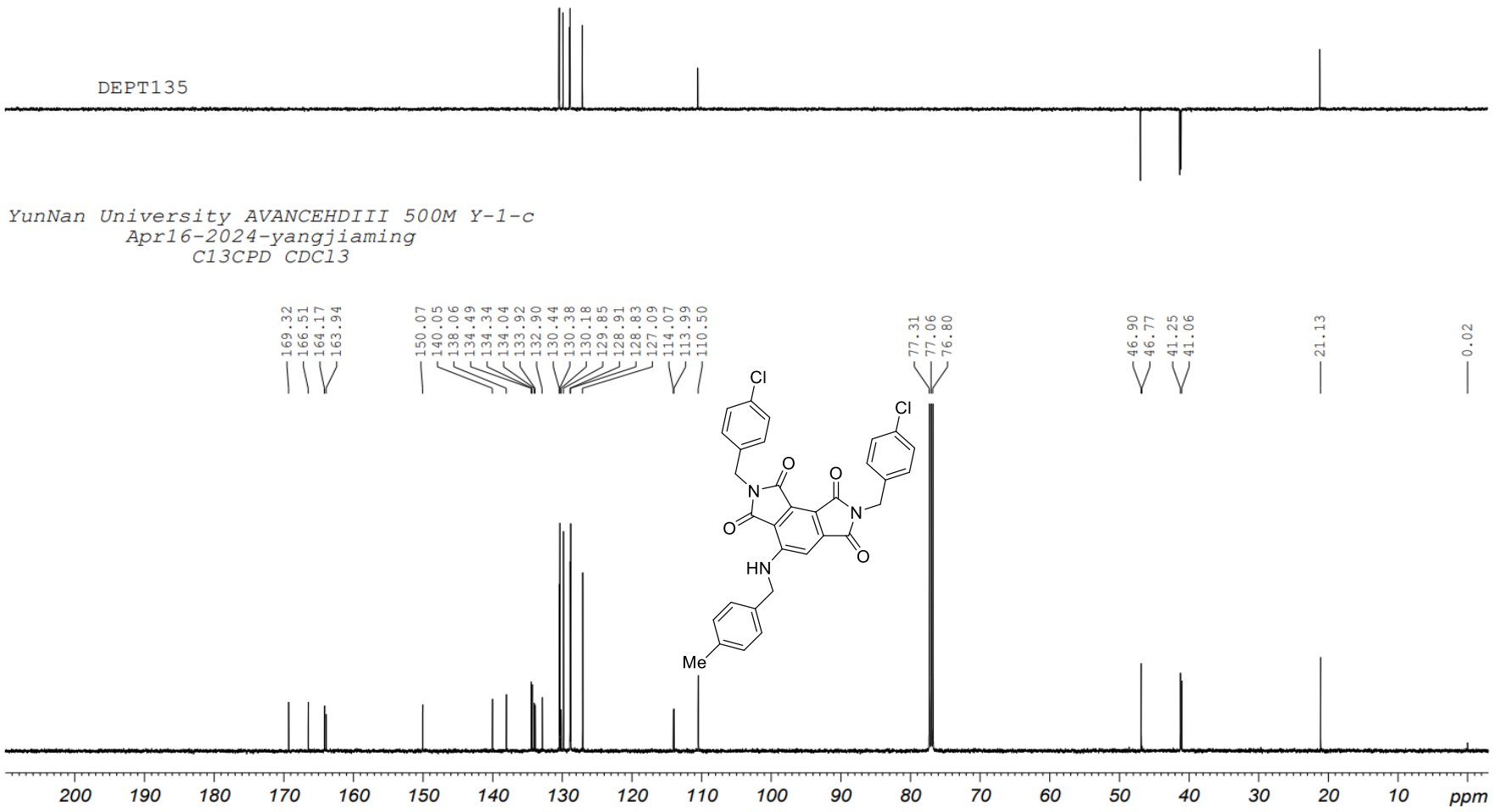


Figure S5. ^{13}C NMR (125 MHz, $CDCl_3$) spectra of compound **3b**

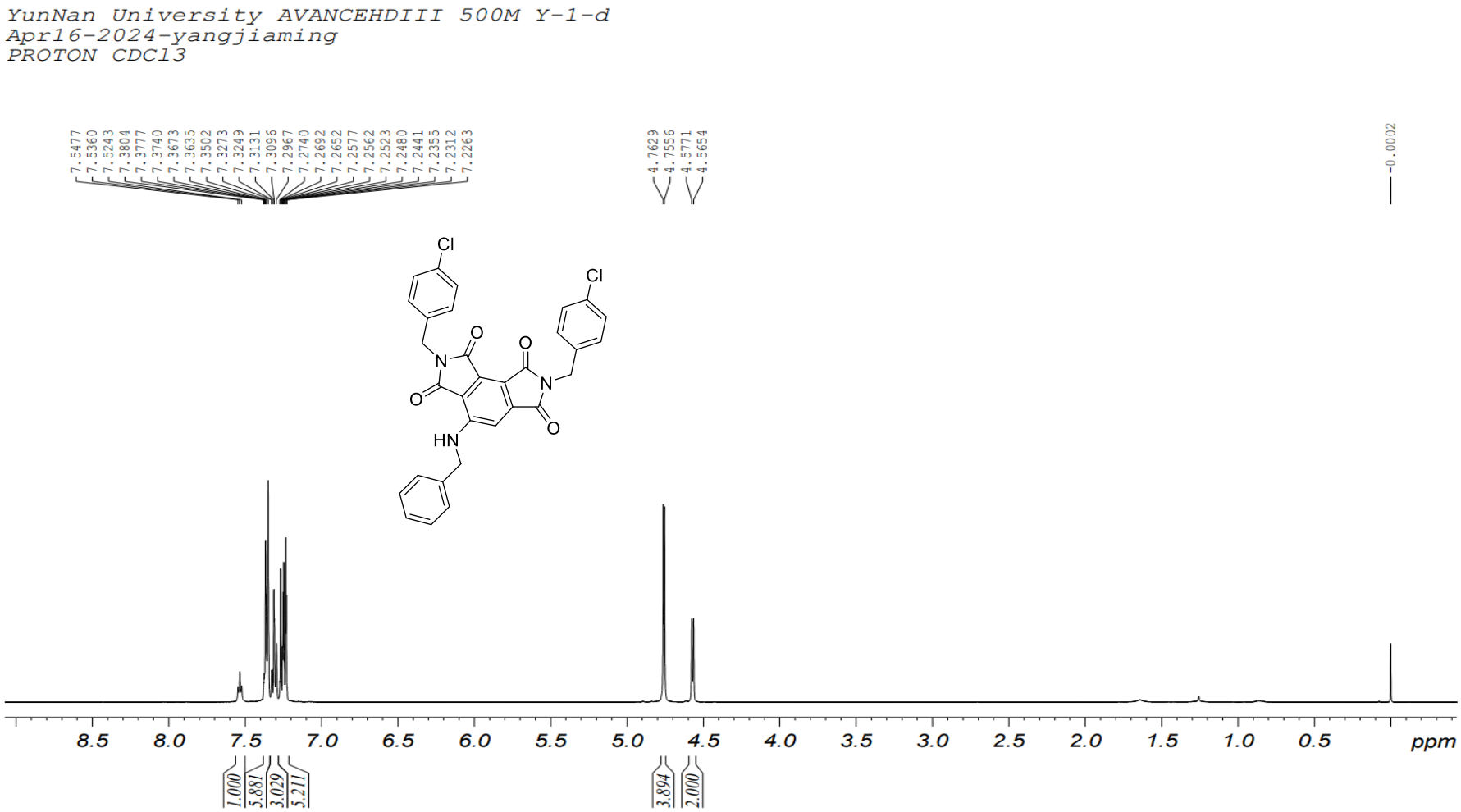


Figure S6. ^{1}H NMR (500 MHz, $CDCl_3$) spectra of compound **3c**

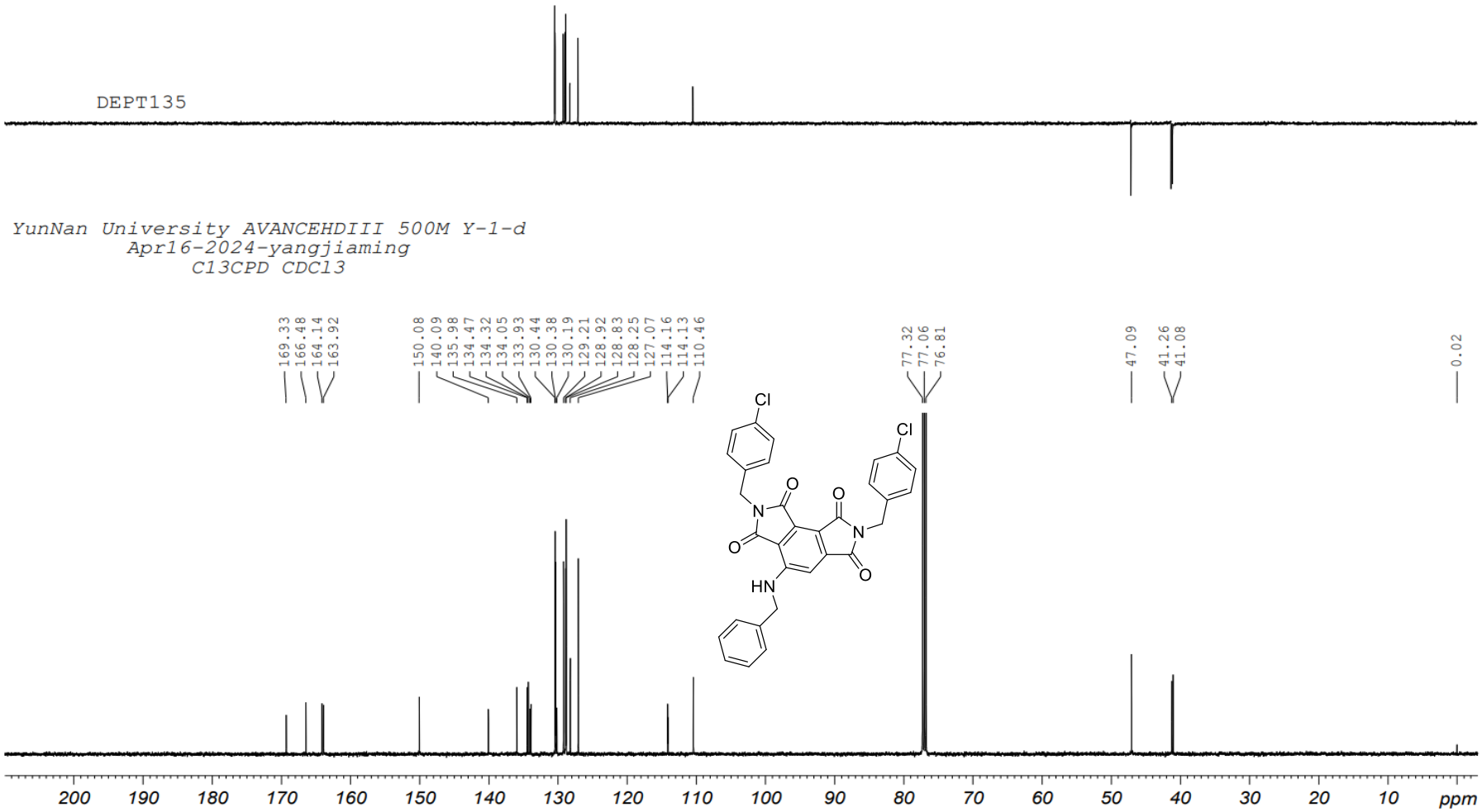


Figure S7. ^{13}C NMR (125 MHz, $CDCl_3$) spectra of compound **3c**

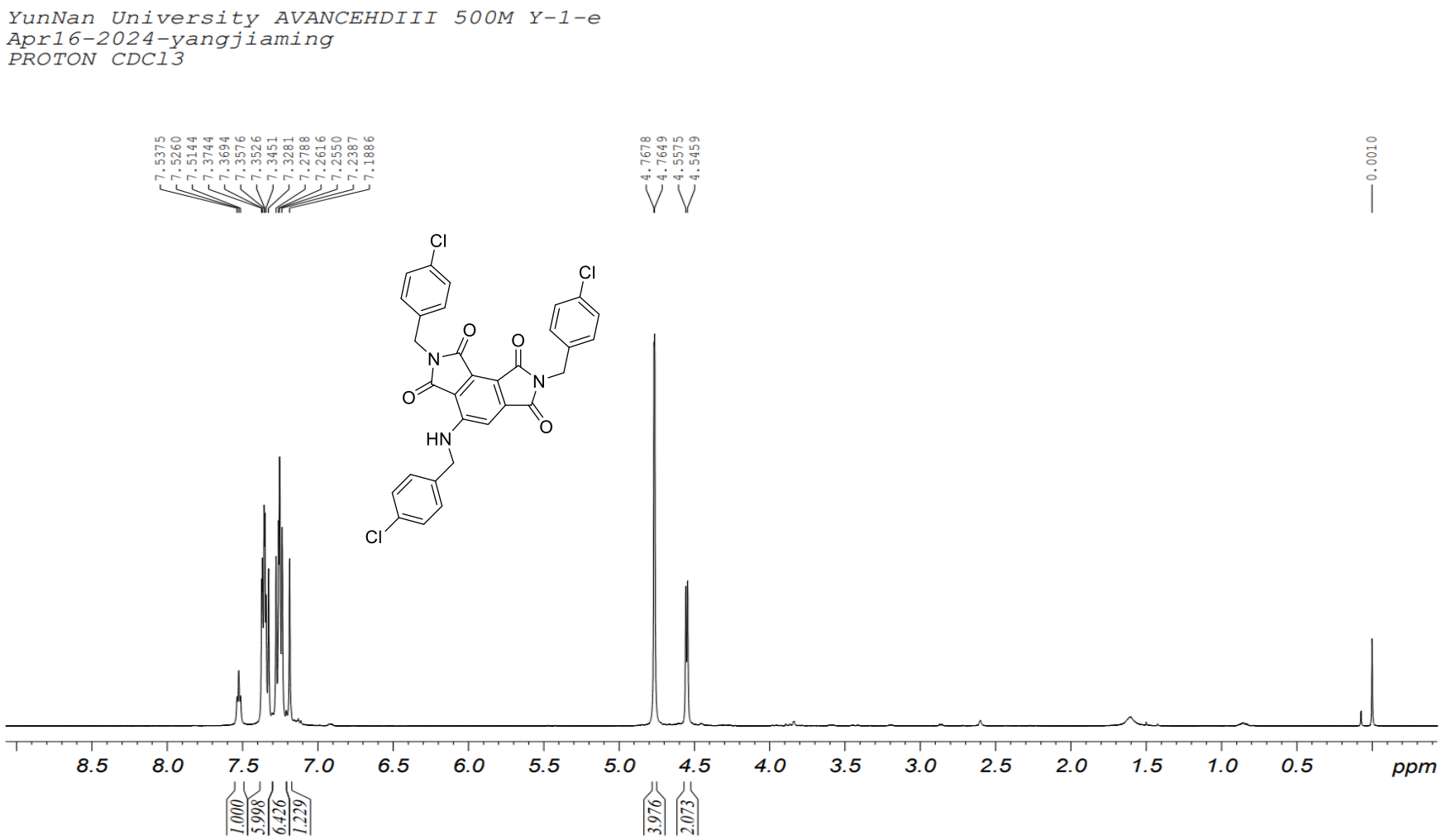


Figure S8. ^{1}H NMR (500 MHz, $CDCl_3$) spectra of compound **3d**

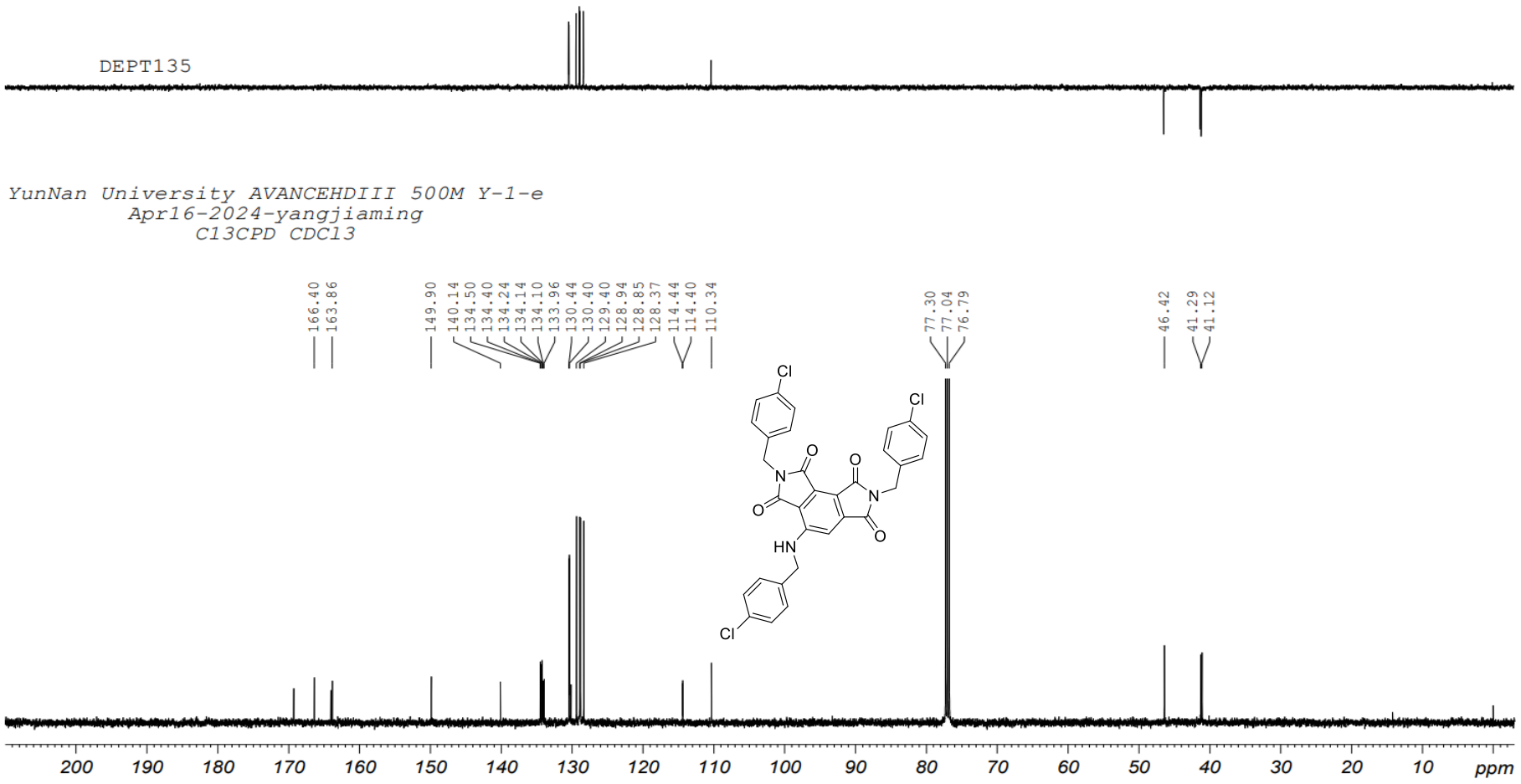


Figure S9. ^{13}C NMR (125 MHz, $CDCl_3$) spectra of compound **3d**

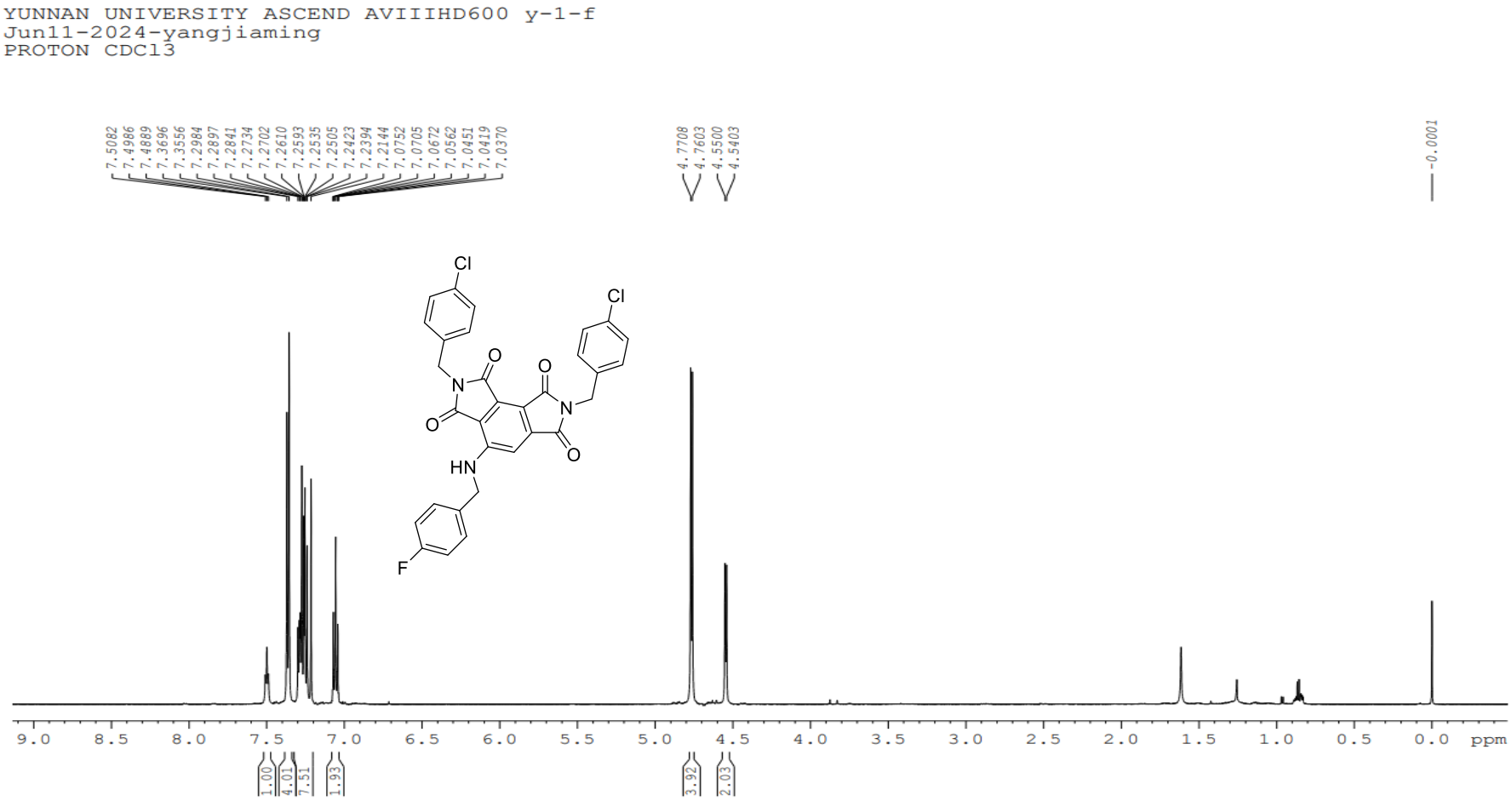


Figure S10. ^{1}H NMR (600 MHz, $CDCl_3$) spectra of compound **3e**

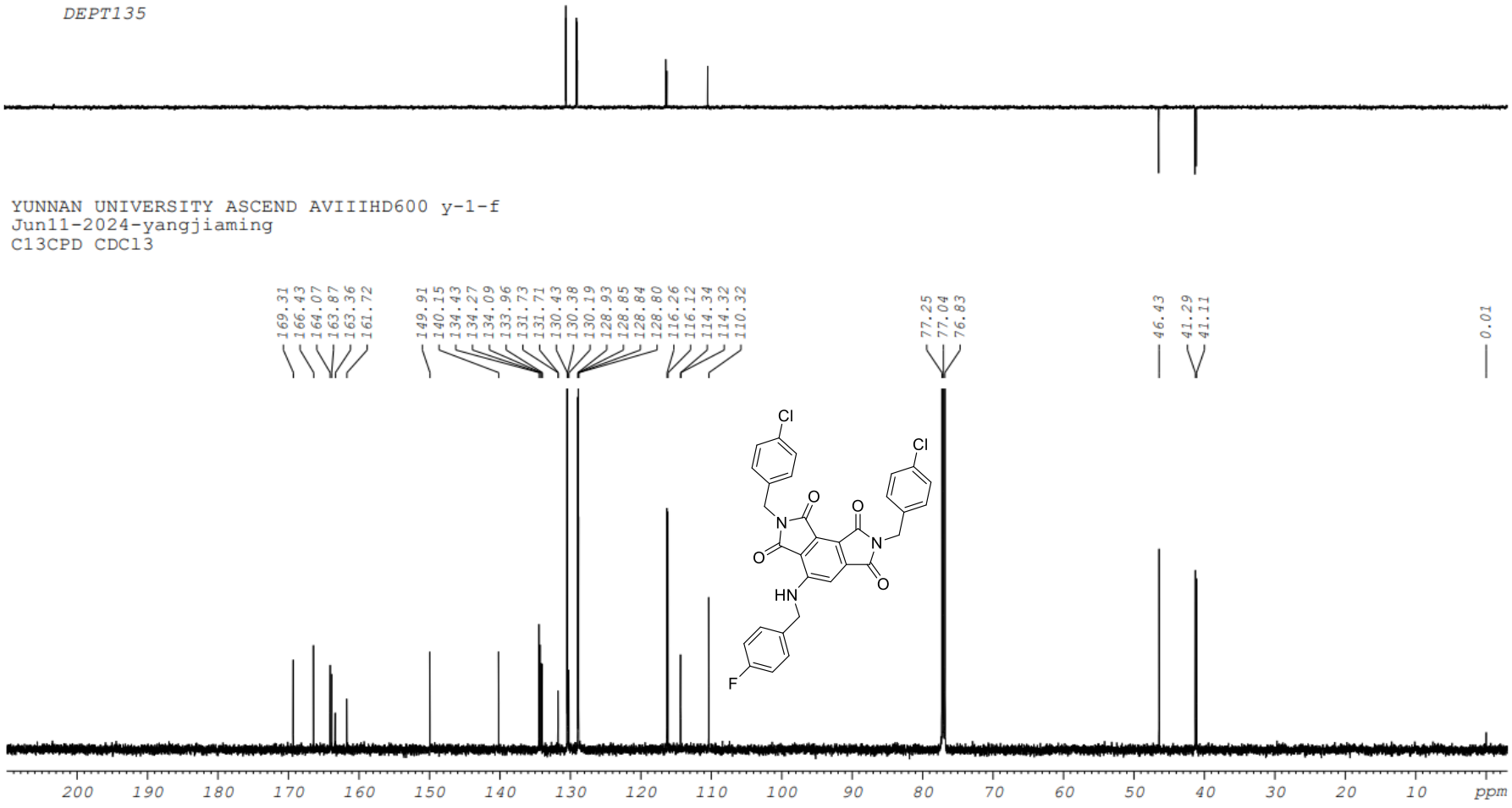


Figure S11. ^{13}C NMR (150 MHz, $CDCl_3$) spectra of compound **3e**

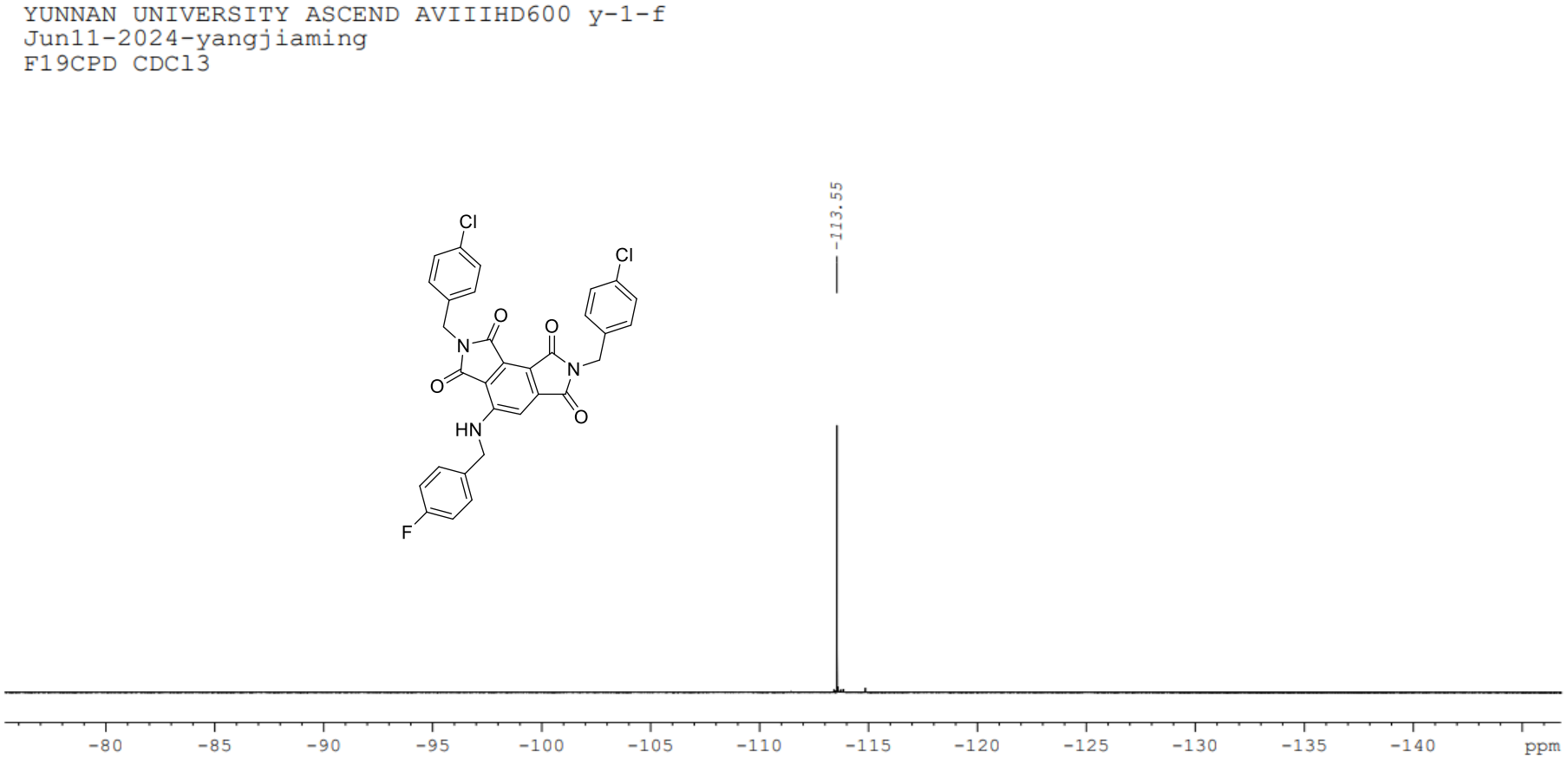


Figure S12. ^{19}F NMR (564 MHz, $CDCl_3$) spectra of compound **3e**

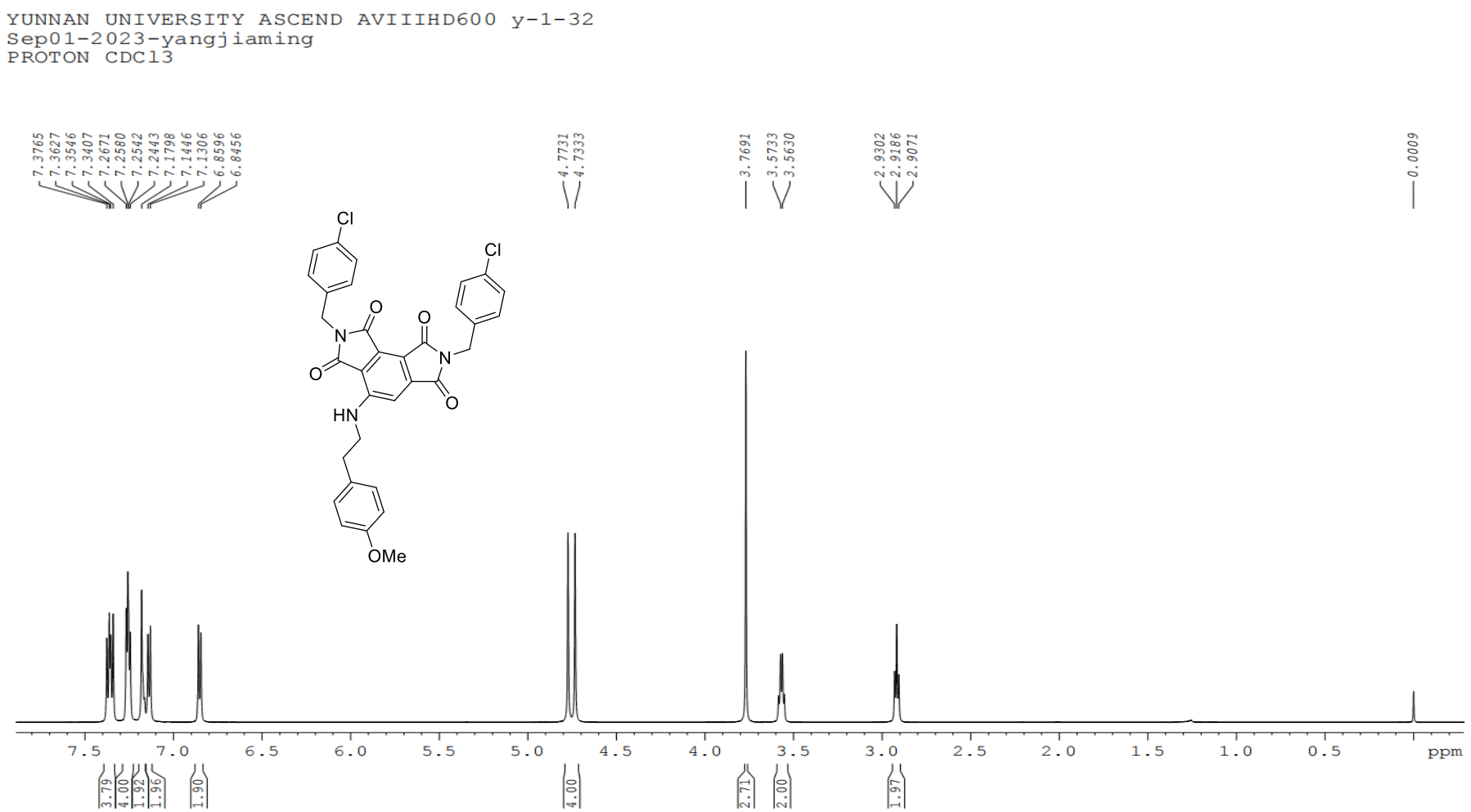


Figure S13. ^{1}H NMR (600 MHz, $CDCl_3$) spectra of compound **3f**

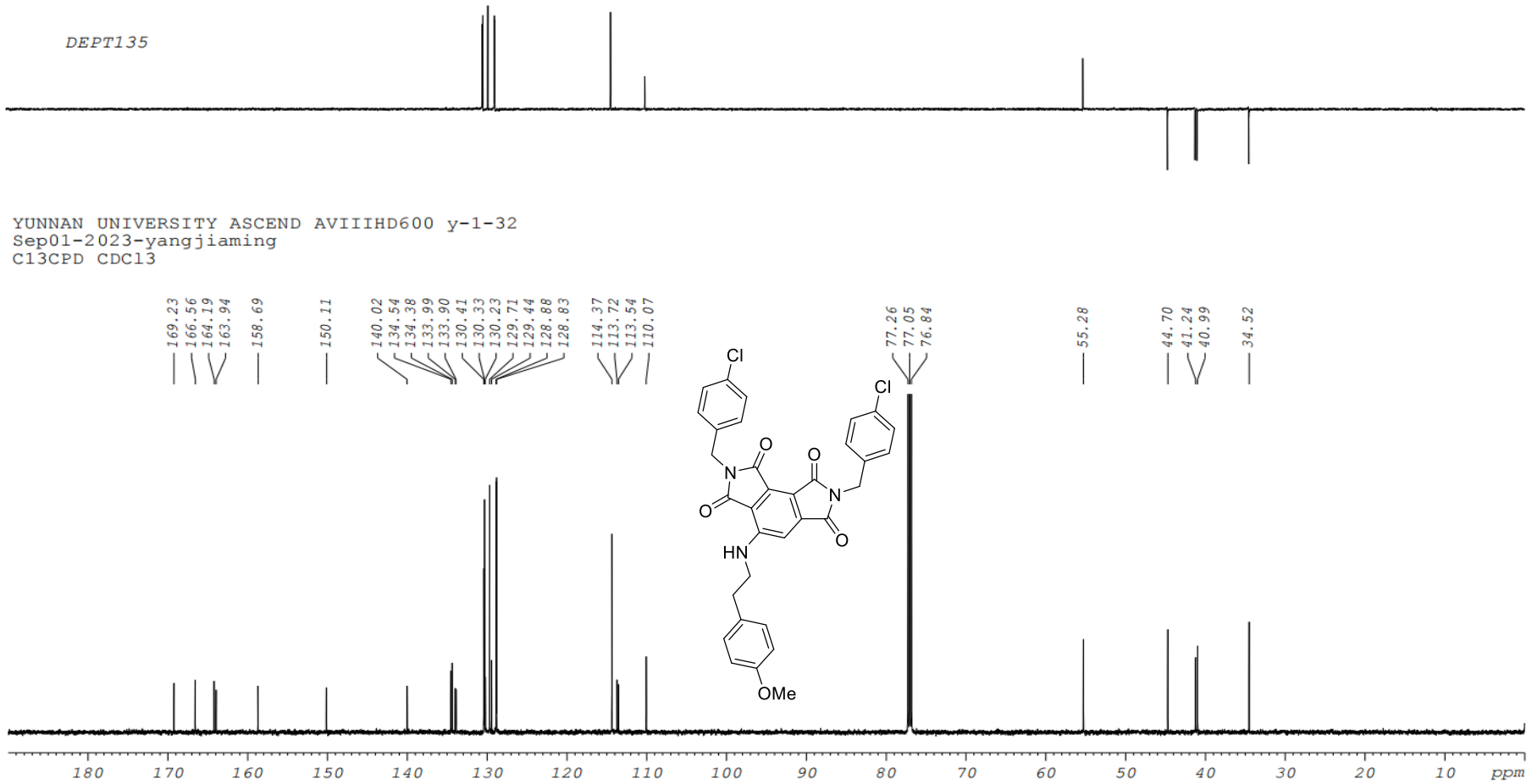


Figure S14. ^{13}C NMR (150 MHz, $CDCl_3$) spectra of compound **3f**

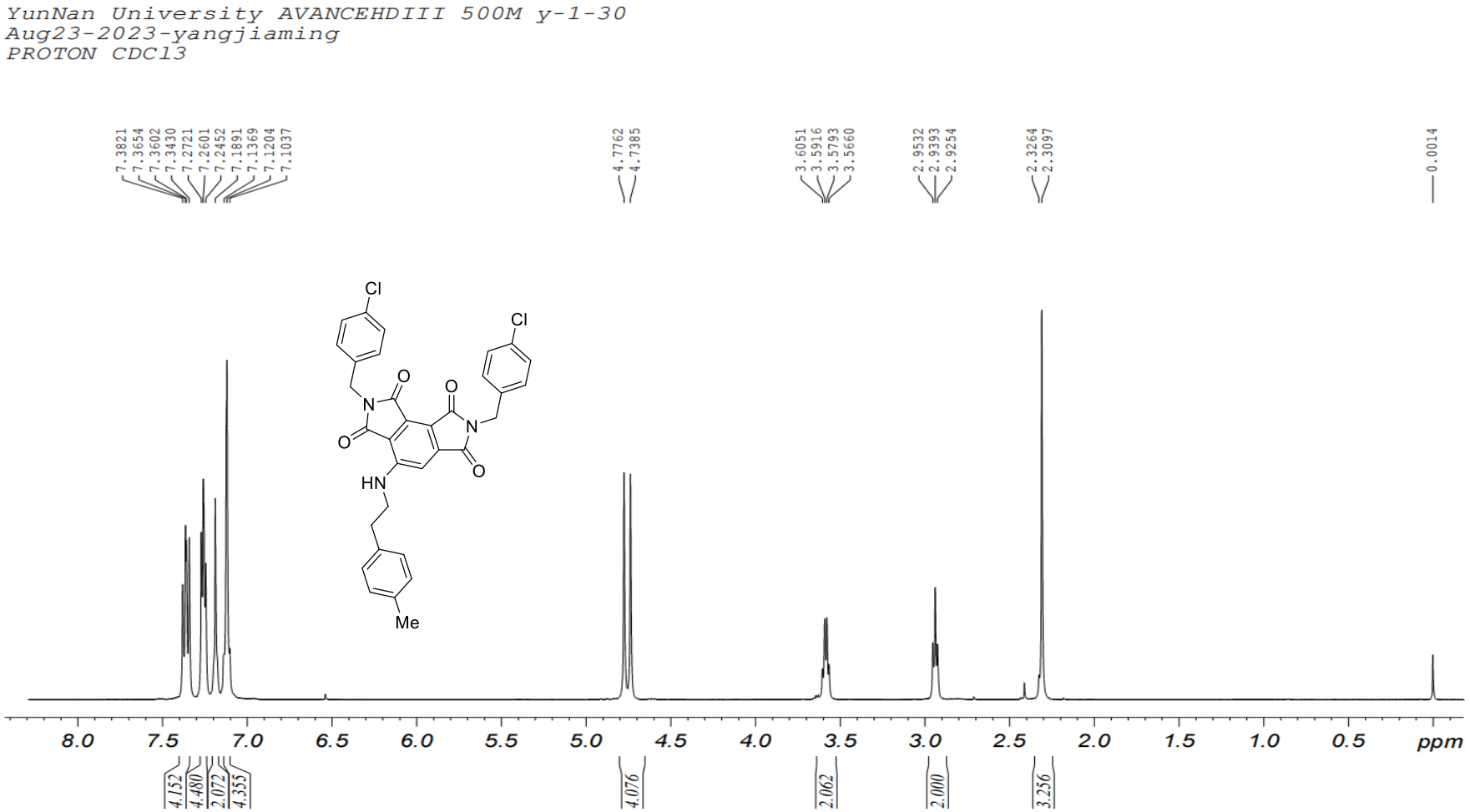


Figure S15. ^{1}H NMR (500 MHz, $CDCl_3$) spectra of compound **3g**

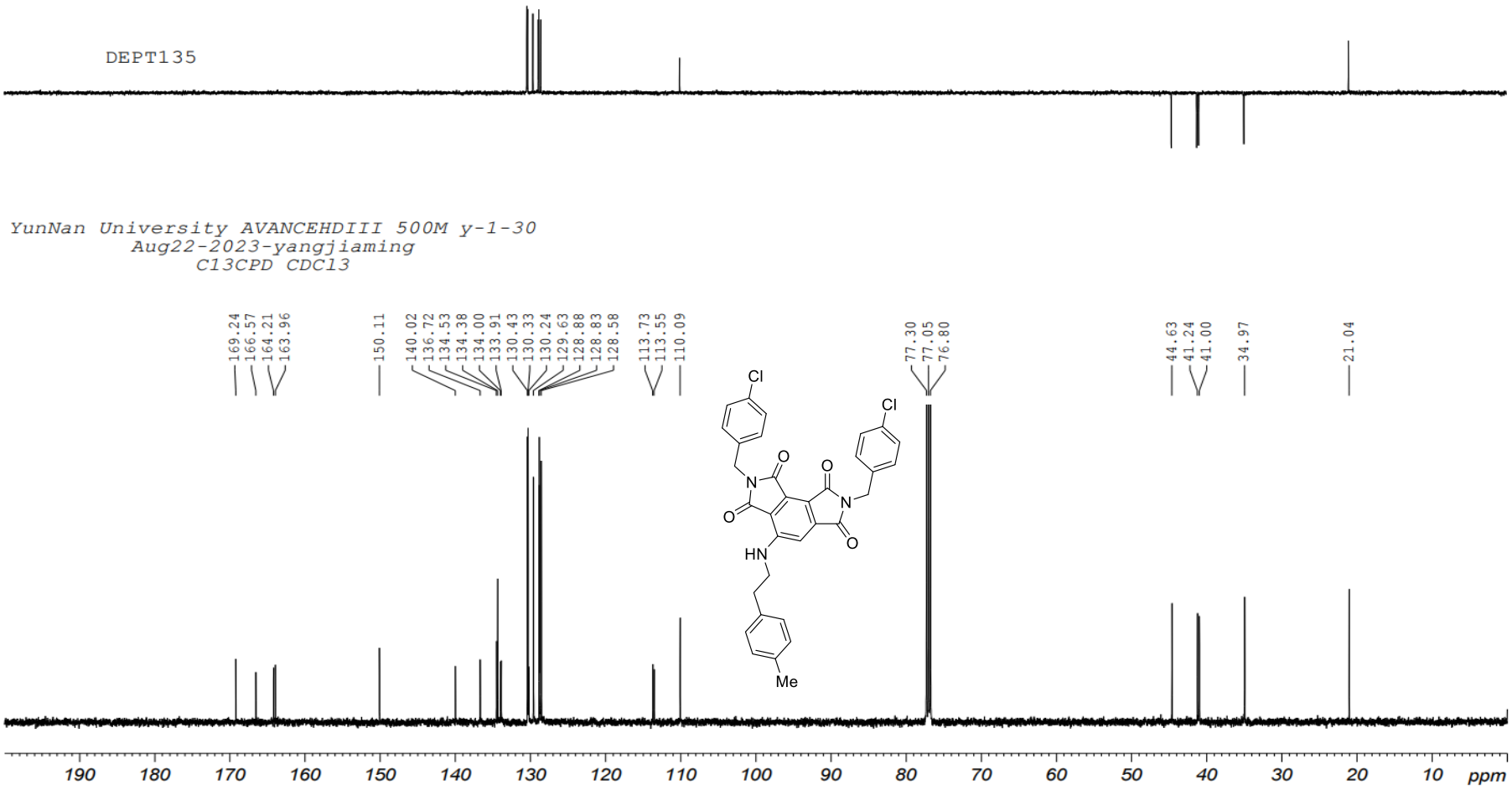


Figure S16. ^{13}C NMR (125 MHz, $CDCl_3$) spectra of compound **3g**

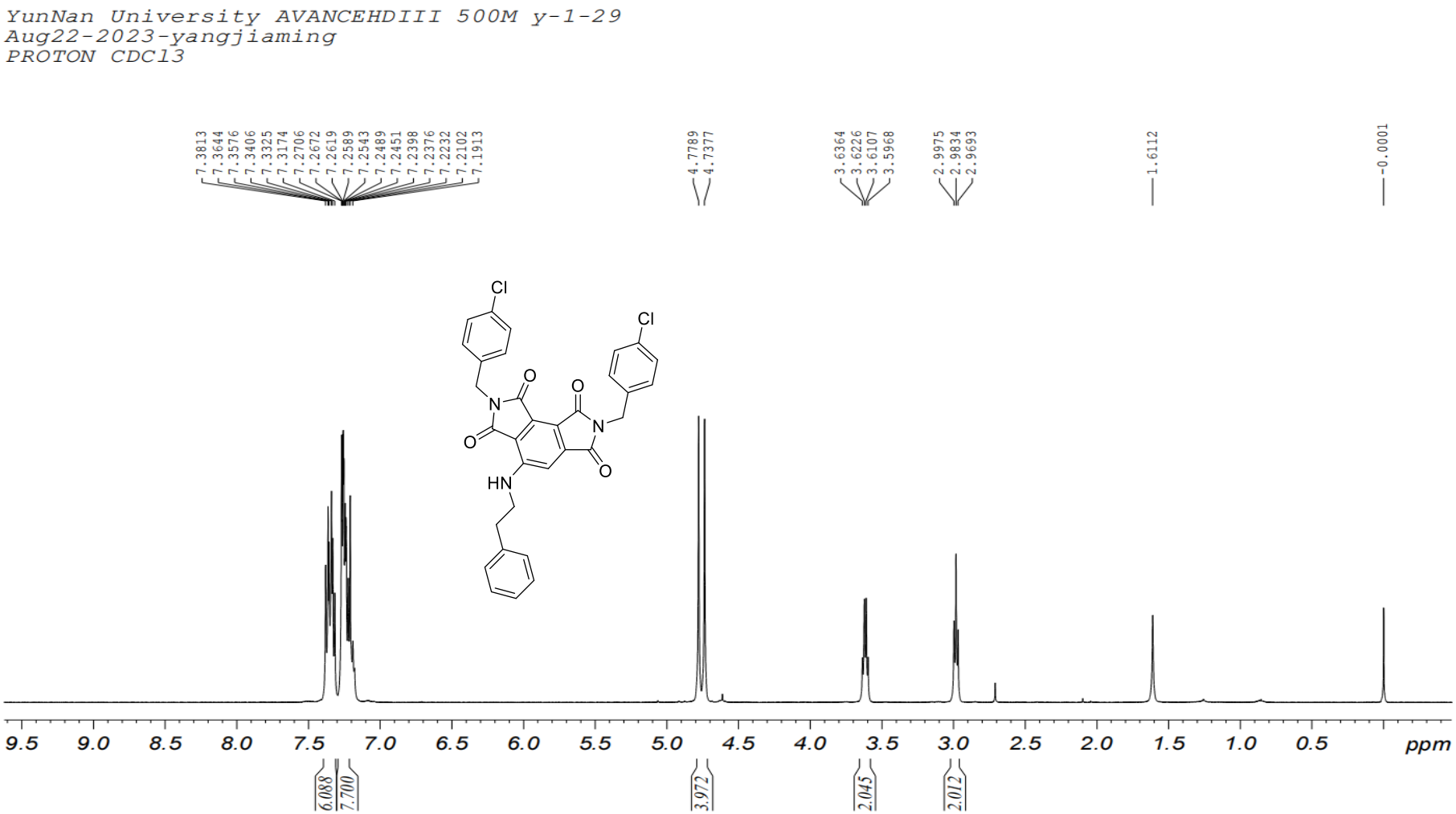


Figure S17. ^{1}H NMR (500 MHz, $CDCl_3$) spectra of compound **3h**

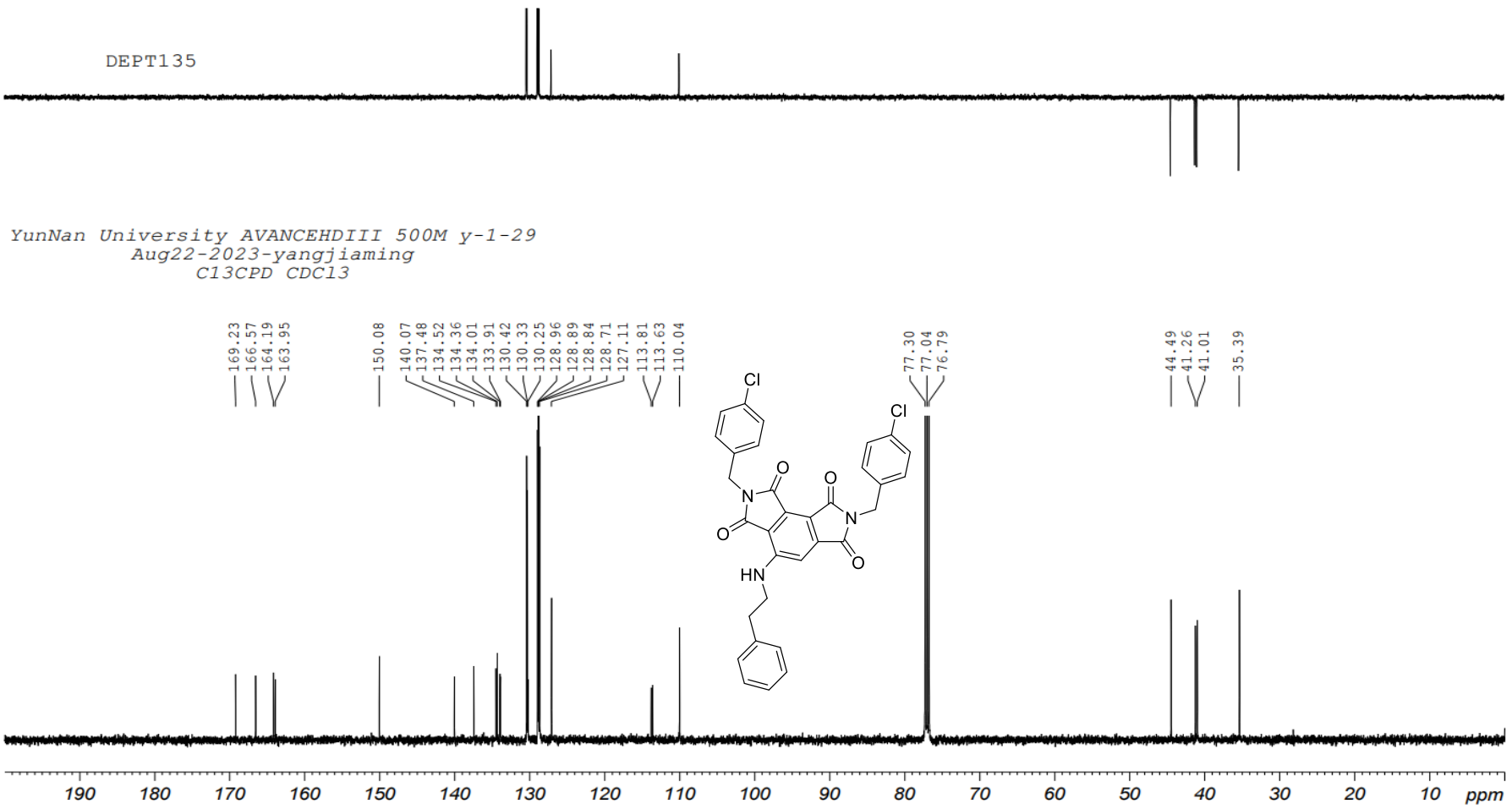


Figure S18. ^{13}C NMR (125 MHz, $CDCl_3$) spectra of compound **3h**

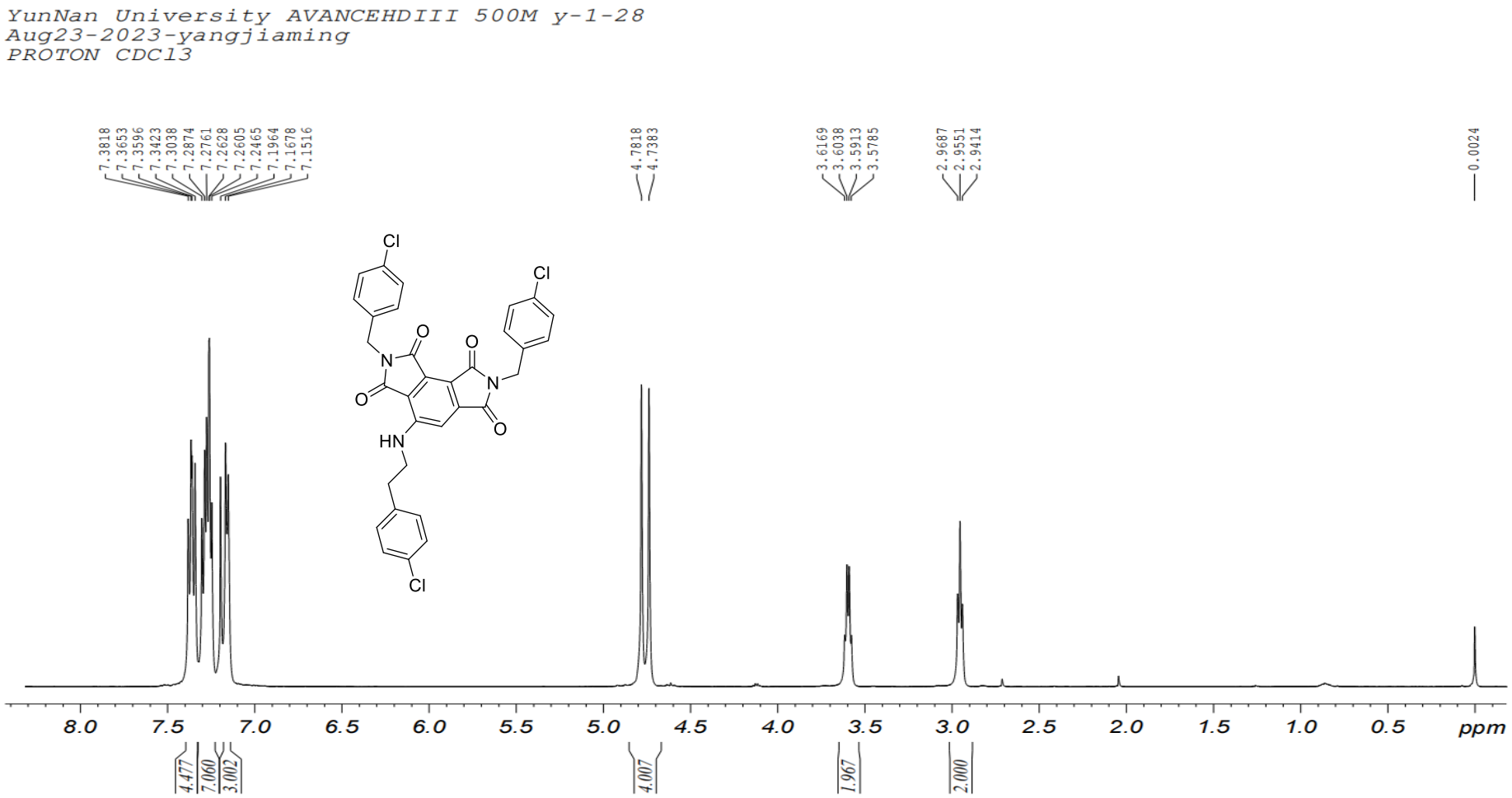


Figure S19. ^{1}H NMR (500 MHz, $CDCl_3$) spectra of compound **3i**

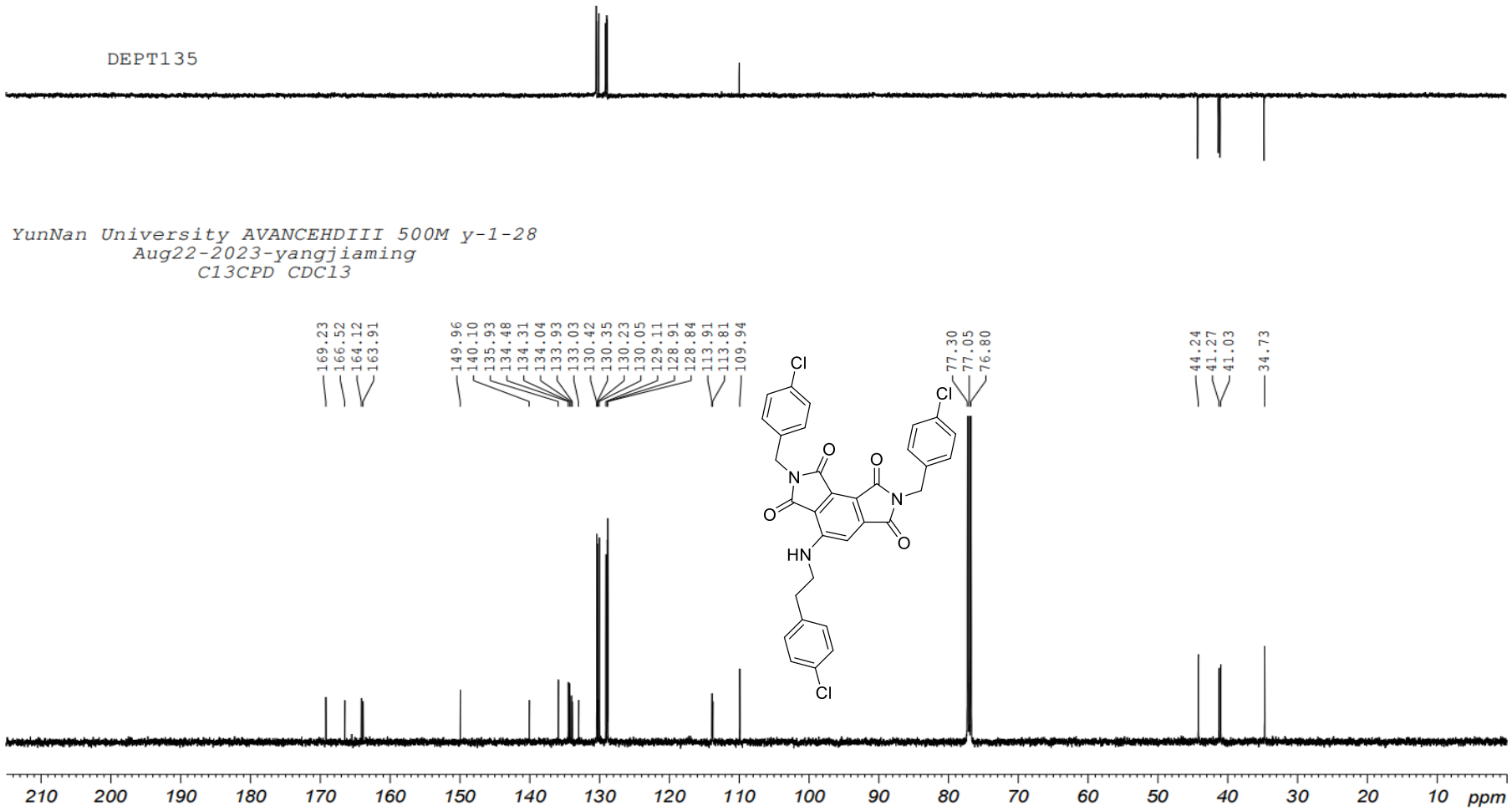


Figure S20. ^{13}C NMR (125 MHz, $CDCl_3$) spectra of compound **3i**

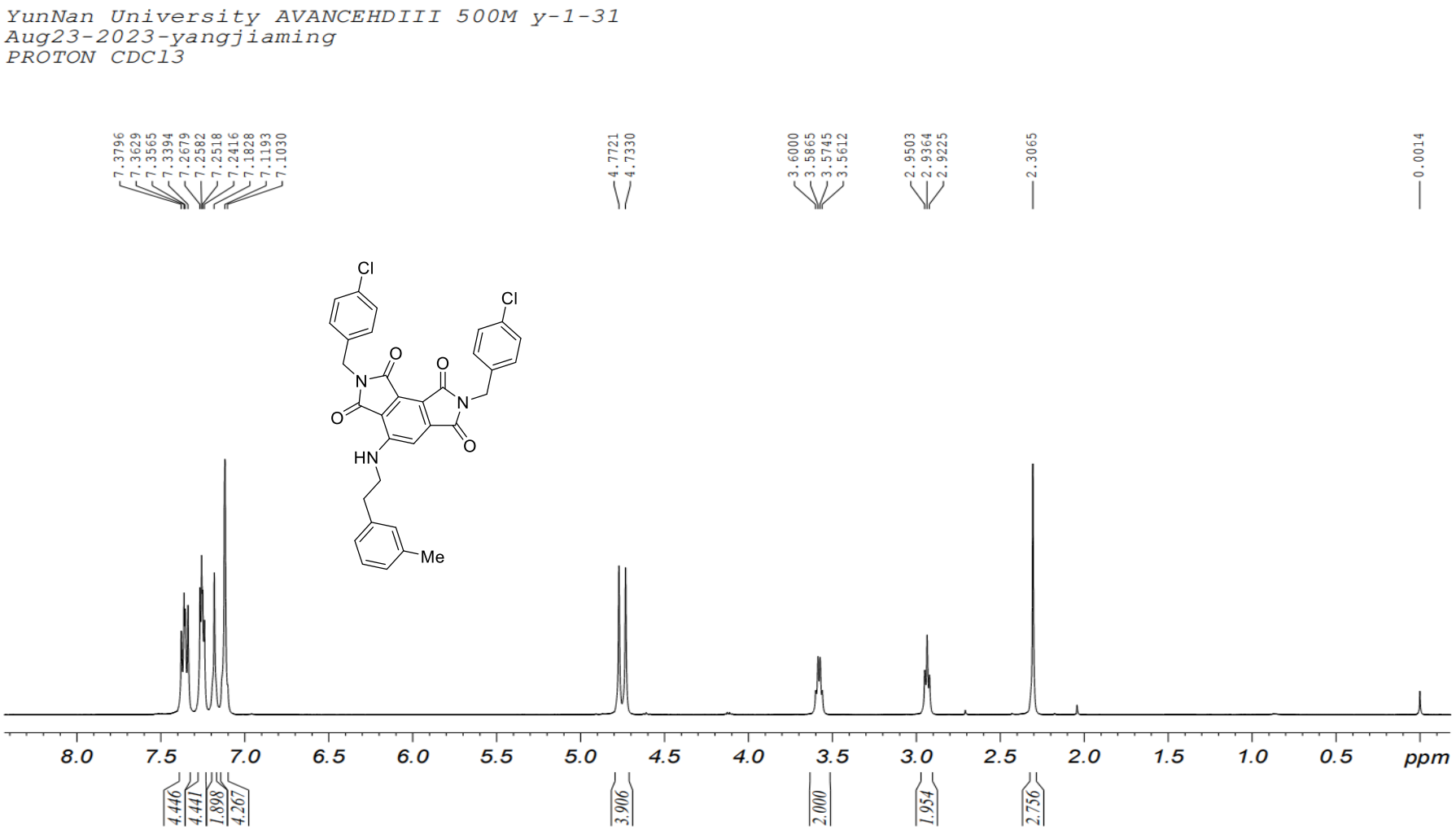


Figure S21. ^{1}H NMR (500 MHz, $CDCl_3$) spectra of compound **3j**

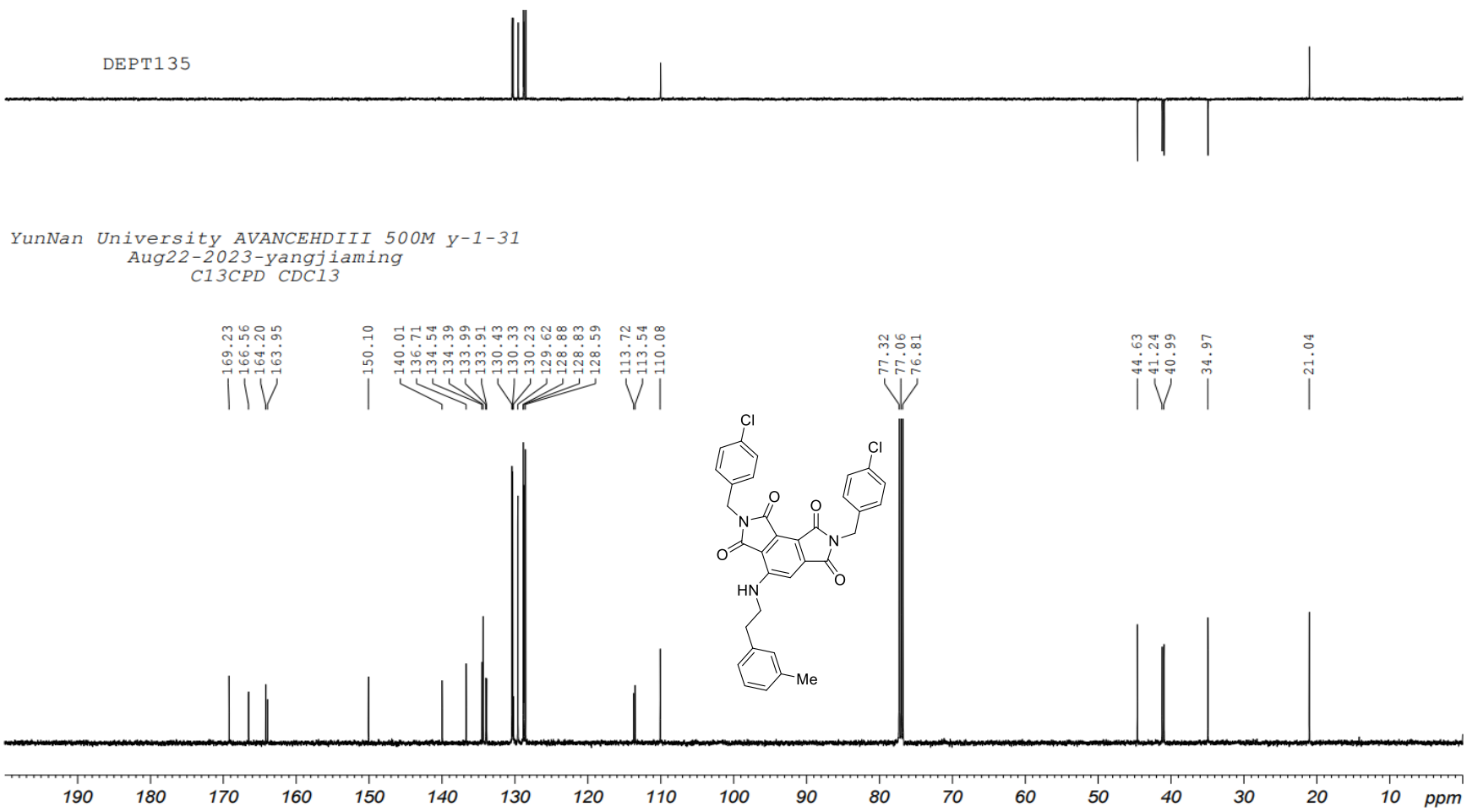


Figure S22. ^{13}C NMR (125 MHz, $CDCl_3$) spectra of compound **3j**

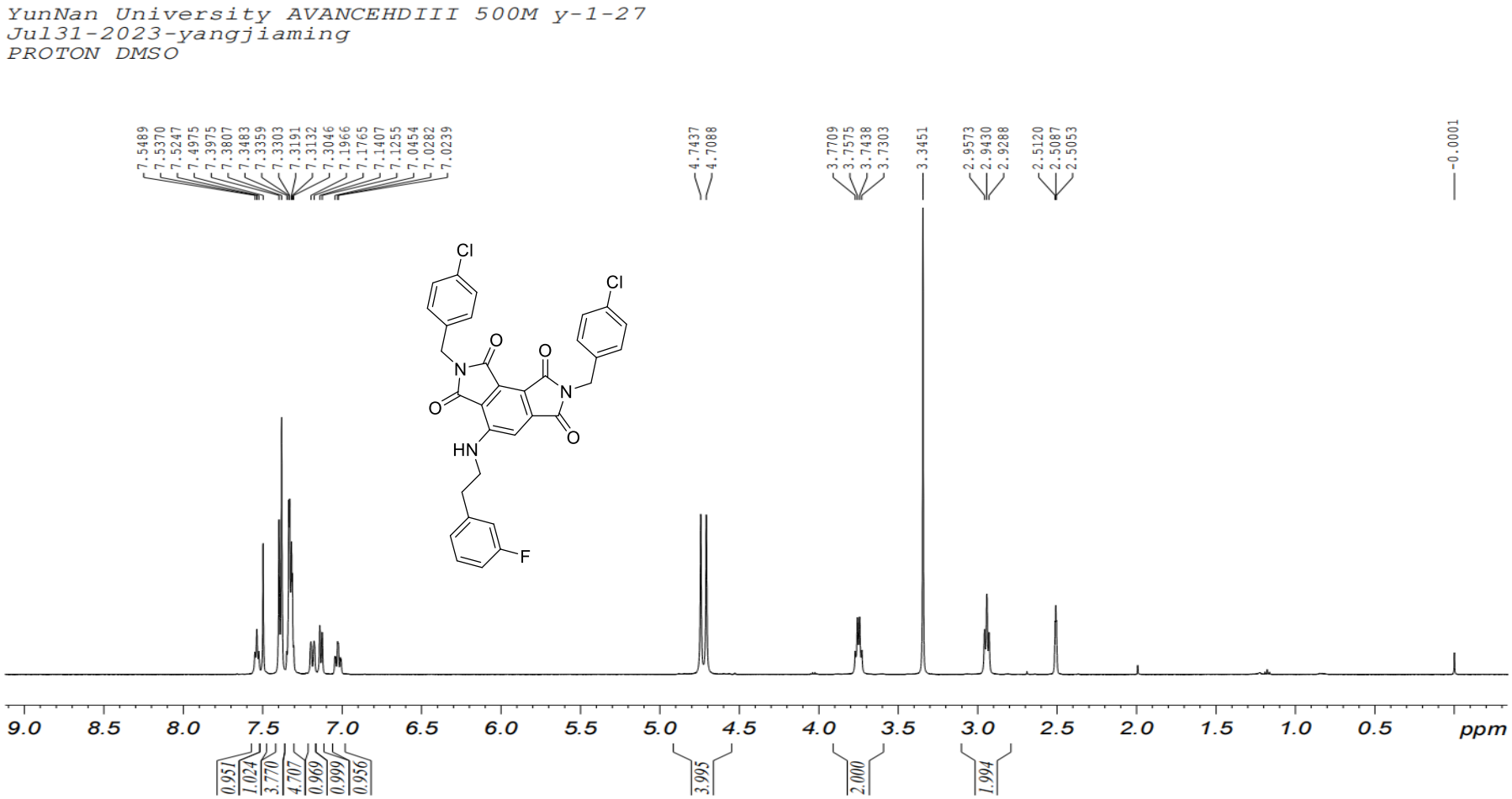


Figure S23. ^{1}H NMR (500 MHz, DMSO-d_6) spectra of compound **3k**

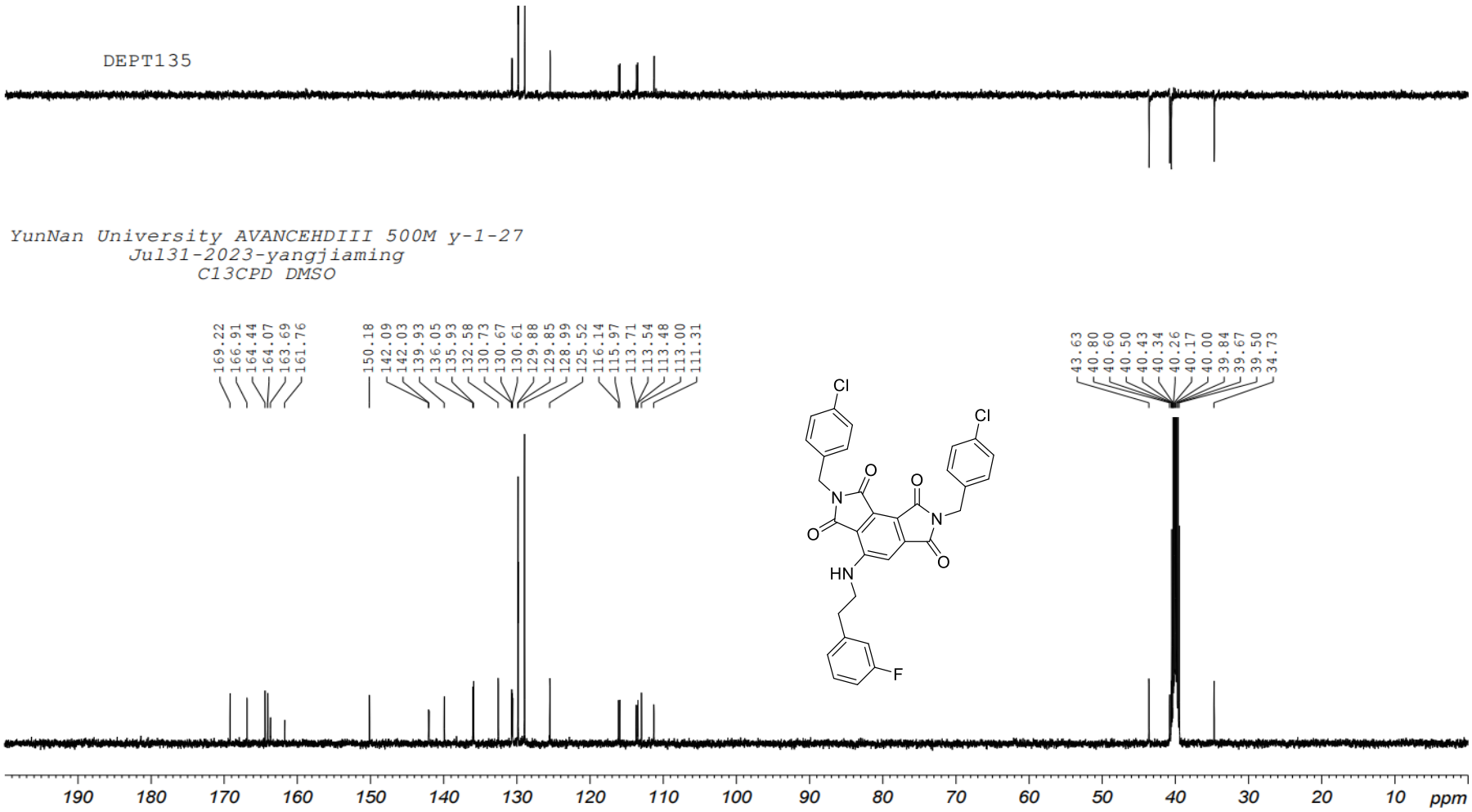


Figure S24. ^{13}C NMR (125 MHz, DMSO-d_6) spectra of compound **3k**

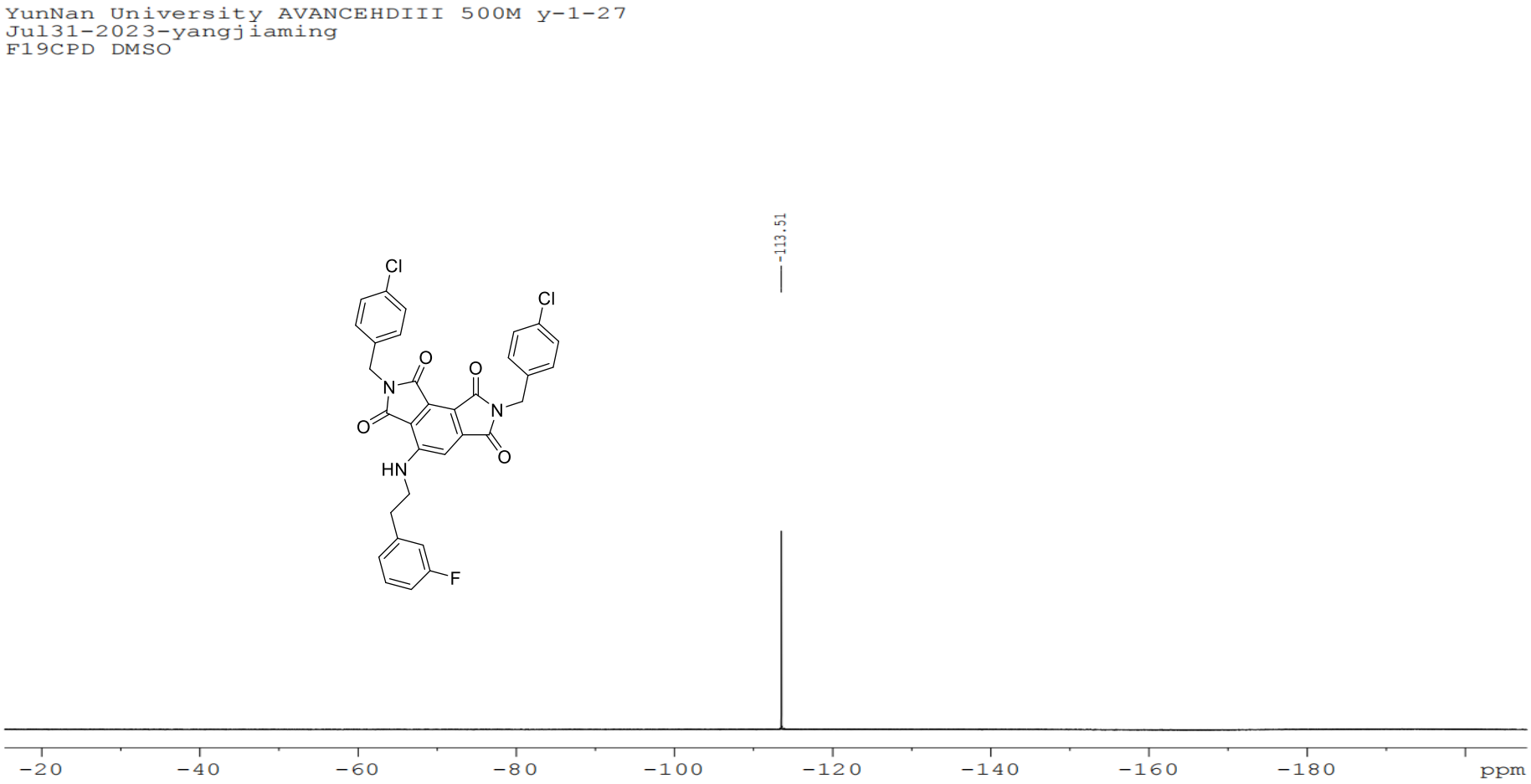


Figure S25. ^{19}F NMR (470 MHz, DMSO-d_6) spectra of compound 3**k**

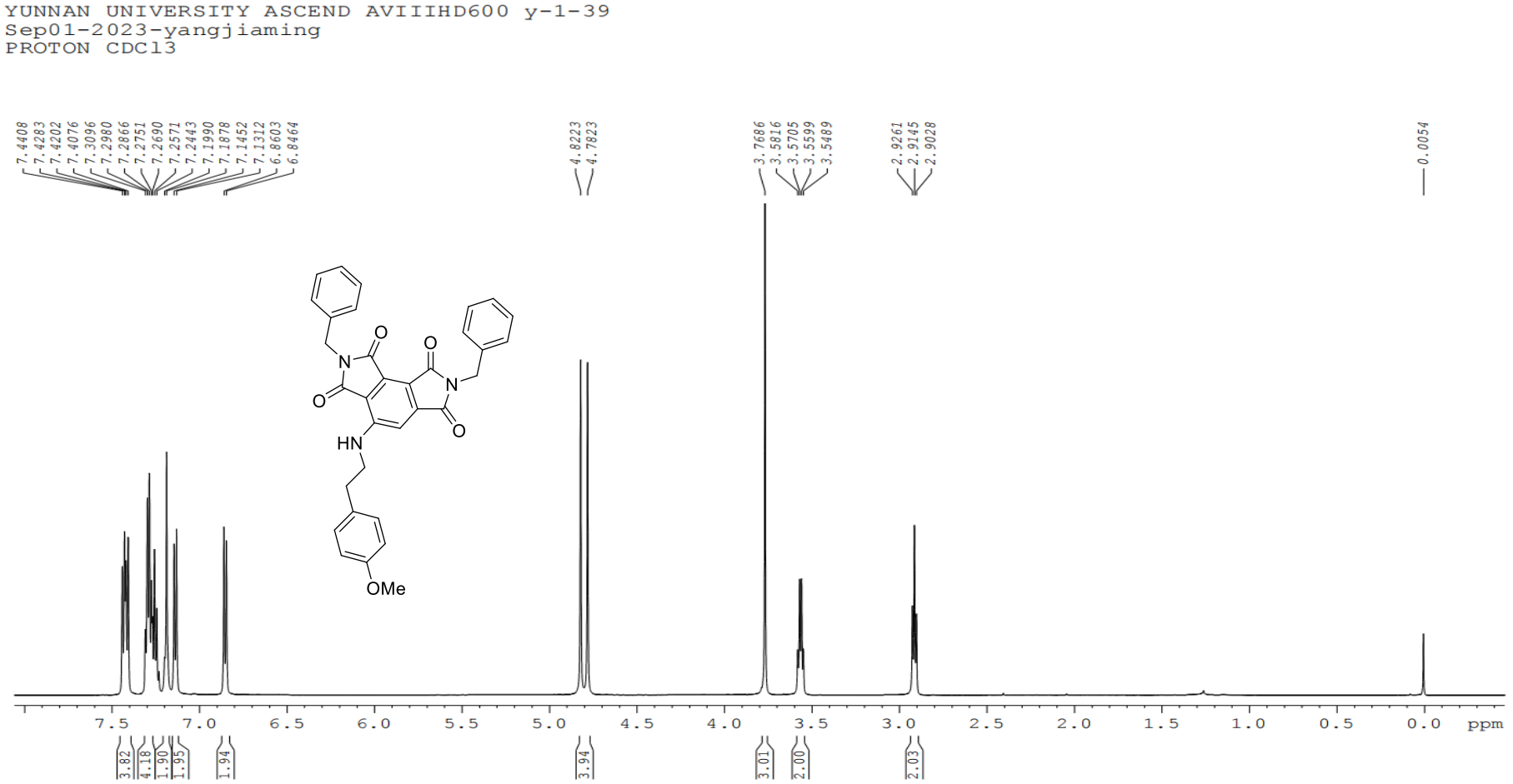


Figure S26. ^{1}H NMR (600 MHz, $CDCl_3$) spectra of compound **3l**

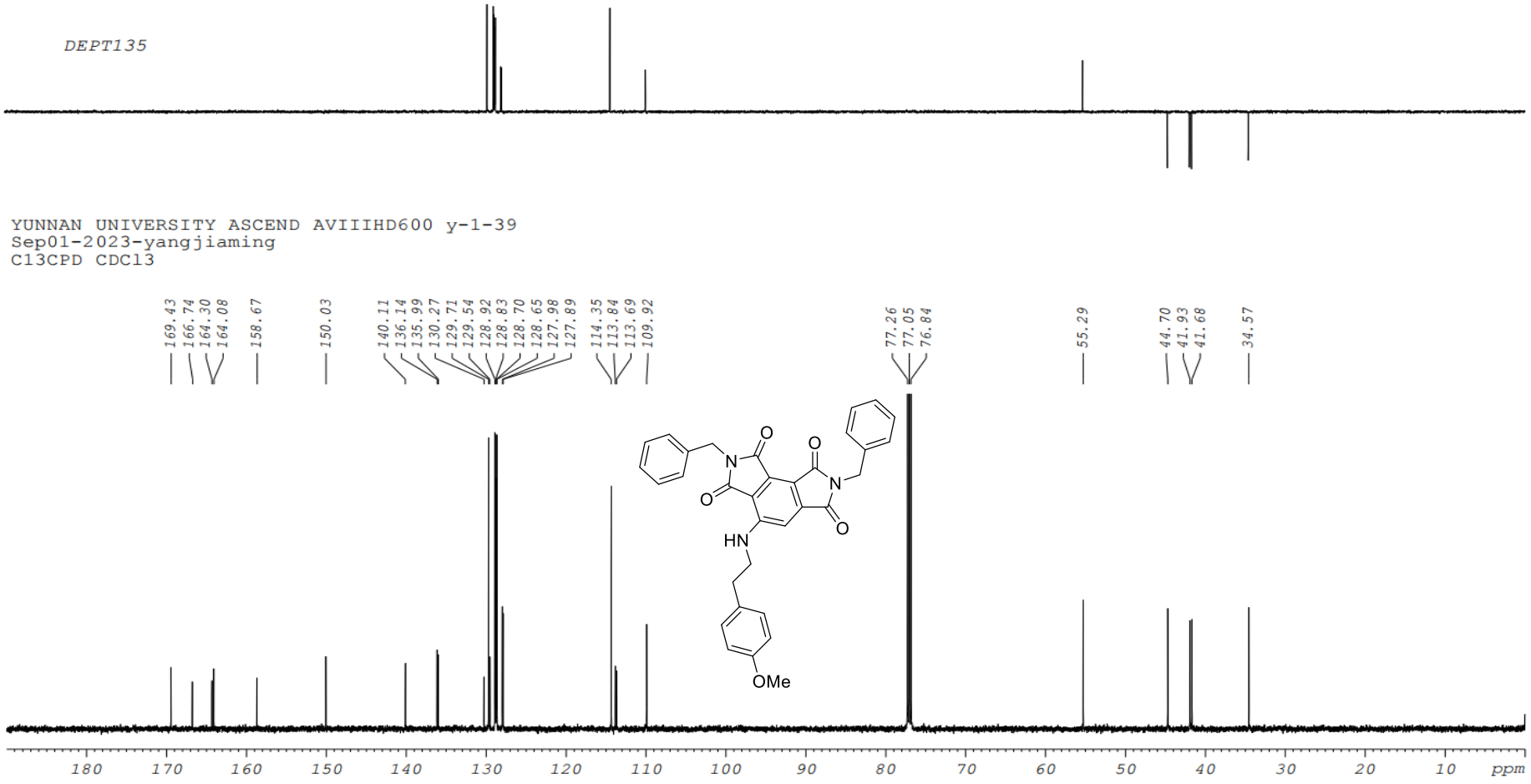


Figure S27. ^{13}C NMR (150 MHz, $CDCl_3$) spectra of compound **3l**

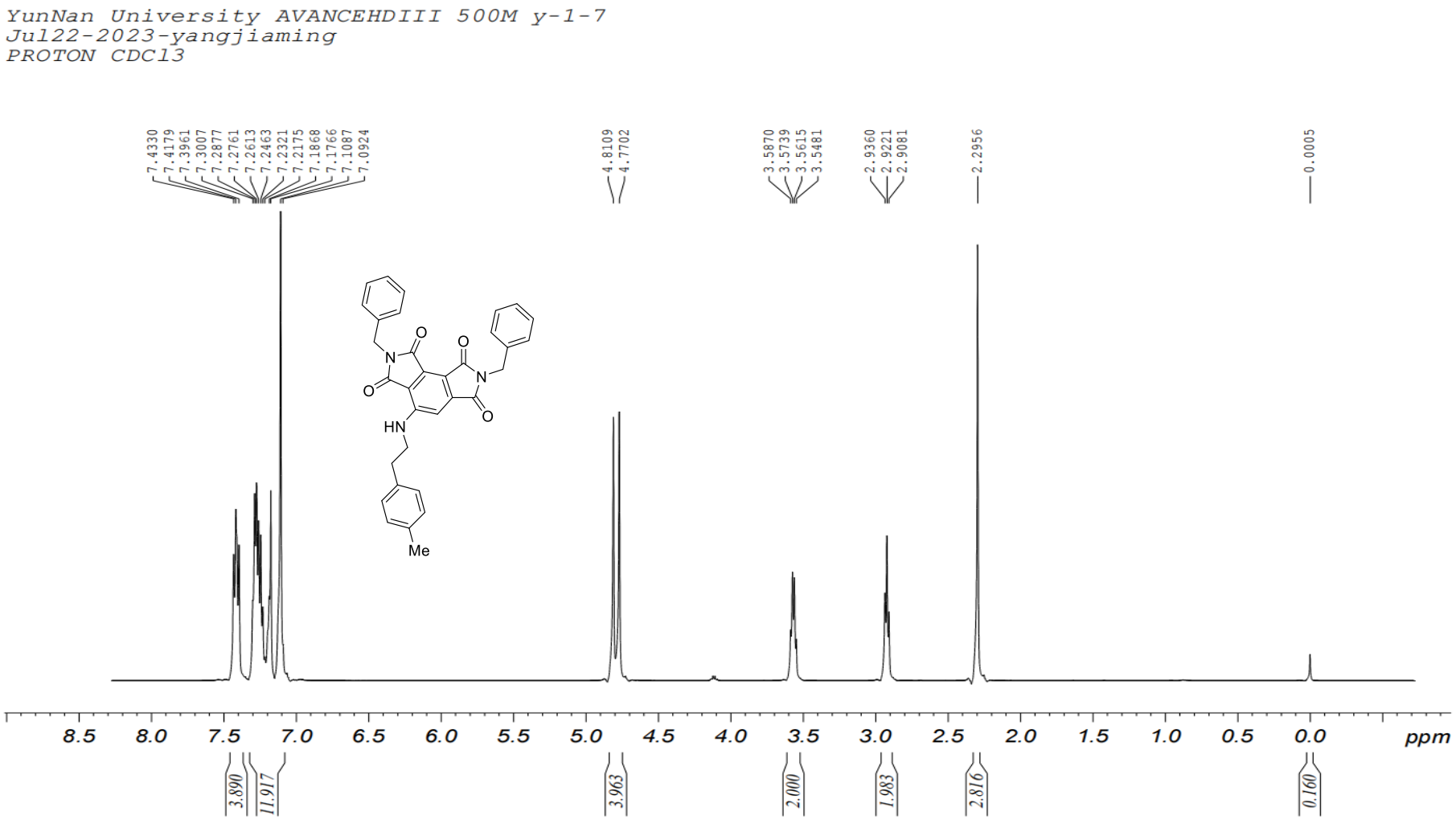


Figure S28. ^{1}H NMR (500 MHz, $CDCl_3$) spectra of compound **3m**

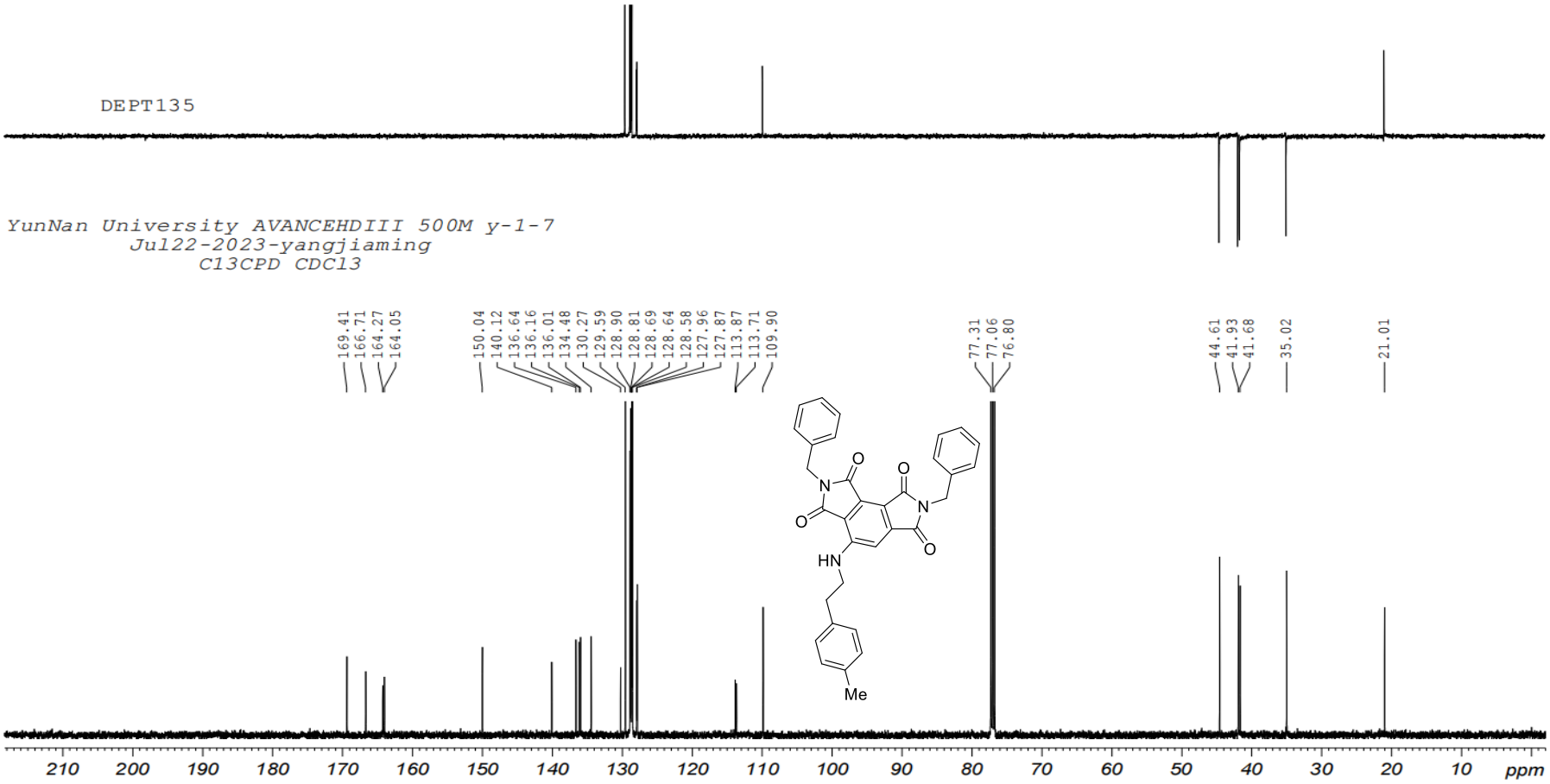


Figure S29. ^{13}C NMR (125 MHz, $CDCl_3$) spectra of compound **3m**

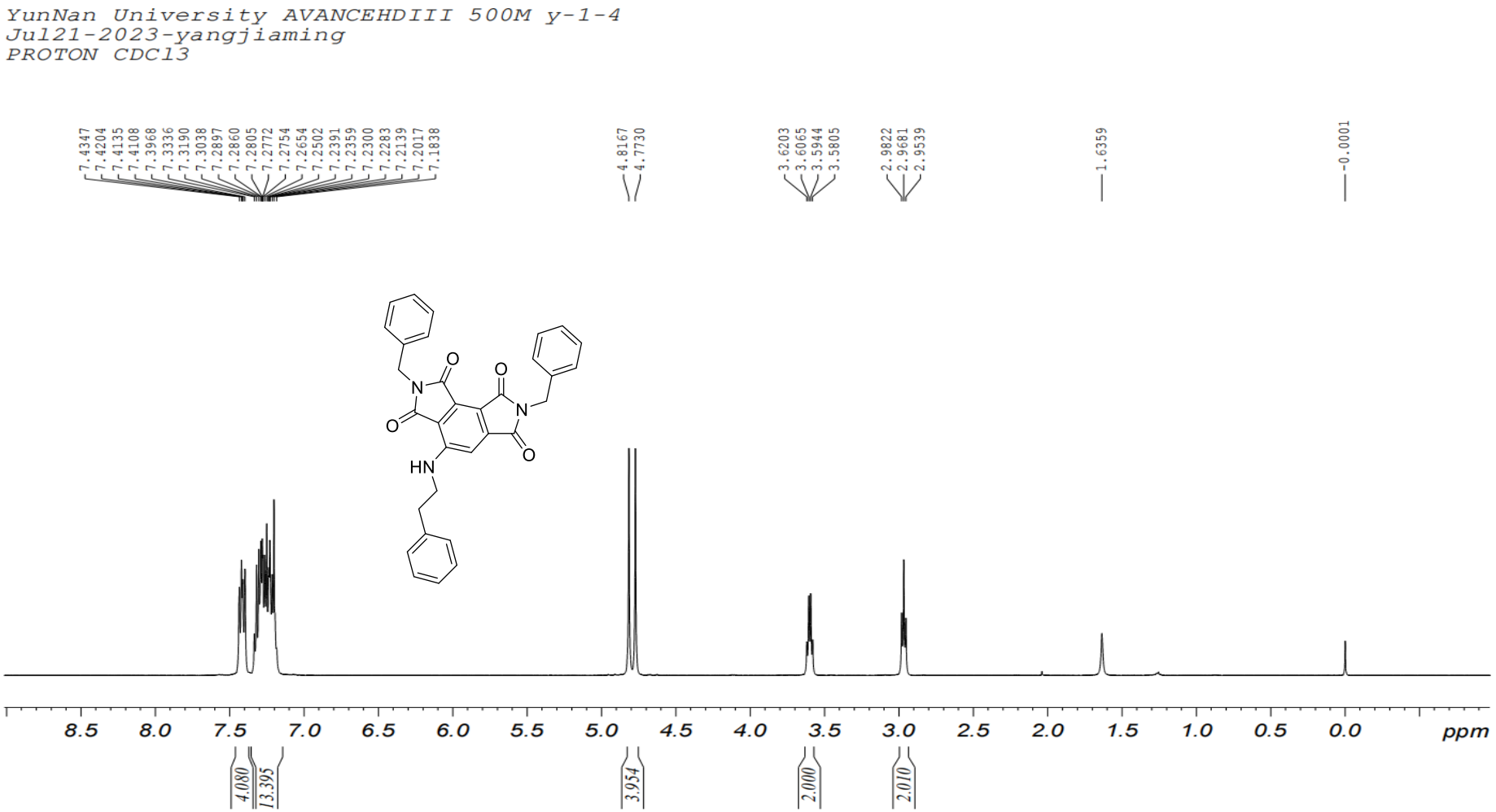


Figure S30. ^{1}H NMR (500 MHz, $CDCl_3$) spectra of compound **3n**

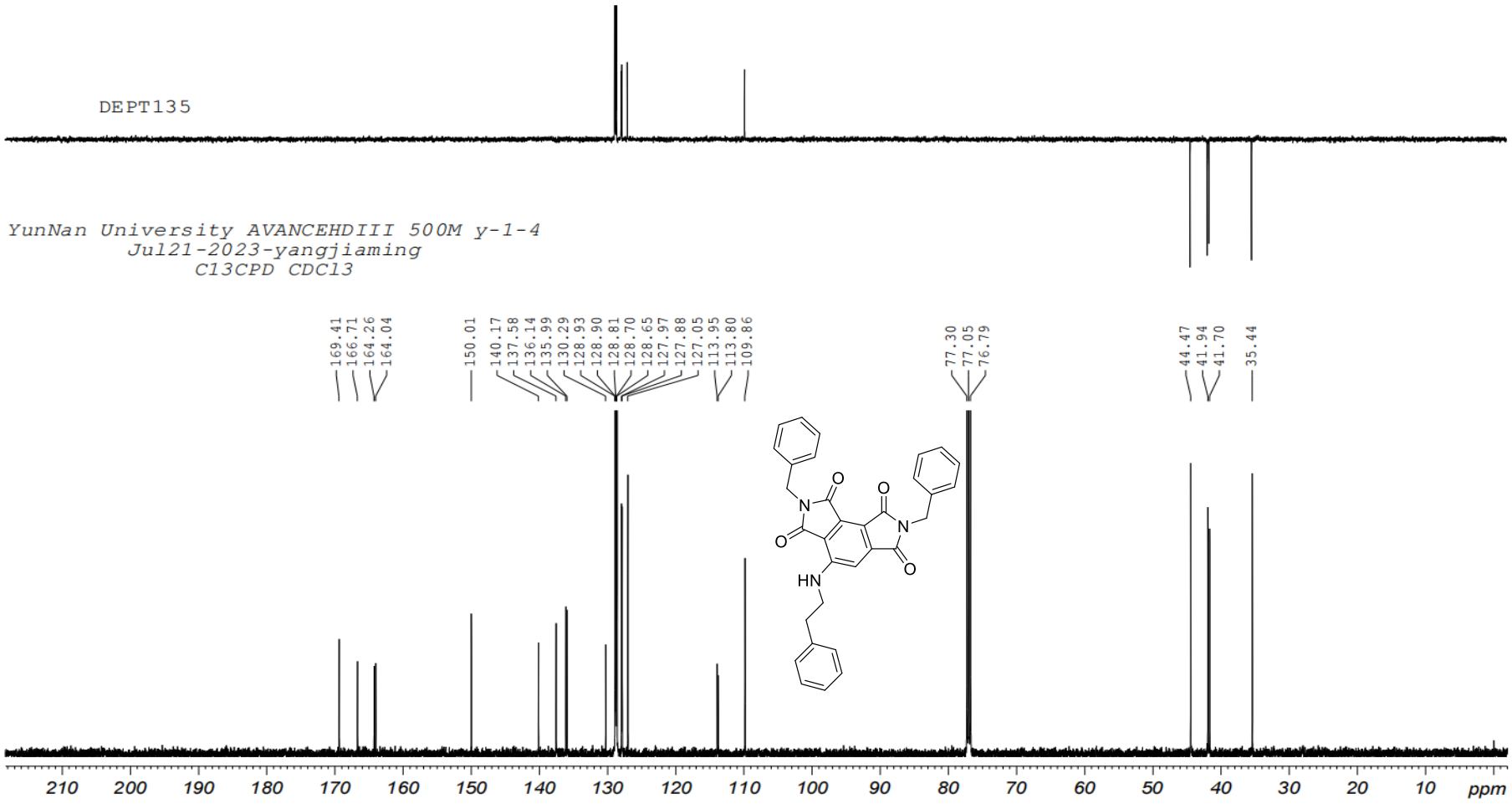


Figure S31. ^{13}C NMR (125 MHz, $CDCl_3$) spectra of compound **3n**

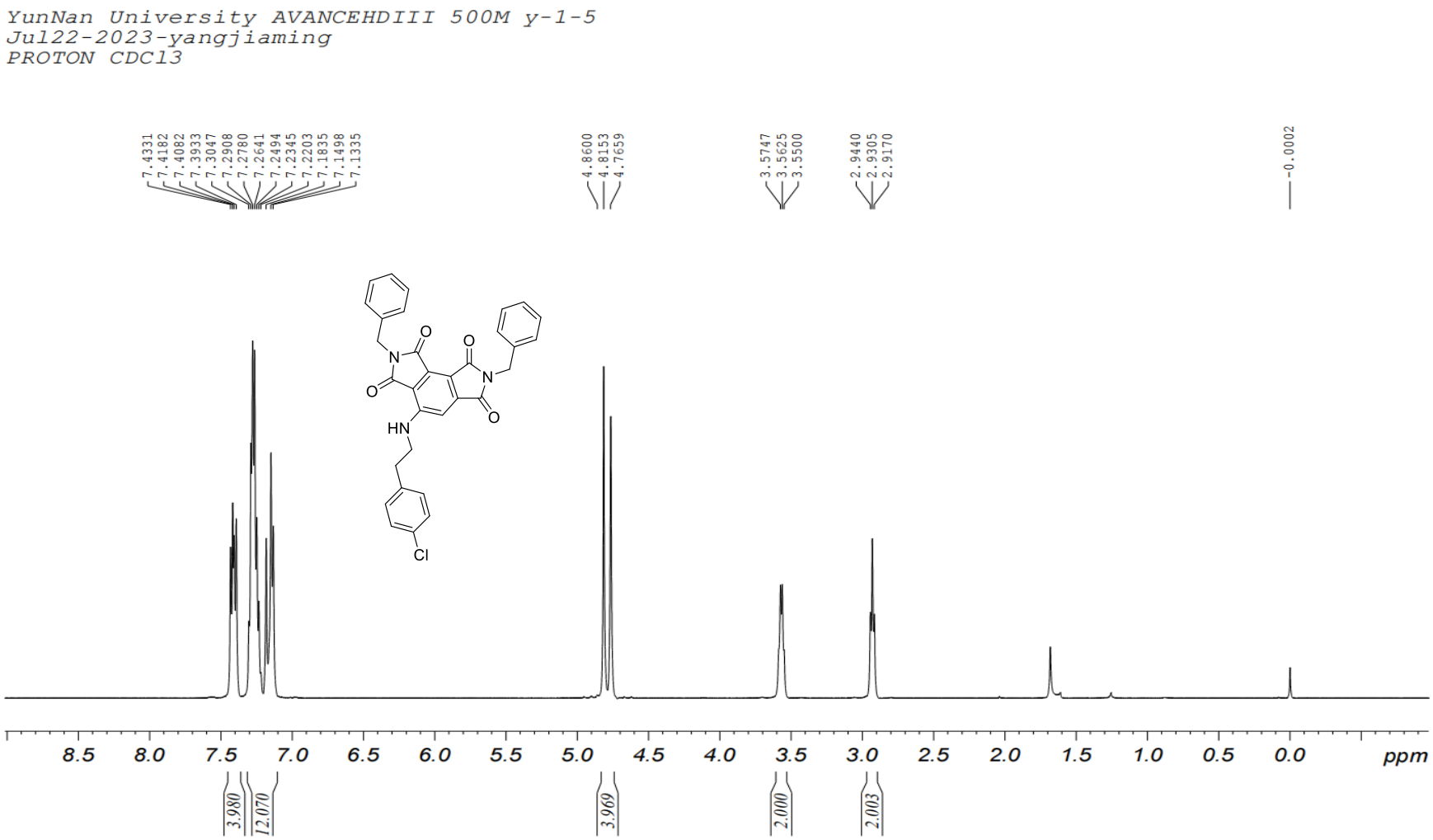


Figure S32. ^{1}H NMR (500 MHz, $CDCl_3$) spectra of compound **3o**

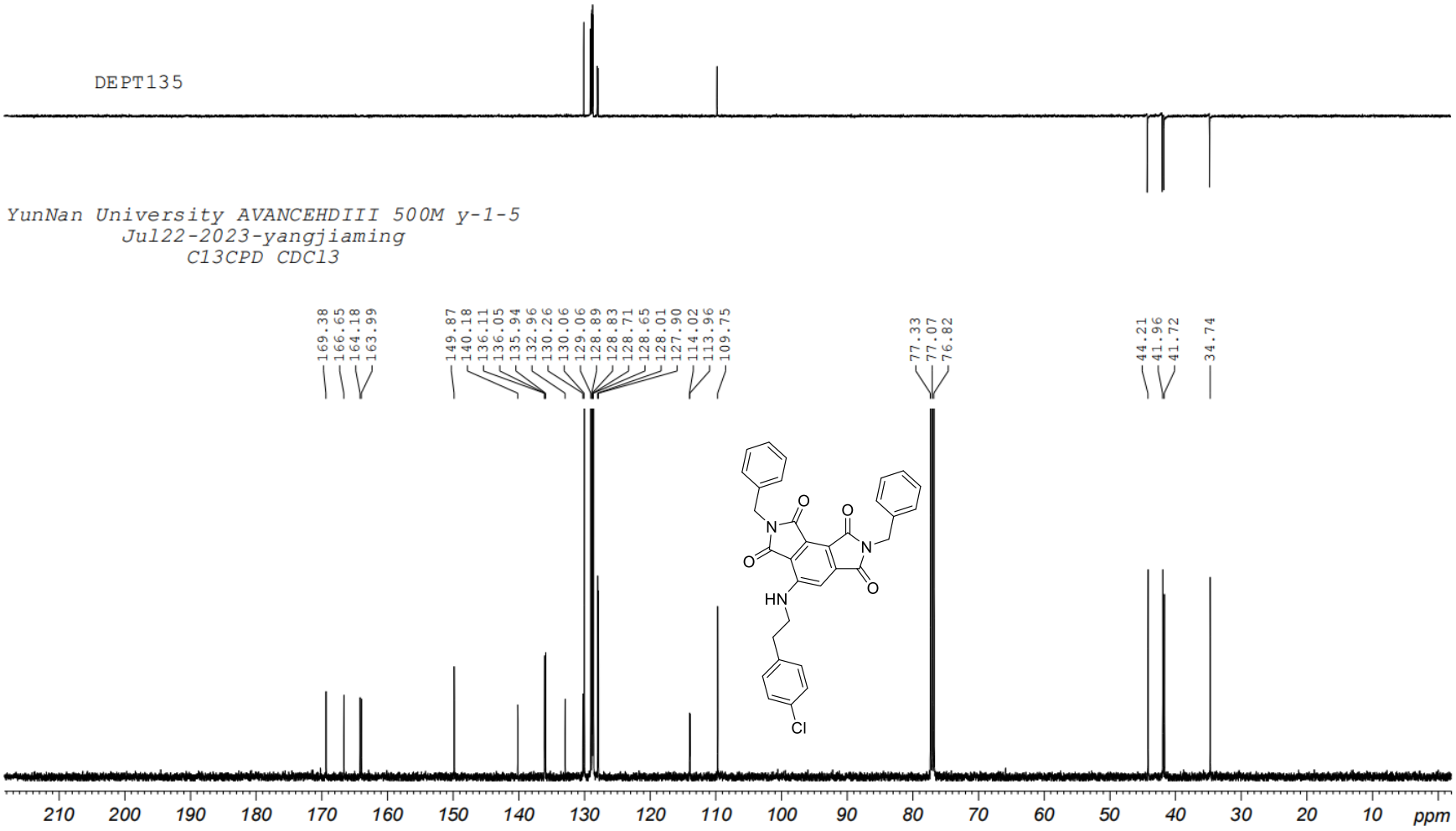


Figure S33. ^{13}C NMR (125 MHz, $CDCl_3$) spectra of compound **3o**

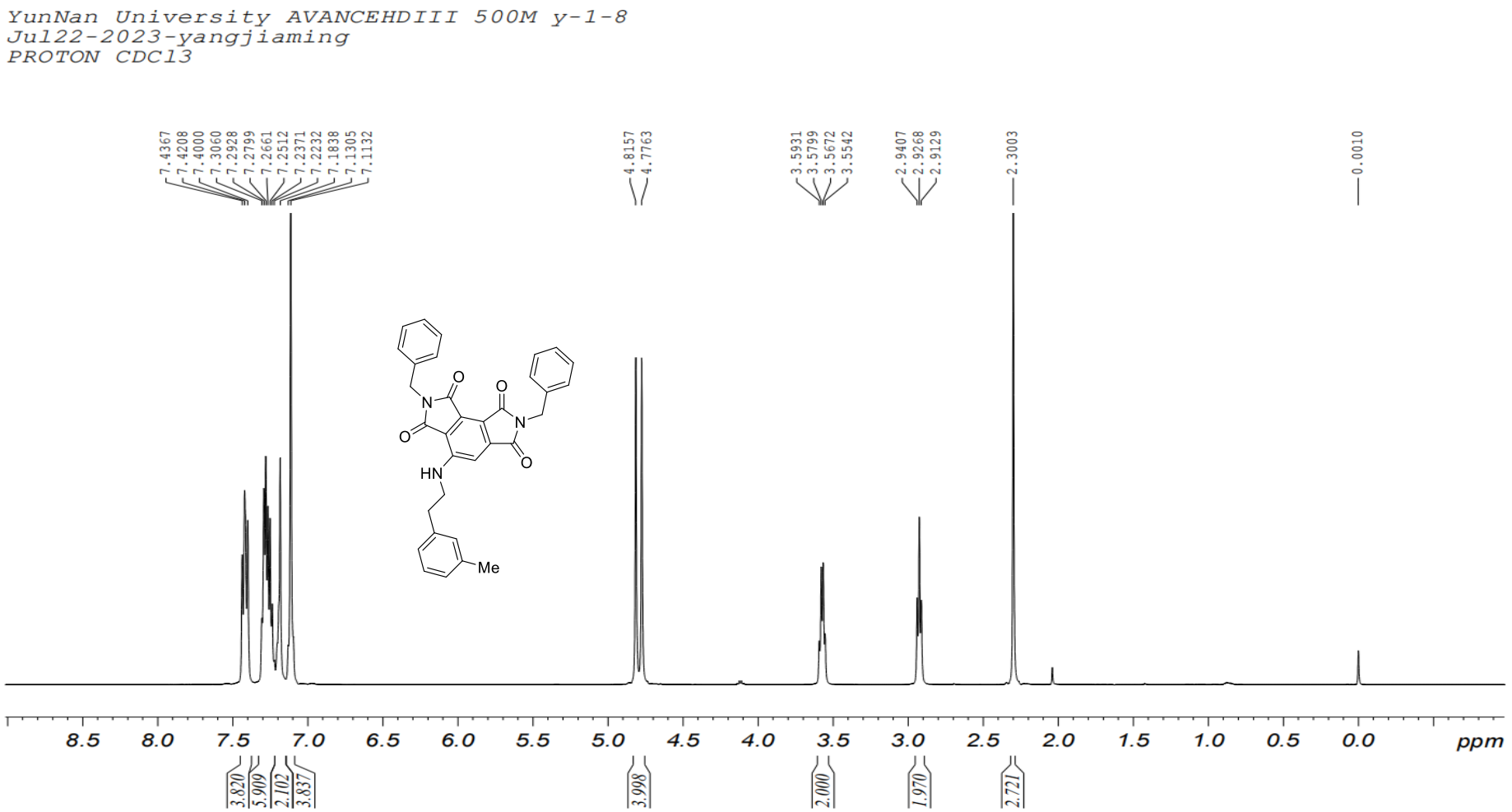


Figure S34. ^{1}H NMR (500 MHz, $CDCl_3$) spectra of compound **3p**

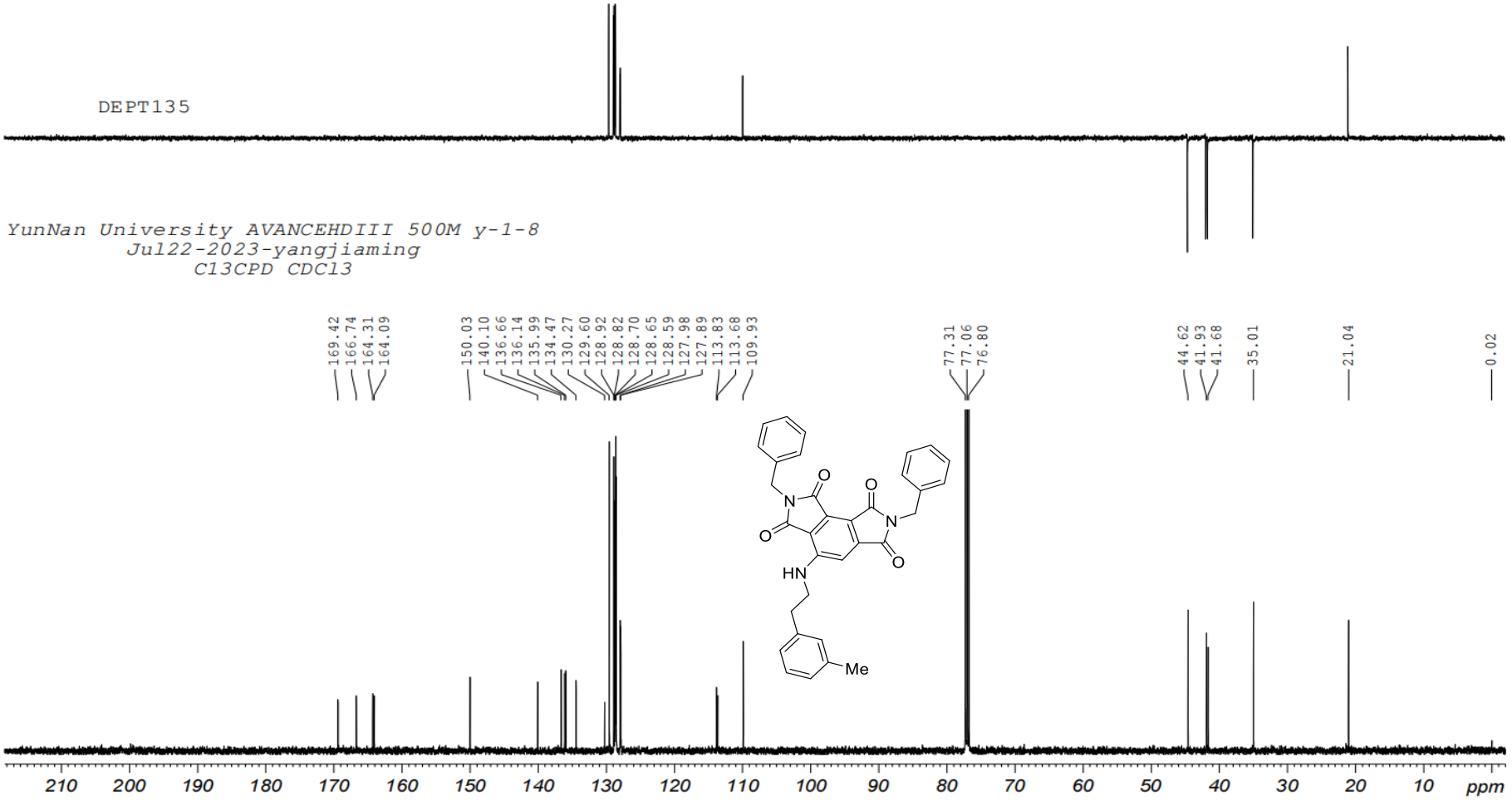


Figure S35. ^{13}C NMR (125 MHz, $CDCl_3$) spectra of compound **3p**

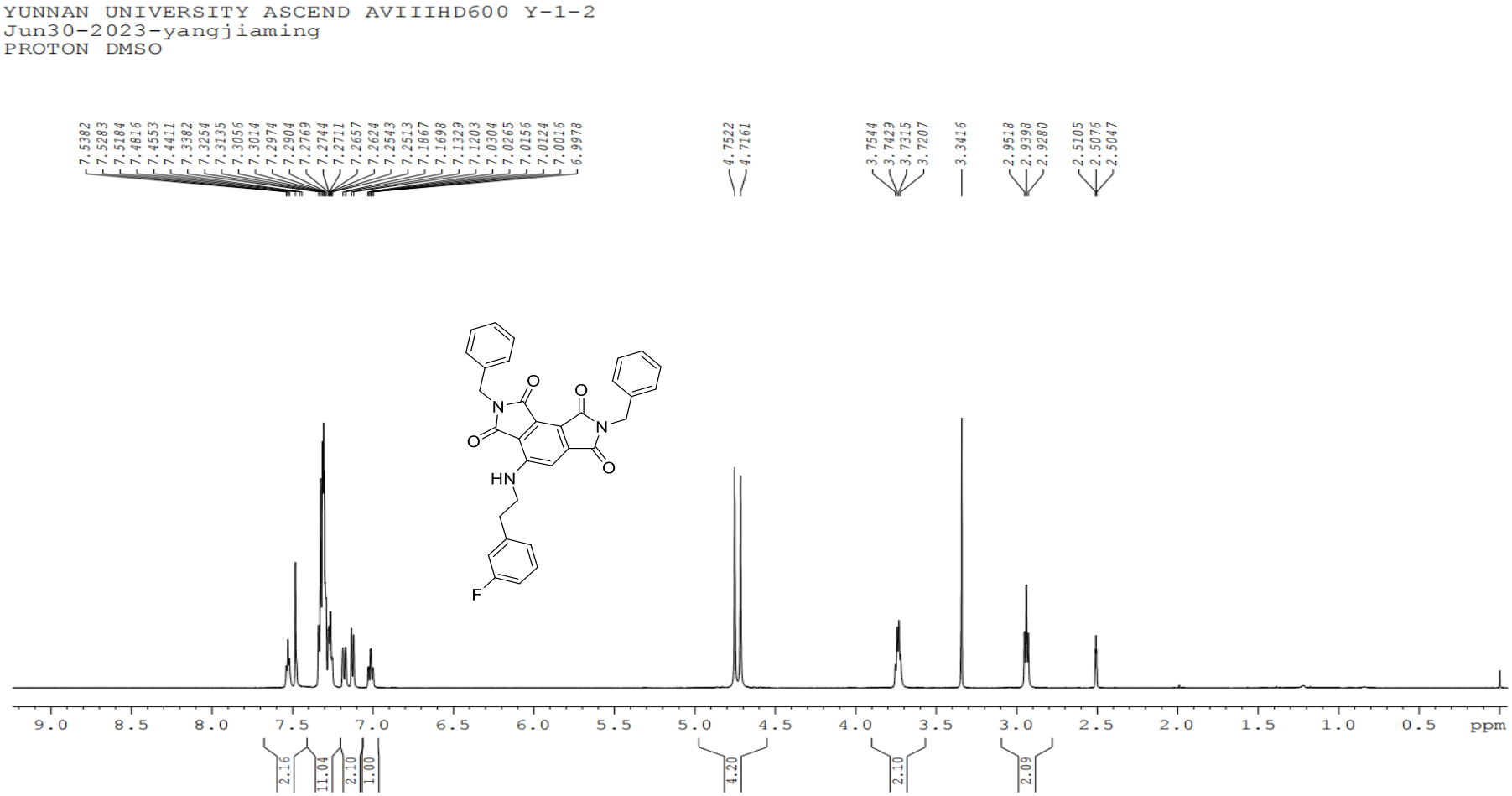


Figure S36. ^{1}H NMR (600 MHz, DMSO-d_6) spectra of compound **3q**

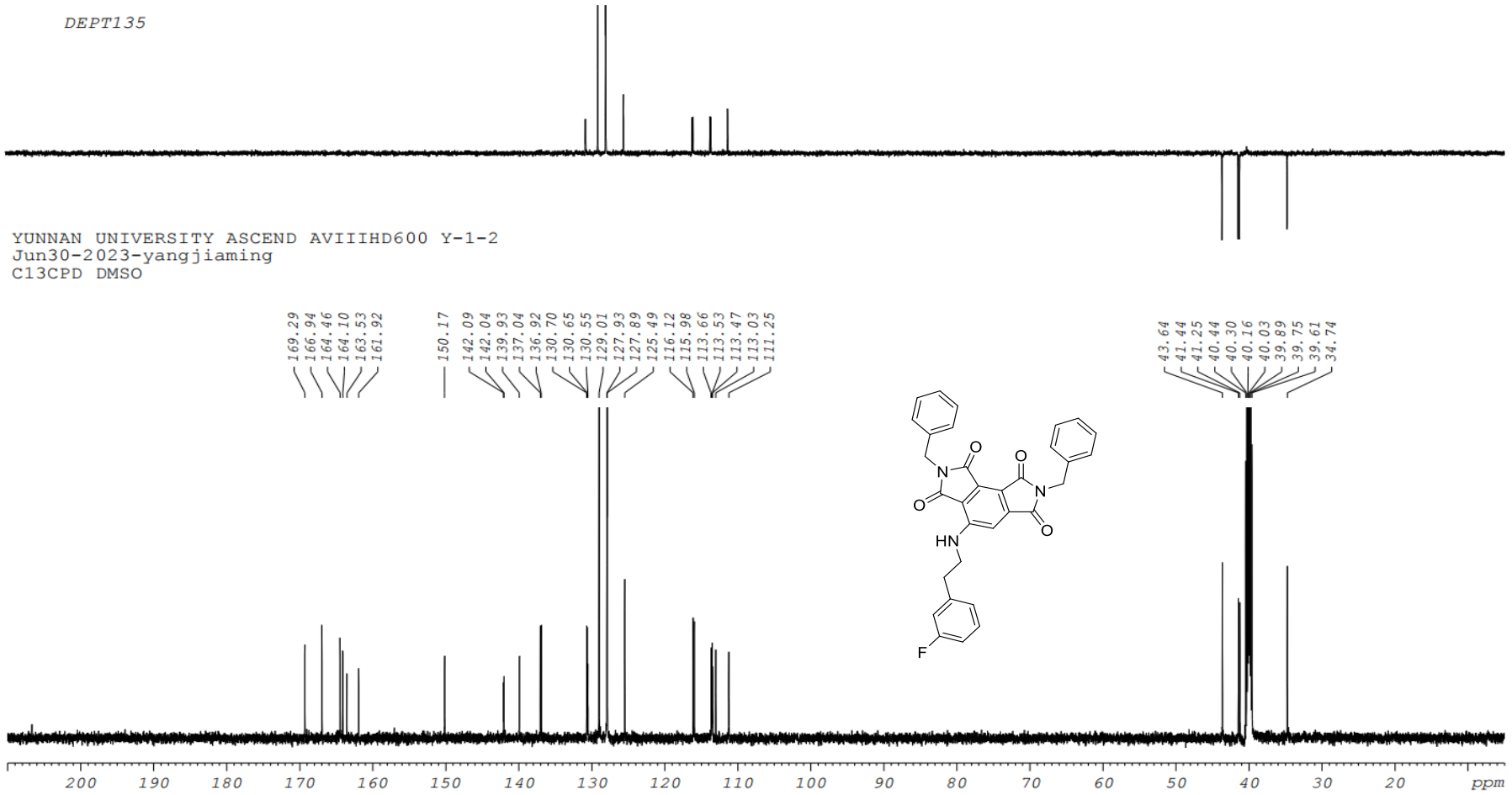


Figure S37. ^{13}C NMR (125 MHz, DMSO-d_6) spectra of compound **3q**

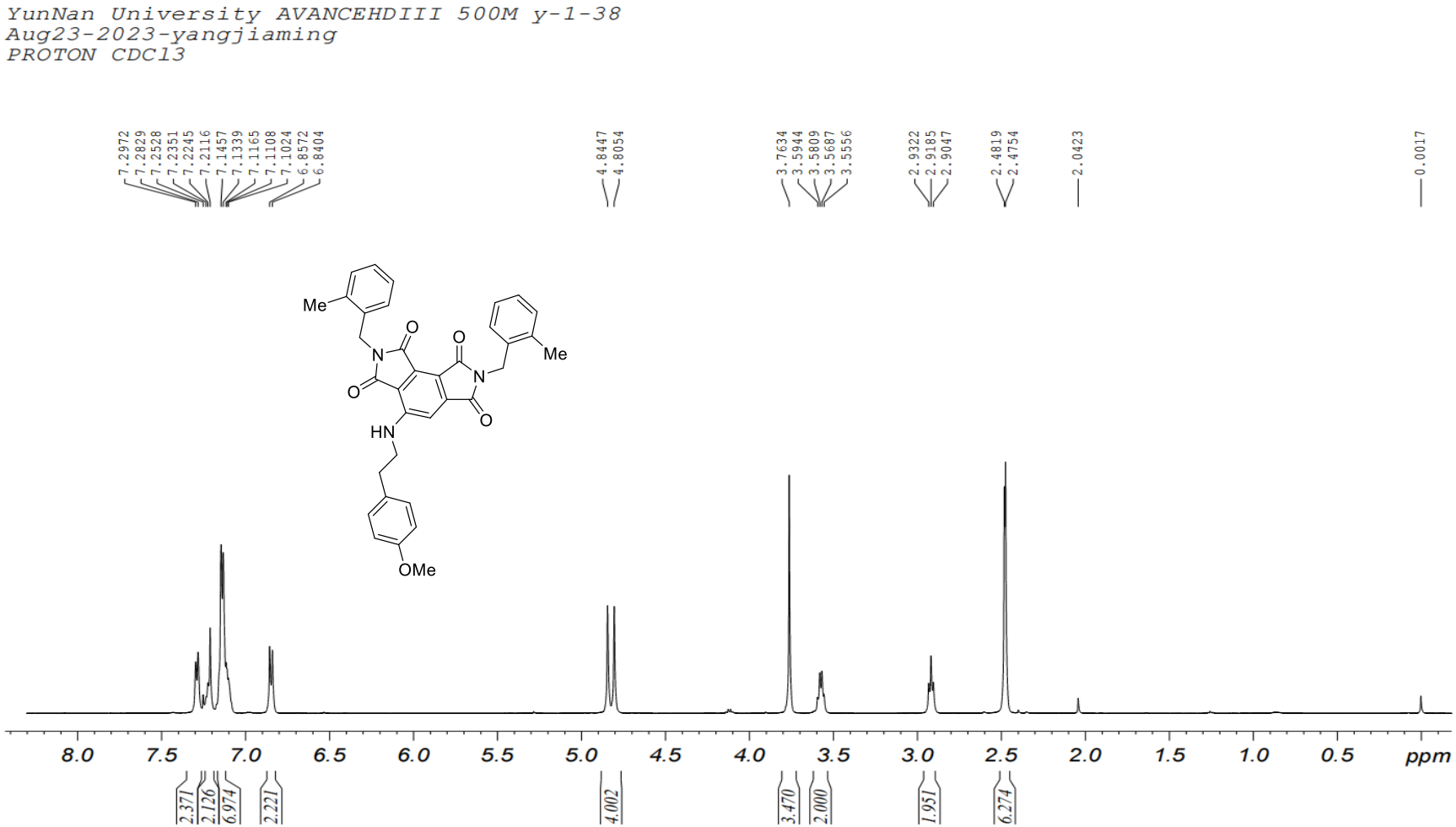


Figure S38. ^{1}H NMR (500 MHz, $CDCl_3$) spectra of compound **3r**

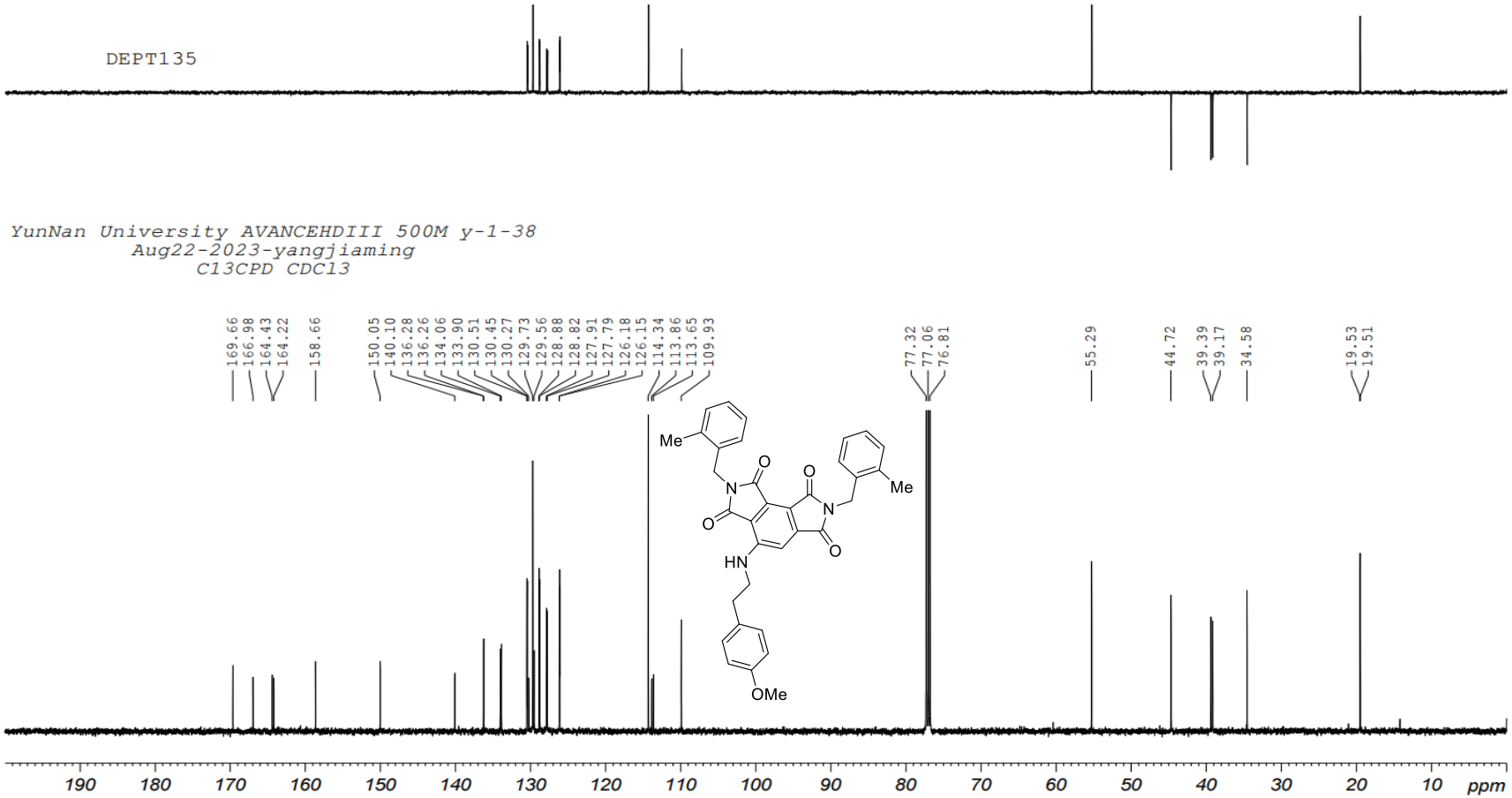


Figure S39. ^{13}C NMR (125 MHz, $CDCl_3$) spectra of compound **3r**

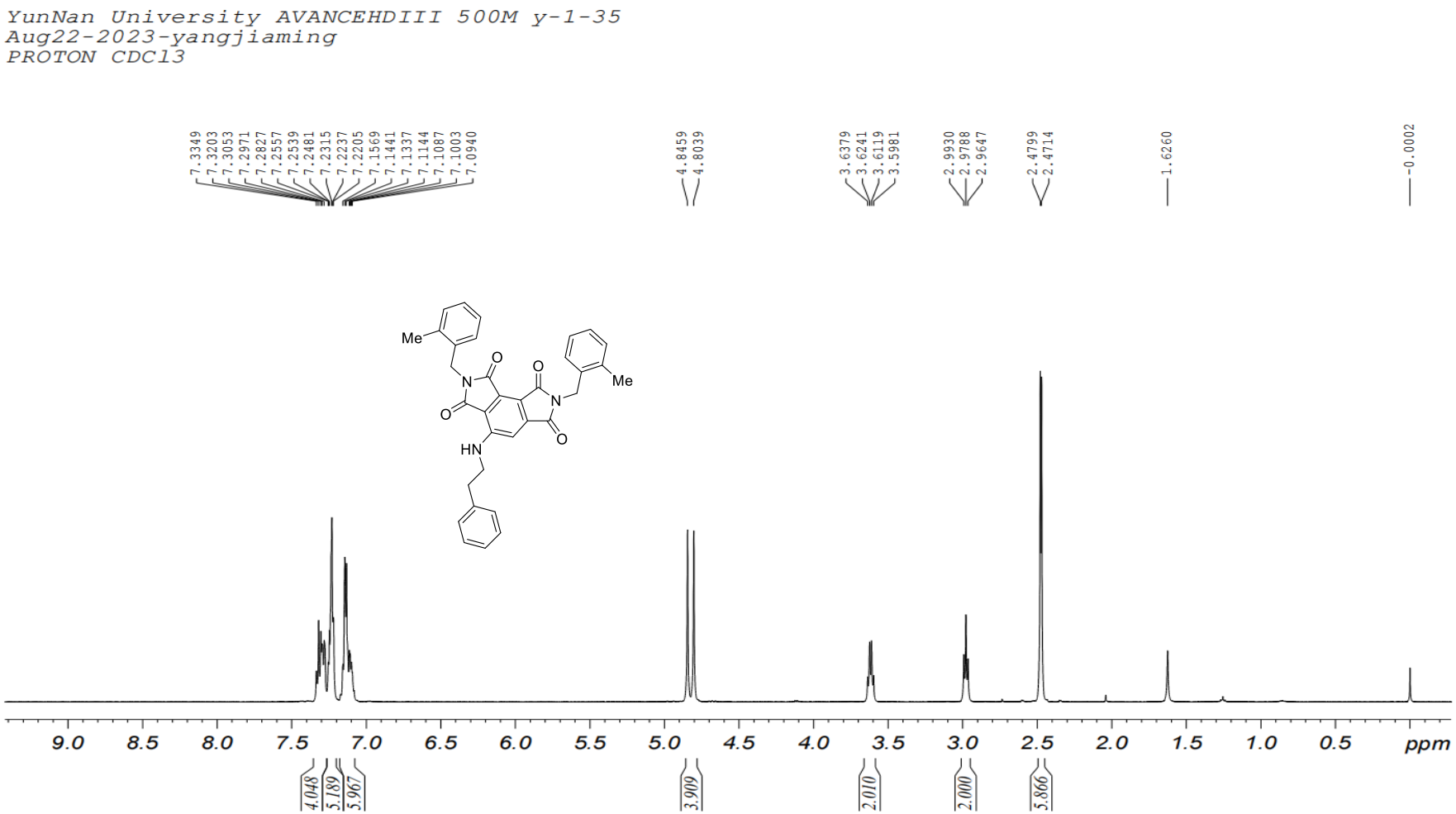


Figure S40. ^{1}H NMR (500 MHz, $CDCl_3$) spectra of compound **3s**

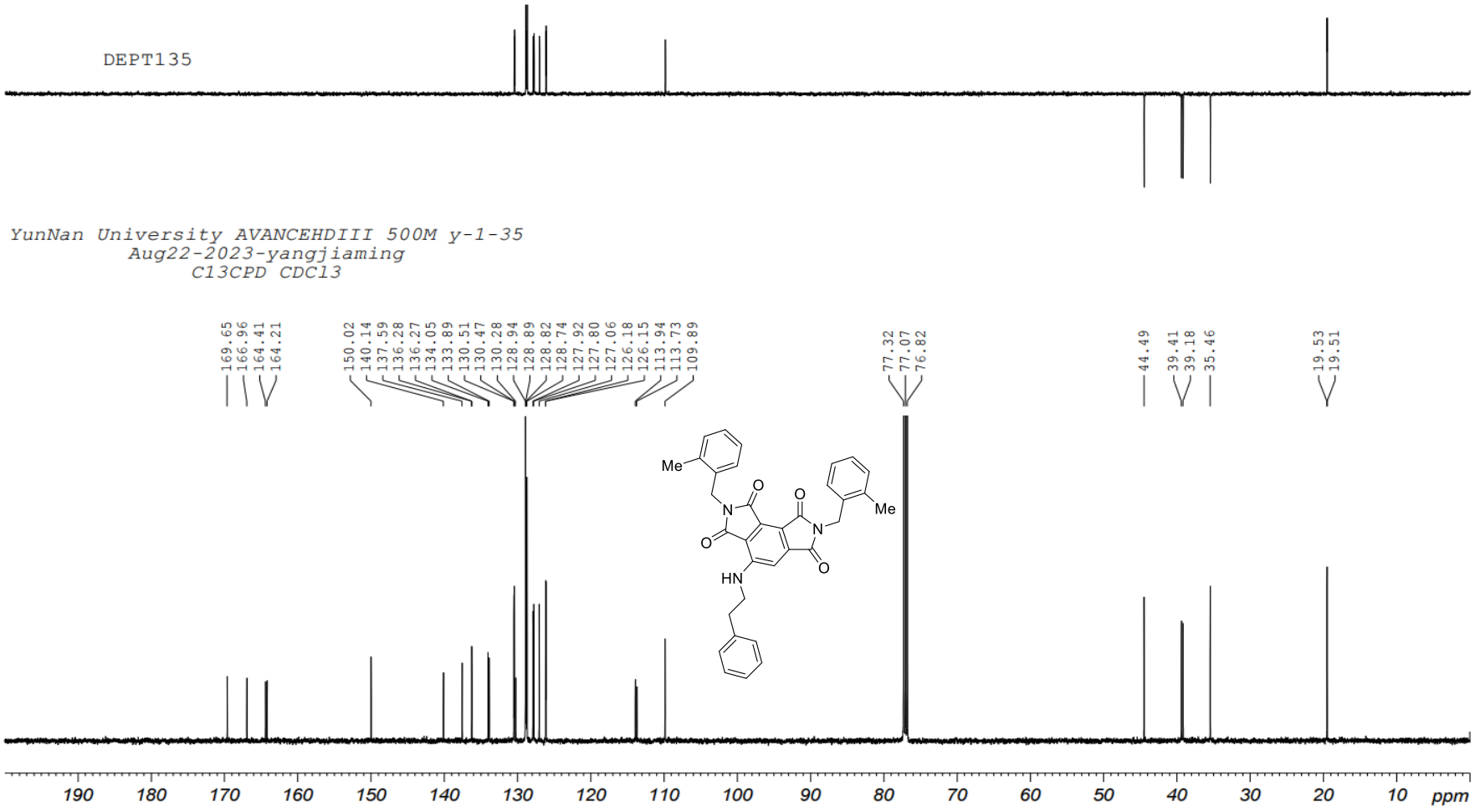


Figure S41. ^{13}C NMR (125 MHz, $CDCl_3$) spectra of compound **3s**

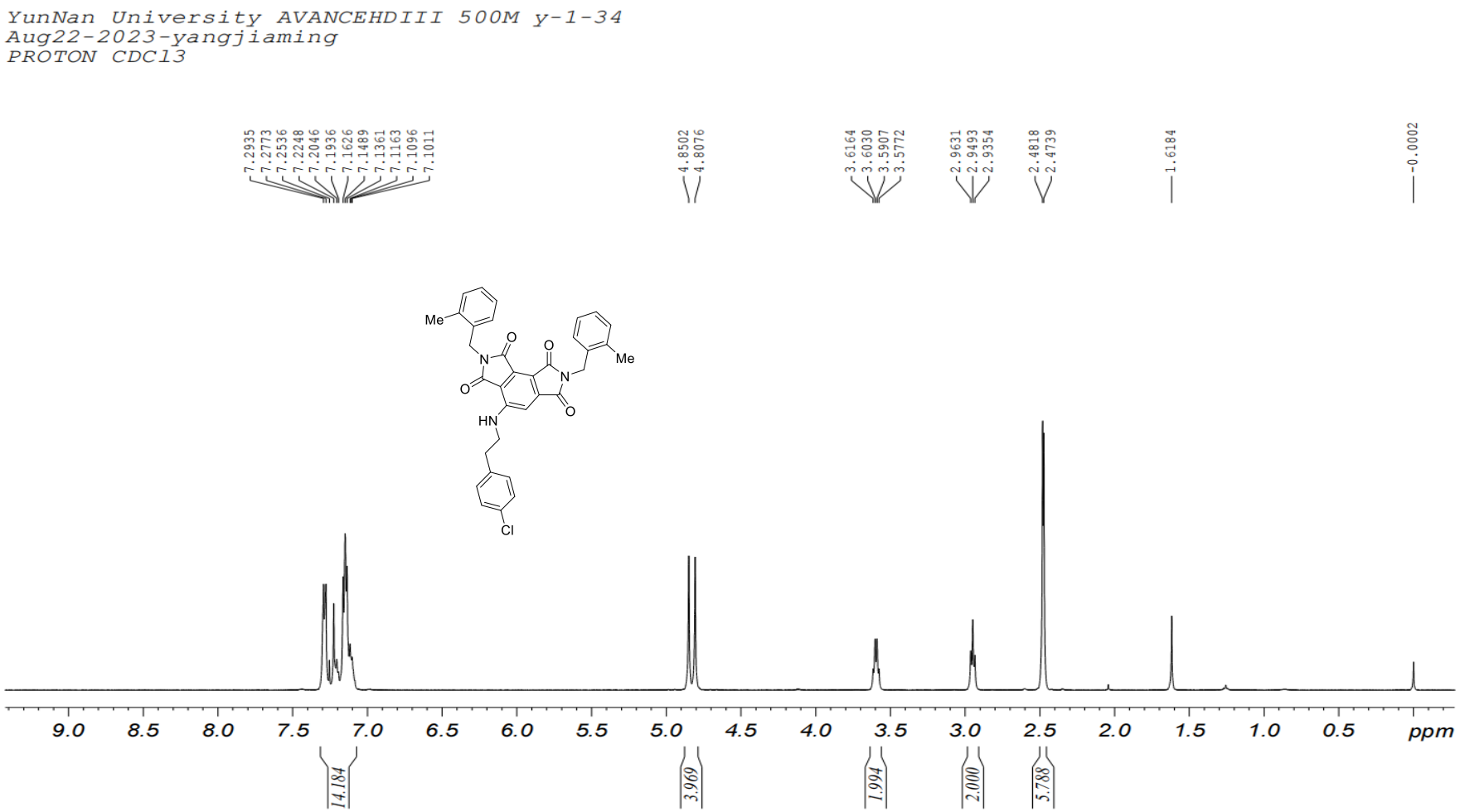


Figure S42. ^{1}H NMR (500 MHz, $CDCl_3$) spectra of compound **3t**

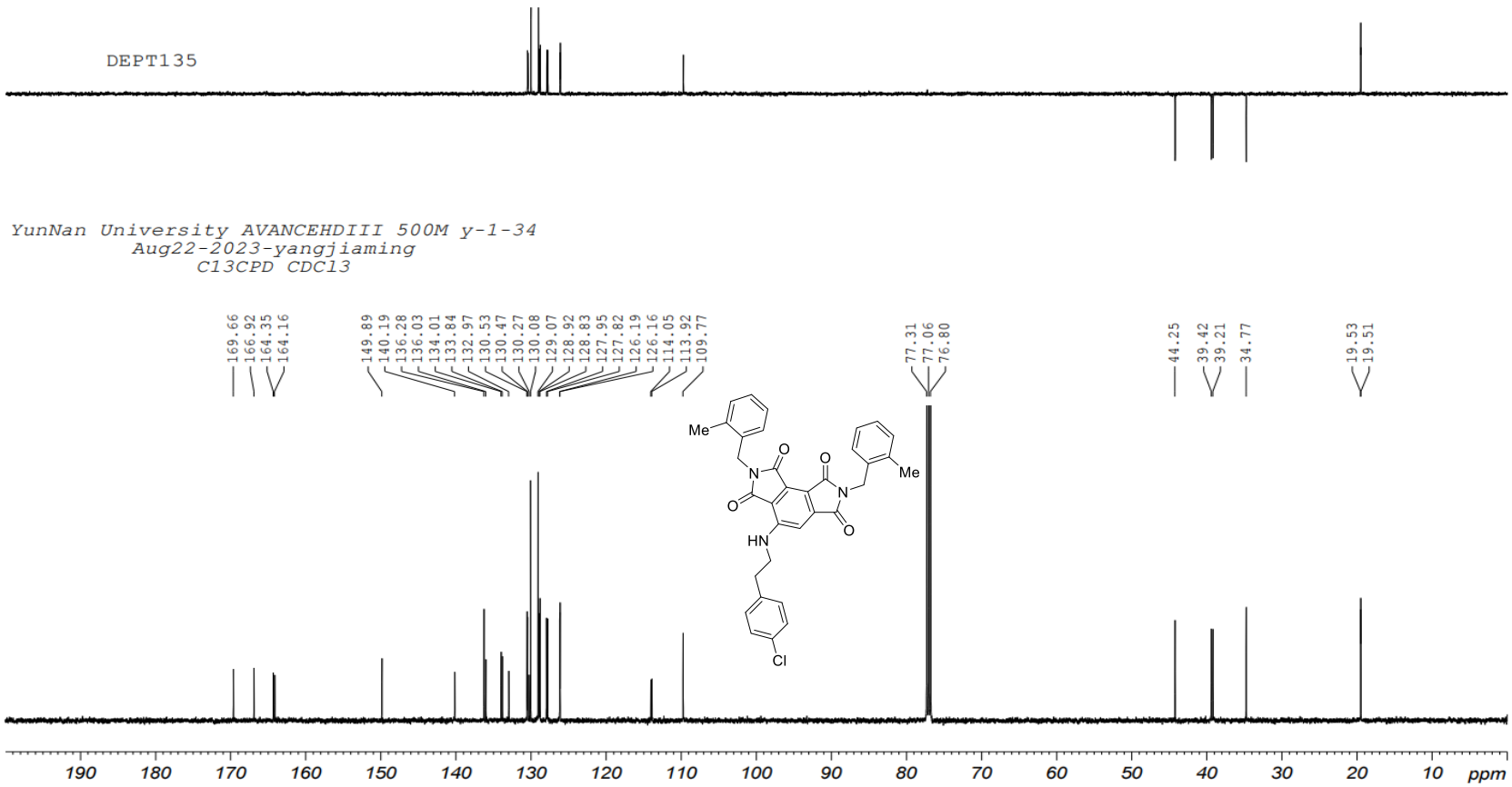


Figure S43. ^{13}C NMR (125 MHz, $CDCl_3$) spectra of compound **3t**

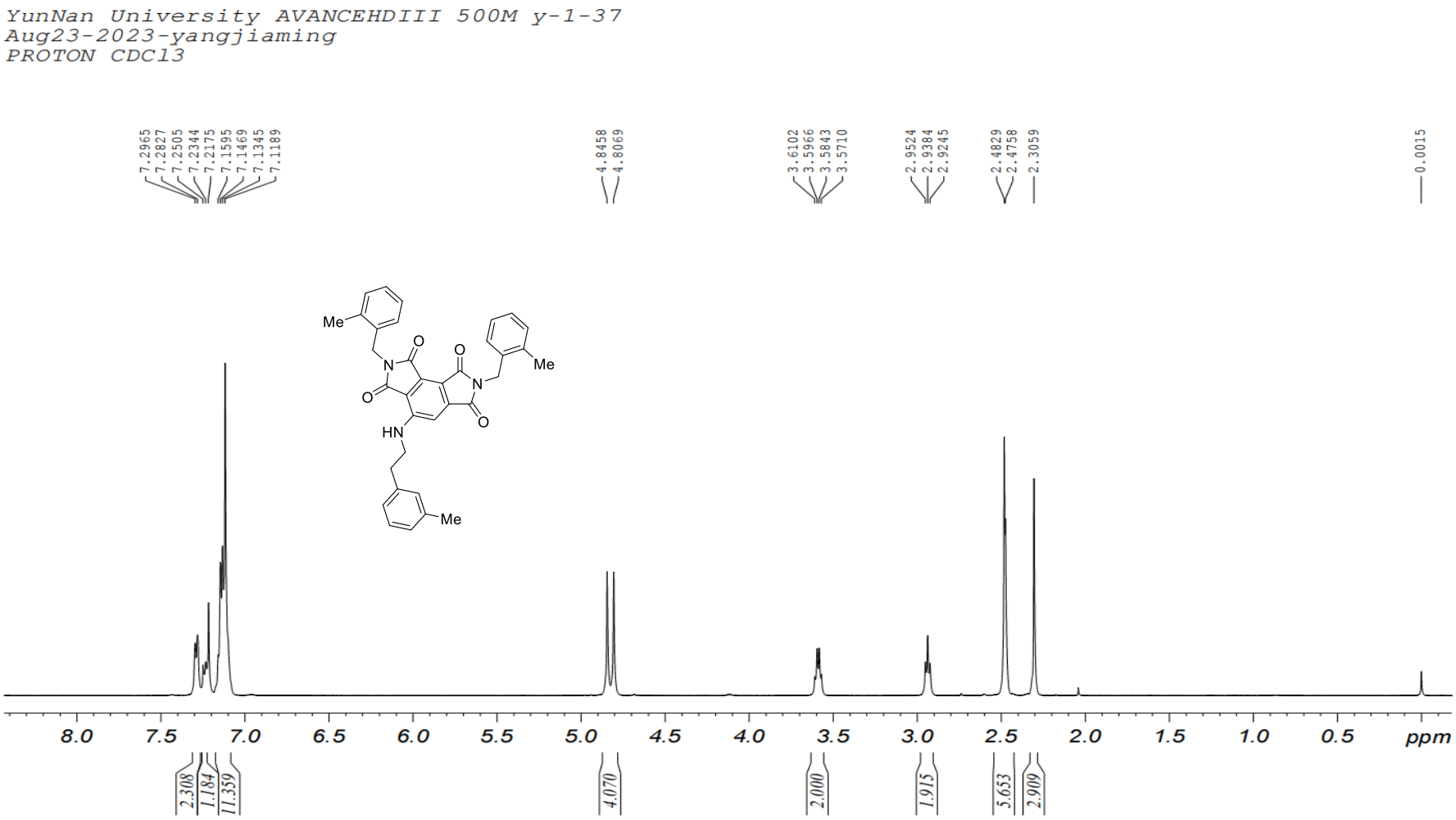


Figure S44. ^{1}H NMR (500 MHz, $CDCl_3$) spectra of compound **3u**

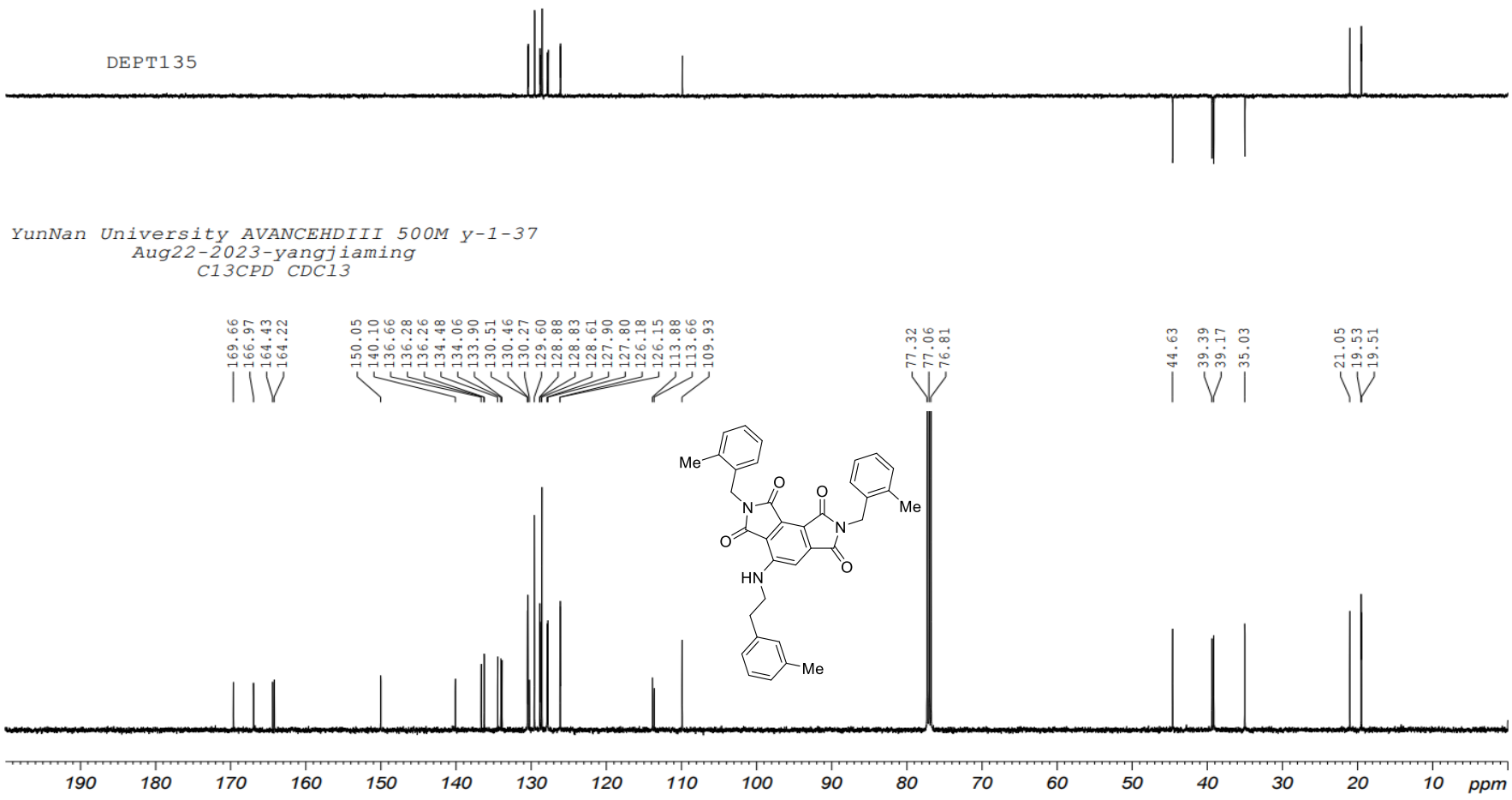


Figure S45. ^{13}C NMR (125 MHz, $CDCl_3$) spectra of compound **3u**

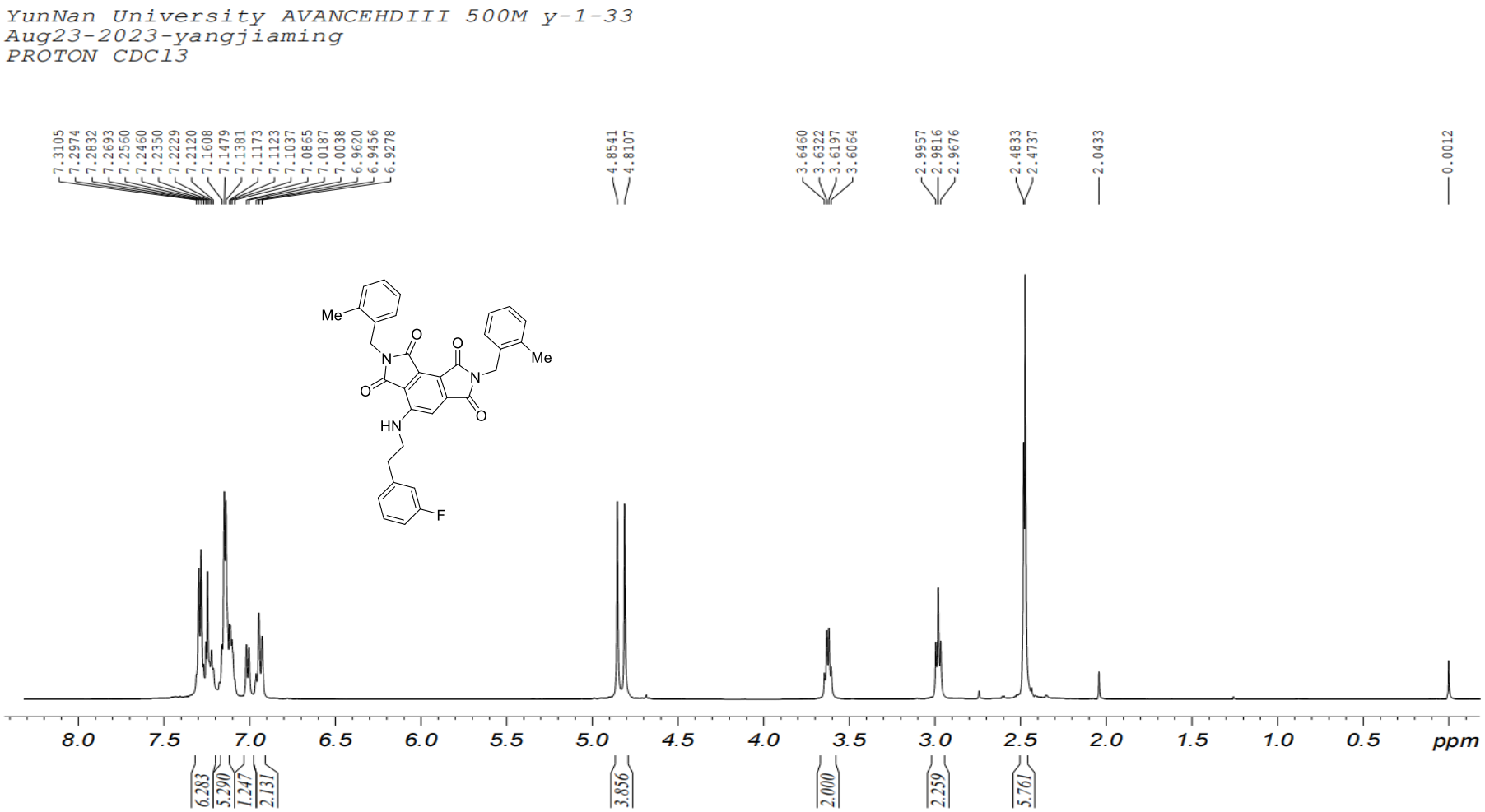


Figure S46. ^{1}H NMR (500 MHz, $CDCl_3$) spectra of compound **3v**

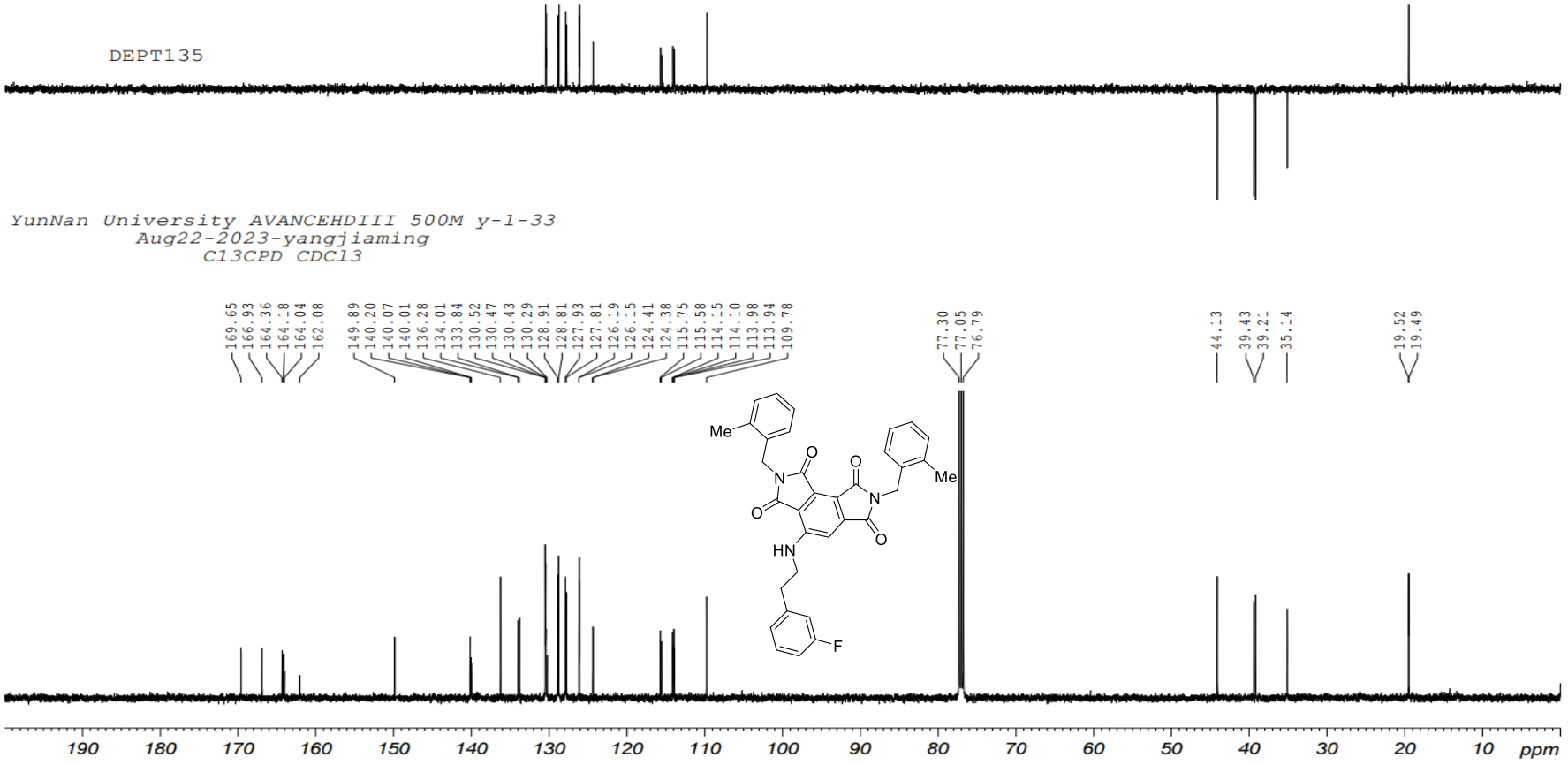


Figure S47. ^{13}C NMR (125 MHz, $CDCl_3$) spectra of compound **3v**

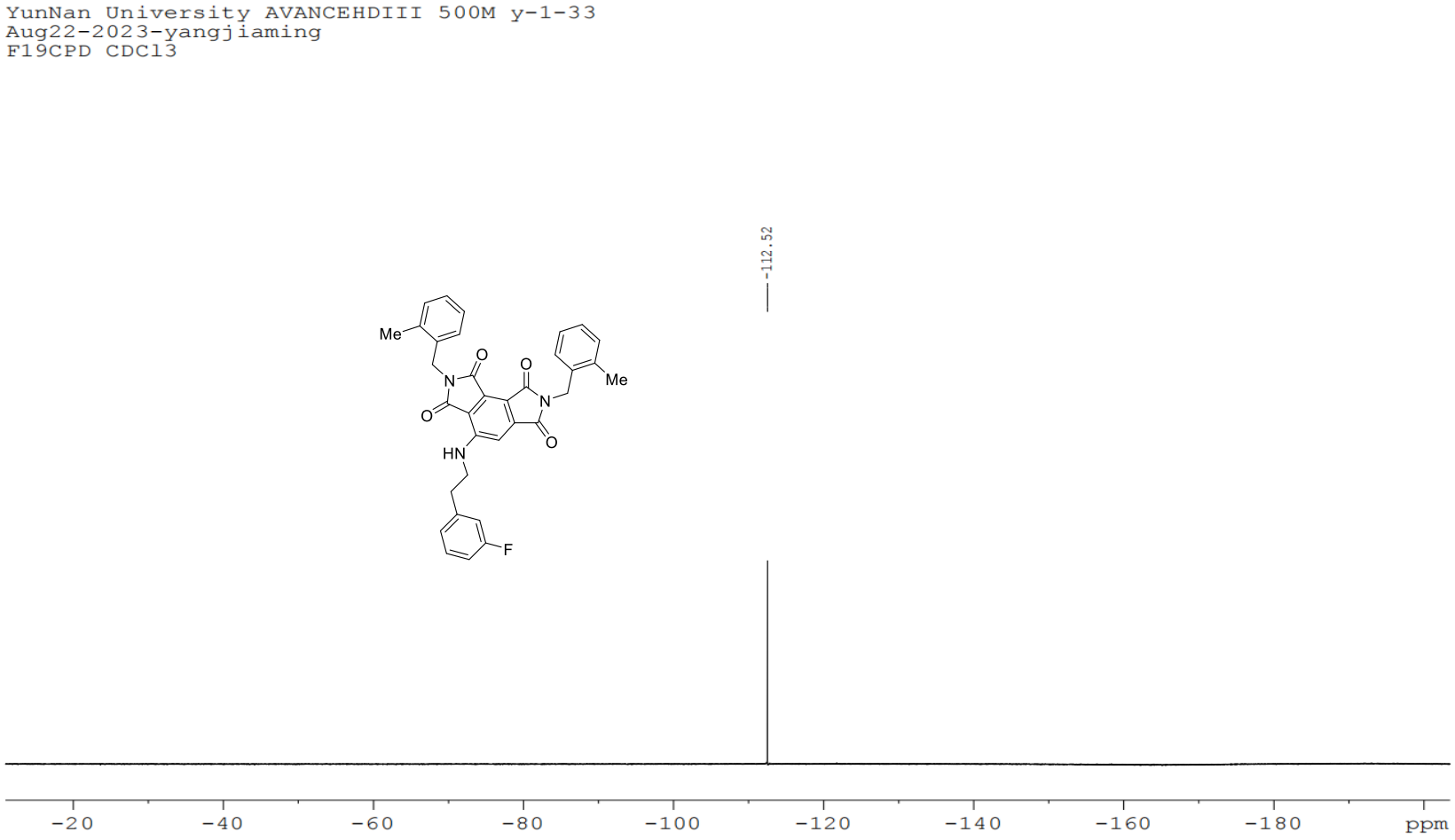


Figure S48. ^{19}F NMR (470 MHz, $CDCl_3$) spectra of compound **3v**

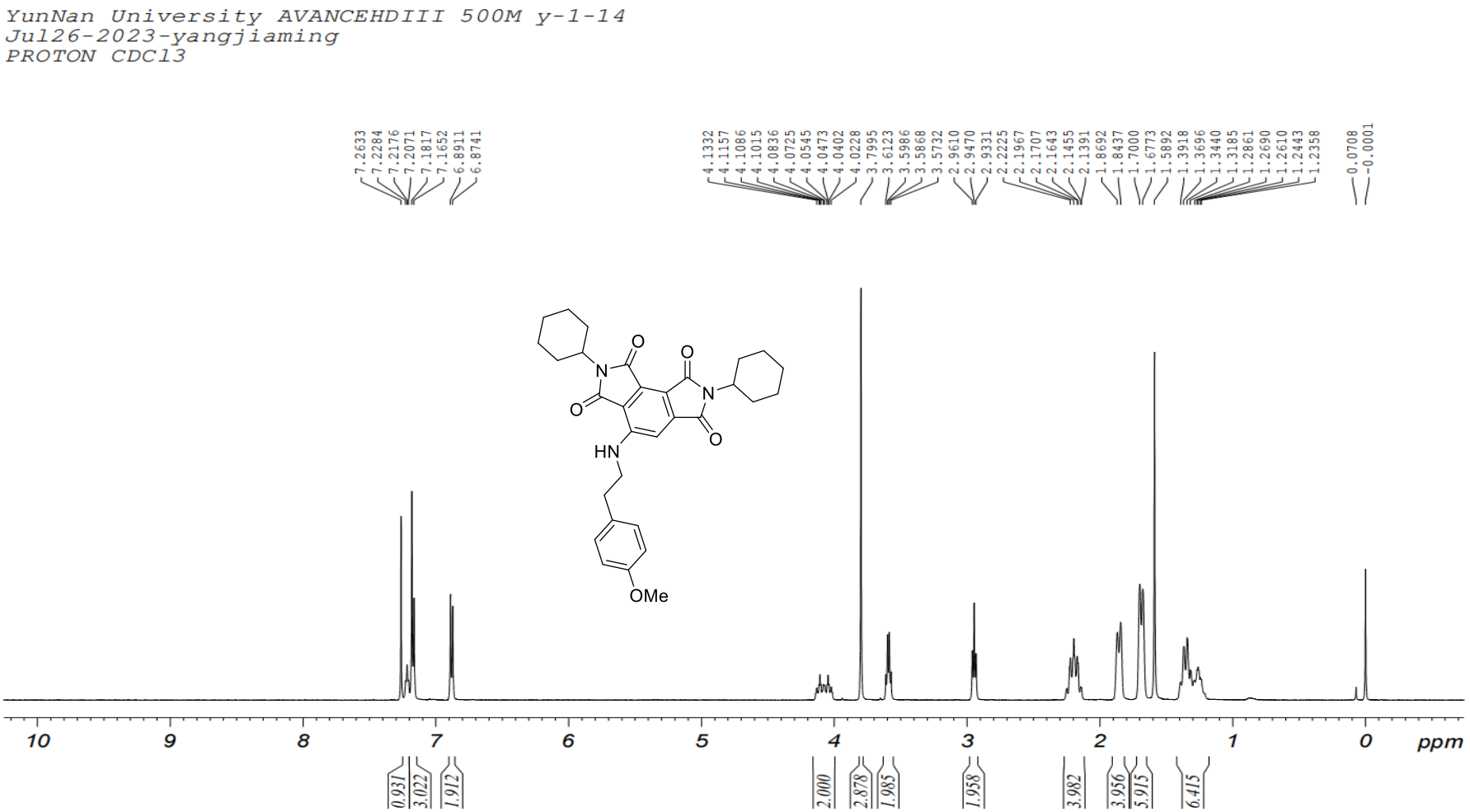


Figure S49. ^{1}H NMR (500 MHz, $CDCl_3$) spectra of compound **3w**

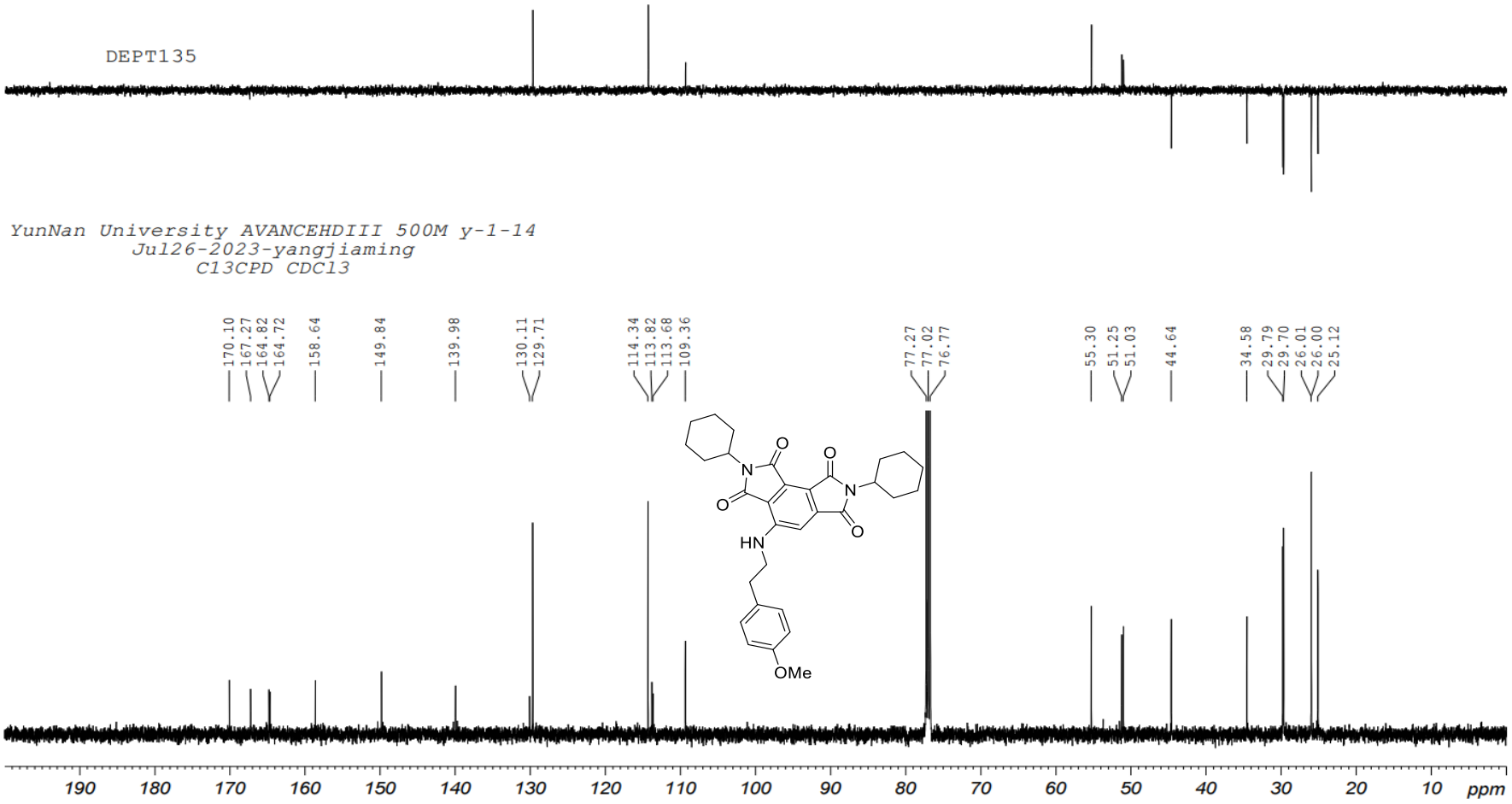


Figure S50. ^{13}C NMR (125 MHz, $CDCl_3$) spectra of compound **3w**

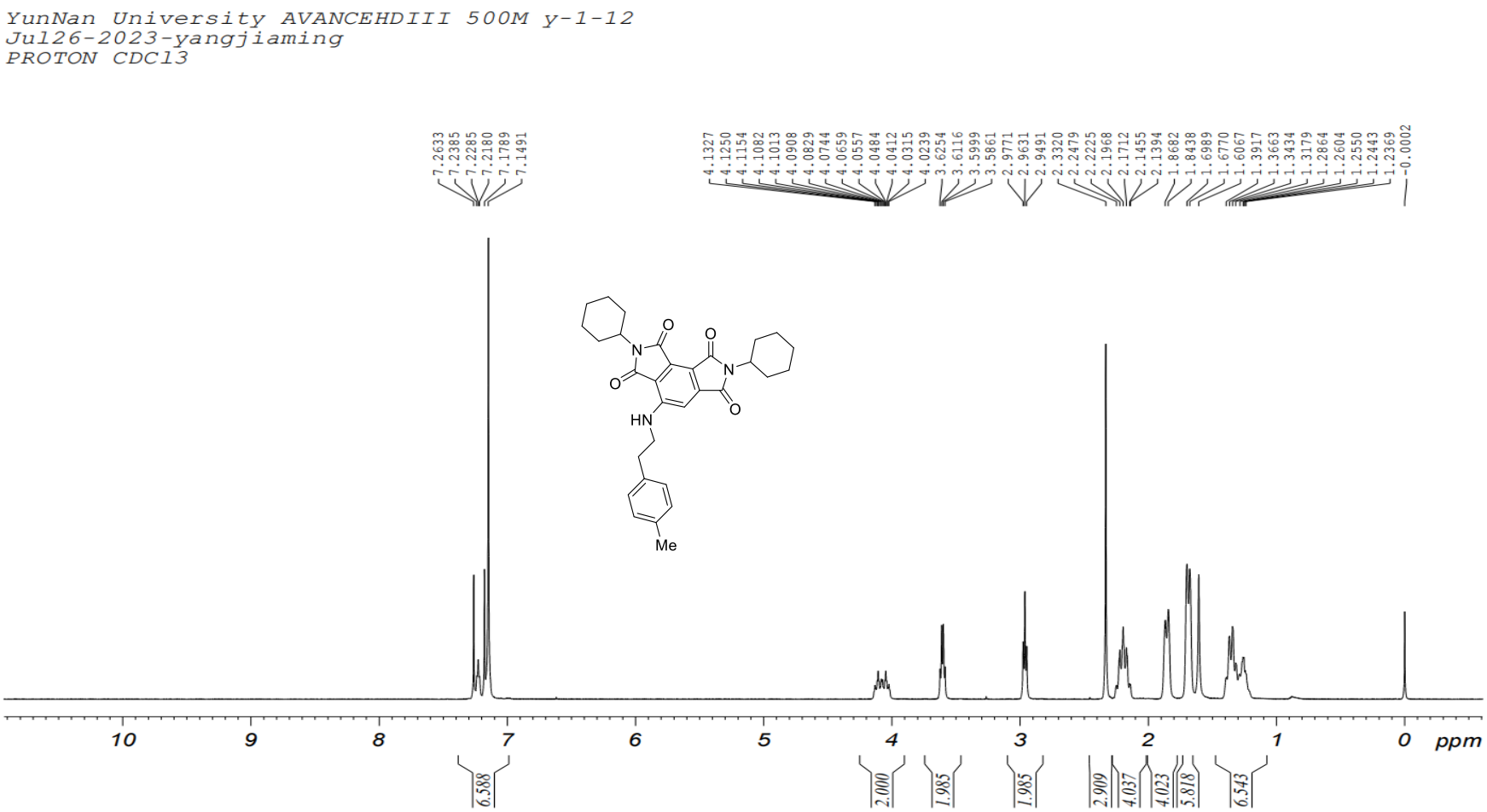


Figure S51. ^{1}H NMR (500 MHz, $CDCl_3$) spectra of compound **3x**

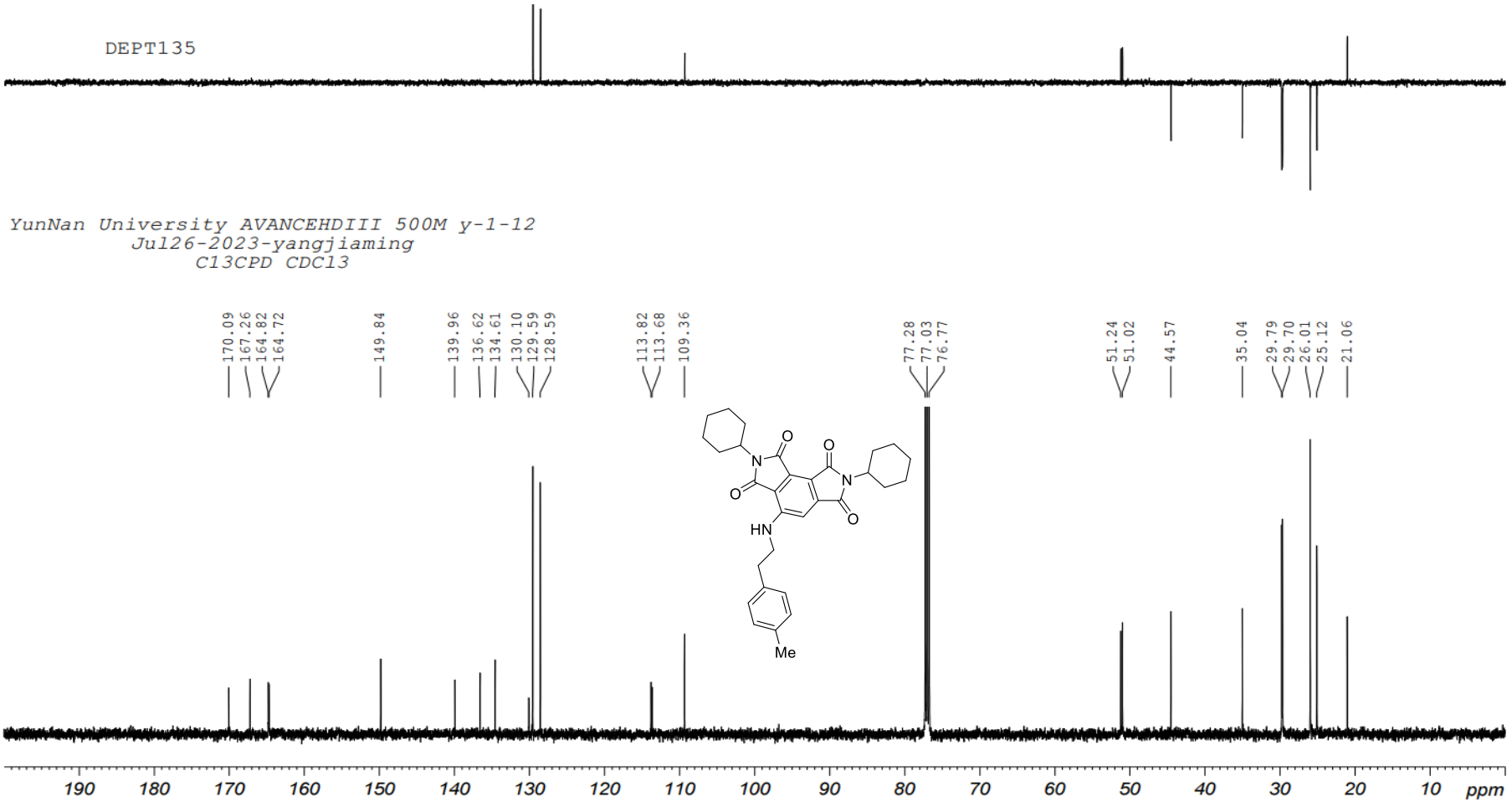


Figure S52. ^{13}C NMR (125 MHz, $CDCl_3$) spectra of compound **3x**

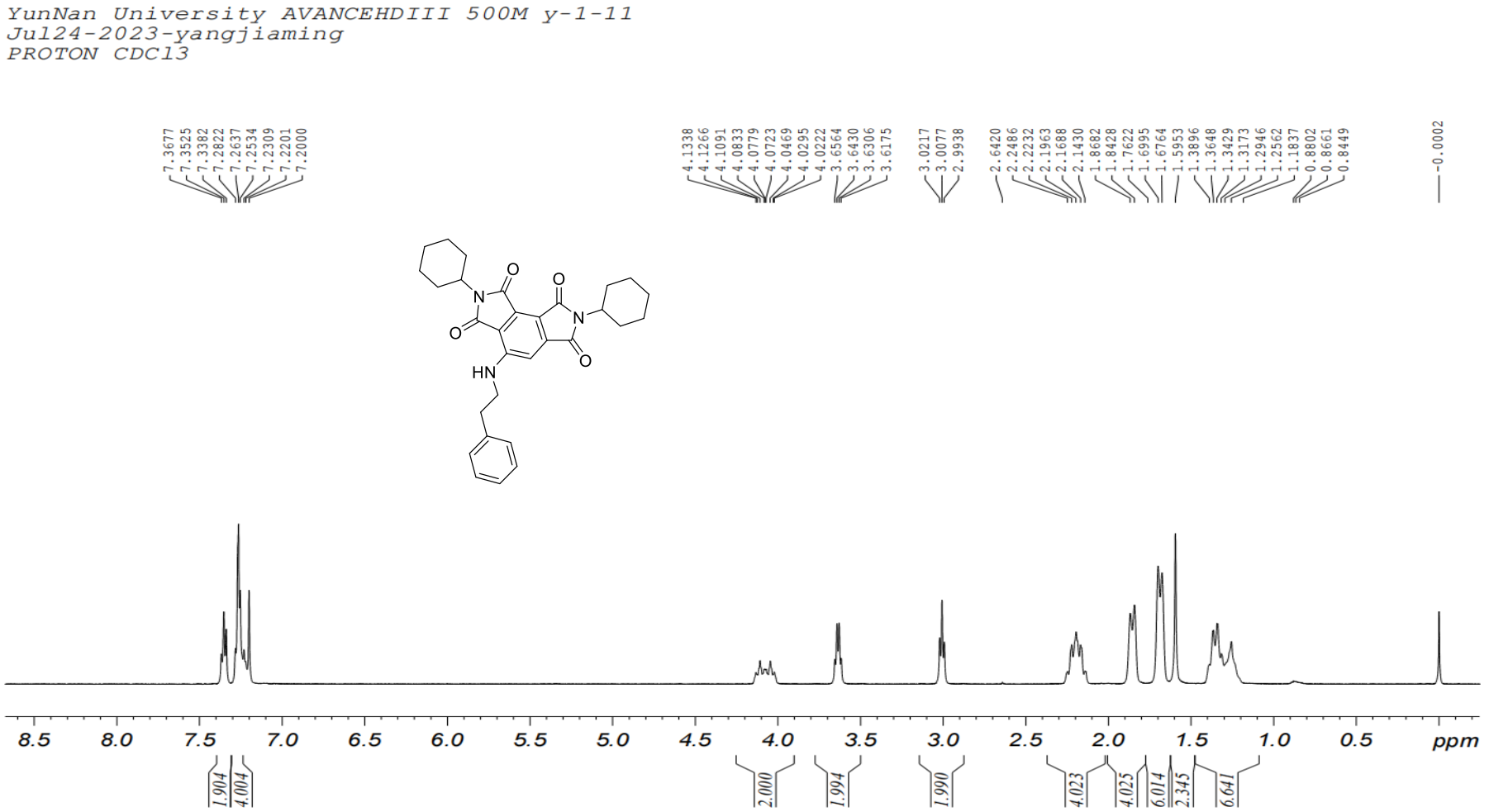


Figure S53. ^{1}H NMR (500 MHz, $CDCl_3$) spectra of compound **3y**

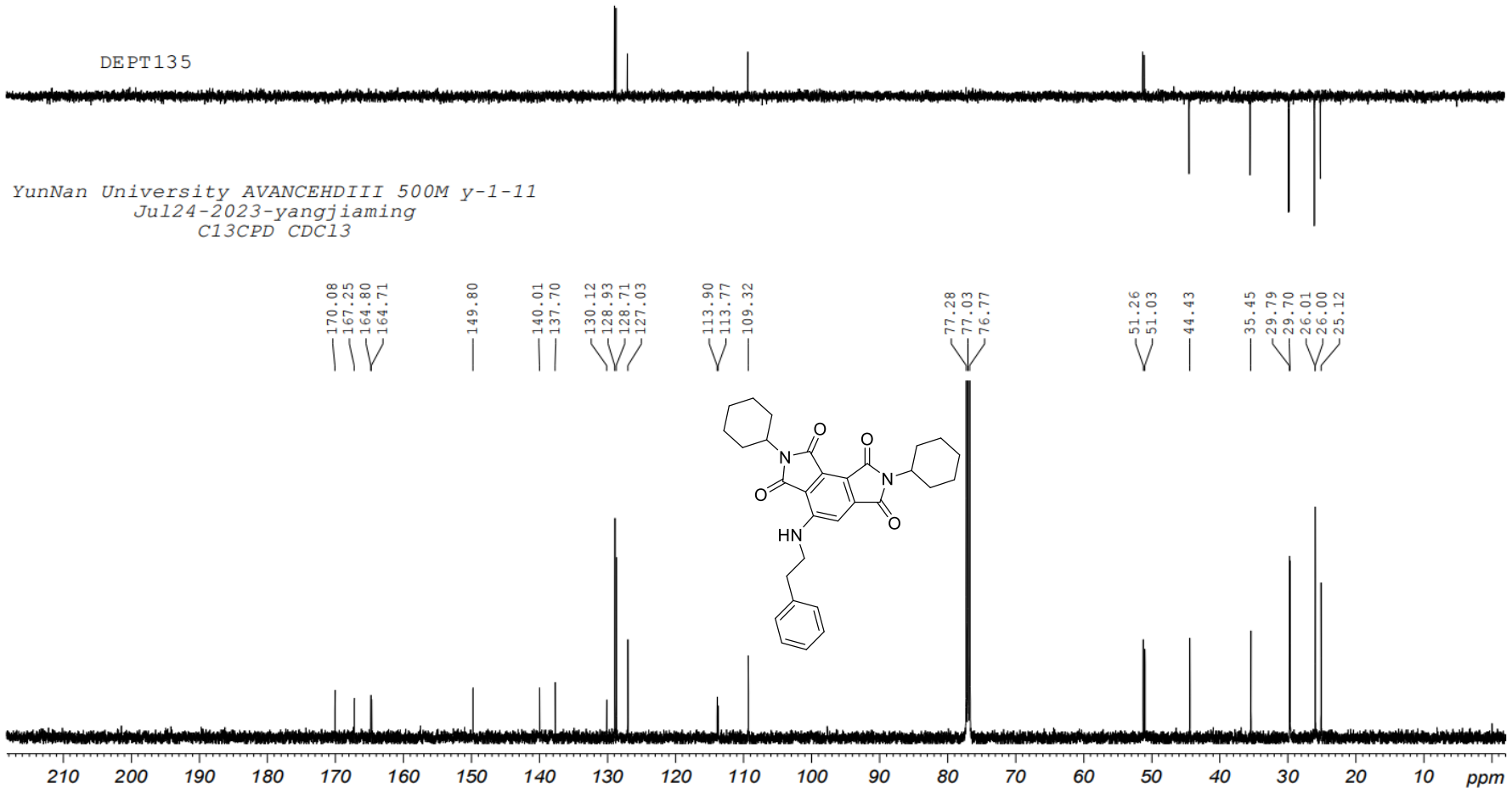


Figure S54. ^{13}C NMR (125 MHz, $CDCl_3$) spectra of compound **3y**

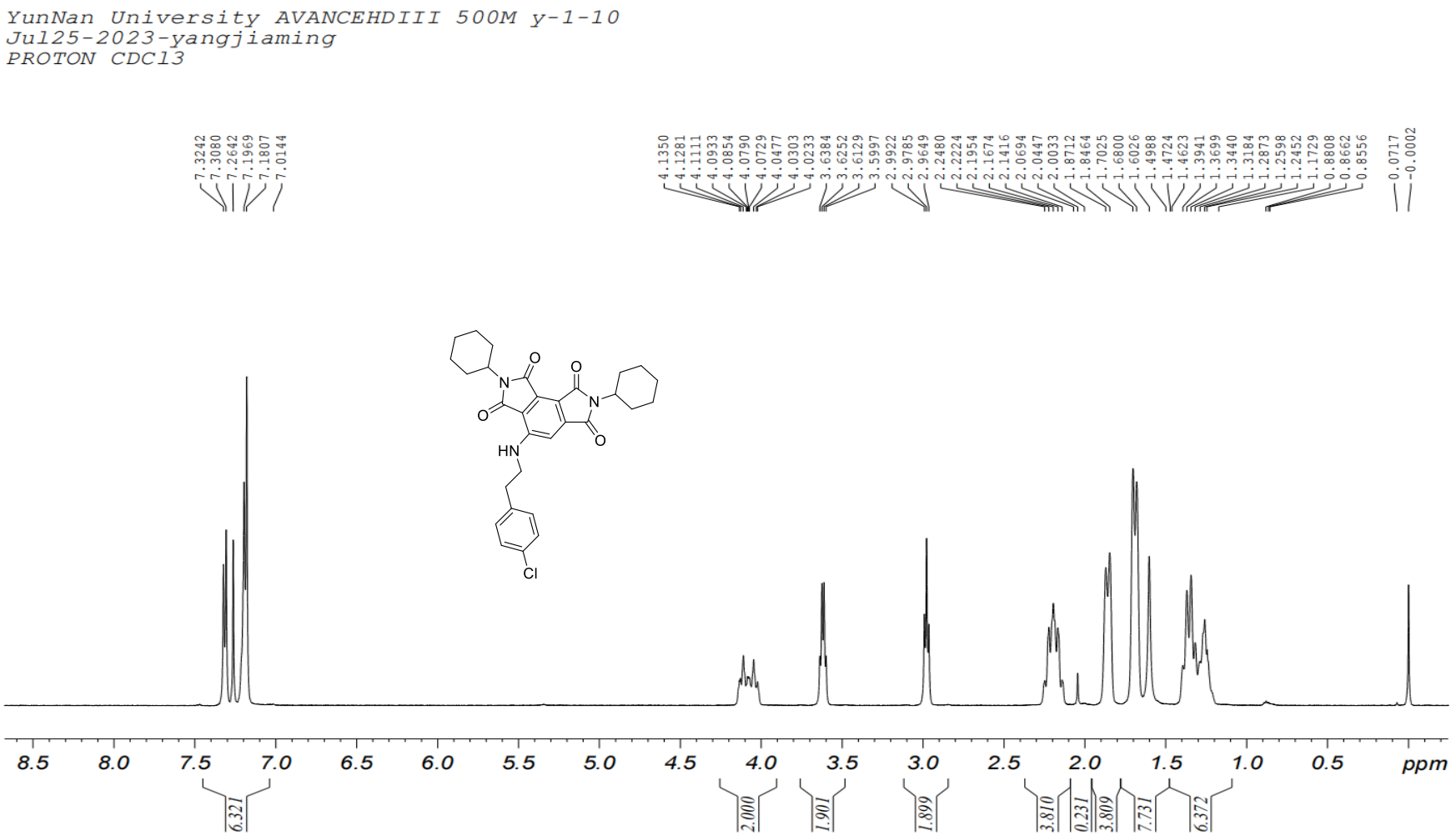


Figure S55. ^{1}H NMR (500 MHz, $CDCl_3$) spectra of compound **3z**

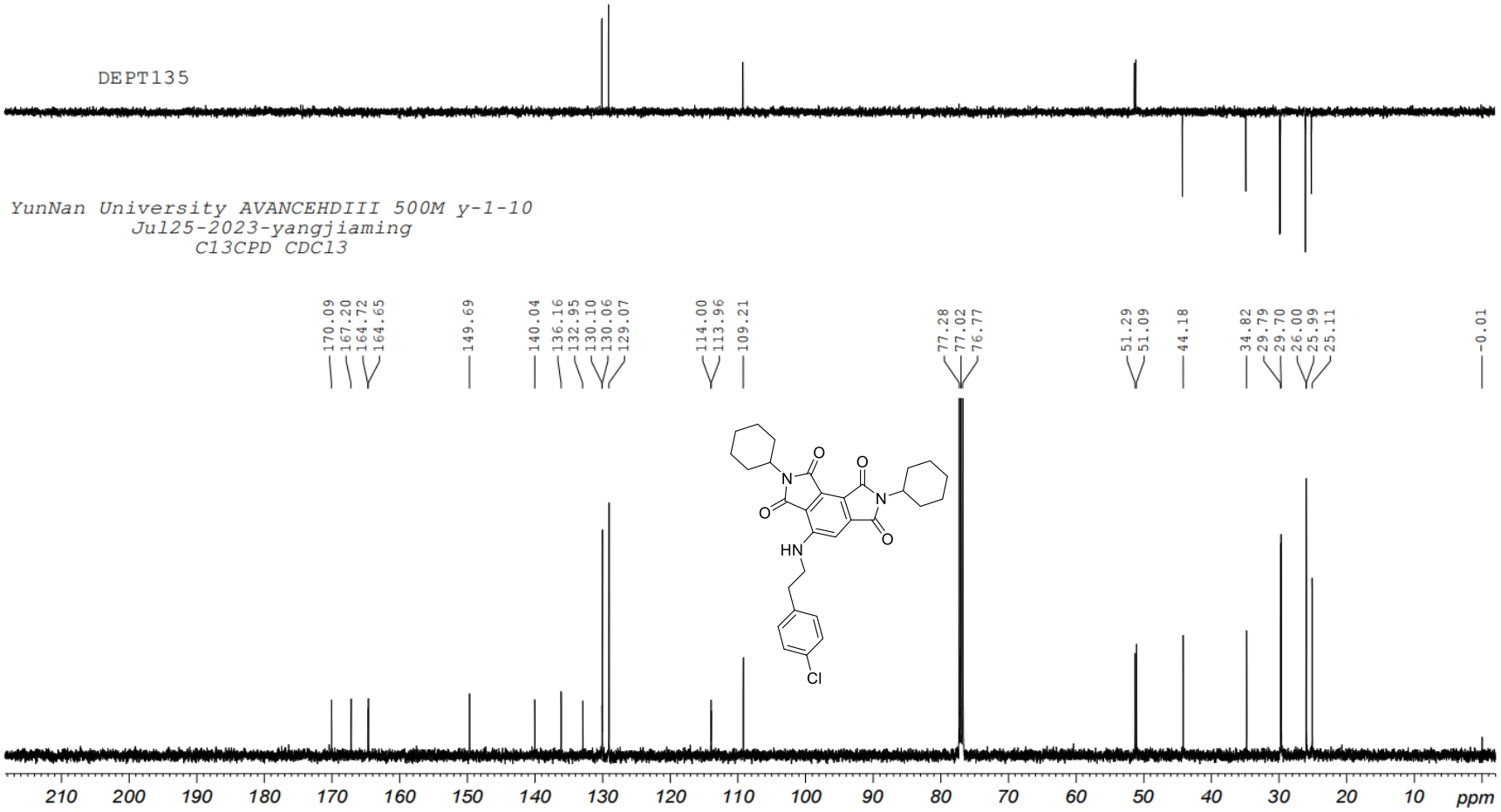


Figure S56. ^{13}C NMR (125 MHz, $CDCl_3$) spectra of compound **3z**

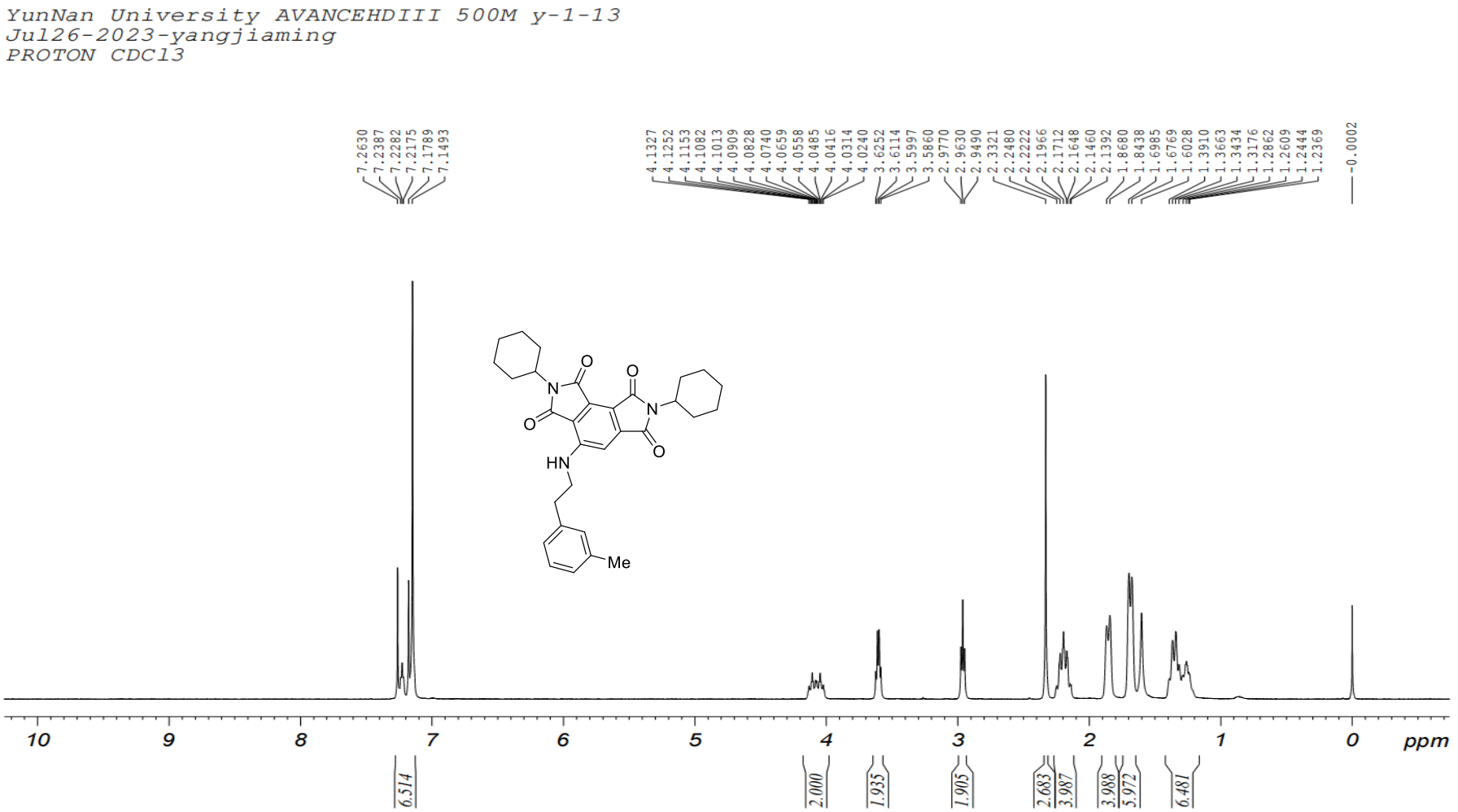


Figure S57. ^{1}H NMR (500 MHz, $CDCl_3$) spectra of compound **3a'**

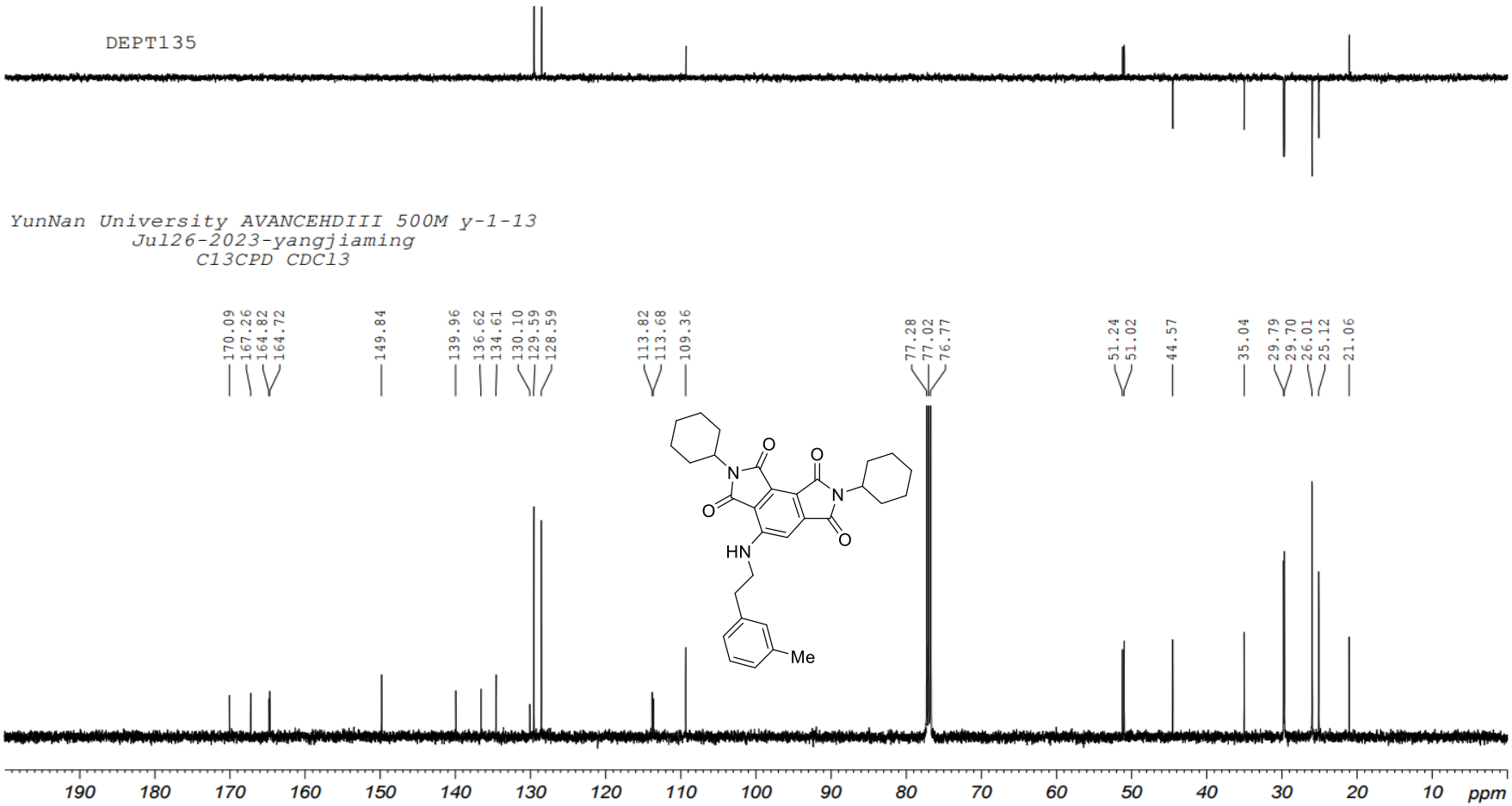


Figure S58. ^{13}C NMR (125 MHz, $CDCl_3$) spectra of compound **3a'**

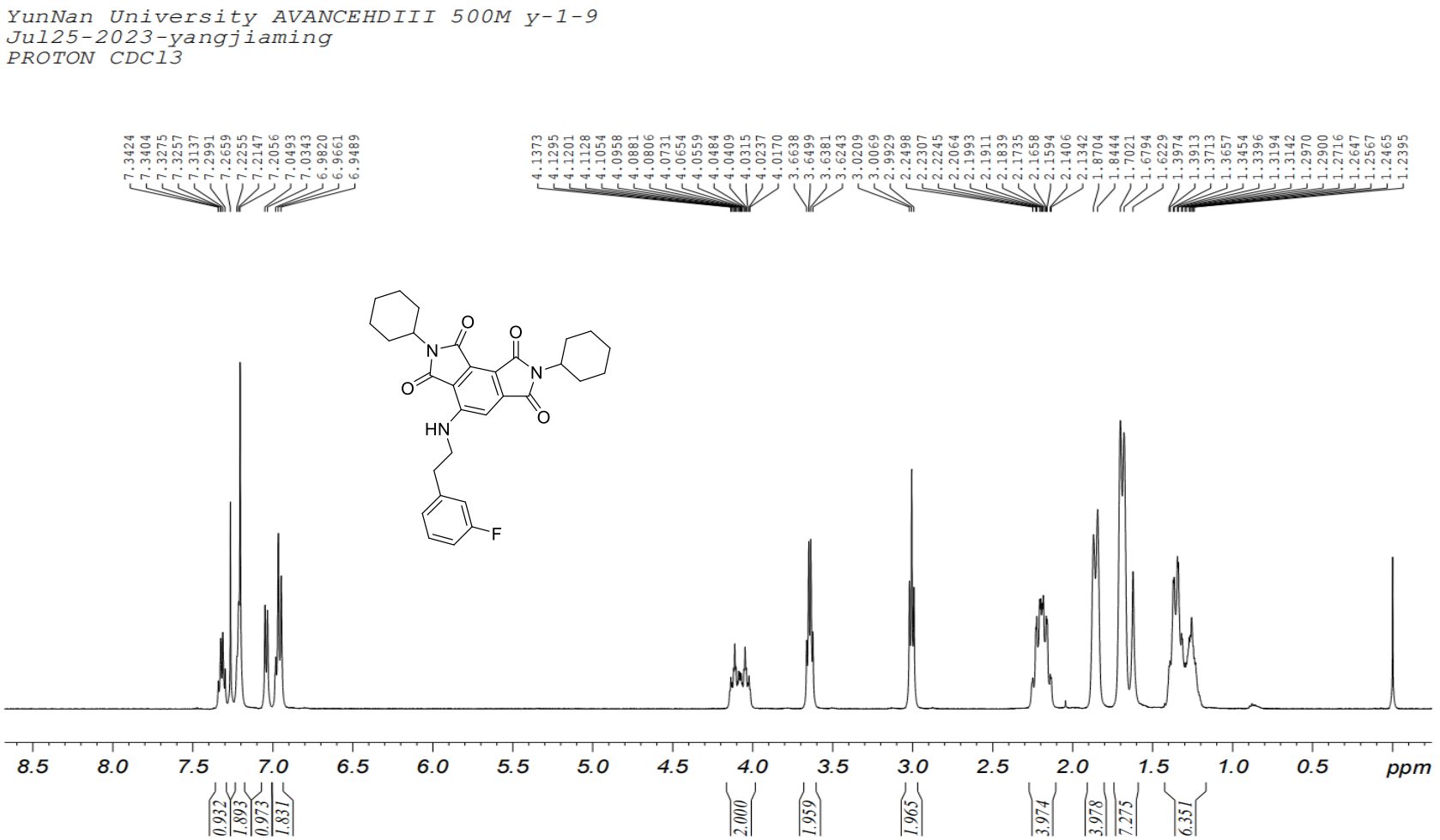


Figure S59. ^{1}H NMR (500 MHz, $CDCl_3$) spectra of compound **3b'**

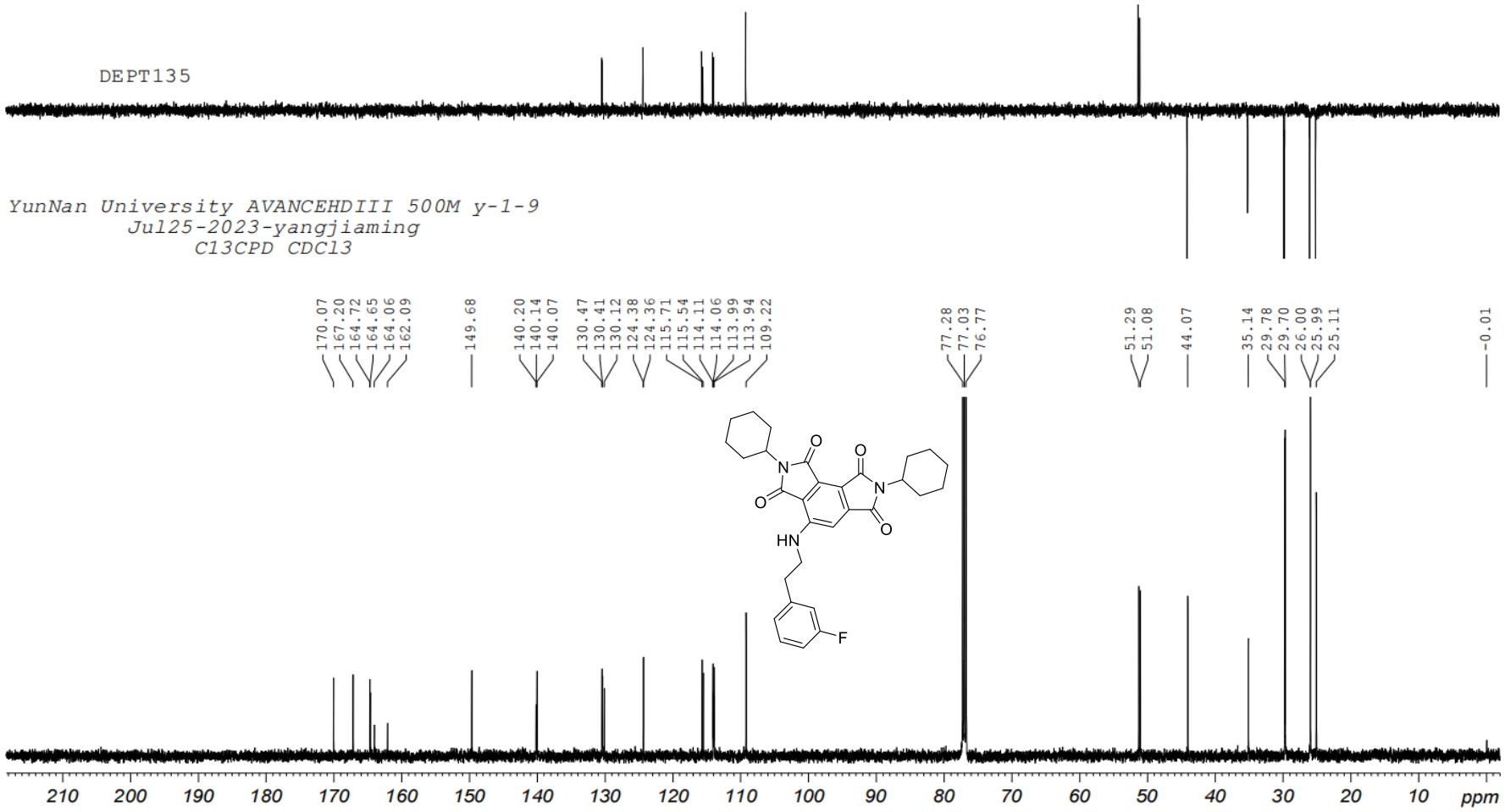


Figure S60. ^{13}C NMR (125 MHz, $CDCl_3$) spectra of compound **3b'**

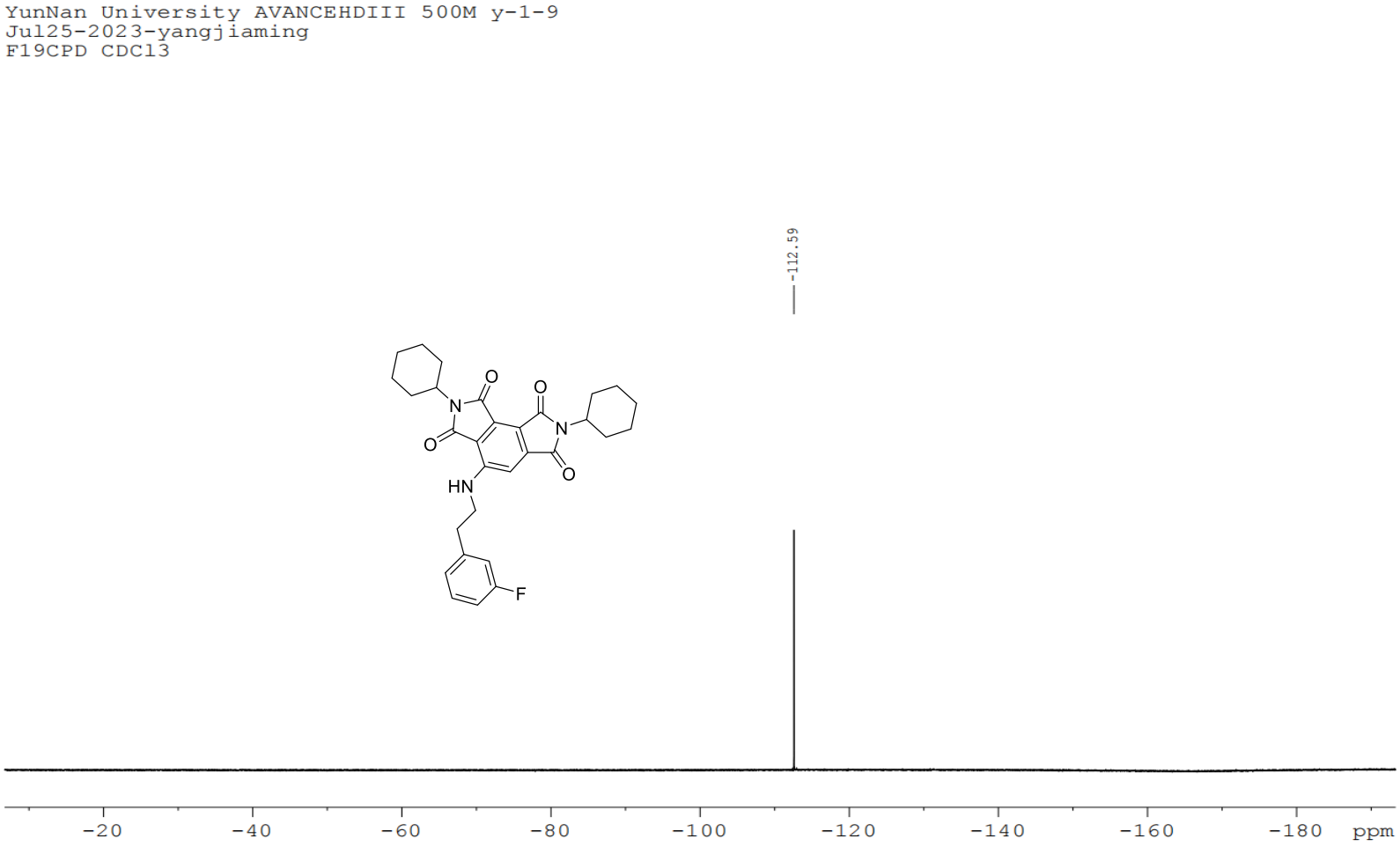


Figure S61. ^{19}F NMR (470 MHz, $CDCl_3$) spectra of compound **3b'**

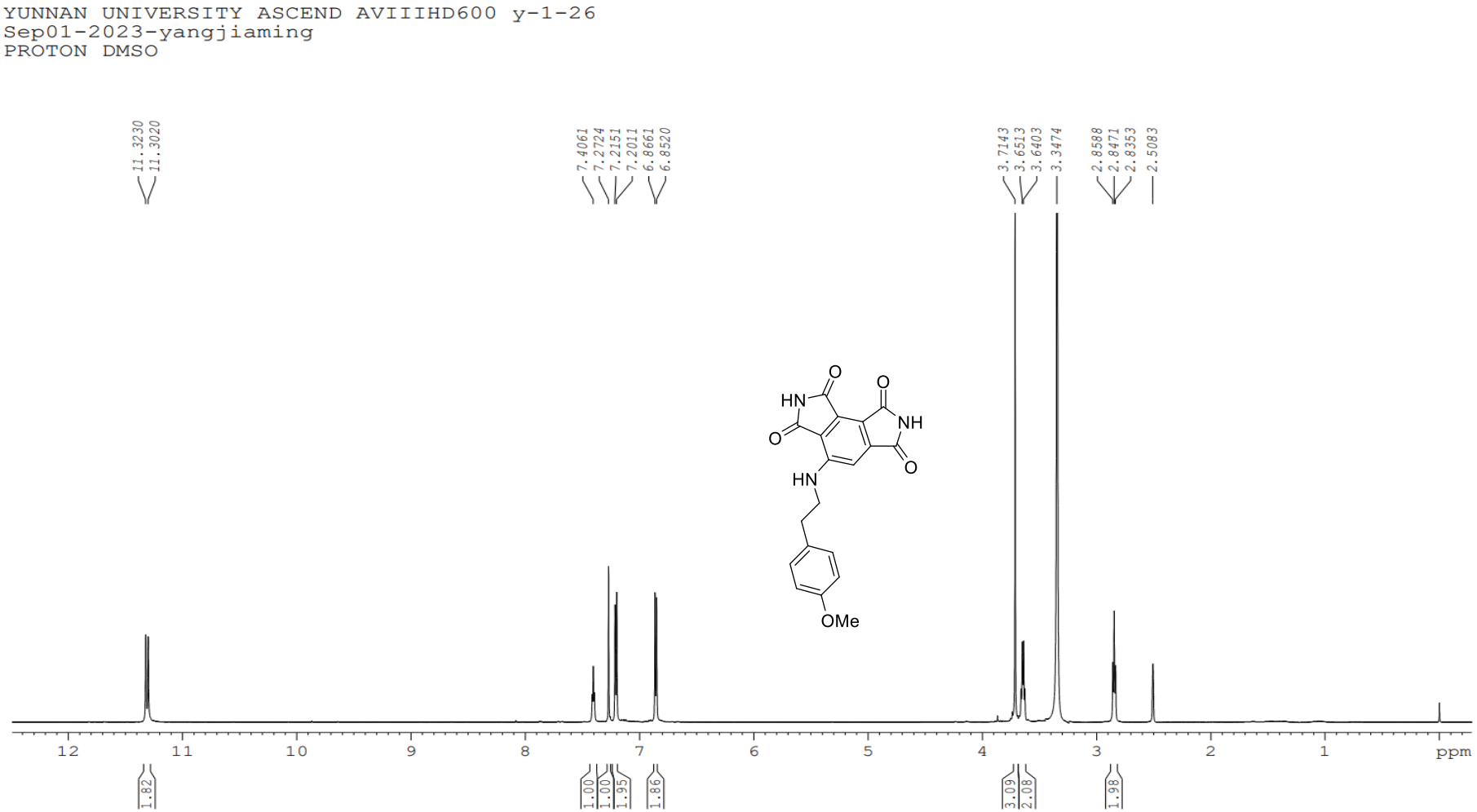


Figure S62. ^{1}H NMR (600 MHz, DMSO-d_6) spectra of compound **3c'**

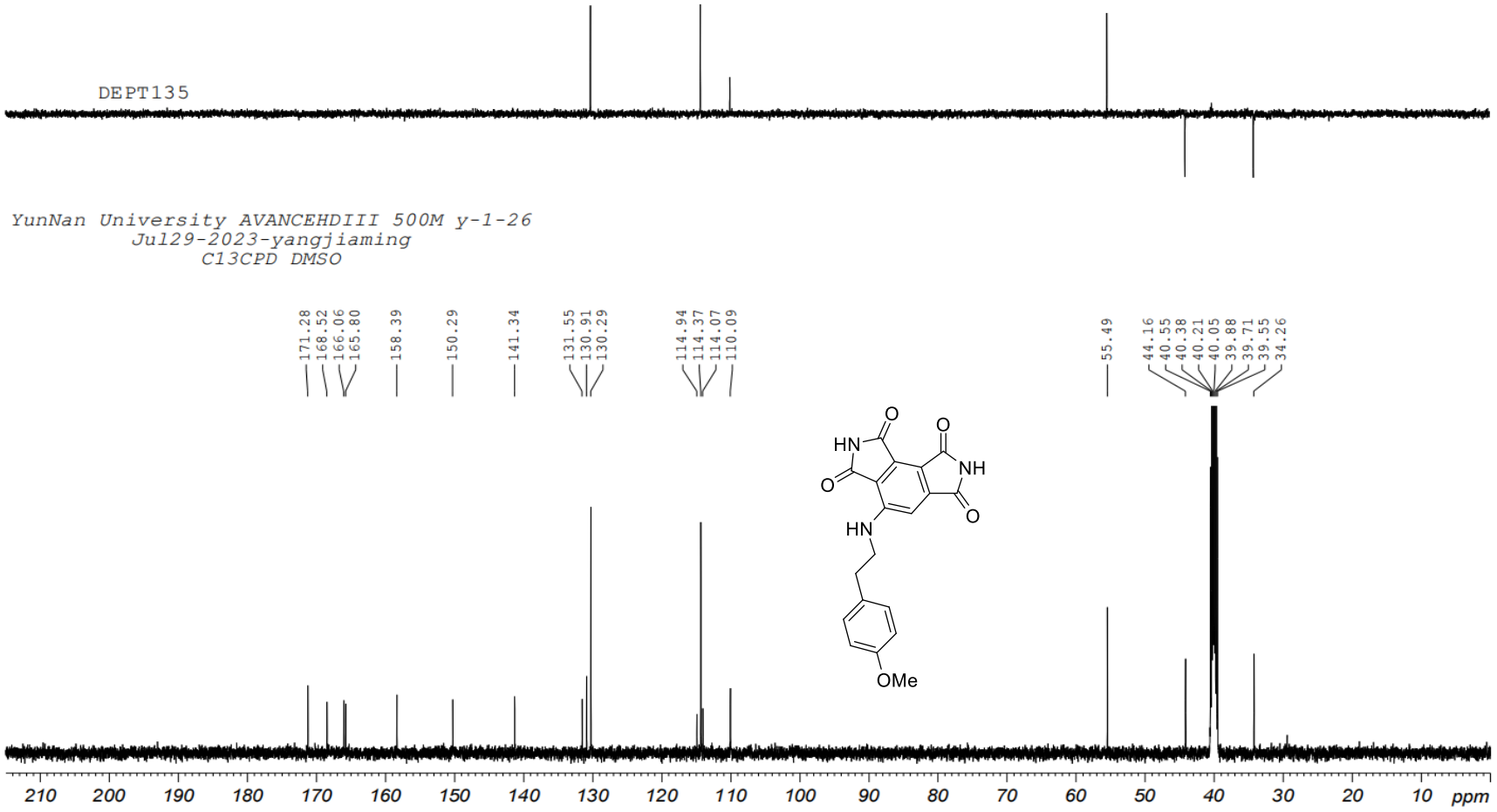


Figure S63. ^{13}C NMR (150 MHz, DMSO-d_6) spectra of compound **3c'**

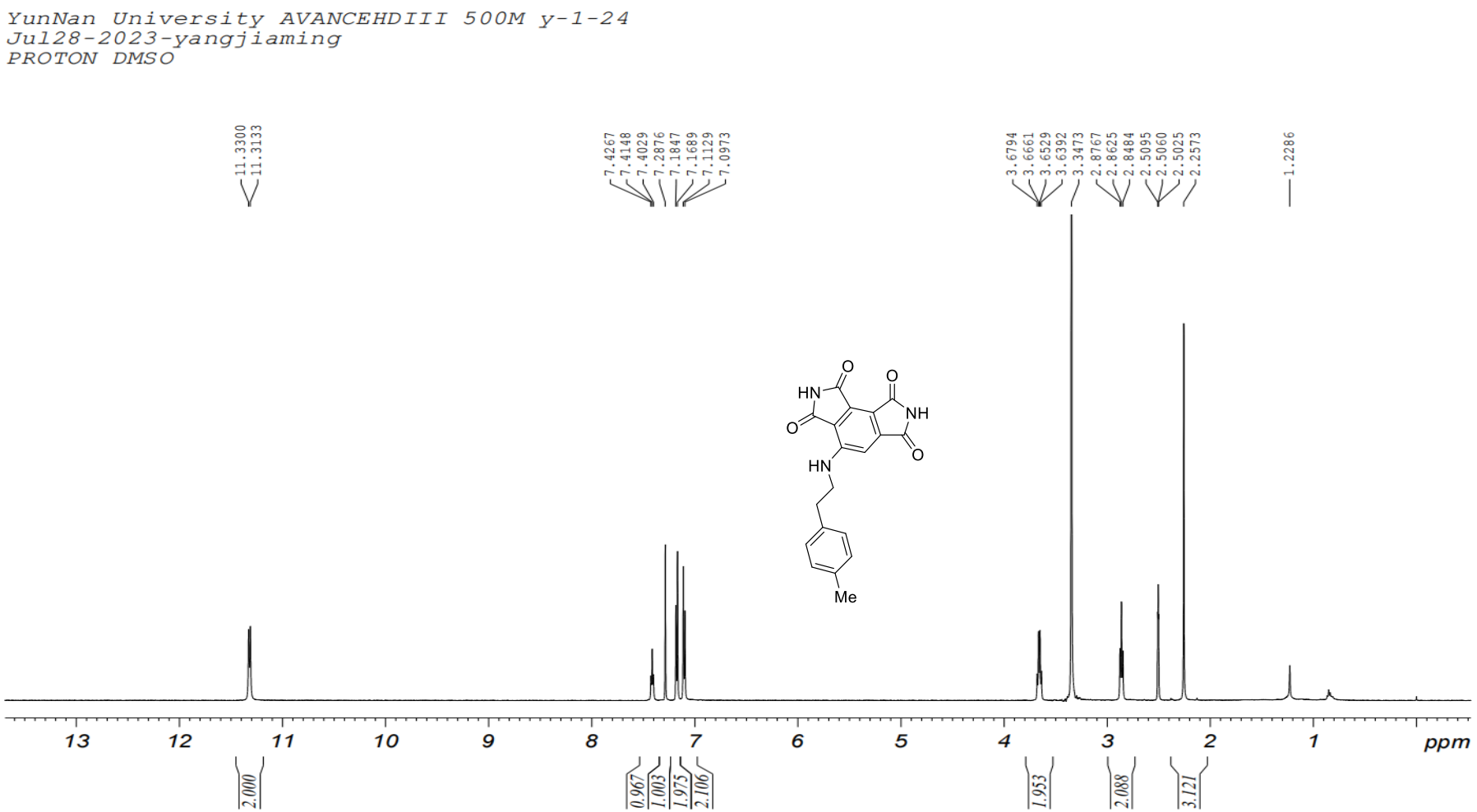


Figure S64. ^{1}H NMR (500 MHz, DMSO-d_6) spectra of compound **3d'**

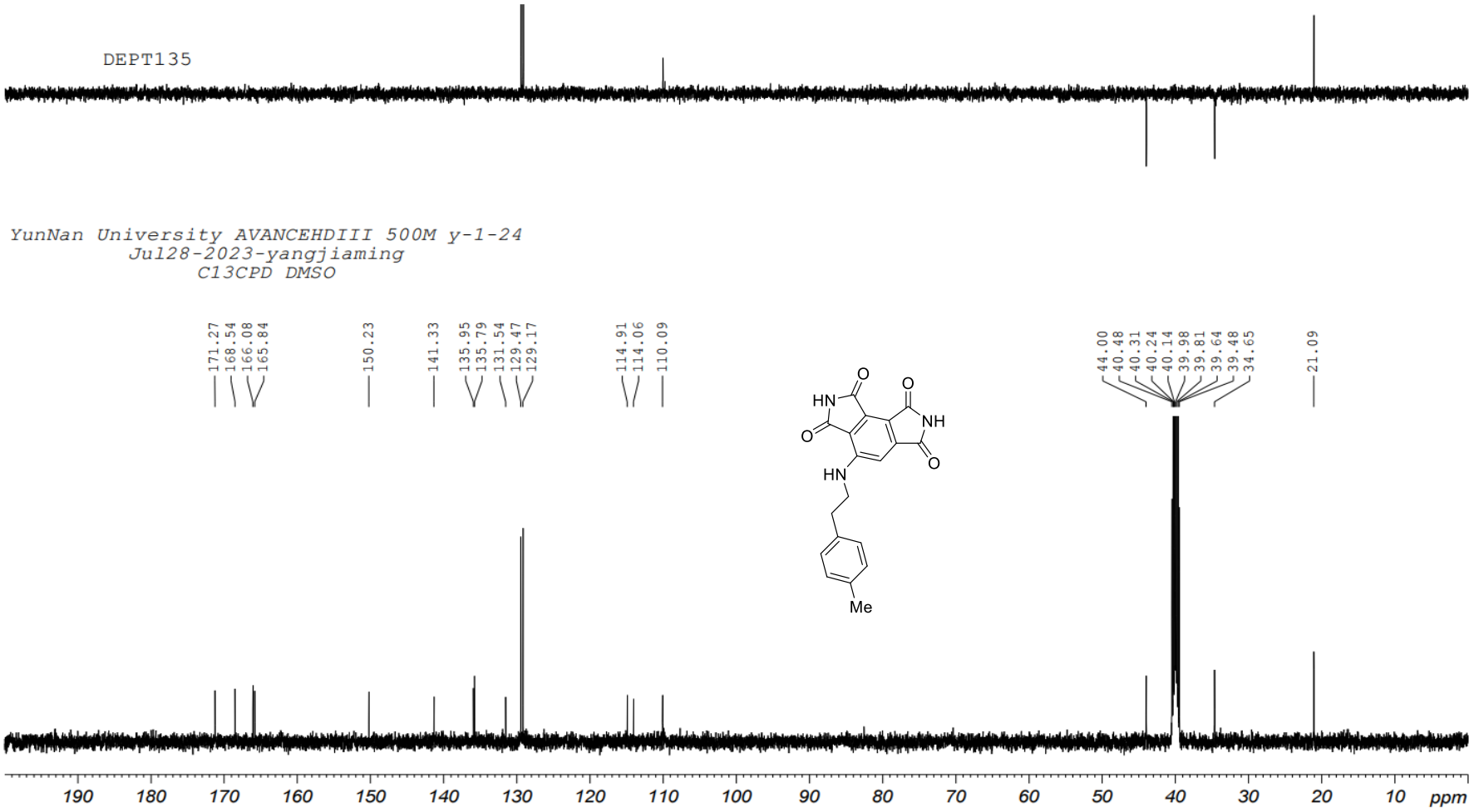


Figure S65. ^{13}C NMR (125 MHz, DMSO-d_6) spectra of compound **3d'**

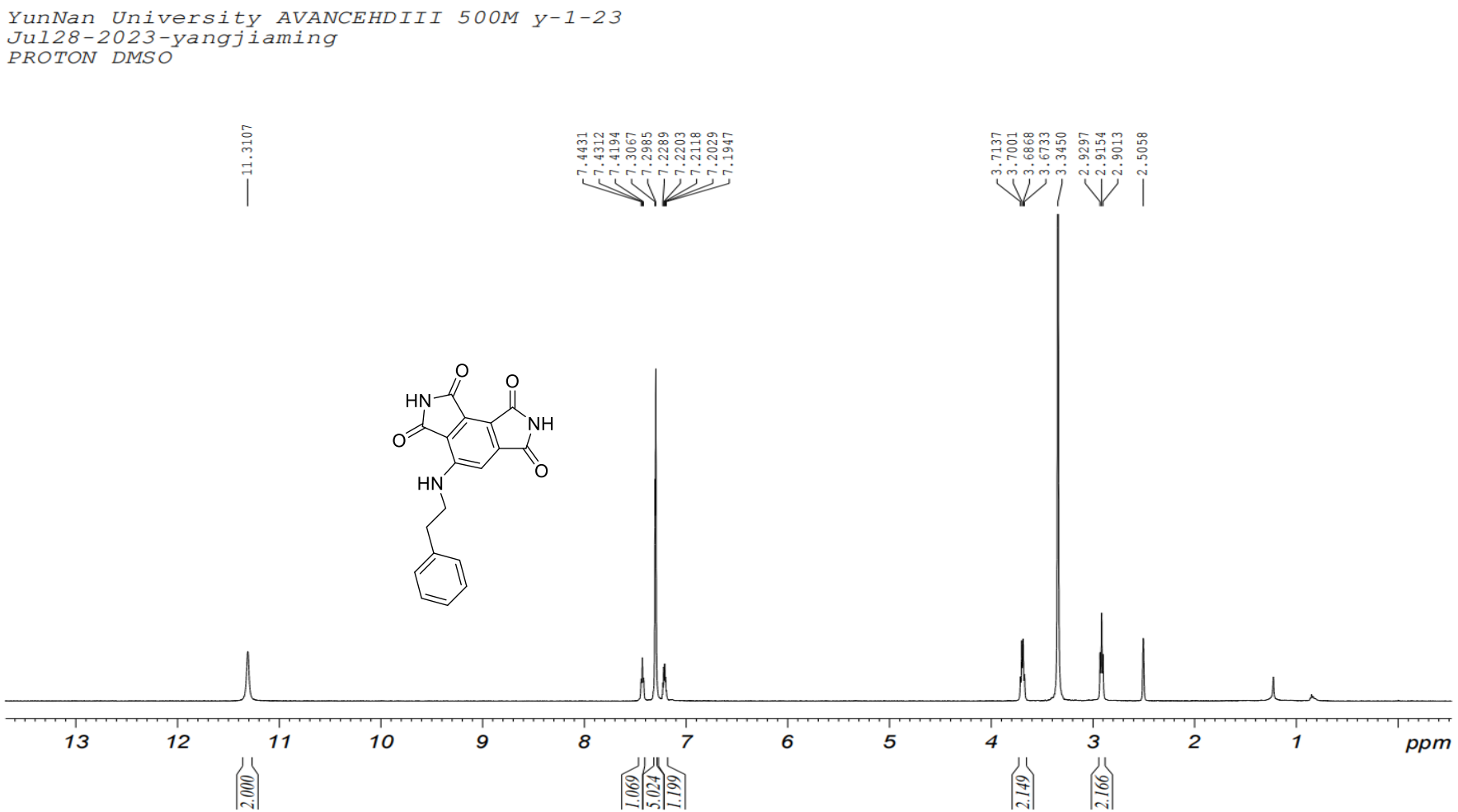


Figure S66. ^{1}H NMR (500 MHz, DMSO-d_6) spectra of compound **3e'**

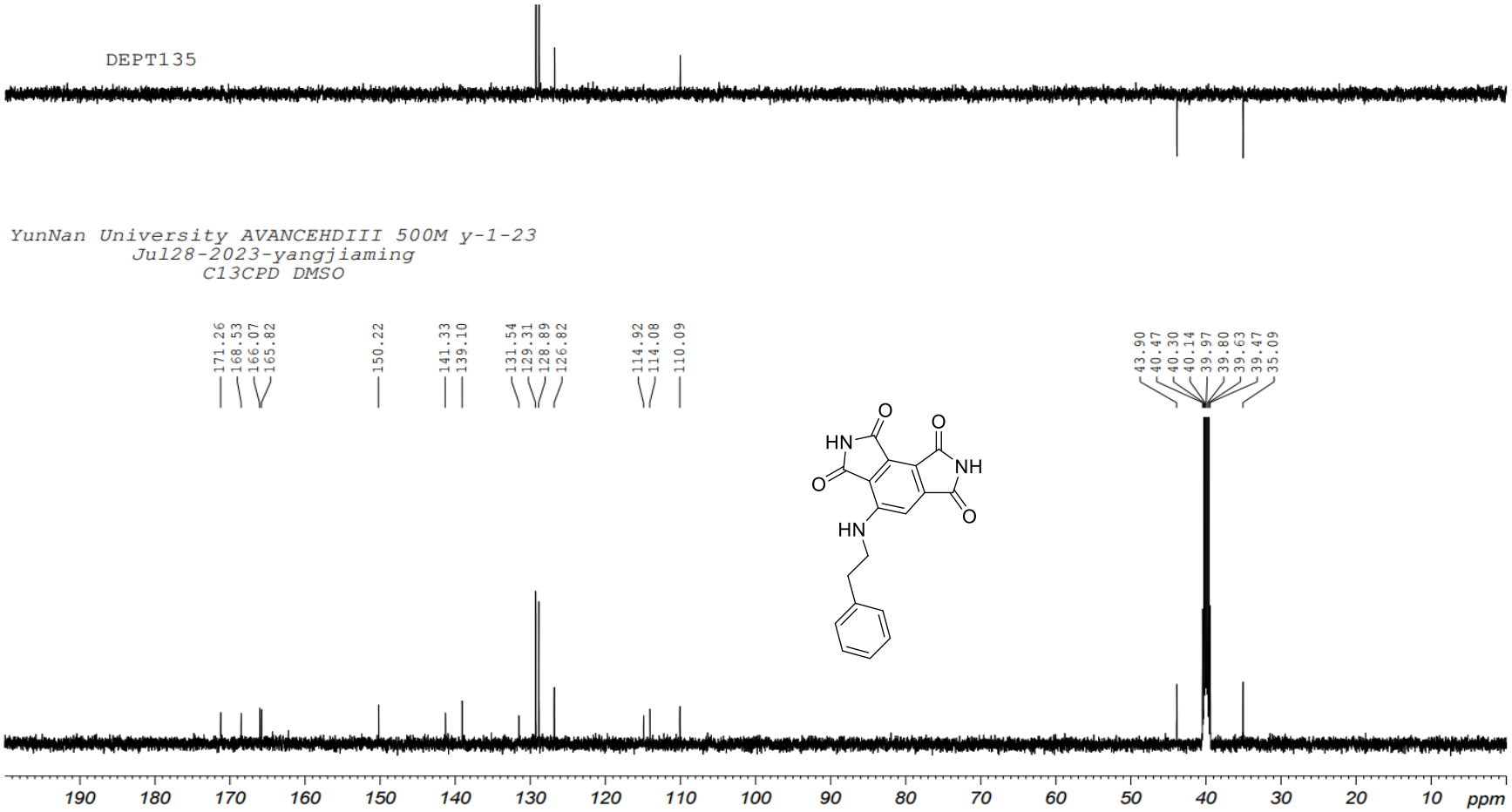


Figure S67. ^{13}C NMR (125 MHz, DMSO-d_6) spectra of compound **3e'**

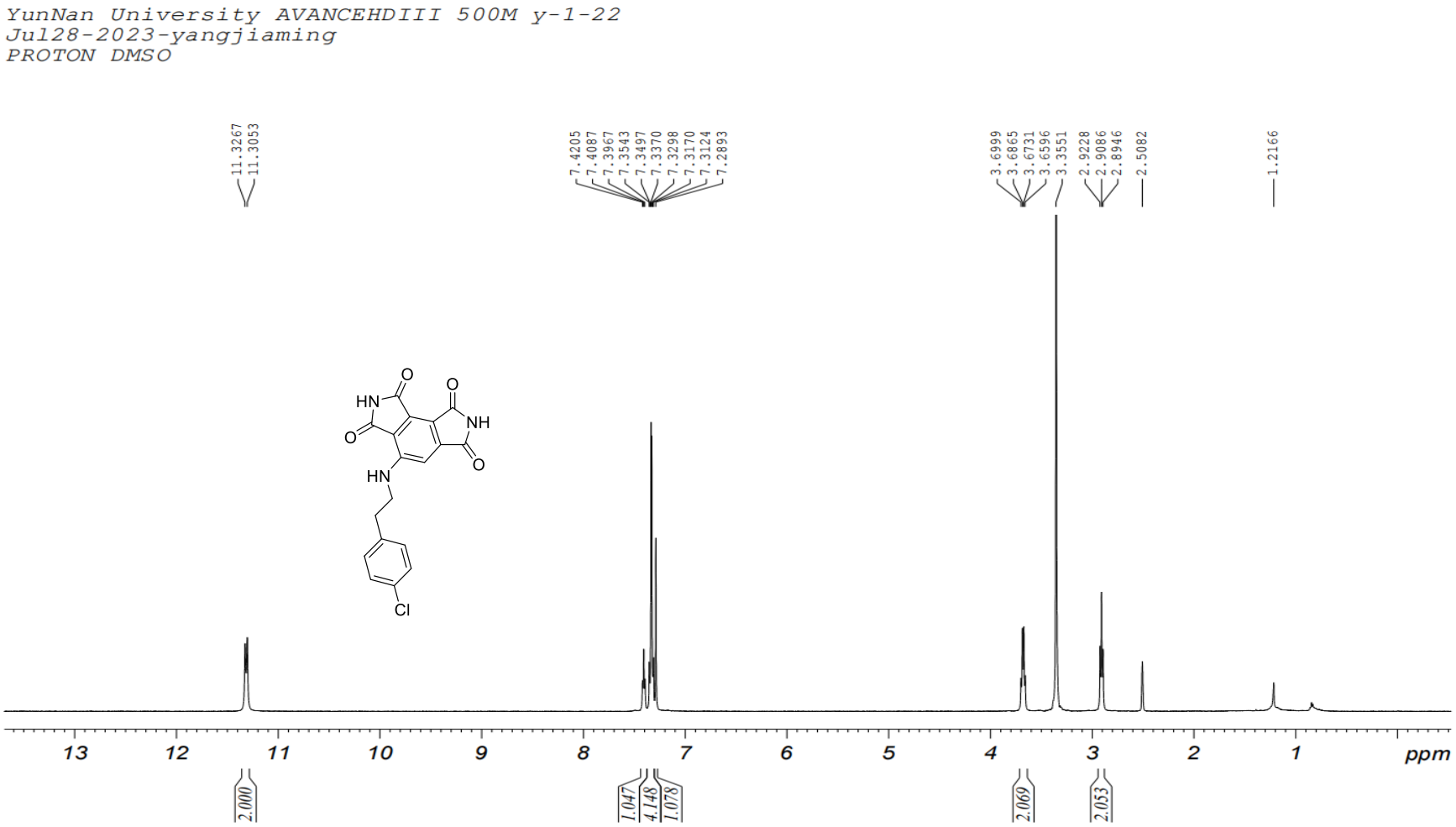


Figure S68. ^{1}H NMR (500 MHz, DMSO-d_6) spectra of compound **3f'**

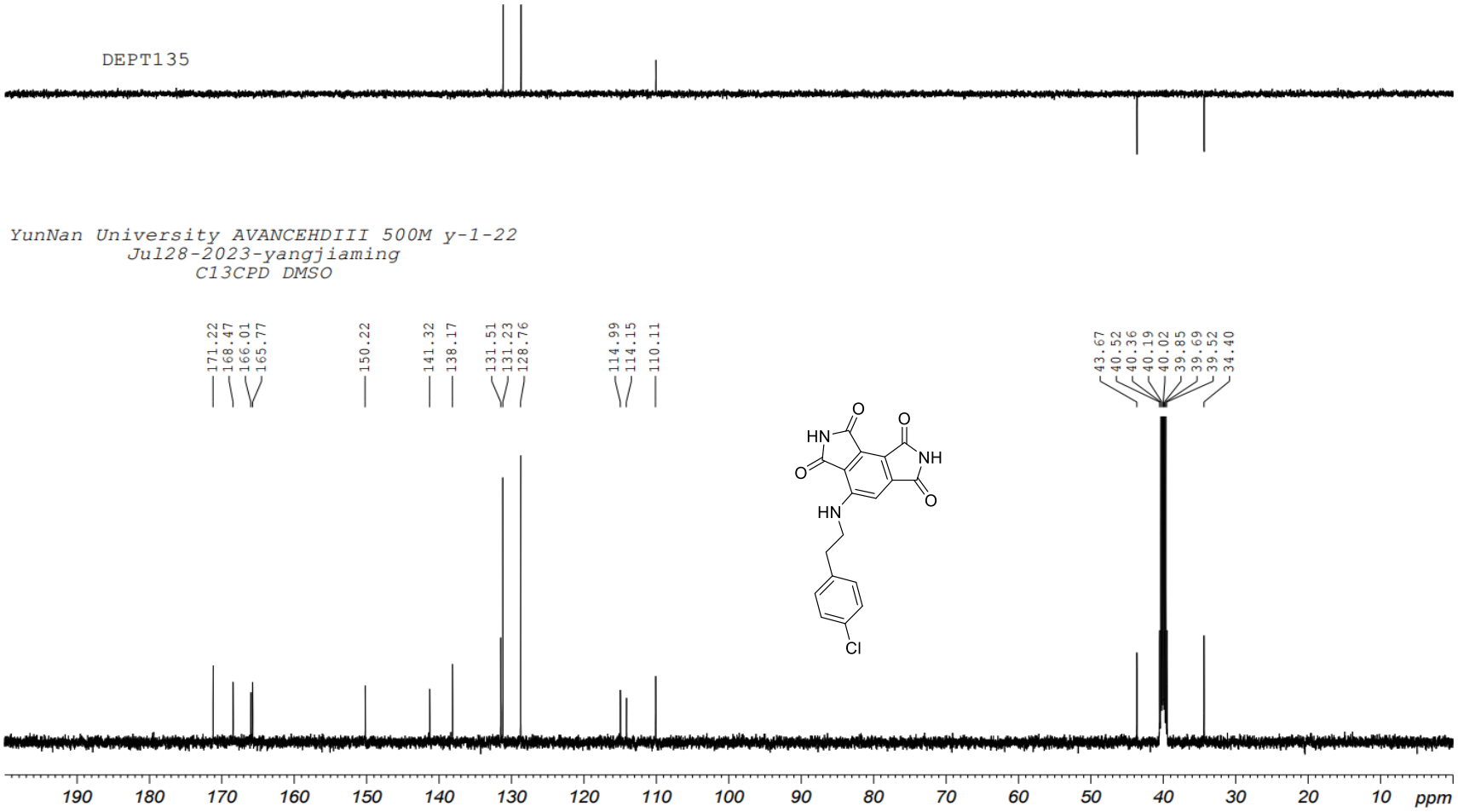


Figure S69. ^{13}C NMR (125 MHz, DMSO-d_6) spectra of compound **3f'**

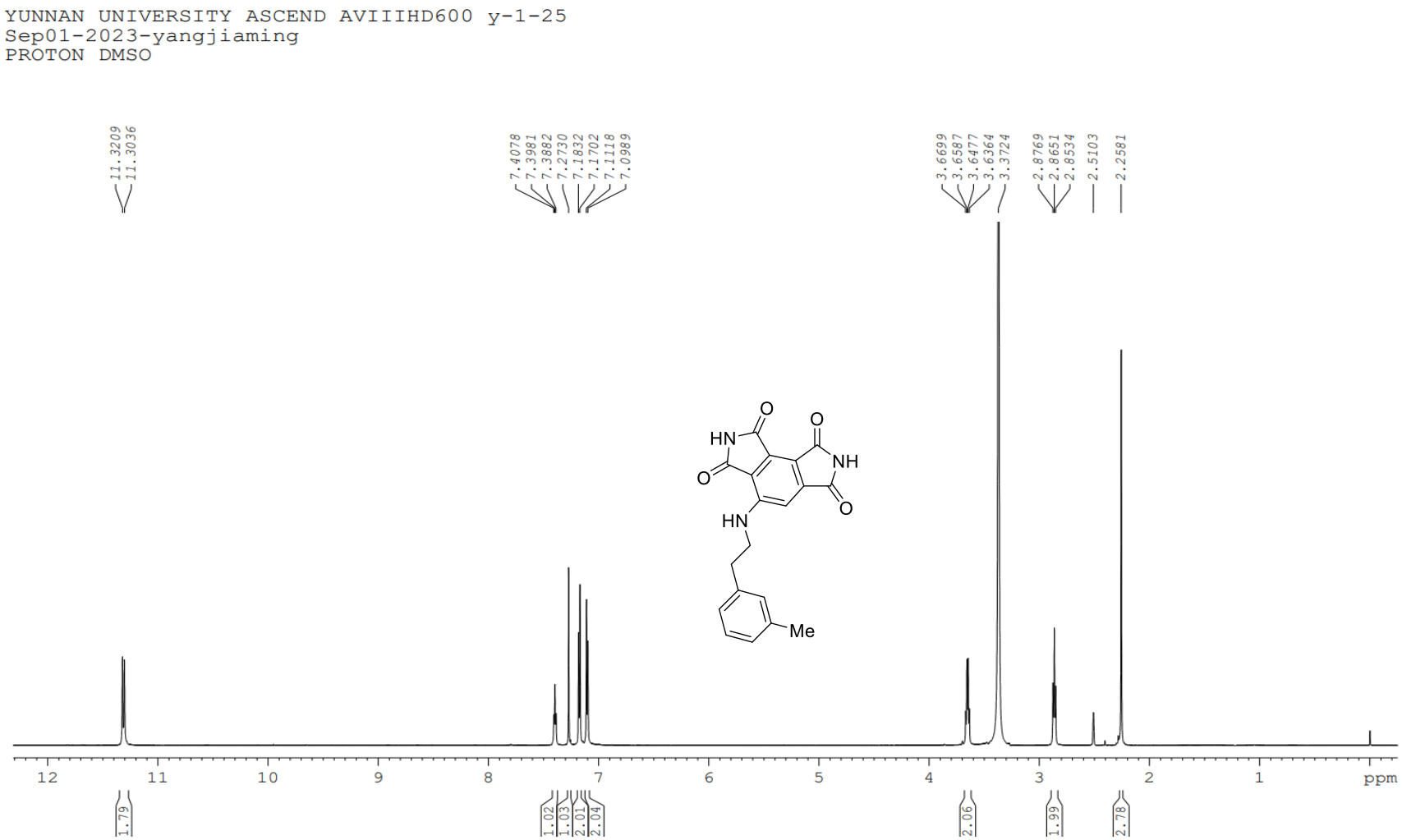


Figure S70. ^{1}H NMR (600 MHz, DMSO-d_6) spectra of compound **3g'**

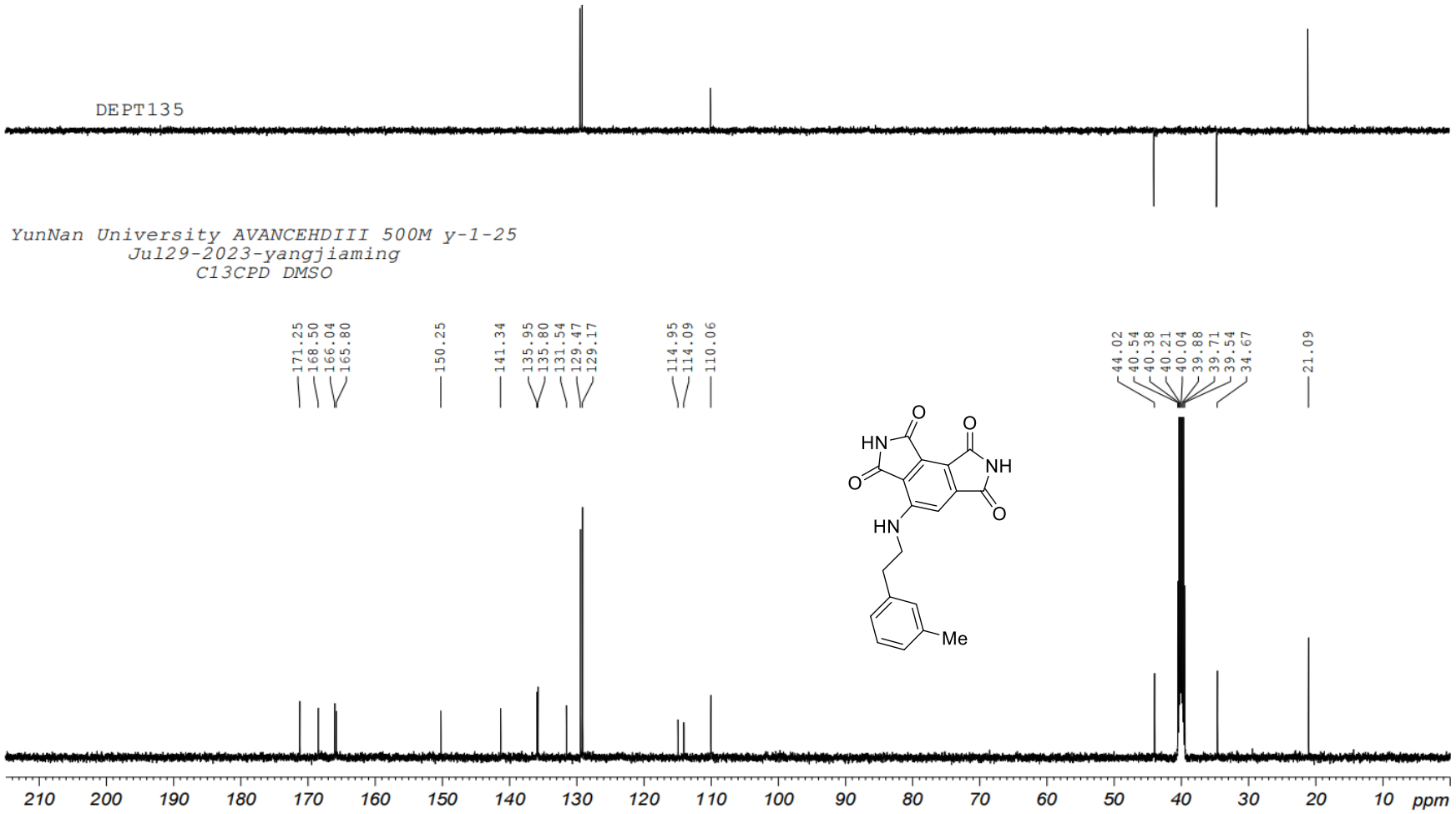


Figure S71. ^{13}C NMR (125 MHz, DMSO-d_6) spectra of compound **3g'**

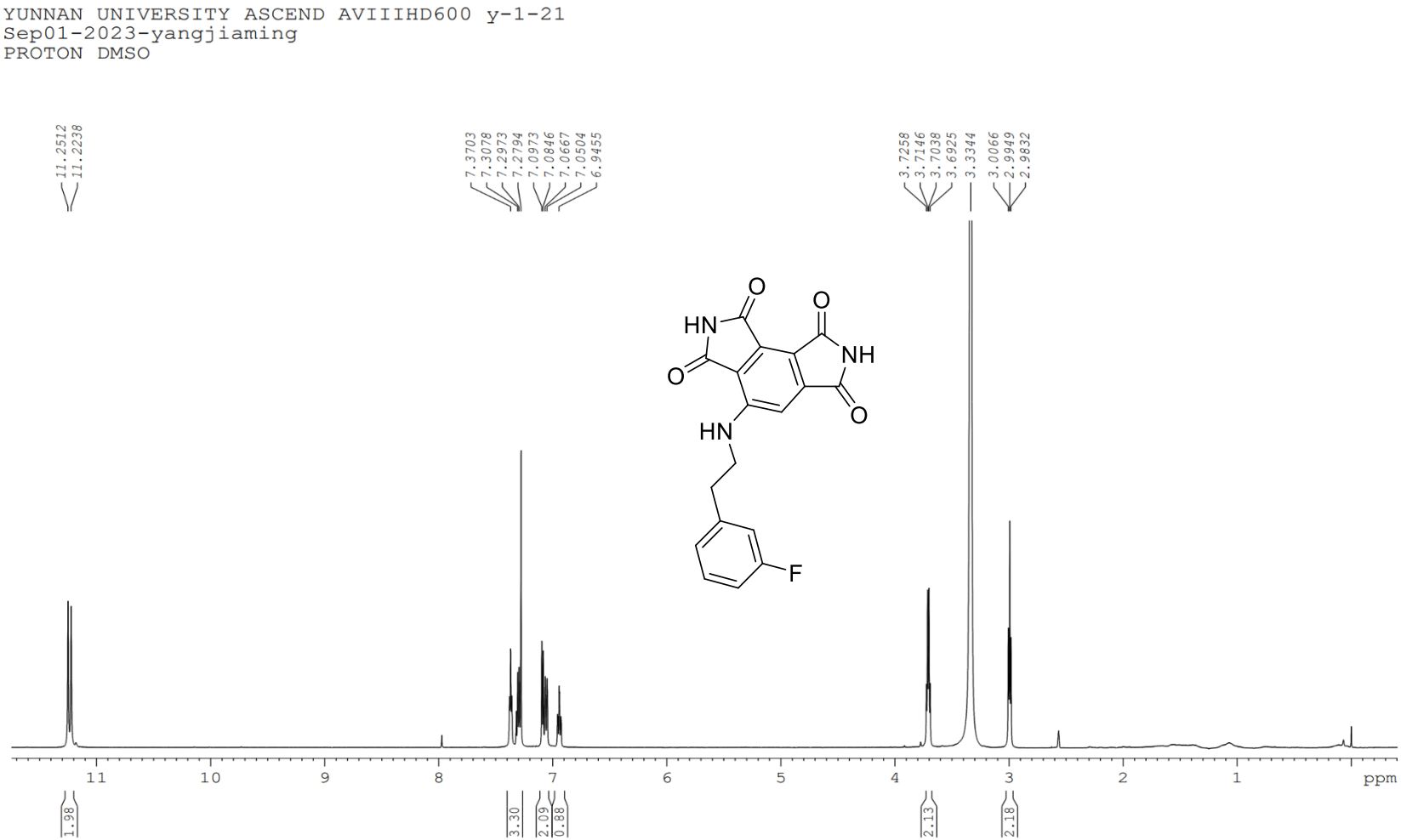


Figure S72. ^{1}H NMR (600 MHz, DMSO-d_6) spectra of compound **3h'**

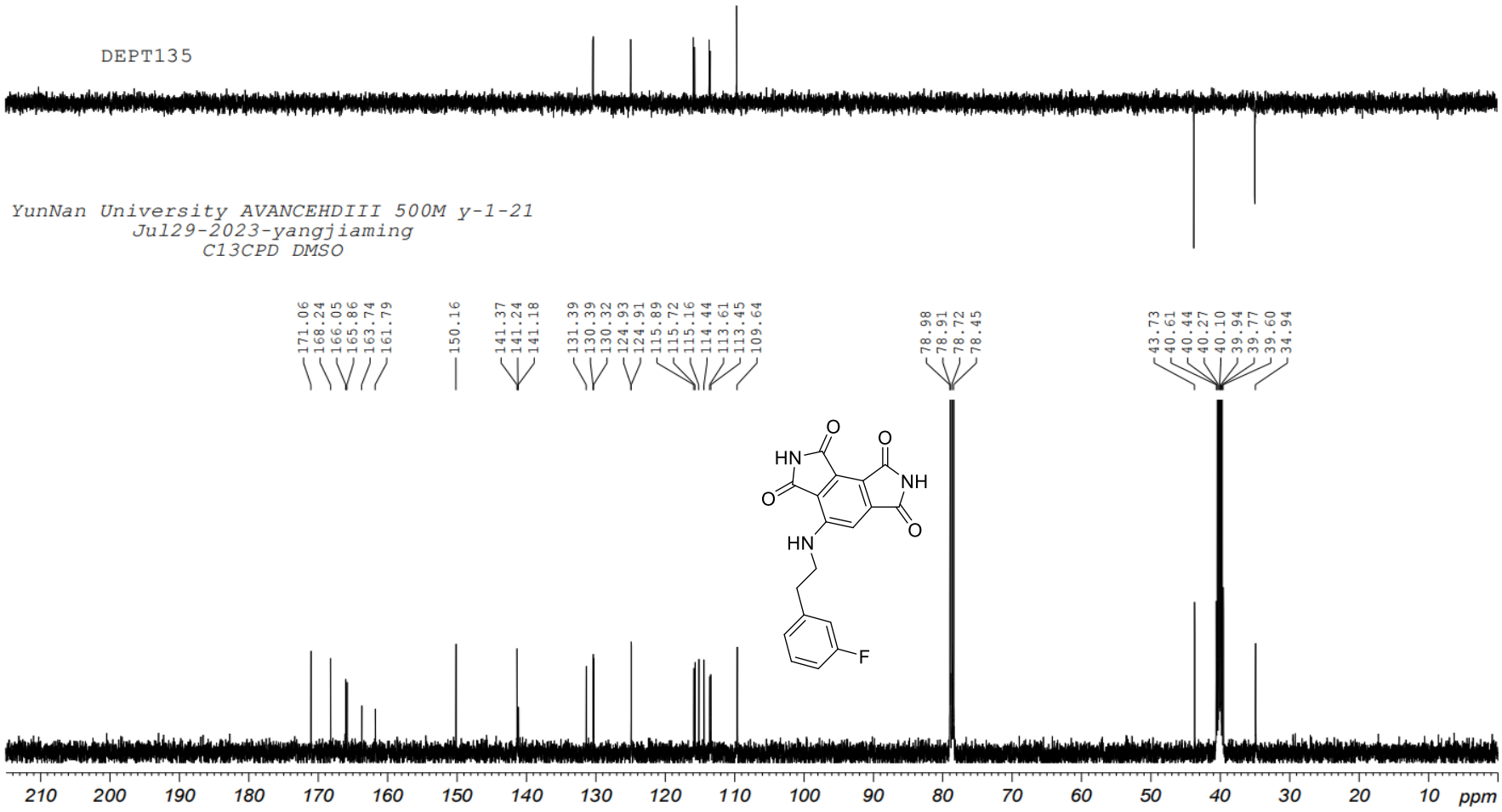


Figure S73. ^{13}C NMR (150 MHz, DMSO-d_6) spectra of compound **3h'**

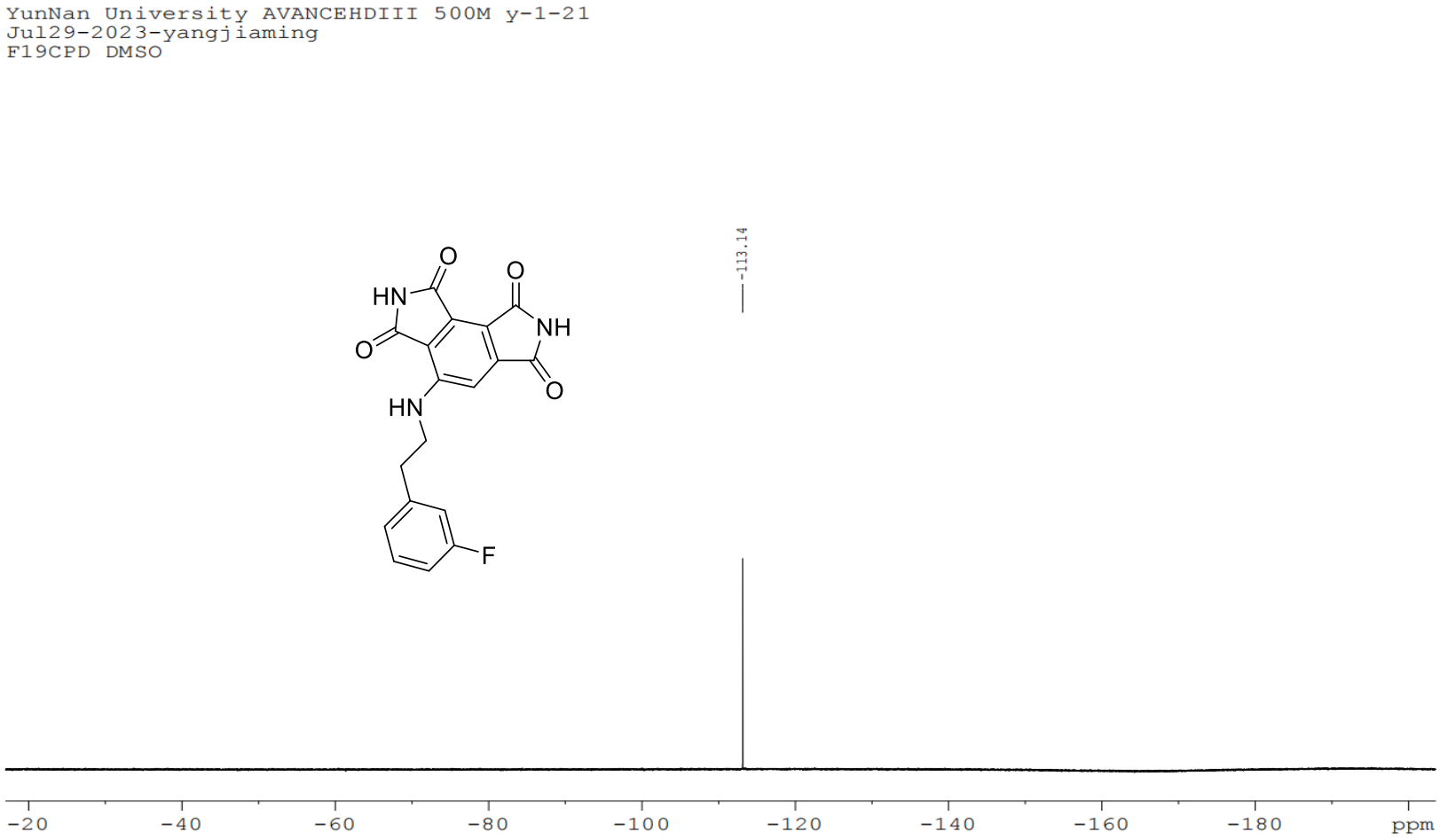


Figure S74. ^{19}F NMR (564 MHz, DMSO-d_6) spectra of compound **3h'**

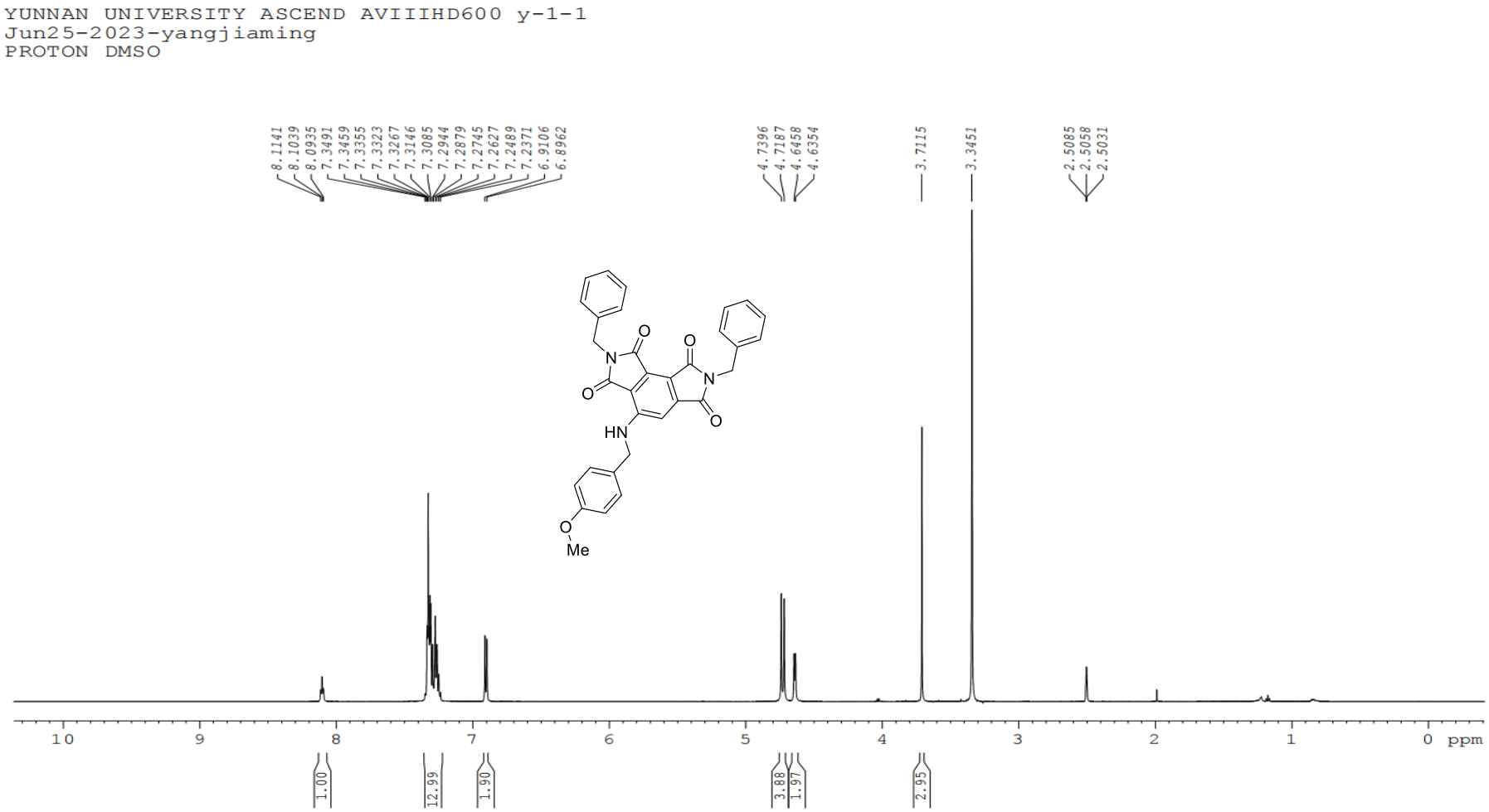


Figure S75. ^{1}H NMR (600 MHz, DMSO-d_6) spectra of compound **3i'**

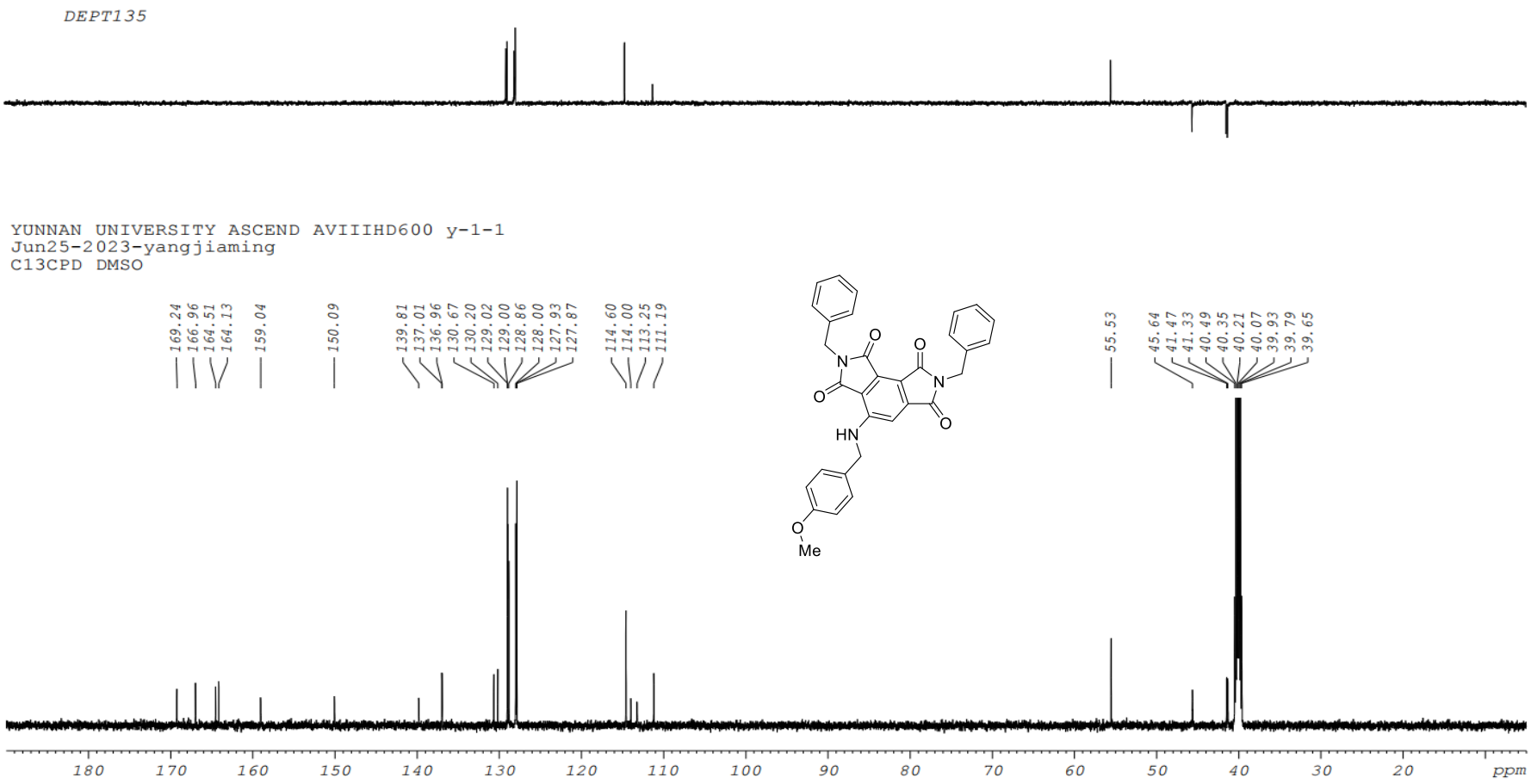


Figure S76. ^{13}C NMR (150 MHz, DMSO-d_6) spectra of compound **3i'**

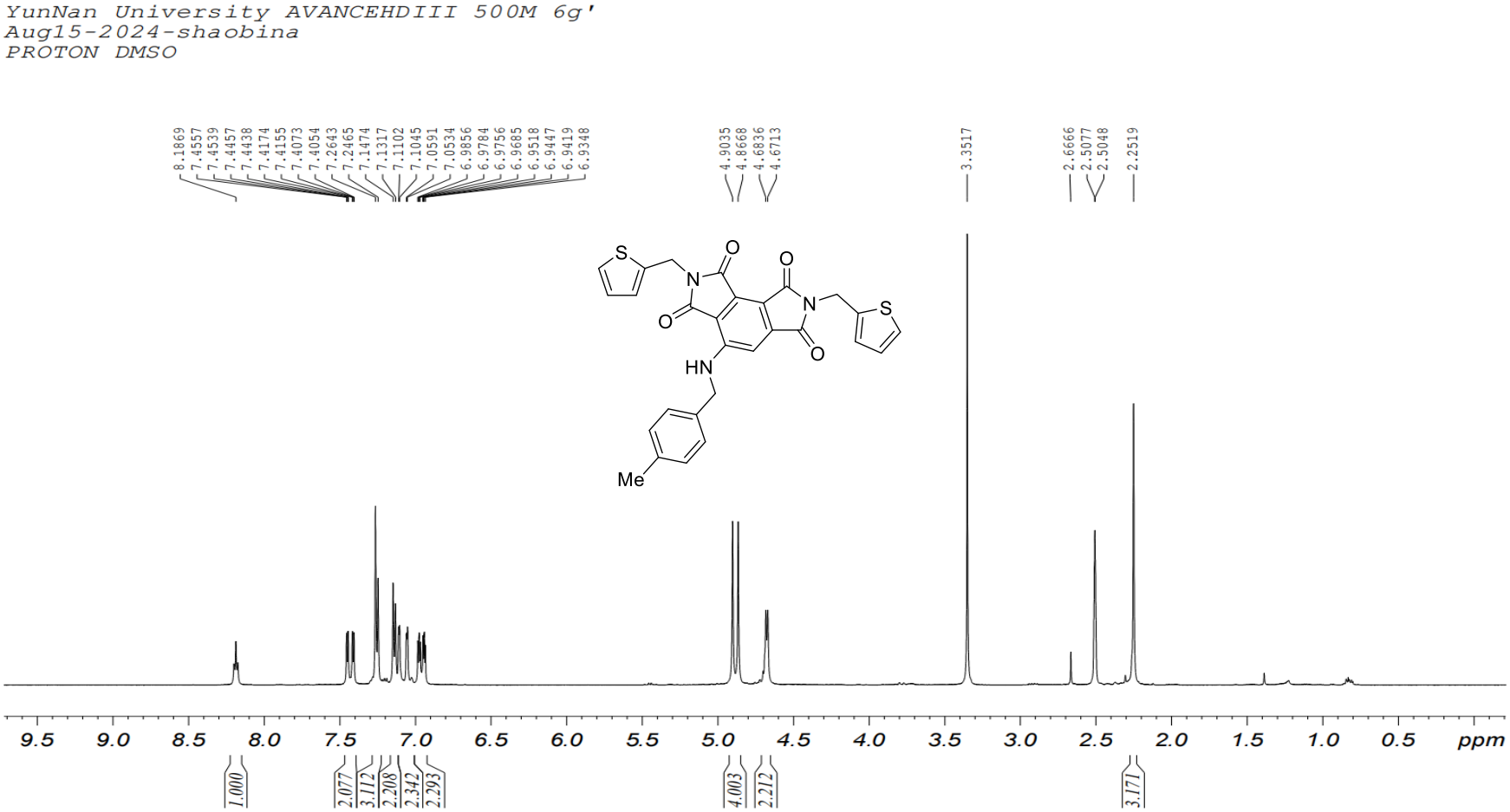


Figure S77. ^{1}H NMR (500 MHz, DMSO-d_6) spectra of compound **3j'**

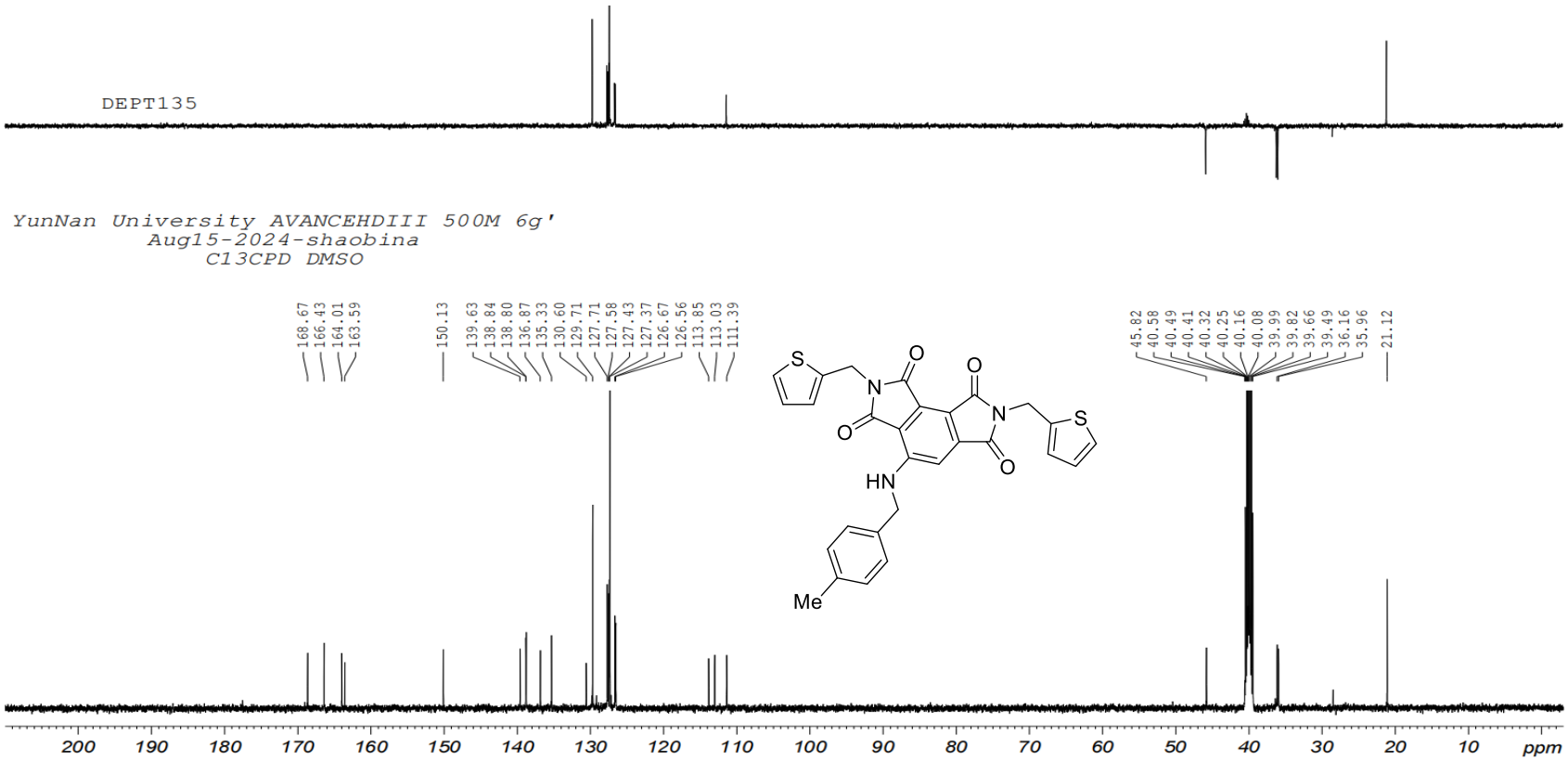


Figure S78. ^{13}C NMR (125 MHz, DMSO-d_6) spectra of compound **3j'**

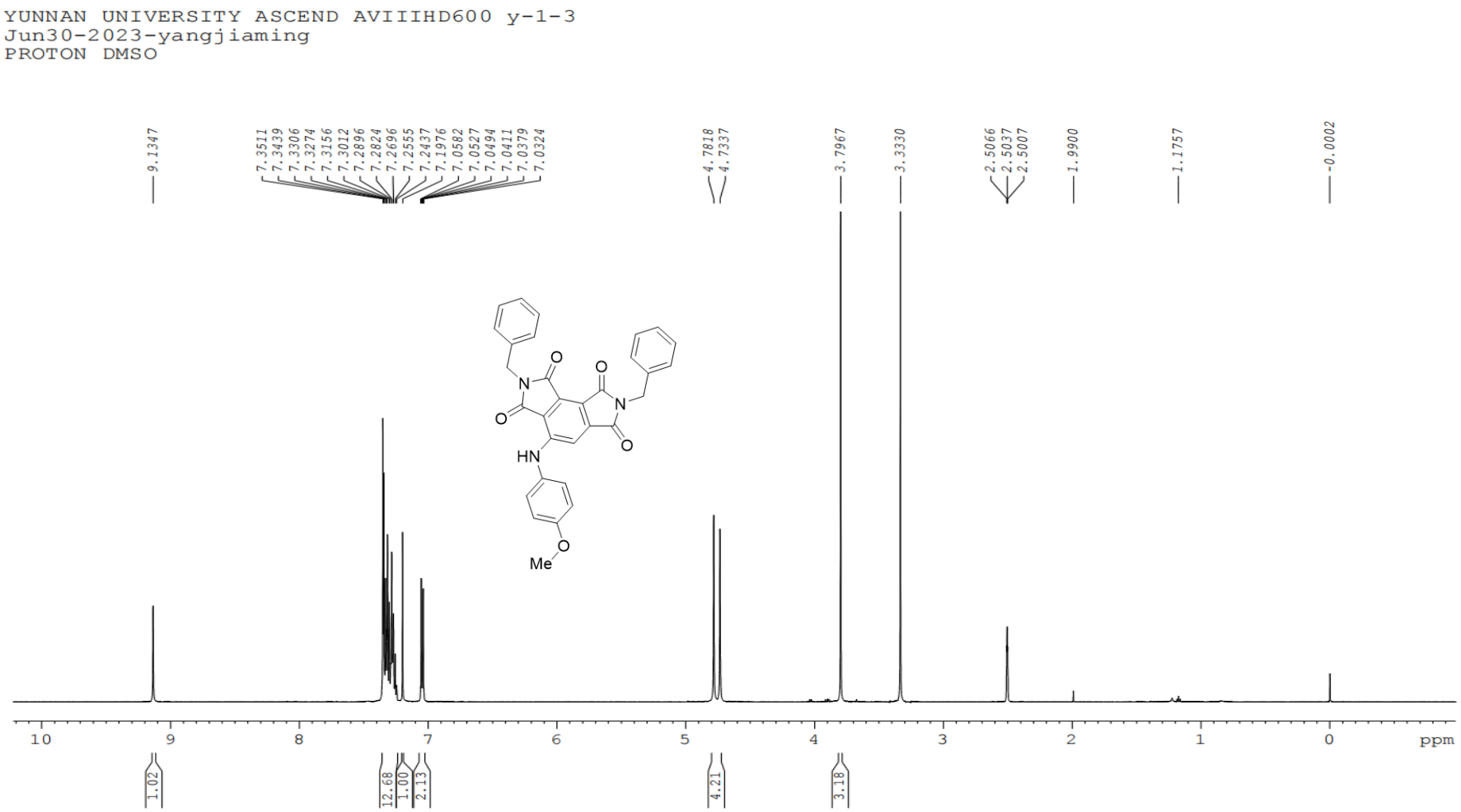


Figure S79. ^{1}H NMR (600 MHz, DMSO-d_6) spectra of compound **3k'**

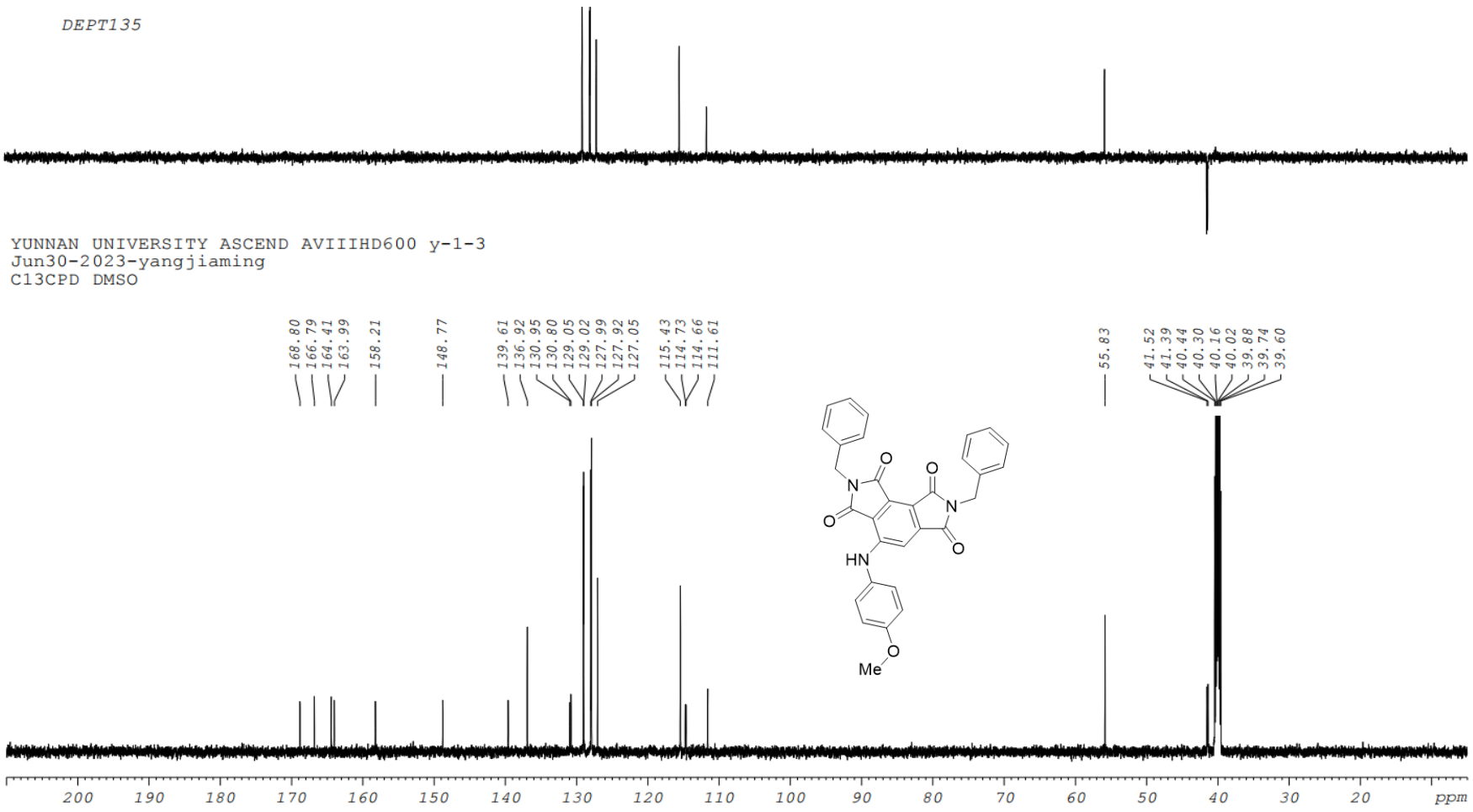


Figure S80. ^{13}C NMR (150 MHz, DMSO-d_6) spectra of compound **3k'**

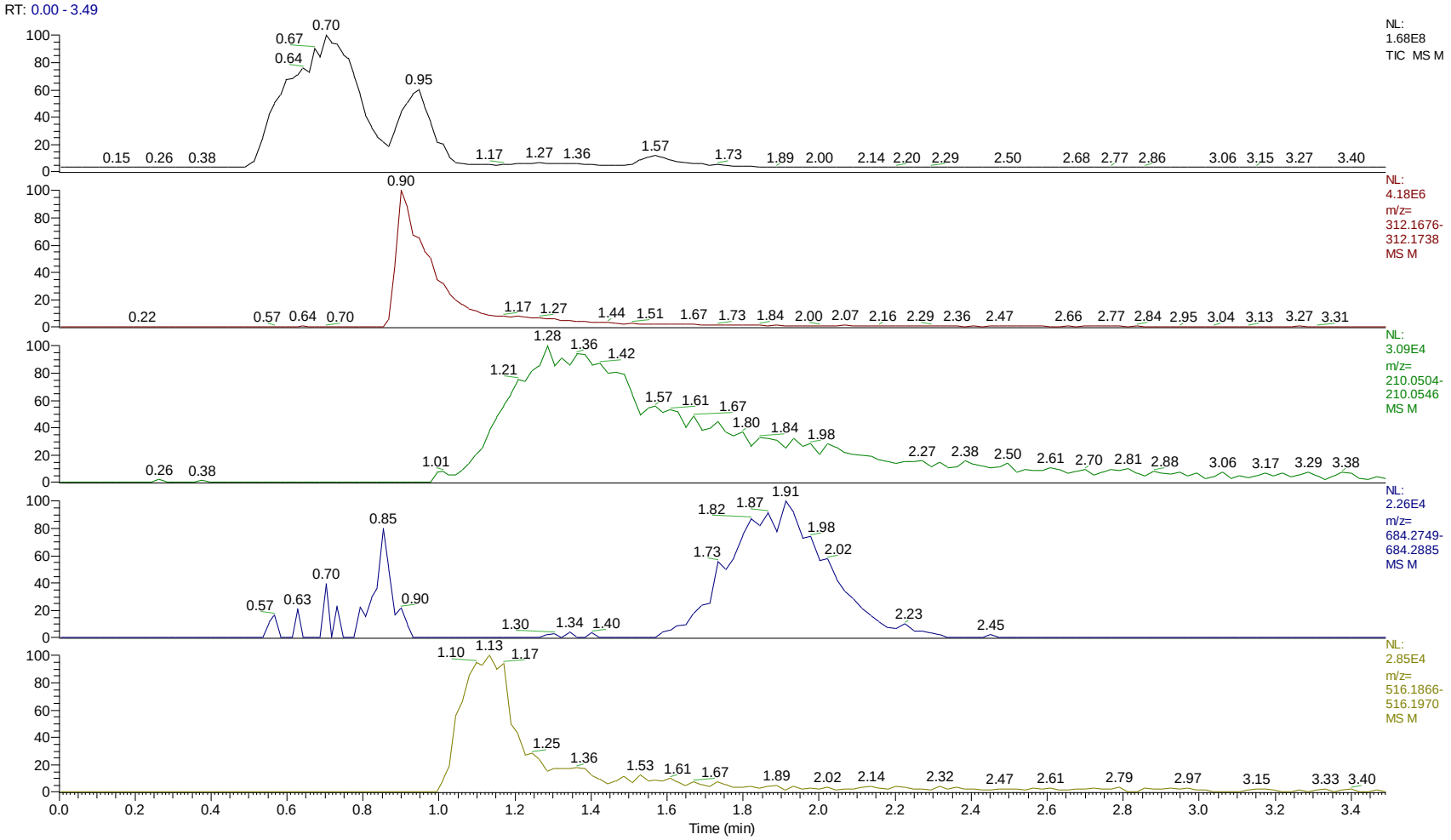


Figure S81. HPLC of the reaction mixture

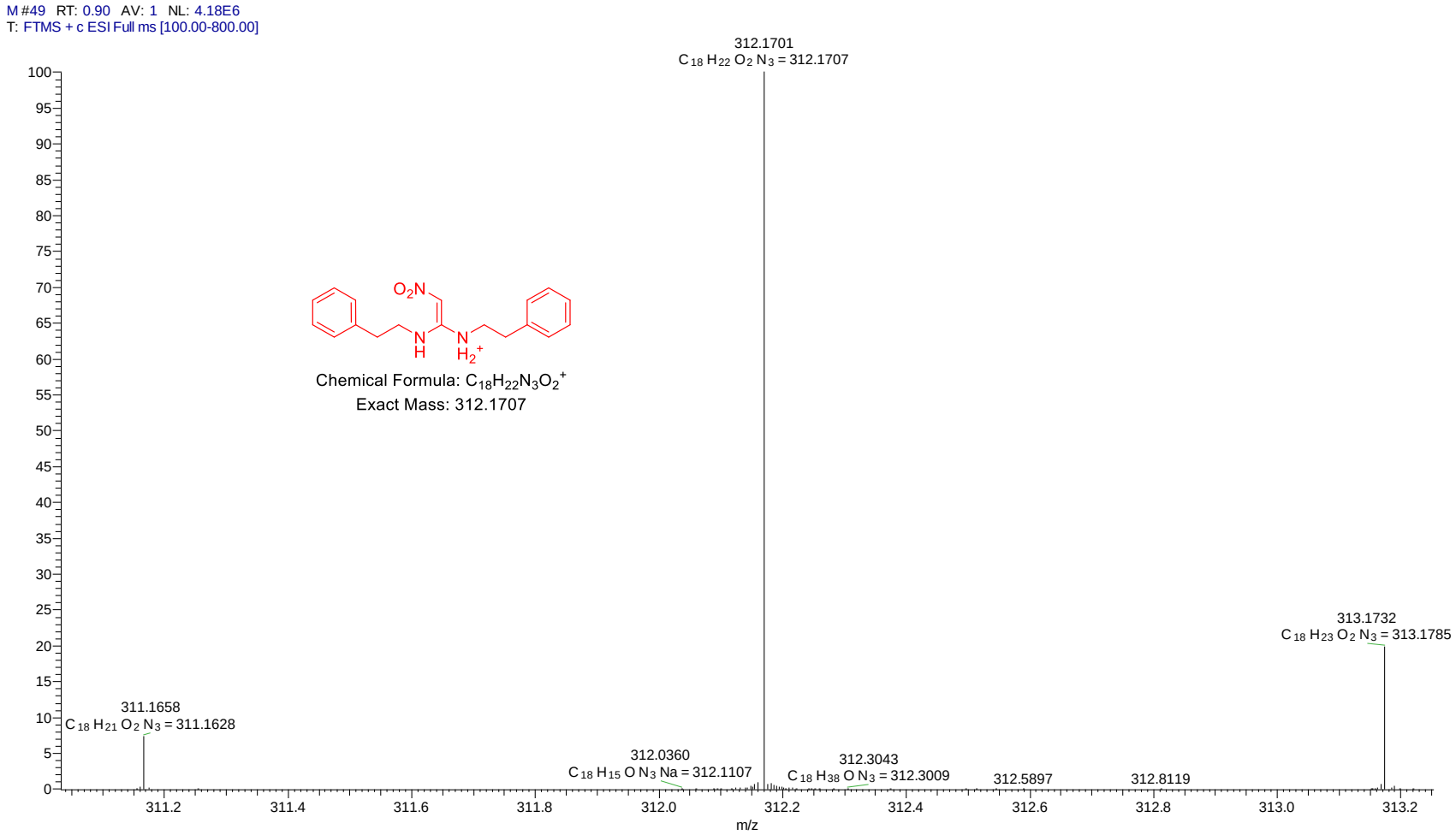


Figure S82. HRMS of substrate **1h**

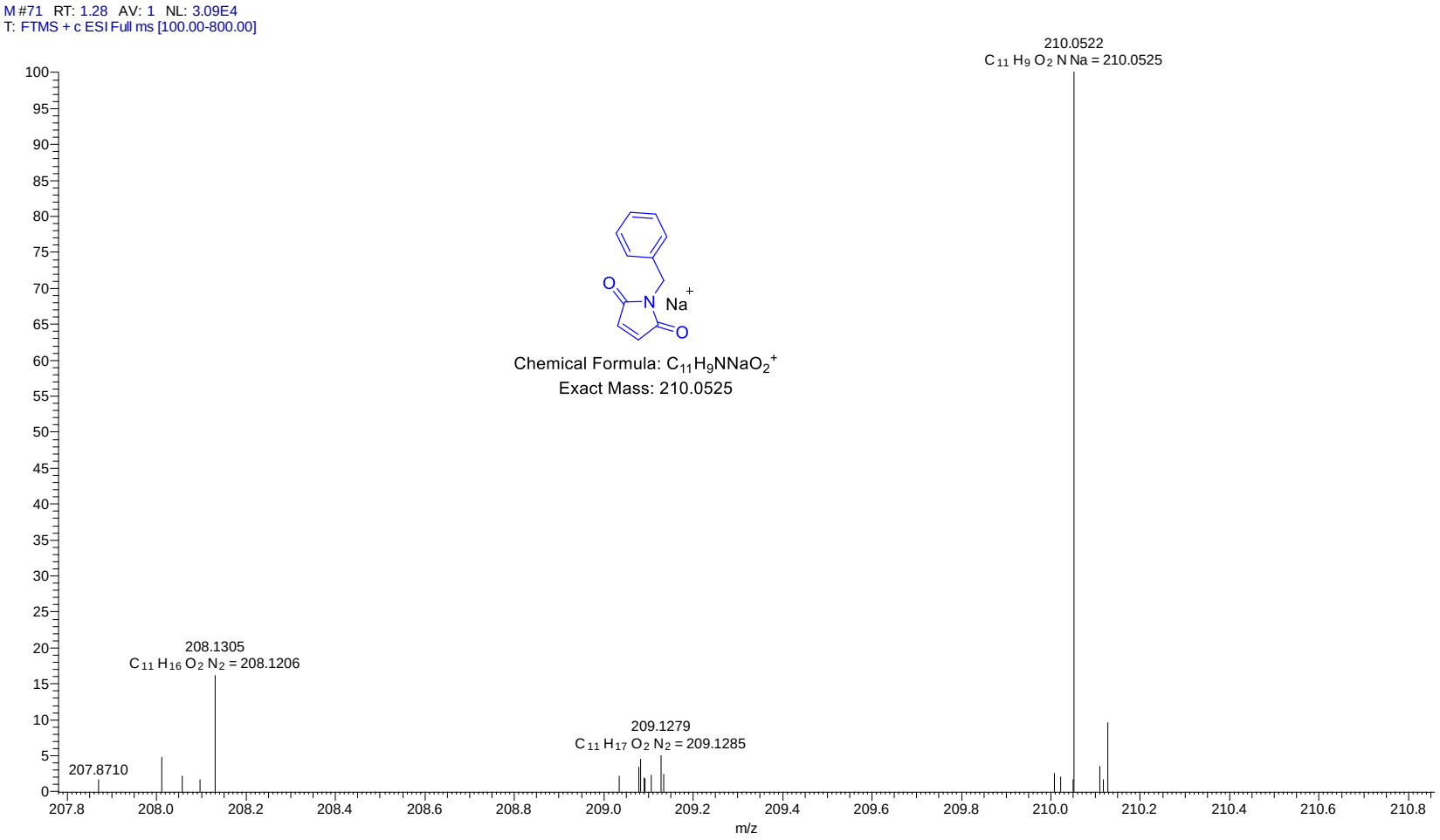


Figure S83. HRMS of substrate **2b**

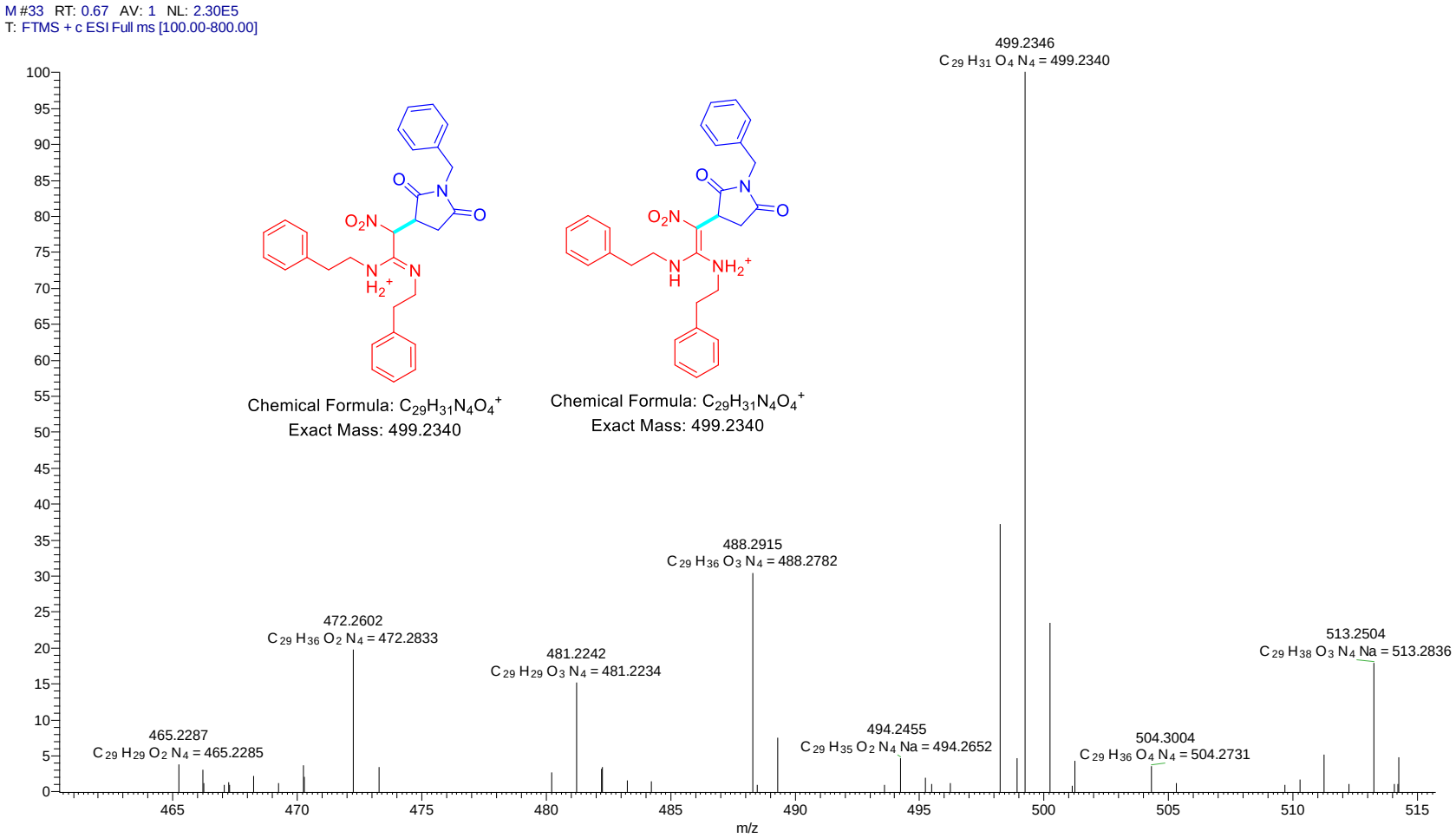


Figure S84. HRMS of intermediate **4n/5n**

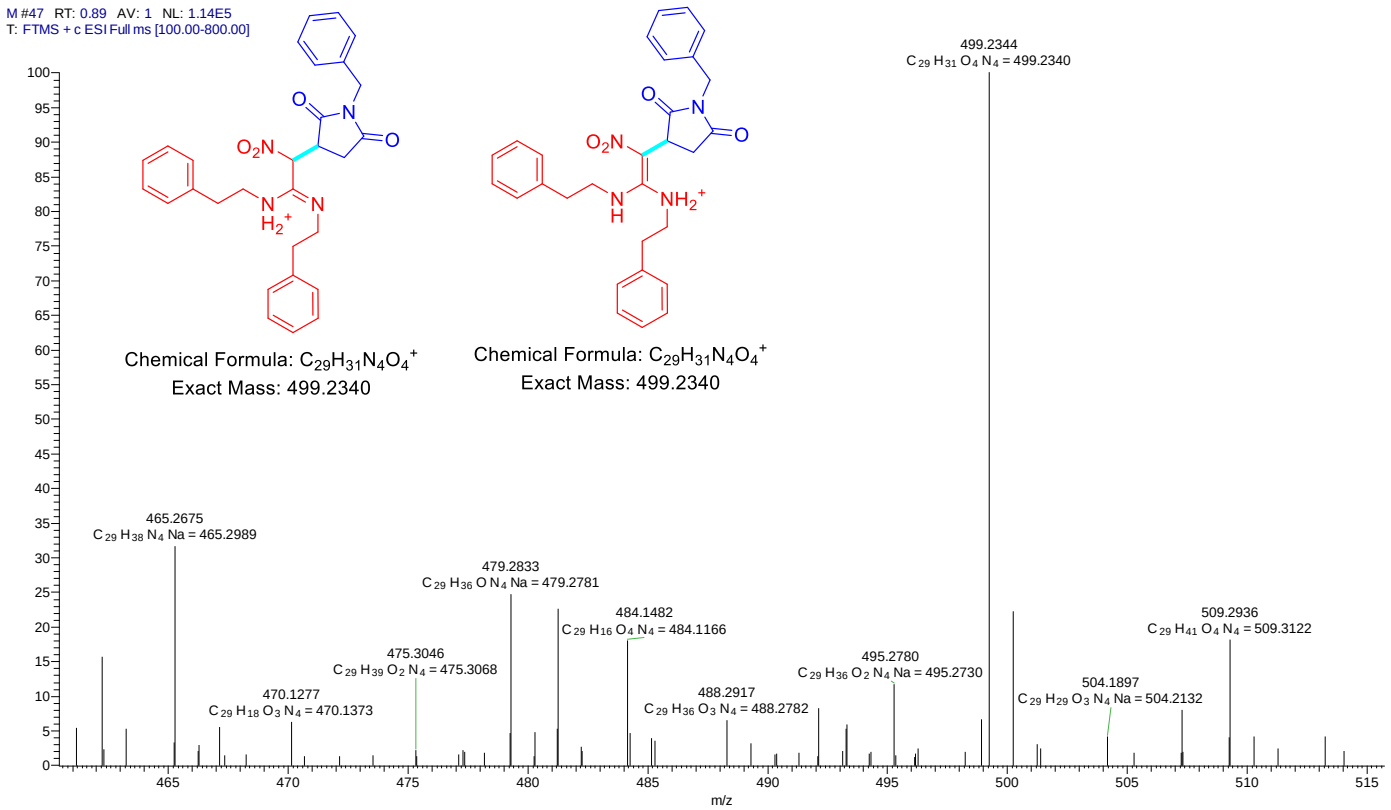


Figure S85. HRMS of intermediate **4n**/**5n**

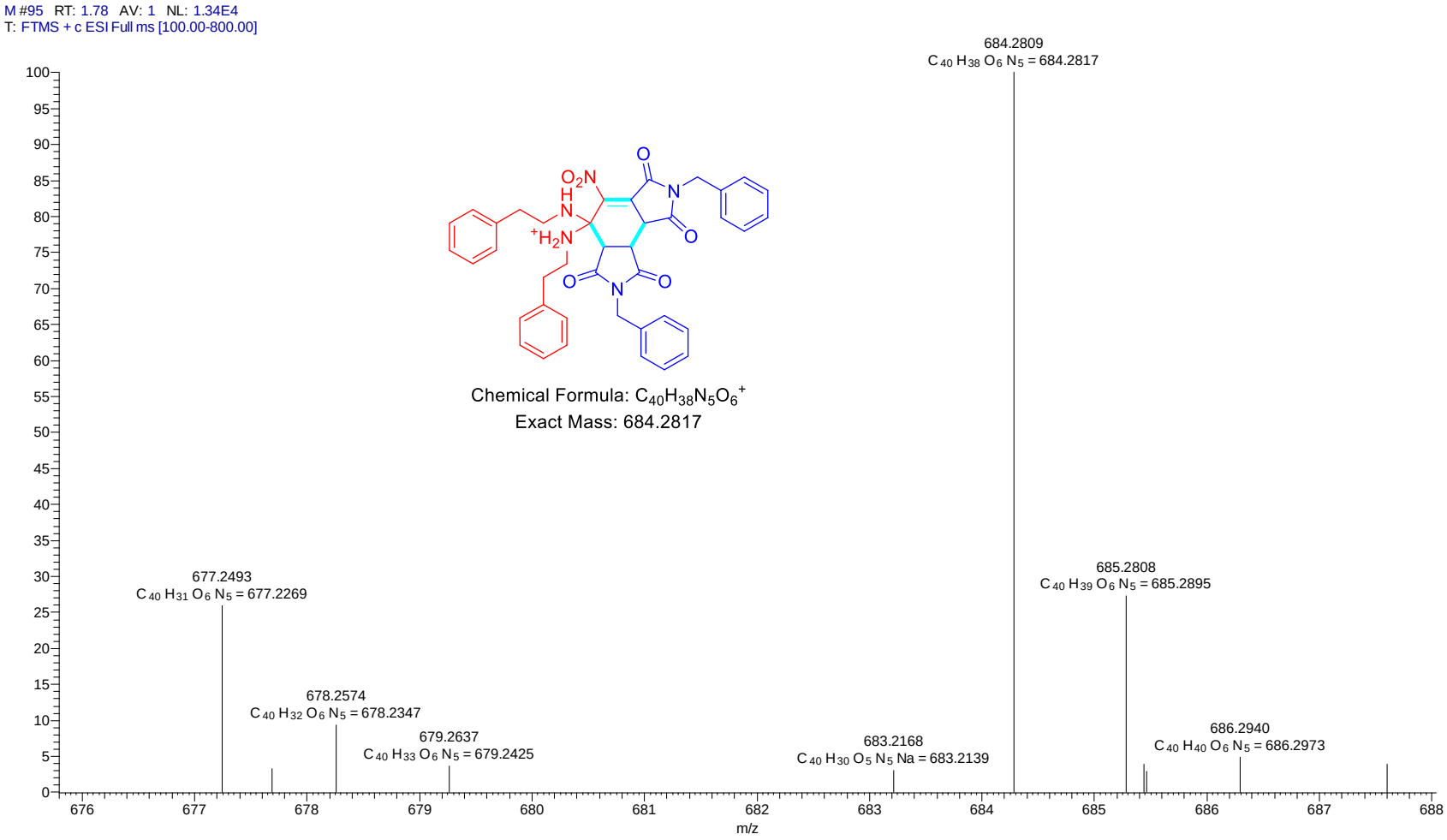


Figure S86. HRMS of intermediate **6n**

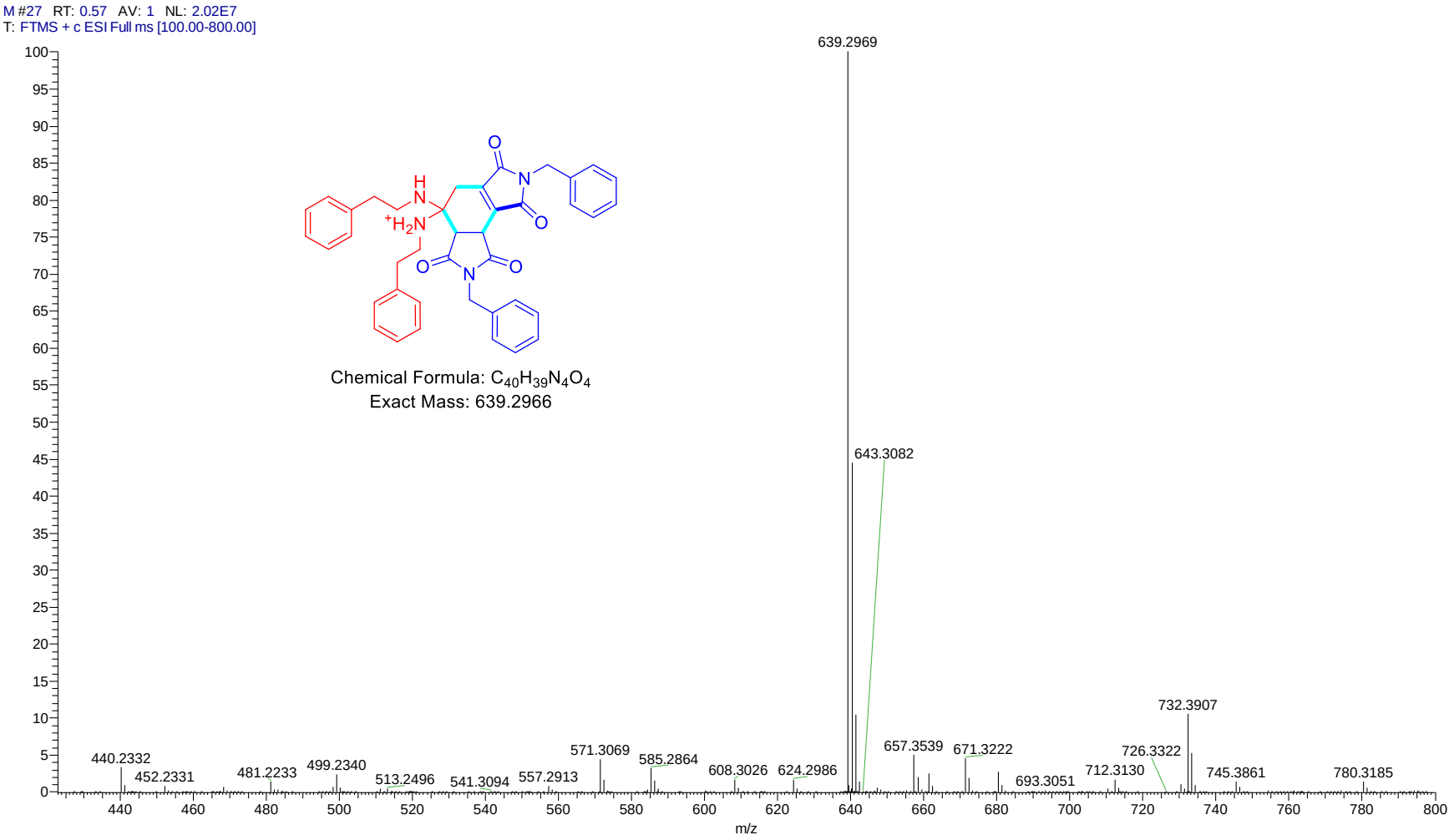


Figure S87. HRMS of intermediate **7n**

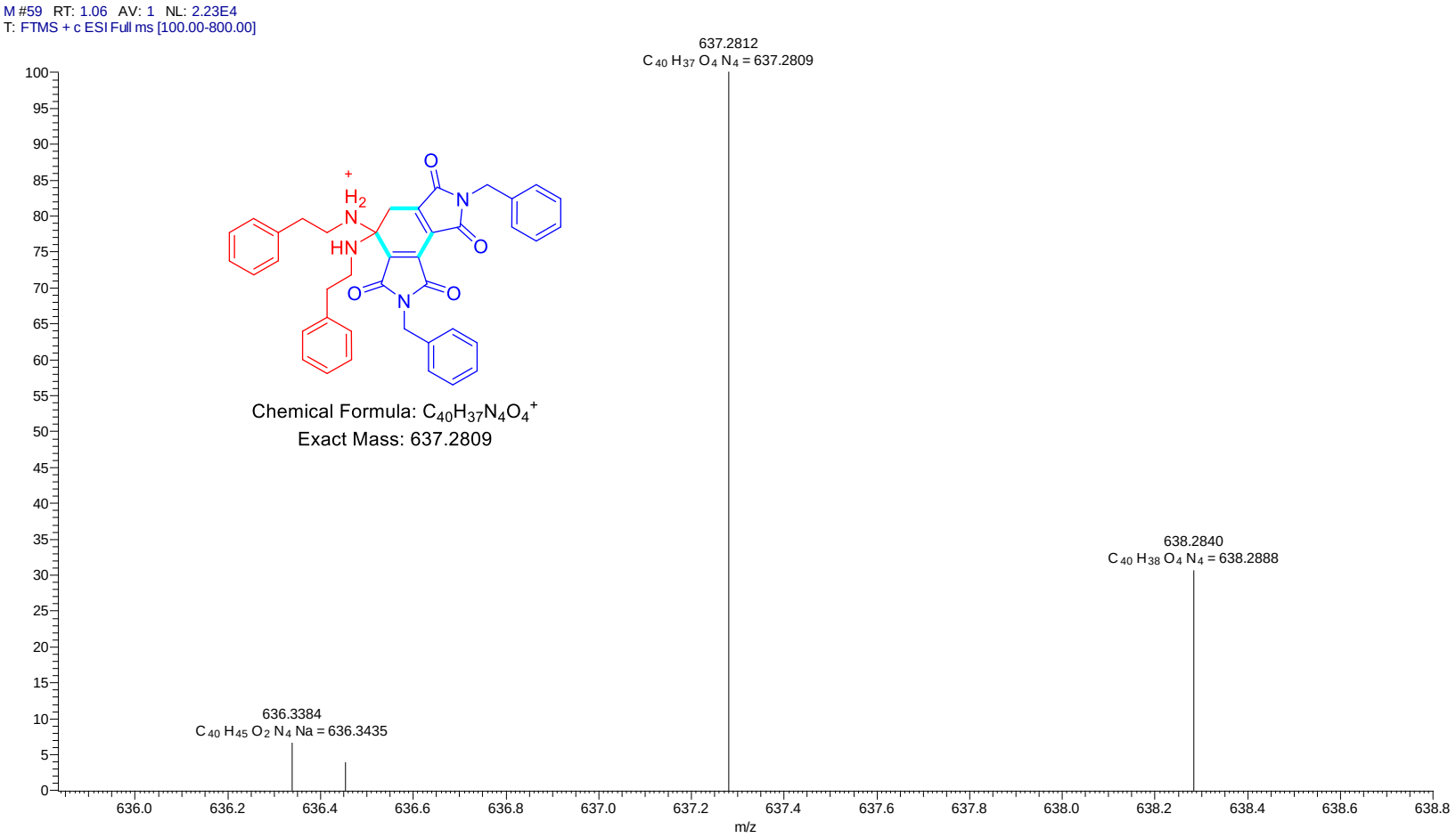


Figure S88. HRMS of intermediate **8n**

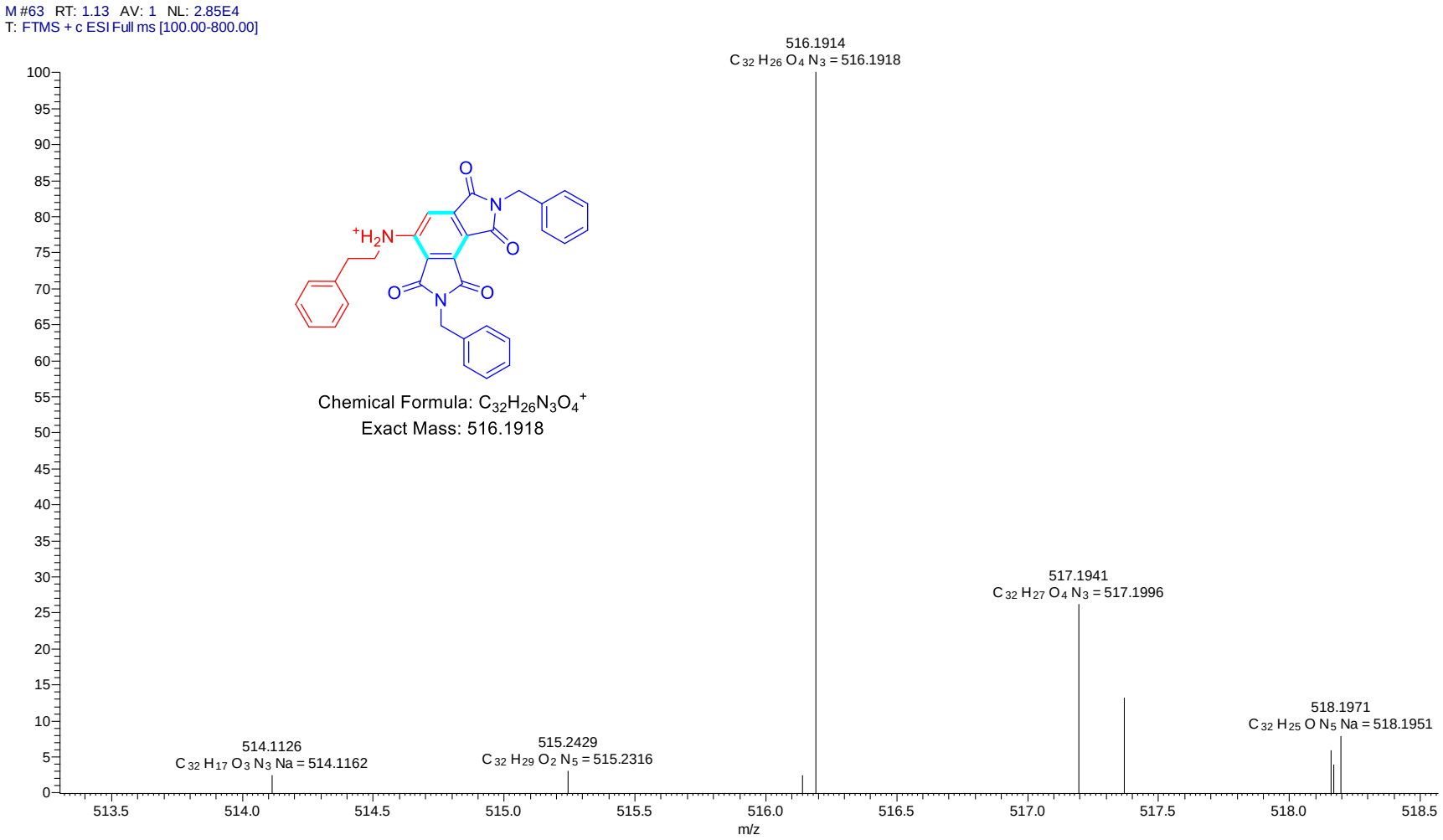


Figure S89. HRMS of the target compound **3n**

References

1. X.-M. Hu, D.-Y.Luo, Q.-X. Zi, J. Lin, S.-J. Yan, Diastereoselective Synthesis of Morphan Derivatives by Michael and Hetero-Michael Addition of 1,1-Enediamines to Quinone Monoketals, *ACS Omega*, 2018, **3**, 8.

2. CCDC2371133 contain the supplementary crystallographic data for compound **3n**. These data can be obtained free of charge from The Cambridge Crystallographic Data Center *via* www.ccdc.cam.ac.uk/data_request/cif