Supporting Information

Unexpected amine-triggered skeletal modification of fascaplysin and its derivatives: a rapid access to δ,γ-biscarbolines

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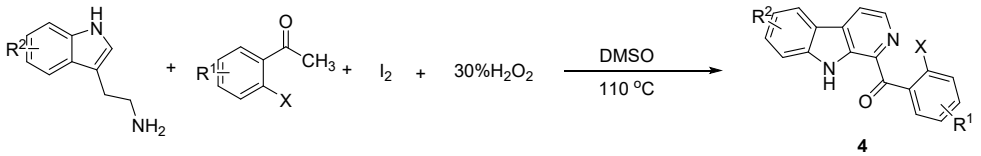
Column chromatographic purifications were performed on SDZF silica gel 160. ^{1}H, ^{13}C and ^{19}F NMR spectra were obtained on a Bruker NMR spectrometer at 600 MHz, 150 MHz and 565 MHz, respectively, referenced internally based on the residual solvent signal. The data reported for the ^{1}H NMR spectra are as follows: chemical shift (δ, ppm), multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; and m, multiplet), coupling constant in hertz, and number of protons. The data reported for the ^{13}C spectra are given as chemical shift (δ, ppm). The data reported for the ^{19}F spectra are given as chemical shift (δ, ppm). High-resolution mass spectra (HRMS) were obtained on an Agilent mass spectrometer by electrospray ionization-time of flight (ESI-TOF) analysis. Melting points were measured with a melting point instrument without correction. All the chemical reagents and solvents were purchased from commercial sources and used as received.

1. Experimental and spectroscopic data for compounds **4a-j, 2a-j and 1**: **Page S2-15**.

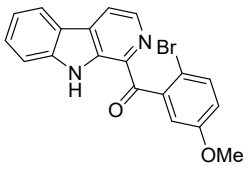
1.1 Synthesis of compounds **4a-j**



4c-f, X=Cl
4a-b, 4g-j, X=Br

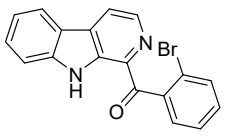
To a solution of tryptamine (12.5 mmol) in 20 mL DMSO was added acetophenone (12.5 mmol), iodine (2.5 g, 10 mmol), 30% H_2O_2 (425 mg, 0.38 mL, 18.8 mmol) and the reaction mixture was stirred at 110 °C until TLC indicated the complete consumption of acetophenone. Then the reaction mixture was cooled to room temperature, diluted with H_2O, extracted with DCM. The combined organic layer was washed with 10% $Na_2S_2O_3$, H_2O and brine, dried over anhydrous Na_2SO_4, concentrated. The obtained crude products was purified by flash column silica gel chromatography to give compound **4**.

(2-bromo-5-methoxyphenyl) (9*H*-pyrido[3,4-*b*] indol-1-yl) methanone (4a)



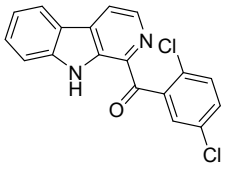
Purification by flash column silica gel chromatography (PE: EA=3:1) to give **4a** as a yellow solid (3.23 g, yield 68%). m.p.190.8-191.3 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.23 (s, 1H), 8.51 – 8.40 (m, 2H), 8.33 (d, *J* = 7.8 Hz, 1H), 7.85 (d, *J* = 8.2 Hz, 1H), 7.63 (t, *J* = 7.6 Hz, 1H), 7.59 (d, *J* = 8.9 Hz, 1H), 7.34 (t, *J* = 7.5 Hz, 1H), 7.18 (d, *J* = 3.0 Hz, 1H), 7.05 (dd, *J* = 8.9, 3.1 Hz, 1H), 3.79 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 196.6, 158.3, 142.3, 142.0, 137.9, 135.3, 135.1, 133.1, 131.3, 129.2, 122.0, 120.5, 120.0, 119.7, 116.8, 115.0, 113.2, 109.2, 55.7. HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{19}H_{14}BrN_2O_2$ 381.0233; Found 381.0229.

(2-bromophenyl) (9*H*-pyrido[3,4-*b*] indol-1-yl) methanone (4b)



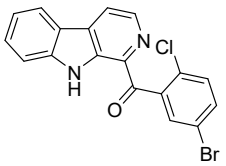
Purification by flash column silica gel chromatography (PE: EA=4:1) to give **4b** as a yellow solid (3.59 g, yield 82 %). ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.24 (s, 1H), 8.45 (dd, *J* = 11.1, 4.8 Hz, 2H), 8.33 (d, *J* = 7.8 Hz, 1H), 7.86 (d, *J* = 8.2 Hz, 1H), 7.73 (dd, *J* = 8.0, 0.7 Hz, 1H), 7.67 – 7.61 (m, 1H), 7.59 (dd, *J* = 7.5, 1.7 Hz, 1H), 7.53 (td, *J* = 7.5, 1.0 Hz, 1H), 7.47 (td, *J* = 7.8, 1.8 Hz, 1H), 7.37 – 7.31 (m, 1H). The ^{1}H NMR data is consistent with literature values.[1]

(2,5-dichlorophenyl) (9*H*-pyrido[3,4-*b*] indol-1-yl) methanone (4c)



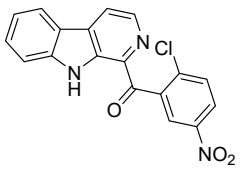
Purification by flash column silica gel chromatography (PE: EA=4:1) to give **4c** as a yellow solid (3.78 g, yield 75%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.26 (s, 1H), 8.47 (dd, J = 11.8, 4.8 Hz, 2H), 8.34 (d, J = 7.8 Hz, 1H), 7.85 (d, J = 8.2 Hz, 1H), 7.79 (d, J = 1.8 Hz, 1H), 7.66 – 7.60 (m, 3H), 7.34 (t, J = 7.5 Hz, 1H). The ^{1}H NMR data is consistent with literature values.[2]

(5-bromo-2-chlorophenyl) (9*H*-pyrido[3,4-*b*] indol-1-yl) methanone (4d)



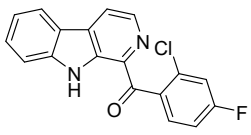
Purification by flash column silica gel chromatography (PE: EA=3:1) to give **4d** as a yellow solid (3.44 g, yield 72%). m.p.265.4-265.9 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.26 (s, 1H), 8.47 (q, J = 4.8 Hz, 2H), 8.33 (d, J = 7.8 Hz, 1H), 7.90 (d, J = 2.4 Hz, 1H), 7.86 (d, J = 8.2 Hz, 1H), 7.74 (dd, J = 8.6, 2.3 Hz, 1H), 7.64 (t, J = 7.7 Hz, 1H), 7.54 (d, J = 8.6 Hz, 1H), 7.34 (t, J = 7.5 Hz, 1H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 194.4, 142.0, 141.3, 138.0, 135.3, 134.9, 133.7, 131.8, 131.4, 131.3, 129.4, 129.3, 122.0, 120.6, 120.0, 119.9, 119.7, 113.2. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{18}H_{11}BrClN_2O$ 384.9738; Found 384.9733.

(2-chloro-5-nitrophenyl) (9H-pyrido[3,4-b] indol-1-yl) methanone(4e)



Purification by flash column silica gel chromatography (DCM: MeOH =300:1-DCM: MeOH=150:1) to give **4e** as a yellow solid (219.4 mg, yield 5%). m.p.248.9-249.5°C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.31 (s, 1H), 8.59 (d, J = 1.6 Hz, 1H), 8.47 (dd, J = 23.7, 4.6 Hz, 2H), 8.36 (dd, J = 19.7, 8.3 Hz, 2H), 7.88 (dd, J = 17.6, 8.5 Hz, 2H), 7.64 (t, J = 7.7 Hz, 1H), 7.35 (t, J = 7.4 Hz, 1H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 193.7, 146.1, 142.1, 140.4, 138.0, 137.0, 135.3, 134.7, 131.5, 131.0, 129.4, 125.7, 124.5, 122.0, 120.7, 120.2, 119.9, 113.2. HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{18}H_{10}ClN_3O_3Na$ 374.0303; Found 374.0294.

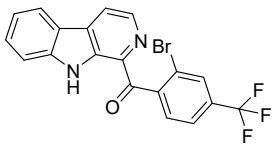
(2-chloro-4-fluorophenyl) (9*H*-pyrido[3,4-*b*] indol-1-yl) methanone (4f)



Purification by flash column silica gel chromatography (PE: EA=3:1) to give **4f** as a yellow solid (2.83 g, yield 70%). m.p.180.9-181.8 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.23 (s, 1H), 8.46 (dd, J = 10.8, 4.8 Hz, 2H), 8.33 (d, J = 7.8 Hz, 1H), 7.85 (d, J

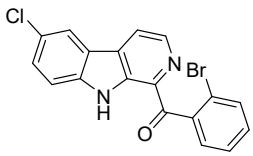
= 8.2 Hz, 1H), 7.73 (dd, *J* = 8.5, 6.2 Hz, 1H), 7.63 (t, *J* = 7.7 Hz, 1H), 7.60 (dd, *J* = 9.0, 2.4 Hz, 1H), 7.39 (td, *J* = 8.5, 2.4 Hz, 1H), 7.34 (t, *J* = 7.5 Hz, 1H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 195.2, 163.3(d, *J* = 248.2 Hz), 142.0, 137.9, 135.7(d, *J* = 3.2 Hz), 135.3, 135.2, 131.7, 131.6, 131.4, 129.2, 122.0, 120.5, 119.9, 119.8, 117.0, (d, *J* = 25.3 Hz), 114.2(d, *J* = 21.1 Hz), 113.1. ^{19}F NMR (565 MHz, DMSO-d_6) δ -109.1. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{18}H_{11}ClFN_2O$ 384.9738; Found 384.9733.

(2-bromo-4-(trifluoromethyl) phenyl) (9H-pyrido[3,4-b] indol-1-yl) methanone(4g)



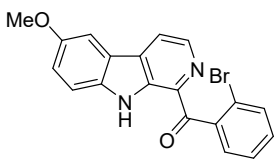
Purification by flash column silica gel chromatography (DCM) to give **4g** as a yellow solid (2.72 g, yield 52%). m.p.211.3-211.8°C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.31 (s, 1H), 8.49 (d, *J* = 4.8 Hz, 1H), 8.44 (d, *J* = 4.8 Hz, 1H), 8.34 (d, *J* = 7.8 Hz, 1H), 8.15 (s, 1H), 7.93 (d, *J* = 7.9 Hz, 1H), 7.86 (t, *J* = 7.7 Hz, 2H), 7.69 – 7.59 (m, 1H), 7.35 (t, *J* = 7.5 Hz, 1H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 195.8, 145.7, 142.1, 138.1, 135.3, 134.6, 131.5, 131.2(d, *J* = 32.3 Hz), 130.1, 129.3, 129.1(d, *J* = 3.6 Hz), 124.4(d, *J* = 3.5 Hz), 124.0, 122.2(d, *J* = 27.8 Hz), 120.7, 120.1, 119.9, 119.5, 113.2. ^{19}F NMR (565 MHz, DMSO-d_6) δ -61.2. HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{19}H_{10}BrF_3N_2ONa$ 440.9821; Found 440.9814.

(2-bromophenyl) (6-chloro-9*H*-pyrido[3,4-*b*] indol-1-yl) methanone (4h)



Purification by flash column silica gel chromatography (PE: EA=2:1) to give **4h** as a yellow solid (3.11 g, yield 65 %). m.p.254.2-254.7 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.37 (s, 1H), 8.50 (d, *J* = 4.9 Hz, 1H), 8.47 (dd, *J* = 8.2, 3.4 Hz, 2H), 7.85 (d, *J* = 8.7 Hz, 1H), 7.73 (dd, *J* = 8.0, 0.6 Hz, 1H), 7.65 (dd, *J* = 8.7, 2.1 Hz, 1H), 7.59 (dd, *J* = 7.5, 1.7 Hz, 1H), 7.53 (td, *J* = 7.5, 0.9 Hz, 1H), 7.47 (td, *J* = 7.8, 1.7 Hz, 1H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 196.8, 141.2, 140.4, 138.1, 135.6, 135.5, 132.3, 131.2, 130.4, 129.5, 129.1, 127.2, 124.8, 121.6, 121.3, 120.2, 119.0, 114.73. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{18}H_{11}BrClN_2O$ 384.9738; Found 384.9732.

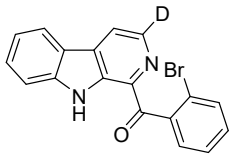
(2-bromophenyl) (6-methoxy-9*H*-pyrido[3,4-*b*] indol-1-yl) methanone (4i)



Purification by flash column silica gel chromatography (PE: EA=2:1) to give **4i** as a yellow solid (2.72 g, yield 68%). m.p.195.3-196.2 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.07 (s, 1H), 8.44 (d, *J* = 4.9 Hz, 1H), 8.40 (d, *J* = 4.8 Hz, 1H), 7.90 (d, *J* = 2.5 Hz, 1H), 7.75 (d, *J* = 8.8 Hz, 1H), 7.61 (dd, *J* = 7.5, 1.4 Hz, 1H), 7.56 (m,

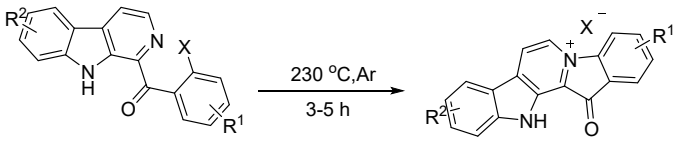
J = 9.8, 8.1, 1.5 Hz, 2H), 7.49 (td, *J* = 7.3, 1.6 Hz, 1H), 7.28 (dd, *J* = 8.9, 2.5 Hz, 1H), 3.88 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 196.8, 154.2, 141.4, 137.2, 136.7, 135.7, 135.1, 132.3, 131.2, 131.1, 129.4, 127.2, 120.4, 119.8,119.0, 119.0, 114.0, 103.8, 55.6. HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{19}H_{14}BrN_2O_2$ 381.0233; Found 381.0237

(2-bromophenyl) (9*H*-pyrido[3,4-*b*] indol-1-yl-3-*d*) methanone (4j)



4j was obtained from 2-bromoacetophenone and tryptamine-α, α-d_2 (prepared according to the literature[3] through the reduction of 3-indoleacetamide by lithium aluminum deuteride). Purification by flash column silica gel chromatography (DCM) to give a yellow solid (2.72 g, yield 62 %). m.p.207.8-208.3 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.23 (s, 1H), 8.46 (s, 1H), 8.33 (d, *J* = 7.8 Hz, 1H), 7.85 (d, *J* = 8.2 Hz, 1H), 7.73 (dd, *J* = 8.0, 0.7 Hz, 1H), 7.66 – 7.61 (m, 1H), 7.59 (dd, *J* = 7.5, 1.7 Hz, 1H), 7.53 (td, *J* = 7.5, 1.0 Hz, 1H), 7.50 – 7.44 (m, 1H), 7.34 (t, *J* = 7.5 Hz, 1H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 196.9, 142.0, 141.4, 135.3, 135.1, 132.3, 131.3, 131.2, 129.5, 129.2, 127.2, 122.0, 120.5, 120.0, 119.6, 119.0, 113.2. HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{18}H_{10}DBrN_2O$ 352.0190; Found 352.0186.

1.2 Synthesis of compounds **2a-j**



4

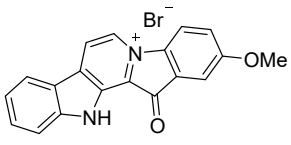
4c-f, X=Cl
4a-b, 4g-j, X=Br

2

2c-f, X=Cl
2a-b, 2g-j, X=Br

Compound **4** (2.86 mmol) was heated in sealed tube and under an argon atmosphere at 230 °C for 3-5 h. After cooling, the reaction mixture was purified by trituration with MeOH and EA to give compound **2**.

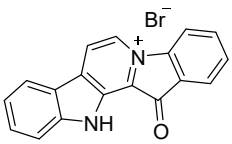
2-methoxy-13-oxo-12,13-dihydropyrido[1,2-*a*:3,4-*b*'] diindol-5-ium (2a)



Purified by trituration with MeOH and EA to give **2a** as a red solid (1.52 g, yield 76 %). m.p. > 420 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.87 (s, 1H), 9.54 (d, *J* = 6.2 Hz, 1H), 9.16 (d, *J* = 6.1 Hz, 1H), 8.58 (d, *J* = 7.9 Hz, 1H), 8.29 (d, *J* =

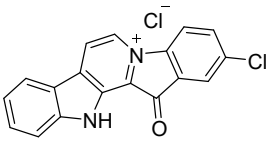
8.6 Hz, 1H), 8.01 – 7.88 (m, 2H), 7.56 (t, *J* = 7.2 Hz, 1H), 7.37 – 7.24 (m, 2H), 4.44 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$ + CF_3CO_2D) δ 182.0, 162.1, 148.2, 142.0, 139.6, 136.2, 135.9, 125.8, 125.3, 125.1, 124.7, 124.2, 120.1, 117.5, 116.4, 115.6, 113.7, 111.9, 35.3. HRMS (ESI-TOF) *m/z*: [M]$^+$ Calcd for $C_{19}H_{13}N_2O_2^+$ 301.0972; Found 301.0966.

13-oxo-12,13-dihydropyrido[1,2-*a*:3,4-*b*'] diindol-5-ium (2b)



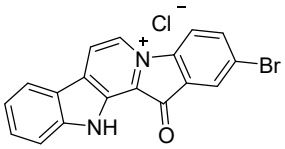
Purified by trituration with MeOH and EA to give **2b** as red solid (1.8 g, yield 90%). ^{1}H NMR (600 MHz, DMSO-d_6 + CF_3CO_2D) δ 9.63 (d, *J* = 6.2 Hz, 1H), 9.09 (d, *J* = 6.2 Hz, 1H), 8.49 (d, *J* = 8.0 Hz, 2H), 8.00 (d, *J* = 7.4 Hz, 1H), 7.95 (t, *J* = 7.8 Hz, 1H), 7.78 (t, *J* = 7.6 Hz, 1H), 7.73 (d, *J* = 8.2 Hz, 1H), 7.68 (t, *J* = 7.5 Hz, 1H), 7.43 (t, *J* = 7.5 Hz, 1H). The ^{1}H NMR data is consistent with literature values.[4]

2-chloro-13-oxo-12,13-dihydropyrido[1,2-*a*:3,4-*b*'] diindol-5-ium (2c)



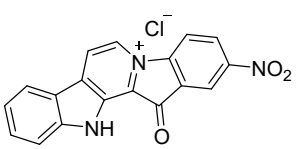
Purified by trituration with MeOH and EA to give **2c** as a red solid (1.6 g, yield 80%). ^{1}H NMR (600 MHz, DMSO-d_6 + CF_3CO_2D) δ 9.60 (dd, *J* = 6.3, 2.3 Hz, 1H), 9.07 (d, *J* = 6.2 Hz, 1H), 8.50 (d, *J* = 8.5 Hz, 1H), 8.46 (d, *J* = 8.0 Hz, 1H), 8.04 (d, *J* = 2.1 Hz, 1H), 8.00 (dd, *J* = 8.5, 2.1 Hz, 1H), 7.82 – 7.75 (m, 1H), 7.73 (d, *J* = 8.3 Hz, 1H), 7.46 – 7.37 (m, 1H). The ^{1}H NMR data is consistent with literature values.[5]

2-bromo-13-oxo-12,13-dihydropyrido[1,2-*a*:3,4-*b*'] diindol-5-ium (2d)



Purified by trituration with MeOH and EA to give **2d** as a red solid. (1.78 g, yield 89 %). ^{1}H NMR (600 MHz, DMSO-d_6 + CF_3CO_2D) δ 9.61 (d, *J* = 6.2 Hz, 1H), 9.08 (d, *J* = 6.2 Hz, 1H), 8.48 (d, *J* = 8.0 Hz, 1H), 8.43 (d, *J* = 8.5 Hz, 1H), 8.22 – 8.11 (m, 2H), 7.80 (t, *J* = 7.6 Hz, 1H), 7.75 (d, *J* = 8.3 Hz, 1H), 7.44 (t, *J* = 7.5 Hz, 1H). The ^{1}H NMR data is consistent with literature values.[6]

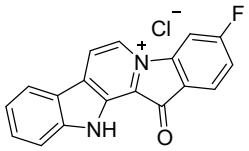
2-nitro-13-oxo-12,13-dihydropyrido[1,2-a:3,4-b'] diindol-5-ium (2e)



Purified by trituration with MeOH and EA to give **2e** as a black solid (1.80g, yield 90%). m.p.>420^{o}C. ^{1}H NMR (600 MHz, DMSO-d_6 + CF_3CO_2D) δ 9.75 (d, *J* = 6.3 Hz, 1H), 9.14 (d, *J* = 6.2 Hz, 1H), 8.82 (dd, *J* = 8.7, 1.8 Hz, 1H), 8.75 (d, *J* =

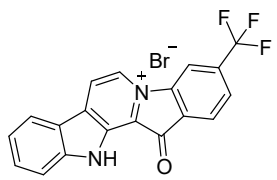
8.8 Hz, 1H), 8.67 (d, *J* = 1.9 Hz, 1H), 8.50 (d, *J* = 8.0 Hz, 1H), 7.82 (t, *J* = 7.6 Hz, 1H), 7.77 (d, *J* = 8.3 Hz, 1H), 7.45 (t, *J* = 7.4 Hz, 1H). ^{13}C NMR (150 MHz, DMSO-d_6 + CF_3CO_2D) δ 181.1, 151.1, 150.1, 148.4, 142.4, 135.8, 132.9, 131.9, 128.8, 126.3, 125.4, 124.1, 121.1, 120.4, 118.6, 116.7, 114.8, 112.9. HRMS (ESI-TOF) *m/z*: $[M]^+$ Calcd for $C_{18}H_{10}N_3O_3^+$ 316.0717; Found 316.0714.

3-fluoro-13-oxo-12,13-dihydropyrido[1,2-*a*:3,4-*b*'] diindol-5-ium (2f)



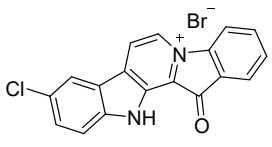
Purified by trituration with MeOH and EA to give **2f** as a red solid (1.64 g, yield 82 %). m.p. > 420 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 13.59 (s, 1H), 9.79 (d, *J* = 5.8 Hz, 1H), 9.23 (d, *J* = 6.1 Hz, 1H), 8.82 – 8.67 (m, 1H), 8.57 (d, *J* = 7.9 Hz, 1H), 8.15 (dd, *J* = 8.2, 5.1 Hz, 1H), 7.88 (t, *J* = 7.5 Hz, 1H), 7.81 (d, *J* = 8.3 Hz, 1H), 7.60 (td, *J* = 8.7, 1.9 Hz, 1H), 7.52 (t, *J* = 7.5 Hz, 1H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 180.7, 167.8(d, *J* = 255.3 Hz), 149.3(d, *J* = 13.2 Hz), 147.1, 140.8, 134.5, 130.7, 128.0(d, *J* = 10.9 Hz), 127.5, 124.6, 123.3, 123.1, 120.8, 120.4, 119.4, 118.2(d, *J* = 23.4 Hz), 113.8, 105.7(d, *J* = 29.8 Hz). ^{19}F NMR (565 MHz, DMSO-d_6) δ -98.0. HRMS (ESI-TOF) *m/z*: [M]$^+$ Calcd for $C_{18}H_{10}FN_2O^+$ 289.0772 Found 289.0767.

13-oxo-3-(trifluoromethyl)-12,13-dihydropyrido[1,2-a:3,4-b'] diindol-5-ium (2g)



Purified by trituration with MeOH and EA to give **2g** as a red solid (1.84 g, yield 92 %). m.p.>420°C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 13.65 (d, *J* = 8.8 Hz, 1H), 9.85 (s, 1H), 9.30 (d, *J* = 5.7 Hz, 1H), 9.09 (s, 1H), 8.59 (d, *J* = 7.6 Hz, 1H), 8.29 (d, *J* = 7.5 Hz, 1H), 8.14 (d, *J* = 7.7 Hz, 1H), 7.91 (d, *J* = 5.8 Hz, 1H), 7.81 (d, *J* = 8.1 Hz, 1H), 7.63 – 7.45 (m, 1H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 181.1, 147.3(d, *J* = 30.8 Hz), 140.8, 135.6(d, *J* = 32.5 Hz), 134.7, 130.9, 128.5, 127.5, 126.4, 124.6, 124.0, 123.3(d, *J* = 35.0 Hz), 122.2, 120.7, 119.5, 113.8(d, *J* = 39.0 Hz). ^{19}F NMR (565 MHz, DMSO-d_6) δ -61.6. HRMS (ESI-TOF) *m/z*: $[M]^+$ Calcd for $C_{19}H_{10}F_3N_2O^+$ 339.0740; Found 339.0738.

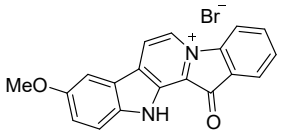
9-chloro-13-oxo-12,13-dihydropyrido[1,2-*a*:3,4-*b*'] diindol-5-ium (2h)



Purified by trituration with MeOH and EA to give **2h** as a red solid (1.70 g, yield 85 %).^{1}H NMR (600 MHz, DMSO-d_6 + CF_3CO_2D) δ 9.60 (d, *J* = 6.3 Hz, 1H), 9.06 (d, *J* = 6.2 Hz, 1H), 8.58 (s, 1H), 8.43 (d, *J* = 8.1 Hz, 1H), 7.97 (d, *J* = 7.4 Hz, 1H), 7.94 – 7.86 (m, 1H), 7.80 – 7.70 (m, 2H), 7.65 (t, *J* = 7.5 Hz, 1H). The ^{1}H NMR data is consistent with literature

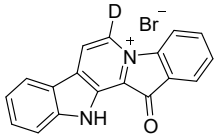
values.[7]

9-methoxy-13-oxo-12,13-dihydropyrido[1,2-*a*:3,4-*b*'] diindol-5-ium (2i)



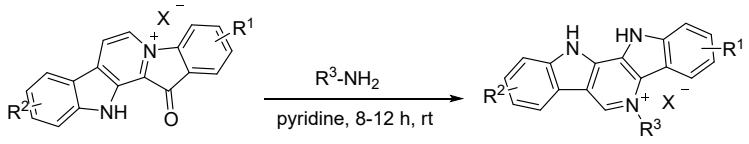
Purified by trituration with MeOH and EA to give **2i** as a black solid (1.52 g, yield 76 %). m.p. > 420 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 13.31 (s, 1H), 9.62 (s, 1H), 9.07 (s, 1H), 8.50 (d, J = 7.7 Hz, 1H), 8.03 (d, J = 23.8 Hz, 3H), 7.80 – 7.56 (m, 2H), 7.40 (s, 1H), 3.87 (s, 3H). HRMS (ESI-TOF) *m/z*: [M]$^+$ Calcd for $C_{19}H_{13}N_2O_2^+$ 301.0972 Found 301.0975. The ^{13}C NMR spectra of **2i** could not be obtained due to its poor solubility.

13-oxo-12,13-dihydropyrido[1,2-*a*:3,4-*b*'] diindol-5-ium-6-*d* (2j)



Purified by trituration with MeOH and EA to give **2j** as a red solid (1.46 g, yield 73%). m.p. > 420 °C. ^{1}H NMR (600 MHz, DMSO-d_6 + CF_3CO_2D) δ 9.10 (s, 1H), 8.50 (dd, J = 12.0, 8.0 Hz, 2H), 8.01 (d, J = 7.4 Hz, 1H), 7.96 (td, J = 7.9, 1.1 Hz, 1H), 7.84 – 7.78 (m, 1H), 7.76 (d, J = 8.3 Hz, 1H), 7.69 (t, J = 7.5 Hz, 1H), 7.49 – 7.42 (m, 1H). ^{13}C NMR (150 MHz, DMSO-d_6 + CF_3CO_2D) δ 182.6, 147.5, 147.3, 141.0, 137.3, 134.5, 131.6, 131.4, 125.9, 124.7, 124.4, 123.3, 120.7, 119.8, 118.1, 116.2, 114.3, 112.4. HRMS (ESI-TOF) *m/z*: [M]$^+$ Calcd for $C_{18}H_{10}DN_2O^+$ 272.0929 Found 272.0924.

1.3 Synthesis of compounds **1**



2

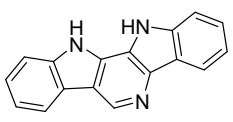
2c-f, X=Cl
2a-b, 2g-j, X=Br

1

1b-f, 1h-j, 1m-q, 1w, 1x, X=Br
1r-s, 1v, X=Cl

To a solution of fascaplysin or its derivatives (0.28 mmol) in 4 mL pyridine was added 14.8 mmol NH_3 (2.11 mL, 7 M in MeOH) or amine (0.84 mmol), and the reaction mixture was stirred at room temperature for 8-12 h under air, then the reaction mixture was concentrated. The obtained crude products was purified by trituration with DCM and PE to give compound **1.**

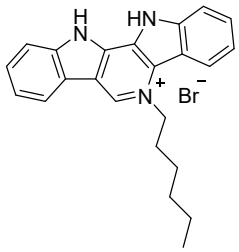
11,12-dihydropyrido[3,2-*b*:4,5-*b*'] diindole (1a)



Purification by flash column silica gel chromatography (DCM: MeOH=40:1-20:1)

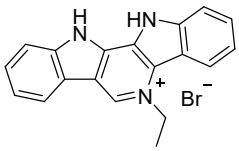
to give **1a** as a brown solid (7.4 mg, yield 10%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 11.61 (s, 1H), 11.24 (s, 1H), 9.29 (s, 1H), 8.27 (dd, J = 30.1, 7.7 Hz, 2H), 7.82 – 7.70 (m, 2H), 7.47 (t, J = 7.5 Hz, 2H), 7.29 (dt, J = 15.0, 7.4 Hz, 2H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 139.1, 139.1, 137.0, 135.8, 130.0, 125.8, 125.6, 123.0, 122.3, 120.2, 120.0, 119.5, 119.5, 119.3, 116.9, 112.2, 112.1. HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{17}H_{12}N_3$ 258.1026; Found 258.1018.

5-pentyl-11,12-dihydropyrido[3,2-*b*:4,5-*b*'] diindol-5-ium. (1b)



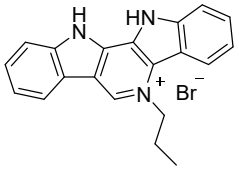
Purified by trituration with DCM and PE to give **1b** as a white solid (108.3 mg, yield 90%). m.p. 256.3-257.1 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.73 (s, 2H), 9.92 (s, 1H), 8.34 (dd, J = 57.3, 8.1 Hz, 2H), 7.96 (dd, J = 33.5, 8.2 Hz, 2H), 7.69 (dt, J = 16.2, 7.8 Hz, 2H), 7.50 (t, J = 7.5 Hz, 2H), 5.15 (t, J = 7.4 Hz, 2H), 2.16 – 2.00 (m, 2H), 1.49 (dt, J = 15.2, 7.4 Hz, 2H), 1.29 (qd, J = 14.5, 7.0 Hz, 4H), 0.84 (t, J = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 140.4, 139.1, 133.4, 132.7, 128.5, 128.2, 125.8, 122.5, 121.7, 121.6, 121.3, 121.1, 120.7, 116.3, 114.9, 113.5, 113.3, 57.3, 30.7, 29.1, 25.2, 21.9, 13.8. HRMS (ESI-TOF) *m/z*: [M]$^+$ Calcd for $C_{23}H_{24}N_3^+$ 342.1965; Found 342.1961.

5-ethyl-11,12-dihydropyrido[3,2-*b*:4,5-*b*'] diindol-5-ium (1c)



Purified by trituration with DCM and PE to give **1c** as a white solid (78.2 mg, yield 75%). m.p. 346.3-347.1 °C. ^{1}H NMR (600 MHz, DMSO-d_6 + CF_3CO_2D) δ 9.75 (s, 1H), 8.44 – 8.16 (m, 2H), 7.84 (dd, J = 39.1, 8.2 Hz, 2H), 7.61 (dt, J = 39.0, 7.7 Hz, 2H), 7.41 (dd, J = 12.6, 7.3 Hz, 2H), 5.14 (q, J = 7.1 Hz, 2H), 1.70 (t, J = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$ + CF_3CO_2D) δ 140.5, 139.9, 130.2, 130.1, 129.5, 123.7, 123.1, 121.3, 120.9, 120.7, 117.9, 117.5, 115.7, 115.0, 113.8, 113.1, 111.9, 54.0, 15.4. HRMS (ESI-TOF) *m/z*: [M]$^+$ Calcd for $C_{19}H_{16}N_3^+$ 286.1339; Found 286.1333.

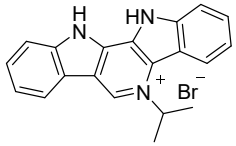
5-propyl-11,12-dihydropyrido[3,2-*b*:4,5-*b*'] diindol-5-ium (1d)



Purified by trituration with DCM and PE to give **1d** as a white solid (84.5 mg, yield 78%). m.p. 311.6-312.4 °C. ^{1}H NMR (600 MHz, DMSO-d_6 + CF_3CO_2D) δ 9.83 (s, 1H), 8.25 (dd, J = 57.0, 8.0 Hz, 2H), 7.85 (dd, J = 32.8, 8.2 Hz, 2H), 7.61 (dt, J = 32.0, 7.7 Hz, 2H), 7.41 (t, J = 7.2 Hz, 2H), 5.06 (t, J = 7.3 Hz, 2H), 2.18 – 2.00 (m, 2H), 1.04 (t, J

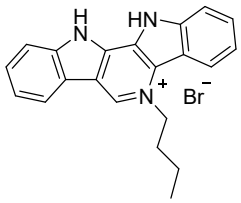
= 7.3 Hz, 3H). ^{13}C NMR (150 MHz, DMSO-d_6+ CF_3CO_2D) δ 140.7, 139.5, 133.8, 128.8, 128.6, 126.1, 122.8, 122.0, 121.4, 118.3, 116.4, 114.5, 113.8, 113.5, 112.5, 58.9, 23.0, 10.7. HRMS (ESI-TOF) *m/z*: [M]$^+$ Calcd for $C_{20}H_{18}N_3^+$ 300.1495; Found 300.1490.

5-isopropyl-11,12-dihydropyrido[3,2-*b*:4,5-*b*'] diindol-5-ium (1e)



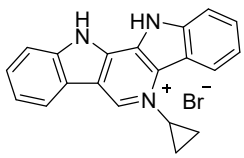
Purified by trituration with DCM and PE to give **1e** as a beige solid (65.0 mg, yield 60%). m.p. 328.9-329.5 °C. ^{1}H NMR (600 MHz, DMSO-d_6+ CF_3CO_2D) δ 9.88 (s, 1H), 8.50 (dd, *J* = 74.3, 7.6 Hz, 2H), 7.89 (dd, *J* = 45.4, 7.7 Hz, 2H), 7.63 (dt, *J* = 42.5, 7.0 Hz, 2H), 7.44 (s, 2H), 5.89 (s, 1H), 1.88 (d, *J* = 5.7 Hz, 6H).^{13}C NMR (150 MHz, DMSO-d_6+ CF_3CO_2D) δ140.8, 139.6, 129.3, 128.8, 128.5, 126.6, 122.6, 122.6, 122.1, 121.9, 118.2, 117.3, 116.3, 115.5, 114.4, 113.8, 113.5, 112.5, 57.9, 22.5. HRMS (ESI-TOF) *m/z*: [M]$^+$ Calcd for $C_{20}H_{18}N_3^+$ 300.1495; Found 300.1492.

5-butyl-11,12-dihydropyrido[3,2-*b*:4,5-*b*'] diindol-5-ium (1f)



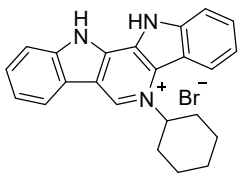
Purified by trituration with DCM and PE to give **1f** as a white solid (79.7 mg, yield 71%). m.p. 256.3-257.1 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.71 (s, 2H), 9.92 (s, 1H), 8.37 (d, *J* = 44.8 Hz, 2H), 7.98 (d, *J* = 32.2 Hz, 2H), 7.71 (d, *J* = 32.2 Hz, 2H), 7.52 (s, 2H), 5.18 (s, 2H), 2.08 (s, 2H), 1.50 (s, 2H), 0.96 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 140.4, 139.1, 133.4, 132.6, 128.5, 128.2, 125.8, 122.4, 121.7, 121.3, 121.1, 120.7, 116.3, 114.9, 113.5, 113.3, 57.1, 31.2, 19.0, 13.6. HRMS (ESI-TOF) *m/z*: [M]$^+$ Calcd for $C_{21}H_{20}N_3^+$ 314.1652; Found 314.1646.

5-cyclopropyl-11,12-dihydropyrido[3,2-*b*:4,5-*b*'] diindol-5-ium (1h)



Purified by trituration with DCM and PE to give **1h** as a beige solid (50.6 mg, isolated yield 47%). m.p. > 420 °C. ^{1}H NMR (600 MHz, DMSO-d_6+ CF_3CO_2D) δ 9.74 (s, 1H), 8.54 (dd, *J* = 112.2, 8.0 Hz, 2H), 7.83 (dd, *J* = 41.0, 8.2 Hz, 2H), 7.60 (dt, *J* = 45.8, 7.7 Hz, 2H), 7.40 (dd, *J* = 12.9, 7.3 Hz, 2H), 1.61 (d, *J* = 7.2 Hz, 5H). HRMS (ESI-TOF) *m/z*: [M]$^+$ Calcd for $C_{20}H_{16}N_3^+$ 298.1339; found 298.1336. The ^{13}C NMR spectra of **1h** could not be obtained due to its poor solubility.

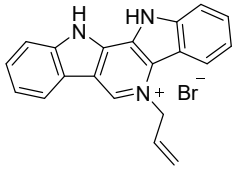
5-cyclohexyl-11,12-dihydropyrido[3,2-*b*:4,5-*b*'] diindol-5-ium (1i)



Purified by trituration with DCM and PE to give **1i** as a light pink solid (98.2 mg, yield 82%). m.p. 321.8-322.5 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.78 (s, 2H), 9.91

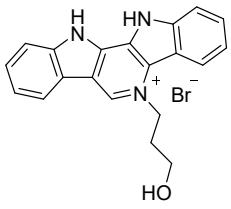
(s, 1H), 8.45 (dd, *J* = 172.6, 8.0 Hz, 2H), 7.95 (dd, *J* = 47.0, 8.2 Hz, 2H), 7.69 (dt, *J* = 42.2, 7.6 Hz, 2H), 7.60 – 7.42 (m, 2H), 5.45 (t, *J* = 11.7 Hz, 1H), 2.39 (d, *J* = 11.0 Hz, 2H), 2.24 (q, *J* = 11.4 Hz, 2H), 2.06 (d, *J* = 12.6 Hz, 2H), 1.86 (dd, *J* = 27.1, 12.6 Hz, 3H), 1.44 (t, *J* = 12.9 Hz, 1H).^{13}C NMR (150 MHz, DMSO-d_6) δ 140.5, 139.2, 132.6, 129.3, 128.5, 128.3, 126.2, 122.4, 121.9, 121.7, 121.7, 120.7, 116.8, 115.1, 113.6, 113.3, 64.3, 32.4, 25.1, 24.9. HRMS (ESI-TOF) *m/z*: [M]$^+$ Calcd for $C_{23}H_{22}N_3^+$ 340.1808; Found 340.1806.

5-allyl-11,12-dihydropyrido[3,2-*b*:4,5-*b*'] diindol-5-ium bromide (1j).



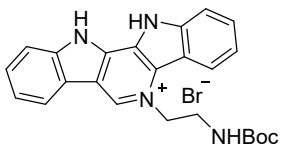
Purified by trituration with DCM and PE to give **1j** as a beige solid (62.5 mg, yield 58%). m.p. > 420 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.75 (s, 1H), 8.27 (dd, *J* = 66.3, 8.0 Hz, 2H), 7.82 (dd, *J* = 13.8, 8.2 Hz, 2H), 7.58 (dd, *J* = 19.2, 7.7 Hz, 2H), 7.44 – 7.29 (m, 2H), 6.52 – 6.31 (m, 1H), 5.77 (s, 2H), 5.27 (d, *J* = 10.6 Hz, 1H), 4.89 (d, *J* = 17.3 Hz, 1H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 138.9, 132.8, 132.4, 127.4, 124.6, 122.7, 122.2, 121.8, 121.3, 120.8, 120.7, 117.6, 117.2, 115.3, 114.7, 113.1, 58.1. HRMS (ESI-TOF) *m/z*: [M]$^+$ Calcd for $C_{20}H_{16}N_3^+$ 298.1339; found 298.1336.

5-(3-hydroxypropyl)-11,12-dihydropyrido[3,2-*b*:4,5-*b*'] diindol-5-ium (1m)



Purified by trituration with DCM and PE to give **1m** as a white solid (73.4 mg, yield 65%). m.p. 296.2-297.1 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.77 (s, 2H), 9.86 (s, 1H), 8.39 (dd, *J* = 44.6, 8.0 Hz, 2H), 7.92 (dd, *J* = 36.7, 8.2 Hz, 2H), 7.66 (dt, *J* = 37.5, 7.7 Hz, 2H), 7.46 (t, *J* = 7.5 Hz, 2H), 5.22 (t, *J* = 7.4 Hz, 2H), 5.04 (s, 1H), 3.64 (s, 2H), 2.32 – 2.18 (m, 2H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 140.4, 139.2, 133.6, 132.7, 128.5, 128.3, 125.9, 122.5, 122.0, 121.7, 121.3, 121.1, 120.7, 116.4, 115.0, 113.5, 113.3, 57.4, 55.1, 32.2. HRMS (ESI-TOF) *m/z*: [M]$^+$Calcd for $C_{20}H_{18}N_3O^+$ 316.1444; Found 316.1441.

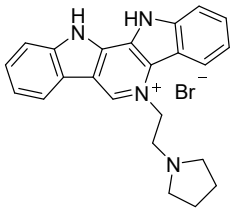
5-(2-((tert-butoxycarbonyl) amino) ethyl)-11,12-dihydropyrido[3,2-*b*:4,5-*b*'] diindol-5-ium (1n)



Purified by trituration with DCM and PE to give **1n** as a white solid (82.3 mg, yield 60%). m.p. 246.7-247.3 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.63 (s, 1H), 8.40 (dd, *J* = 53.5, 8.0 Hz, 2H), 7.95 (dd, *J* = 32.1, 8.2 Hz, 2H), 7.69 (dt, *J* = 33.7, 7.6 Hz, 2H), 7.49 (dt, *J* = 20.0, 7.5 Hz, 2H), 7.13 (t, *J* = 5.9 Hz, 1H), 5.19 (t, *J* = 5.2 Hz, 2H), 3.70 (dd, *J* = 10.7, 5.4 Hz, 2H), 1.04 (s, 9H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 156.0, 141.4, 139.6, 134.2, 133.8, 128.8, 128.6, 126.7, 122.9, 122.3, 122.0, 122.0, 121.3, 121.3, 116.9, 115.7, 114.0, 113.9, 78.5, 57.8, 28.2. HRMS (ESI-TOF) *m/z*: [M]$^+$

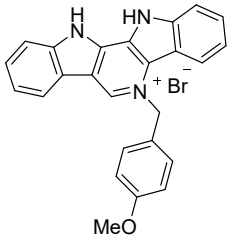
Calcd for $C_{24}H_{25}N_4O_2^+$ 401.1972; Found 401.1970.

5-(2-(pyrrolidin-1-yl) ethyl)-11,12-dihydropyrido[3,2-*b*:4,5-*b*'] diindol-5-ium (1o)



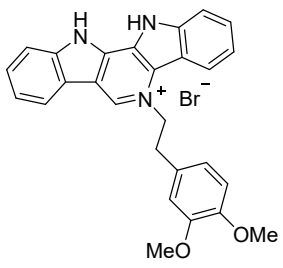
Purified by trituration with DCM and PE to give **1o** as a white solid (68.2 mg, yield 55%). m.p. 248.6-249.4 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.73 (s, 2H), 9.85 (s, 1H), 8.37 (dd, J = 46.7, 8.1 Hz, 2H), 7.96 (dd, J = 34.5, 8.2 Hz, 2H), 7.69 (dt, J = 32.2, 7.5 Hz, 2H), 7.50 (dd, J = 12.7, 7.4 Hz, 2H), 5.28 (s, 2H), 3.20 (s, 2H), 2.61 (s, 4H), 1.67 (s, 4H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 140.5, 139.2, 134.0, 132.9, 128.6, 128.3, 125.8, 122.6, 121.7, 121.6, 121.4, 121.1, 120.7, 116.2, 115.0, 113.6, 113.4, 56.0, 53.9, 53.8, 23.3. HRMS (ESI-TOF) *m/z*: [M]$^+$ Calcd for $C_{23}H_{23}N_4^+$ 355.1917; Found 355.1912.

5-(4-methoxybenzyl)-11,12-dihydropyrido[3,2-*b*:4,5-*b*'] diindol-5-ium (1p)



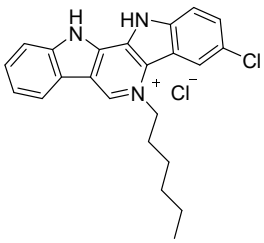
Purified by trituration with DCM and PE to give **1p** as a white solid (73.2 mg, yield 56%). m.p. 267.5-268.2 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.84 (d, J = 142.1 Hz, 2H), 10.02 (s, 1H), 8.41 (d, J = 7.6 Hz, 1H), 8.23 (d, J = 8.0 Hz, 1H), 8.09 – 7.86 (m, 2H), 7.68 (dt, J = 27.2, 7.3 Hz, 2H), 7.53 (t, J = 7.2 Hz, 1H), 7.36 (t, J = 7.3 Hz, 1H), 7.19 (d, J = 8.0 Hz, 2H), 6.90 (d, J = 8.1 Hz, 2H), 6.42 (s, 2H), 3.68 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 159.1, 140.7, 139.3, 134.1, 133.2, 128.6, 128.5, 127.7, 126.6, 126.5, 122.7, 122.2, 121.5, 121.4, 121.2, 121.0, 116.8, 115.0, 114.5, 113.5, 59.3, 55.1. HRMS (ESI-TOF) *m/z*: [M]$^+$ Calcd for $C_{25}H_{20}N_3O^+$ 378.1601; Found 378.1598.

5-(3,4-dimethoxyphenethyl)-11,12-dihydropyrido[3,2-*b*:4,5-*b*'] diindol-5-ium (1q)



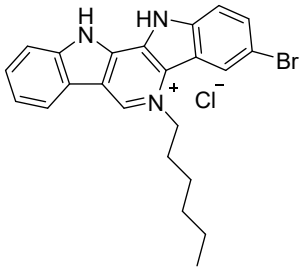
Purified by trituration with DCM and PE to give **1q** as a white solid (87.2 mg, yield 61%). m.p. 188.7-189.3 °C. ^{1}H NMR (600 MHz, DMSO-d_6+CF_3CO_2D) δ 9.52 (s, 1H), 8.21 (dd, J = 67.9, 8.0 Hz, 2H), 7.82 (dd, J = 52.6, 8.2 Hz, 2H), 7.58 (dt, J = 51.1, 7.6 Hz, 2H), 7.39 (dt, J = 36.0, 7.5 Hz, 2H), 6.79 (s, 1H), 6.71 (d, J = 8.1 Hz, 1H), 6.59 (d, J = 8.0 Hz, 1H), 5.30 (t, J = 7.3 Hz, 2H), 3.60 (d, J = 6.4 Hz, 6H), 3.28 (t, J = 7.3 Hz, 2H). ^{13}C NMR (150 MHz, DMSO-d_6+CF_3CO_2D) δ 149.2, 148.3, 140.6, 139.5, 133.5, 129.0, 128.7, 128.4, 126.0, 122.7, 121.8, 121.6, 121.2, 121.1, 118.1, 116.2, 115.2, 114.3, 113.8, 113.5, 113.0, 112.4, 112.2, 58.4, 55.6, 55.5, 35.1. HRMS (ESI-TOF) *m/z*: [M]$^+$ Calcd for $C_{27}H_{24}N_3O_2^+$ 422.1863; Found 422.1860.

2-chloro-5-hexyl-11,12-dihydropyrido[3,2-*b*:4,5-*b*'] diindol-5-ium (1r)



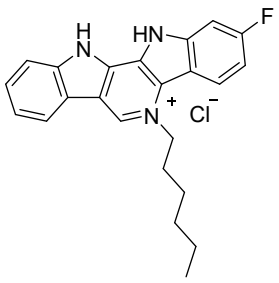
Purified by trituration with DCM and PE to give **1r** as a white solid (52.0 mg, yield 43%). m.p. 272.2-273.1 °C. ^{1}H NMR (600 MHz, DMSO-d_6+CF_3CO_2D) δ 13.24 (d, *J* = 105.0 Hz, 2H), 9.78 (d, *J* = 2.4 Hz, 1H), 8.29 (d, *J* = 7.8 Hz, 1H), 8.17 (s, 1H), 7.87 (dd, *J* = 8.8, 3.1 Hz, 1H), 7.81 (d, *J* = 8.1 Hz, 1H), 7.65 – 7.56 (m, 2H), 7.43 (t, *J* = 7.5 Hz, 1H), 5.07 (t, *J* = 7.4 Hz, 2H), 2.12 – 1.97 (m, 2H), 1.46 (dt, *J* = 15.1, 7.5 Hz, 2H), 1.37 – 1.29 (m, 2H), 1.25 (dt, *J* = 14.3, 6.9 Hz, 2H), 0.83 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$+ CF_3CO_2D) δ 140.9, 138.3, 133.1, 131.5, 130.5, 130.0, 129.2, 126.1, 124.1, 121.7, 121.2, 120.9, 120.9, 117.7, 115.8, 113.9, 112.0, 59.2, 31.6, 30.3, 26.4, 22.7, 13.6. HRMS (ESI-TOF) *m/z*: [M]$^+$ Calcd for $C_{23}H_{23}ClN_3^+$ 376.1575; Found 376.1573.

2-bromo-5-hexyl-11,12-dihydropyrido[3,2-*b*:4,5-*b*'] diindol-5-ium (1s)



Purified by trituration with DCM and PE to give **1s** as a beige solid (77.2 mg, yield 65%). m.p. 297.1-297.9 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 13.28 (s, 2H), 9.87 (s, 1H), 8.43 – 8.33 (m, 2H), 7.89 (dd, *J* = 11.9, 8.5 Hz, 2H), 7.80 (d, *J* = 8.8 Hz, 1H), 7.66 (t, *J* = 7.6 Hz, 1H), 7.49 (t, *J* = 7.5 Hz, 1H), 5.13 (t, *J* = 7.4 Hz, 2H), 2.15 – 1.98 (m, 2H), 1.48 (dt, *J* = 15.0, 7.4 Hz, 2H), 1.39 – 1.31 (m, 2H), 1.27 (dt, *J* = 14.3, 7.1 Hz, 2H), 0.85 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$+CF_3CO_2D) δ 140.8, 138.5, 133.1, 131.5, 130.0, 125.8, 124.1, 123.9, 121.5, 121.1, 120.9, 117.6, 116.8, 115.7, 113.9, 113.5, 112.0, 59.2, 31.6, 30.2, 26.4, 22.7, 13.6. HRMS (ESI-TOF) *m/z*: [M]$^+$ Calcd for $C_{23}H_{23}BrN_3^+$ 420.1070; Found 420.1068.

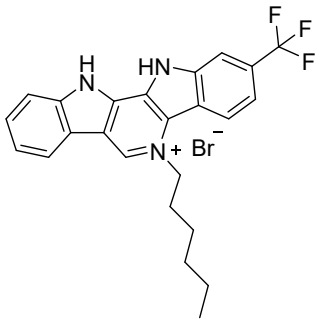
3-fluoro-5-hexyl-11,12-dihydropyrido[3,2-*b*:4,5-*b*'] diindol-5-ium (1v)



Purified by trituration with DCM and PE to give **1v** as a white solid (84.1 mg, yield 69%). m.p. 257.3-258.2 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 13.26 (s, 2H), 9.82 (s, 1H), 8.33 (d, *J* = 7.8 Hz, 1H), 8.28 (dd, *J* = 9.0, 5.1 Hz, 1H), 7.84 (d, *J* = 8.1 Hz, 1H), 7.73 (dd, *J* = 9.4, 1.8 Hz, 1H), 7.63 (t, *J* = 7.6 Hz, 1H), 7.46 (t, *J* = 7.5 Hz, 1H), 7.32 (td, *J* = 9.1, 2.1 Hz, 1H), 5.11 (t, *J* = 7.4 Hz, 2H), 2.15 – 1.92 (m, 2H), 1.48 (dt, *J* = 15.2, 7.5 Hz, 2H), 1.36 – 1.22 (m, 4H), 0.84 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$+CF_3CO_2D) δ 163.5(d, *J* = 249.6 Hz), 141.2(d, *J* = 12.7 Hz), 140.9, 132.9, 131.0, 129.9, 127.2, 124.0, 123.2(d, *J* = 10.4 Hz), 121.5,

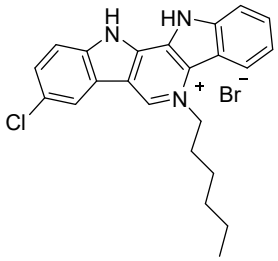
121.1(d, *J* = 29.4 Hz), 118.2, 117.7, 115.8, 113.9, 112.1, 100.5(d, *J* = 26.4 Hz), 59.1, 31.6, 30.2, 26.5, 22.7, 13.5. ^{19}F NMR (565 MHz, DMSO-d_6) δ -110.6. HRMS (ESI-TOF) *m/z*: [M]$^+$ Calcd for $C_{23}H_{23}FN_3^+$ 360.1871; Found 360.1866.

5-hexyl-2-(trifluoromethyl)-11,12-dihydropyrido[3,2-b:4,5-b'] diindol-5-ium (1w)



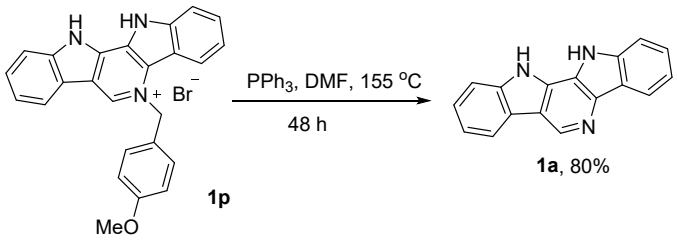
Purified by trituration with DCM and PE to give **1w** as a light pink solid (88.1 mg, yield 76%). m.p.309.2-310.1 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.93 (s, 2H), 10.02 (s, 1H), 8.49 (d, *J* = 8.6 Hz, 1H), 8.44 – 8.33 (m, 2H), 7.93 (d, *J* = 8.2 Hz, 1H), 7.75 (d, *J* = 8.4 Hz, 1H), 7.66 (t, *J* = 7.6 Hz, 1H), 7.49 (t, *J* = 7.5 Hz, 1H), 5.17 (t, *J* = 7.4 Hz, 2H), 2.14 – 2.01 (m, 2H), 1.50 (dt, *J* = 15.2, 7.5 Hz, 2H), 1.35 – 1.22 (m, 4H), 0.84 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 140.5, 138.1, 134.8, 132.8, 128.5, 128.0 (d, *J* = 31.9 Hz), 125.3, 124.9, 123.5, 123.0, 122.8, 122.4, 121.4, 121.2, 117.6 (d, *J* = 9.6 Hz), 116.8, 113.6, 111.3 (d, *J* = 4.4 Hz), 57.4, 30.8, 29.1, 25.3, 21.9, 13.9. ^{19}F NMR (565 MHz, DMSO-d_6) δ -60.1. HRMS (ESI-TOF) *m/z*: [M]$^+$ Calcd for $C_{24}H_{23}F_3N_3^+$ 410.1839; Found 410.1837.

9-chloro-5-hexyl-11,12-dihydropyrido[3,2-*b*:4,5-*b*'] diindol-5-ium (1x)



Purified by trituration with DCM and PE to give **1x** as a beige solid (65.3 mg, yield 54%). m.p.303.1-303.8 °C. ^{1}H NMR (600 MHz, DMSO-d_6+CF_3CO_2D) δ 9.80 (s, 1H), 8.38 (s, 1H), 8.19 (d, *J* = 8.2 Hz, 1H), 7.84 (dd, *J* = 34.2, 8.4 Hz, 2H), 7.64 (t, *J* = 7.6 Hz, 1H), 7.54 (d, *J* = 8.4 Hz, 1H), 7.41 (t, *J* = 7.5 Hz, 1H), 5.05 (t, *J* = 6.9 Hz, 2H), 2.12 – 1.98 (m, 2H), 1.46 (dd, *J* = 13.9, 6.9 Hz, 2H), 1.36 – 1.19 (m, 4H), 0.82 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$+ CF_3CO_2D) δ 139.9, 138.7, 132.9, 131.8, 130.3, 129.6, 129.5, 127.2, 123.3, 122.1, 121.4, 120.9, 120.5, 117.6, 115.7, 113.8, 112.0, 59.5, 31.6, 30.3, 26.5, 22.7, 13.6. HRMS (ESI-TOF) *m/z*: [M]$^+$ Calcd for $C_{23}H_{23}ClN_3^+$ 376.1575; Found 376.1572.

1.4 *N*-dealkylation of **1p**



To a solution of **1p** (100 mg, 0.22 mmol) in 4 mL DMF was added triphenylphosphine (172 mg, 0.66 mmol), and the reaction mixture was stirred at 155 °C for 48 h. Then the reaction mixture was cooled to room temperature, diluted with H_2O, extracted with EA. The combined organic layer was washed with H_2O and brine, dried over anhydrous Na_2SO_4. After evaporation, the obtained crude products were purified by flash column silica gel chromatography (DCM: MeOH=40:1-10:1) to give 45 mg compound **1a** in 80% yield.

References:

(1) Wang X, Qiu H, Yang N, et al. Fascaplysin derivatives binding to DNA via unique cationic five-ring coplanar backbone showed potent antimicrobial/antibiofilm activity against MRSA in vitro and in vivo. European Journal of Medicinal Chemistry, 2022, 230: 114099.

(2) Zhidkov M E, Smirnova P A, Tryapkin O A, et al. Total syntheses and preliminary biological evaluation of brominated fascaplysin and reticulatine alkaloids and their analogues. Marine drugs, 2019, 17(9): 496.

(3) Gynther J, Kanerva L, Undheim K, et al. EI and CI mass fragmentation of tryptamine, tetrahydro-beta-carboline and some of their derivatives. Acta Chemica Scandinavica, 1988, 42: 433-441.

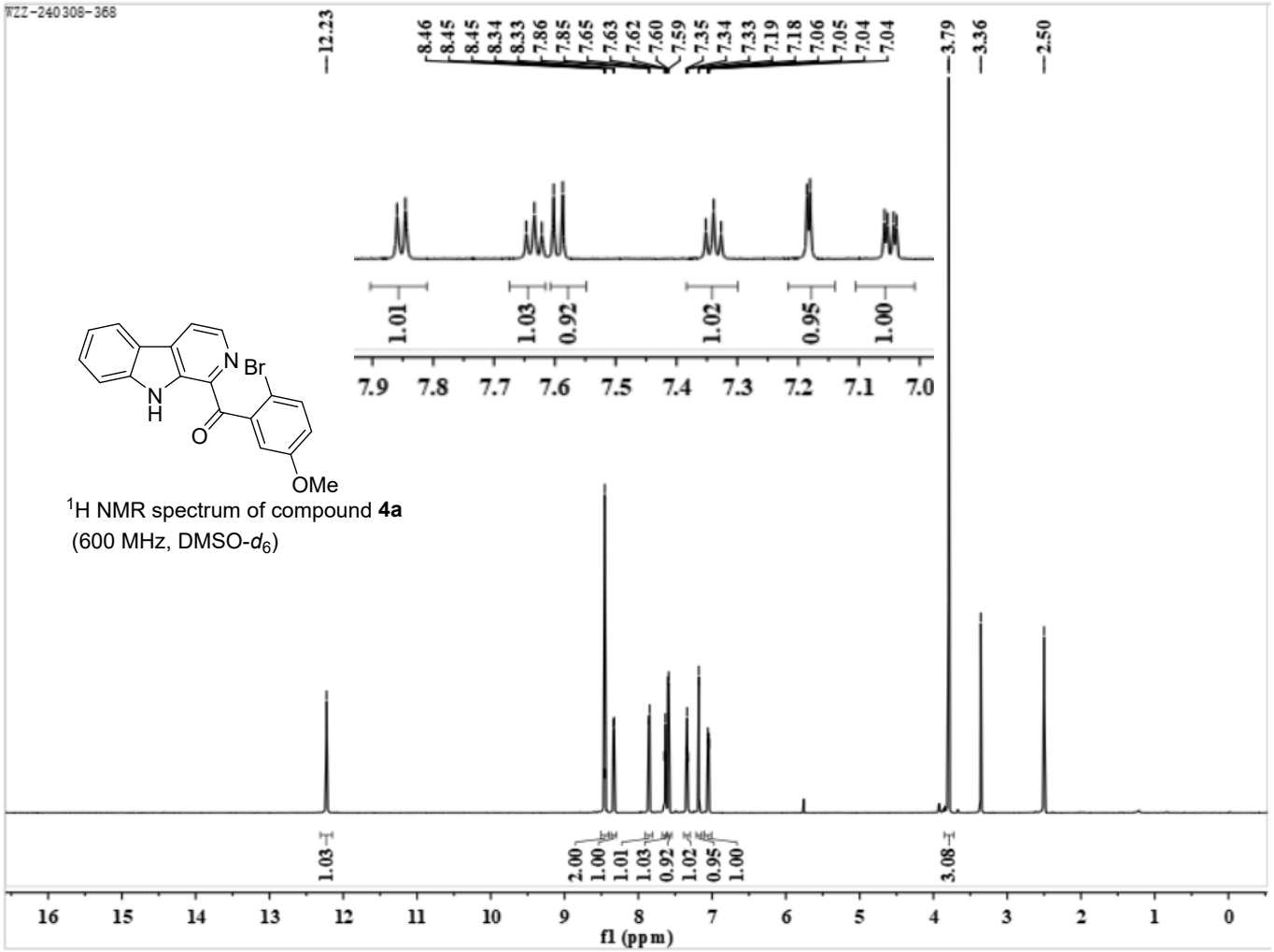
(4) Pan H, Qiu H, Zhang K, et al. Fascaplysin derivatives are potent multitarget agents against Alzheimer's disease: in vitro and in vivo evidence. ACS Chemical Neuroscience, 2019, 10(11): 4741-4756.

(5) Manda S, Sharma S, Wani A, et al. Discovery of a marine-derived bis-indole alkaloid fascaplysin, as a new class of potent P-glycoprotein inducer and establishment of its structure–activity relationship. European journal of medicinal chemistry, 2016, 107: 1-11.

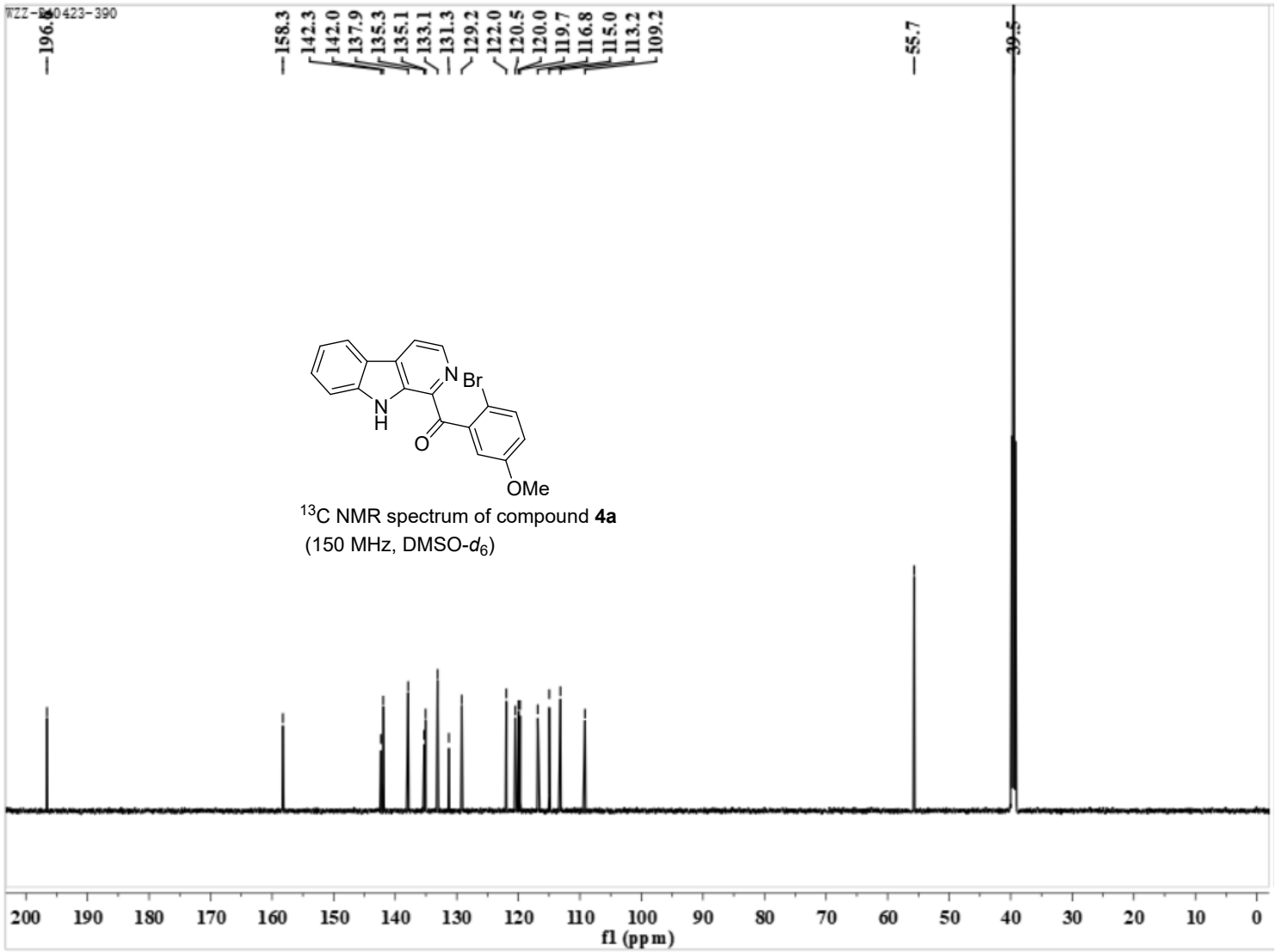
(6) Zhidkov M E, Kaune M, Kantemirov A V, et al. Study of structure–activity relationships of the marine alkaloid fascaplysin and its derivatives as potent anticancer agents. Marine Drugs, 2022, 20(3): 185.

(7) Fretz H, Ucci-Stoll K, Hug P, et al. Investigations on the reactivity of fascaplysin, part I, aromatic electrophilic substitutions occur at position 9. Helvetica Chimica Acta, 2000, 83(11): 3064-3068.

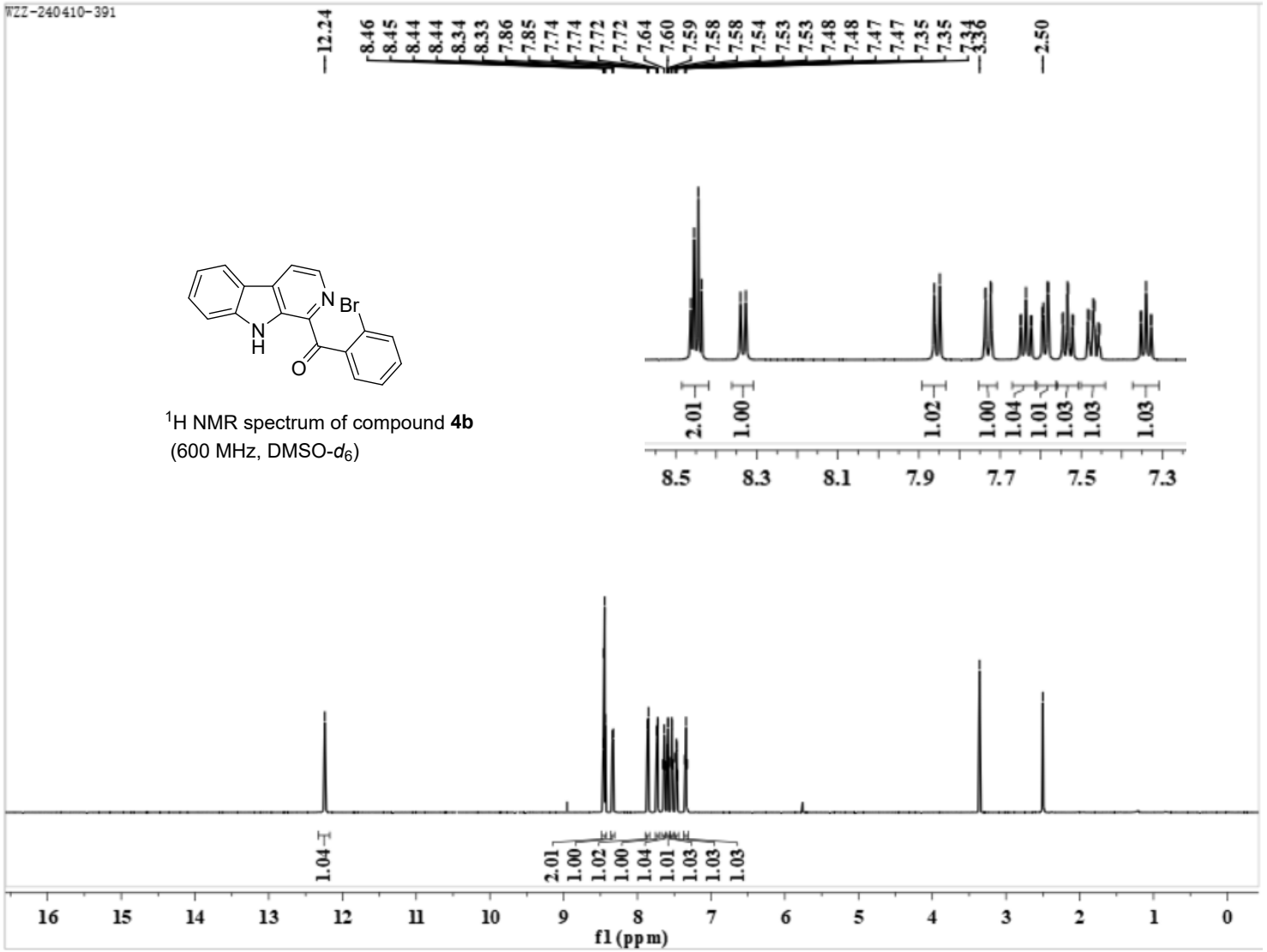
2. NMR spectra for compounds **4a-j, 2a-j and 1**: **Page S16-91**.



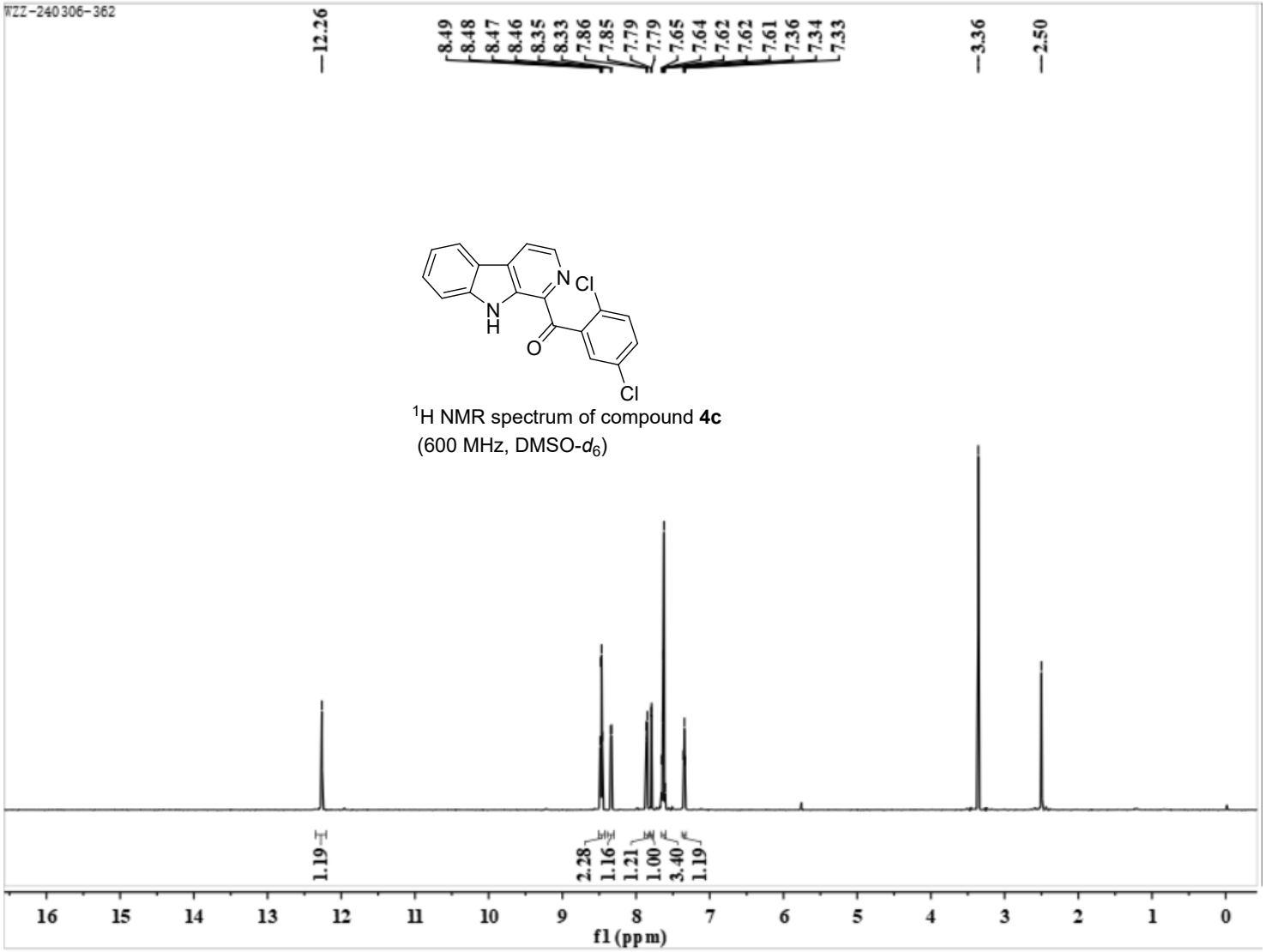
^{1}H NMR spectrum of compound **4a**
(600 MHz, DMSO-d_6)



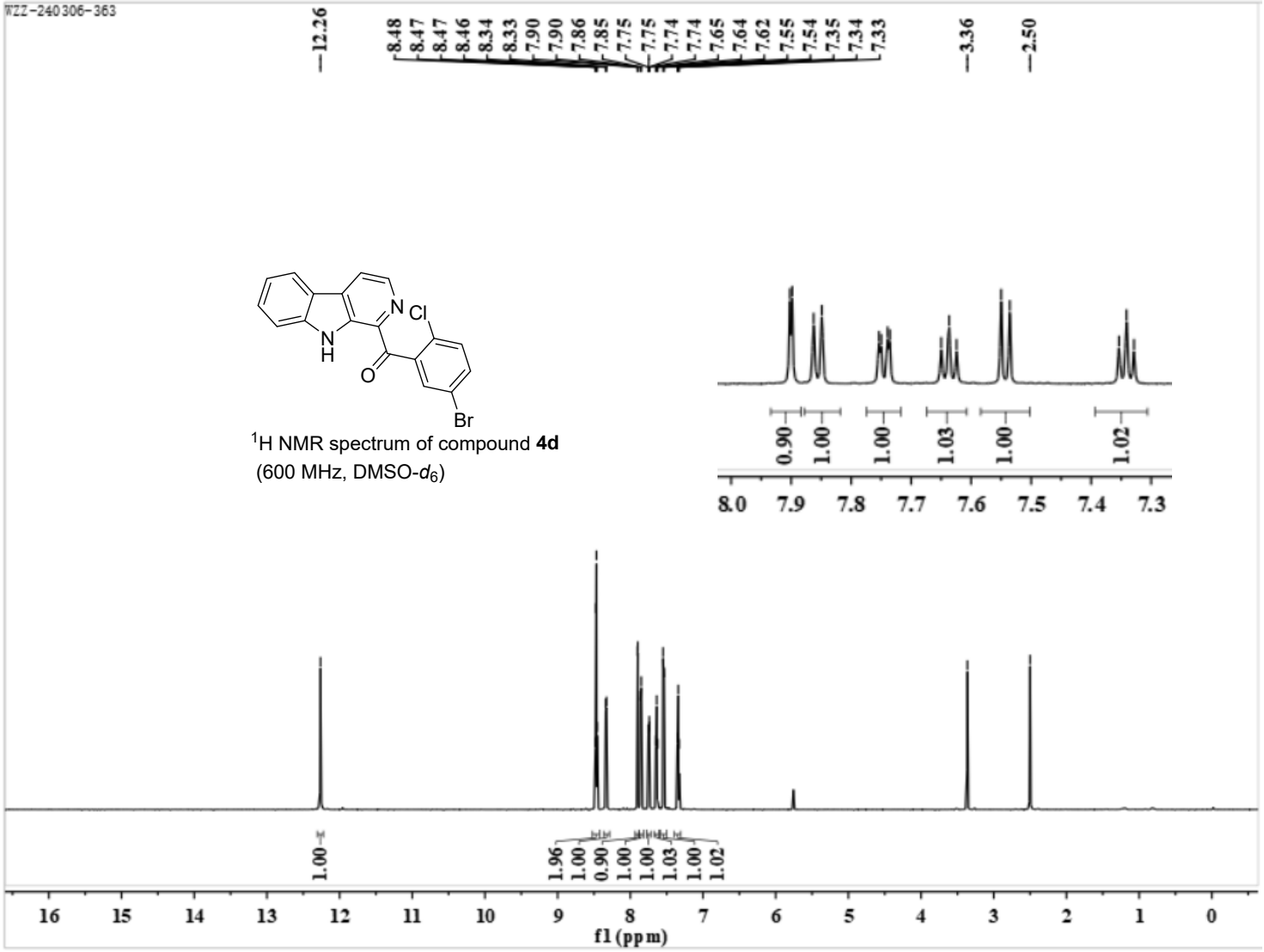
^{13}C NMR spectrum of compound **4a**
(150 MHz, DMSO-d_6)



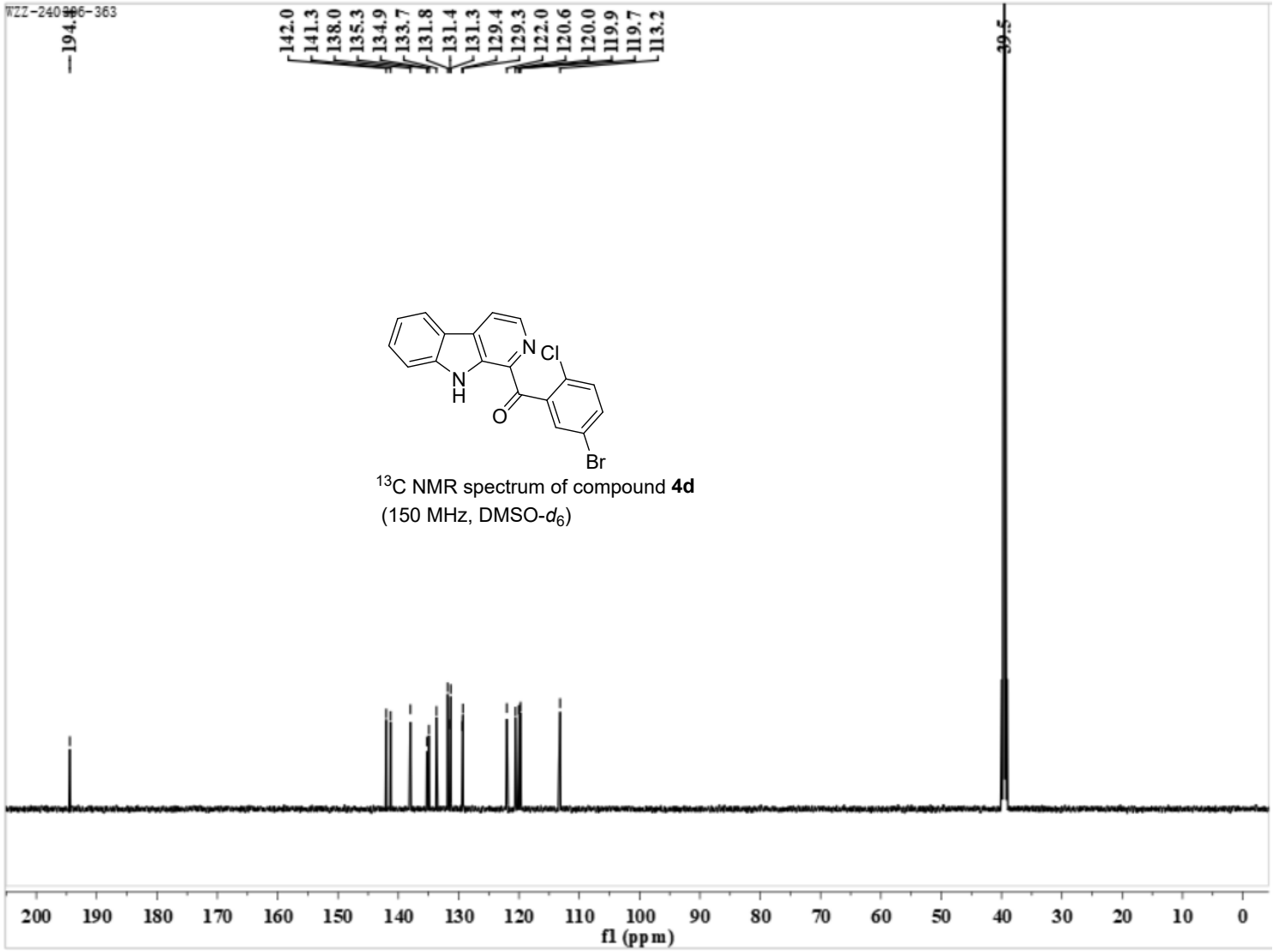
^{1}H NMR spectrum of compound **4b**
(600 MHz, DMSO-d_6)



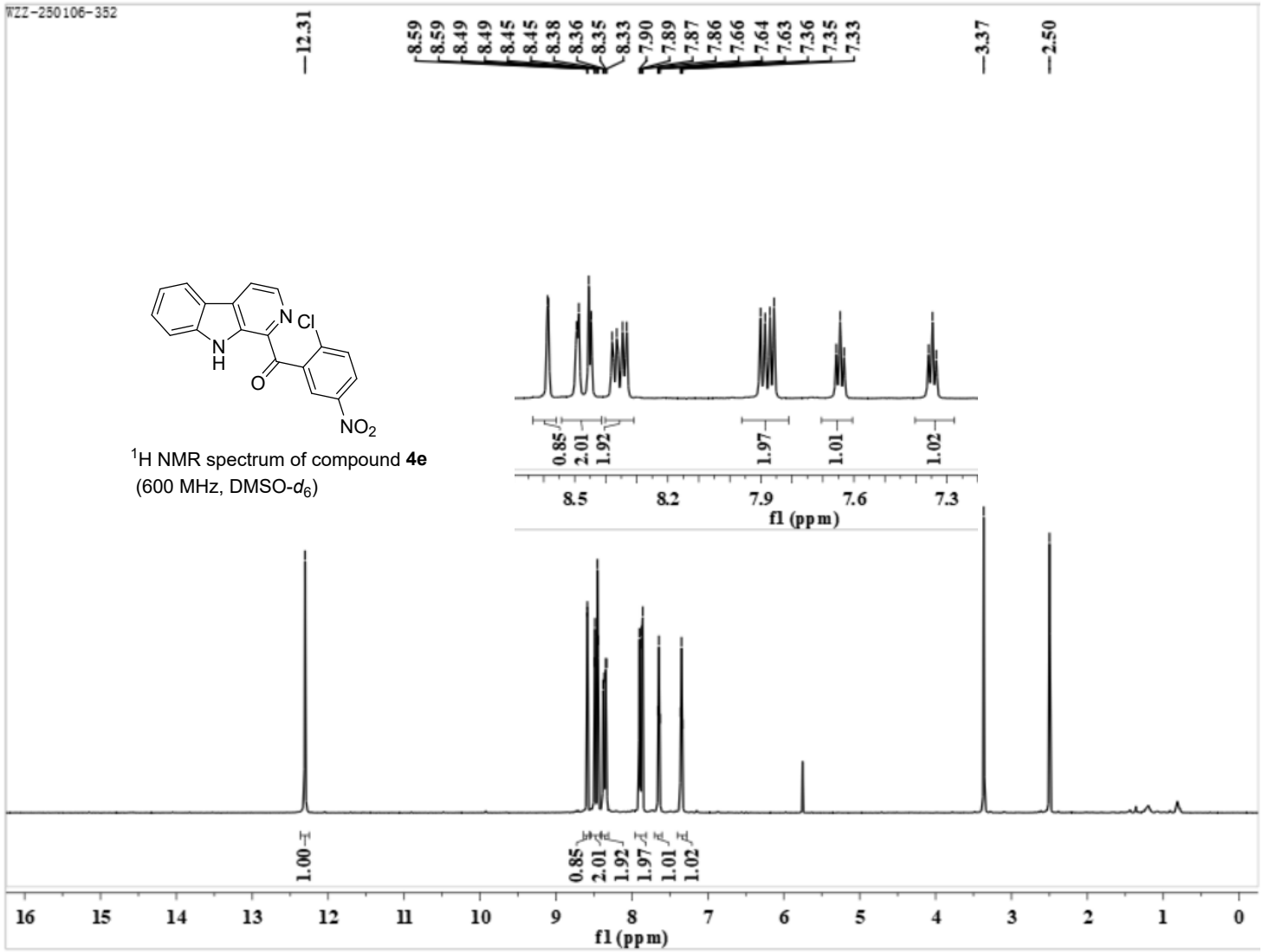
^{1}H NMR spectrum of compound **4c**
(600 MHz, DMSO-d_6)



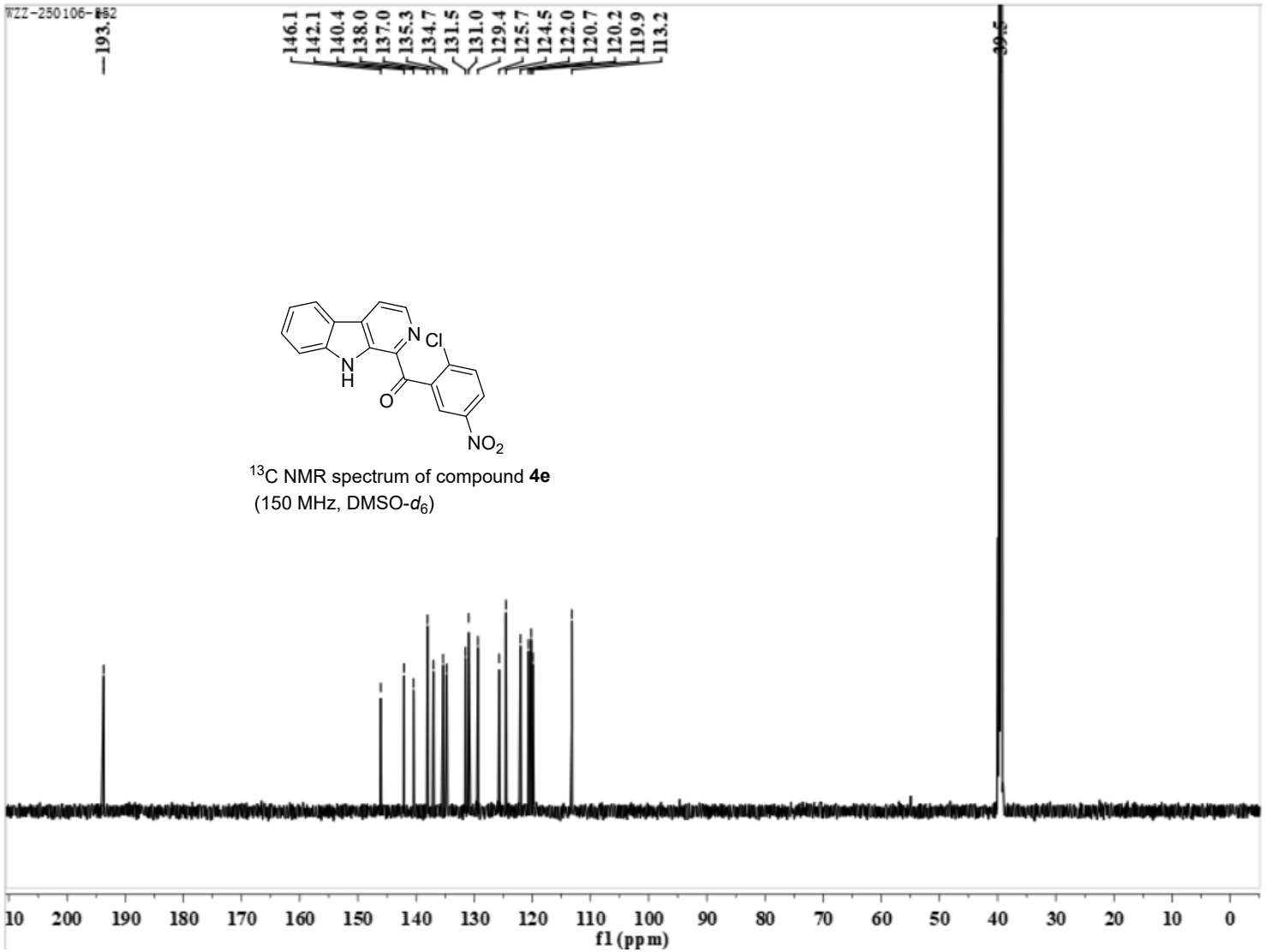
^{1}H NMR spectrum of compound **4d**
(600 MHz, DMSO-d_6)



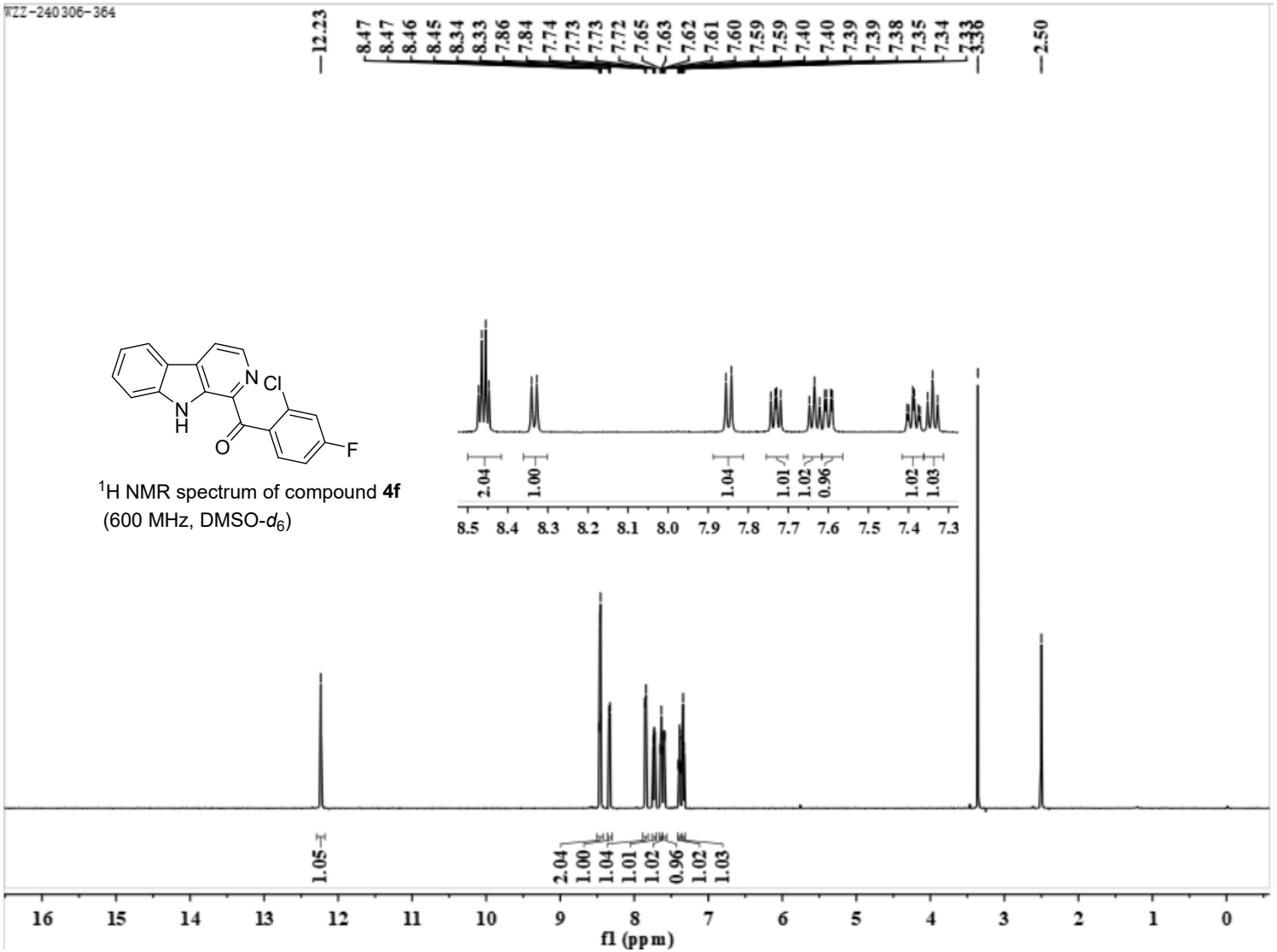
^{13}C NMR spectrum of compound **4d**
(150 MHz, DMSO-d_6)



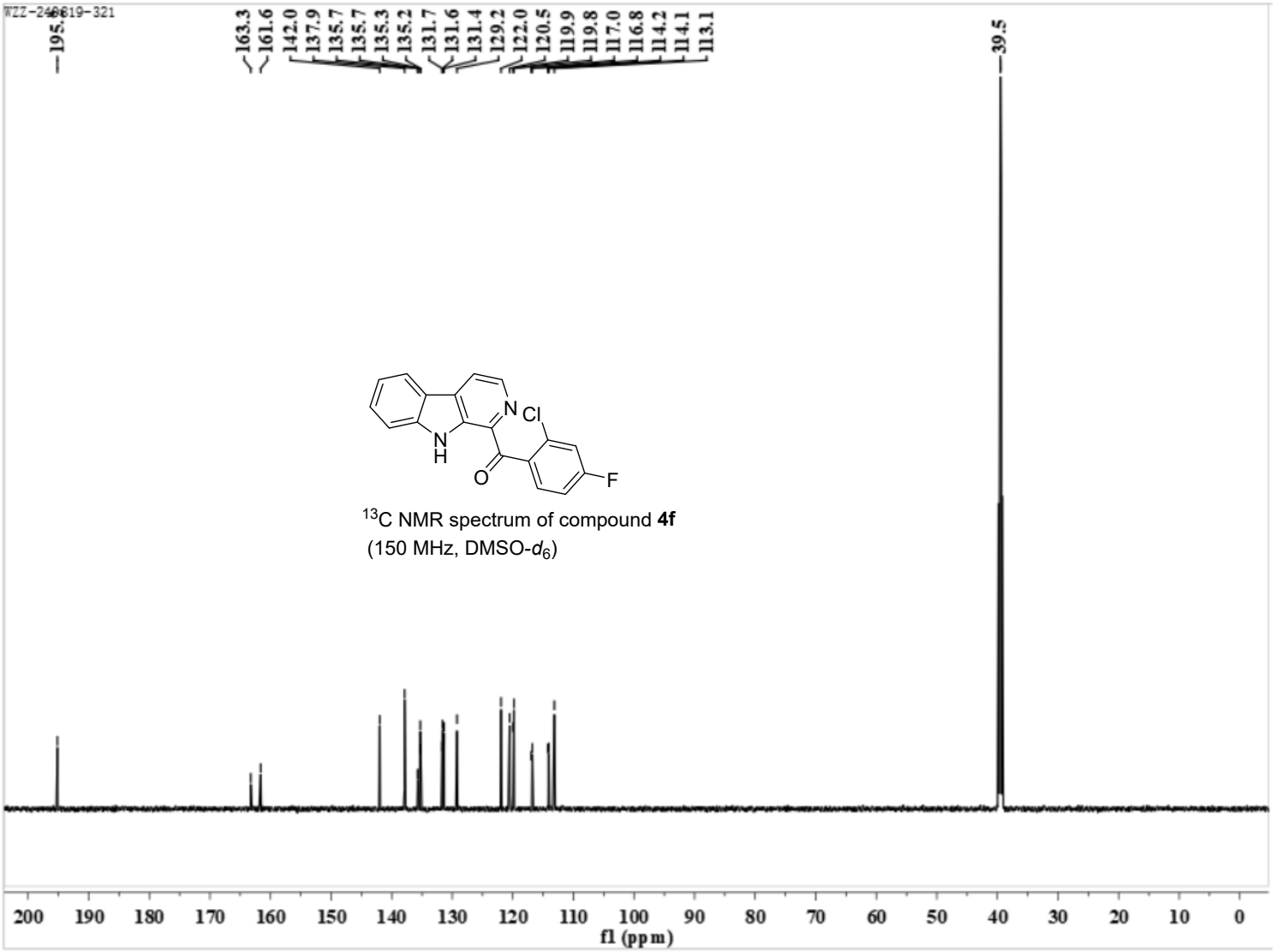
^{1}H NMR spectrum of compound **4e**
(600 MHz, DMSO-d_6)



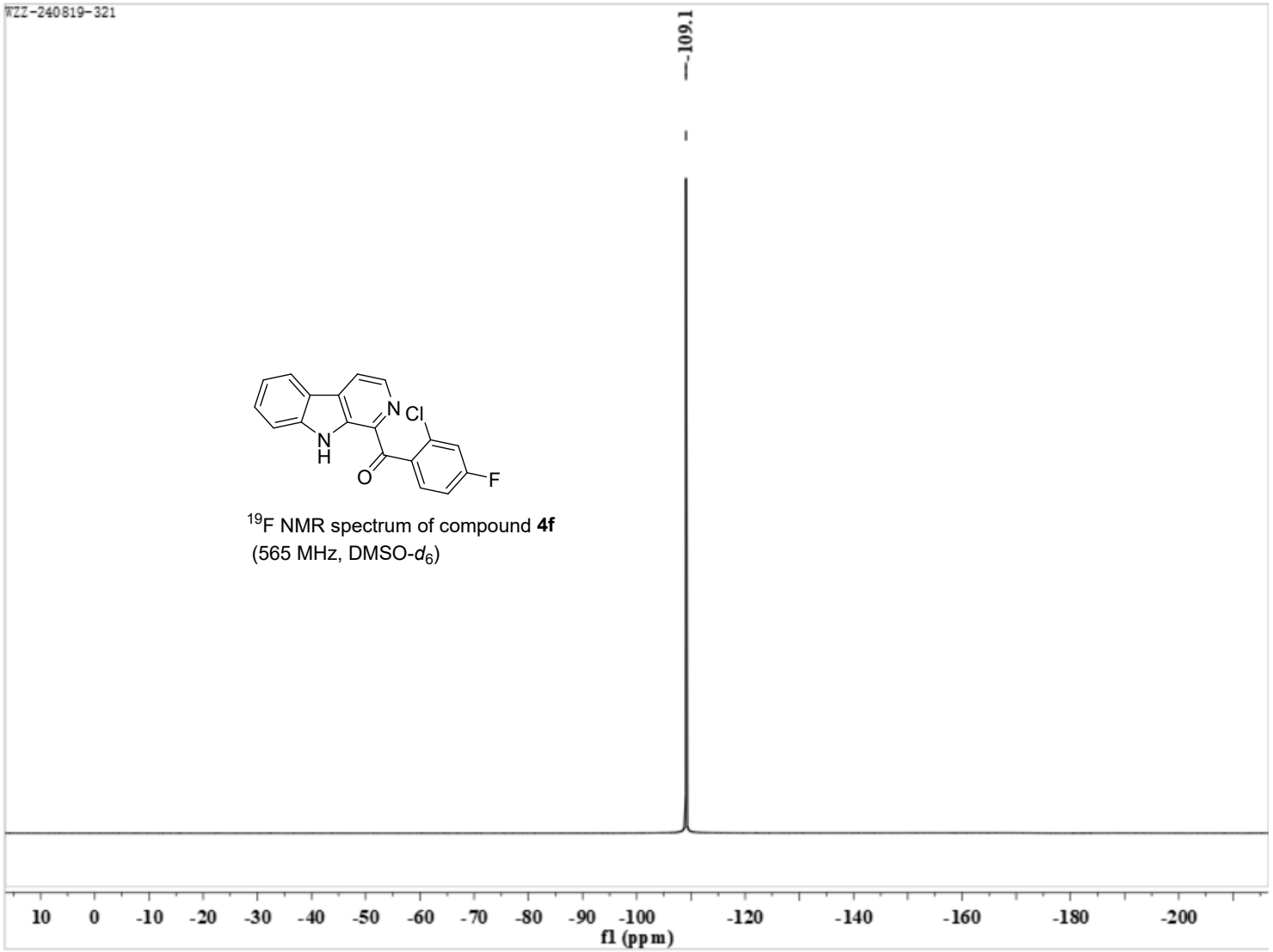
^{13}C NMR spectrum of compound **4e**
(150 MHz, DMSO-d_6)



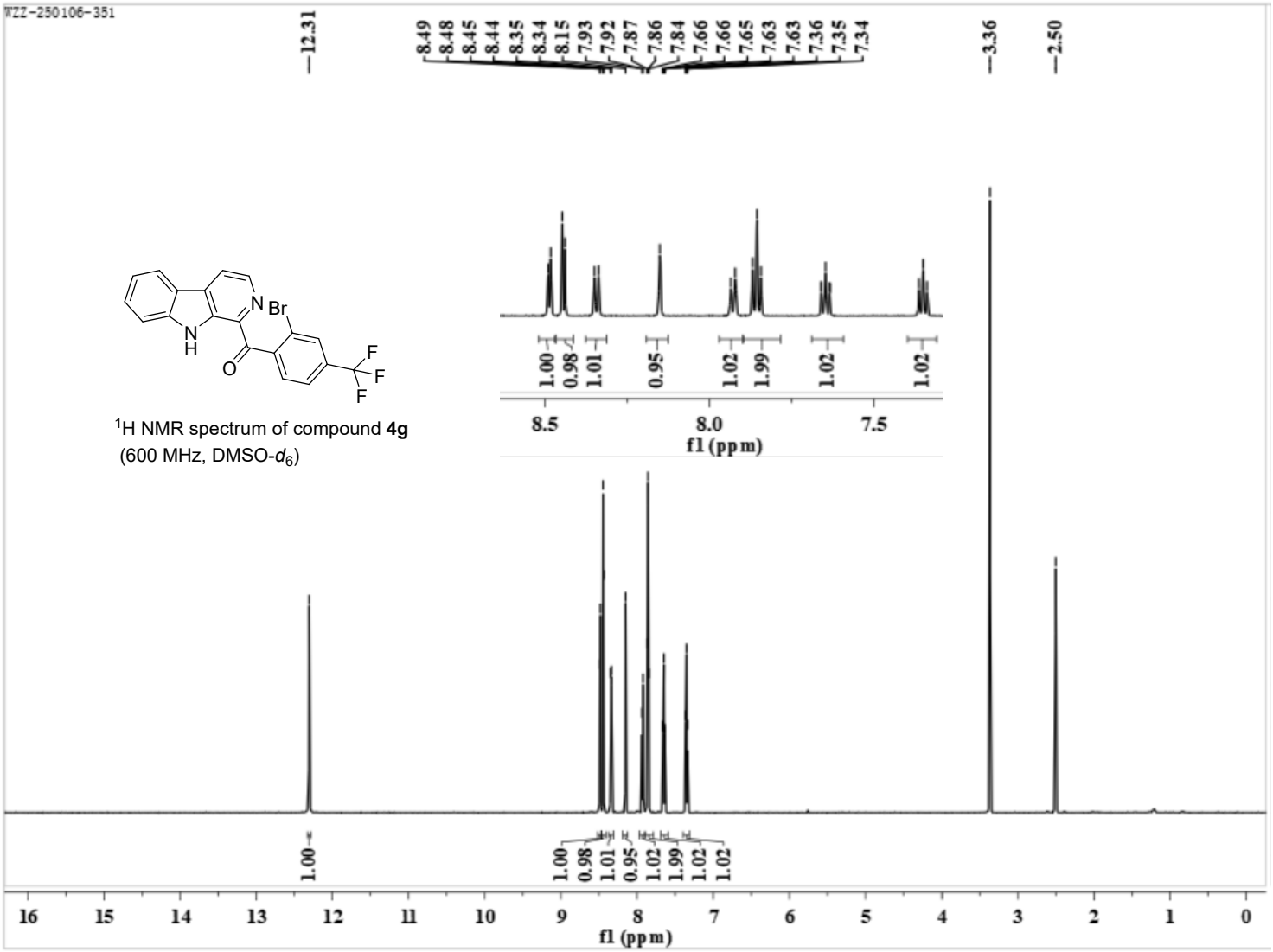
^{1}H NMR spectrum of compound **4f**
(600 MHz, DMSO-d_6)



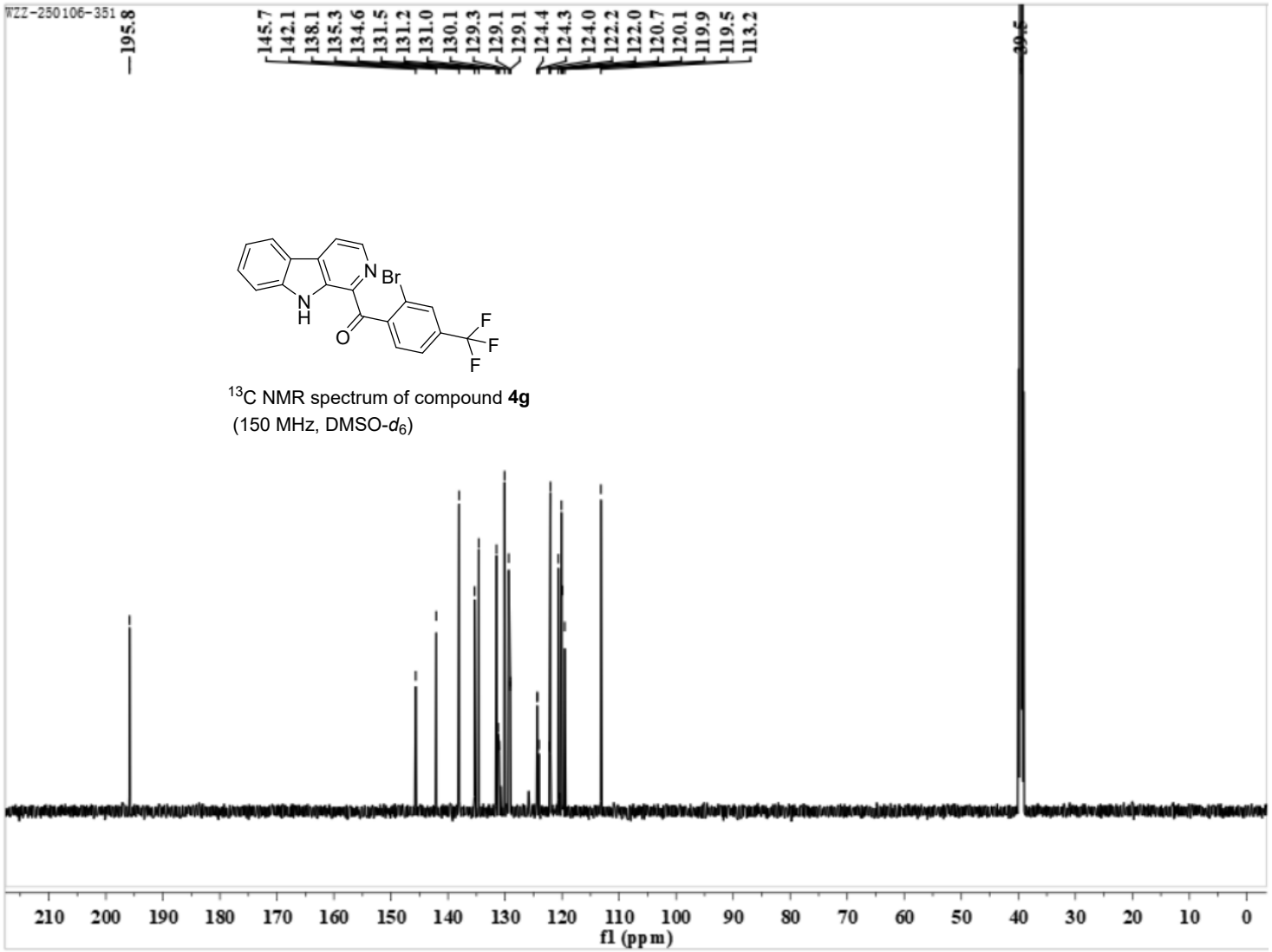
^{13}C NMR spectrum of compound **4f**
(150 MHz, DMSO-d_6)



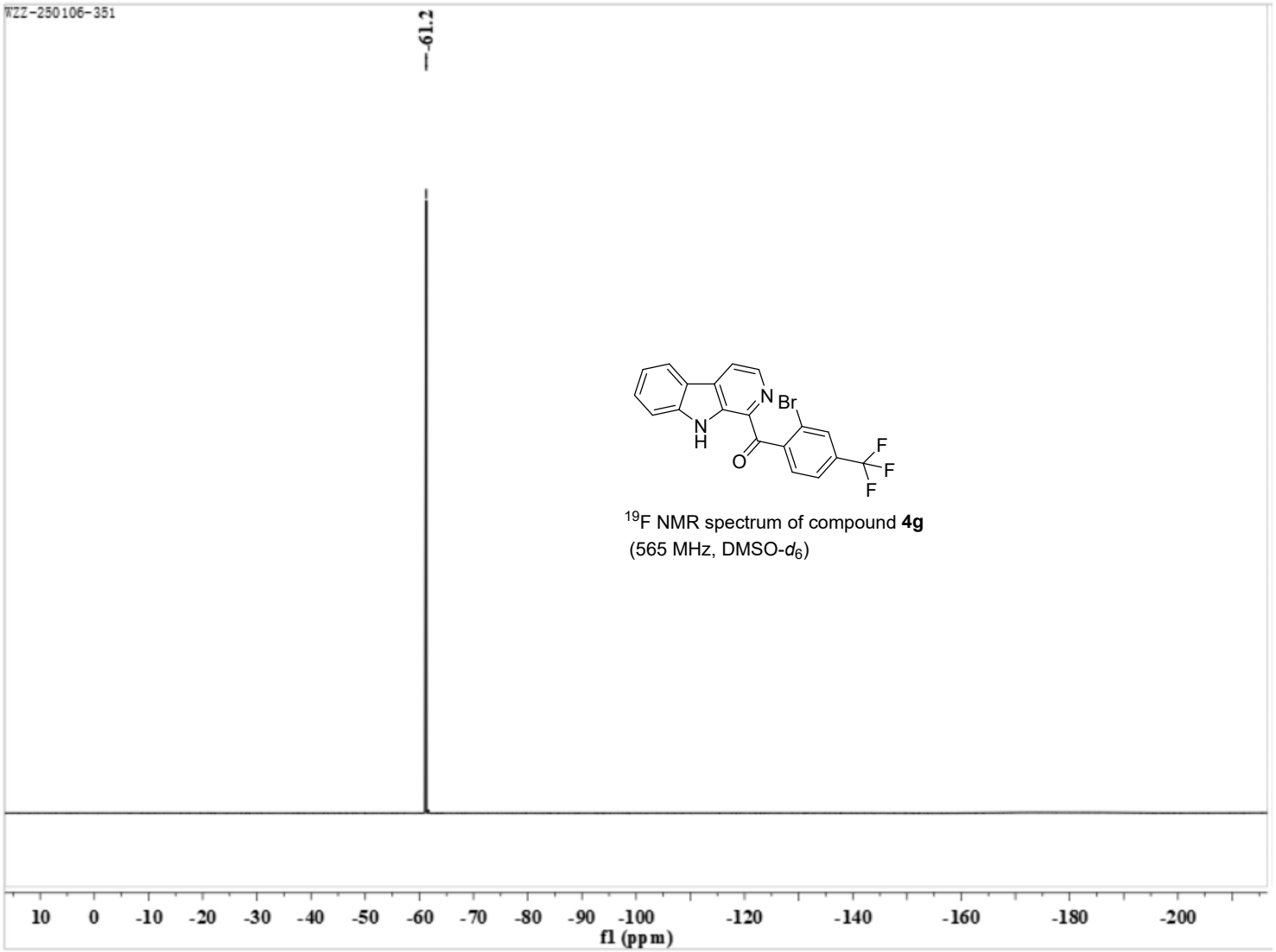
^{19}F NMR spectrum of compound **4f**
(565 MHz, DMSO-d_6)



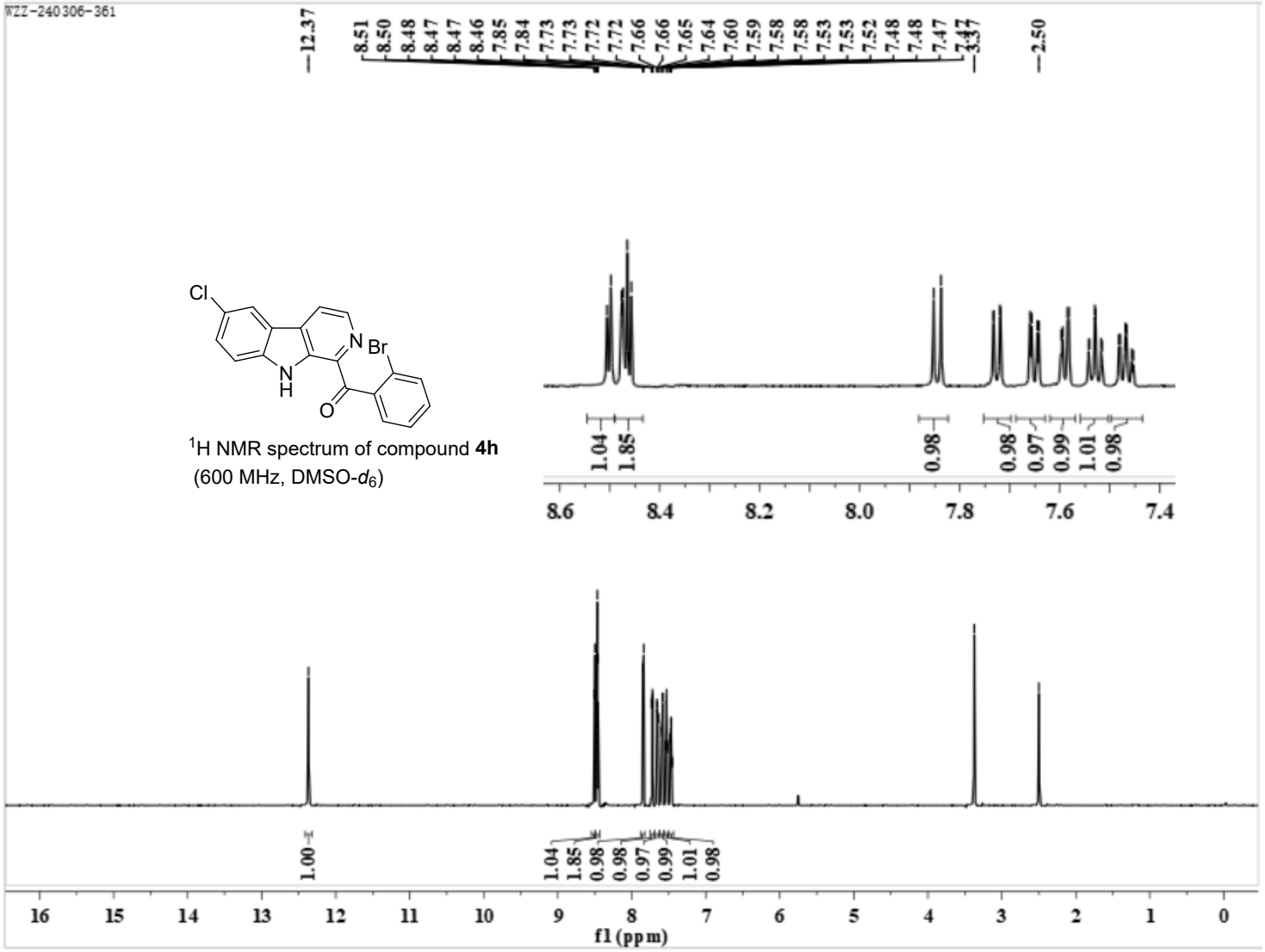
^{1}H NMR spectrum of compound **4g**
(600 MHz, DMSO-d_6)



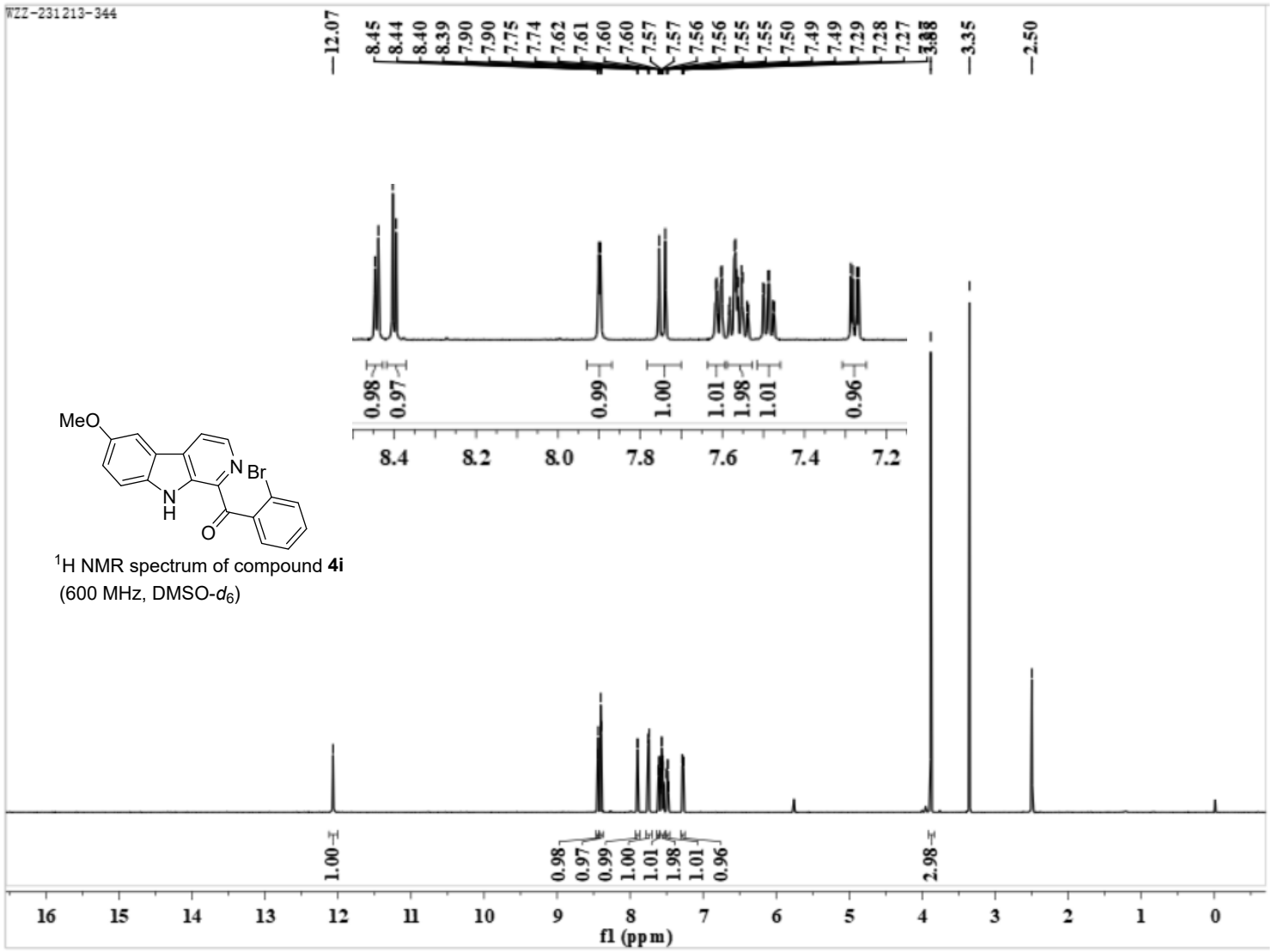
^{13}C NMR spectrum of compound **4g**
(150 MHz, DMSO-d_6)



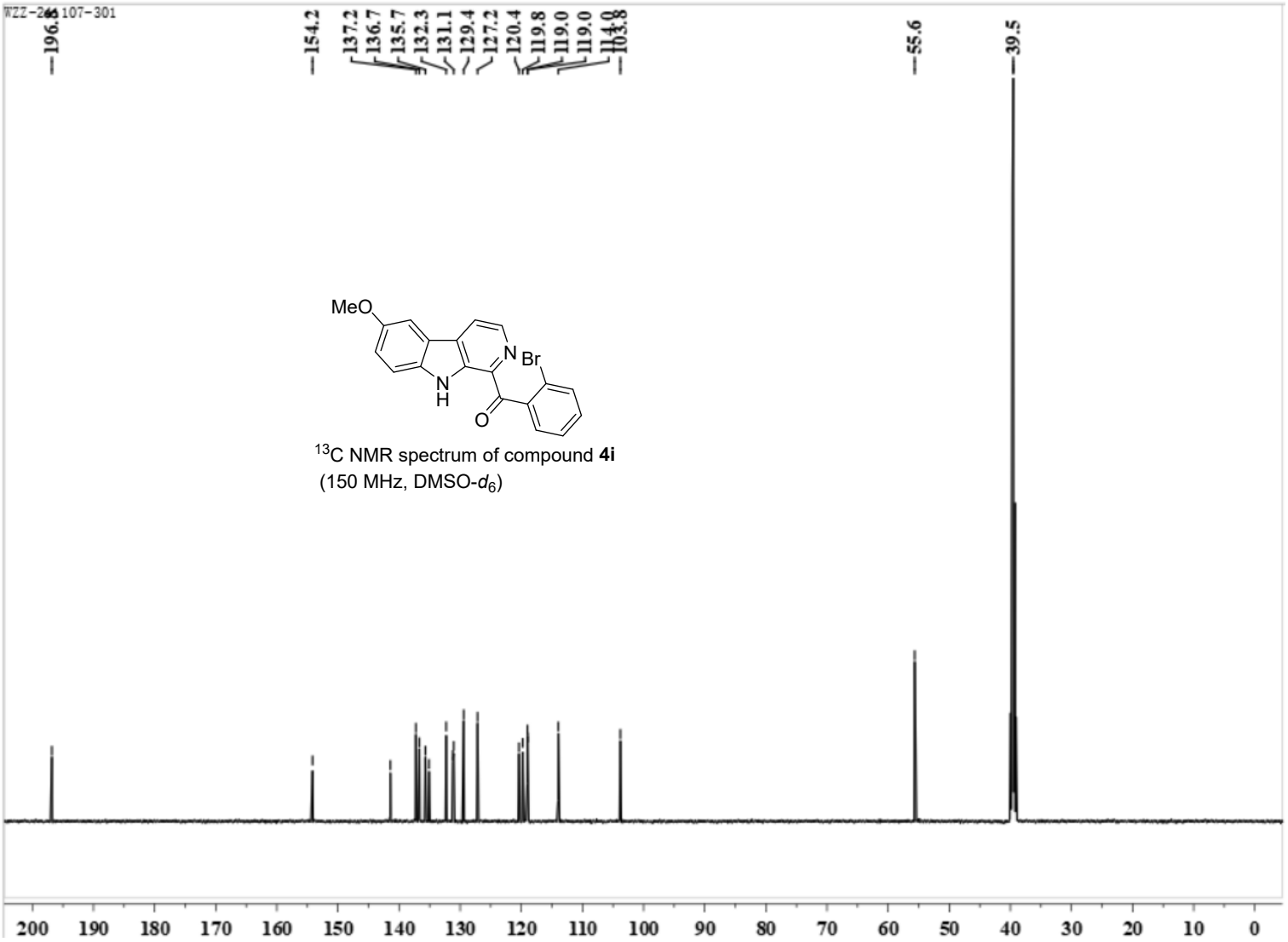
^{19}F NMR spectrum of compound **4g**
(565 MHz, DMSO-d_6)



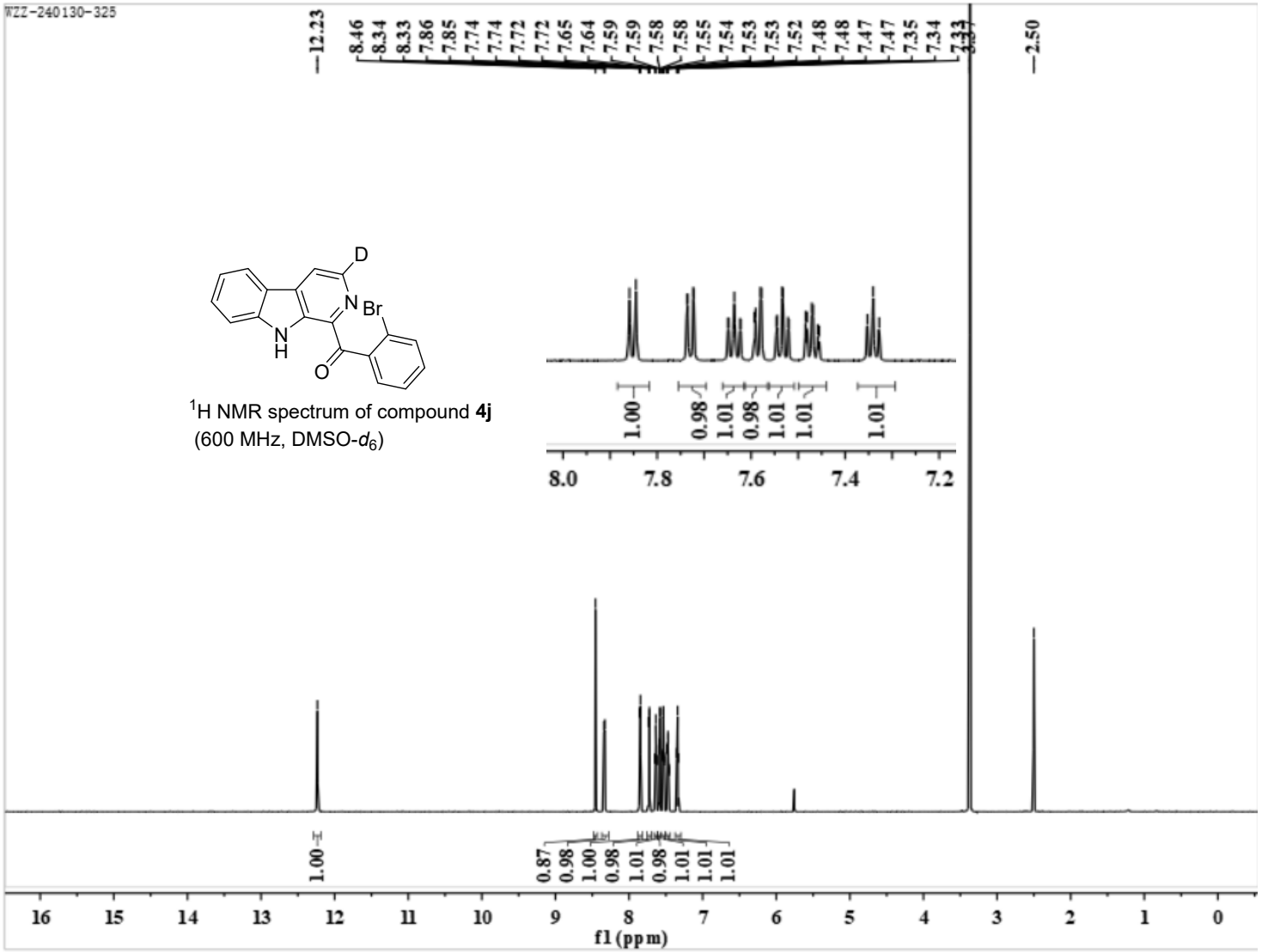
^{1}H NMR spectrum of compound **4h**
(600 MHz, DMSO-d_6)



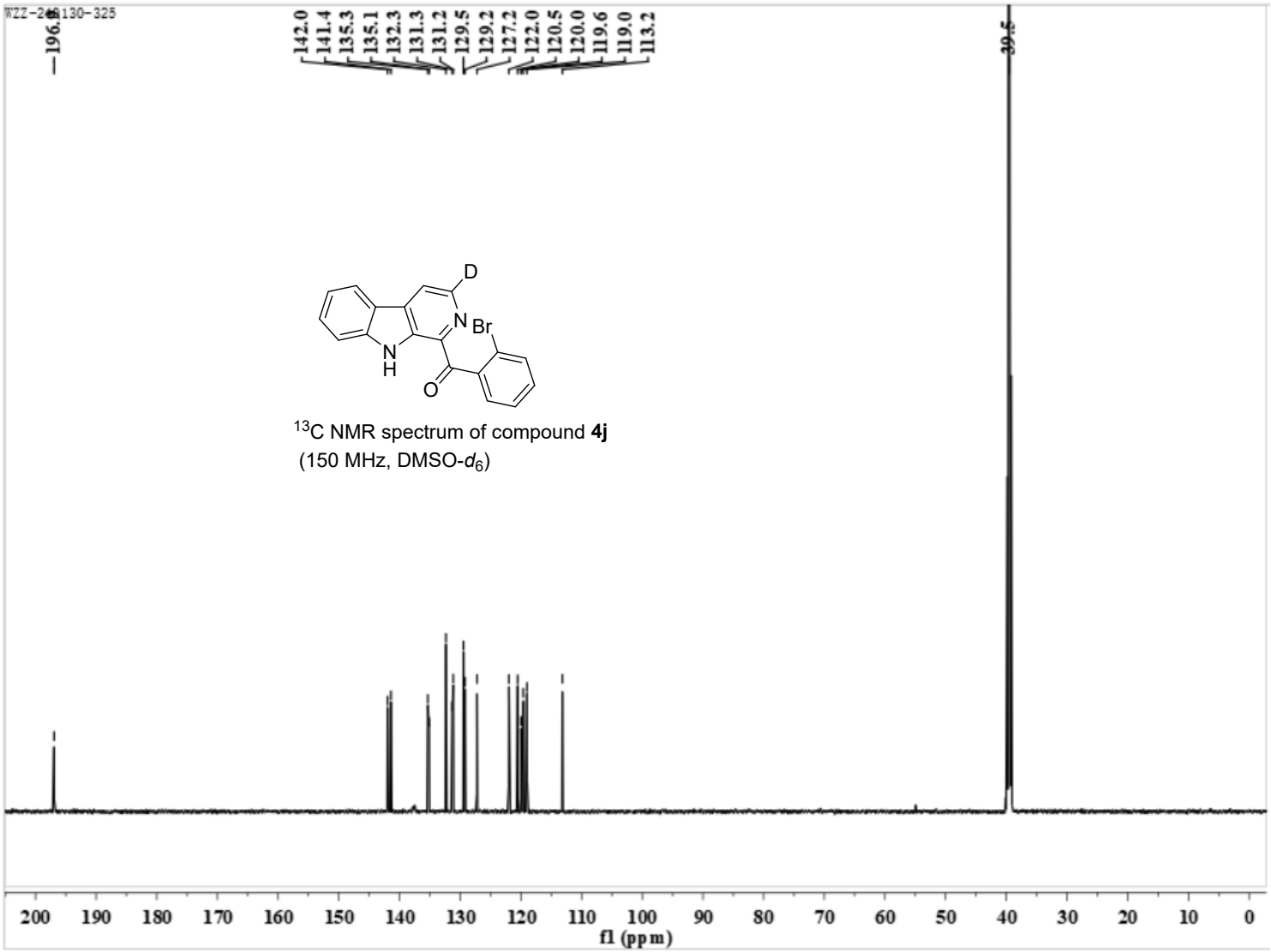
^{1}H NMR spectrum of compound **4i**
(600 MHz, DMSO-d_6)



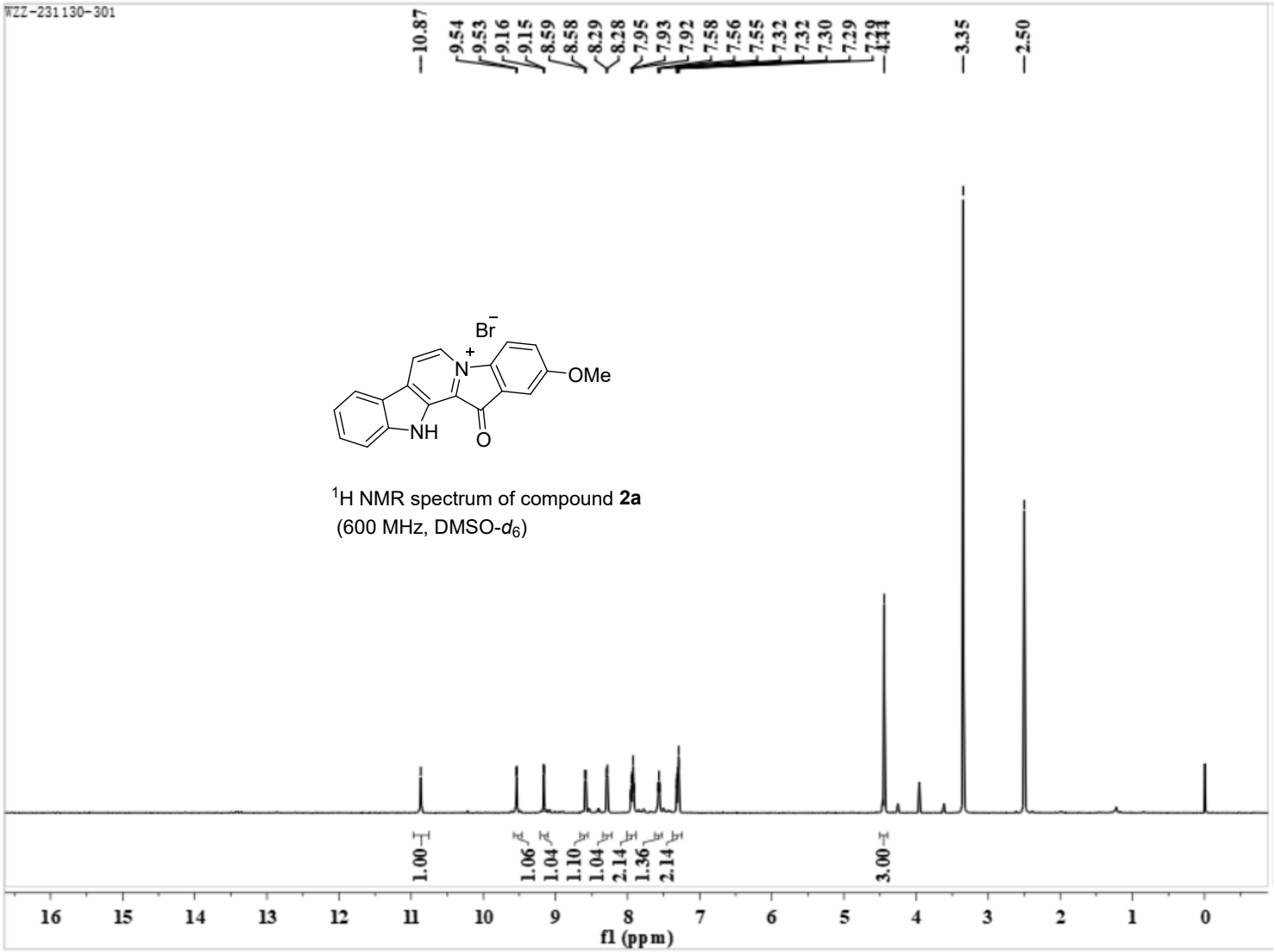
^{13}C NMR spectrum of compound **4i**
(150 MHz, DMSO-d_6)



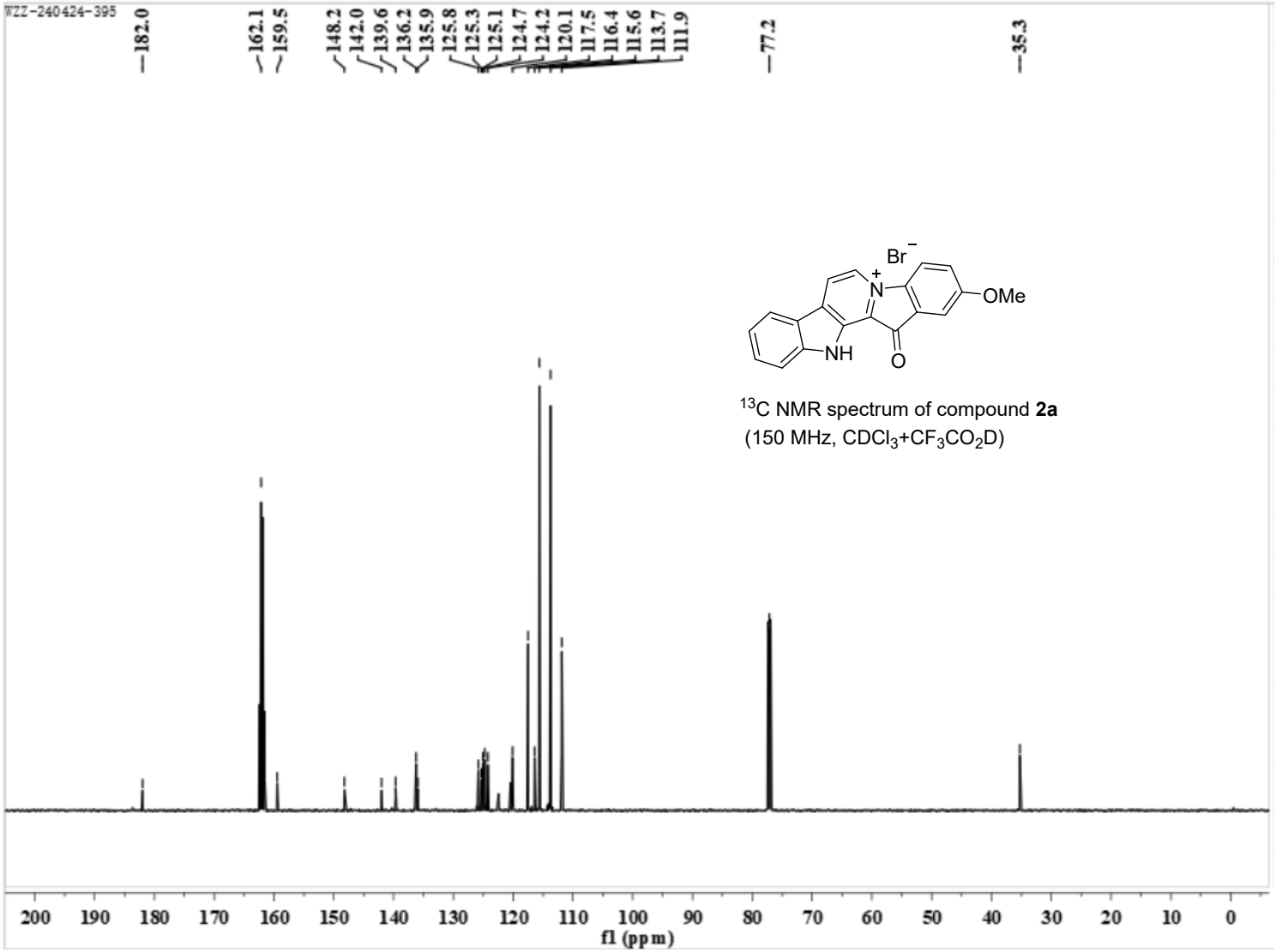
^{1}H NMR spectrum of compound **4j**
(600 MHz, DMSO-d_6)



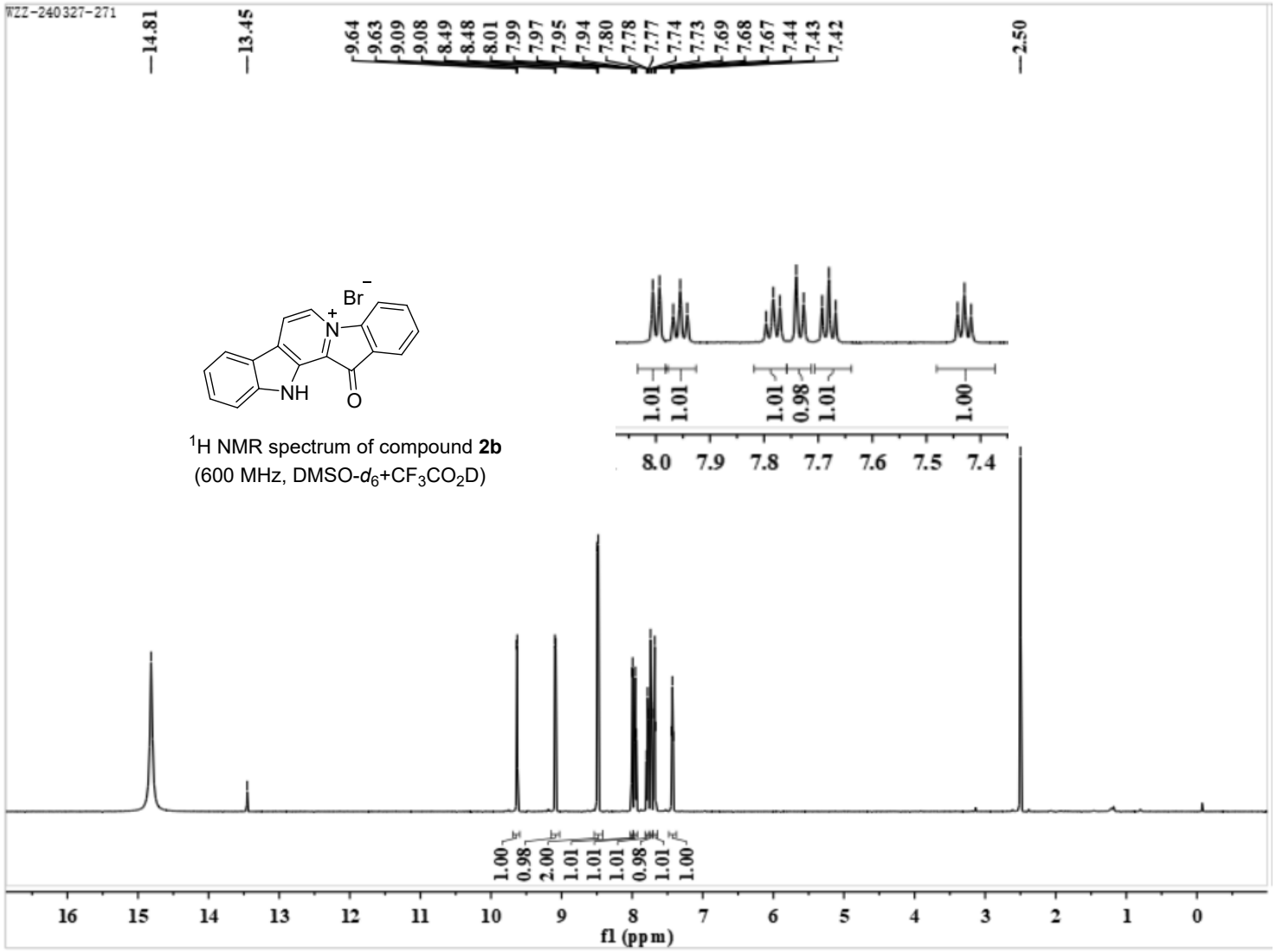
^{13}C NMR spectrum of compound **4j**
(150 MHz, DMSO-d_6)



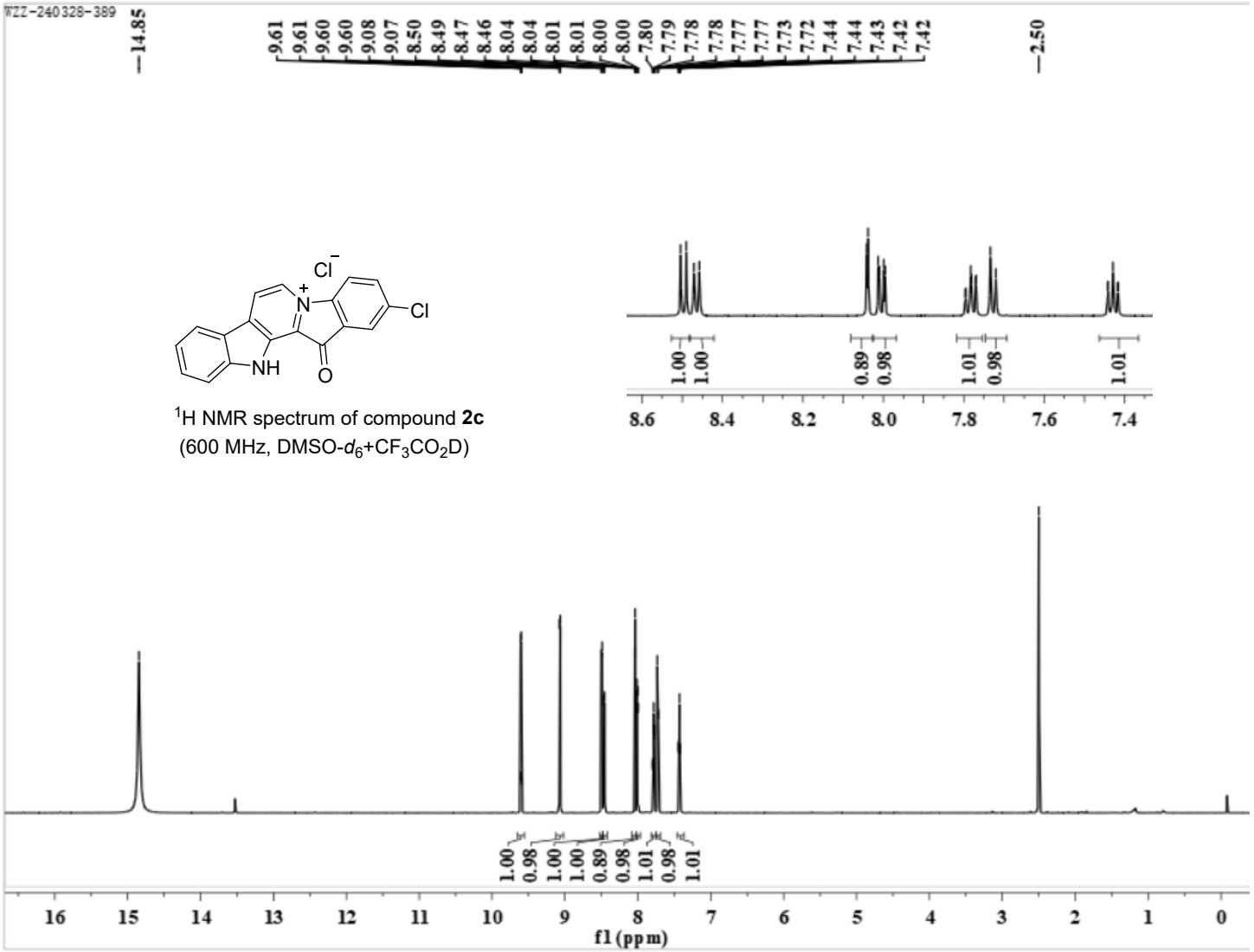
^{1}H NMR spectrum of compound **2a**
(600 MHz, DMSO-d_6)



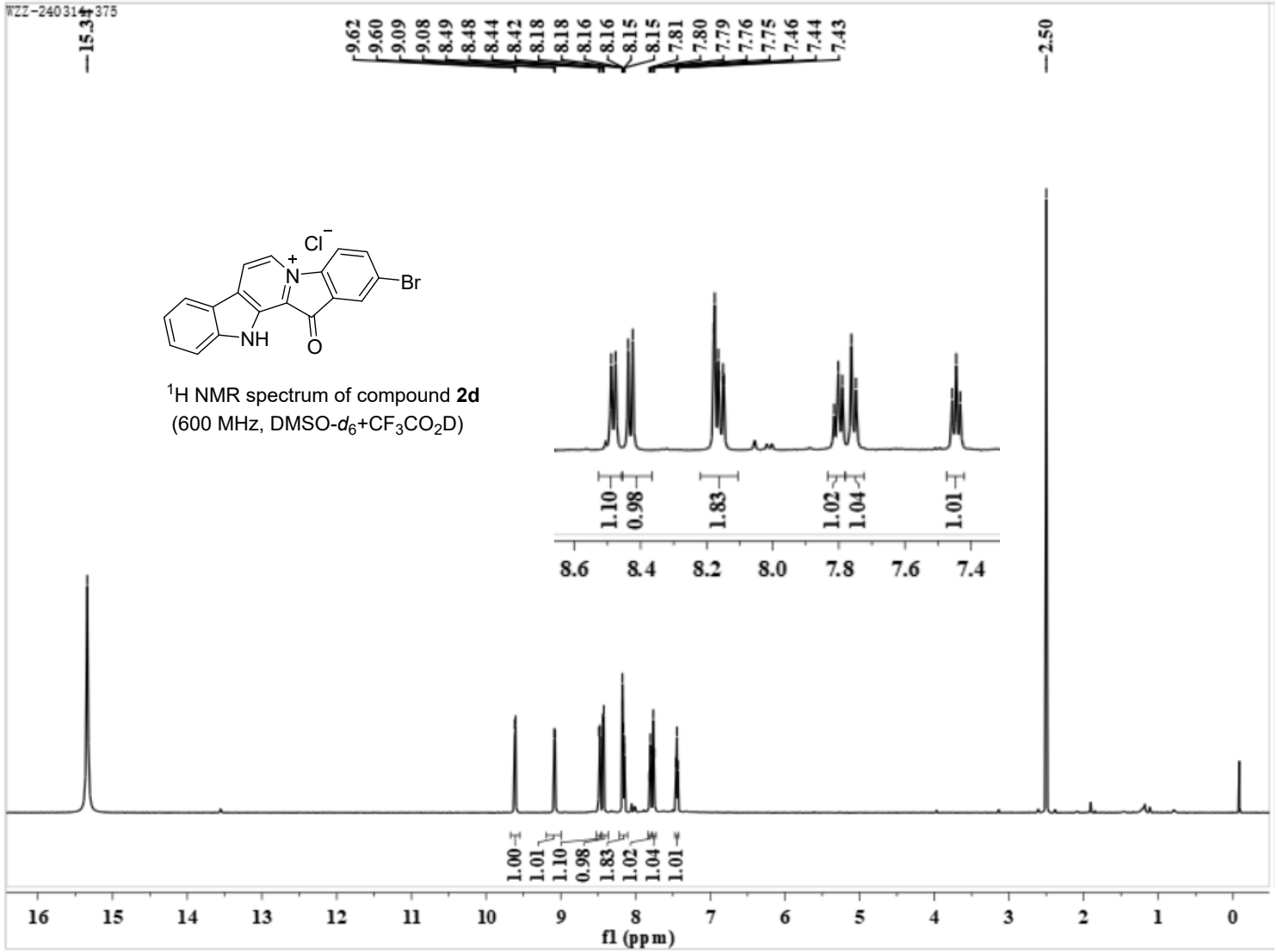
^{13}C NMR spectrum of compound **2a**
(150 MHz, $CDCl_3$+CF_3CO_2D)



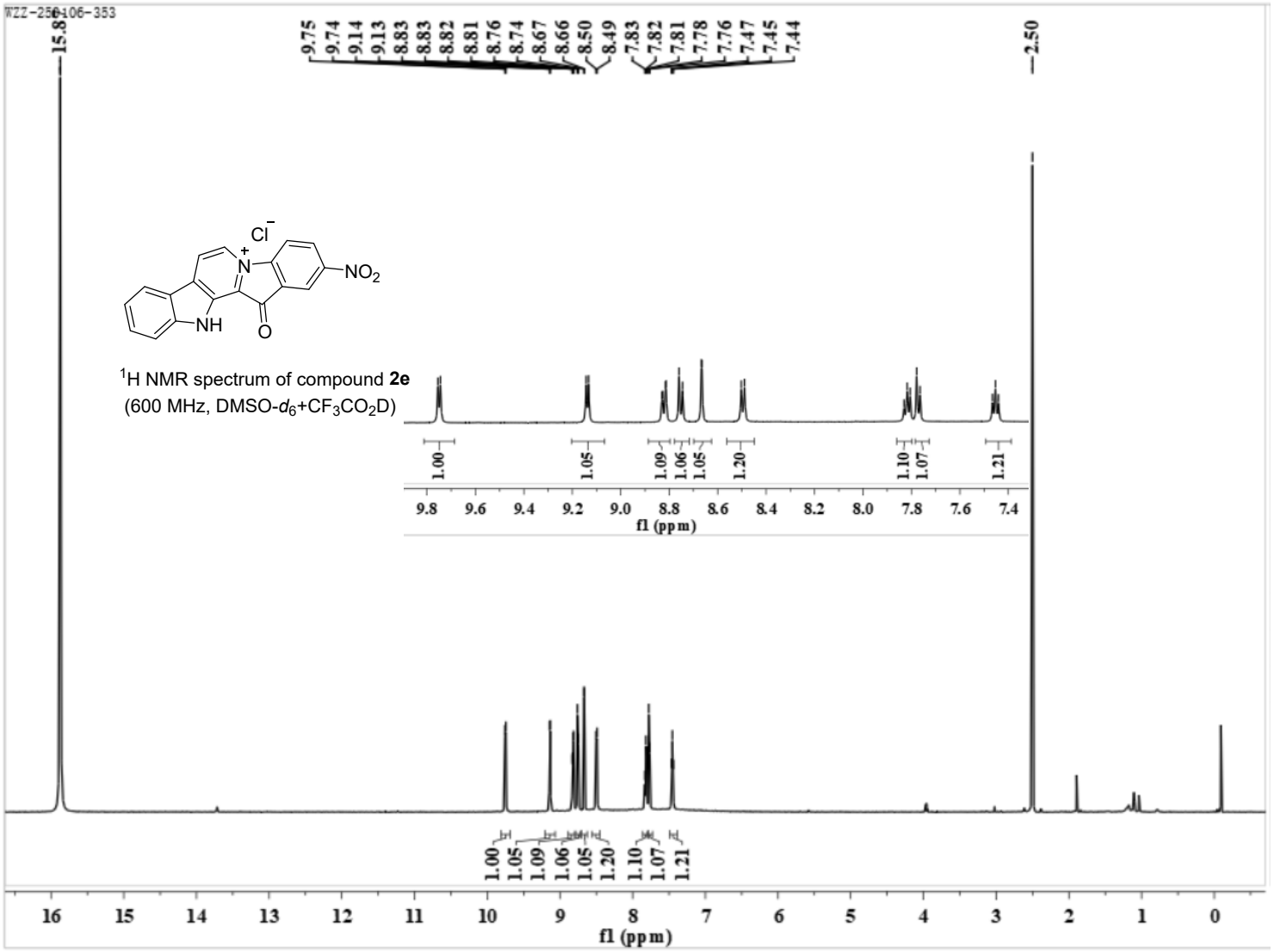
^{1}H NMR spectrum of compound **2b**
(600 MHz, DMSO-d_6+CF_3CO_2D)

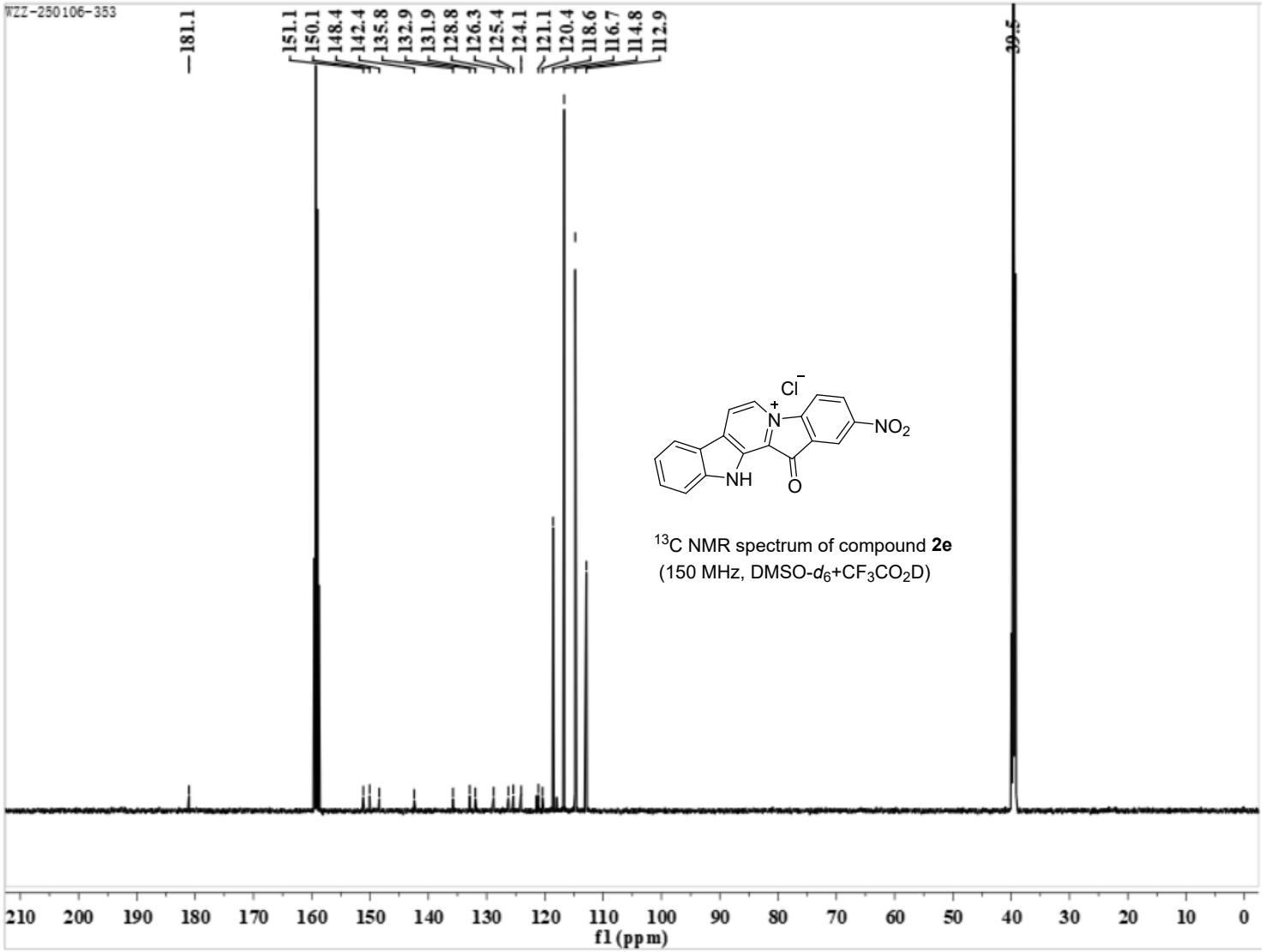


^{1}H NMR spectrum of compound **2c**
(600 MHz, DMSO-d_6+CF_3CO_2D)

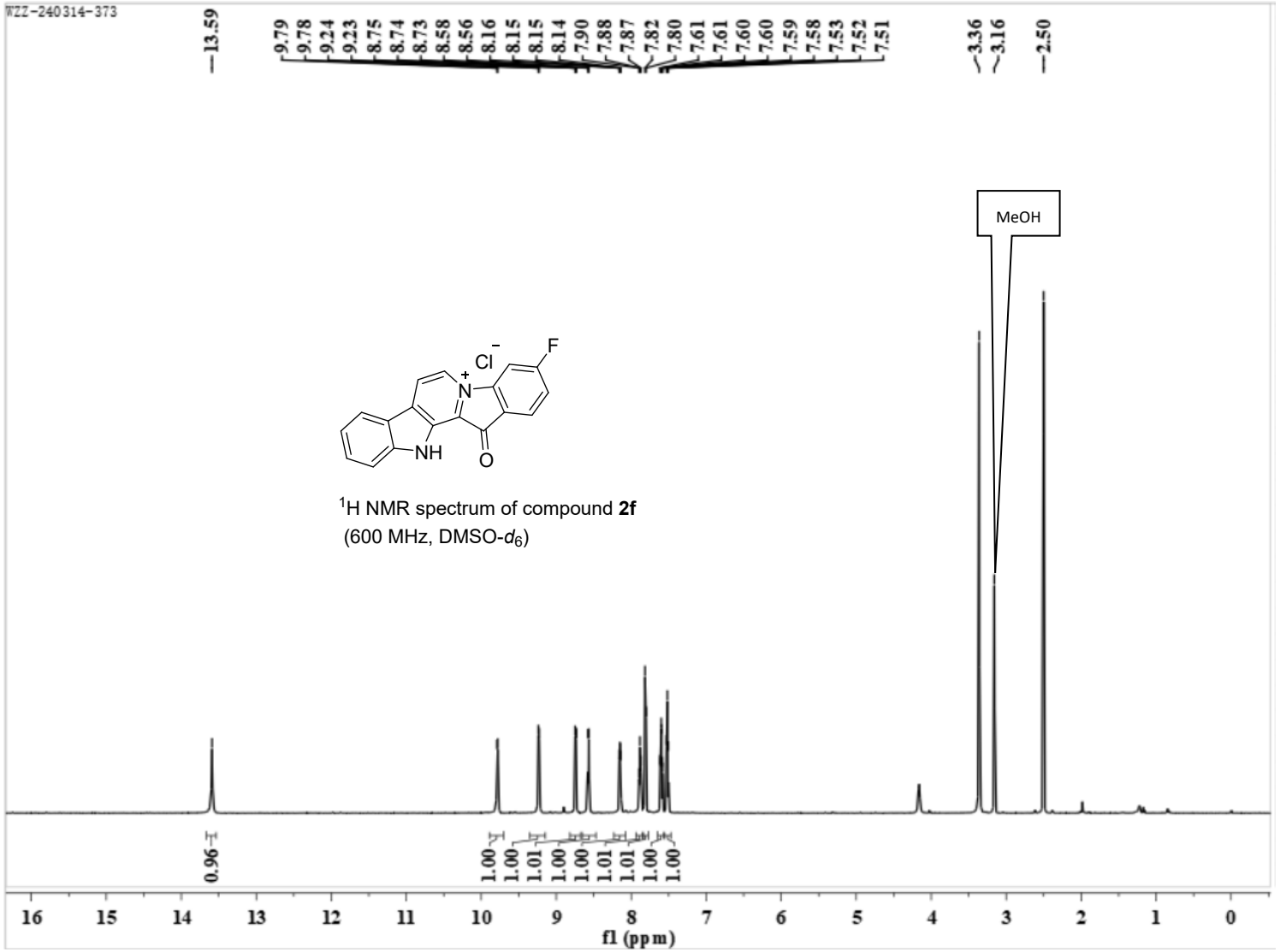


^{1}H NMR spectrum of compound **2d**
(600 MHz, DMSO-d_6+CF_3CO_2D)

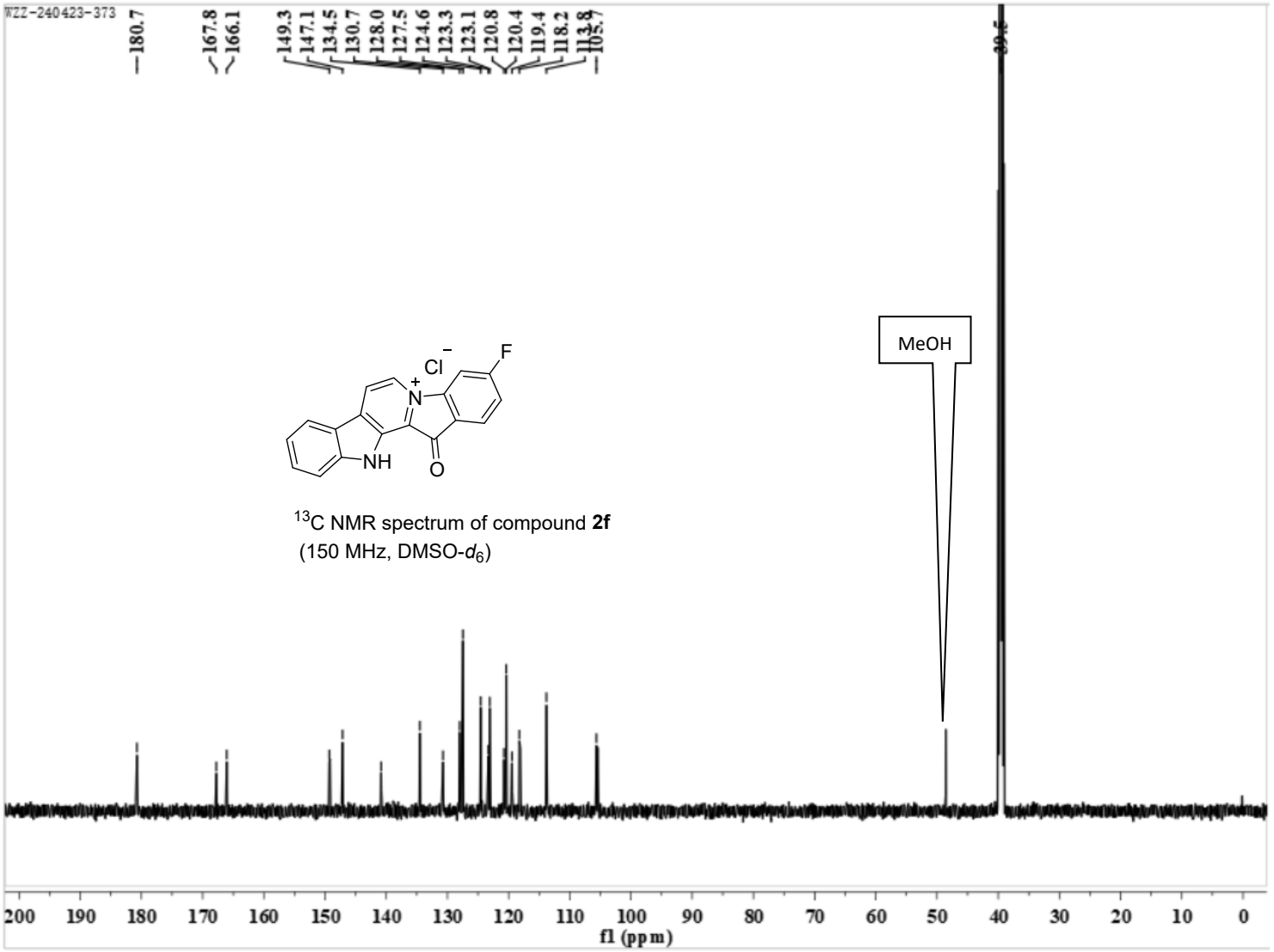

WZZ-250106-353
15.88
9.75
9.74
9.14
9.13
8.83
8.83
8.82
8.81
8.76
8.74
8.67
8.66
8.50
8.49
7.83
7.82
7.81
7.78
7.76
7.47
7.45
7.44
2.50
Cl⁻
N⁺
NO2
NH
O
1H NMR spectrum of compound 2e
(600 MHz, DMSO-d6+CF3CO2D)
1.00
1.05
1.09
1.06
1.05
1.20
1.10
1.07
1.21
9.8 9.6 9.4 9.2 9.0 8.8 8.6 8.4 8.2 8.0 7.8 7.6 7.4
f1 (ppm)
16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0
f1 (ppm)



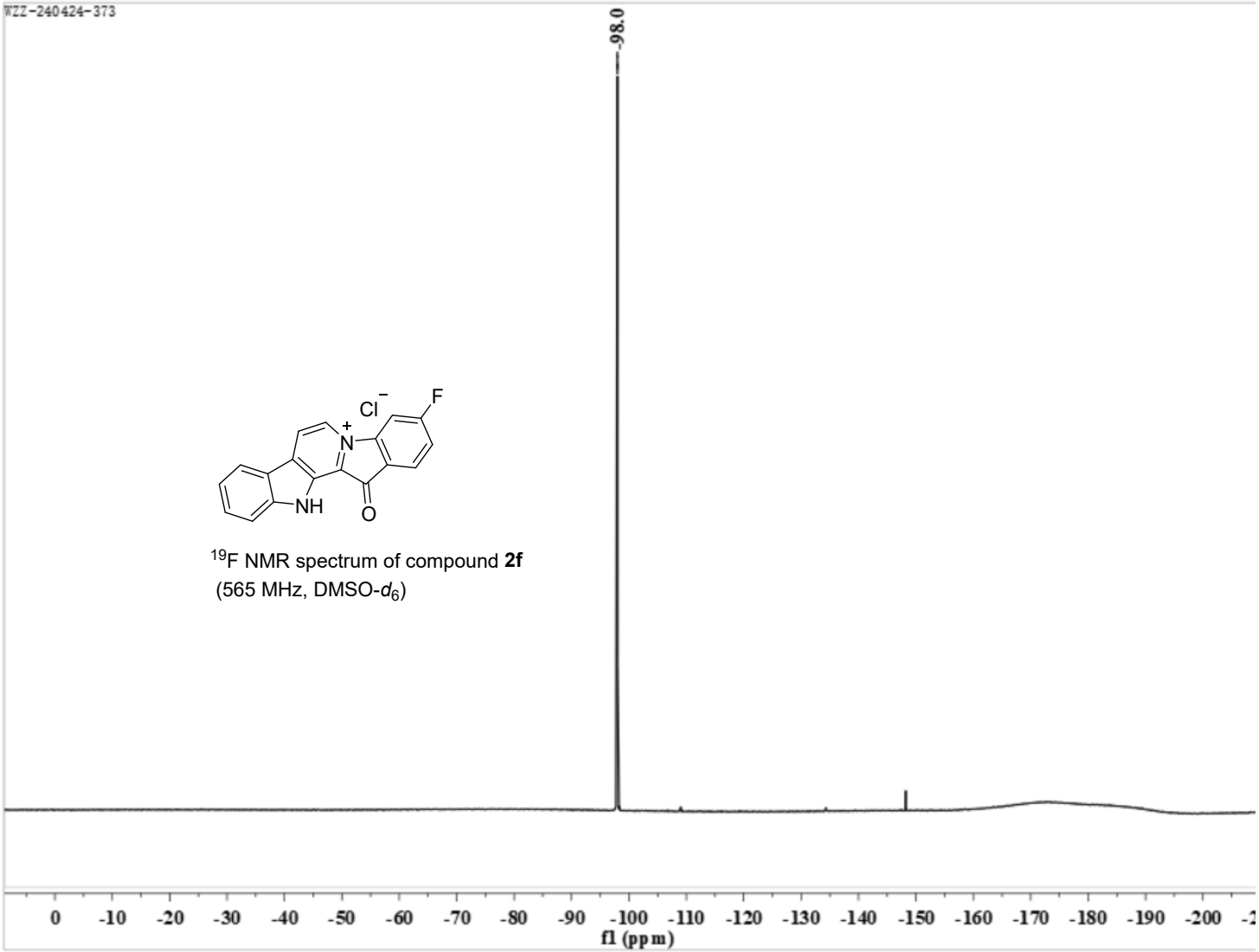
^{13}C NMR spectrum of compound **2e**
(150 MHz, DMSO-d_6+CF_3CO_2D)



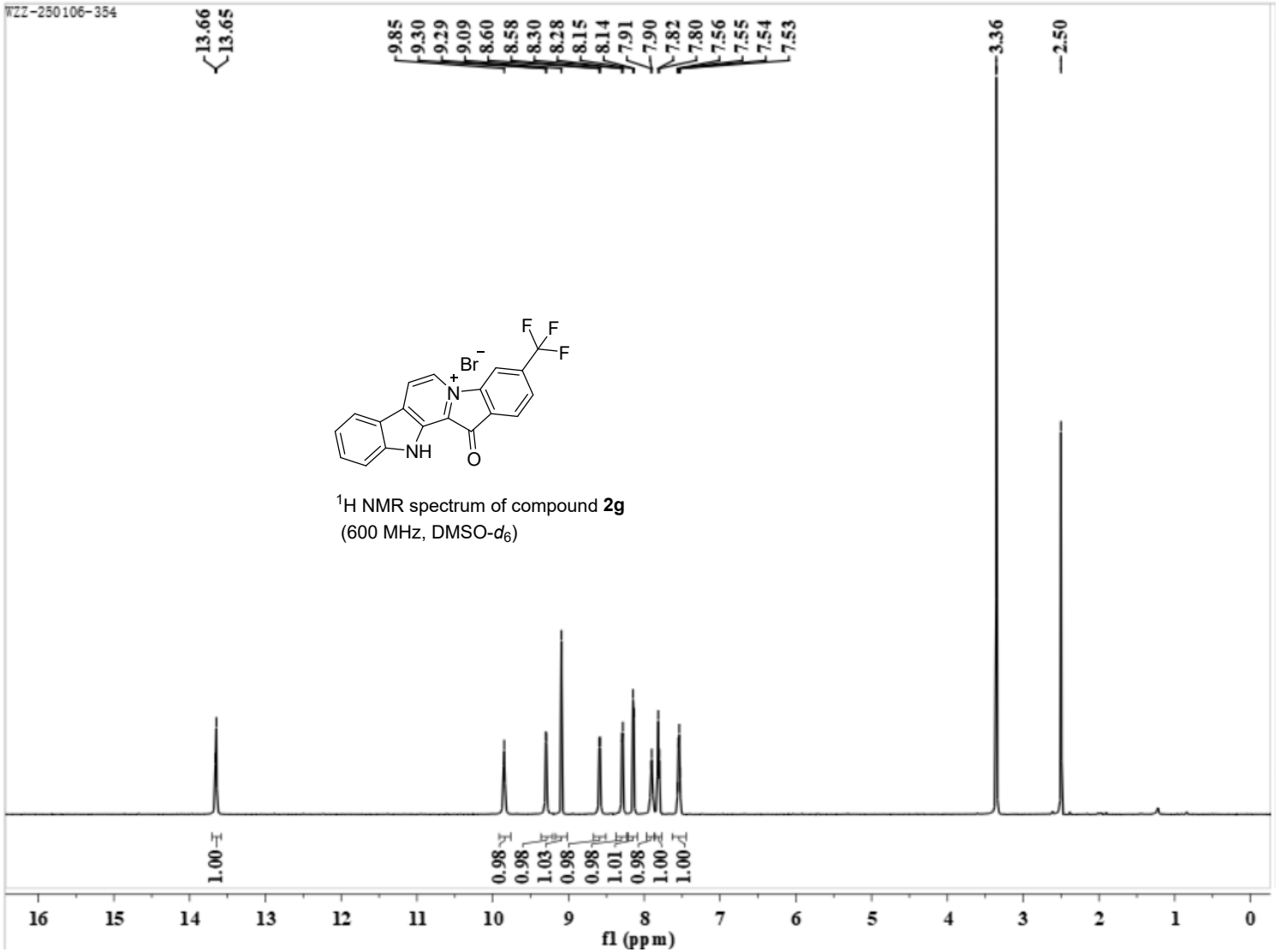
^{1}H NMR spectrum of compound **2f**
(600 MHz, DMSO-d_6)



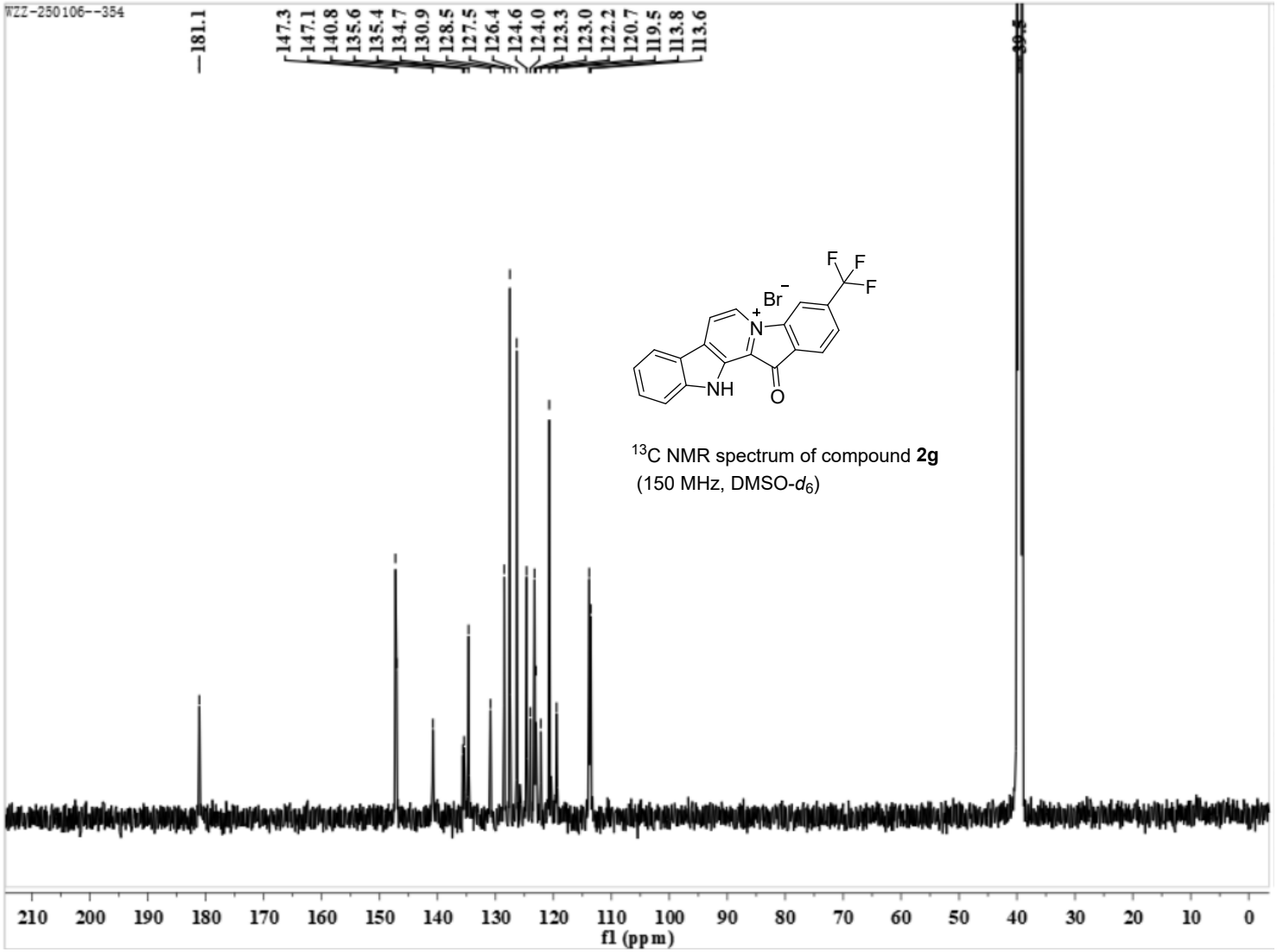
^{13}C NMR spectrum of compound **2f**
(150 MHz, DMSO-d_6)



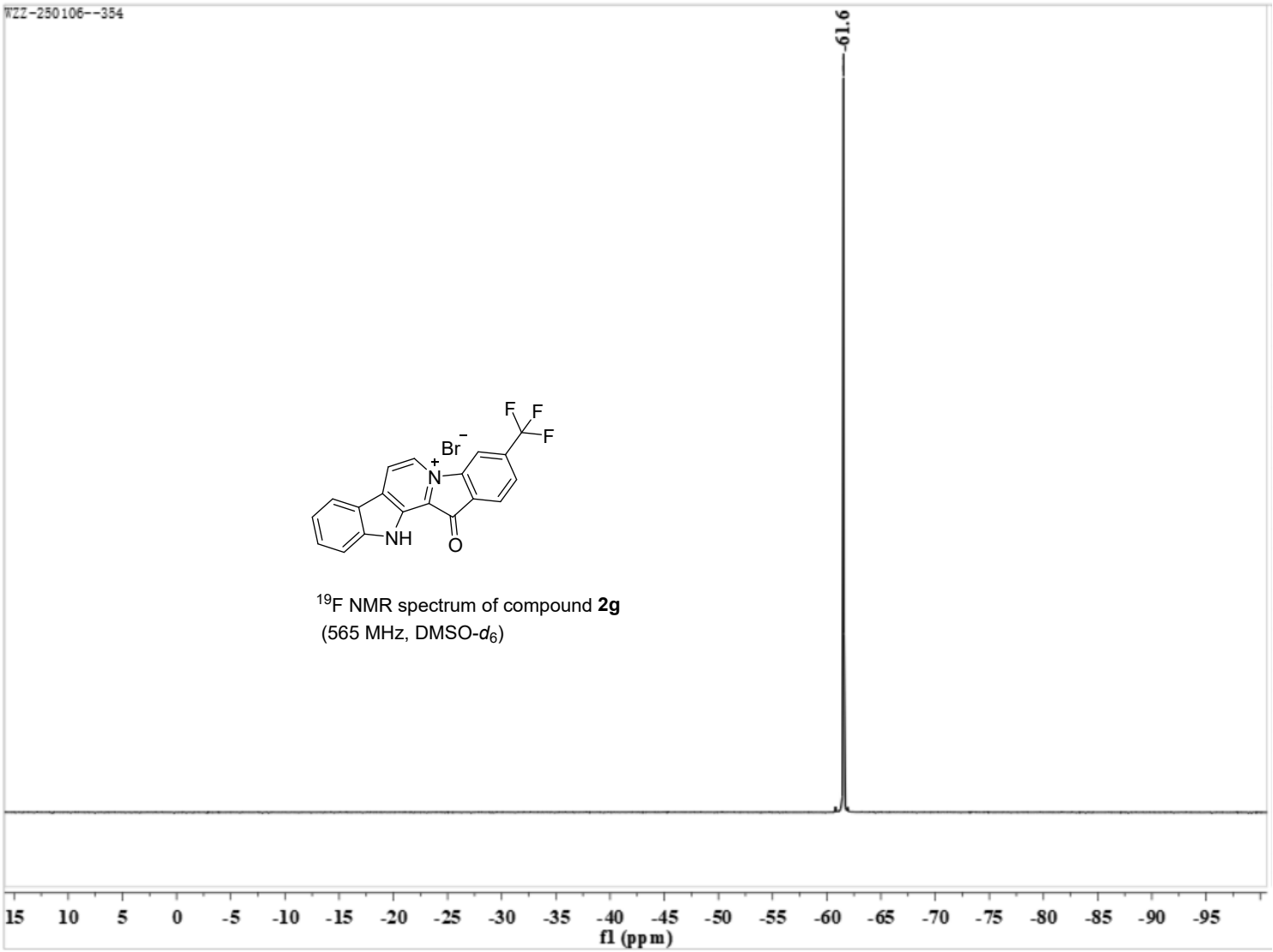
^{19}F NMR spectrum of compound **2f**
(565 MHz, DMSO-d_6)



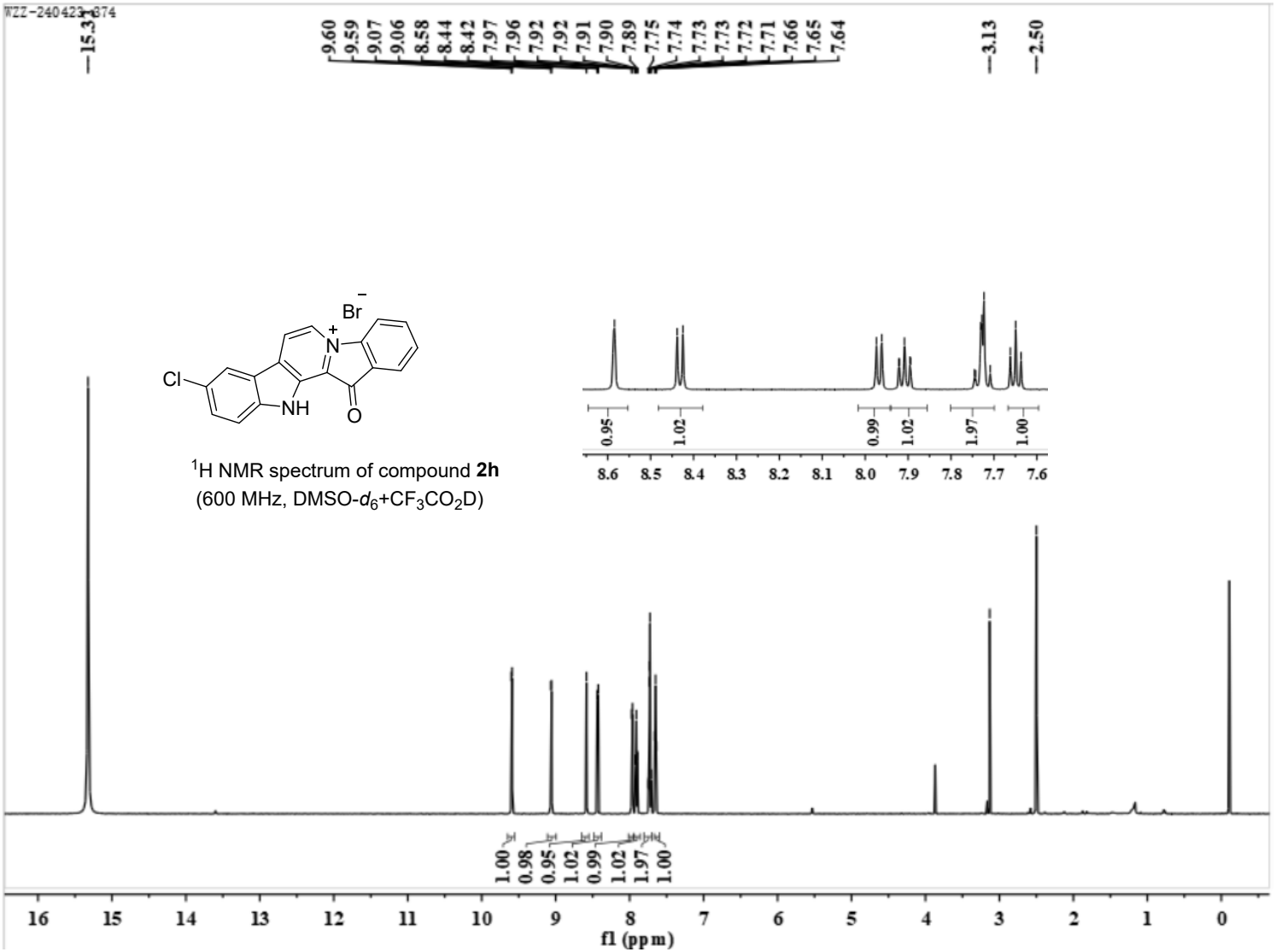
^{1}H NMR spectrum of compound **2g**
(600 MHz, DMSO-d_6)



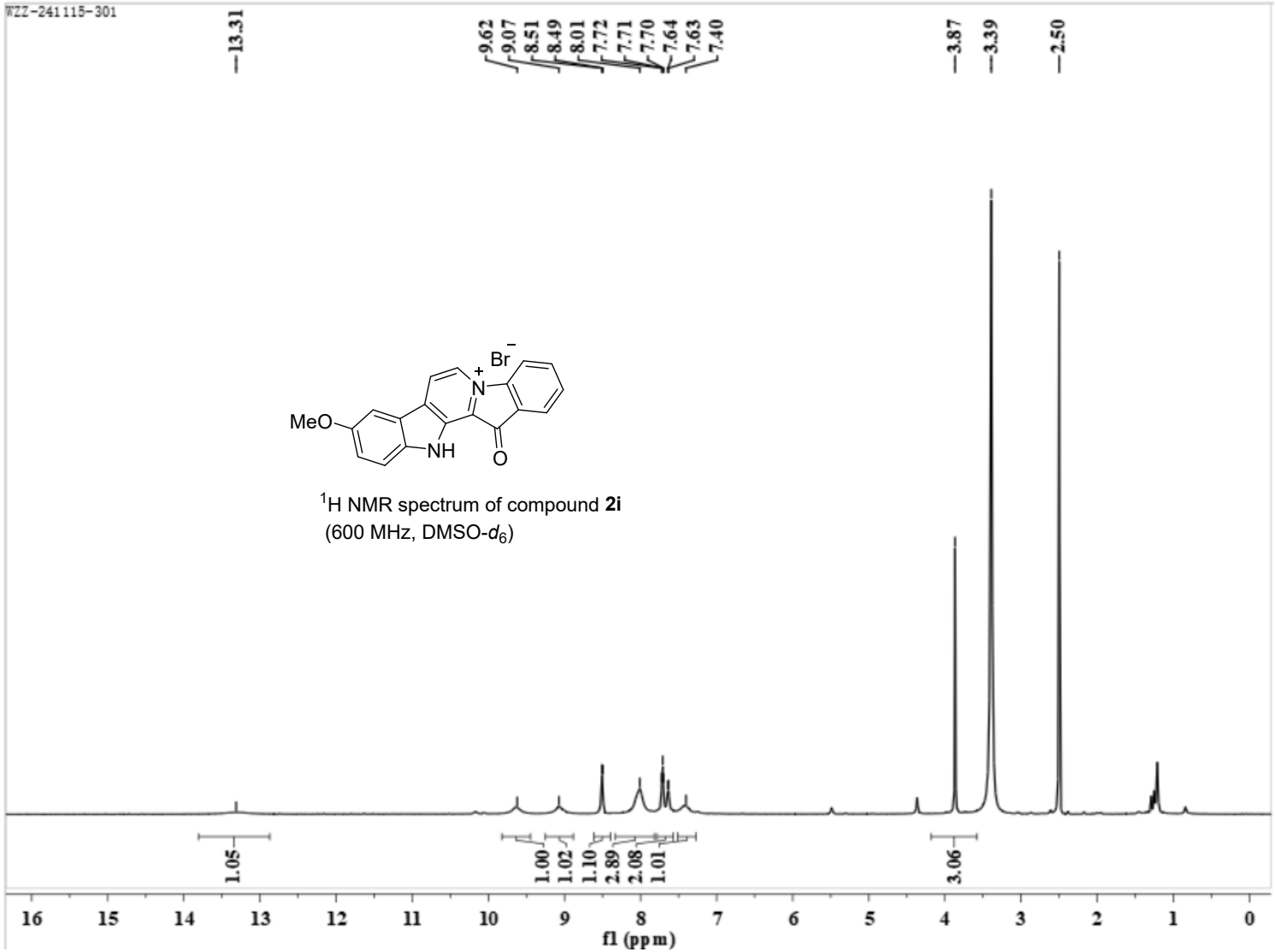
^{13}C NMR spectrum of compound **2g**
(150 MHz, DMSO-d_6)



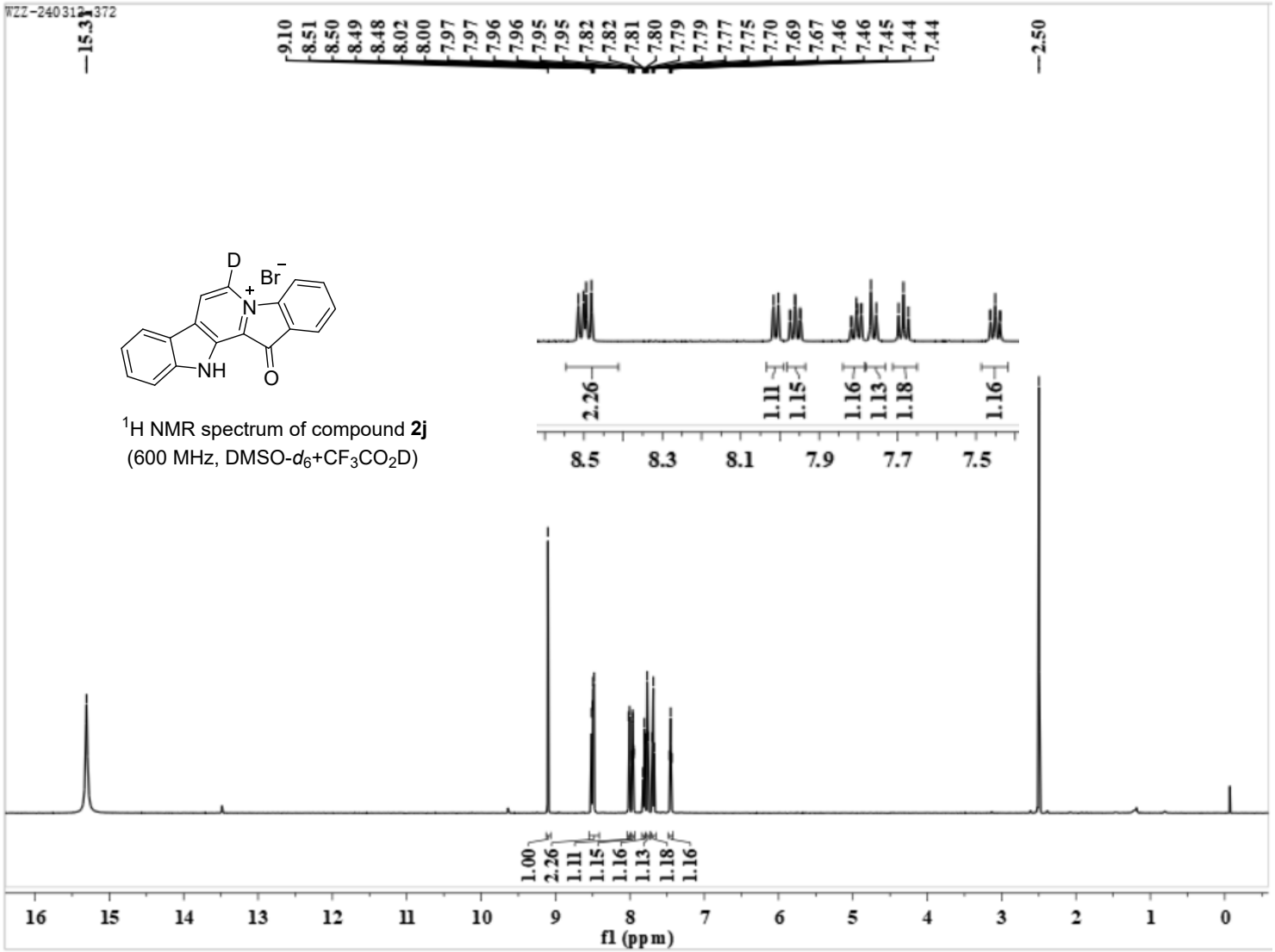
^{19}F NMR spectrum of compound **2g**
(565 MHz, DMSO-d_6)



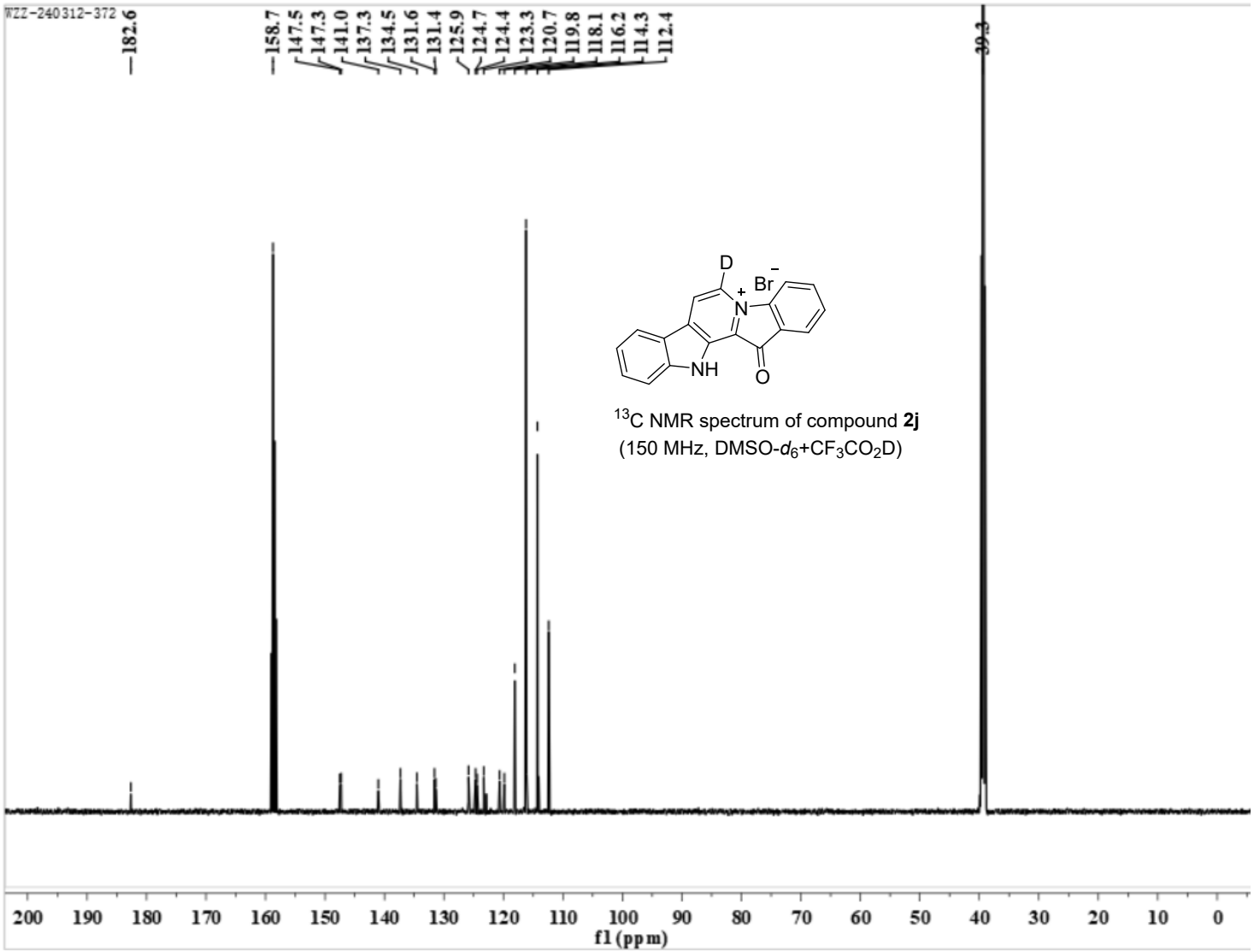
^{1}H NMR spectrum of compound **2h**
(600 MHz, DMSO-d_6+CF_3CO_2D)



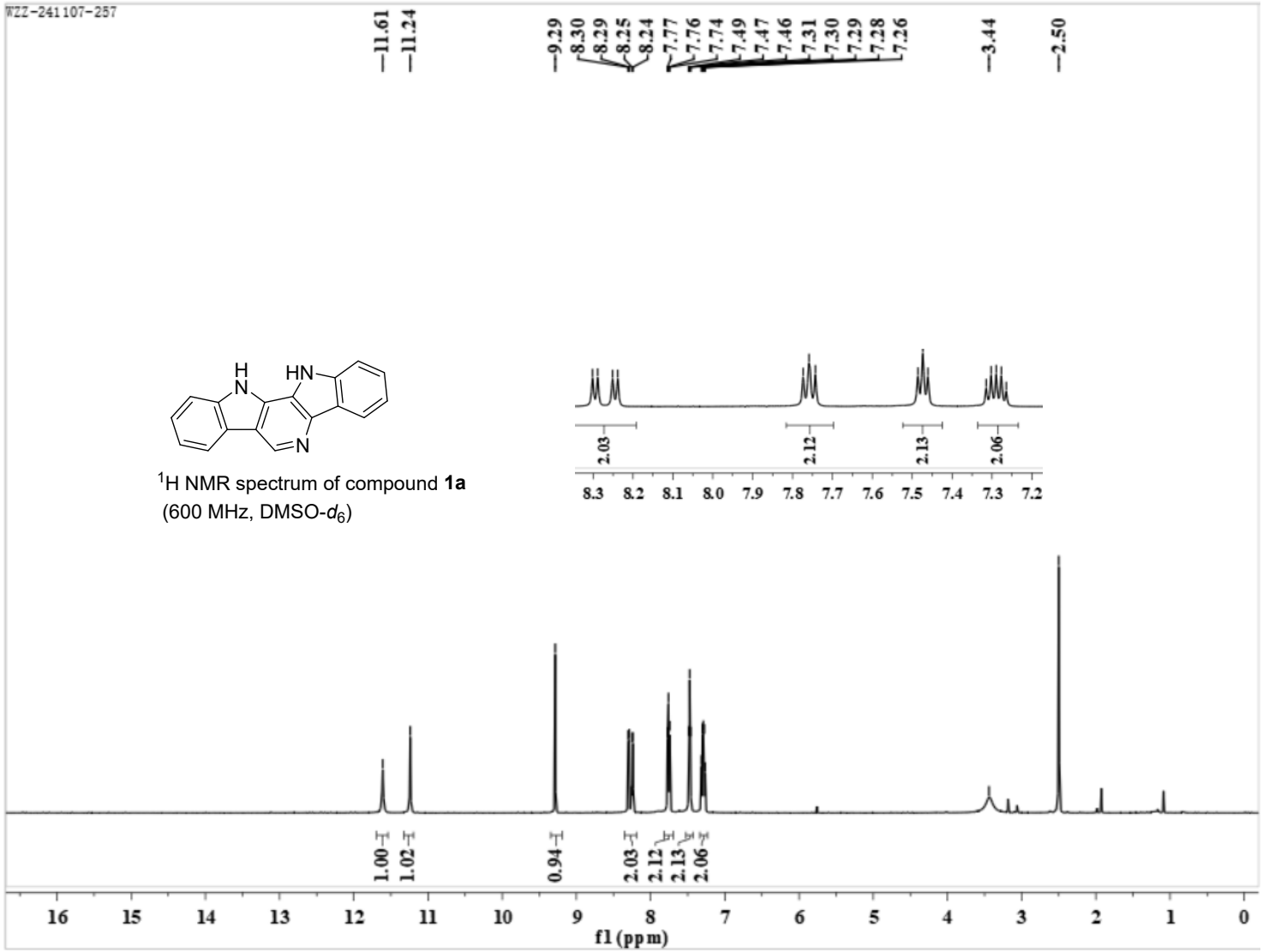
^{1}H NMR spectrum of compound **2i**
(600 MHz, DMSO-d_6)



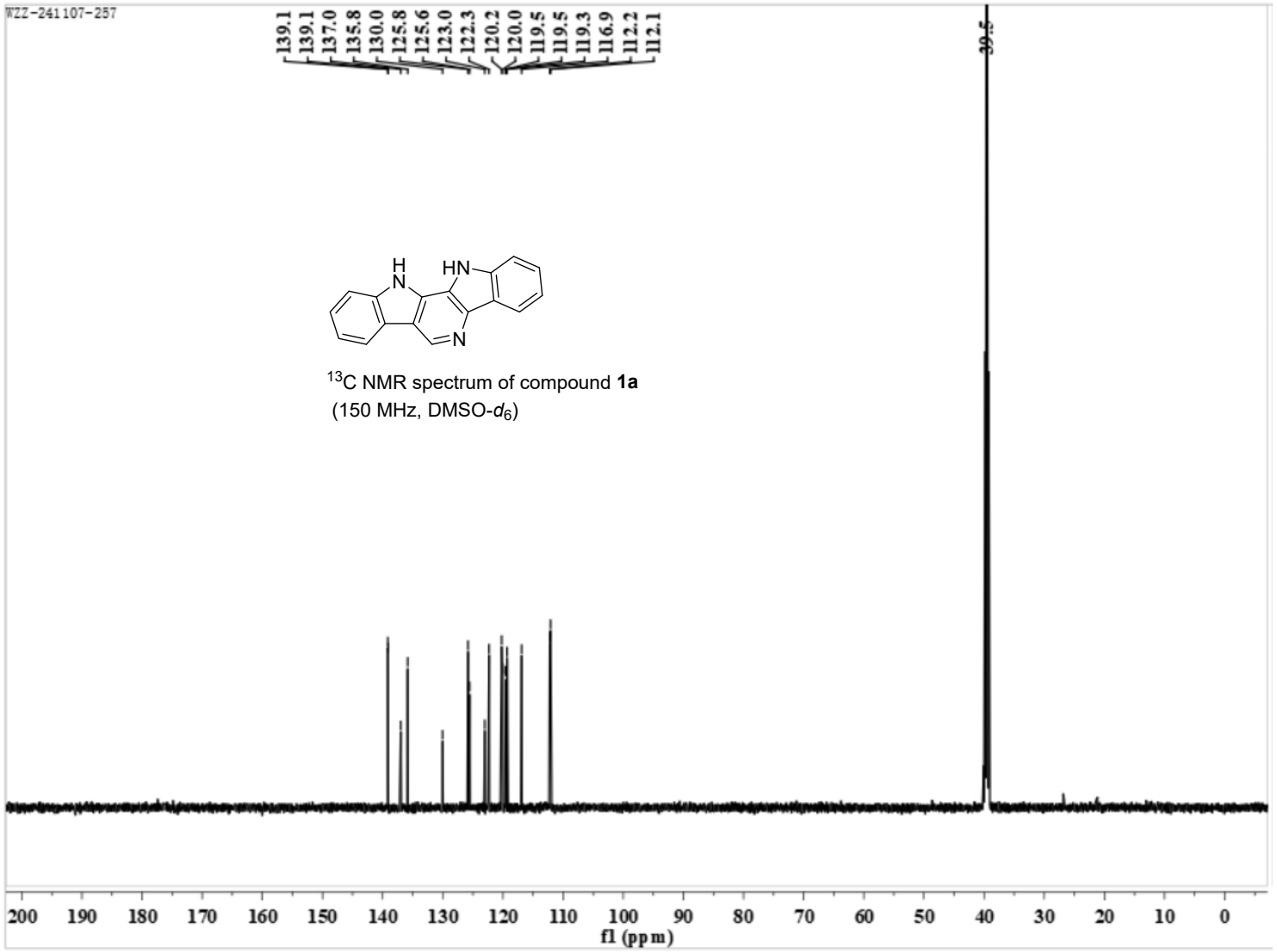
^{1}H NMR spectrum of compound **2j**
(600 MHz, DMSO-d_6+CF_3CO_2D)



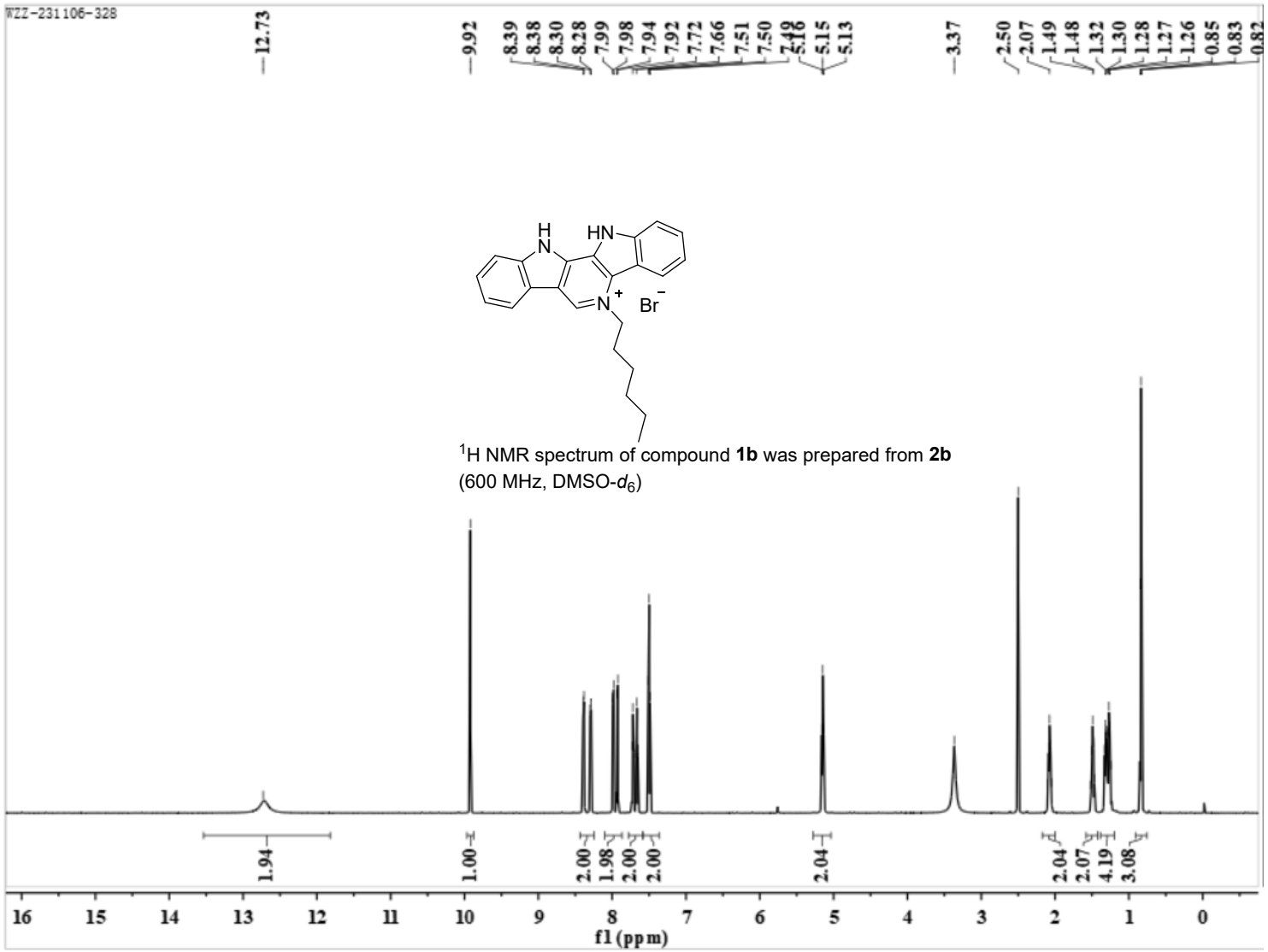
^{13}C NMR spectrum of compound **2j**
(150 MHz, DMSO-d_6+CF_3CO_2D)



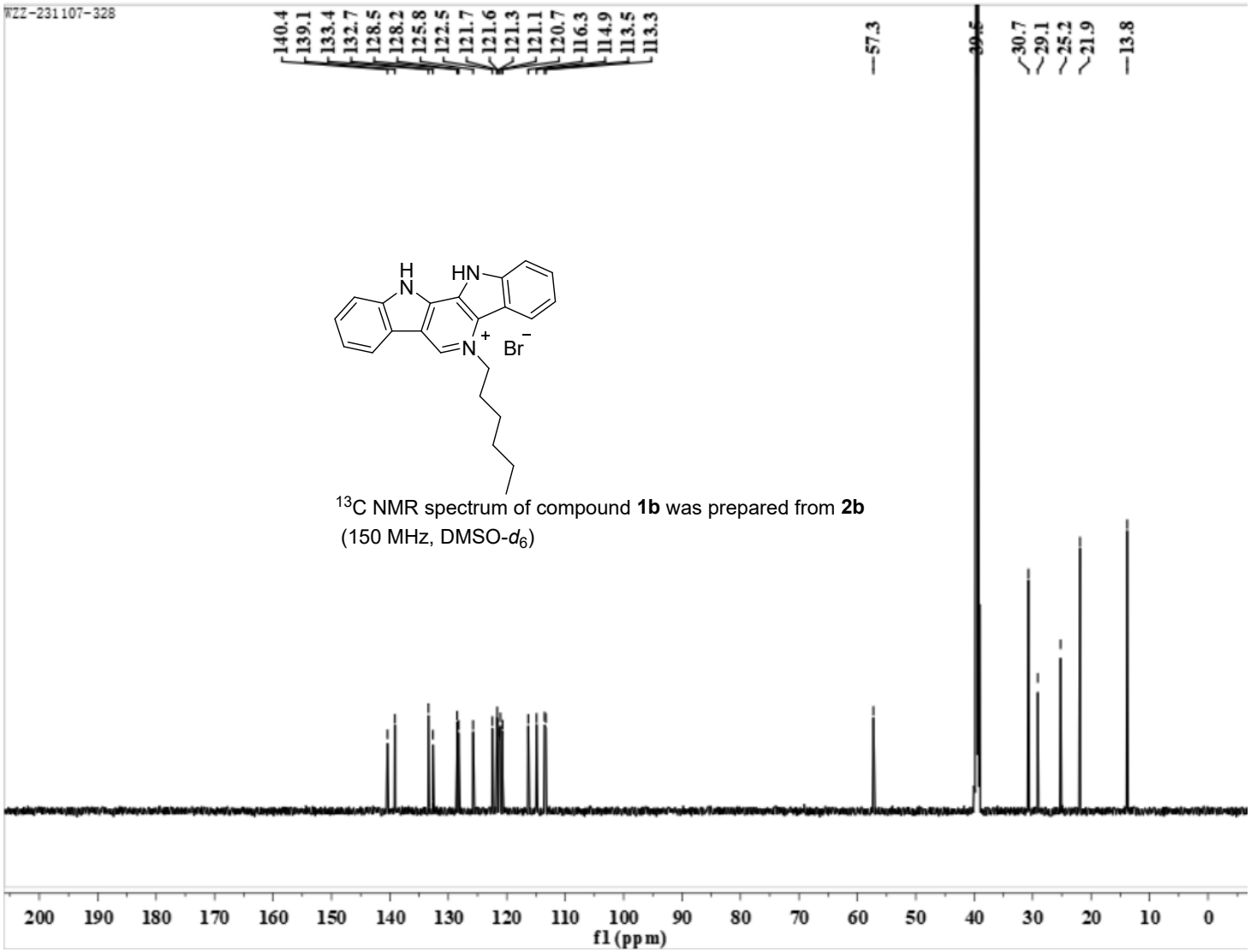
^{1}H NMR spectrum of compound **1a**
(600 MHz, DMSO-d_6)



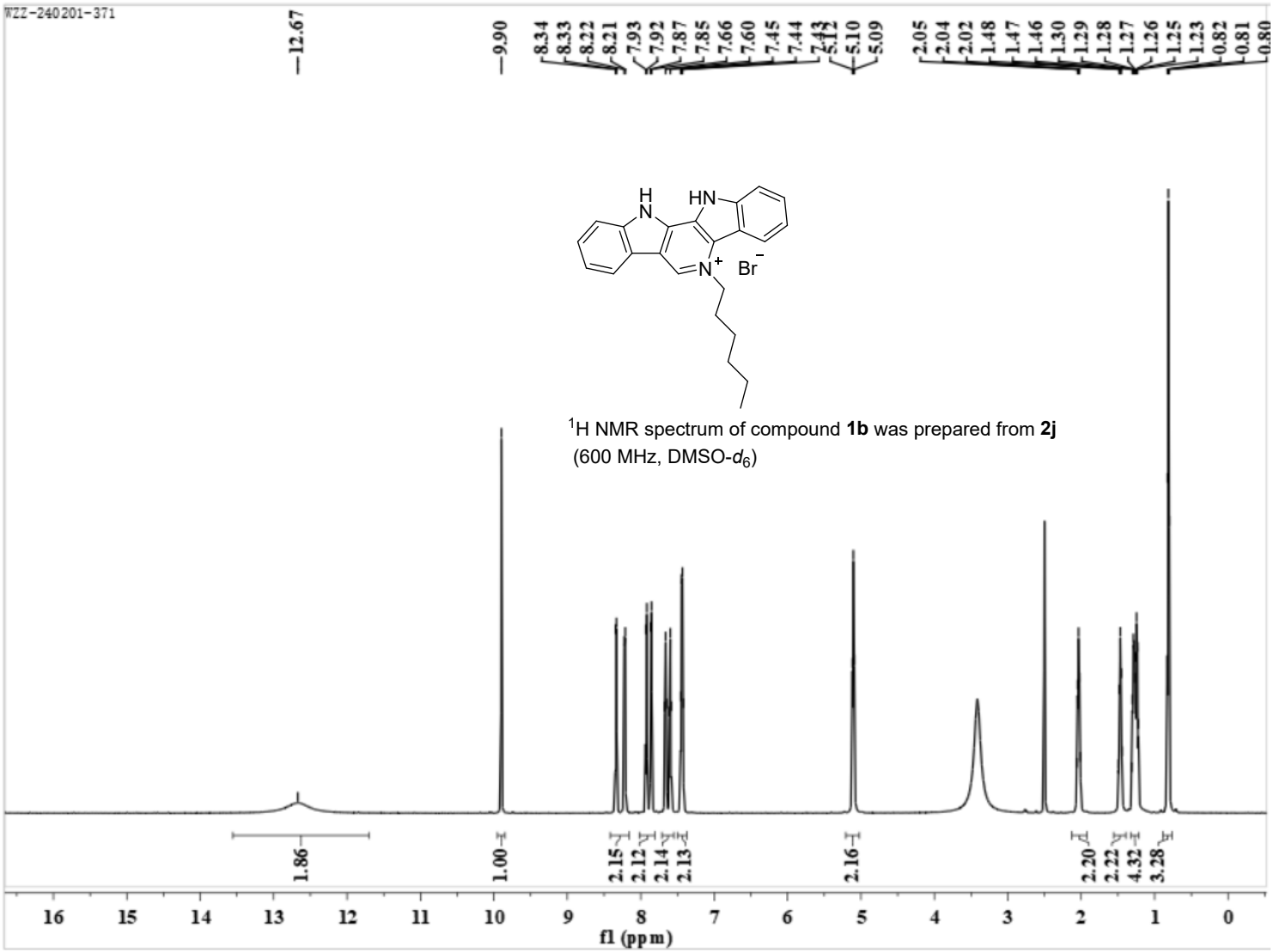
^{13}C NMR spectrum of compound **1a**
(150 MHz, DMSO-d_6)



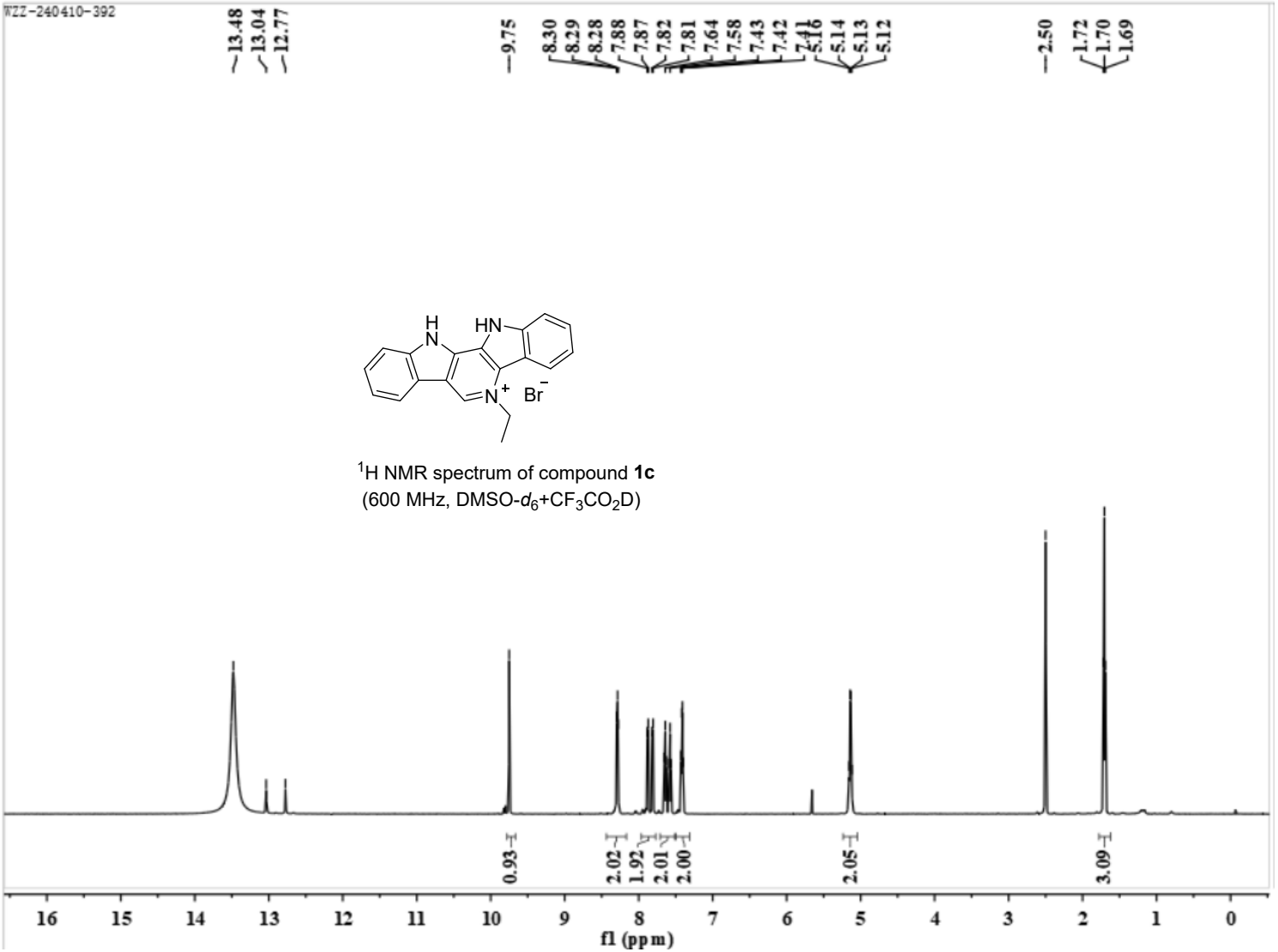
^{1}H NMR spectrum of compound **1b** was prepared from **2b** (600 MHz, DMSO-d_6)



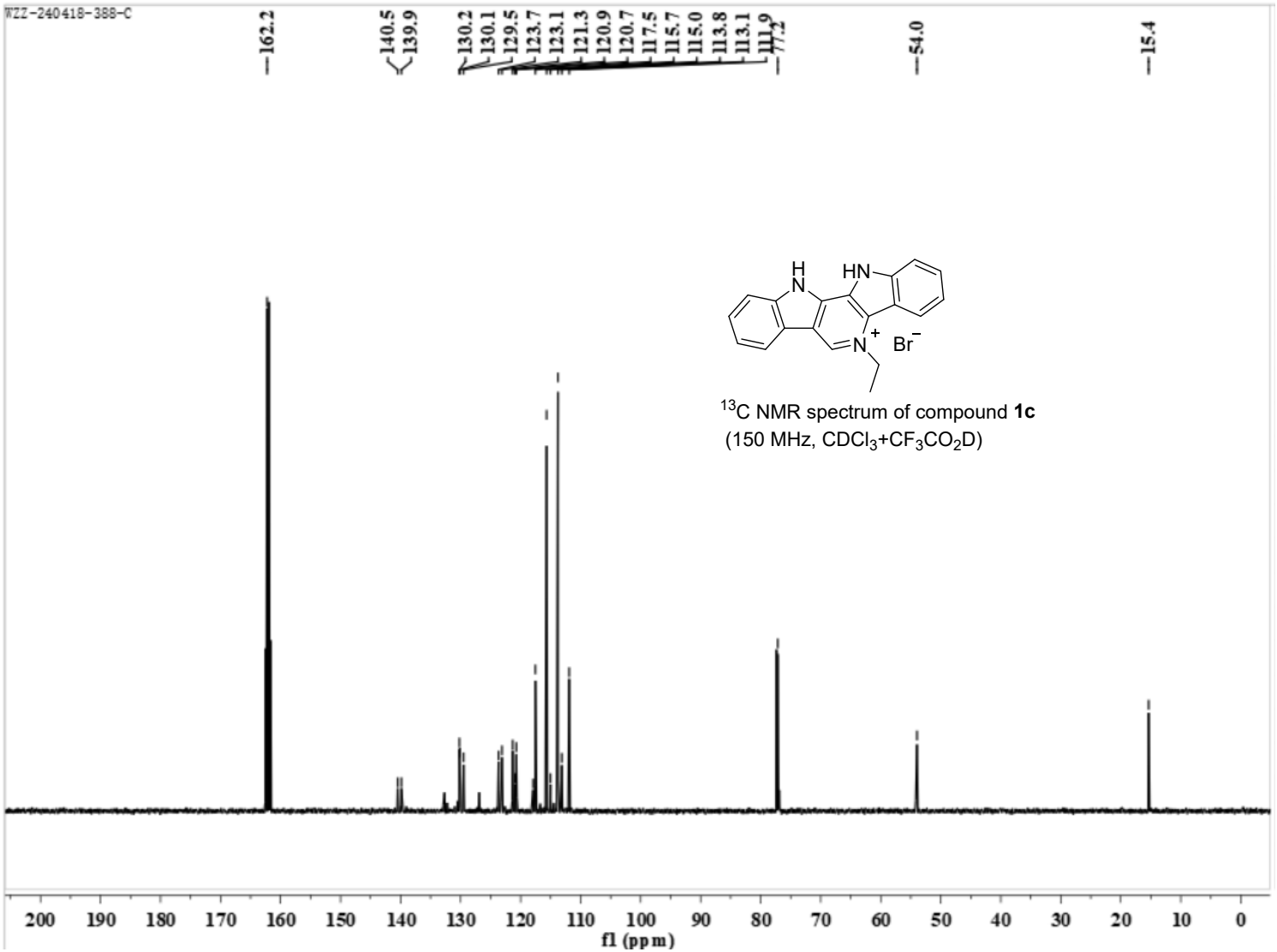
^{13}C NMR spectrum of compound **1b** was prepared from **2b** (150 MHz, DMSO-d_6)



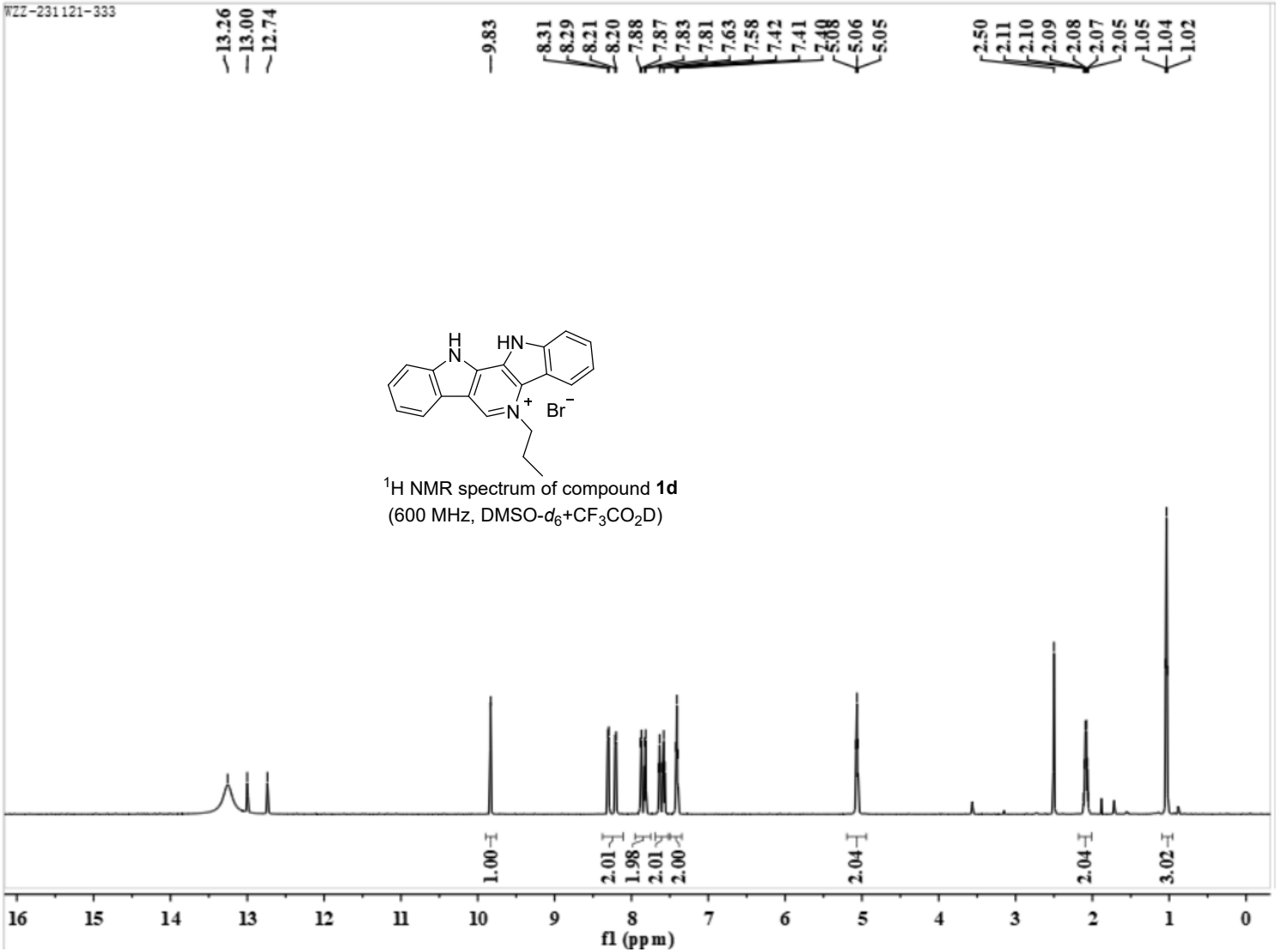
^{1}H NMR spectrum of compound **1b** was prepared from **2j** (600 MHz, DMSO-d_6)



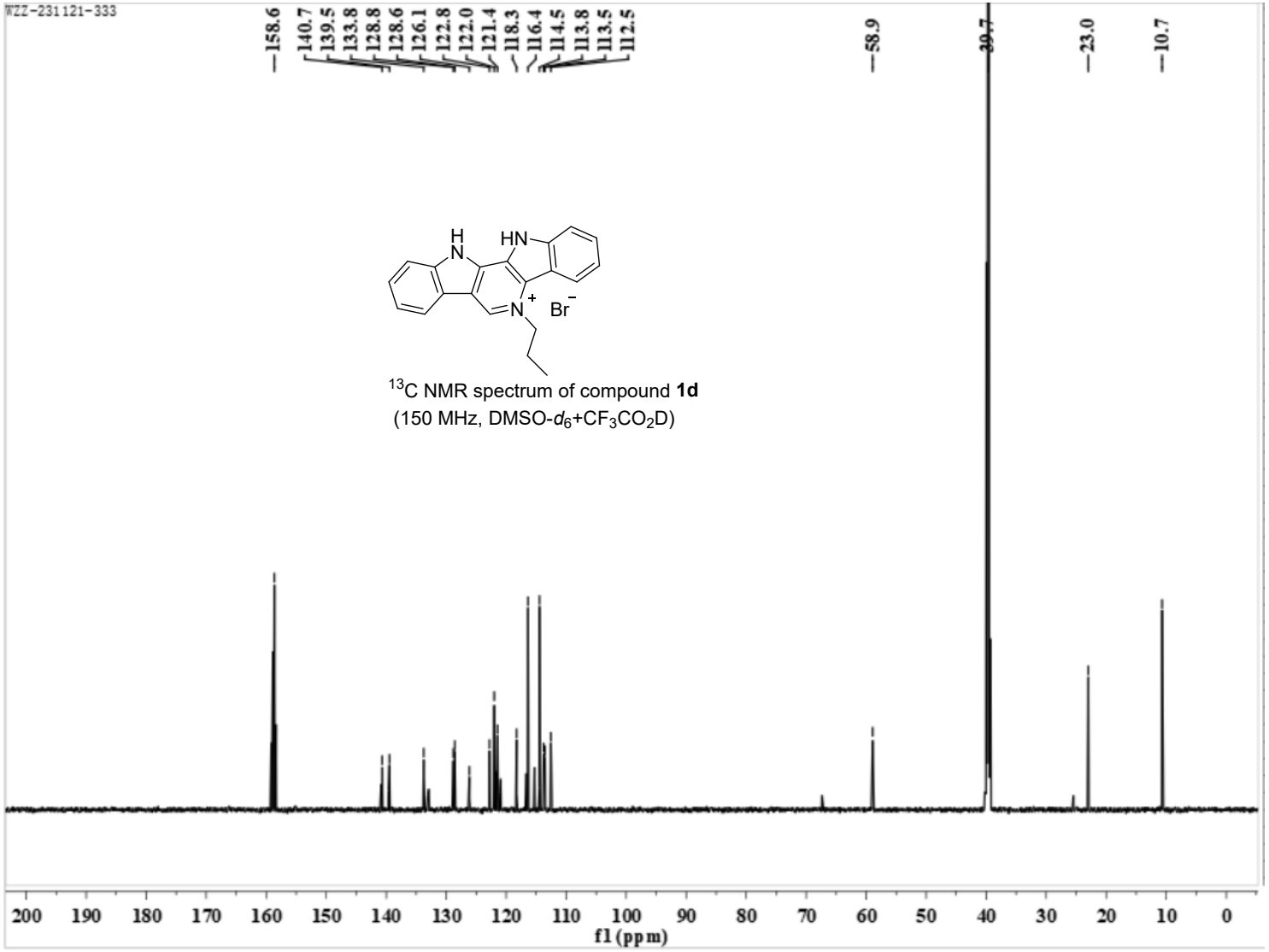
^{1}H NMR spectrum of compound **1c**
(600 MHz, DMSO-d_6+CF_3CO_2D)



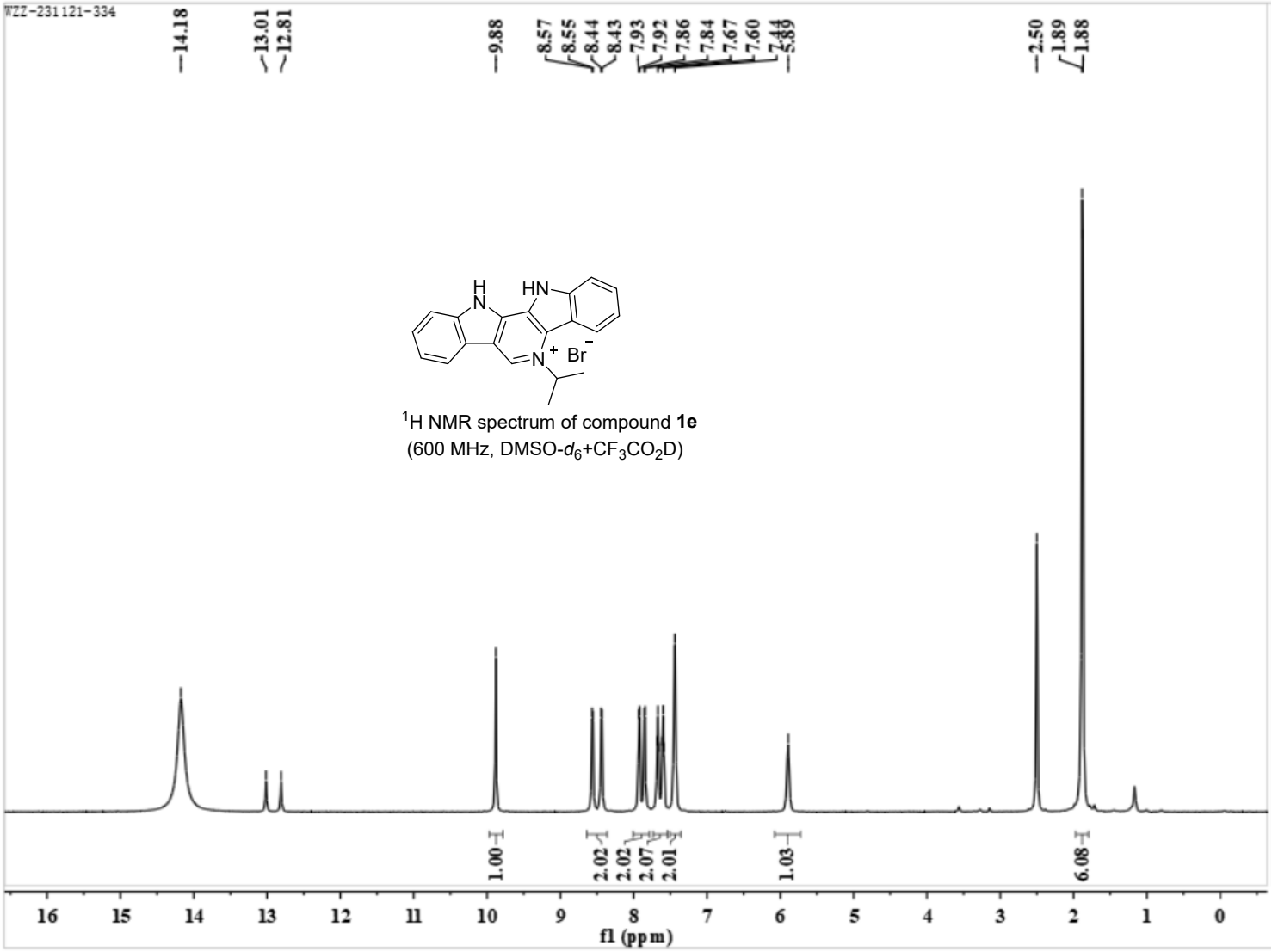
^{13}C NMR spectrum of compound **1c**
(150 MHz, $CDCl_3$+CF_3CO_2D)



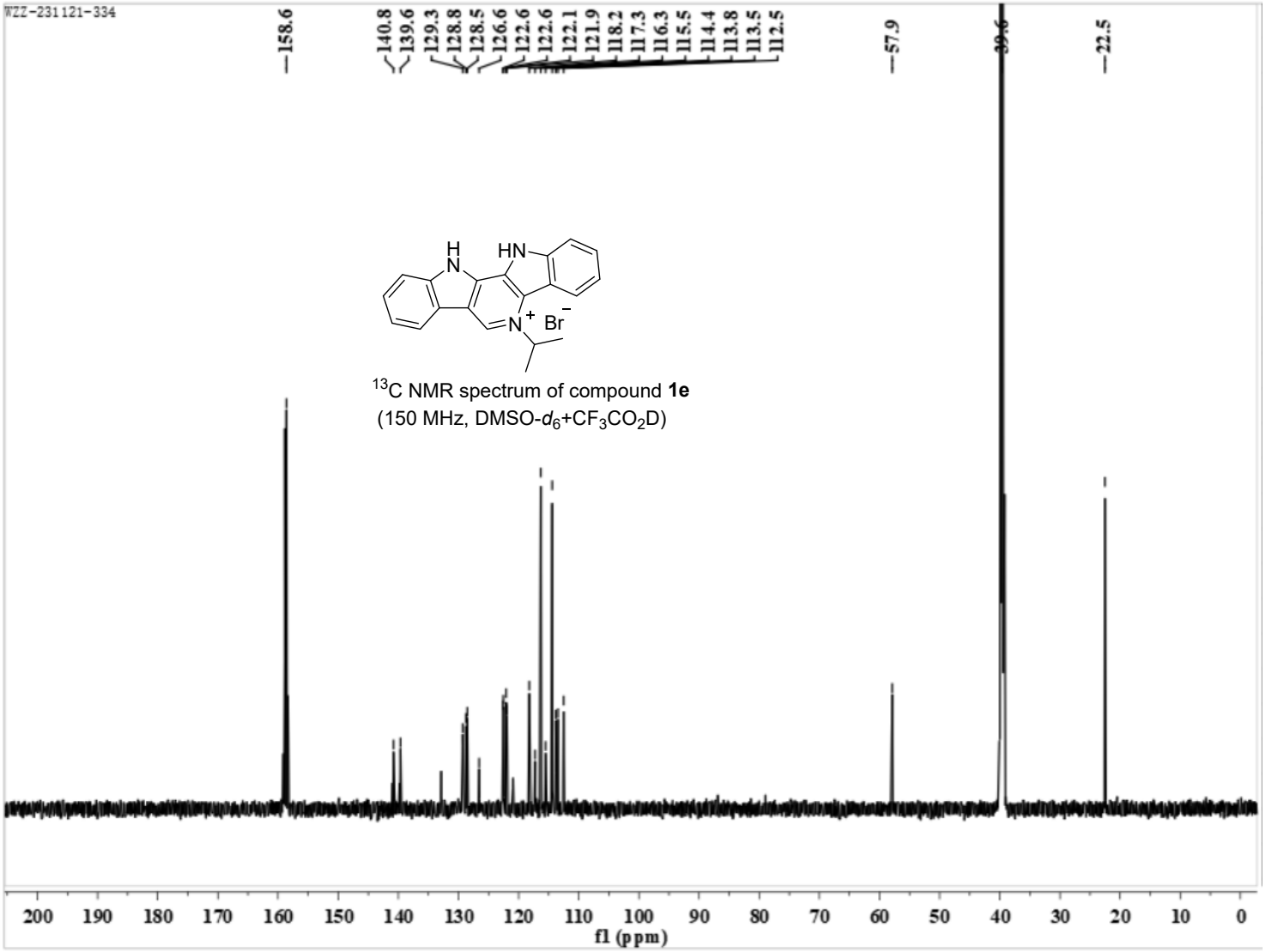
^{1}H NMR spectrum of compound **1d**
(600 MHz, DMSO-d_6+CF_3CO_2D)



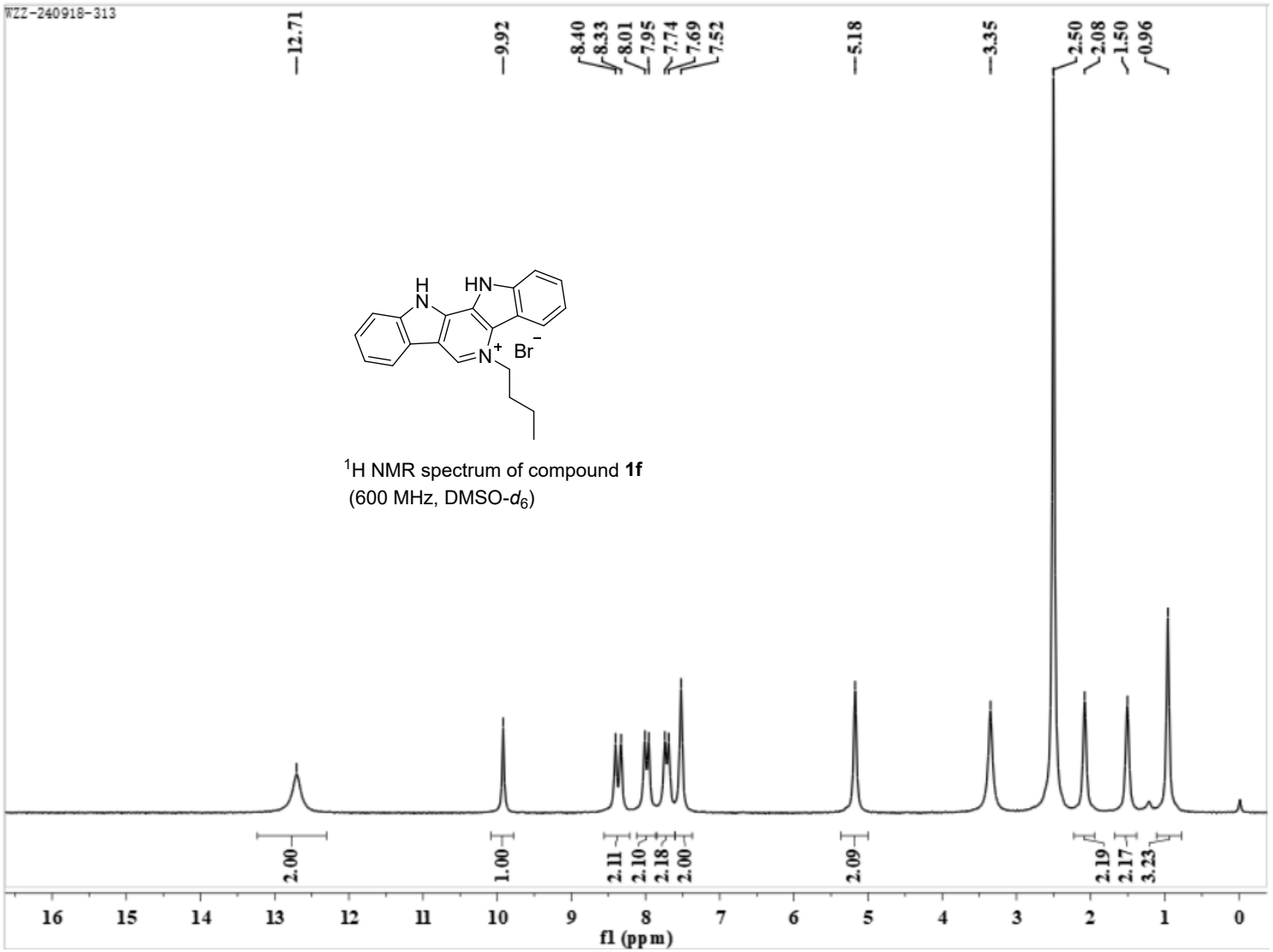
^{13}C NMR spectrum of compound **1d**
(150 MHz, DMSO-d_6+CF_3CO_2D)



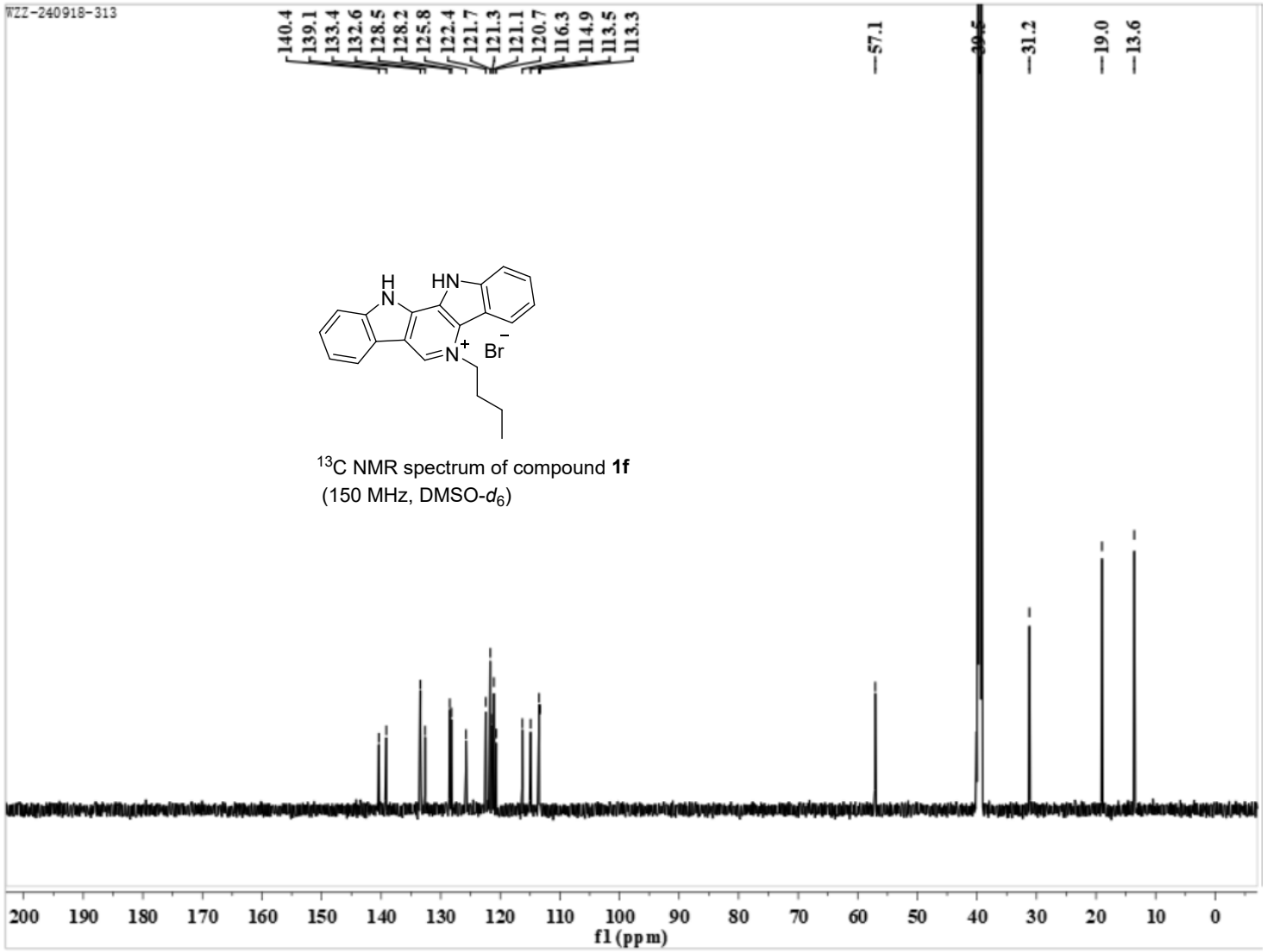
^{1}H NMR spectrum of compound **1e**
(600 MHz, DMSO-d_6+CF_3CO_2D)



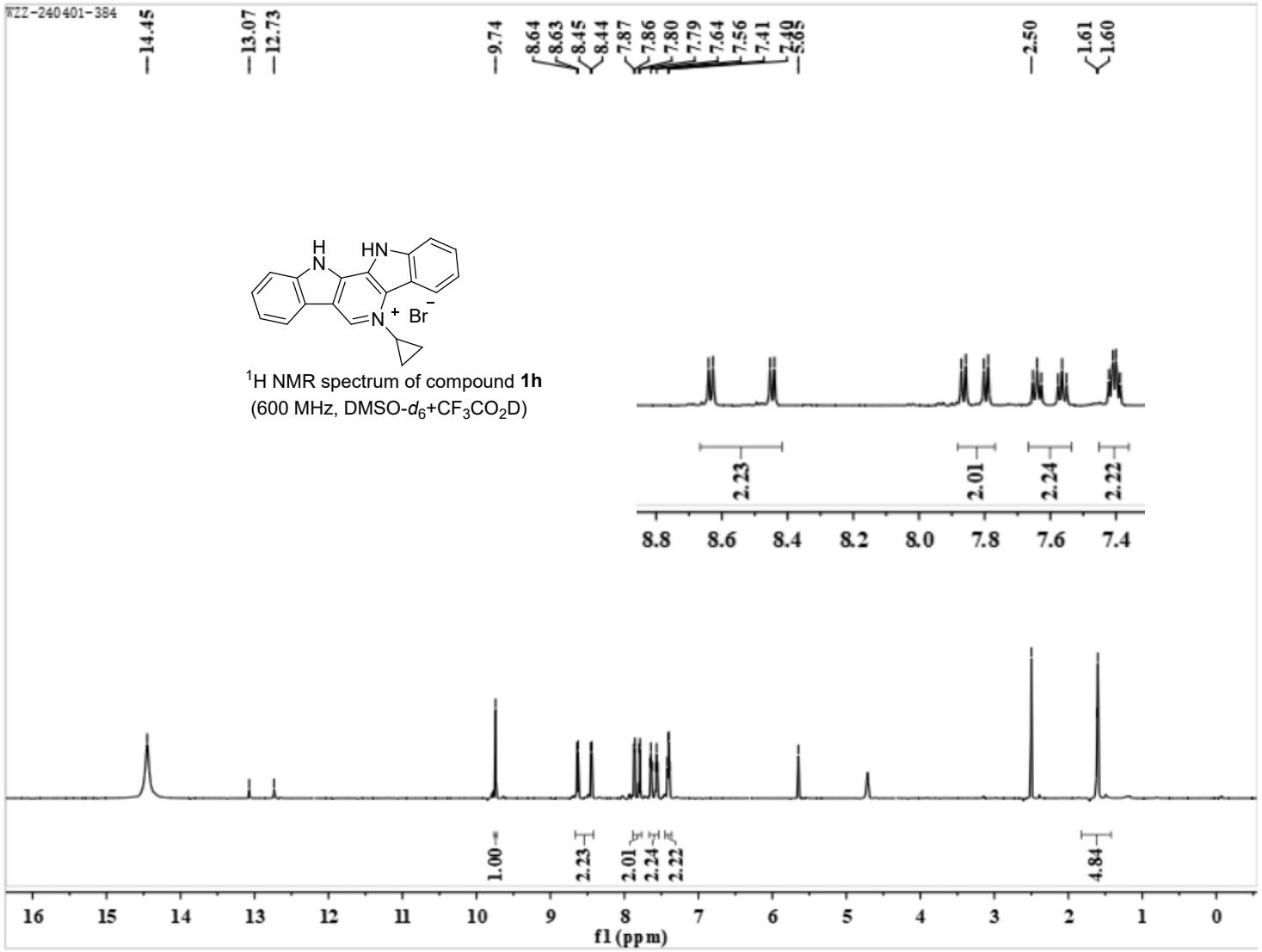
^{13}C NMR spectrum of compound **1e**
(150 MHz, DMSO-d_6+CF_3CO_2D)



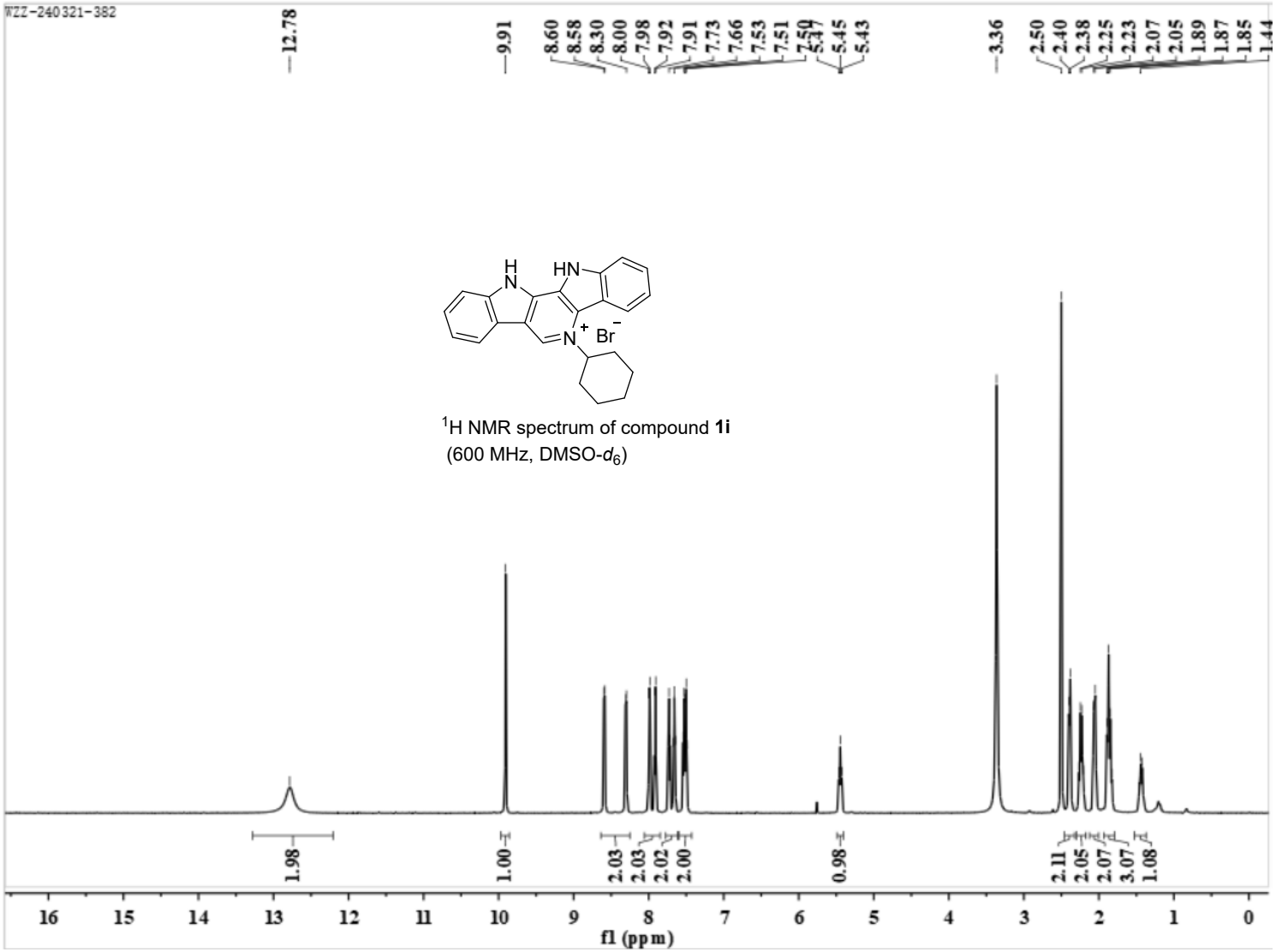
^{1}H NMR spectrum of compound **1f**
(600 MHz, DMSO-d_6)



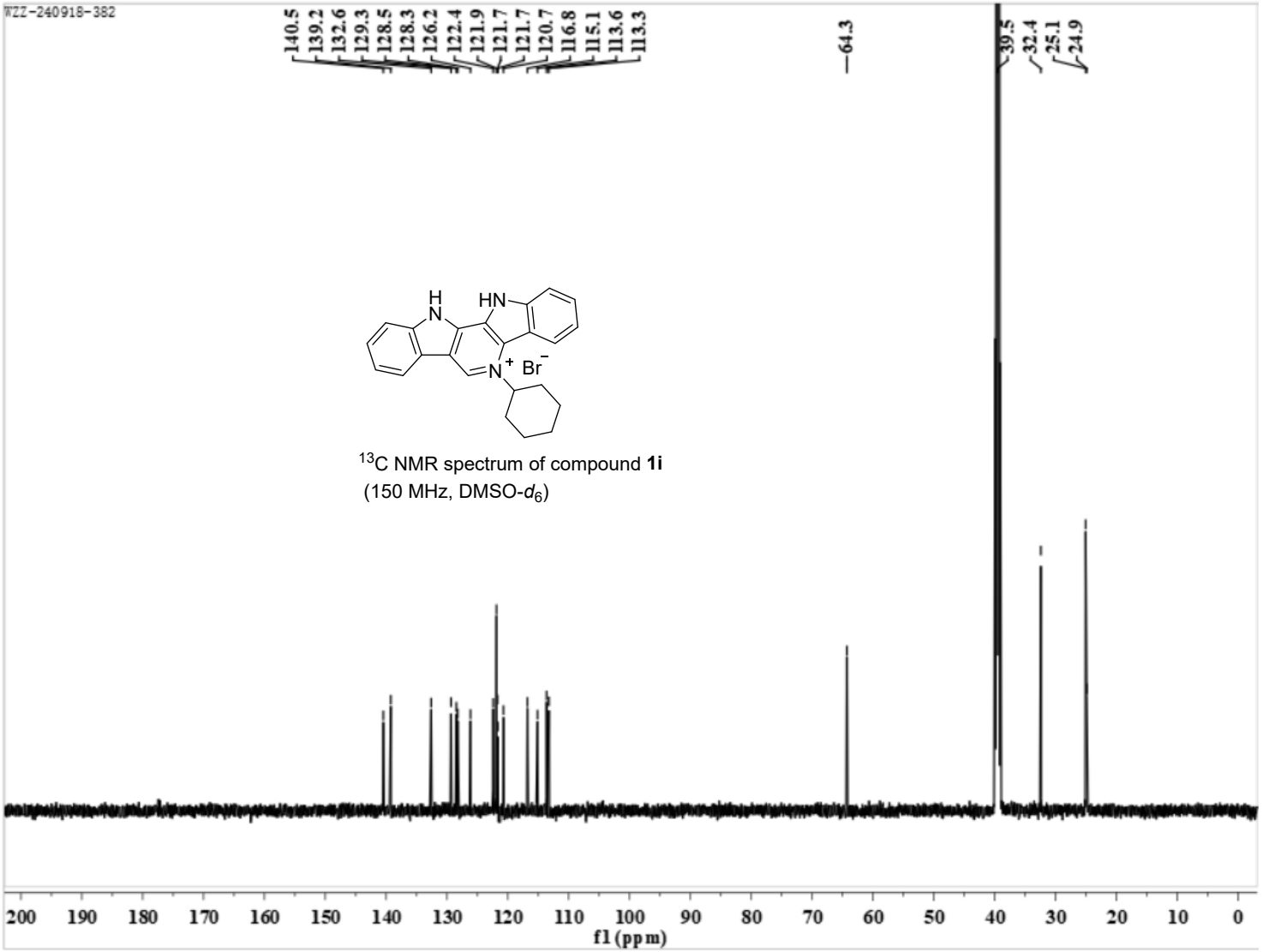
^{13}C NMR spectrum of compound **1f**
(150 MHz, DMSO-d_6)



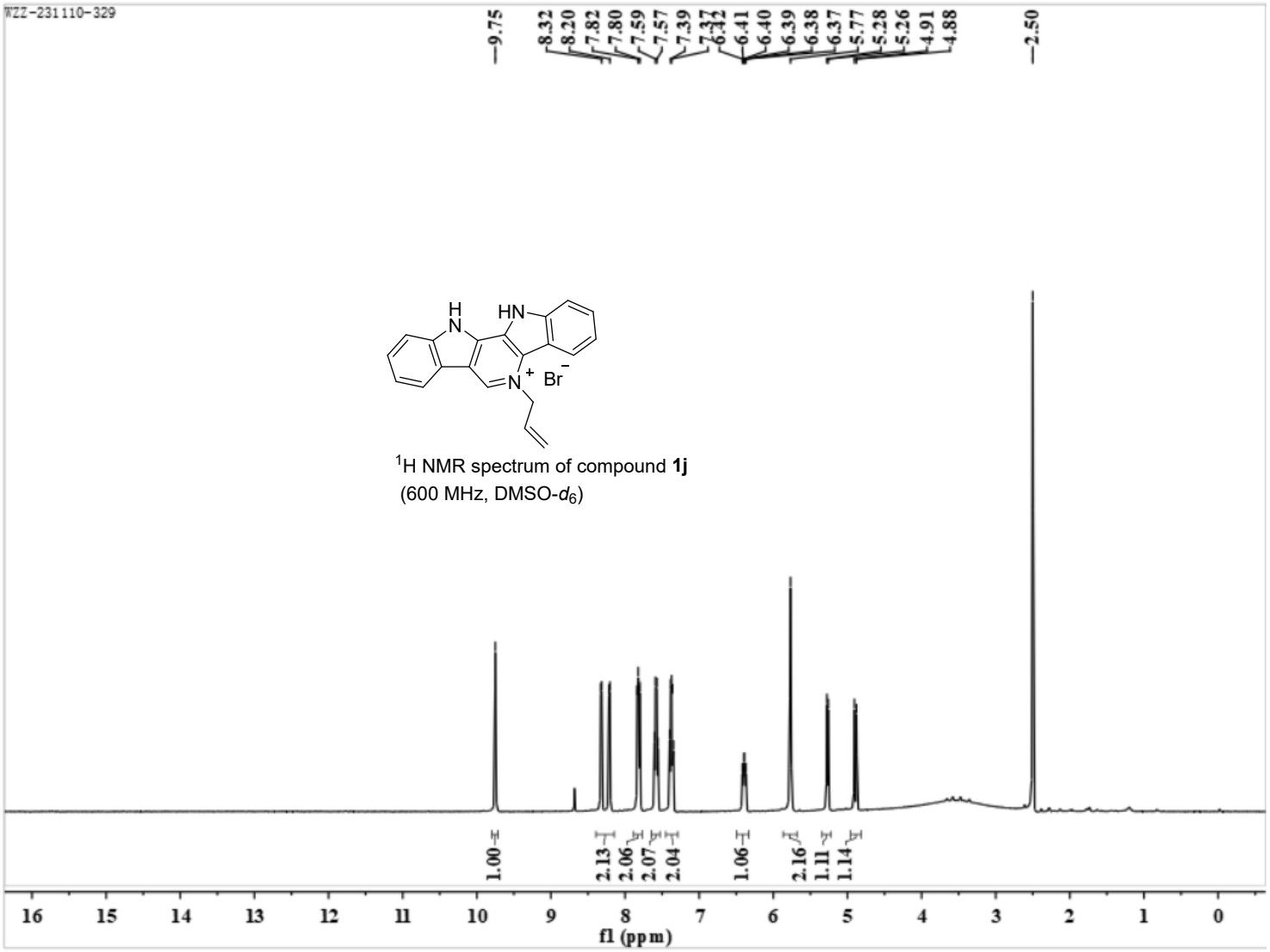
^{1}H NMR spectrum of compound **1h**
(600 MHz, DMSO-d_6+CF_3CO_2D)



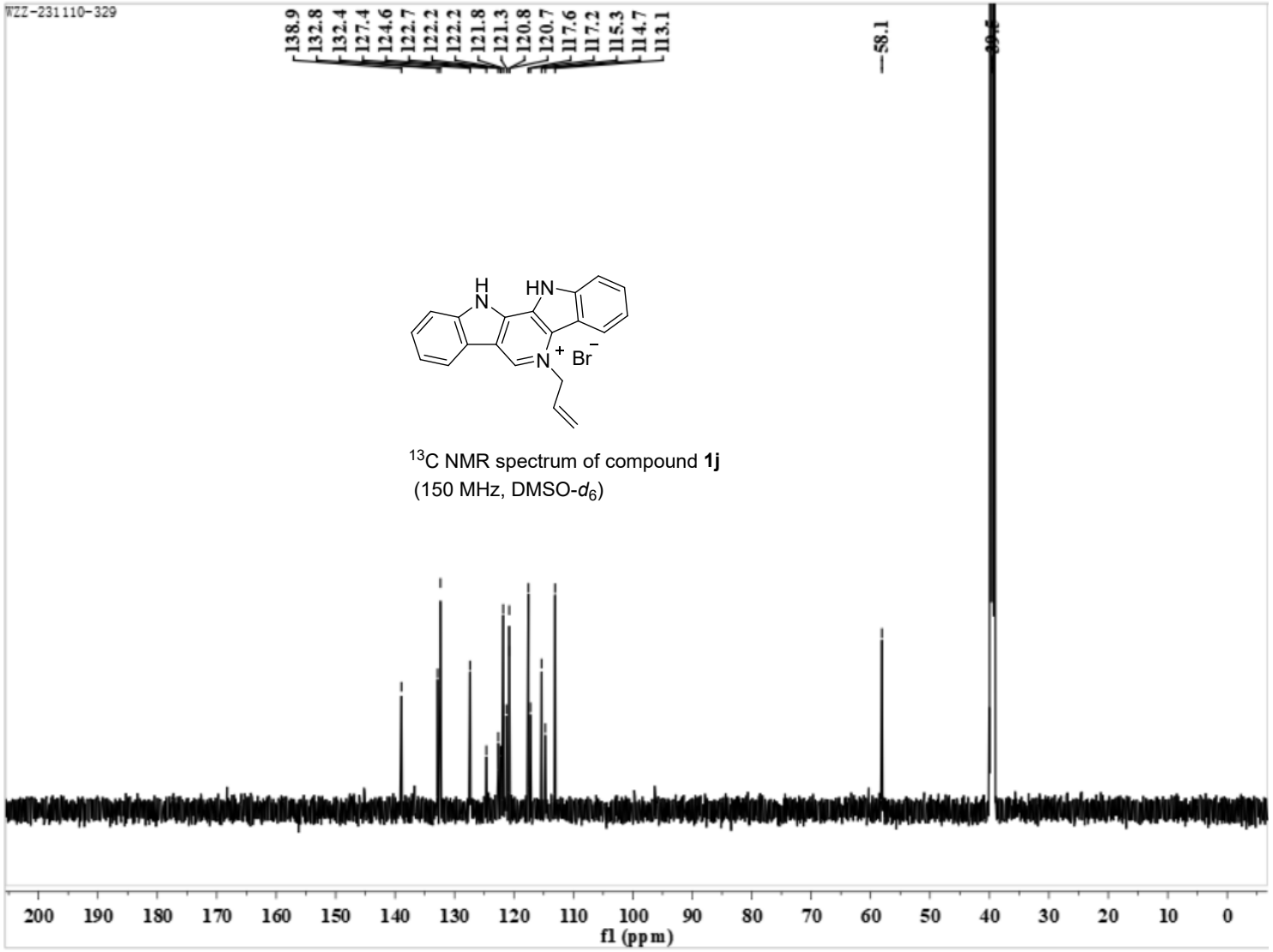
^{1}H NMR spectrum of compound **1i**
(600 MHz, DMSO-d_6)



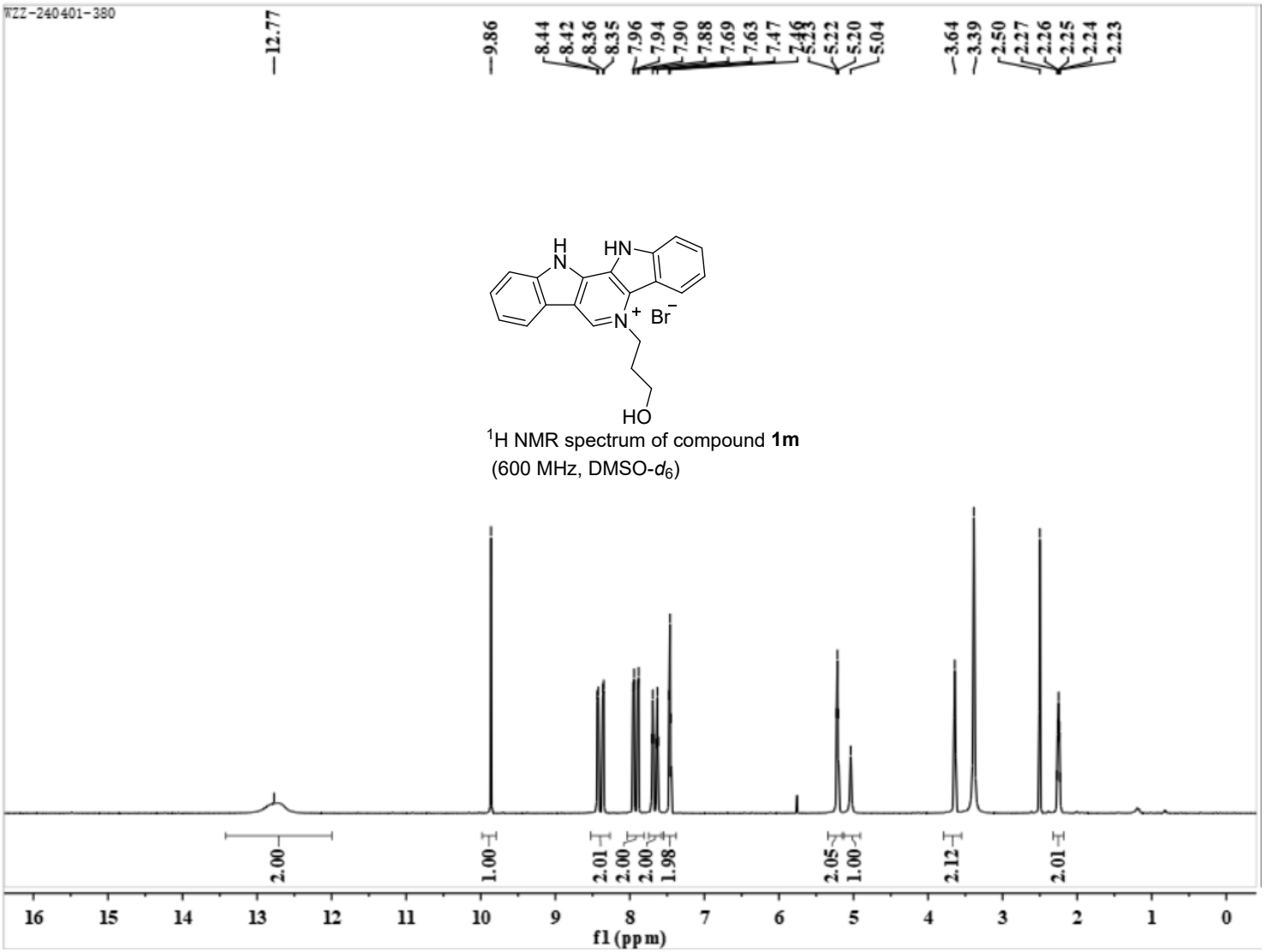
^{13}C NMR spectrum of compound **1i**
(150 MHz, DMSO-d_6)



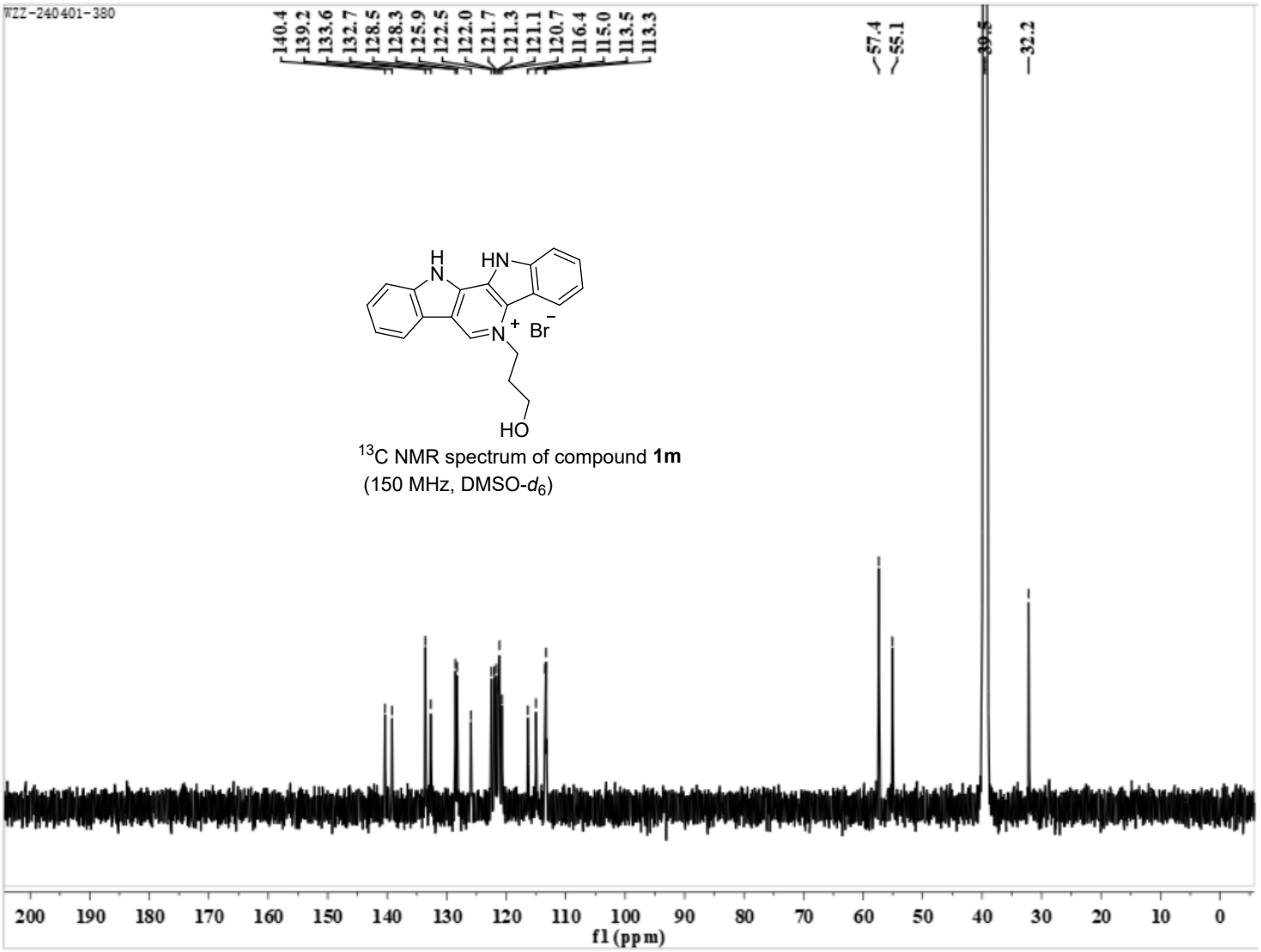
^{1}H NMR spectrum of compound **1j**
(600 MHz, DMSO-d_6)



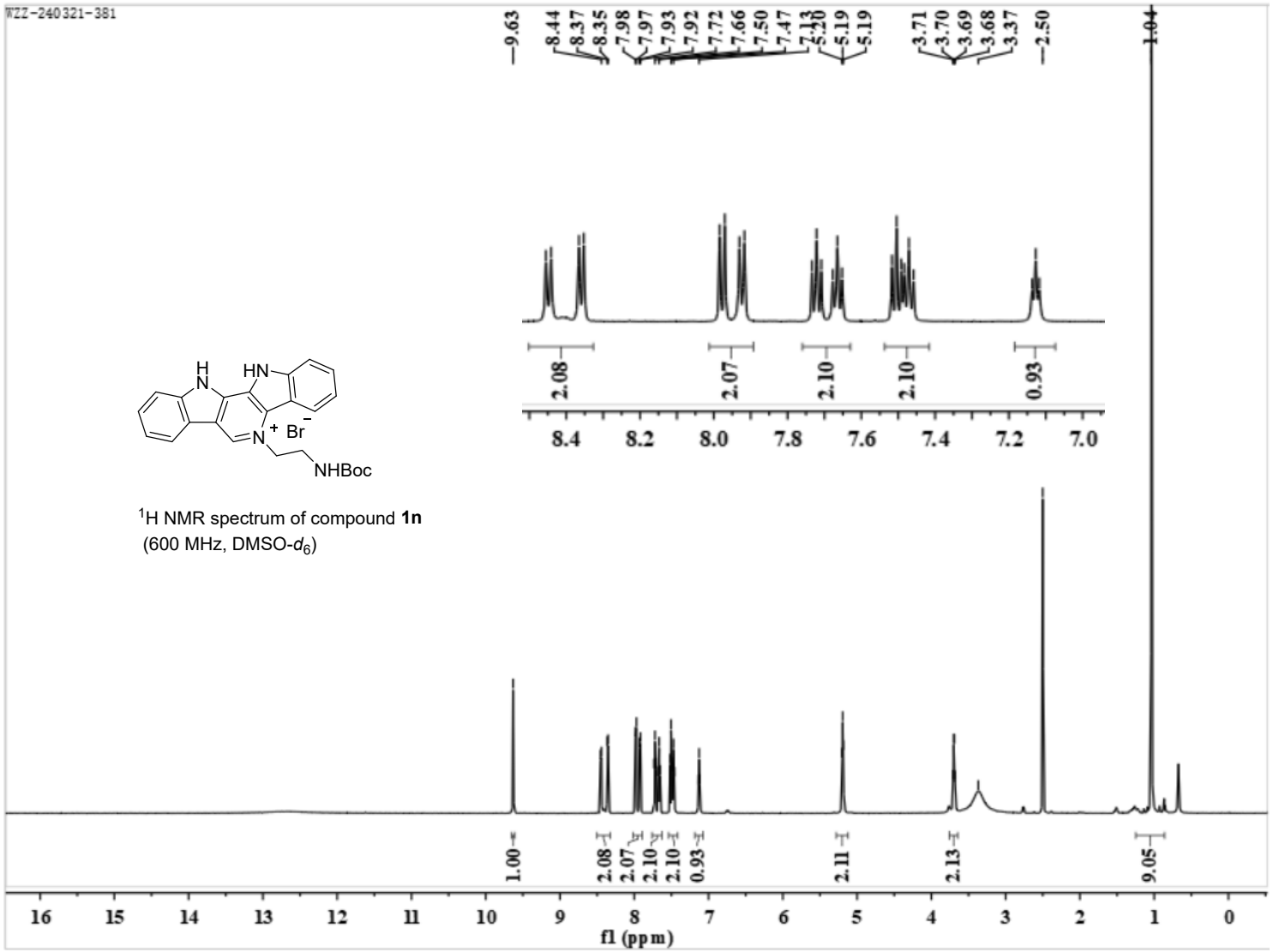
^{13}C NMR spectrum of compound **1j**
(150 MHz, DMSO-d_6)



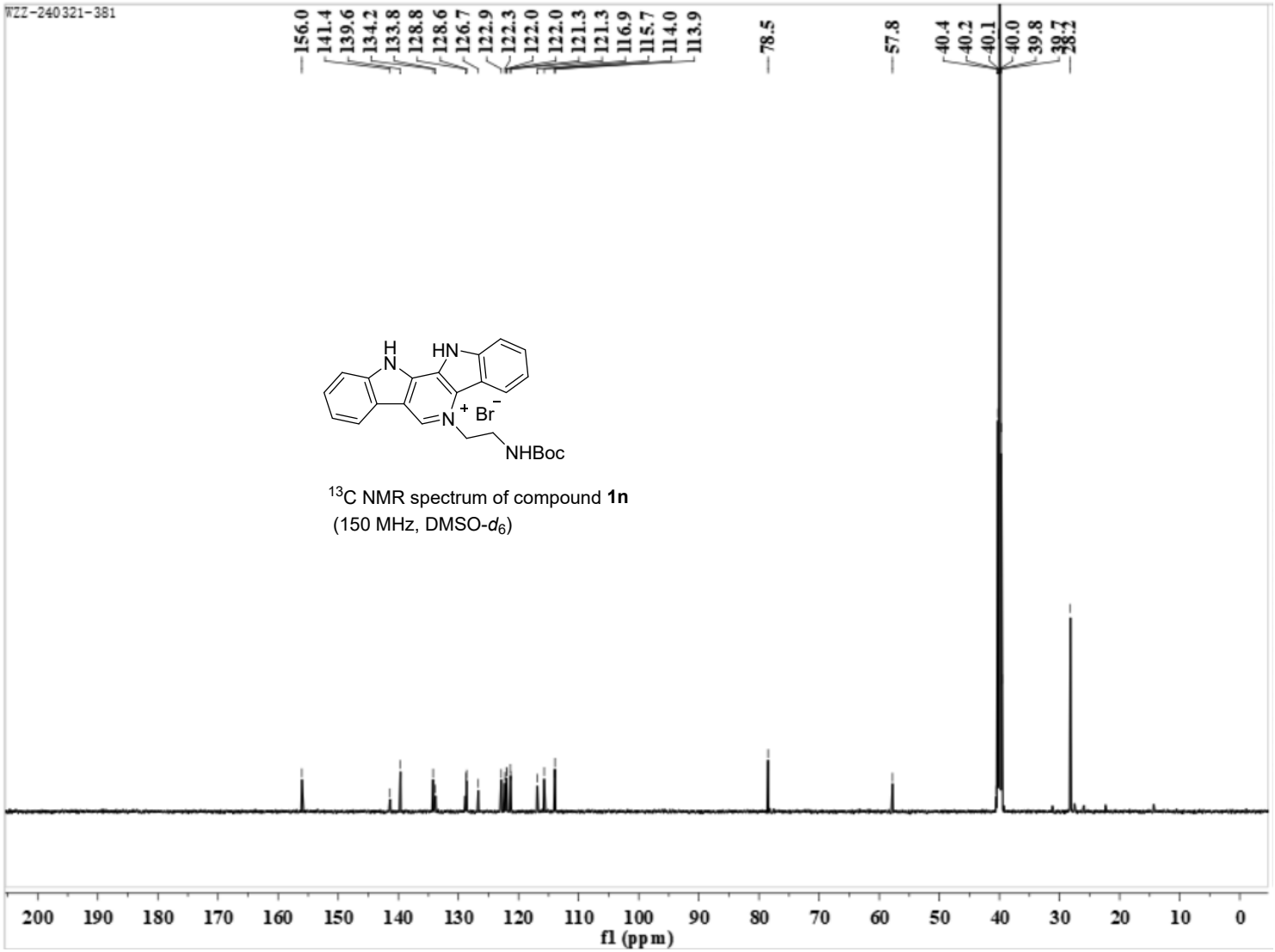
^{1}H NMR spectrum of compound **1m**
(600 MHz, DMSO-d_6)



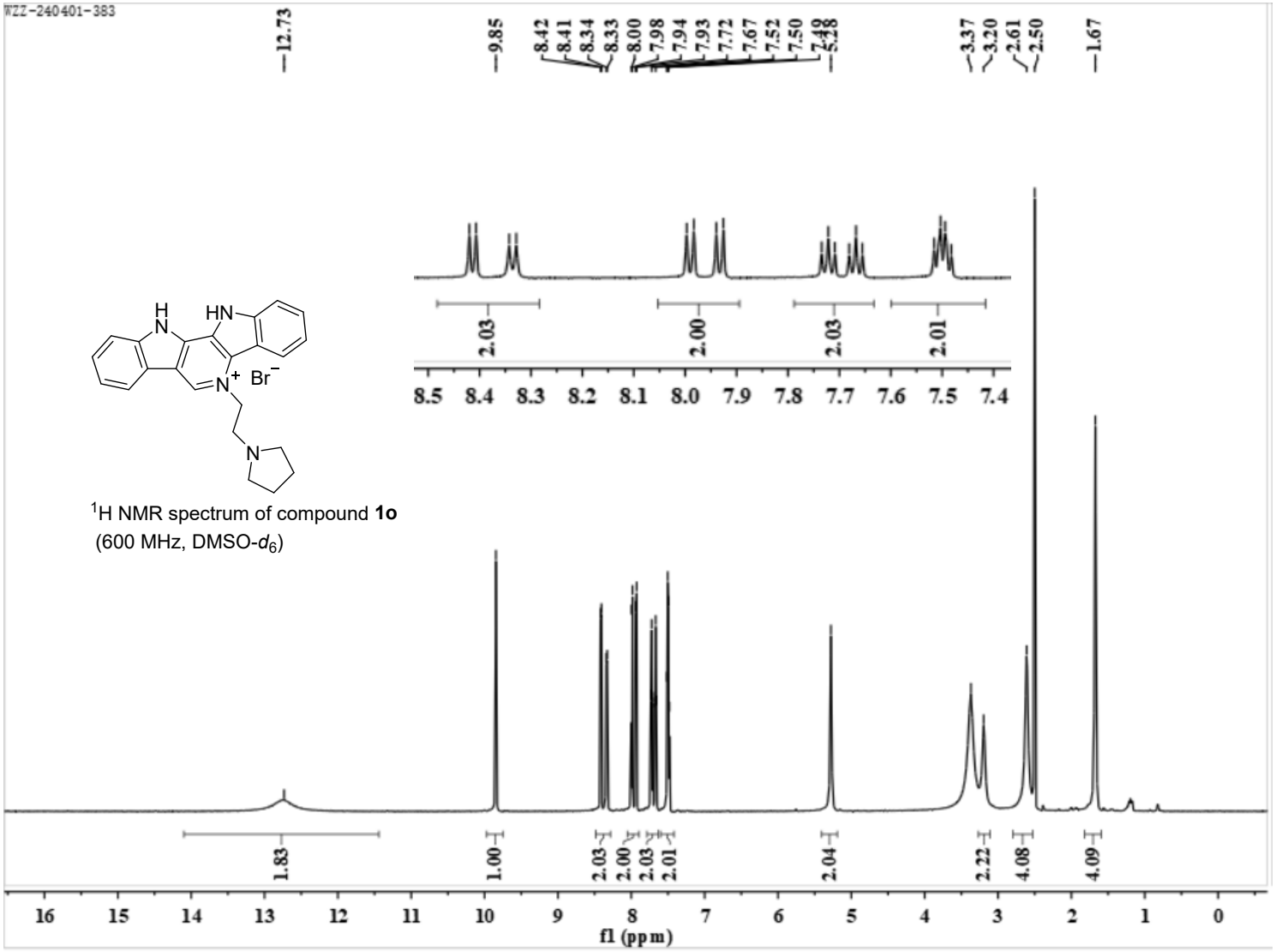
^{13}C NMR spectrum of compound **1m**
(150 MHz, DMSO-d_6)



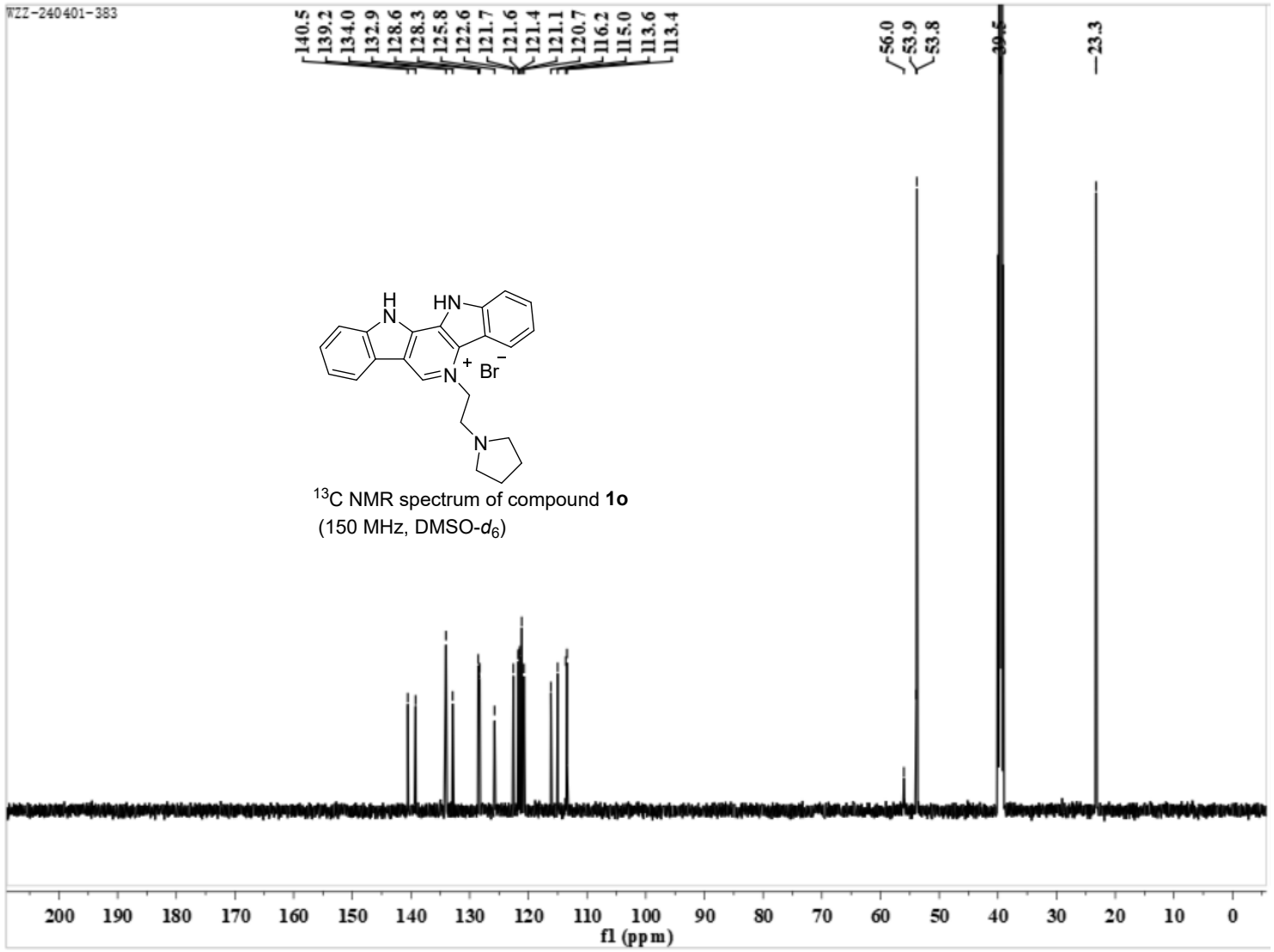
^{1}H NMR spectrum of compound **1n**
(600 MHz, DMSO-d_6)



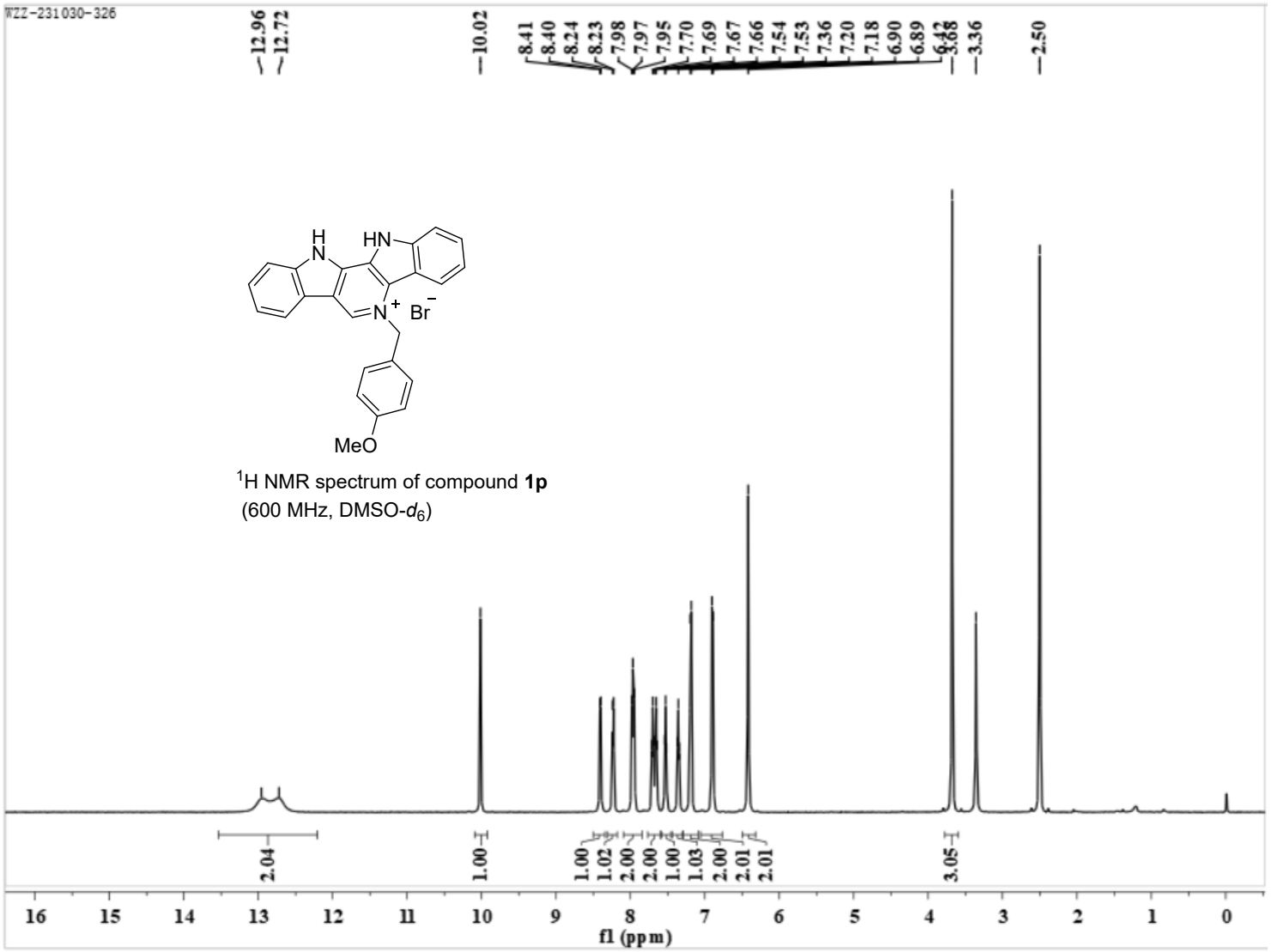
^{13}C NMR spectrum of compound **1n**
(150 MHz, DMSO-d_6)



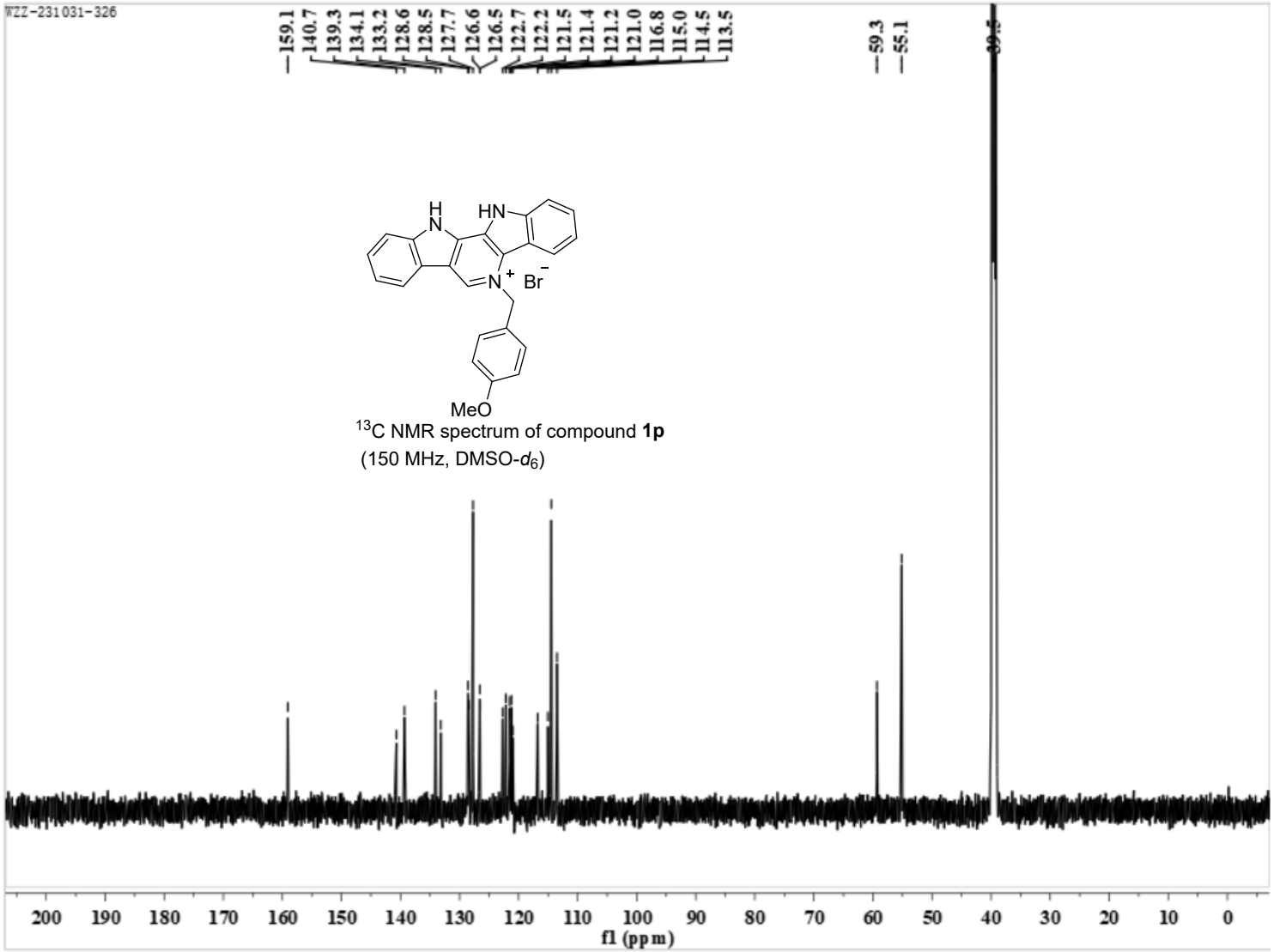
^{1}H NMR spectrum of compound **1o**
(600 MHz, DMSO-d_6)



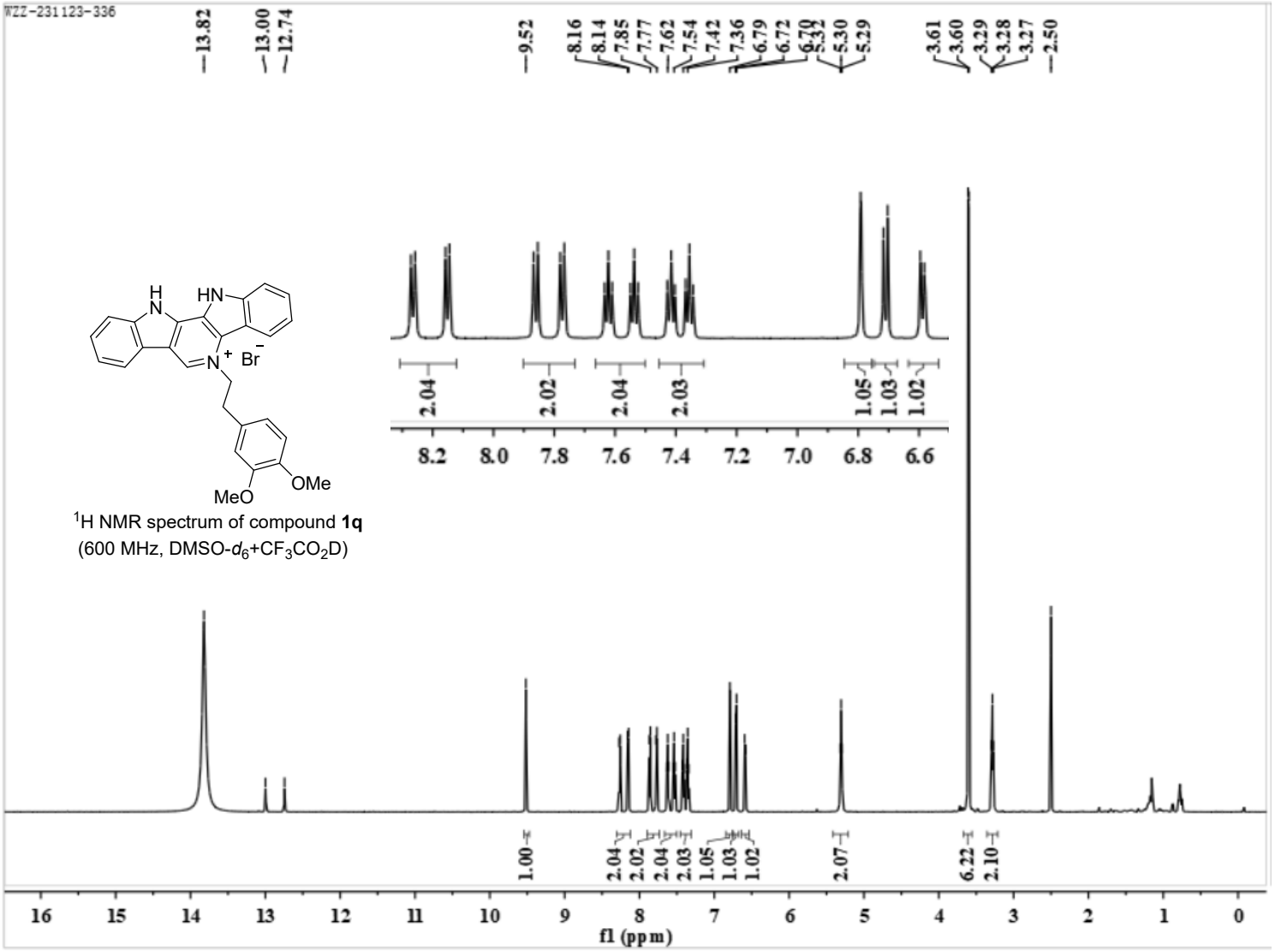
^{13}C NMR spectrum of compound **1o**
(150 MHz, DMSO-d_6)



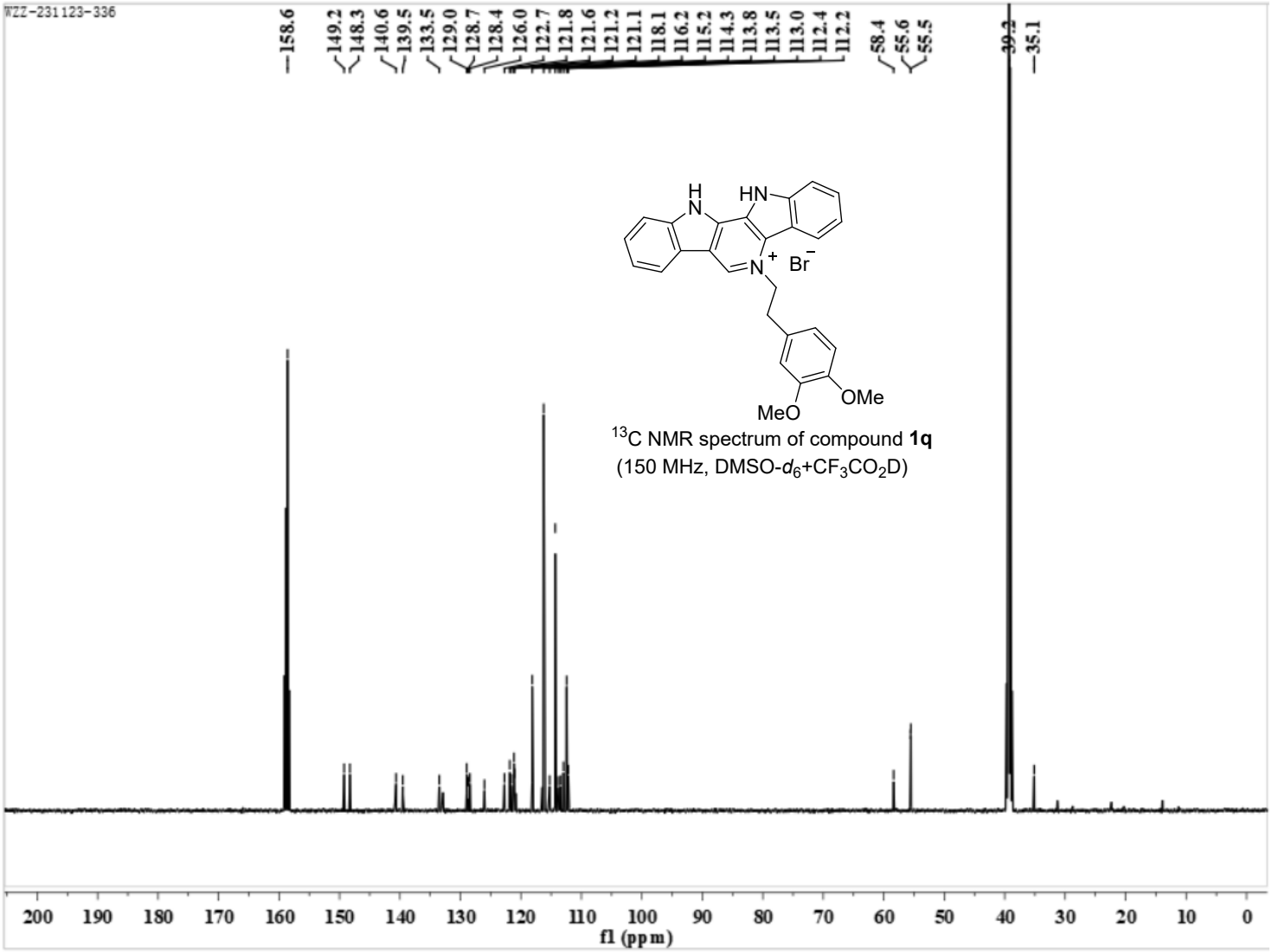
^{1}H NMR spectrum of compound **1p**
(600 MHz, DMSO-d_6)



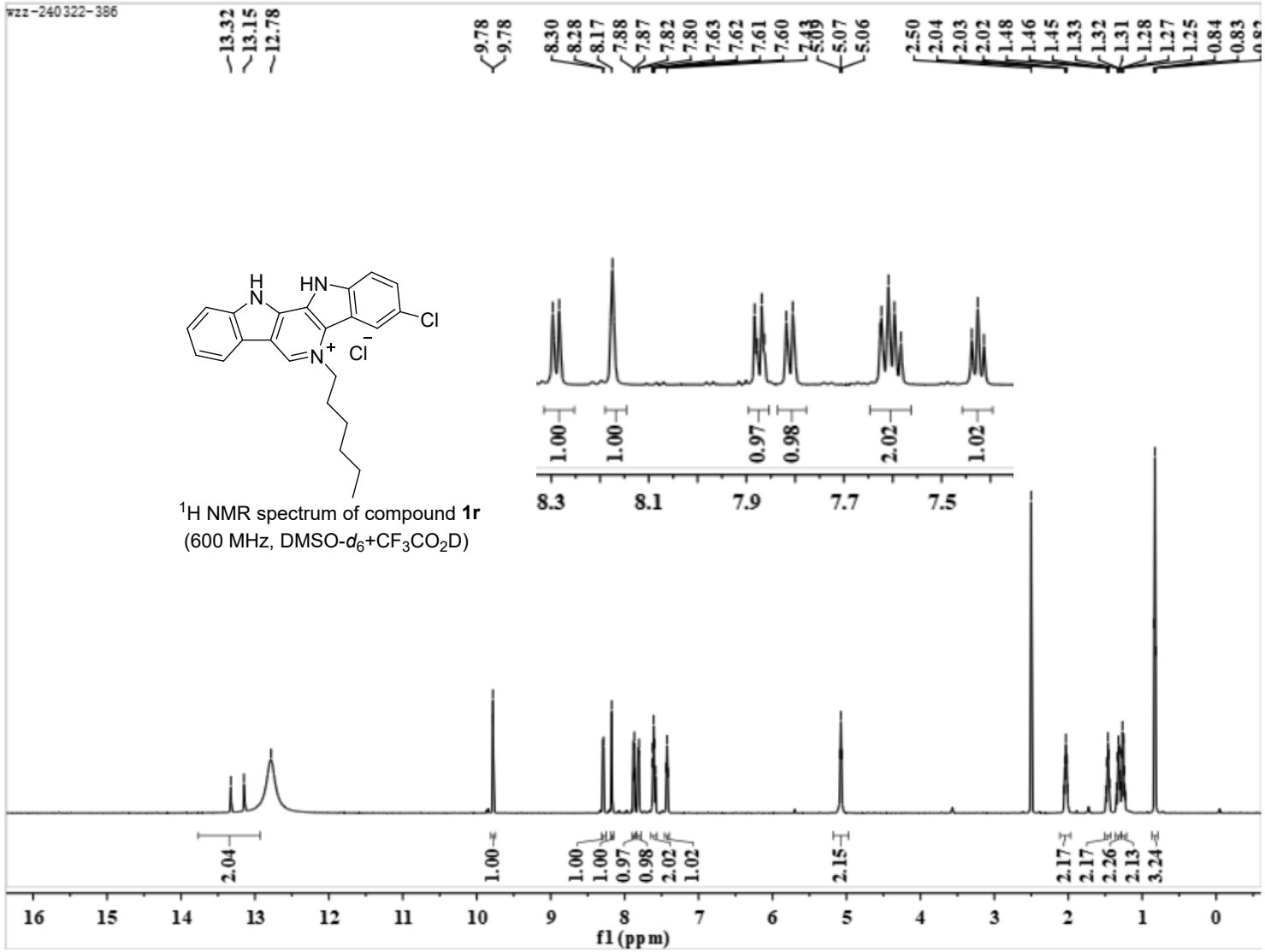
^{13}C NMR spectrum of compound **1p**
(150 MHz, DMSO-d_6)



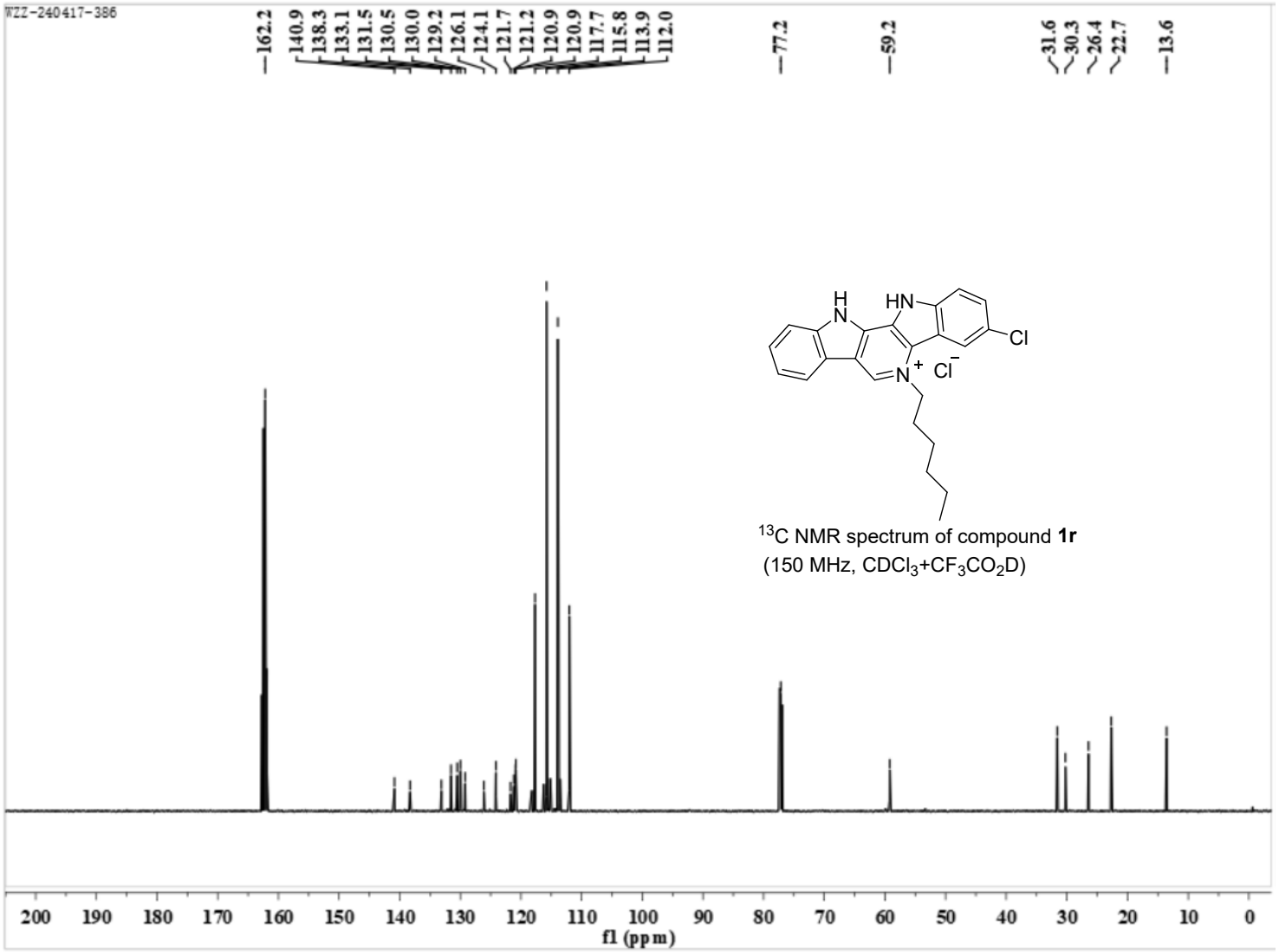
^{1}H NMR spectrum of compound **1q**
(600 MHz, DMSO-d_6+CF_3CO_2D)



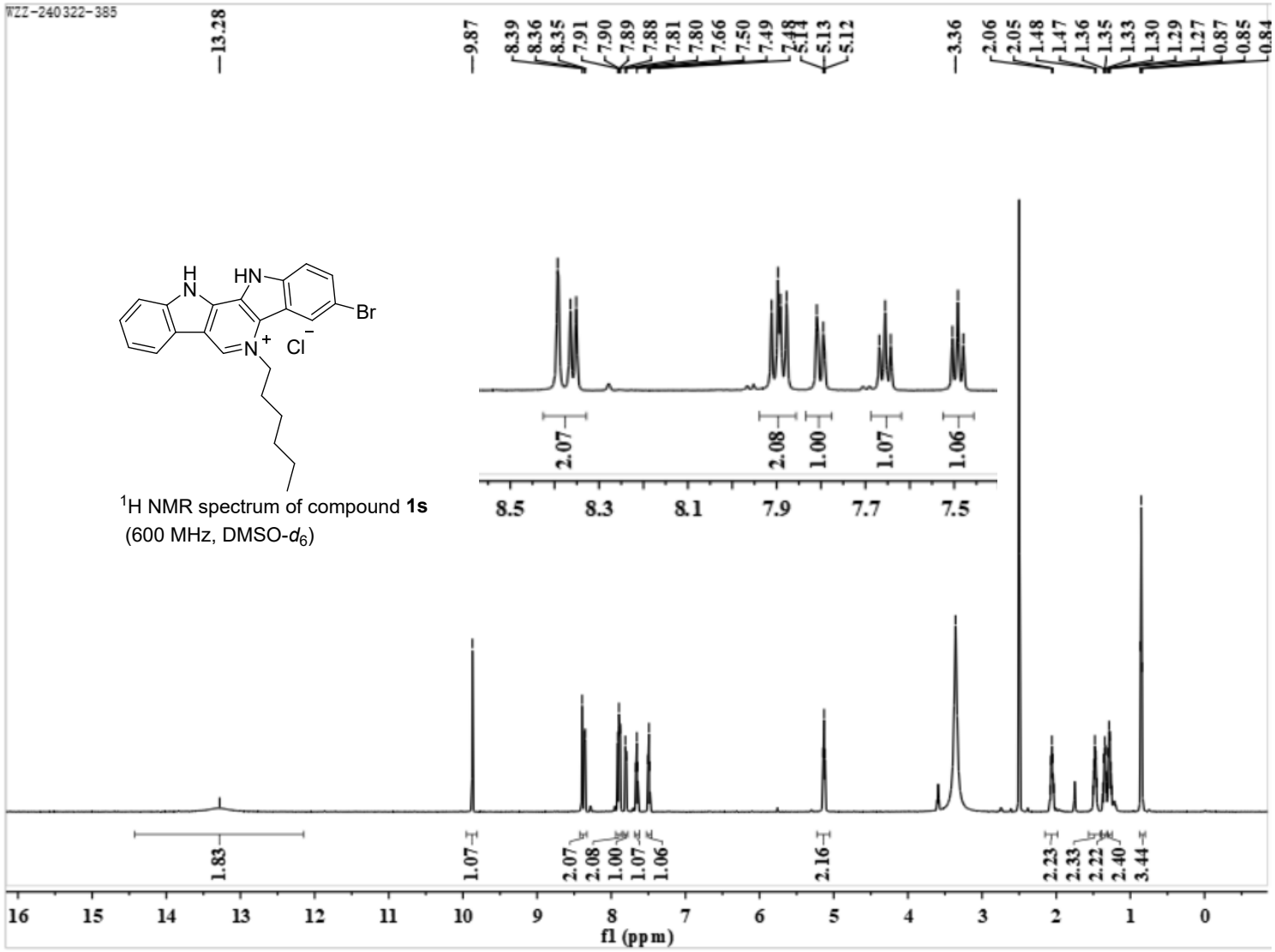
^{13}C NMR spectrum of compound **1q**
(150 MHz, DMSO-d_6+CF_3CO_2D)



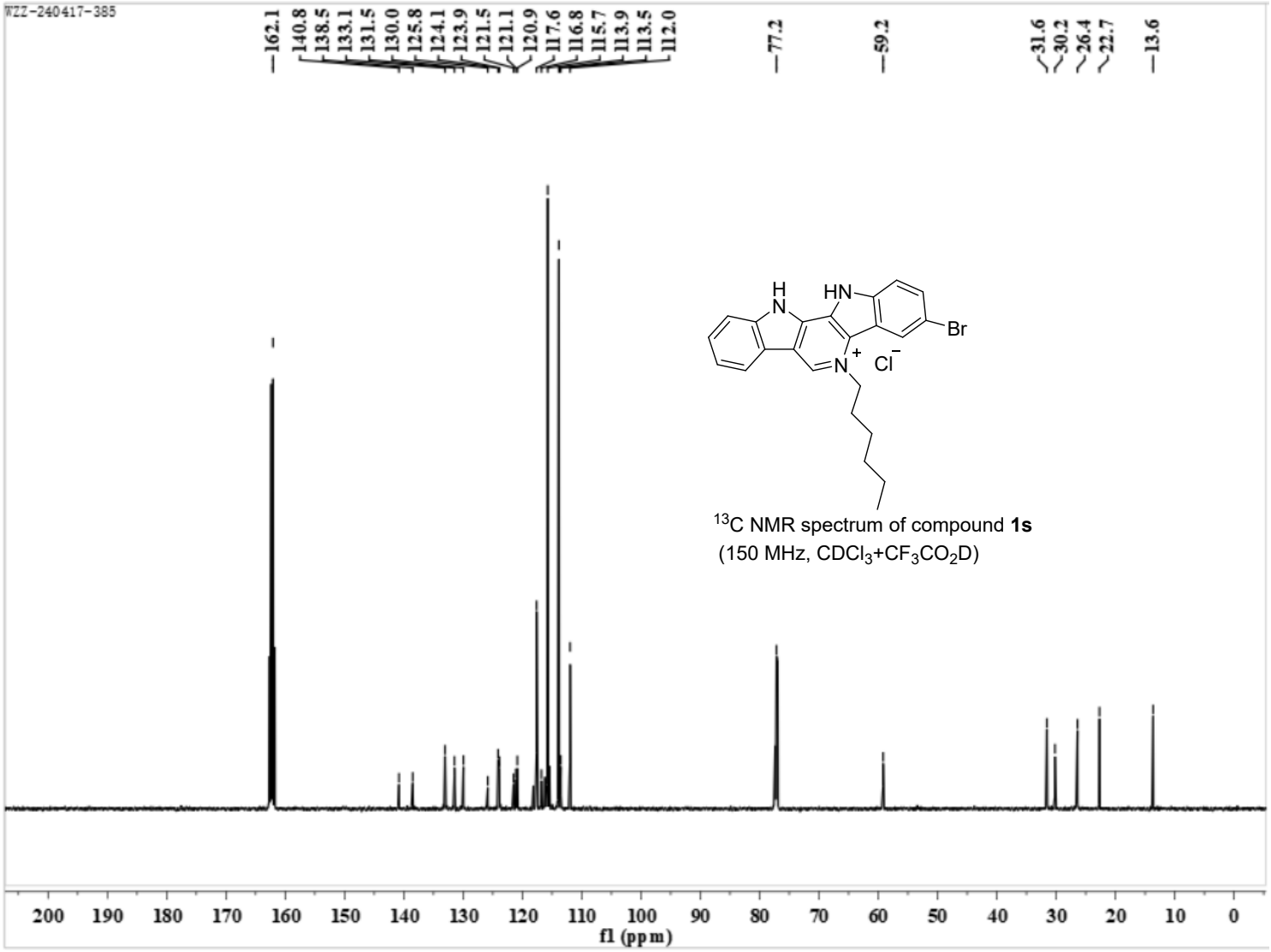
^{1}H NMR spectrum of compound **1r**
(600 MHz, DMSO-d_6+CF_3CO_2D)



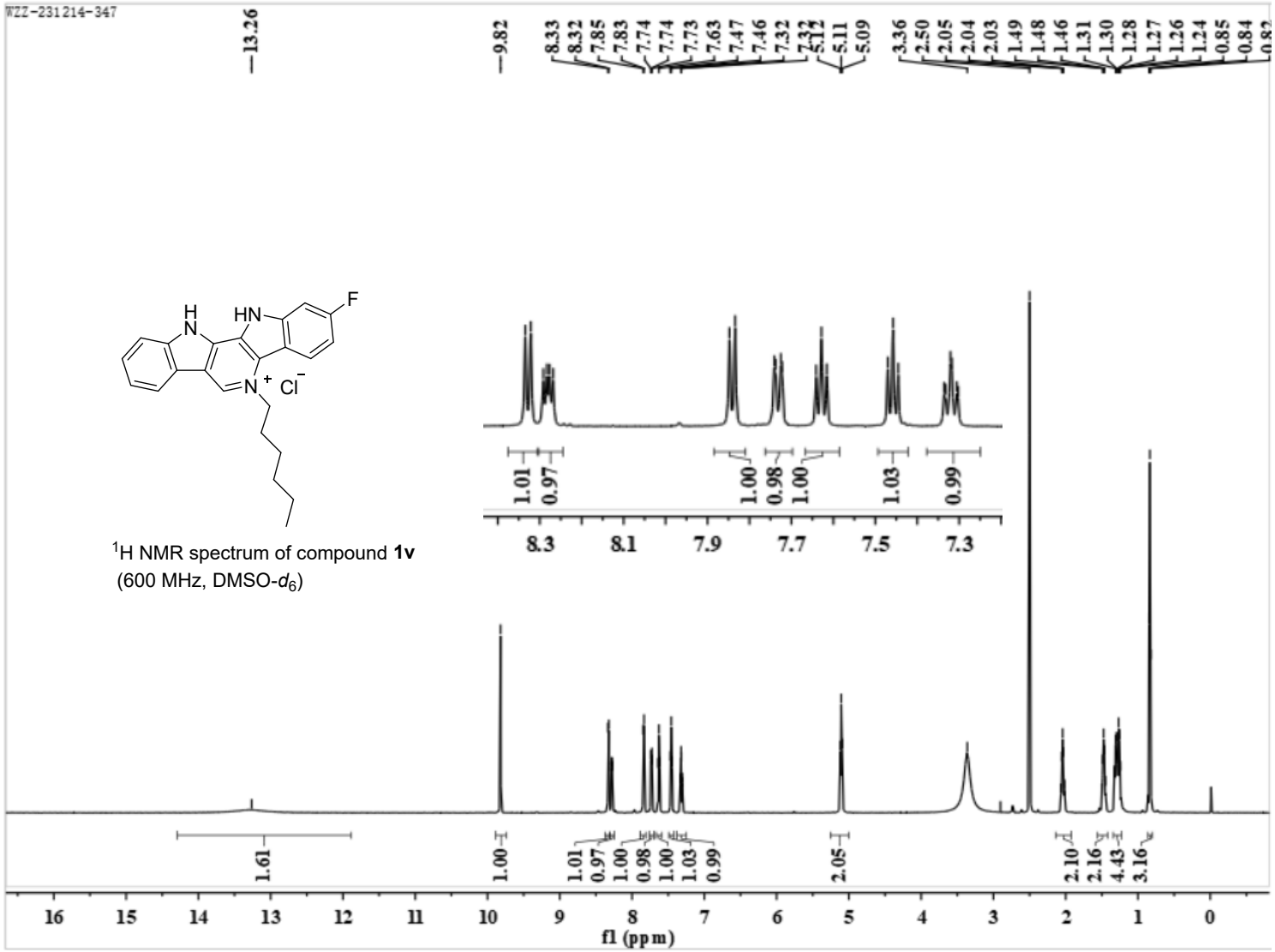
^{13}C NMR spectrum of compound **1r**
(150 MHz, $CDCl_3$+CF_3CO_2D)



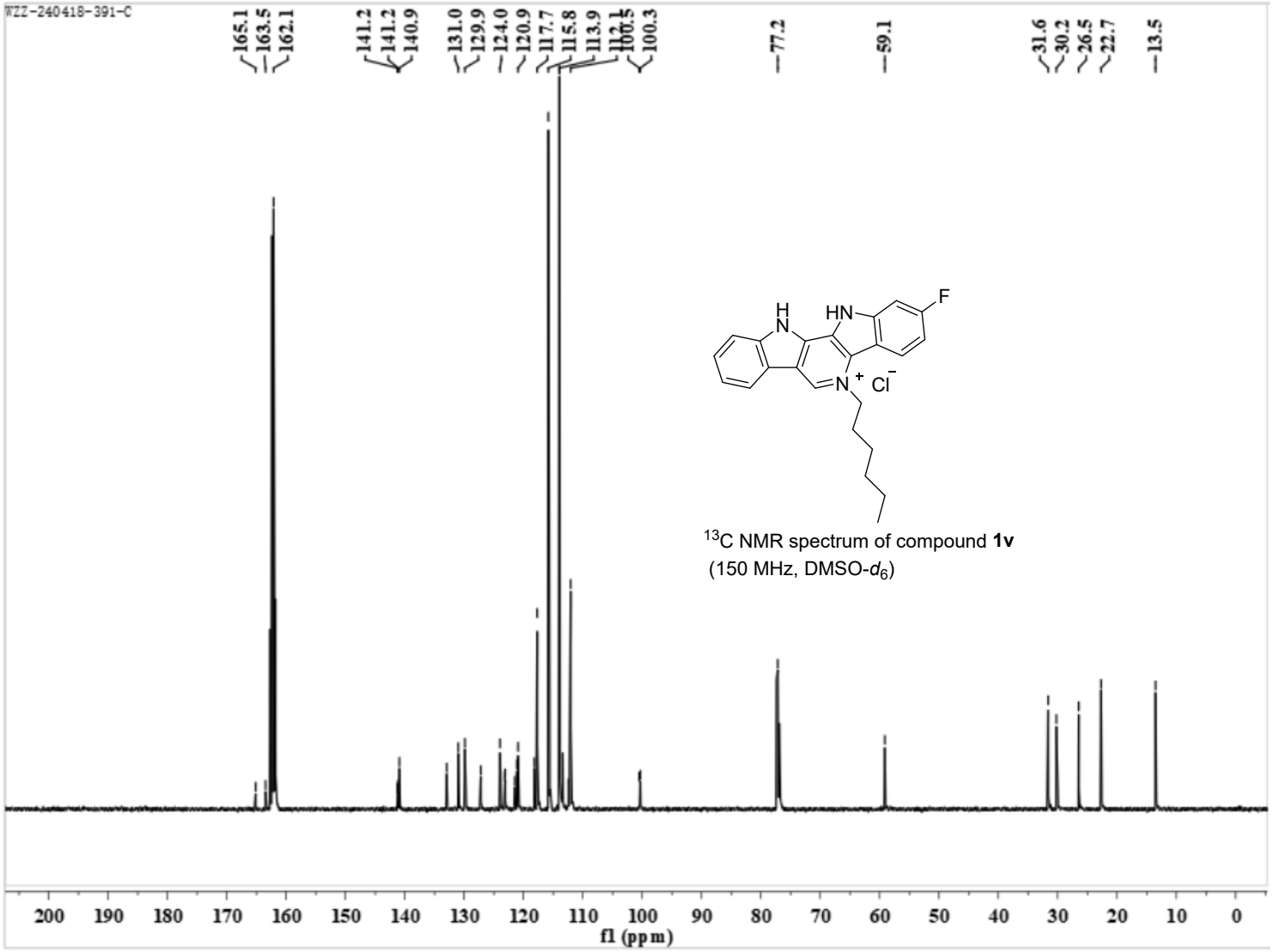
^{1}H NMR spectrum of compound **1s**
(600 MHz, DMSO-d_6)



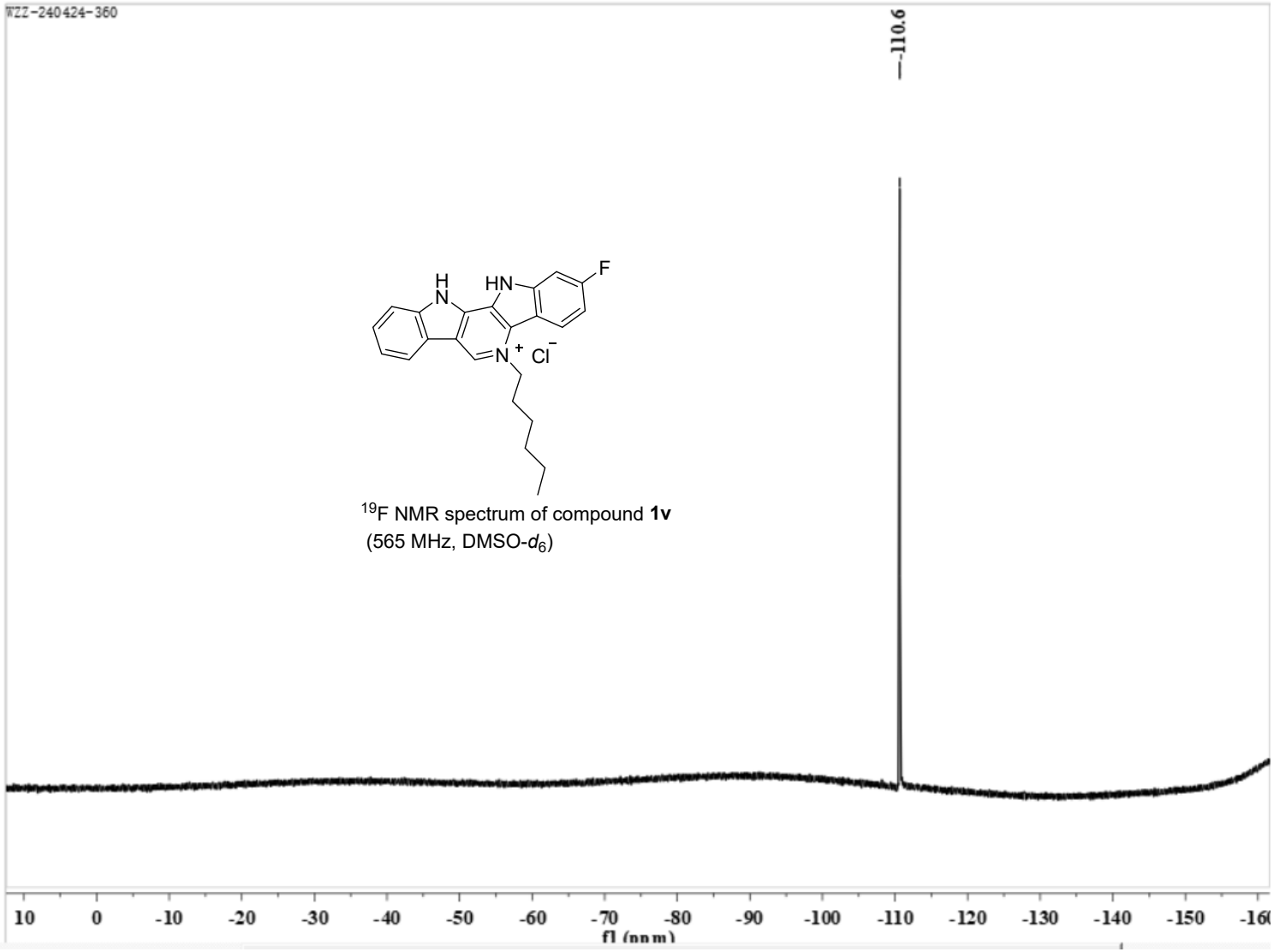
^{13}C NMR spectrum of compound **1s**
(150 MHz, $CDCl_3$+CF_3CO_2D)



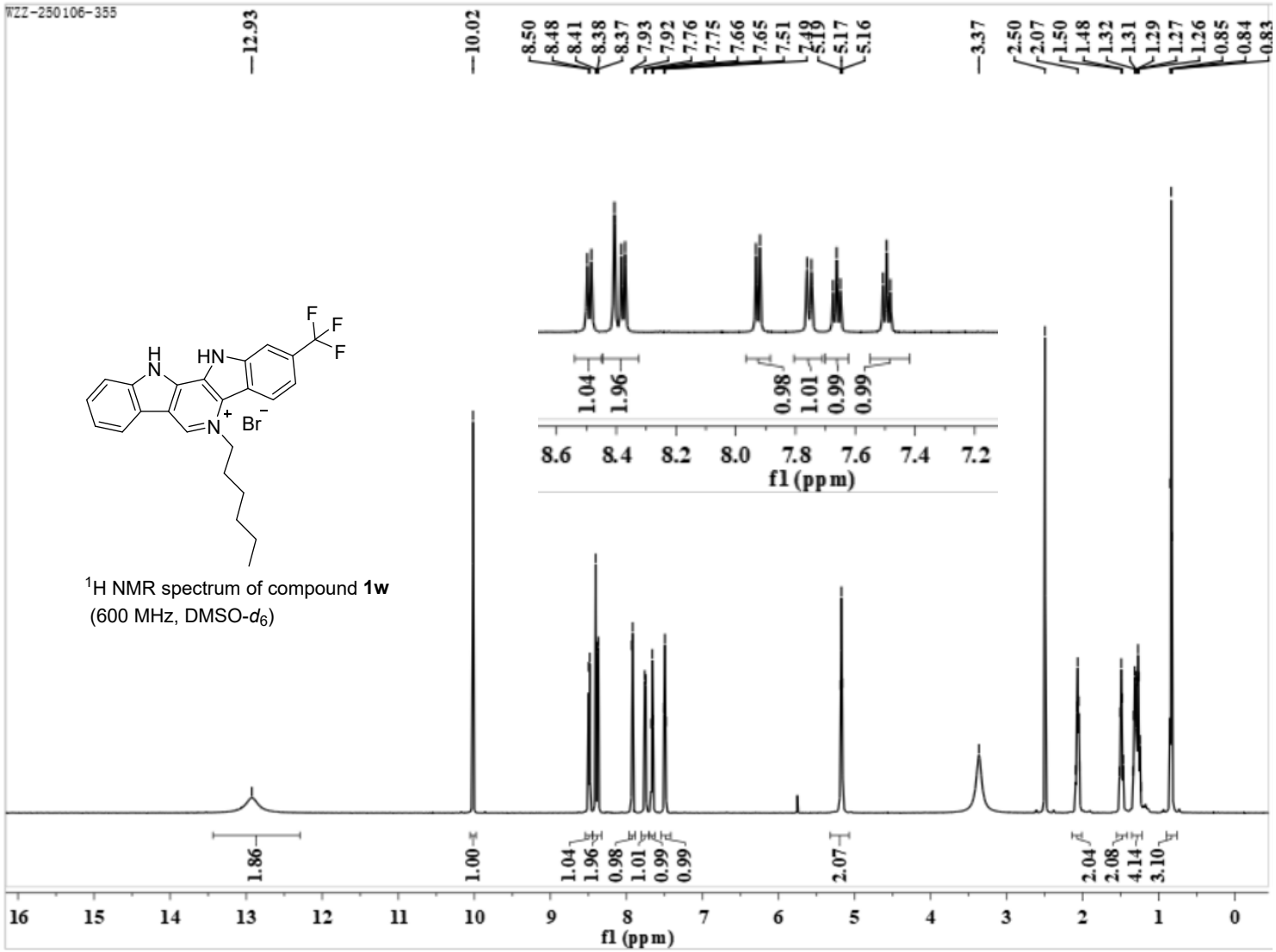
^{1}H NMR spectrum of compound **1v**
(600 MHz, DMSO-d_6)



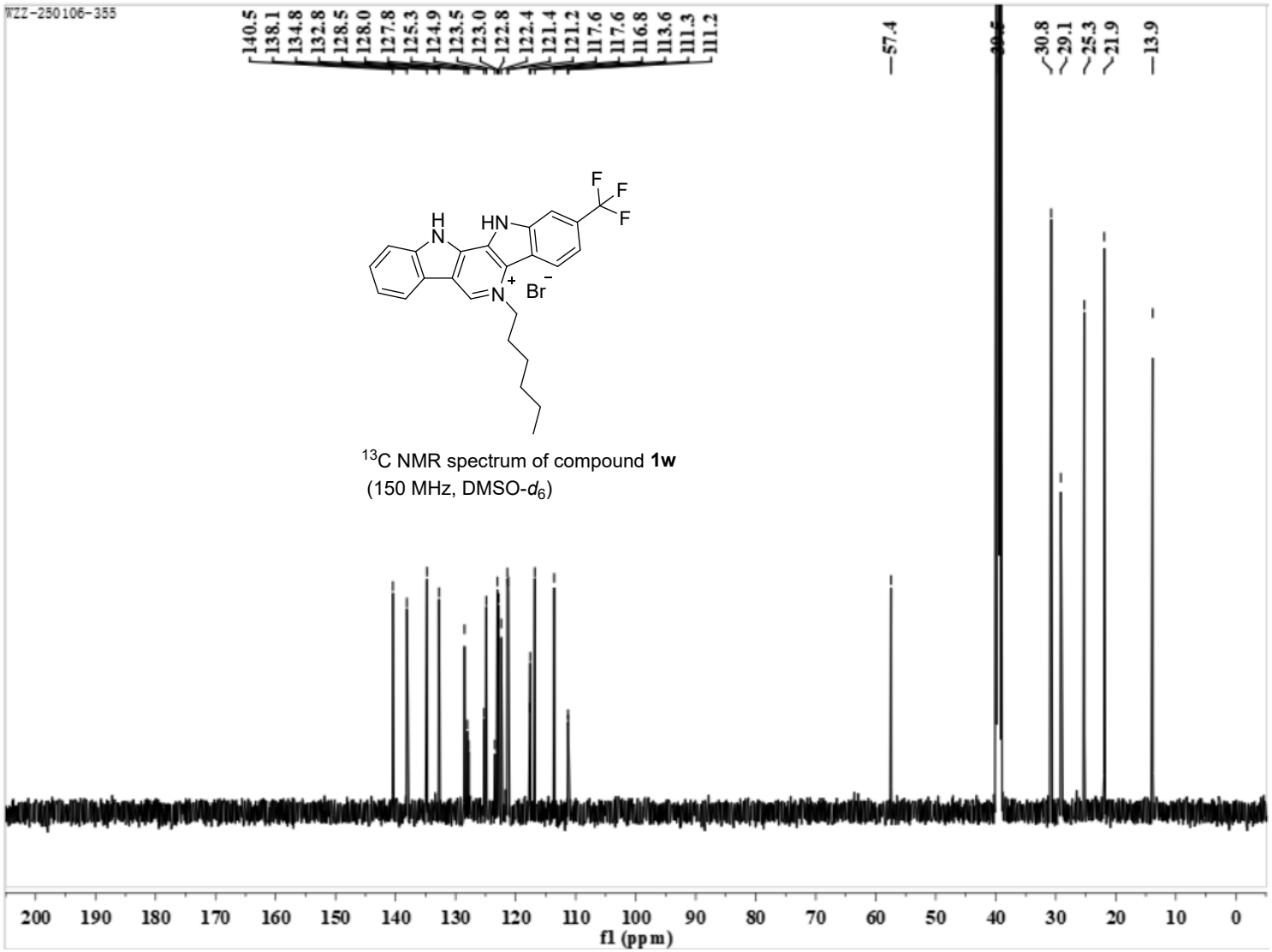
^{13}C NMR spectrum of compound **1v**
(150 MHz, DMSO-d_6)



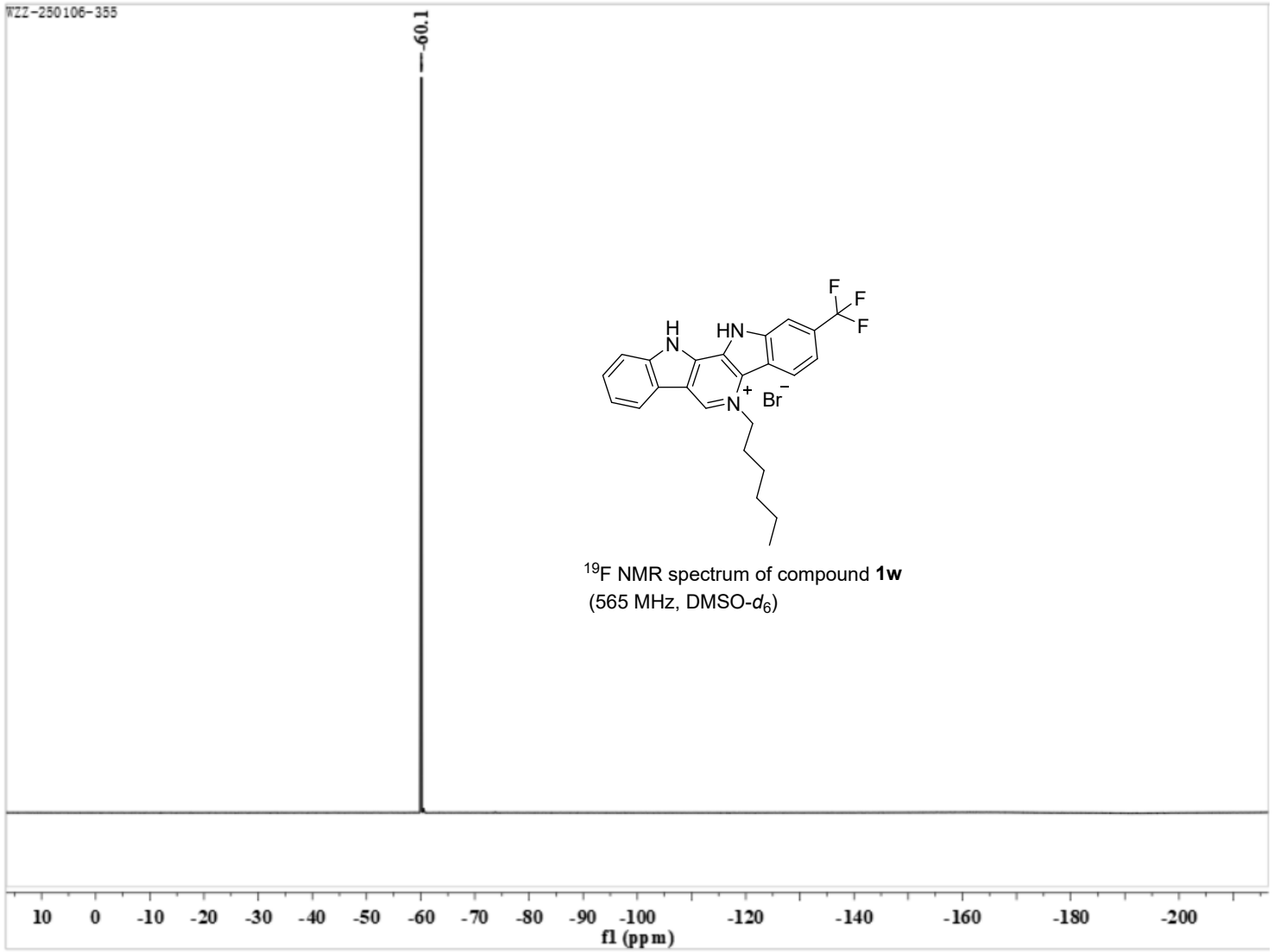
^{19}F NMR spectrum of compound **1v**
(565 MHz, DMSO-d_6)



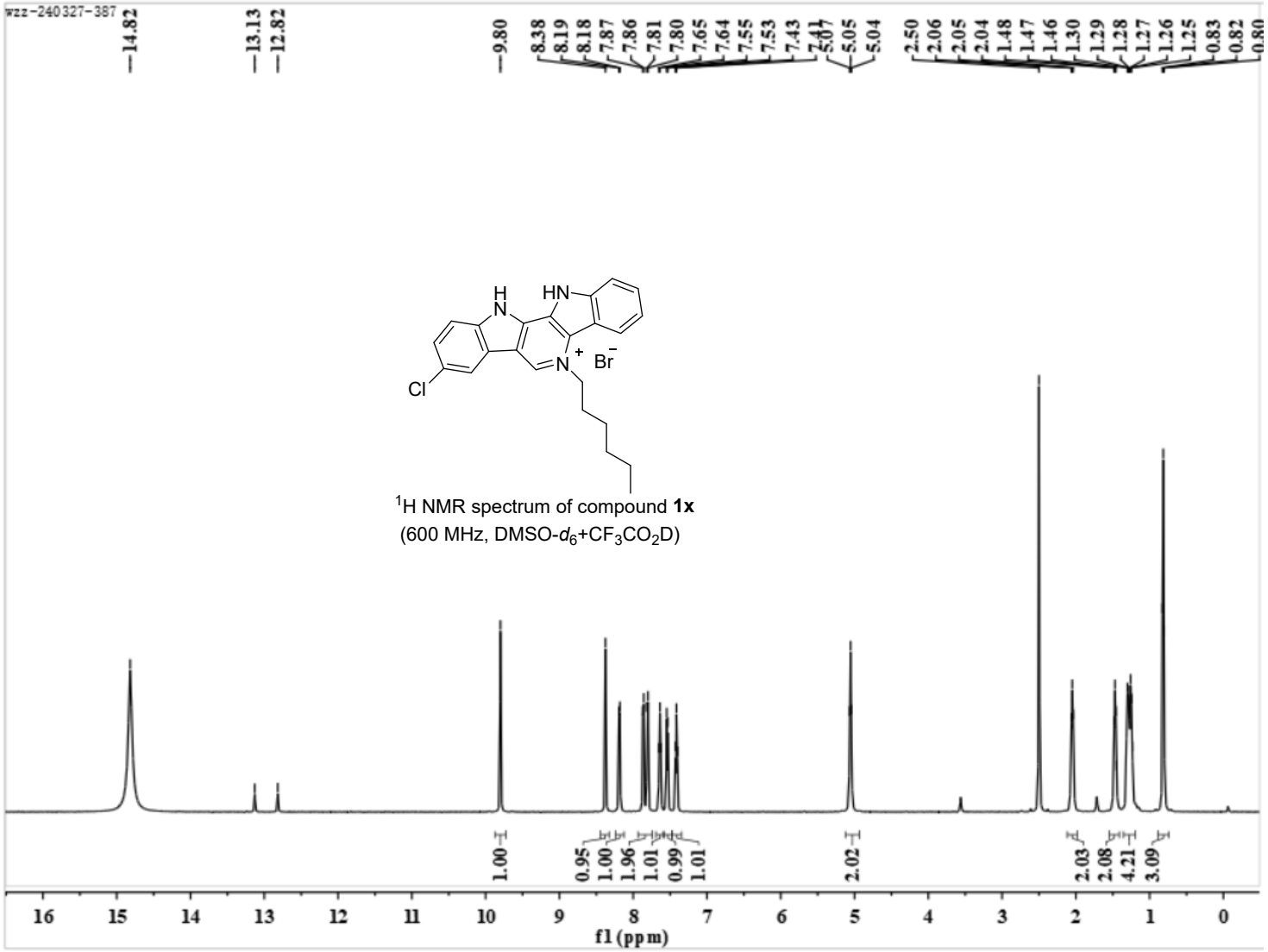
^{1}H NMR spectrum of compound **1w**
(600 MHz, DMSO-d_6)



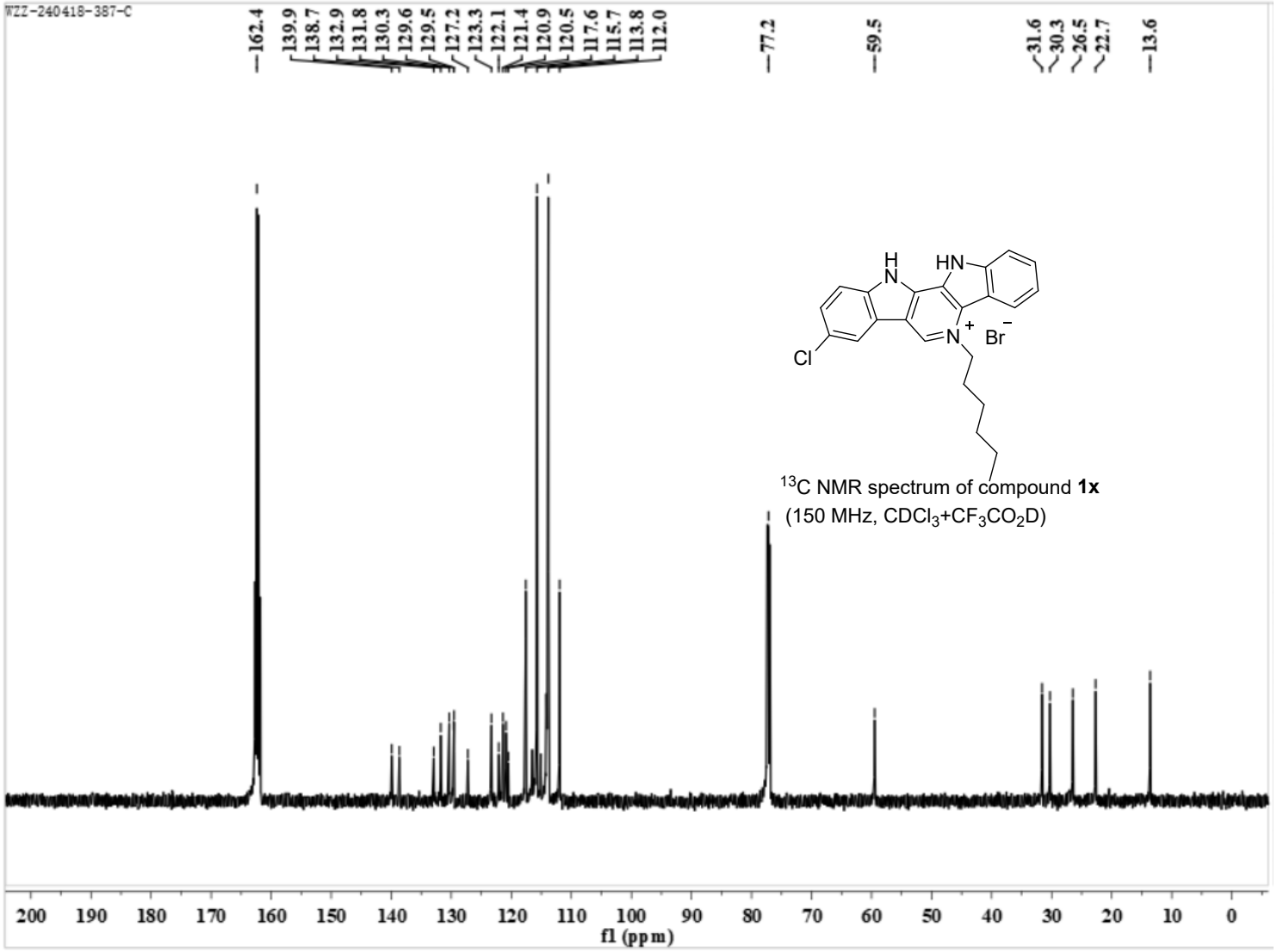
^{13}C NMR spectrum of compound **1w**
(150 MHz, DMSO-d_6)



^{19}F NMR spectrum of compound **1w**
(565 MHz, DMSO-d_6)



^{1}H NMR spectrum of compound **1x**
(600 MHz, DMSO-d_6+CF_3CO_2D)



^{13}C NMR spectrum of compound **1x**
(150 MHz, $CDCl_3$+CF_3CO_2D)