Redox Neutral [4+2] Benzannulation of Dienals and Tertiary Enaminones Toward Benzaldehyde Synthesis

Lu Yang,[a] Li Wei,[a] Jie-Ping Wan[a,*]

[a]College of Chemistry and Chemical Engineering, Jiangxi Normal University, Nanchang 330022, P.R. China

Email: wanjieping@jxnu.edu.cn

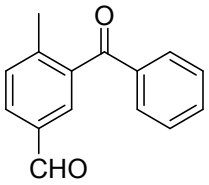
Contents

General experimental information

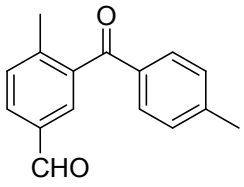
All experiments are performed under air atmosphere, and the reactions are monitored by TLC (GF_{254} silica gel). Enaminones **1**[1] are synthesized following literature procedures, all other chemicals are obtained from commercial sources and used directly without further treatment. Solvents have been treated following standard processes prior to used. The ^{1}H and ^{13}C NMR spectra are recorded on a 400 MHz apparatus by employing $CDCl_3$ as solvent. The chemical shifts are reported in ppm with TMS as internal standard. HRMS data are tested under ESI model in a mass spectrometer equipped with TOF analyzer. Melting points are acquired in X-4A apparatus without correcting temperature.

General procedure for the synthesis of benzaldehydes 3

To a 25 mL round bottom flask equipped with condenser was added enaminone **1** (0.2 mmol), dienal **2** (0.2 mmol), AcOH (1.0 mL) and EtOH(1.0 mL). Then the mixture was stirred at 80 ^{o}C for 12 h. Upon completion, water (10 mL) was poured into the vessel, and K_2CO_3 was added to the vessel to neutralize the mixture until no bubble occurred. Subsequently, the resulting suspension was extracted with ethyl acetate (3×10 mL). The combined organic phase was dried over anhydrous Na_2SO_4 and filtrated. The solution was evaporated under reduced pressure to remove the solvent. Purification of the residue by flash column chromatography using mixed ethyl acetate (EA) and petroleum ether (PET) as eluent (V_{EA} : V_{PET} = 1:10) afforded analytically pure product.

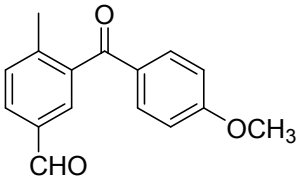


3-Benzoyl-4-methylbenzaldehyde (3a). Yield: 32 mg (73 %); yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.99 (s, 1H), 7.92 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.85-7.77 (m, 3H), 7.63 (d, *J* = 7.2 Hz, 1H), 7.53-7.45 (m, 3H), 2.43 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.3, 191.2, 144.1, 139.5, 137.0, 133.9, 133.7, 131.9, 130.9, 130.1, 129.6, 128.7, 20.4; ESI-HRMS: Calcd for $C_{15}H_{13}O_2$ $[M+H]^+$ 225.0910, found 225.0907.

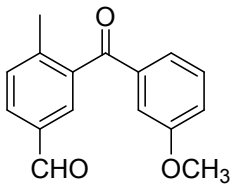


4-Methyl-3-(4-methylbenzoyl)benzaldehyde (3b). Yield: 35 mg (73 %); yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.98 (s, 1 H), 7.94-7.86 (m, 1H), 7.83-7.77 (m, 1H), 7.69 (d, *J* = 8.0 Hz, 2H), 7.47 (d, *J* = 8.0 Hz, 1H), 7.28 (d, *J* = 8.0 Hz, 2H), 2.42 (d, *J* = 13.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.0, 191.3, 144.8, 143.9,

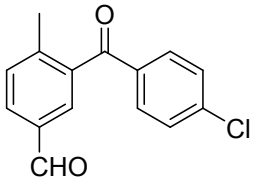
139.8, 134.5, 133.8, 131.8, 130.7, 130.3, 129.5, 129.5, 21.8, 20.4; ESI-HRMS: Calcd for $C_{16}H_{15}O_2$ $[M+H]^+$ 239.1067, found 239.1063.



3-(4-Methoxybenzoyl)-4-methylbenzaldehyde (3c). Yield: 39 mg (77 %); yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) :δ 9.99 (s, 1H), 7.90 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.81-7.78 (m, 2H), 7.77 (s, 1H), 7.47 (d, *J* = 8.0 Hz, 1H), 6.95 (d, *J* = 9.2 Hz, 2H), 3.89 (s, 3H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.9, 191.3, 164.1, 143.6, 140.0, 133.9, 132.5, 131.7, 130.5, 129.8, 129.2, 114.0, 55.6, 20.2; ESI-HRMS: Calcd for $C_{16}H_{15}O_3$ $[M+H]^+$ 255.1016, found 255.1013.

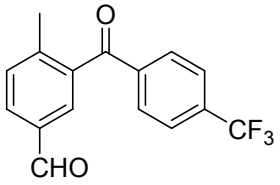


3-(3-Methoxybenzoyl)-4-methylbenzaldehyde (3d). Yield: 36 mg (71 %); yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.99 (s, 1 H), 7.91 (d, *J* = 8.0 Hz, 1H), 7.82 (s, 1 H), 7.48 (d, *J* = 8.0 Hz, 1H), 7.43-7.34 (m, 2H), 7.25 (d, *J* = 7.6 Hz, 1H), 7.17 (d, *J* = 5.6 Hz, 1H), 3.86 (s, 3H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.1, 191.2, 160.0, 144.0, 139.5, 138.3, 133.8, 131.8, 130.9, 129.7, 129.6, 123.2, 120.3, 113.8, 55.5, 20.4； ESI-HRMS: Calcd for $C_{16}H_{15}O_3$ $[M+H]^+$ 255.1016, found 255.1013.

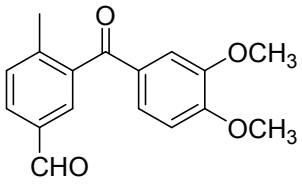


3-(4-Chlorobenzoyl)-4-methylbenzaldehyde (3e). Yield: 36 mg (70 %); yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.99 (s, 1H), 7.93 (d, *J* = 6.8 Hz, 1H), 7.80 (s, 1H), 7.74 (d, *J* = 8.4 Hz, 2H), 7.52-7.44 (m, 3H), 2.42 (s, 3H); ^{13}C NMR (100 MHz,$CDCl_3$): δ 196.0, 191.0, 144.1, 140.3, 138.9, 135.3, 133.9, 132.0, 131.4, 131.2,

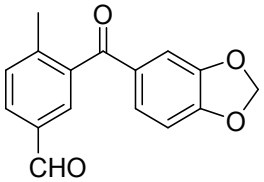
129.4, 129.1, 20.4; ESI-HRMS: Calcd for $C_{16}H_{14}ClO_2$ $[M+CH_3]^+$ 273.0682, found 273.0675.



4-Methyl-3-(4-(trifluoromethyl)benzoyl)benzaldehyde (3f). Yield: 32 mg (67 %); yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.92 (s, 1 H), 7.88 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.83 (d, *J* = 8.0 Hz, 2H), 7.75 (d, *J* = 1.6 Hz, 1H), 7.68 (d, *J* = 8.4 Hz, 2H), 7.45 (d, *J* = 8.0 Hz, 1H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.1 , 190.9, 144.4, 139.9, 138.4, 135.0, 134.7, 134.0, 132.2, 131.6, 130.3, 129.7, 125.8 (q, *J* = 3.7 Hz), 20.6; ESI-HRMS: Calcd for $C_{17}H_{14}F_3O_2$ $[M+CH_3]^+$ 307.0946, found 307.0945.

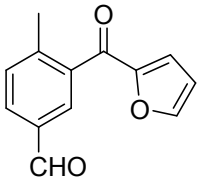


3-(3,4-Dimethoxybenzoyl)-4-methylbenzaldehyde (3g). Yield: 39 mg (69 %); yellow solid; m.p. 121-125^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.92 (s, 1H), 7.85-7.80 (m, 1H), 7.73 (s, 1H), 7.51 (d, *J* = 1.6 Hz, 1H), 7.39 (d, *J* = 8.0 Hz, 1H), 7.11 (dd, *J* = 8.0, 1.6 Hz, 1H), 6.77 (d, *J* = 8.4 Hz, 1H), 3.88 (s, 6H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.9, 191.3, 154.0, 149.4, 143.6, 139.9, 133.8, 131.7, 130.6, 130.0, 129.1, 126.2, 111.0, 110.0, 56.2, 56.1, 20.2; ESI-HRMS: Calcd for $C_{17}H_{17}O_4$ $[M+H]^+$ 285.1121, found 285.1118.

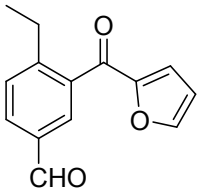


3-(Benzo[d][1,3]dioxole-5-carbonyl)-4-methylbenzaldehyde (3h). Yield: 38 mg (71 %); yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.91 (s, 1H), 7.85-7.77 (m, 1H), 7.71 (d, *J* = 5.2 Hz, 1H), 7.42-7.34 (m, 1H), 7.30 (d, *J* = 5.2 Hz, 1H), 7.21-7.14 (m, 1H), 6.79-6.71 (m, 1H), 6.01 (d, *J* = 5.6 Hz, 2H), 2.32 (d, *J* = 5.2 Hz, 3H); ^{13}C NMR

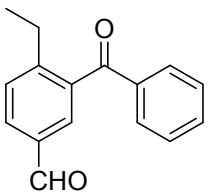
(100 MHz, $CDCl_3$): δ 195.5, 191.2, 165.8, 152.6, 148.4, 143.6, 139.9, 133.4, 131.8, 130.7, 129.0, 127.5, 109.0, 108.0, 102.1, 20.2; ESI-HRMS: Calcd for $C_{16}H_{13}O_4$ $[M+H]^+$ 269.0808, found 269.0806.



3-(Furan-2-carbonyl)-4-methylbenzaldehyde (3i). Yield: 33 mg (77 %); yellow solid; m.p. 113-119°C; ^1H NMR (400 MHz, $CDCl_3$): δ 9.93 (s, 1H), 7.91 (d, *J* = 1.2 Hz, 1H), 7.83 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.66 – 7.63 (m, 1H), 7.40 (d, *J* = 8.0 Hz, 1H), 6.99 (d, *J* = 3.6 Hz, 1H), 6.52 (dd, *J* = 3.6, 1.6 Hz, 1H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.1, 183.7, 152.3, 148.1, 144.6, 138.2, 133.8, 132.0, 131.5, 129.4, 121.6, 112.6, 20.2; ESI-HRMS: Calcd for $C_{13}H_{11}O_3$ $[M+H]^+$ 215.0703, found 215.0701.

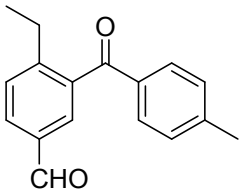


4-Ethyl-3-(furan-2-carbonyl)benzaldehyde (3j). Yield: 26 mg (63 %); yellow liquid; ^1H NMR (400 MHz, $CDCl_3$): δ 10.02 (s, 1H), 7.96 (m, 2H), 7.74-7.71 (m, 1 H), 7.53 (d, *J* = 8.4 Hz, 1H), 7.05 (d, *J* = 3.6 Hz, 1H), 6.63-6.57 (m, 1H), 2.82 (q, *J* = 7.6 Hz, 2H), 1.23 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.1, 183.8, 152.4, 150.6, 148.1, 138.0, 133.7, 131.6, 130.4, 129.3, 121.6, 112.6, 26.6, 15.6; ESI-HRMS: Calcd for $C_{14}H_{13}O_3$ $[M+H]^+$ 229.0859, found 229.0857.

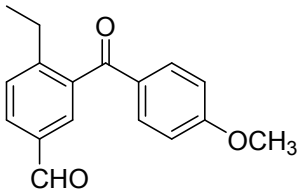


3-Benzoyl-4-ethylbenzaldehyde (3k). Yield: 33 mg (69 %); yellow liquid; ^1H NMR (400 MHz, $CDCl_3$): δ 9.99 (s, 1H), 7.95 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.83-7.77 (m, 3H), 7.62 (d, *J* = 7.6 Hz, 1H), 7.53 (d, *J* = 8.4 Hz, 1H), 7.51-7.45 (m, 2H), 2.75 (q, *J* = 7.6

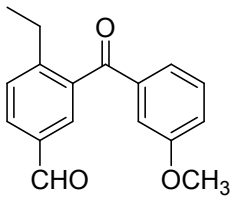
Hz, 2H), 1.20 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.3, 191.2, 150.2, 139.3, 137.1, 133.8, 131.0, 130.3, 130.1, 129.5, 128.7, 26.8, 15.5; ESI-HRMS: Calcd for $C_{16}H_{15}O_2$ $[M+H]^+$ 239.1067, found 239.1064.



4-Ethyl-3-(4-methylbenzoyl)benzaldehyde (3l). Yield: 37 mg (73 %); yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.98 (s, 1 H), 7.94 (dd, J = 8.0, 1.6 Hz, 1H), 7.80-7.66 (m, 3H), 7.52 (d, J = 8.0 Hz, 1H), 7.28 (d, J = 8.0 Hz, 2H), 2.74 (q, J = 7.6 Hz, 2H), 2.44 (s, 3H), 1.19 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.0, 191.2, 150, 144.8, 139.6, 134.6, 133.7, 130.8, 130.3, 130.2, 129.4, 129.4, 26.8, 21.8, 15.5; ESI-HRMS: Calcd for $C_{17}H_{17}O_2$ $[M+H]^+$ 253.1223, found 253.1220.

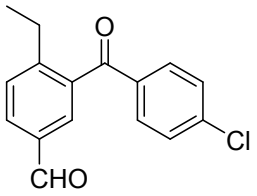


4-Ethyl-3-(4-methoxybenzoyl)benzaldehyde (3m). Yield: 35 mg (65 %); yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.99 (s, 1H), 7.93 (dd, J = 8.0, 1.6 Hz, 1H), 7.81-7.75 (m, 3H), 7.51 (d, J = 8.0 Hz, 1H), 6.95 (d, J = 8.8 Hz, 2H), 3.89 (s, 3H), 2.73 (q, J = 7.6 Hz, 2H), 1.19 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.0, 191.4, 164.2, 149.8, 139.8, 133.7, 132.6, 130.7, 130.2, 130.0, 129.1, 114.0, 55.6, 26.8, 15.5; ESI-HRMS: Calcd for $C_{17}H_{17}O_3$ $[M+H]^+$ 269.1172, found 269.1170.

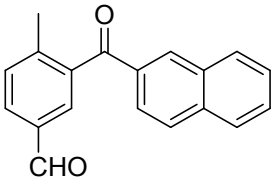


4-Ethyl-3-(3-methoxybenzoyl)benzaldehyde (3n). Yield: 38 mg (71 %); yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.99 (s, 1H), 7.95 (d, J = 8.0 Hz, 1H), 7.79 (s, 1H), 7.53 (d, J = 8.0 Hz, 1H), 7.43 (s, 1H), 7.36 (d, J = 8.0 Hz, 1H), 7.26 (d, J = 7.6 Hz, 1H), 7.17 (dd, J = 8.0, 2.4 Hz, 1H), 3.86 (s, 3H), 2.75 (q, J = 7.6 Hz, 2H), 1.21 (t,

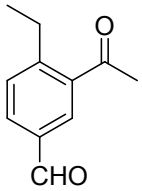
J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.1, 191.2, 159.9, 150.1, 139.3, 138.4, 133.7, 131.0, 130.3, 129.6, 129.4, 123.3, 120.3, 113.8, 55.5, 26.8, 15.5; ESI-HRMS: Calcd for $C_{17}H_{17}O_3$ $[M+H]^+$ 269.1172, found 269.1170.



3-(4-Chlorobenzoyl)-4-ethylbenzaldehyde (3o). Yield: 34 mg (62 %); yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.99 (s, 1H), 7.96 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.77-7.74 (m, 2H), 7.73 (s, 1H), 7.54 (d, *J* = 8.0 Hz, 1H), 7.47 (s, 2H), 2.74 (q, *J* = 7.6 Hz, 2H), 1.20 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.1, 191.2, 150.1, 139.8, 138.5, 135.4, 133.8, 131.5, 131.3, 130.5, 129.2, 129.1, 26.8, 15.5; ESI-HRMS: Calcd for $C_{17}H_{16}ClO_2$ $[M+CH_3]^+$ 287.0839, found 287.0830.

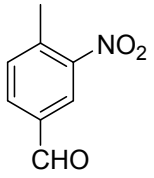


3-(2-Naphthoyl)-4-methylbenzaldehyde (3p). Yield: 41 mg (75 %); yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.99 (s, 1H), 8.15 (s, 1H), 8.00 (d, *J* = 2.0 Hz, 1H), 7.96-7.94 (m, 1H), 7.94-7.92 (m, 1H), 7.91-7.85 (m, 3H), 7.62 (d, *J* = 7.0 Hz, 1H), 7.56-7.48 (m, 2H), 2.44 (s, 3H); ^{13}C NMR (100MHz, $CDCl_3$): δ 197.2, 191.2, 144.0, 139.8, 135.9, 134.4, 134.0, 132.7, 132.4, 131.9, 130.8, 129.7, 129.7, 129.0, 128.8, 127.9, 127.0, 124.8, 20.4; ESI-HRMS: Calcd for $C_{19}H_{15}O_2$ $[M+H]^+$ 275.1067, found 275.1064.

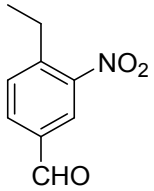


3-Acetyl-4-ethylbenzaldehyde(3q). Yield: 23 mg (66 %); yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.02 (s, 1H), 8.13 (d, *J* = 1.6 Hz, 1H), 7.91 (dd, *J* = 7.8, 2.0

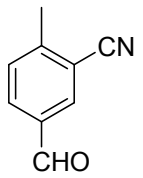
Hz, 1H), 7.47 (d, J = 8.0 Hz, 1H), 2.95 (d, J = 7.4 Hz, 3H), 2.65 (d, J = 2.8 Hz, 3H), 1.25 (t, J = 7.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.2, 191.1, 151.3, 134.1, 132.5, 131.3, 129.6, 29.9, 27.4, 15.6; ESI-HRMS: Calcd for $C_{12}H_{15}O_2$ $[M+CH_3]^+$ 191.1067, found 191.1069.



4-Methyl-3-nitrobenzaldehyde (3r). Yield: 19 mg (58 %); yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.05 (s, 1H), 8.46 (d, J = 1.6 Hz, 1H), 8.03 (dd, J = 7.8, 1.8 Hz, 1H), 7.55 (d, J = 8.0 Hz, 1H), 2.71 (s, 3H); ^{13}C NMR (100MHz, $CDCl_3$): δ 189.5, 140.0, 135.4, 133.8, 132.5, 126.0, 20.8; ESI-HRMS: Calcd for $C_9H_{10}NO_3$ $[M+CH_3]^+$ 180.0655, found 180.0656.



4-Ethyl-3-nitrobenzaldehyde (3s). Yield: 21 mg (59 %); yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.04 (s, 1H), 8.37 (d, J = 1.6 Hz, 1H), 8.05 (dd, J = 8.0, 1.6 Hz, 1H), 7.58 (d, J = 8.0 Hz, 1H), 3.01 (d, J = 7.6 Hz, 2H), 1.34 (d, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.5, 145.3, 135.2, 132.6, 132.2, 125.9, 26.5, 14.6; ESI-HRMS: Calcd for $C_{10}H_{12}NO_3$ $[M+CH_3]^+$ 194.0812, found 194.0813.

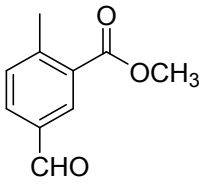


5-Formyl-2-methylbenzonitrile (3t). Yield: 15 mg (54 %); yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.99 (s, 1H), 8.11 (d, J = 1.6 Hz, 1H), 8.00 (dd, J = 8.0, 1.6 Hz, 1H), 7.53 (d, J = 8.0 Hz, 1H), 2.66 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.7,

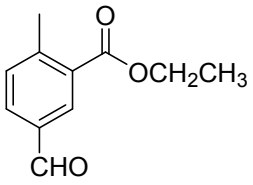
148.5, 134.7, 133.9, 132.9, 131.2, 116.8, 114.0, 21.0; ESI-HRMS: Calcd for $C_{10}H_{10}NO$ $[M+CH_3]^+$ 160.0757, found 160.0758.

General procedure for the synthesis of benzaldehydes 5

To a 25 mL round bottom flask equipped with condenser was added the dienal **2** (0.2 mmol), alkyl propiolate **4** (0.2 mmol), dimethylamine (0.2 mmol, 40% aqueous solution), AcOH (1.0 mL) and EtOH (1.0 mL). The mixture was heated at 80 °C for 12 h. Upon completion, water (10 mL) was poured into the vessel, and K_2CO_3 was added to the vessel to neutralize the mixture until no bubble occurred. Subsequently, the resulting suspension was extracted with ethyl acetate (3×10 mL). The combined organic phase was dried over anhydrous Na_2SO_4 and filtrated. The solution was evaporated under reduced pressure to remove the solvent. Purification of the residue by flash column chromatography using mixed ethyl acetate (EA) and petroleum ether (PET) as eluent (VEA : VPET = 1:10) afforded analytically pure product.

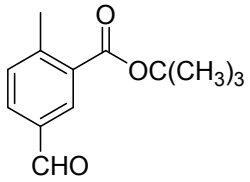


Methyl 5-formyl-2-methylbenzoate (5a). Yield: 25 mg (70 %); yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.01 (s, 1H), 8.42 (d, *J* = 1.2 Hz, 1H), 7.92 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.43 (d, *J* = 8.0 Hz, 1H), 3.94 (s, 3H), 2.70 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.1, 166.9, 147.4, 134.4, 132.7, 132.6, 131.9, 130.4, 52.2, 22.1; ESI-HRMS: Calcd for $C_{11}H_{13}O_3$ $[M+CH_3]^+$ 193.0865, found 193.0860.

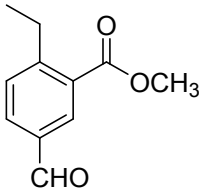


Ethyl 5-formyl-2-methylbenzoate (5b). Yield: 28 mg (73 %); yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.02 (s, 1H), 8.41 (d, *J* = 1.6 Hz, 1H), 7.91 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.42 (d, *J* = 8.0 Hz, 1H), 4.40 (q, *J* = 7.2 Hz, 2H), 2.70 (s, 3H), 1.43 (t, *J*

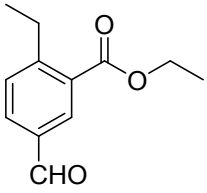
= 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.2, 166.5, 147.3, 147.2, 134.4, 132.6, 131.8, 130.8, 61.2, 22.1, 14.3; ESI-HRMS: Calcd for $C_{11}H_{13}O_3$ $[M+H]^+$ 193.0859, found 193.0860.



***t*-Butyl 5-formyl-2-methylbenzoate (5c)**. Yield: 27 mg (61 %); Yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.93 (s, 1H), 8.22 (s, 1H), 7.82- 7.79 (m, 1H), 7.33 (s, 1H), 2.59 (s, 3H), 1.55 (s, 9H); 13C NMR (100 MHz, $CDCl_3$): δ 191.3, 166.1, 146.5, 134.3, 133.9, 132.6, 132.6, 132.3, 131.3, 82.0, 28.2, 28.1, 22.1; ESI-HRMS: Calcd for $C_{14}H_{19}O_3$ $[M+CH_3]^+$ 235.1334, found 235.1326.



Methyl 2-ethyl-5-formylbenzoate (5d). Yield: 26 mg (68 %); yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.01 (s, 1 H), 8.37 (d, *J* = 1.6 Hz, 1H), 7.95 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.46 (d, *J* = 7.2 Hz, 1H), 3.94 (s, 3H), 3.07 (q, *J* = 7.6 Hz, 2H), 1.27 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.1, 167.0, 153.1, 134.3, 132.7, 132.0, 131.1, 130.2, 52.2, 27.8, 15.5; ESI-HRMS: Calcd for $C_{11}H_{13}O_3$ $[M+H]^+$ 193.0859, found 193.0860.

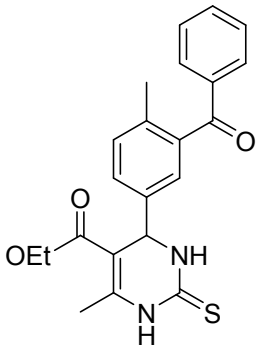


Ethyl 2-ethyl-5-formylbenzoate (5e). Yield: 28 mg (68 %); yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.02 (s, 1H), 8.35 (d, *J* = 1.6 Hz, 1H), 7.94 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.45 (d, *J* = 8.0 Hz, 1H), 4.41 (d, *J* = 7.2 Hz, 2H), 3.07 (d, *J* = 7.6 Hz, 2H), 1.43 (d, *J* = 14.3 Hz, 1H), 1.27 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.2,

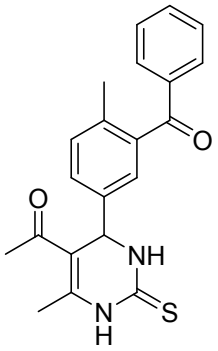
166.6, 152.9, 134.2, 132.6, 131.9, 131.1, 130.7, 61.3, 27.8, 15.5, 14.3; ESI-HRMS: Calcd for $C_{13}H_{17}O_3$ $[M+H]^+$ 207.1016, found 207.1017.

General procedure for Biginelli reaction using aldehyde 3a

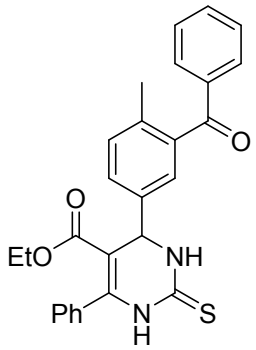
To a 25 mL round bottom flask equipped with condenser was located aldehyde **3a** (0.3 mmol), dicarbonyl compound **7** (0.5 mmol), thiourea **8** (0.5 mmol), TMSCl (0.6 mmol) and THF (3 mL) and DMF (1.0 mL). The resulting mixture was heated at 80 ^oC with stirring for 10 h. Upon completion, the reaction mixture was mixed with water (10 mL), and the resulting suspension was extracted with ethyl acetate (3 × 10 mL). The combined organic phase was dried over anhydrous Na_2SO4 and filtrated. The solution was evaporated under reduced pressure to remove the solvent. Purification of the residue by flash column chromatography using mixed ethyl acetate (EA) and petroleum ether (PET) as eluent (V_{EA} : V_{PET} = 1:3) afforded analytically pure product.



Ethyl 4-(3-benzoyl-4-methylphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (9a). Yield: 85 mg (72 %); white solid; m.p. 116-119^oC; ^1H NMR (400 MHz, $CDCl_3$): δ 8.15 (s, 1H), 7.80-7.74 (m, 2H), 7.71 (s, 1H), 7.59 (d, *J* = 7.4 Hz, 1H), 7.45 (d, *J* = 7.6 Hz, 2H), 7.33 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.30-7.20 (m, 2H), 5.37 (d, *J* = 3.2 Hz, 1H), 4.06 (d, *J* = 7.2 Hz, 2H), 2.31 (d, *J* = 20.8 Hz, 6H), 1.12 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.2, 174.3, 174.3, 165.1, 143.3, 139.7, 138.8, 137.3, 136.9, 133.4, 131.8, 128.6, 128.5, 127.0, 102.6, 60.5, 55.5, 19.7, 18.2, 14.1; ESI-HRMS: Calcd for $C_{22}H_{23}N_2O_3S$ $[M+H]^+$ 395.1424, found 395.1421.



1-(4-(3-Benzoyl-4-methylphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl)ethan-1-one (9b). Yield: 63 mg (58%); yellow solid; m.p. 218-214^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.39 (s, 1H), 8.11 (s, 1H), 7.75 (d, *J* = 8.0 Hz, 2H), 7.58 (d, *J* = 7.2 Hz, 1H), 7.45 (d, *J* = 7.6 Hz, 2H), 7.33-7.28 (m, 1H), 7.27-7.20 (m, 2H), 5.43 (d, *J* = 3.2 Hz, 1H), 2.30 (s, 3H), 2.26 (s, 3H), 2.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.1, 195.2, 174.0, 142.5, 139.1, 138.9, 137.2, 133.5, 132.0, 130.2, 128.6, 127.0, 111.5, 55.6, 30.5, 19.7, 19.3; ESI-HRMS: Calcd for $C_{21}H_{21}N_2O_2S$ $[M+H]^+$ 365.1318, found 365.1315.



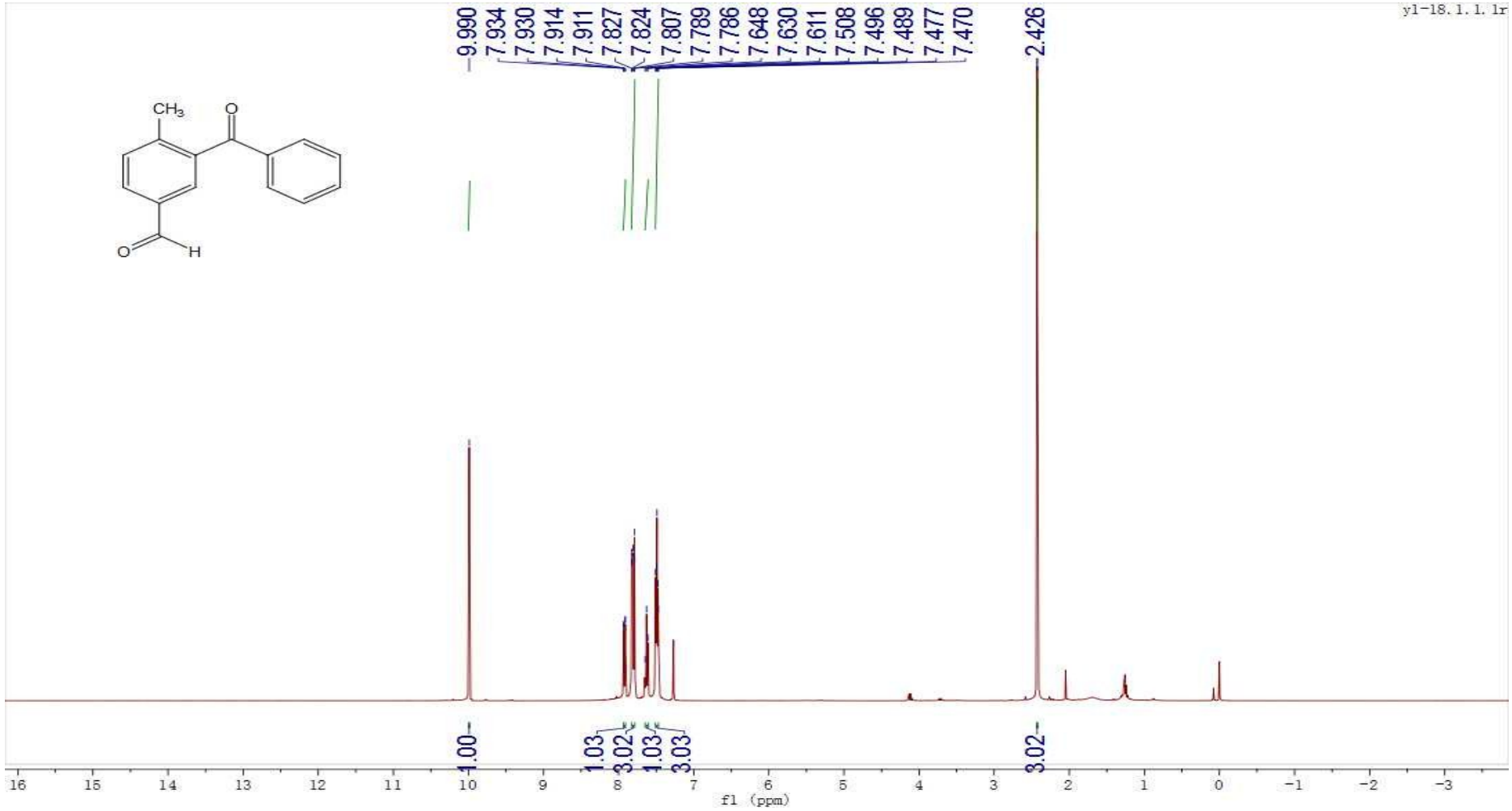
(4-(3-Benzoyl-4-methylphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl)(phenyl)methanone (9c). Yield: 90 mg (65 %); yellow solid; m.p. 213-216 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80-7.78 (m, 3 H), 7.59 (brs, 1H), 7.58 (d, 1H, *J* = 7.6 Hz), 7.47-7.36 (m, 7H), 7.31 (d, *J* = 8.0 Hz, 1H), 7.26-7.23 (m, 2H), 5.51 (d, *J* = 3.2 Hz, 1H), 3.84 (d, *J* = 7.2 Hz, 2H), 2.34 (s, 3 H), 0.80 (d, *J* = 7.0 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.0, 174.7, 164.6, 144.0, 139.3, 138.9, 137.5, 133.9, 133.3, 132.0, 130.2, 129.9, 128.64, 128.56, 128.4, 128.0, 127.2, 103.4, 60.5, 55.8, 19.8, 13.5; ESI-HRMS: Calcd for $C_{27}H_{25}N_2O_3S$ $[M+H]^+$ 457.1580, found 457.1577.

References

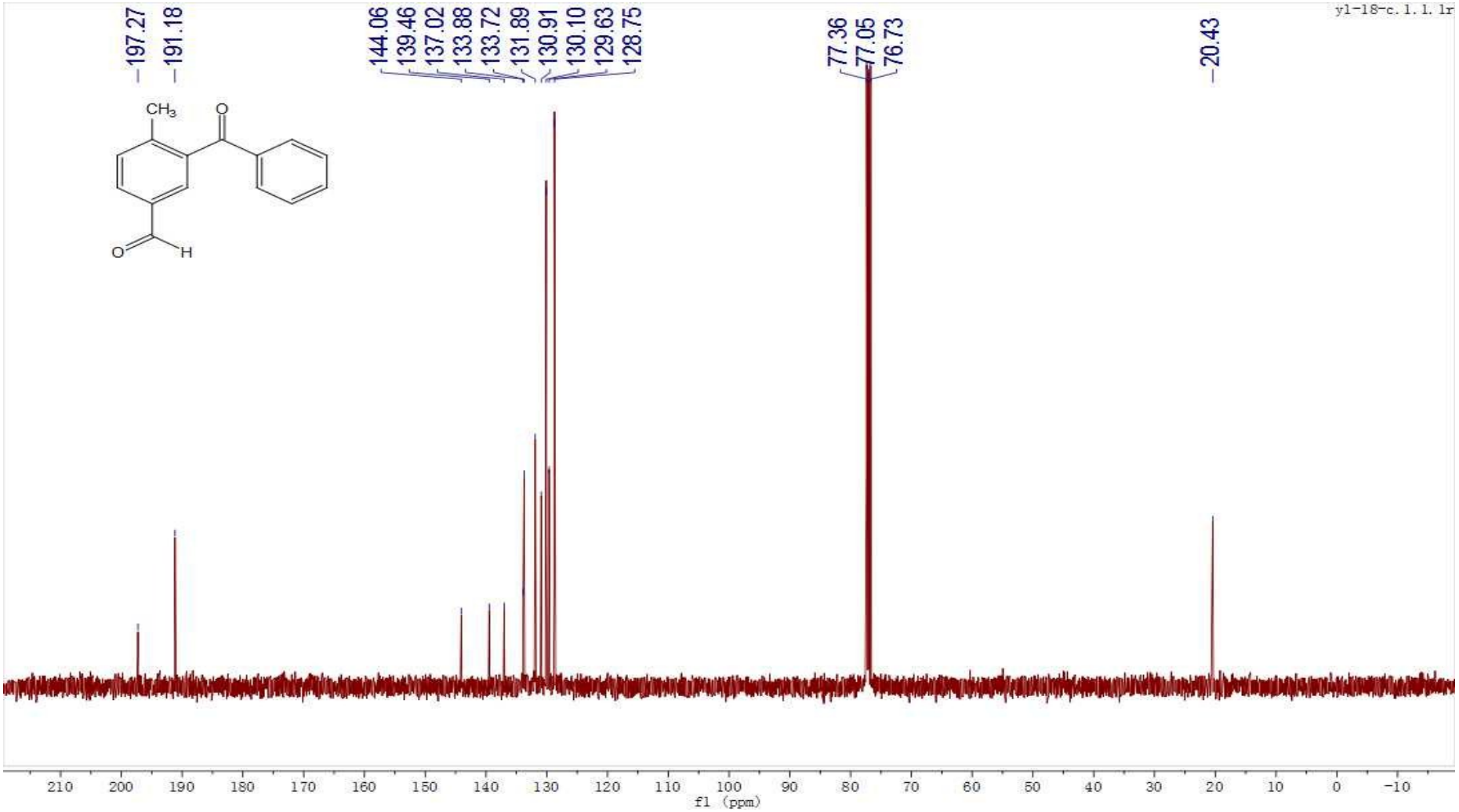
1. El-Taweel, F. M. A. A.; Elnagdi, M. H. *J. Heterocycl. Chem*. **2001**, *38*, 981.

^{1}H and ^{13}C NMR spectra of all products

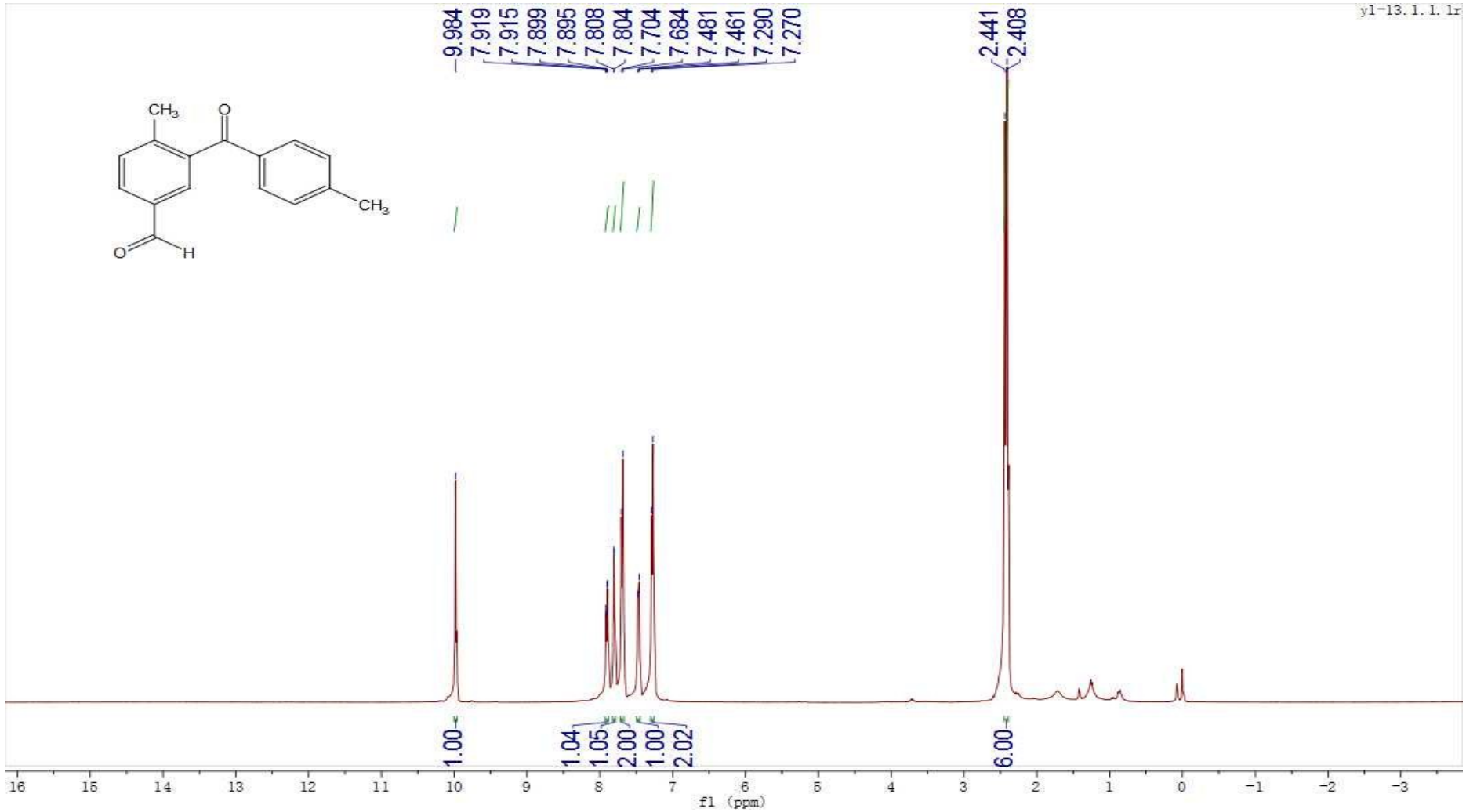
^{1}H NMR spectrum of **3a**



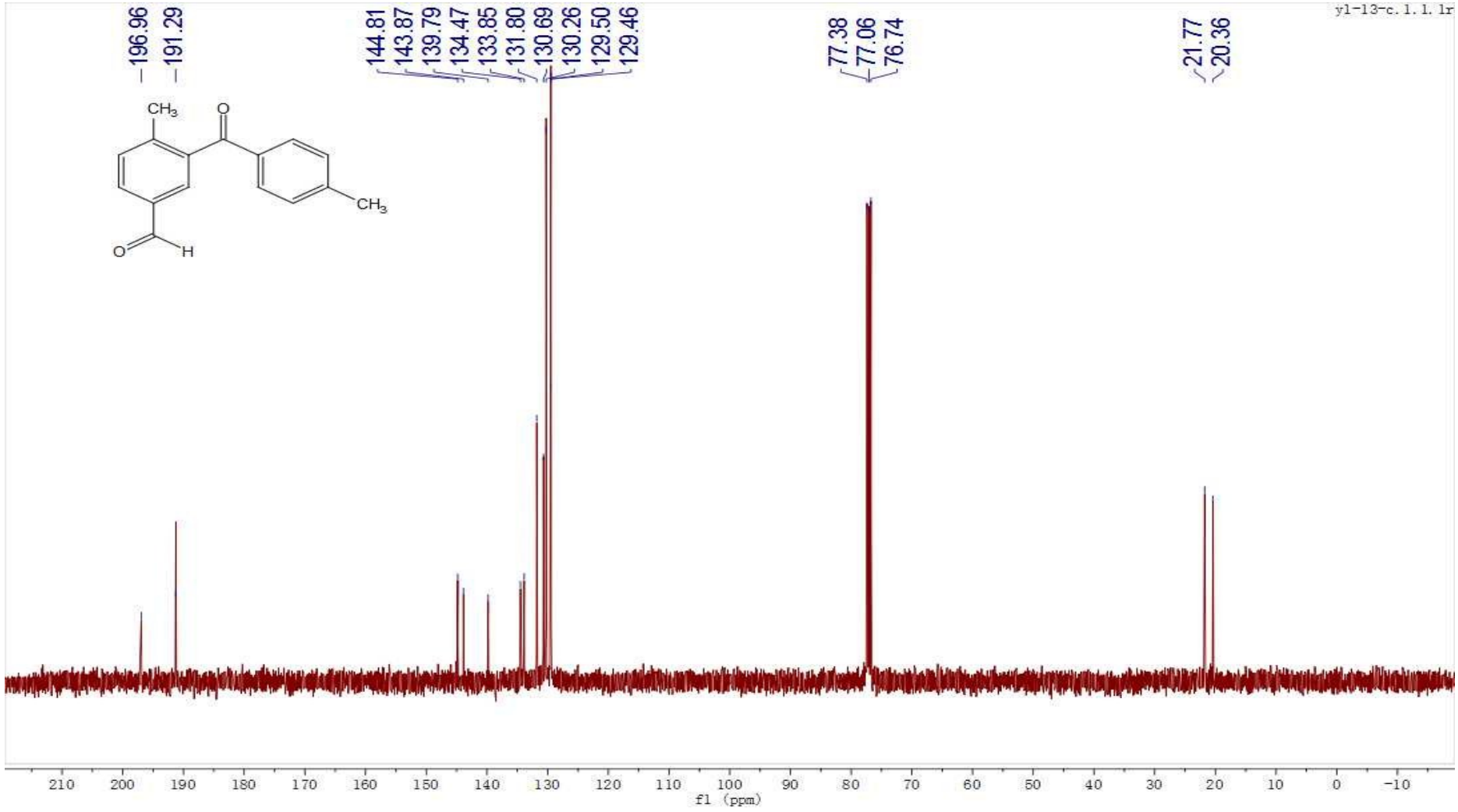
^{13}C NMR spectrum of **3a**



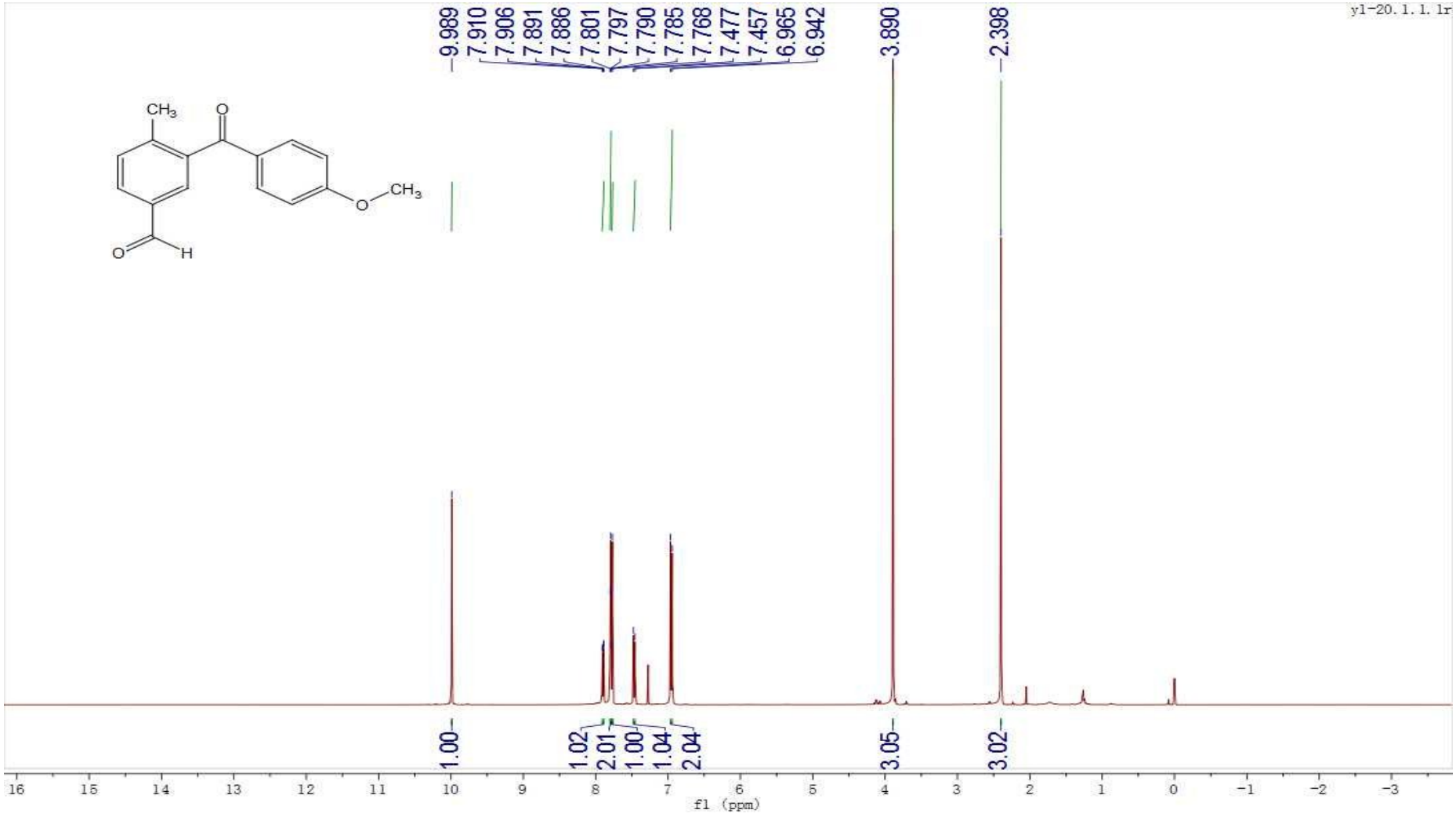
^{1}H NMR spectrum of **3b**



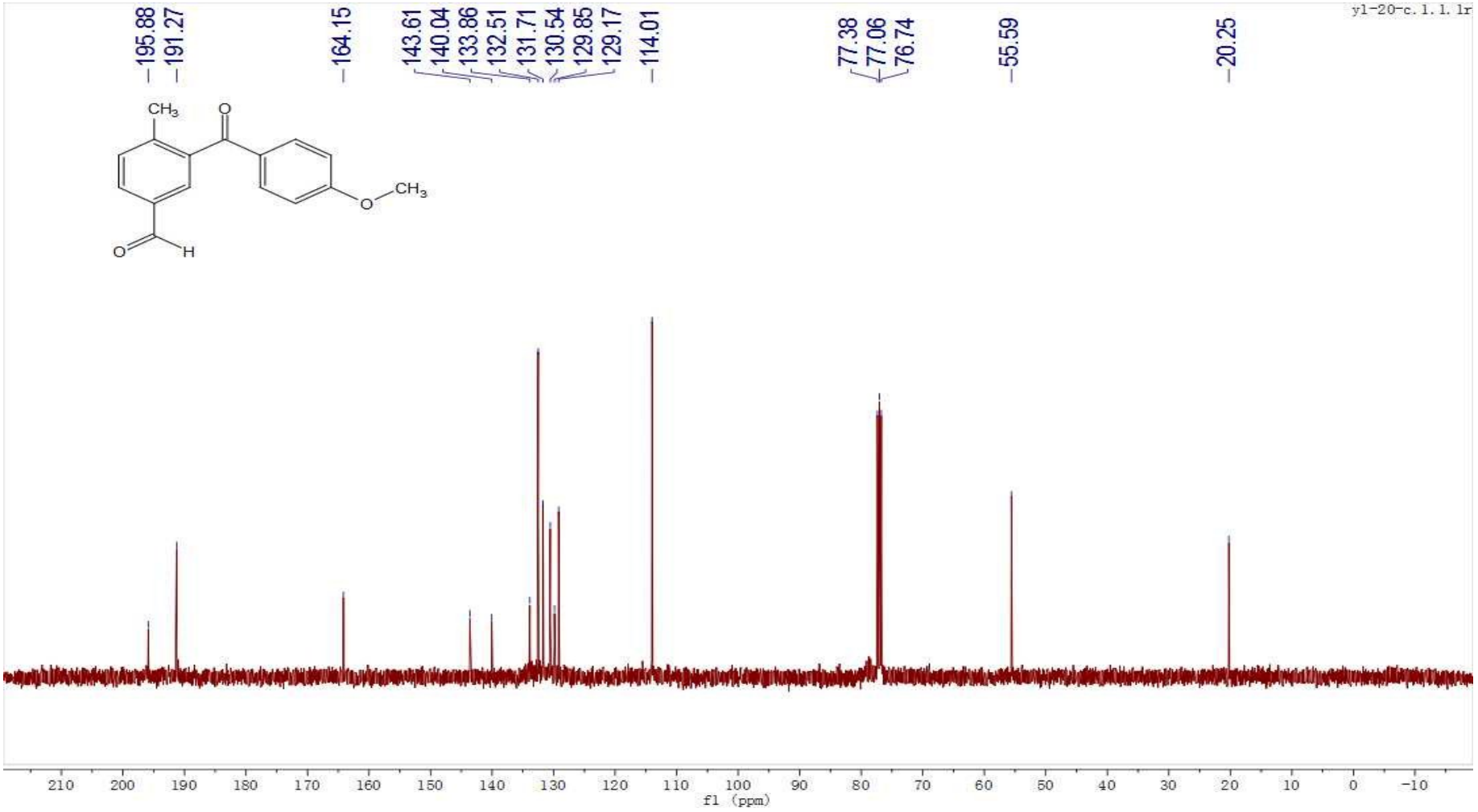
^{13}C NMR spectrum of **3b**



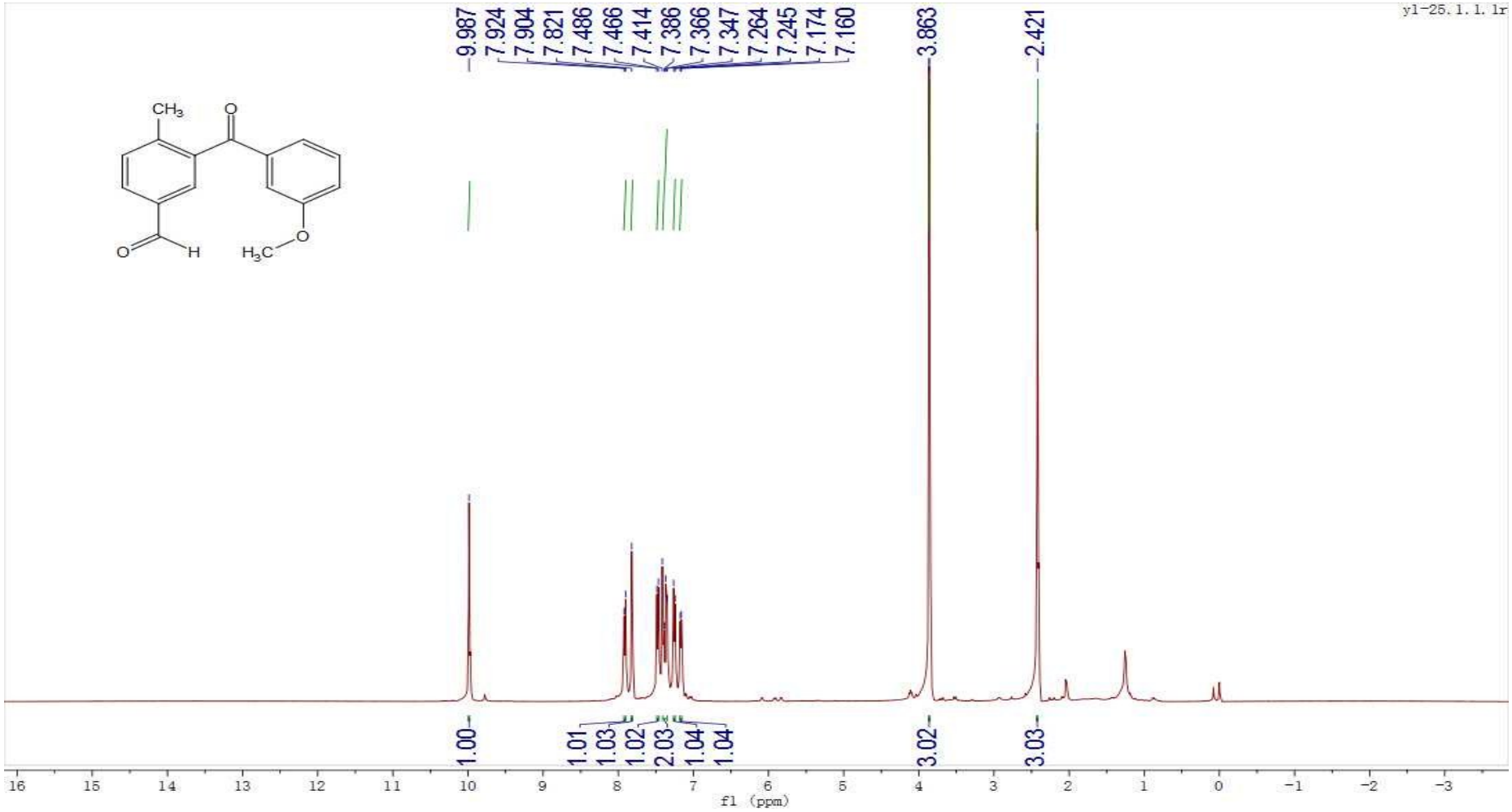
^{1}H NMR spectrum of **3c**



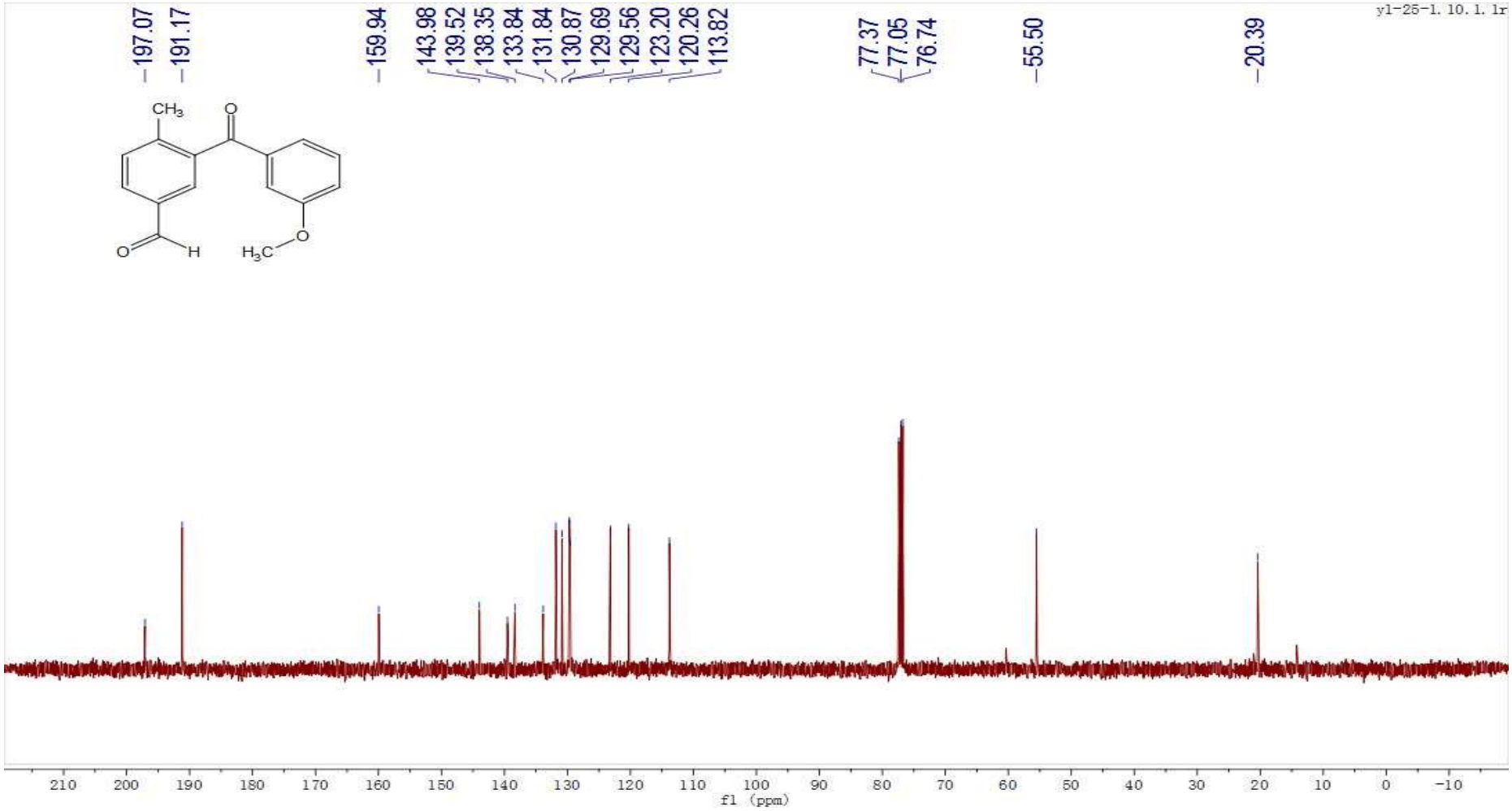
^{13}C NMR spectrum of **3c**



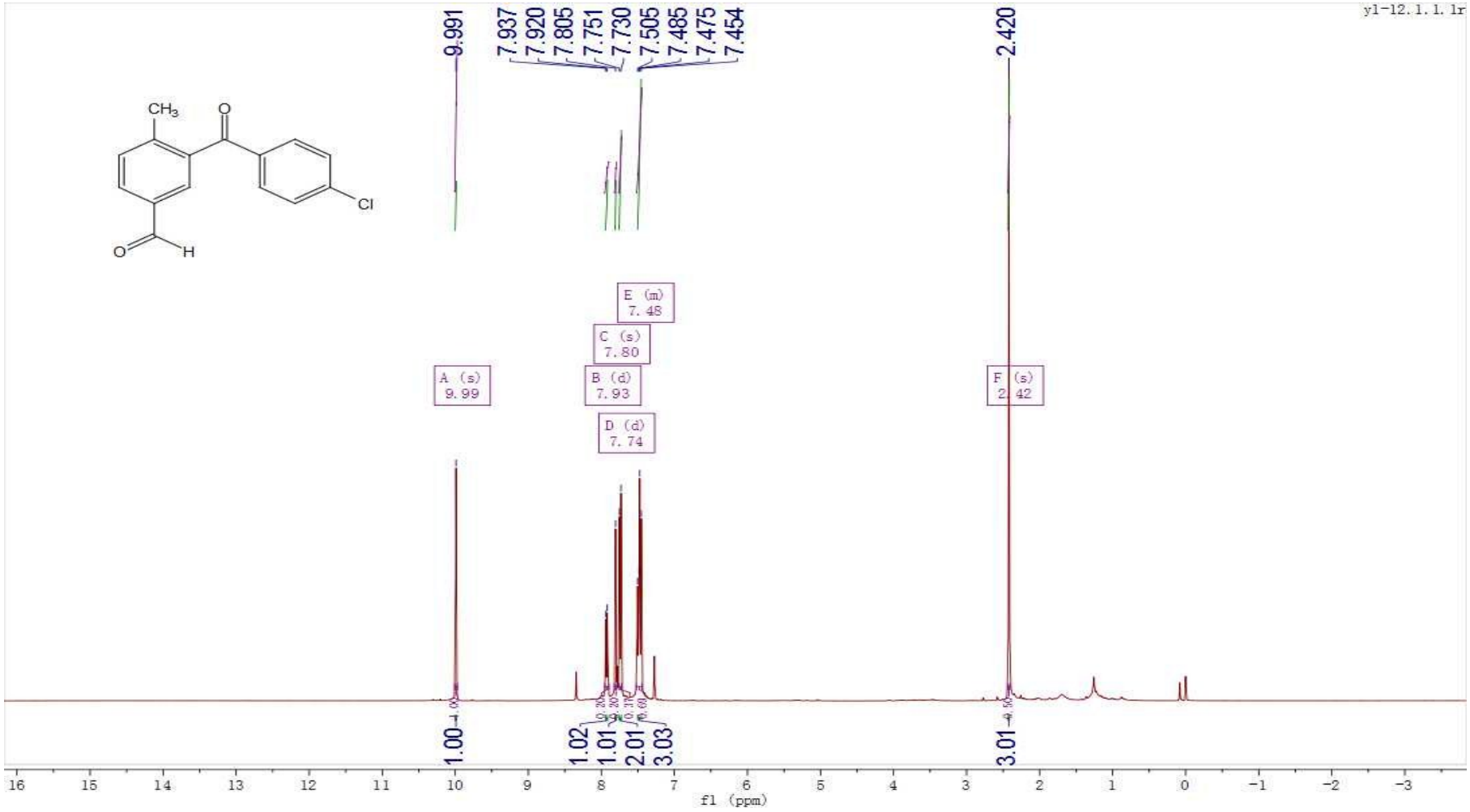
^{1}H NMR spectrum of **3d**



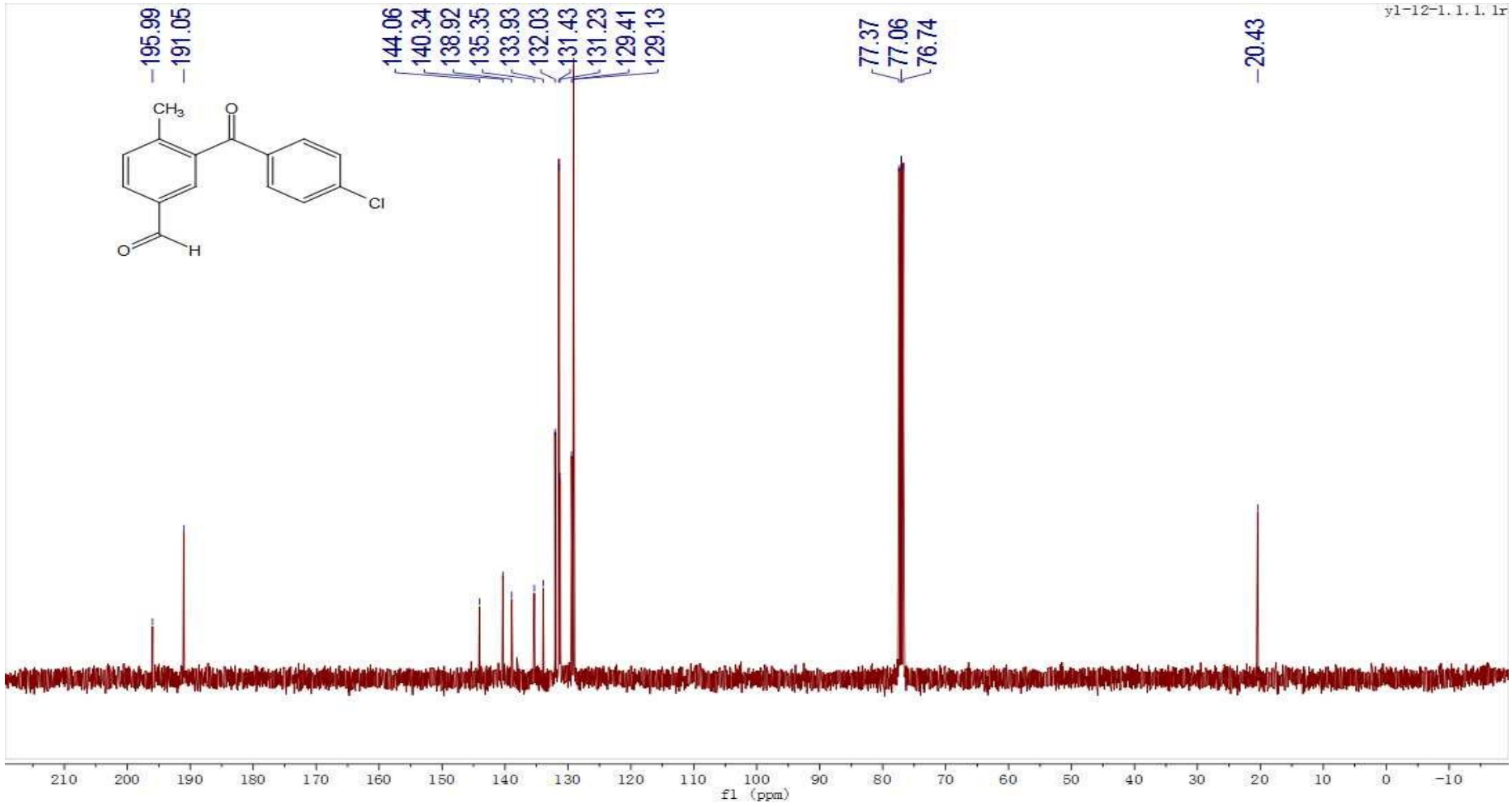
^{13}C NMR spectrum of **3d**



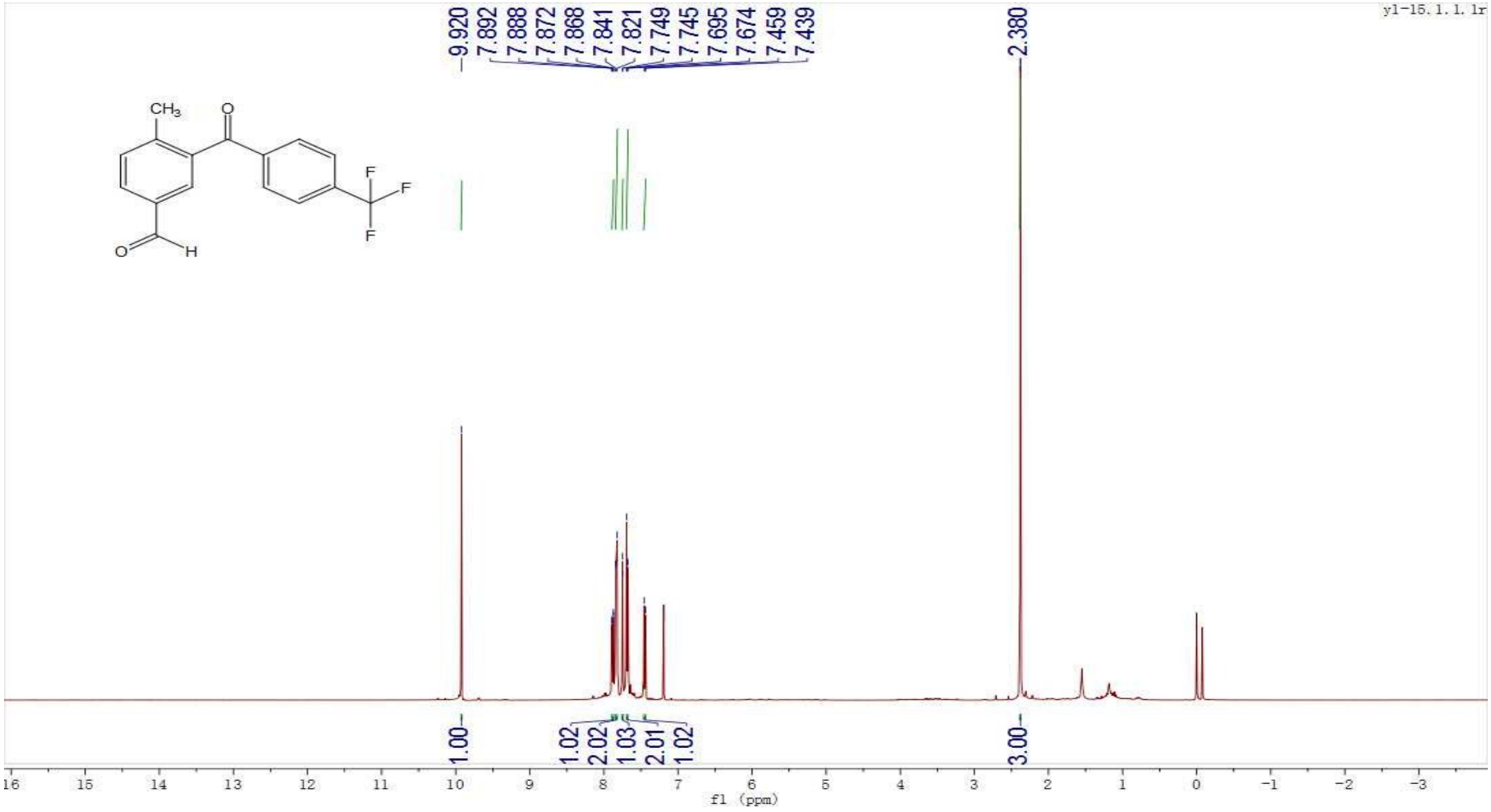
^{1}H NMR spectrum of **3e**



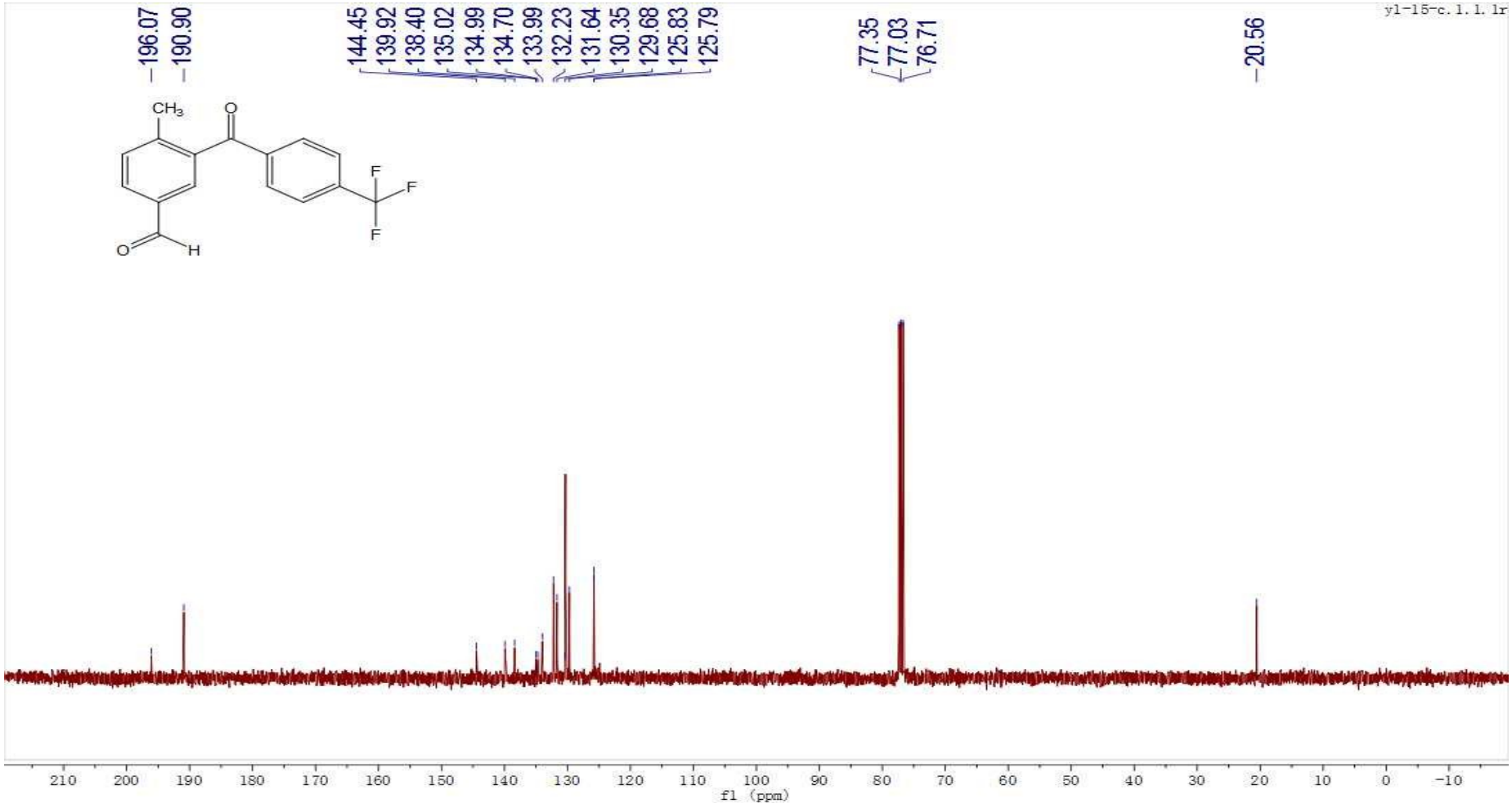
^{13}C NMR spectrum of **3e**



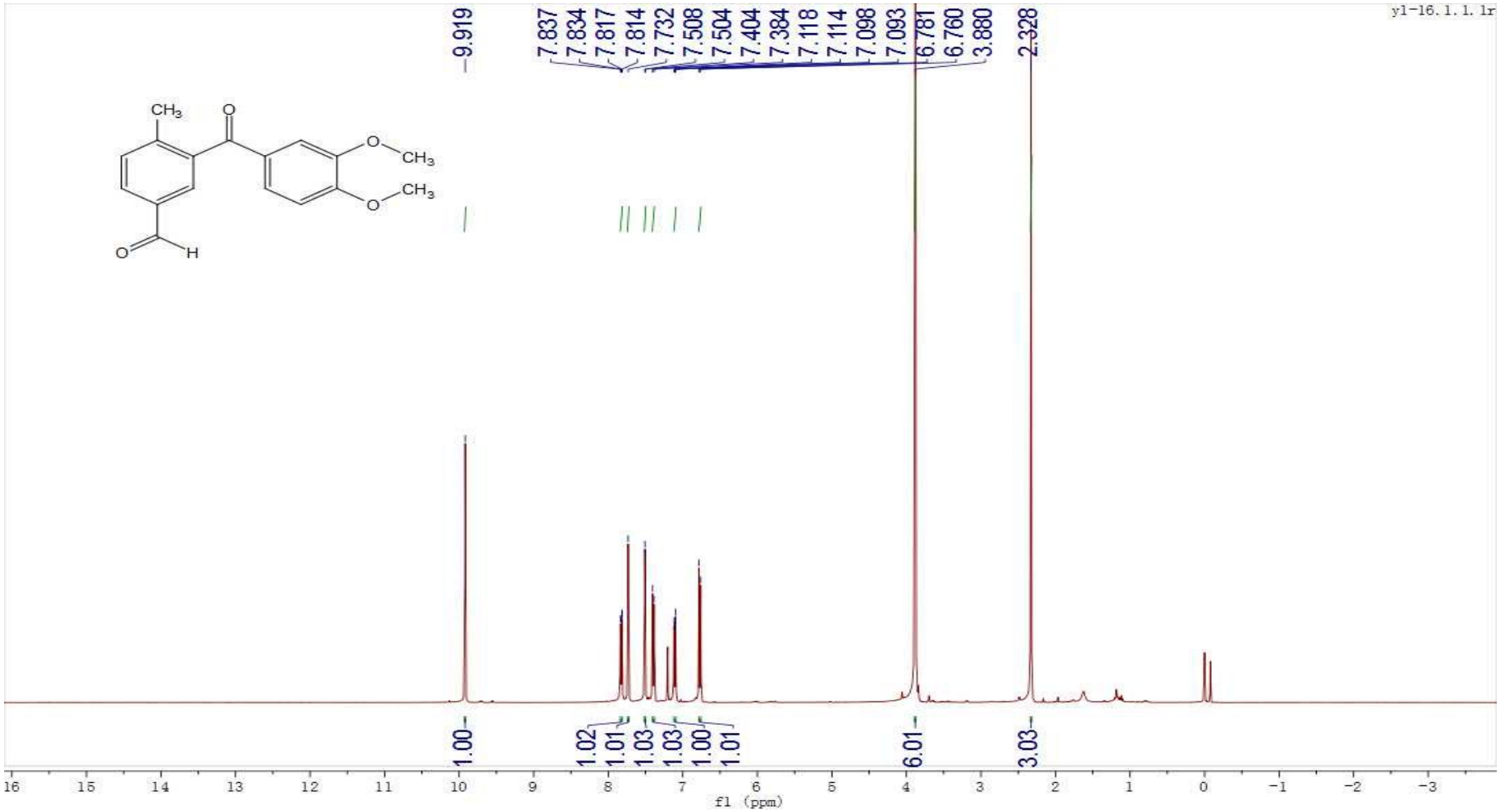
^{1}H NMR spectrum of **3f**



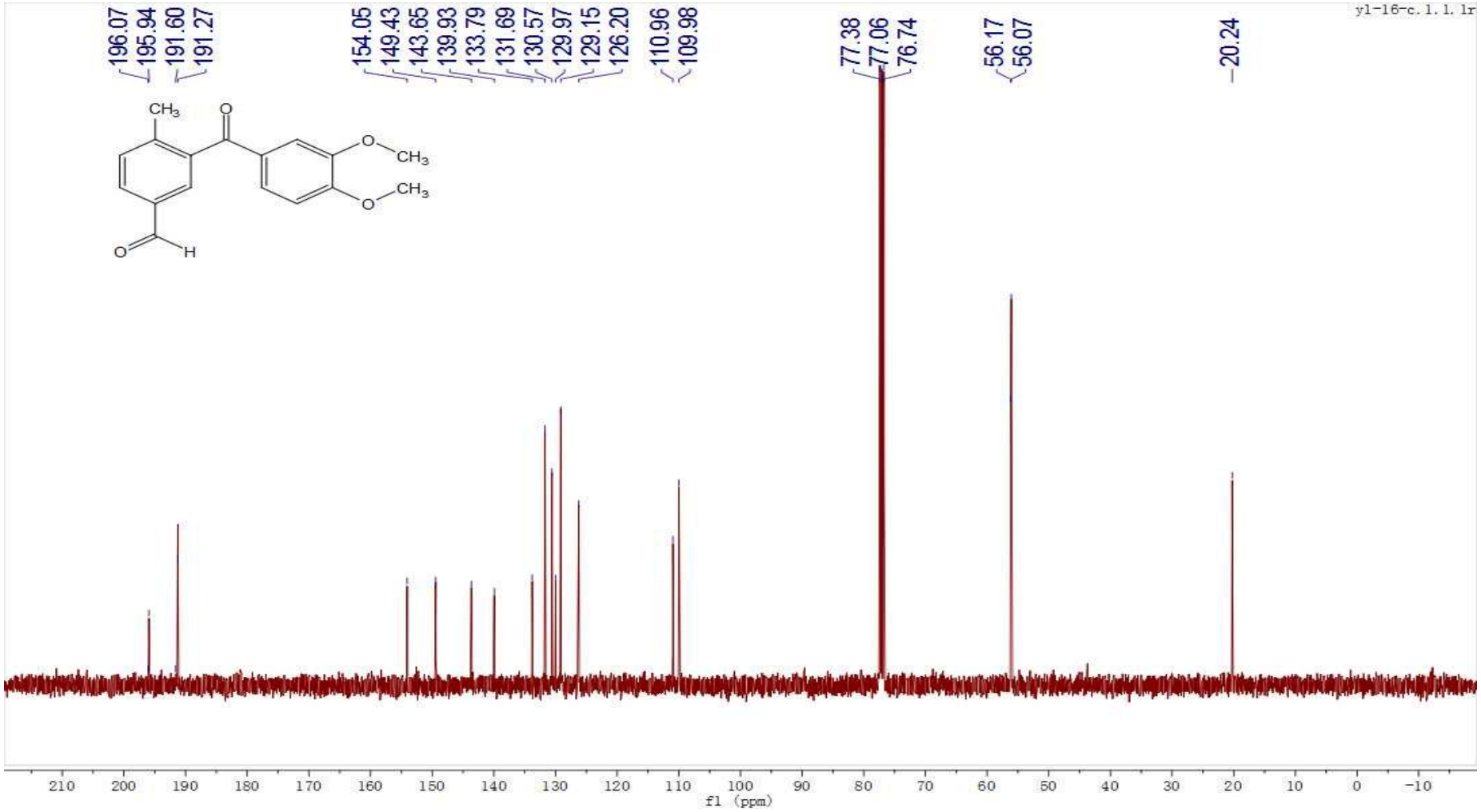
^{13}C NMR spectrum of **3f**



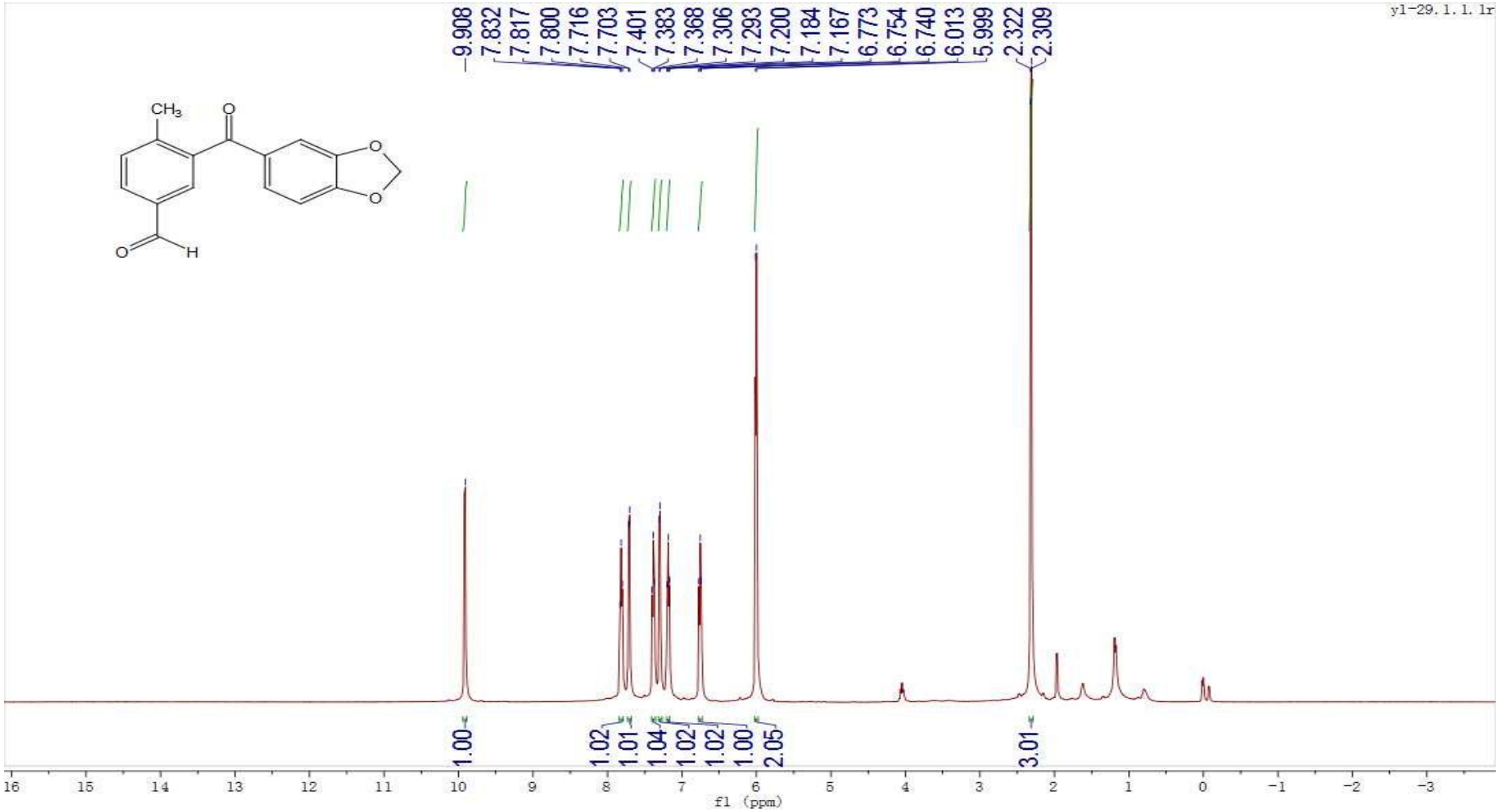
^{1}H NMR spectrum of **3g**



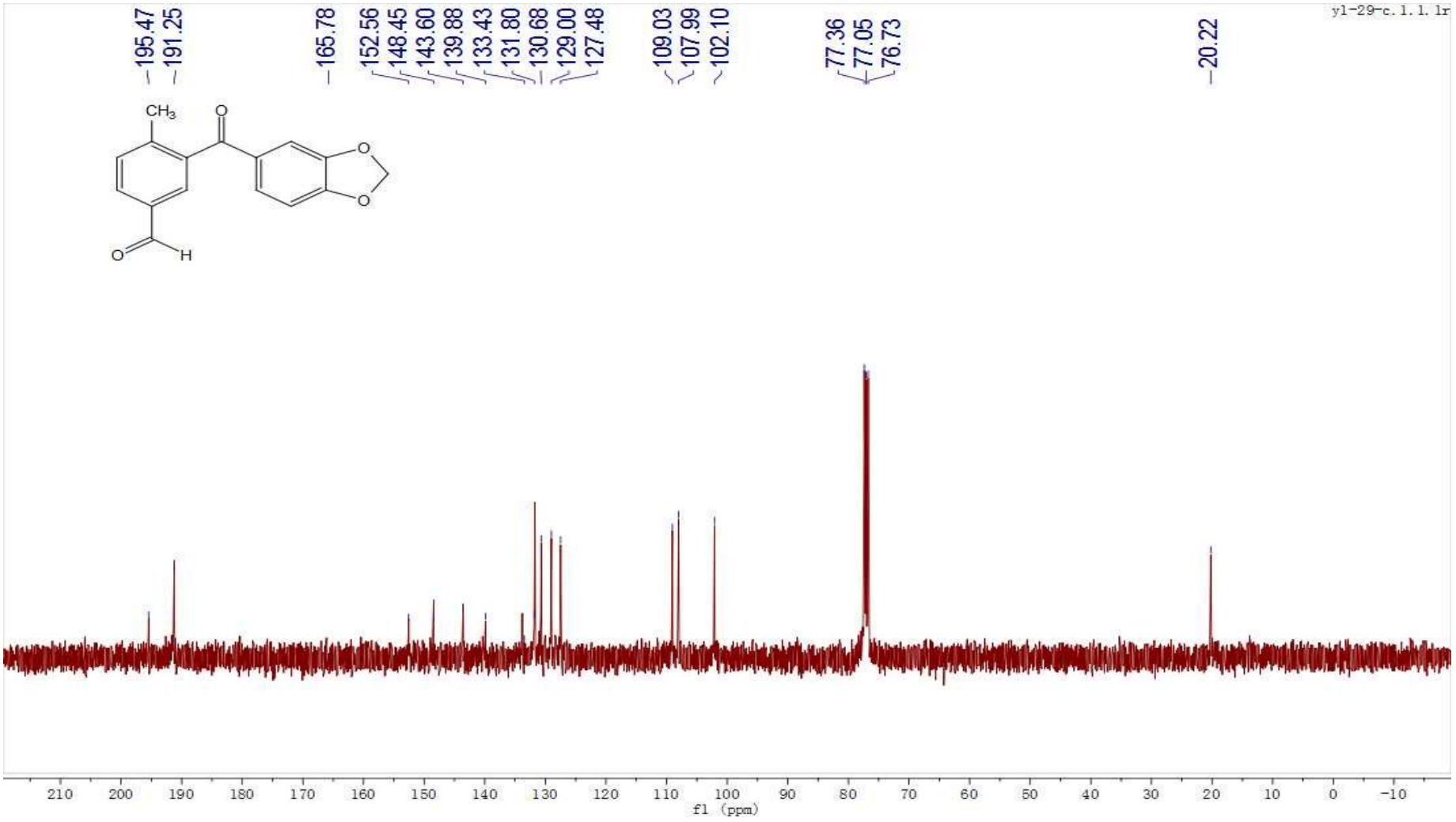
^{13}C NMR spectrum of **3g**



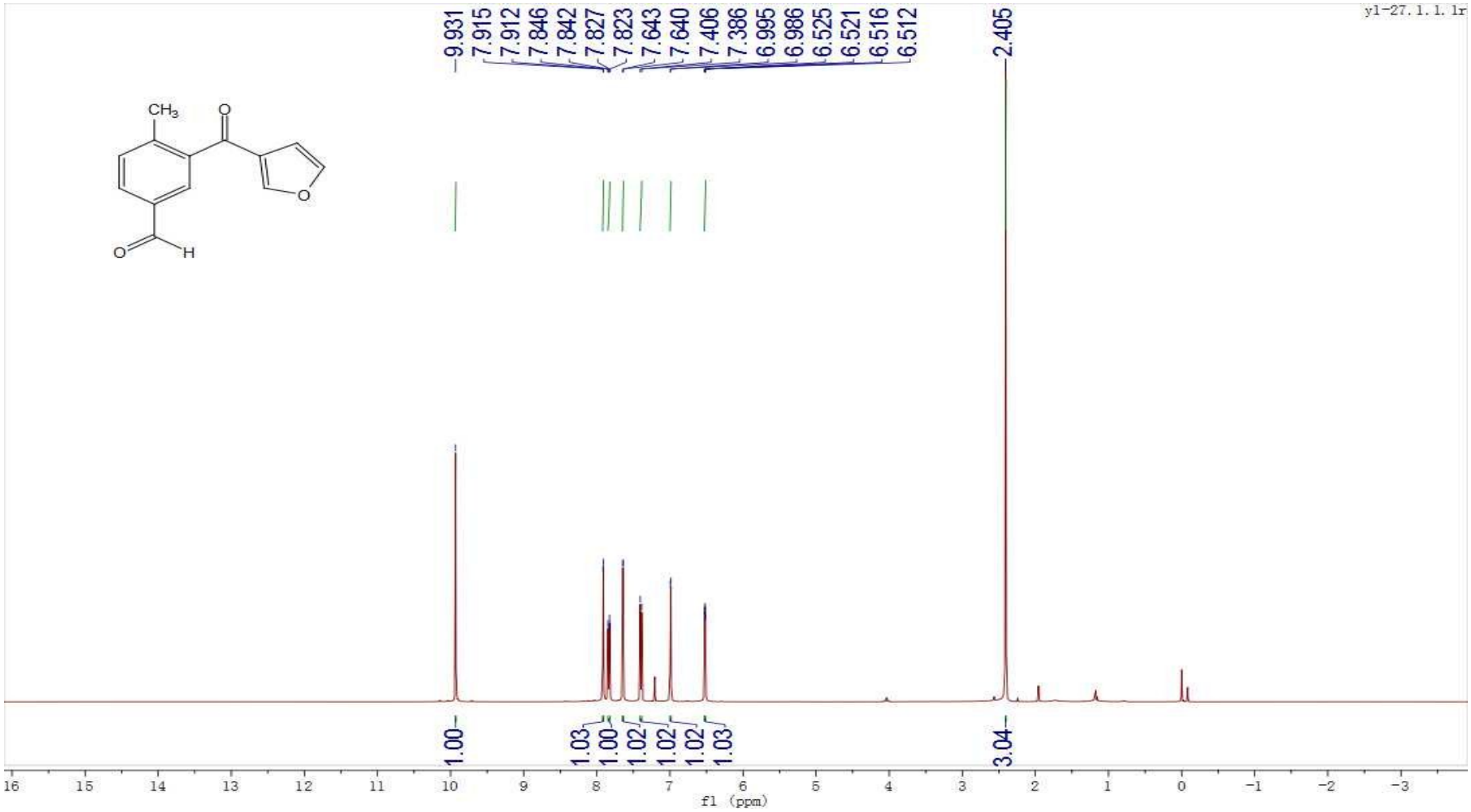
^{1}H NMR spectrum of **3h**



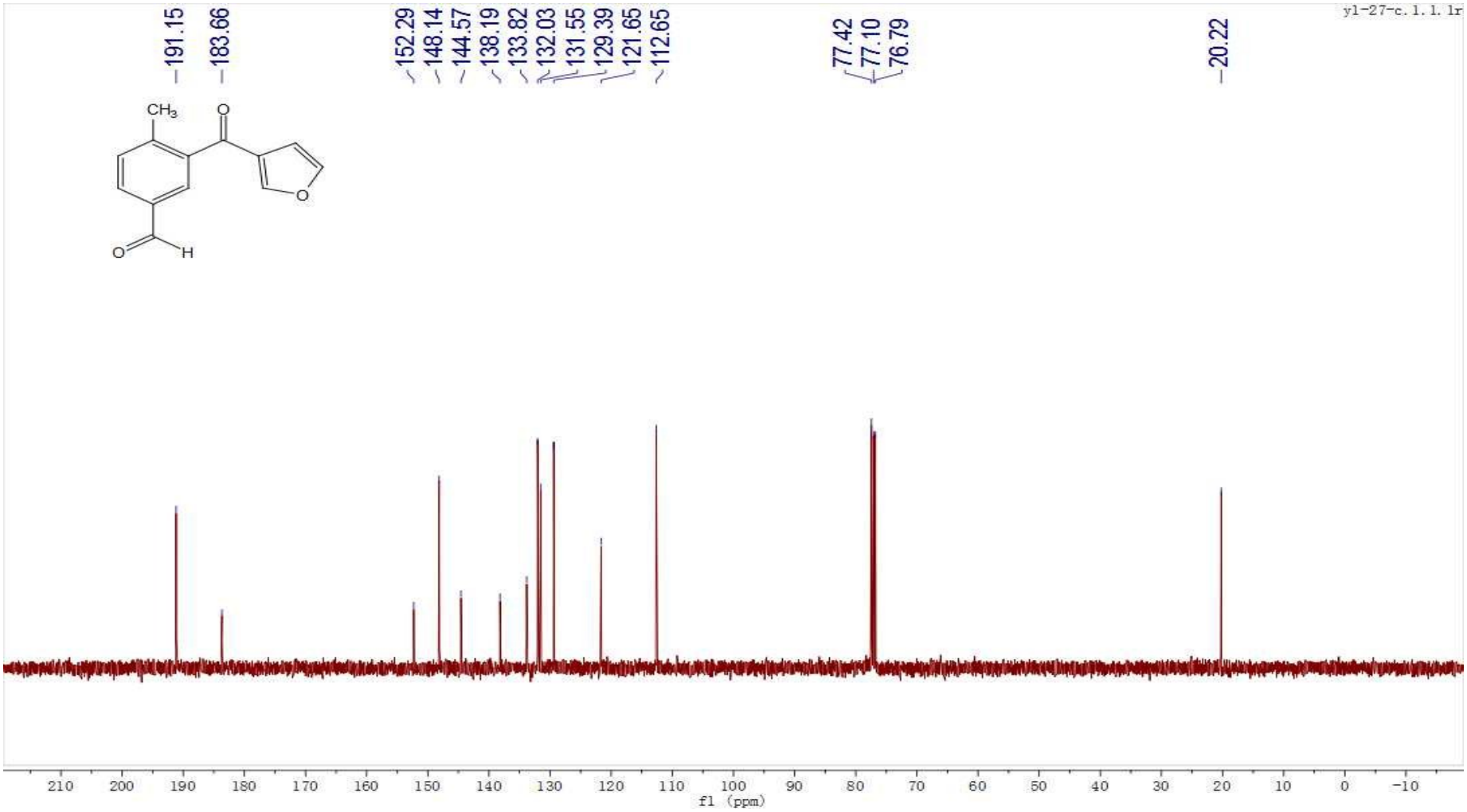
^{13}C NMR spectrum of **3h**



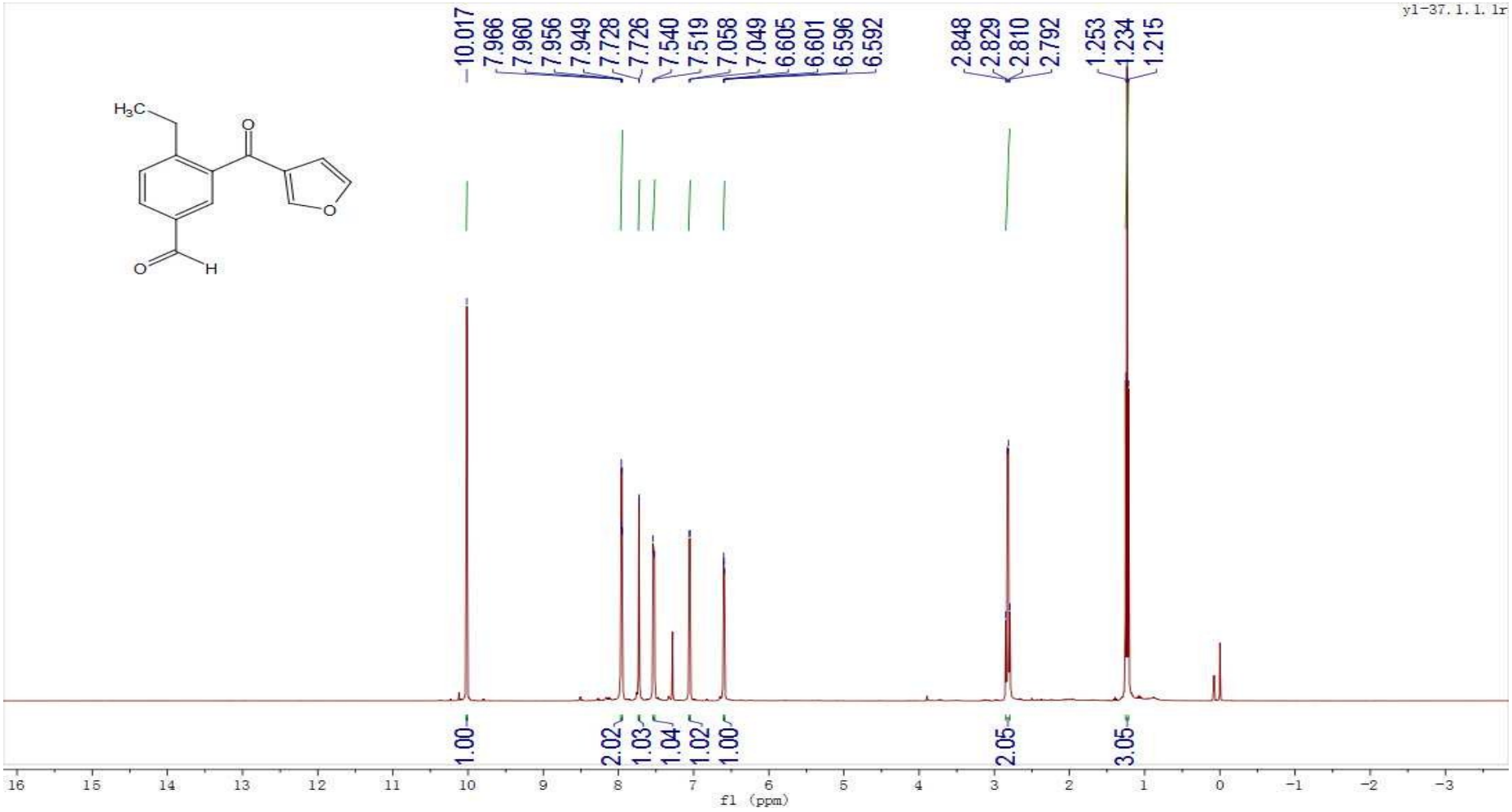
^{1}H NMR spectrum of **3i**



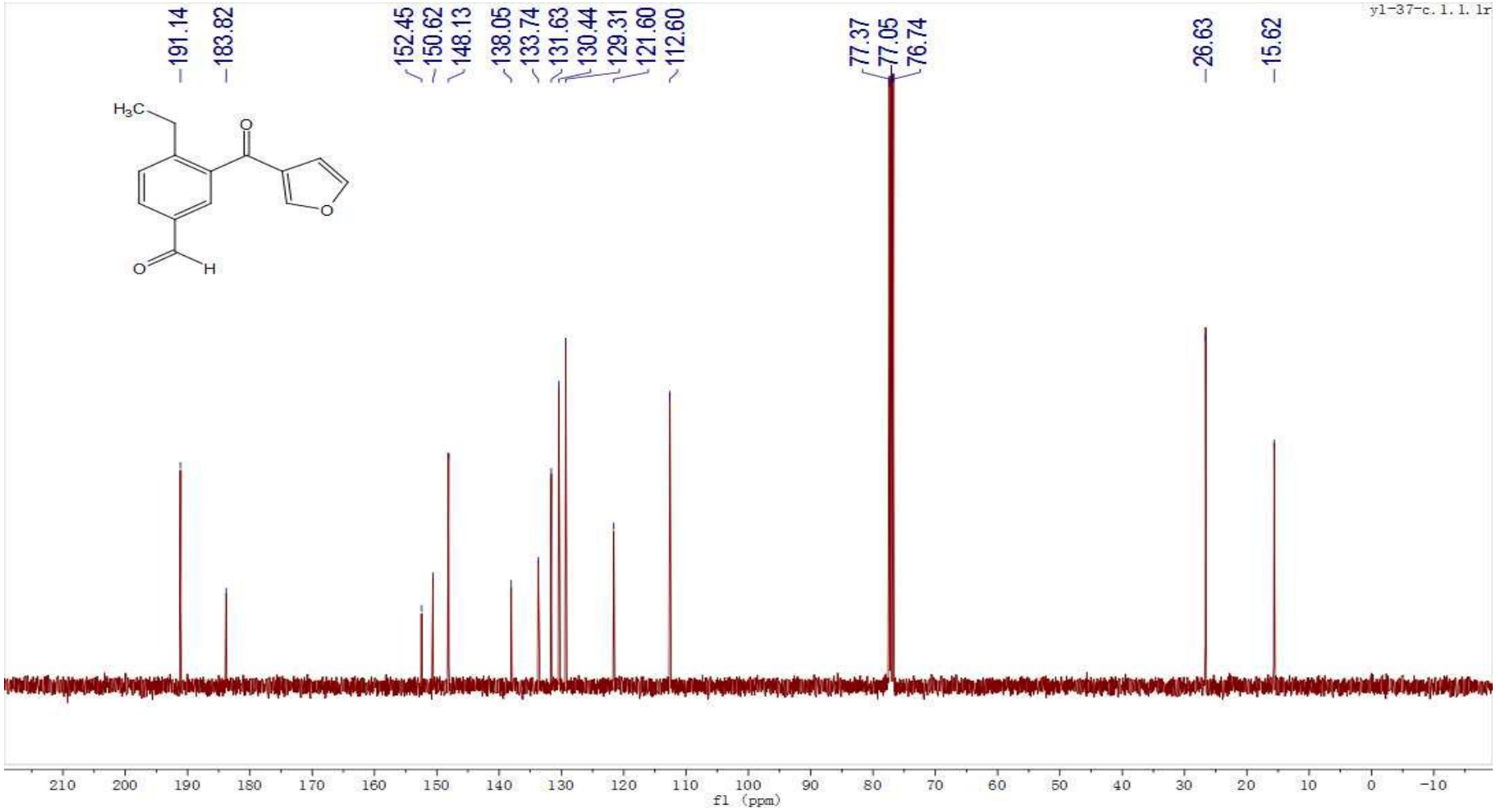
^{13}C NMR spectrum of **3i**



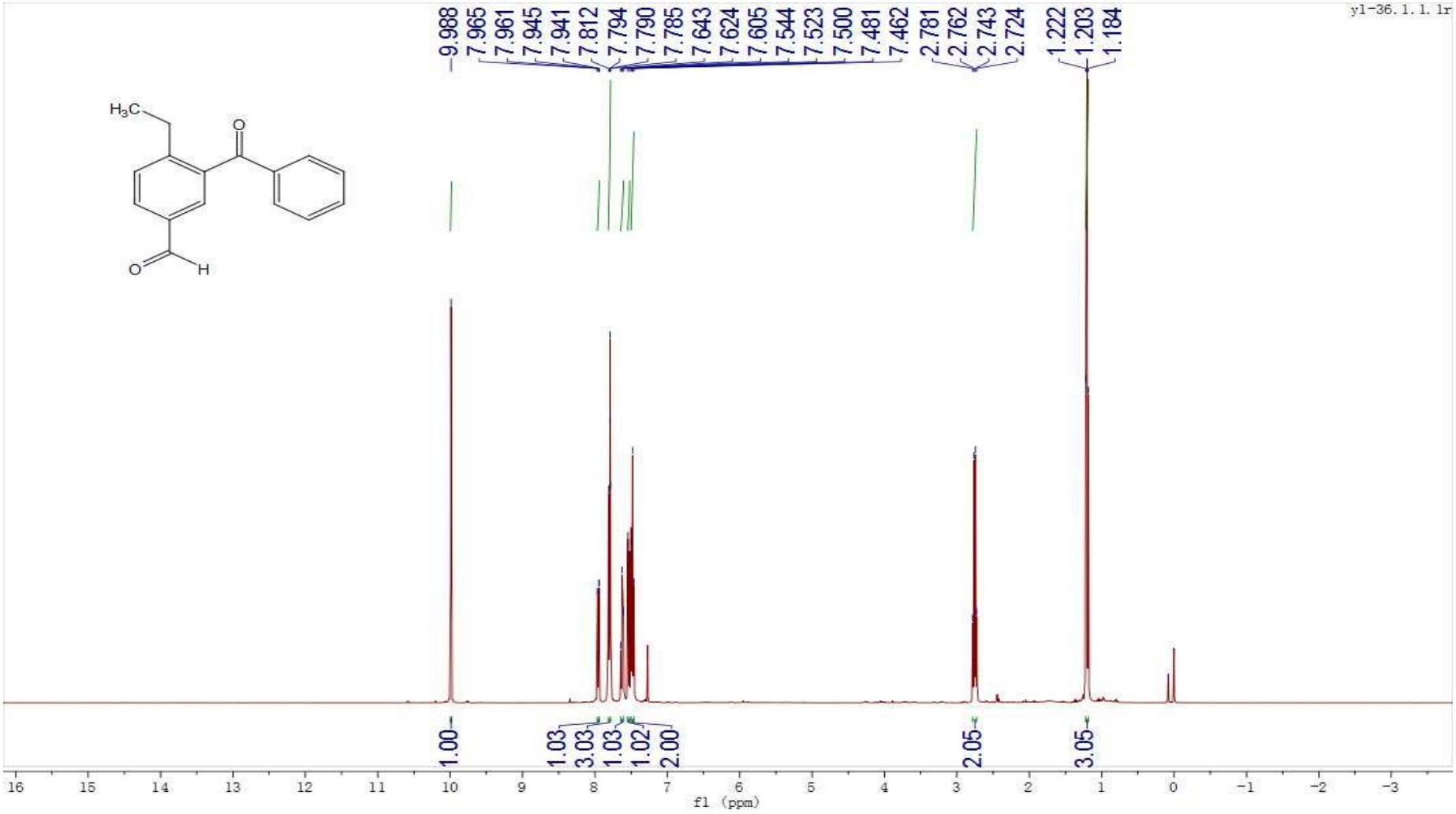
^{1}H NMR spectrum of **3j**



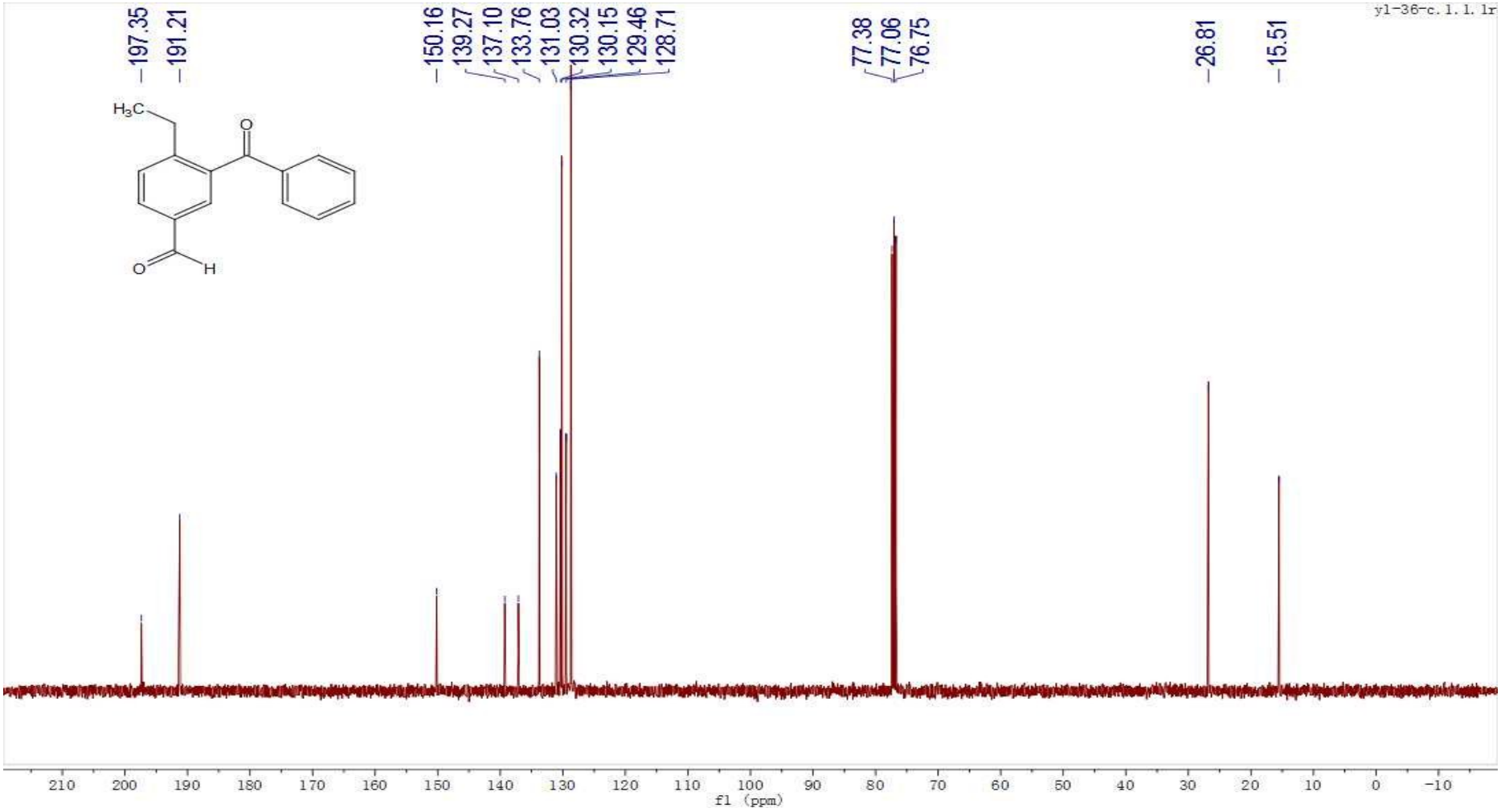
^{13}C NMR spectrum of **3j**



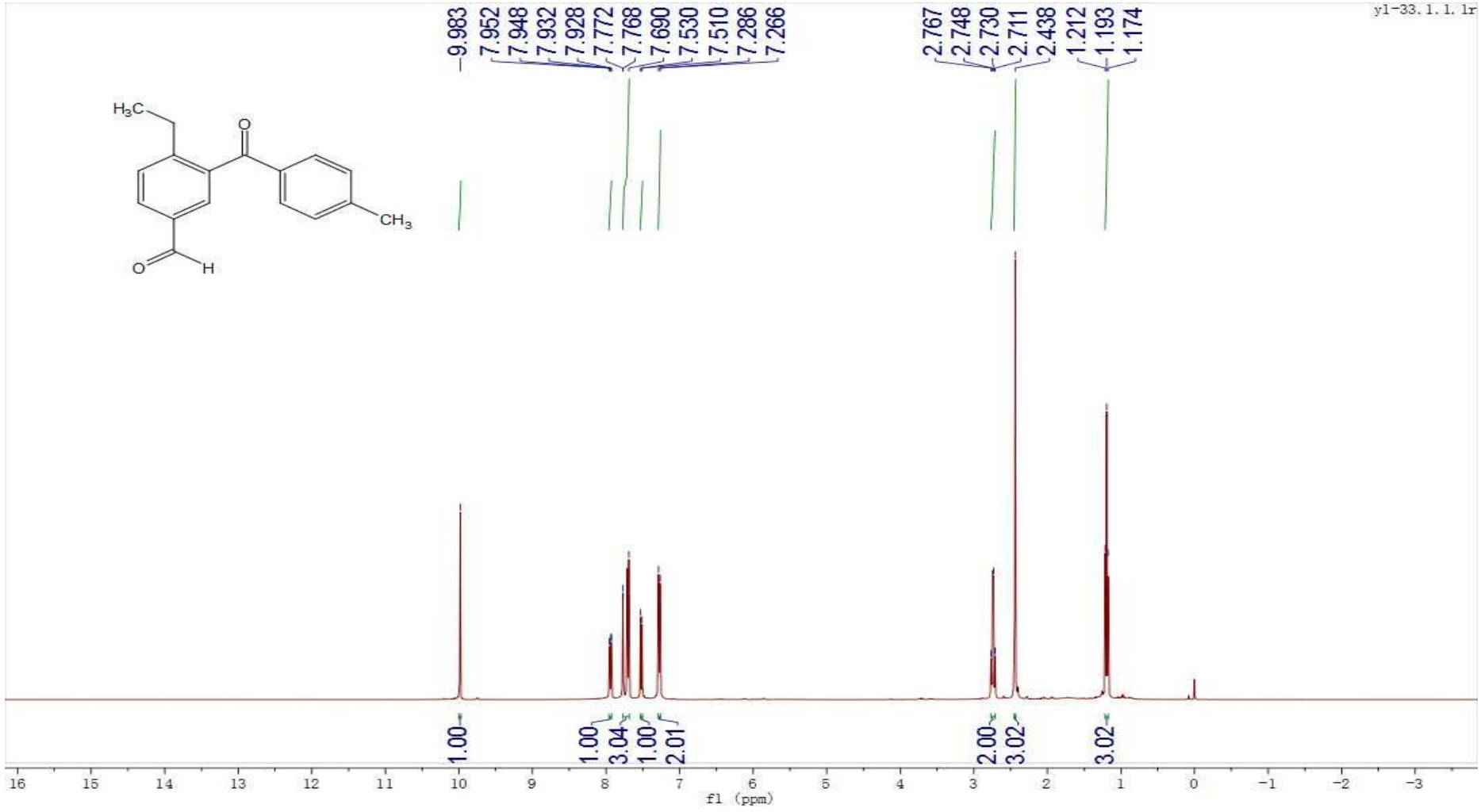
^{1}H NMR spectrum of **3k**



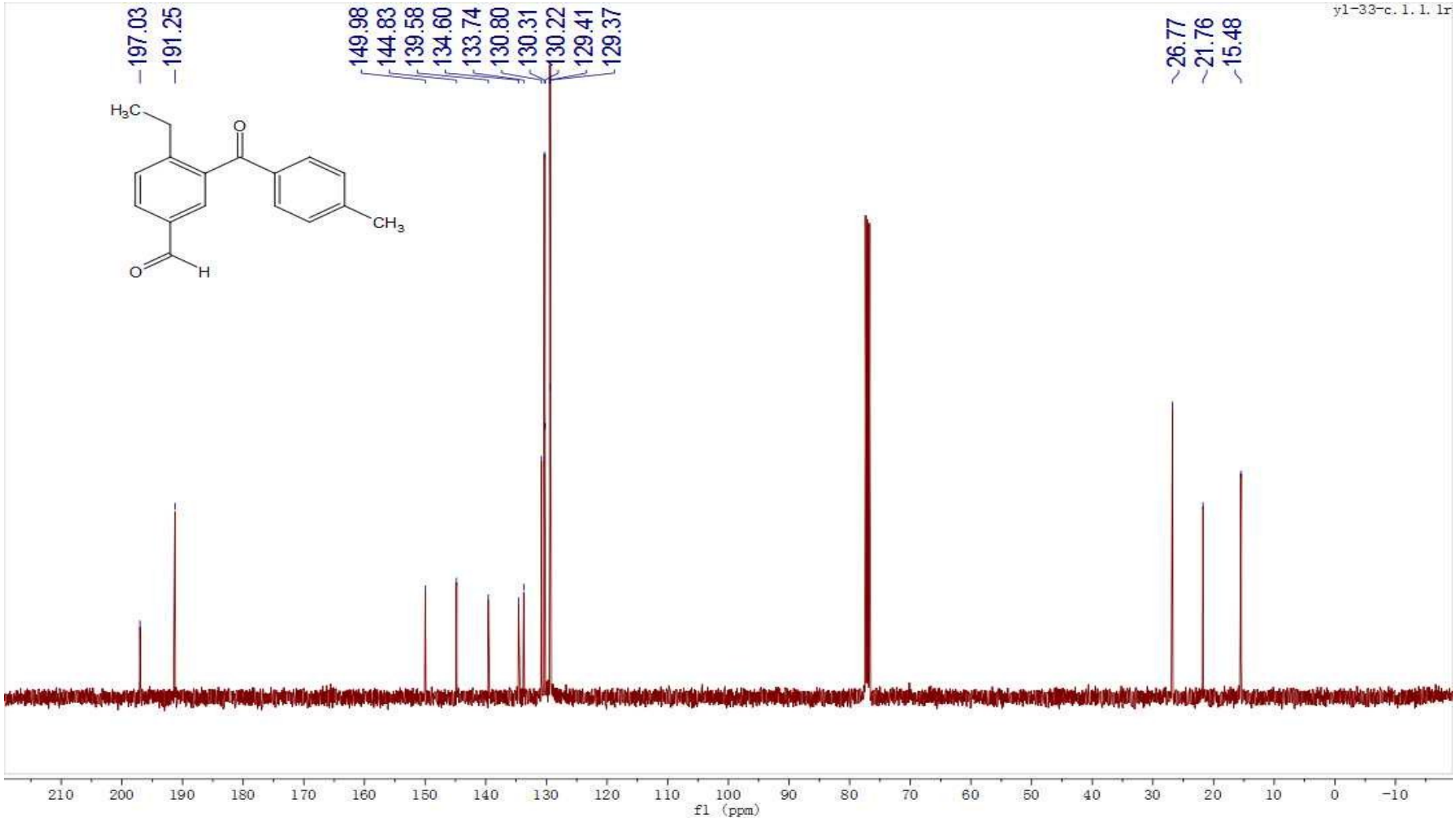
^{13}C NMR spectrum of **3k**



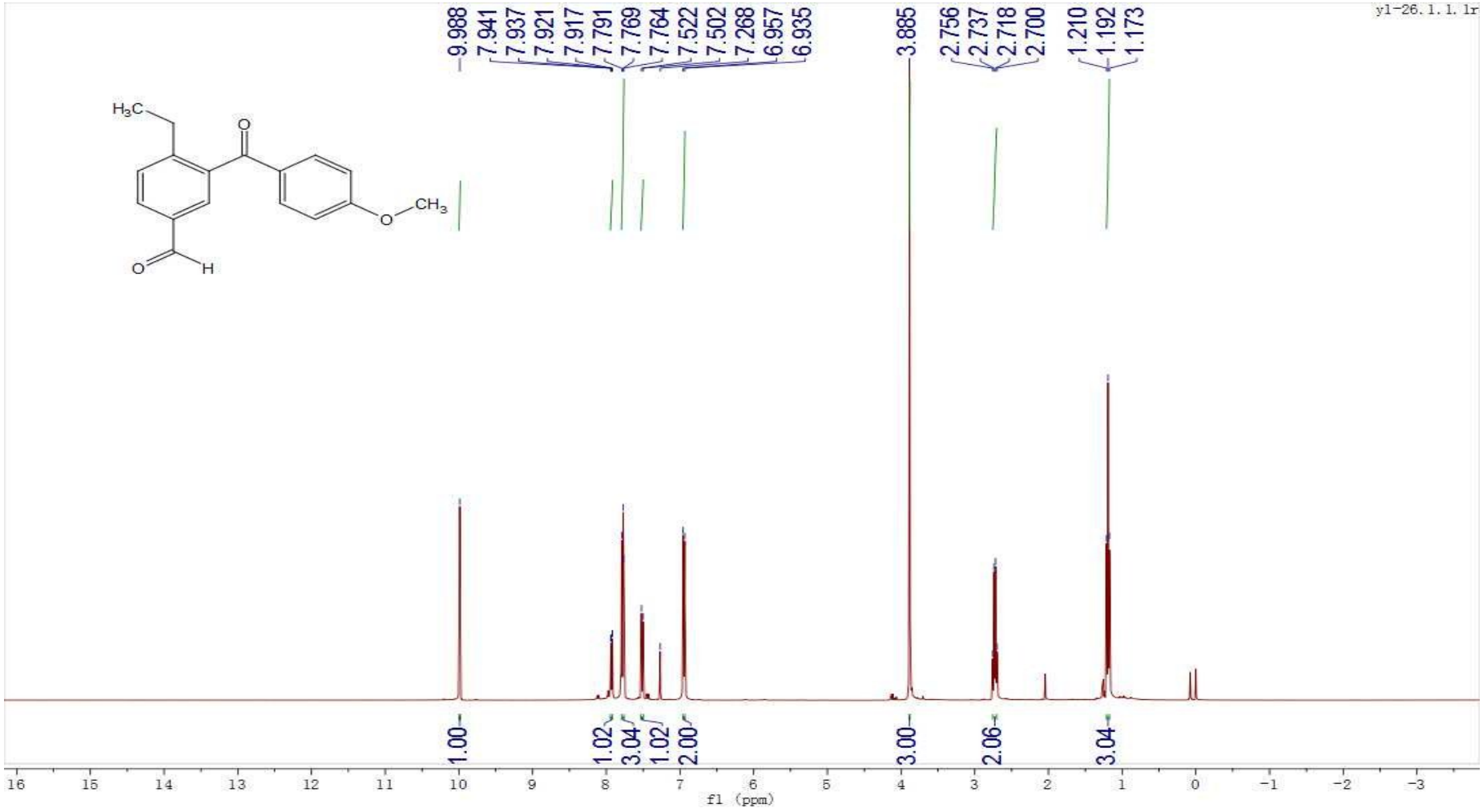
^{1}H NMR spectrum of 3l



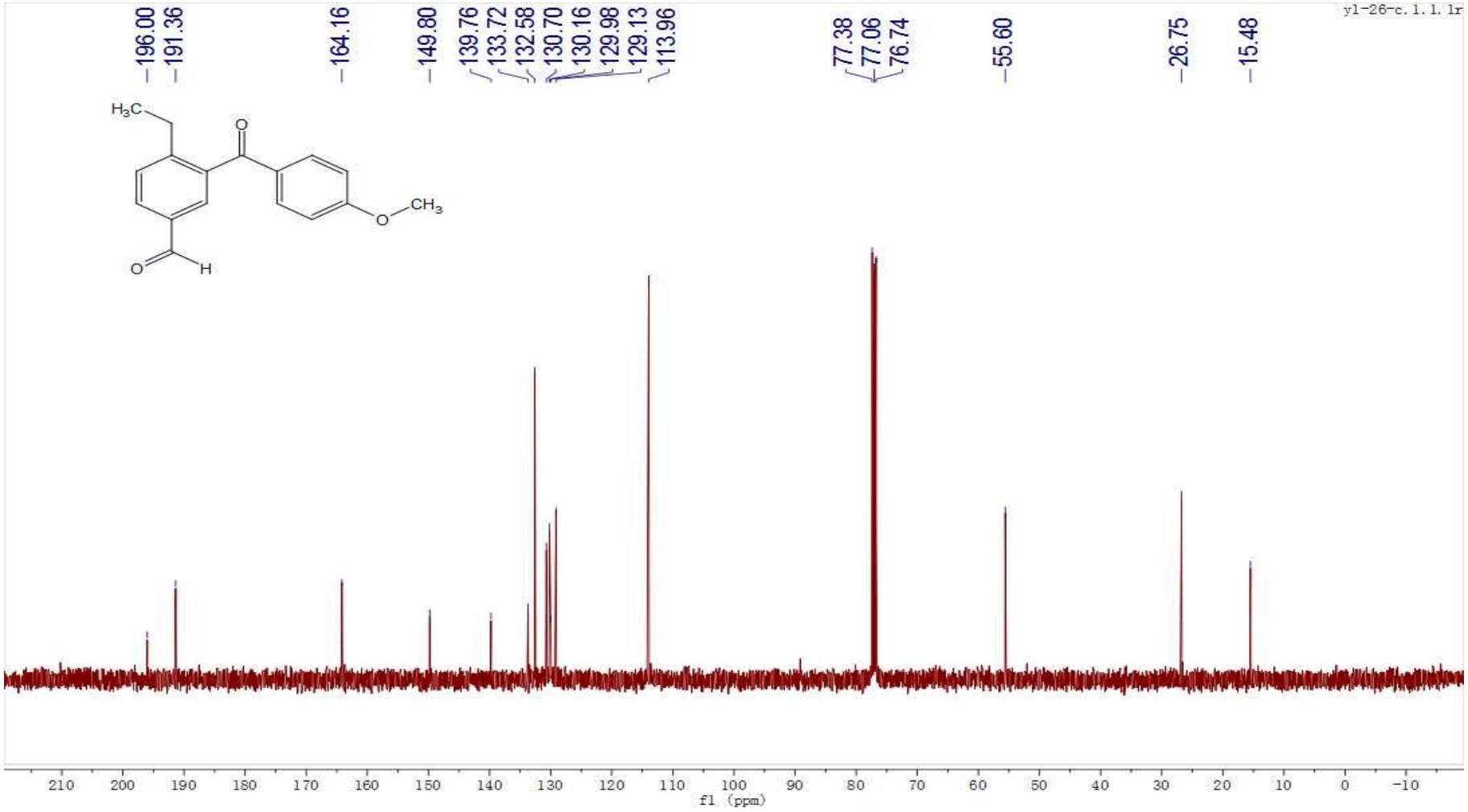
^{13}C NMR spectrum of **3l**



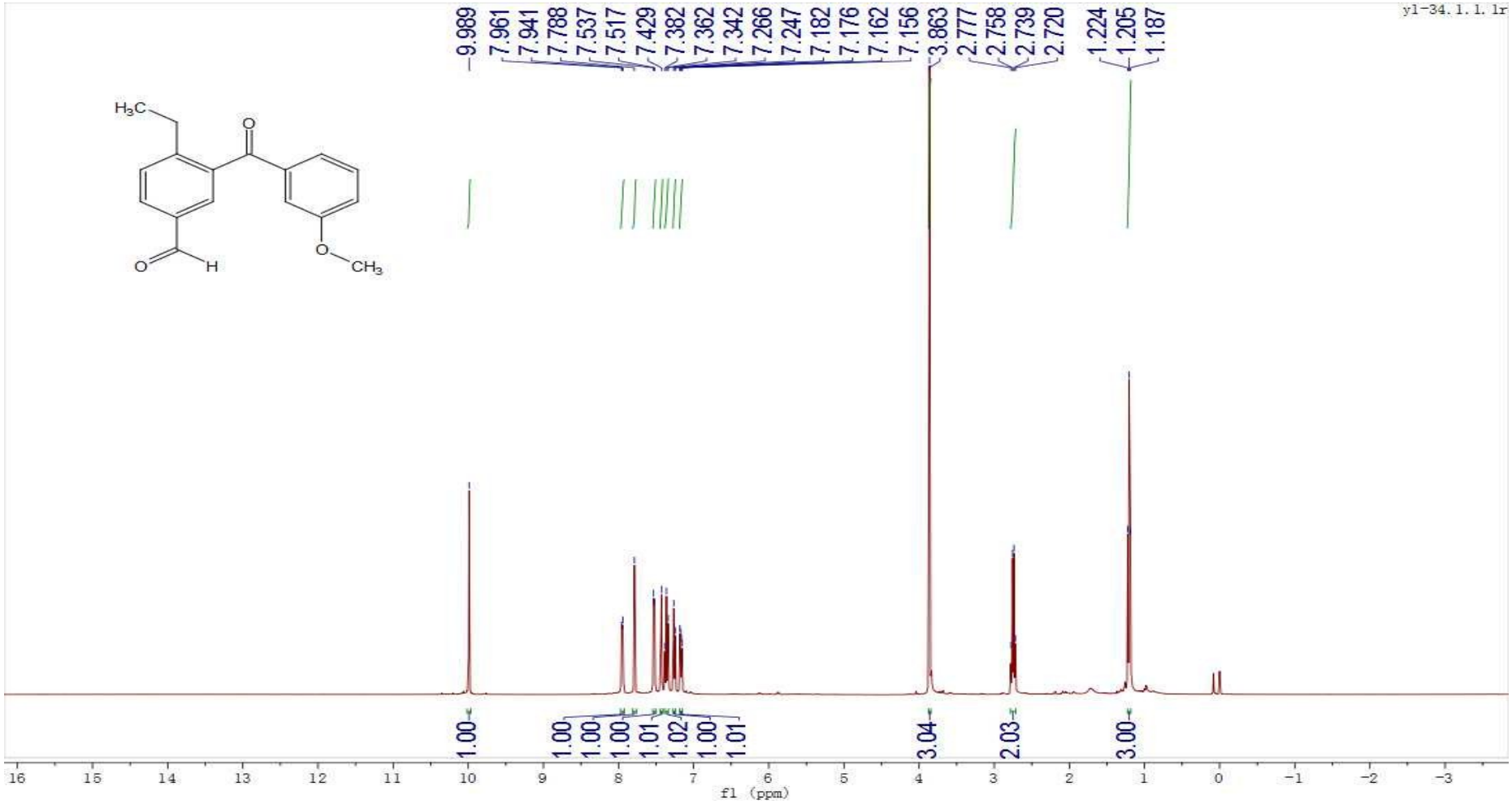
^{1}H NMR spectrum of **3m**



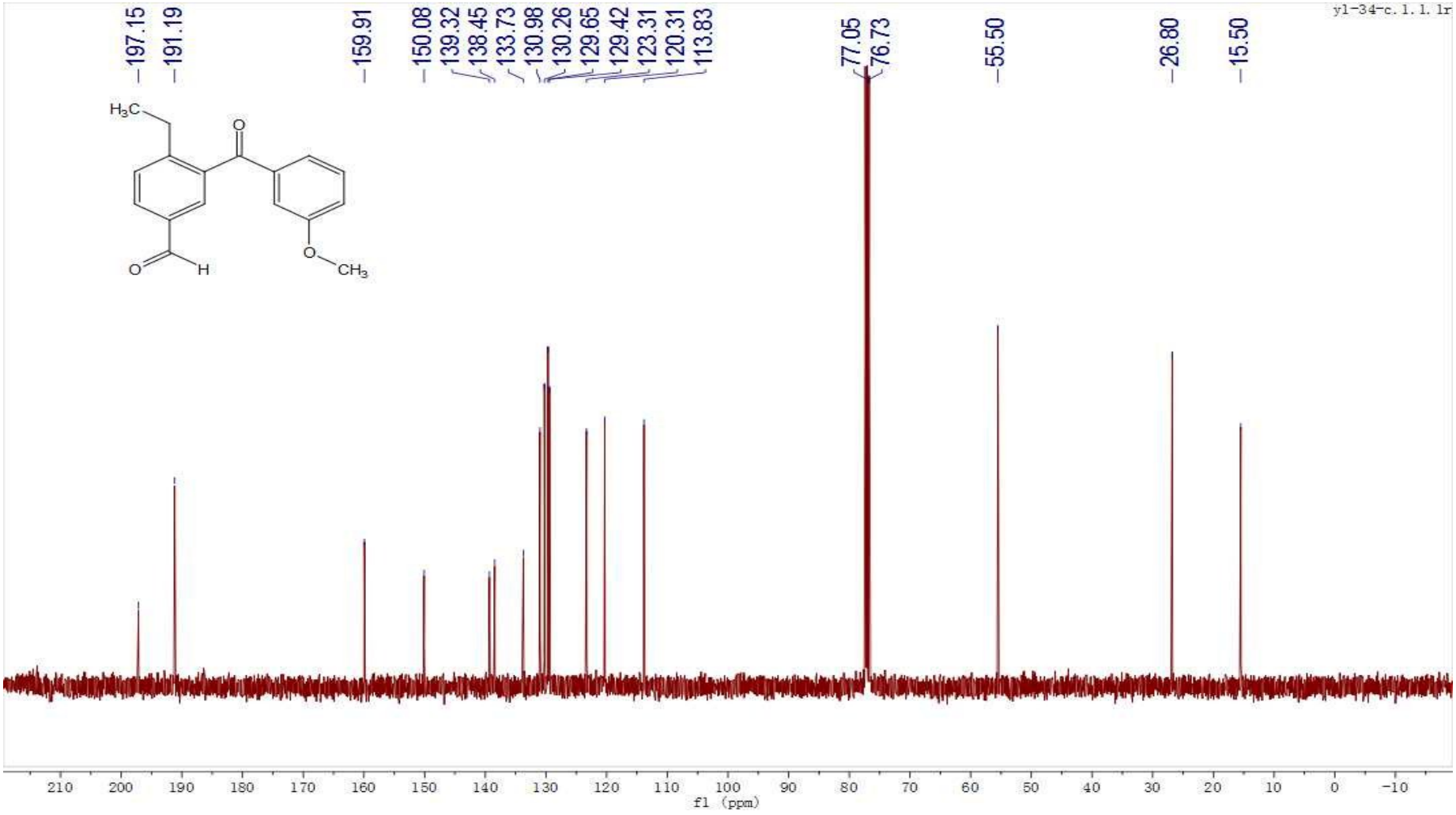
^{13}C NMR spectrum of **3m**



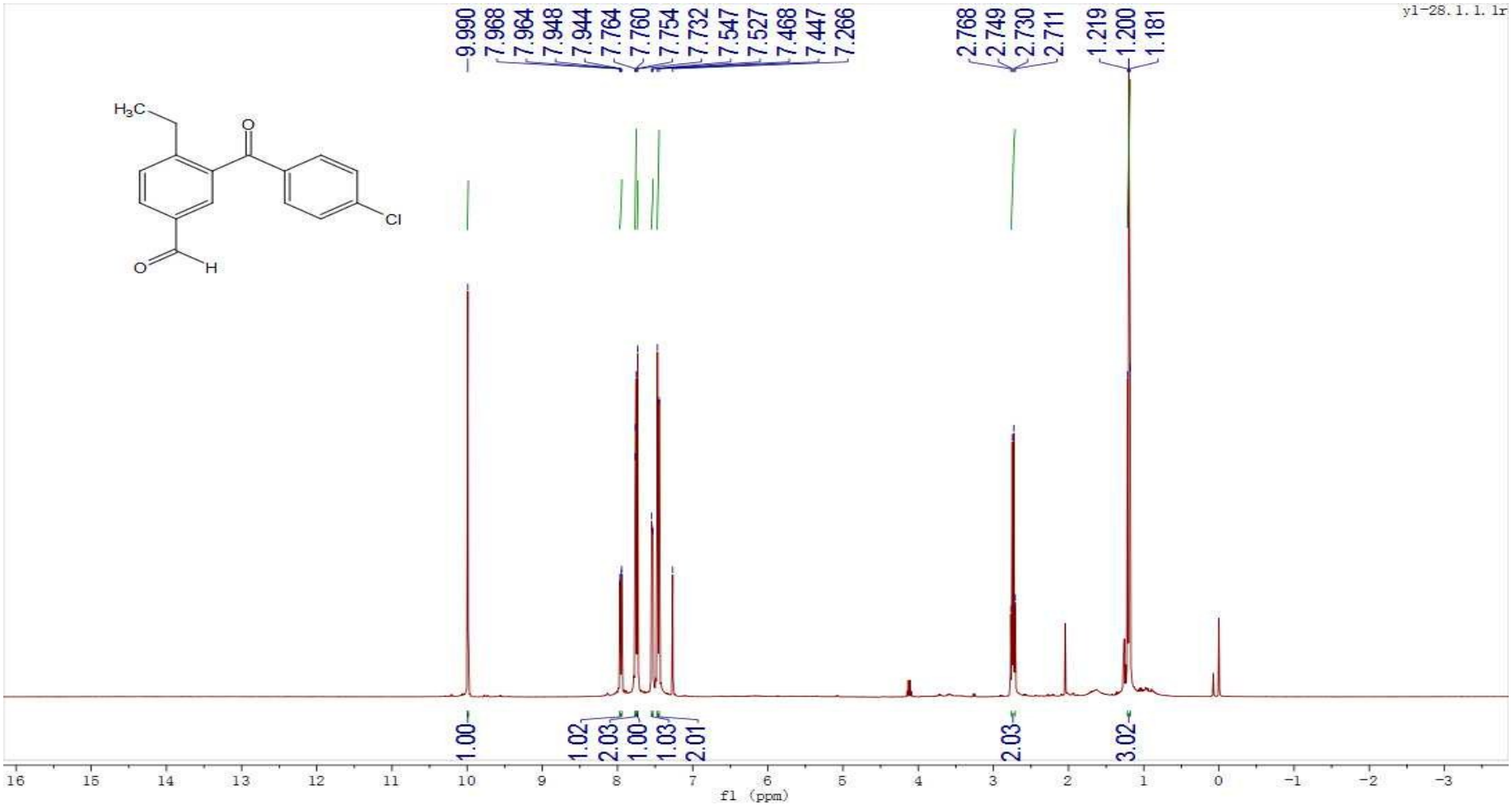
^{1}H NMR spectrum of **3n**



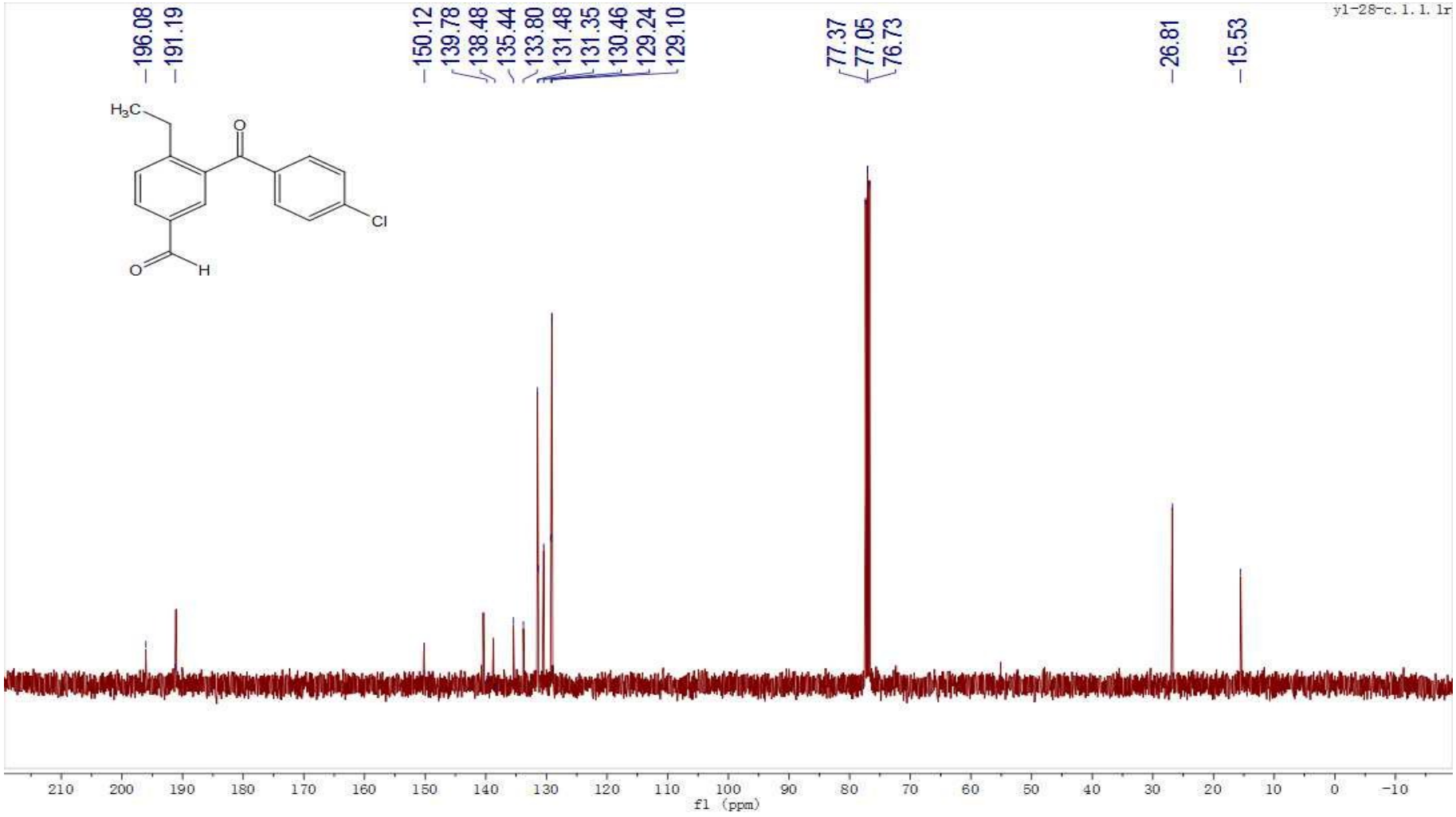
^{13}C NMR spectrum of **3n**



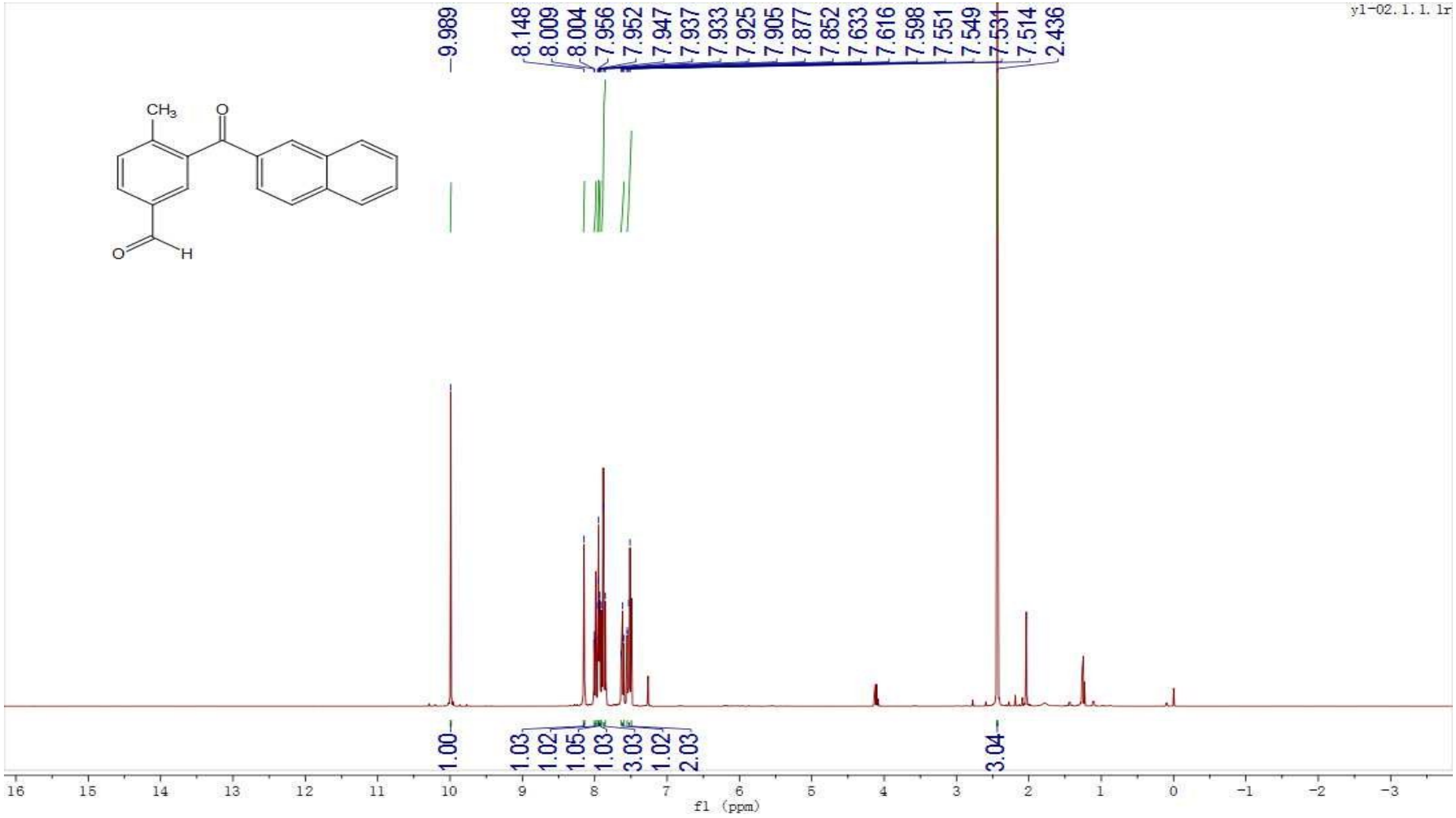
^{1}H NMR spectrum of **3o**



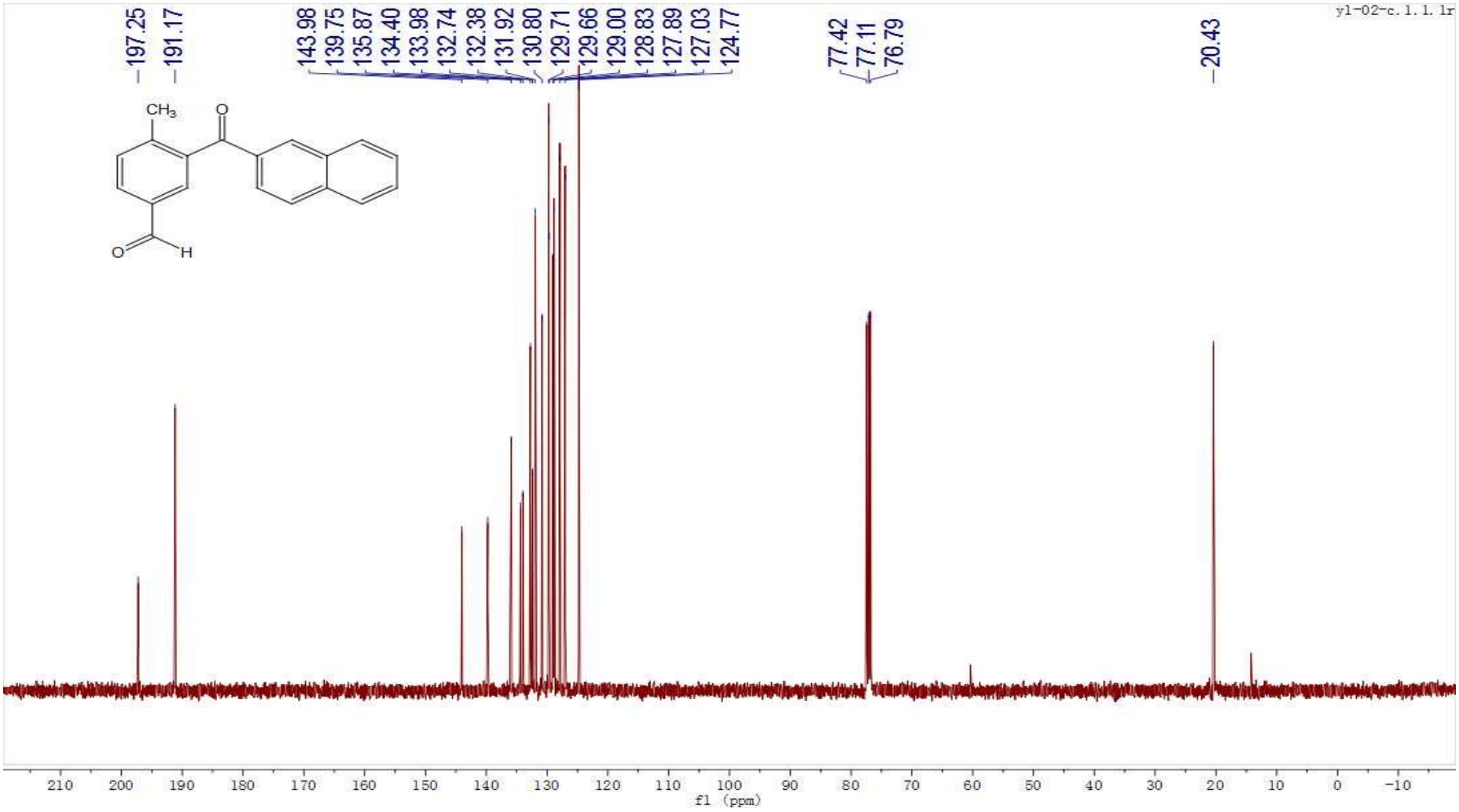
^{13}C NMR spectrum of **3o**



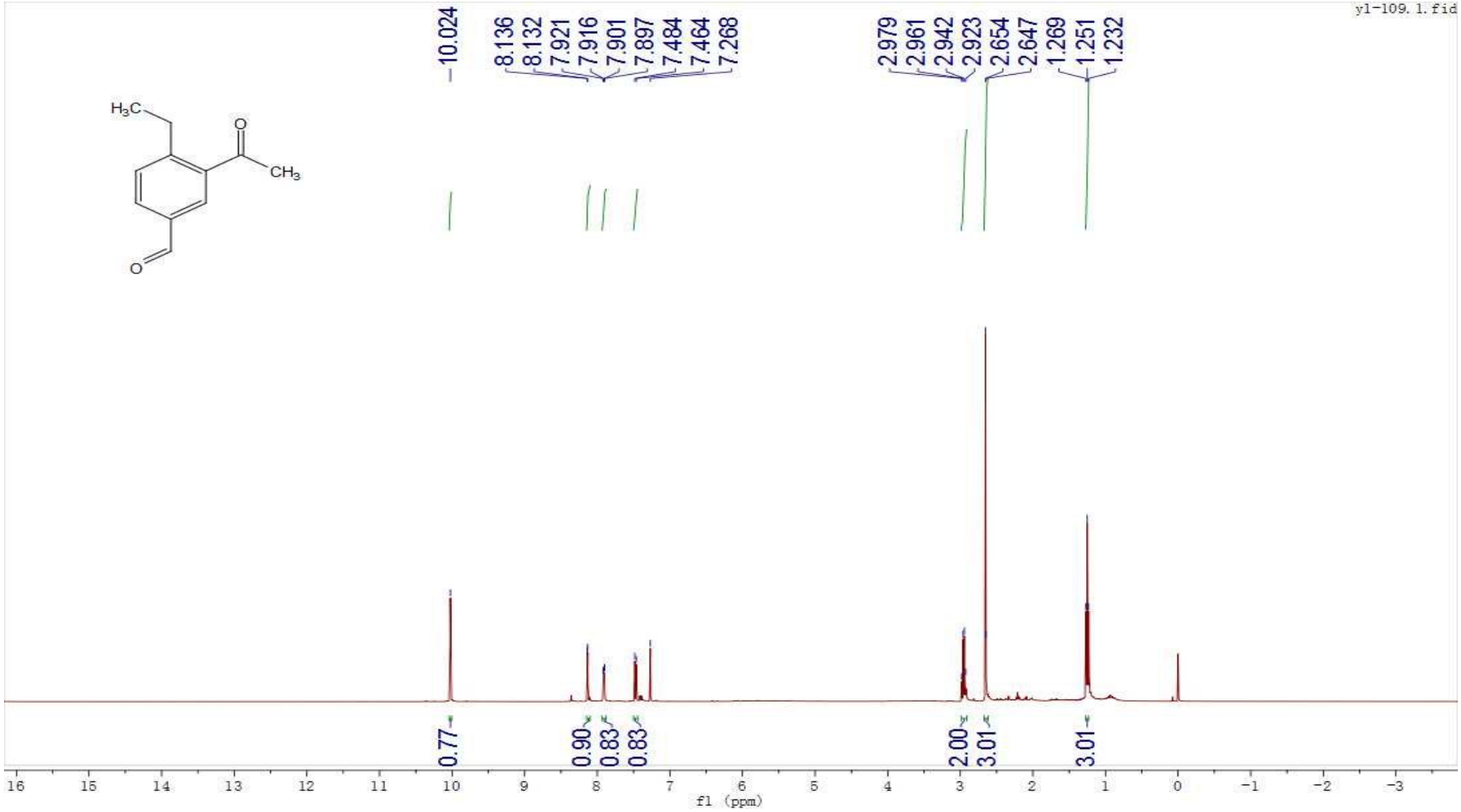
^{1}H NMR spectrum of **3p**



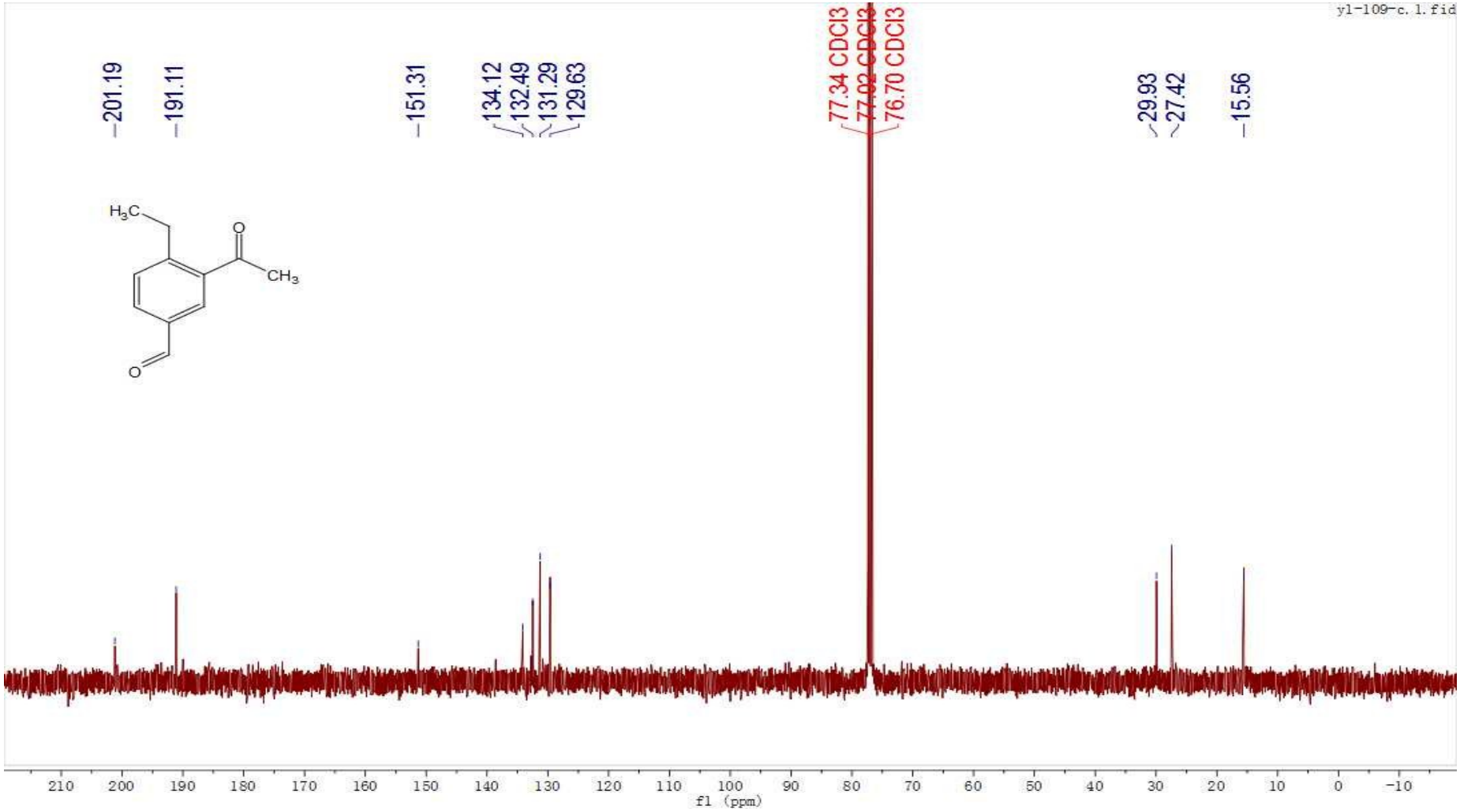
^{13}C NMR spectrum of **3p**



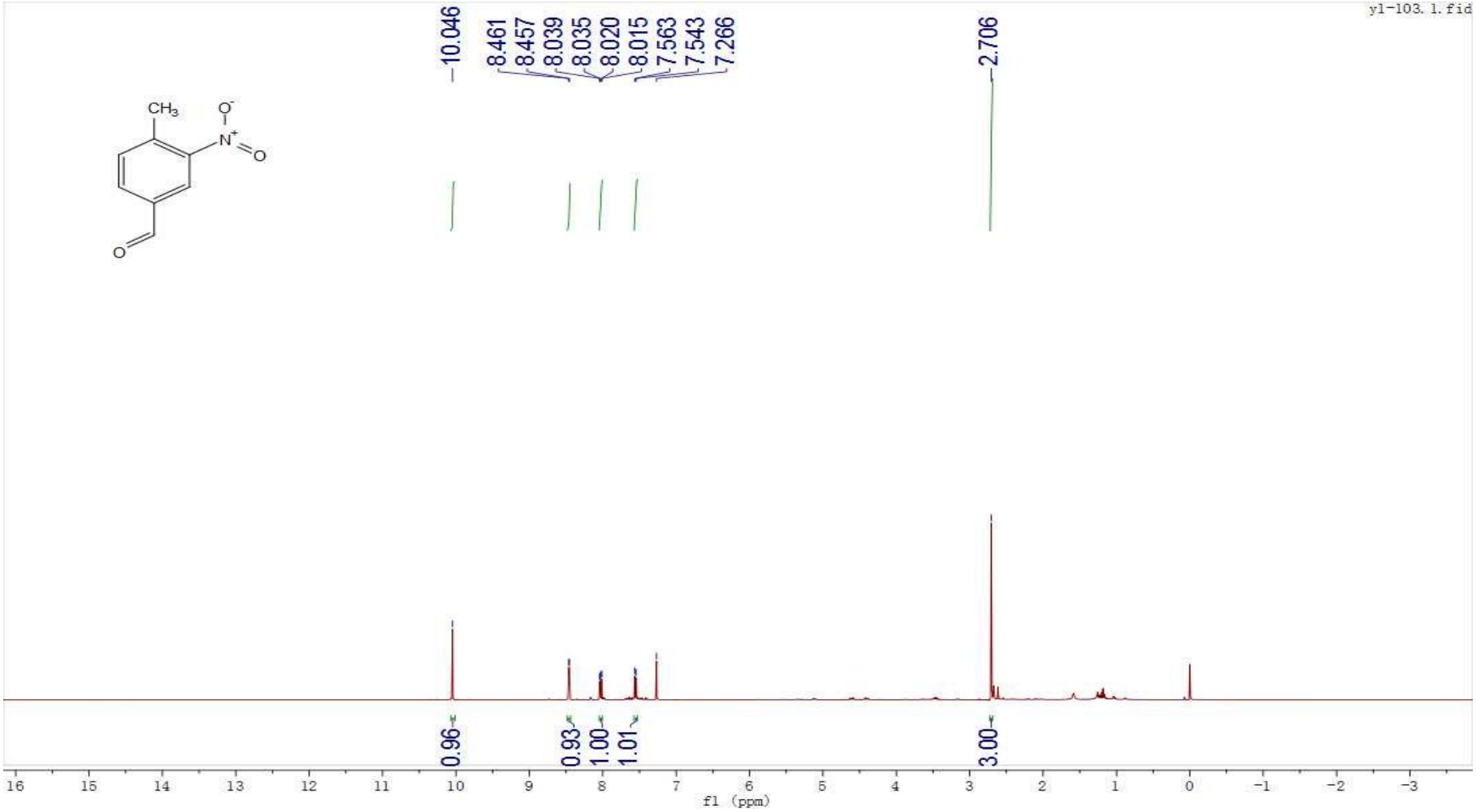
^{1}H NMR spectrum of **3q**



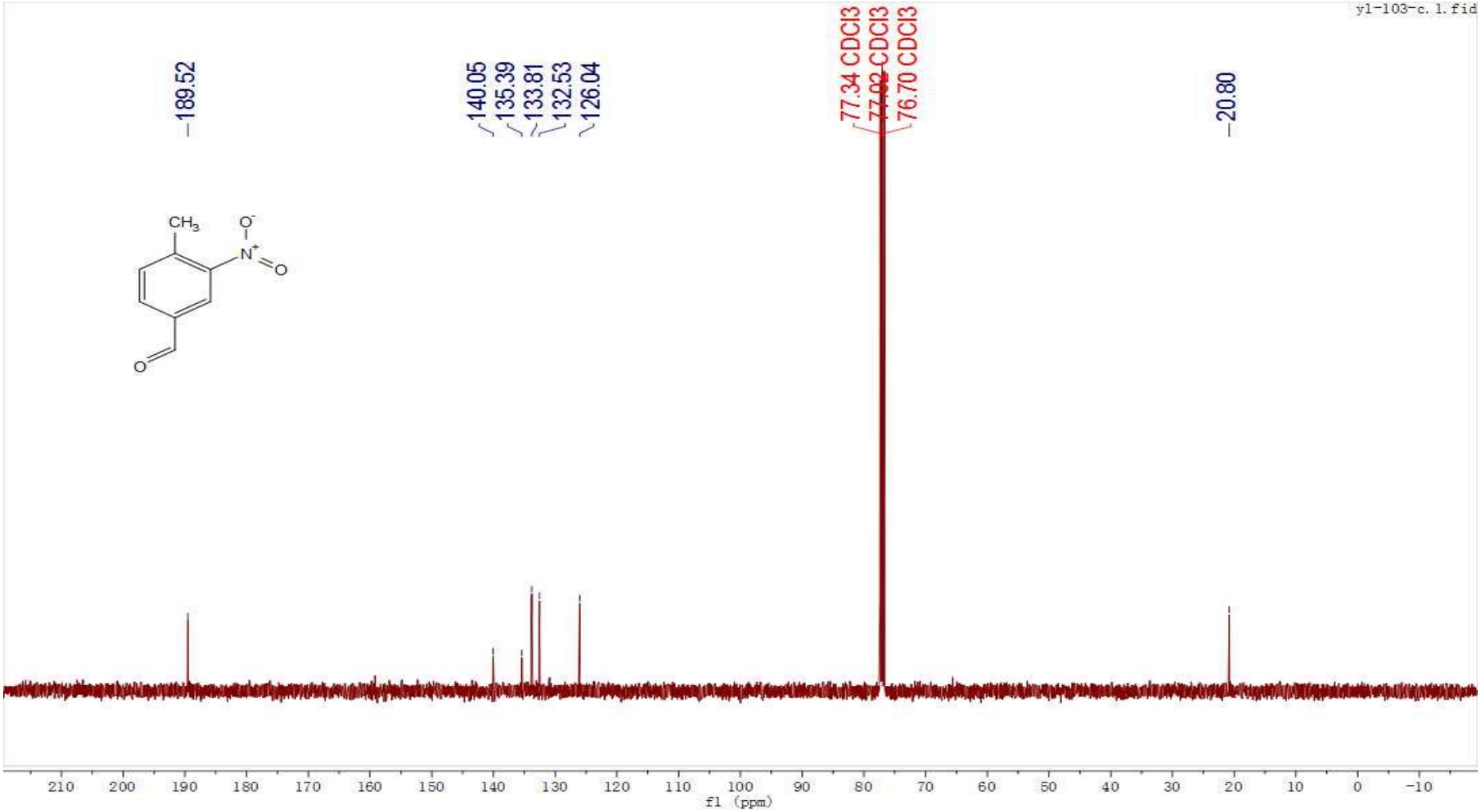
^{13}C NMR spectrum of **3q**



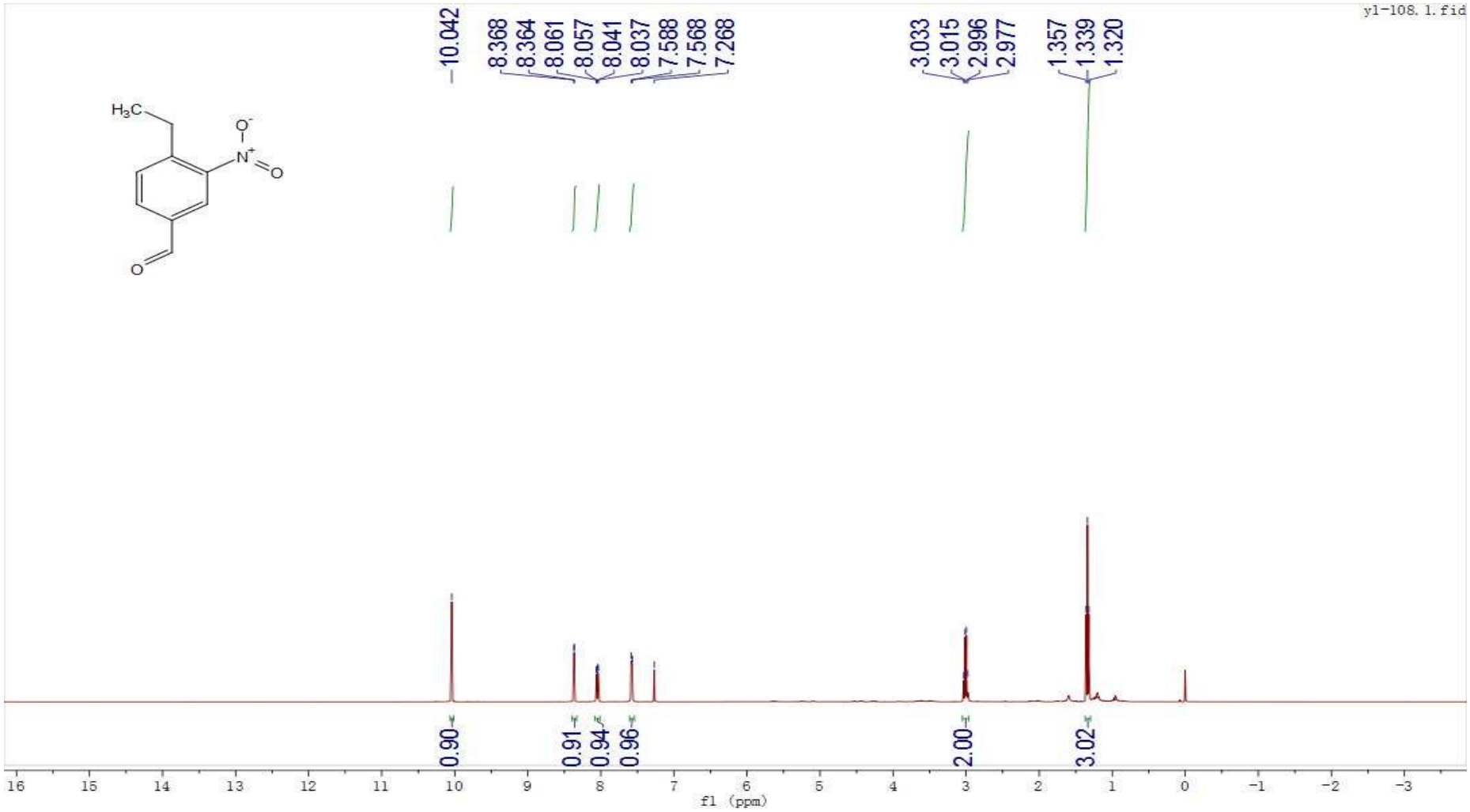
^{1}H NMR spectrum of **3r**



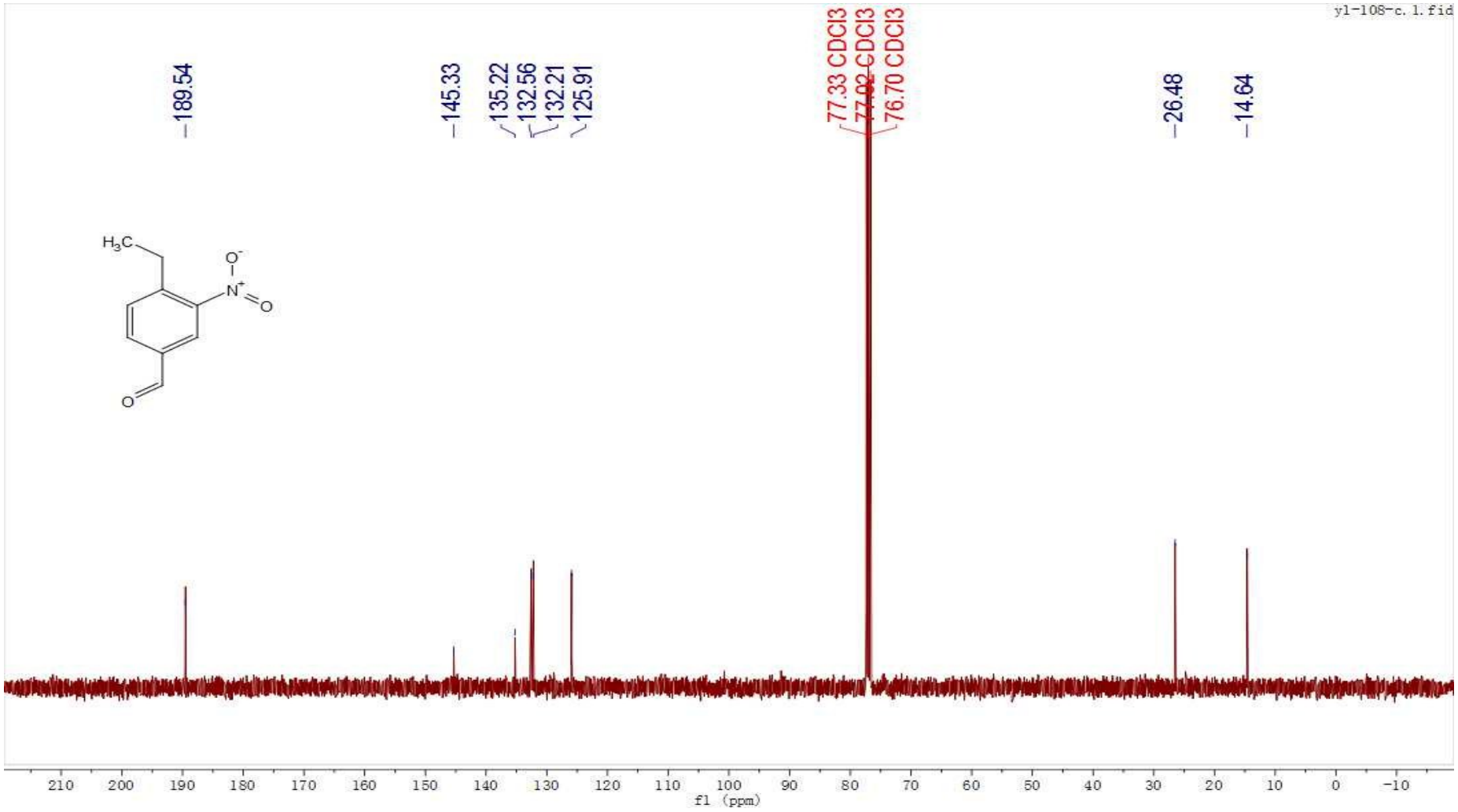
^{13}C NMR spectrum of **3r**



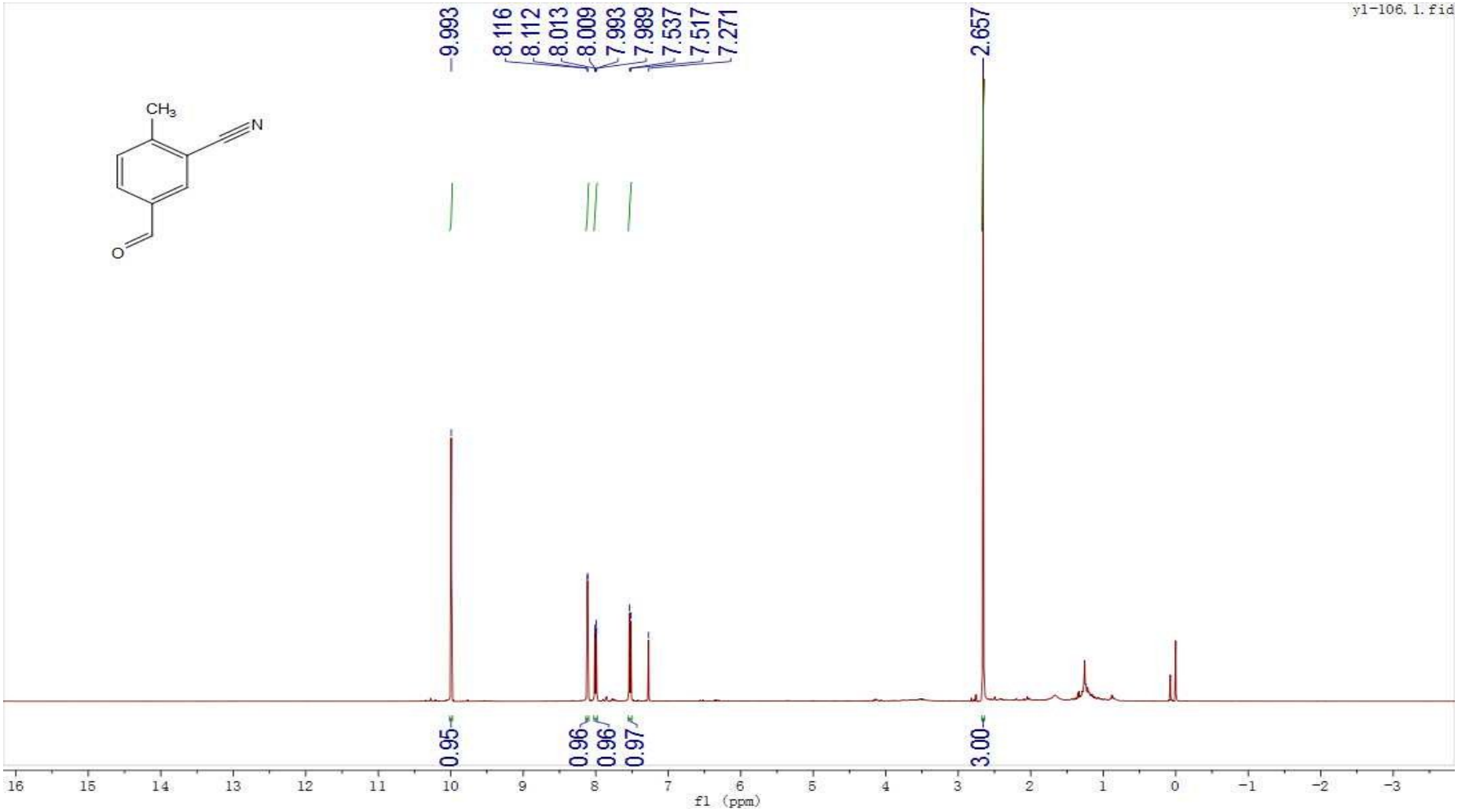
^{1}H NMR spectrum of **3s**



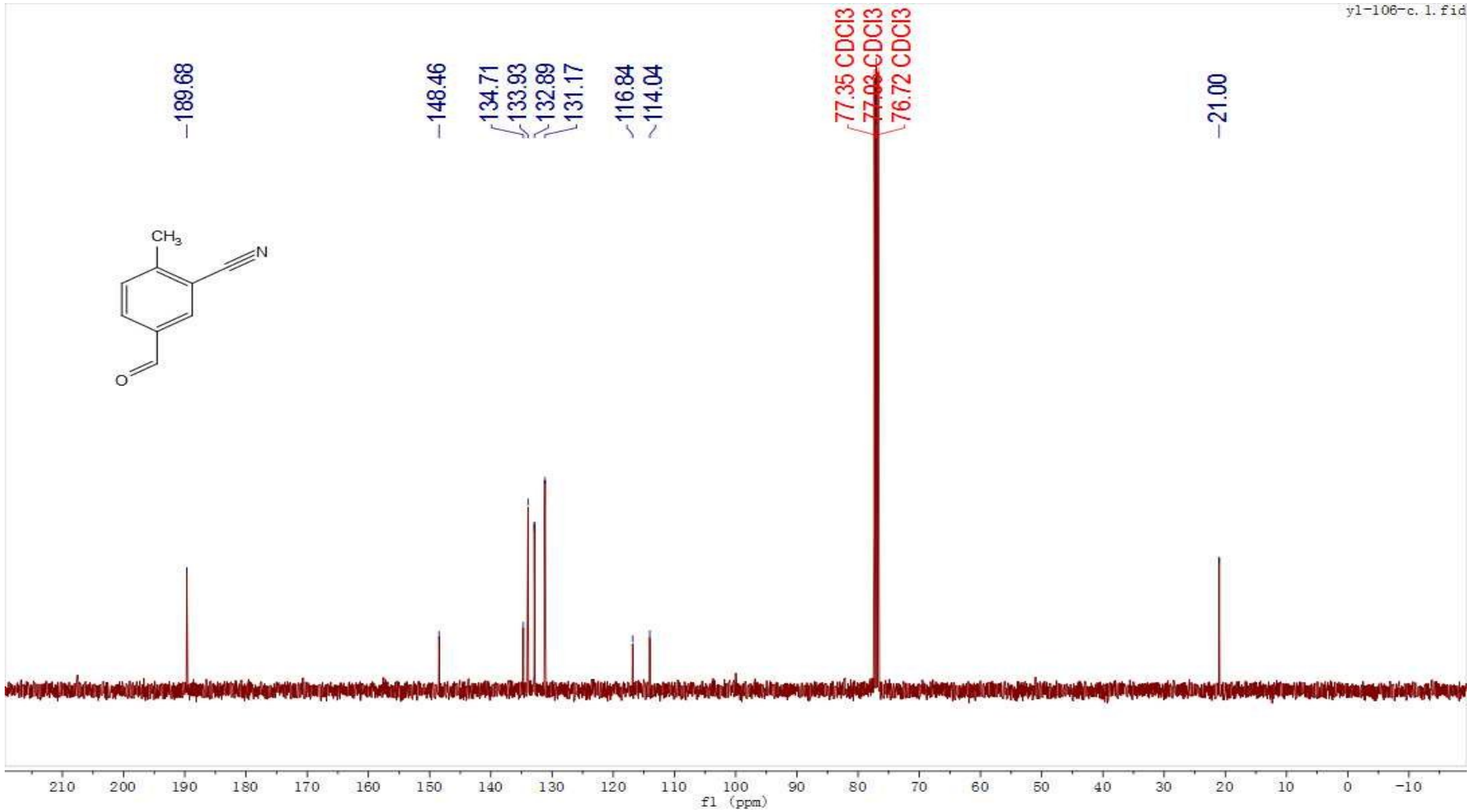
^{13}C NMR spectrum of **3s**



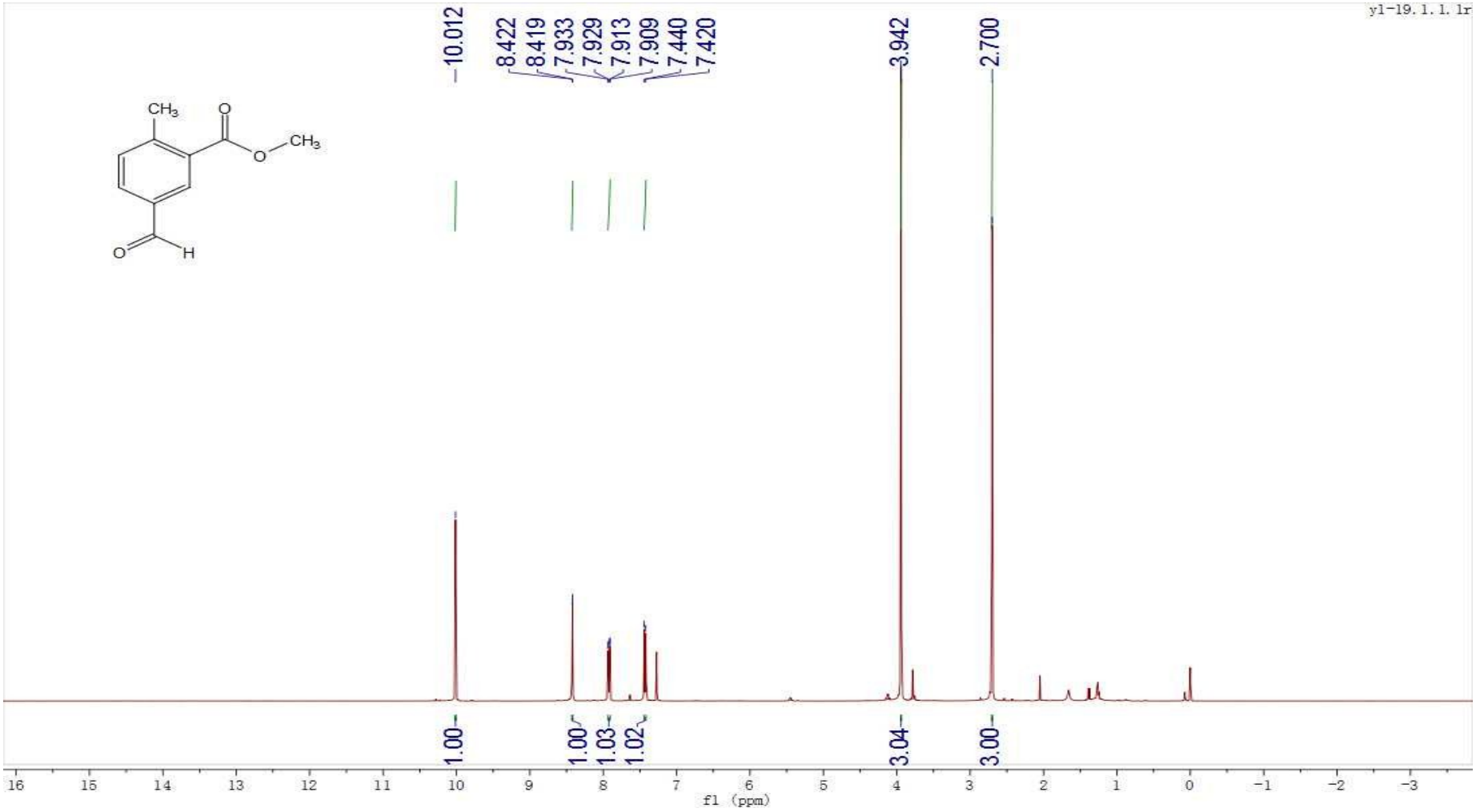
^{1}H NMR spectrum of **3t**



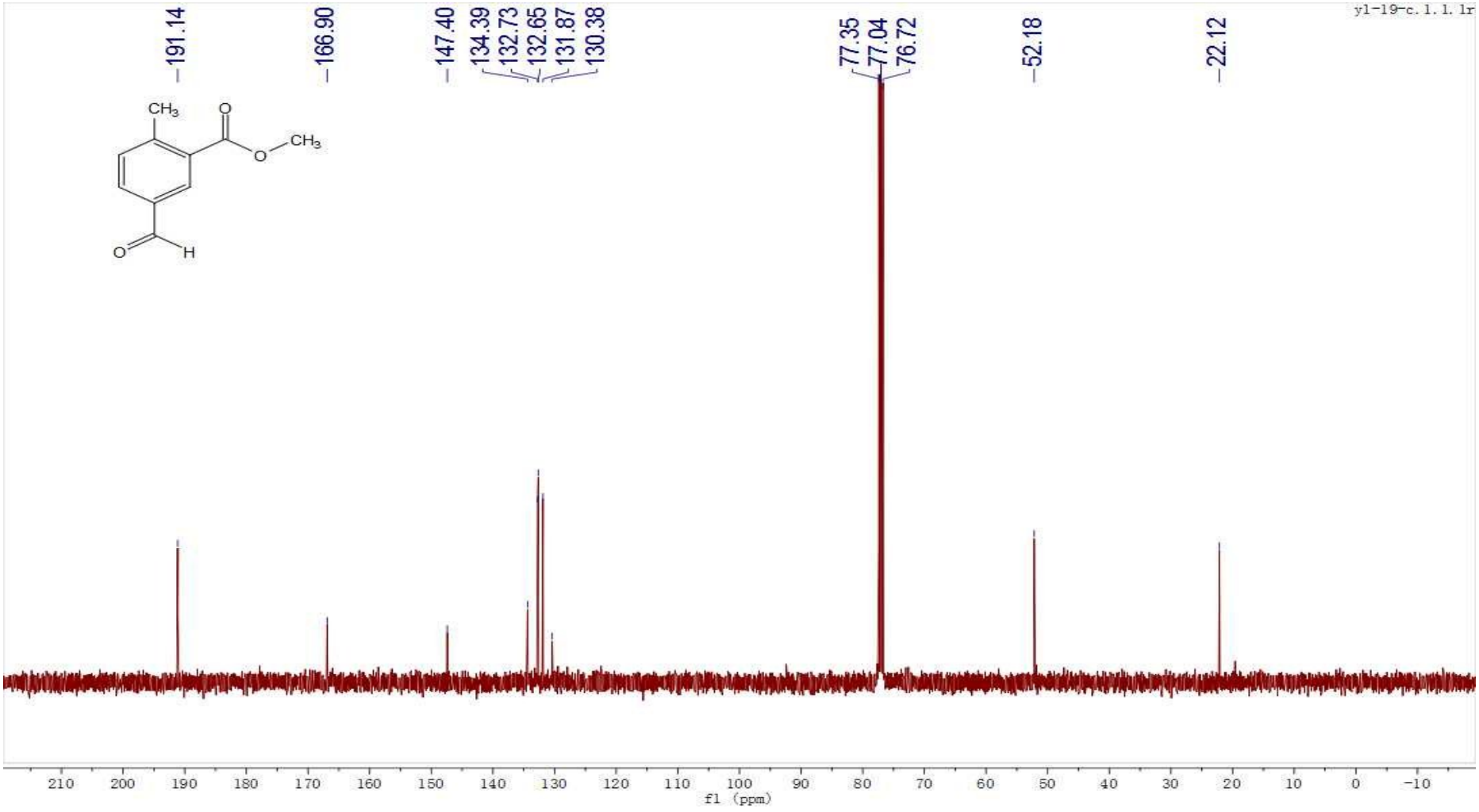
^{13}C NMR spectrum of **3t**



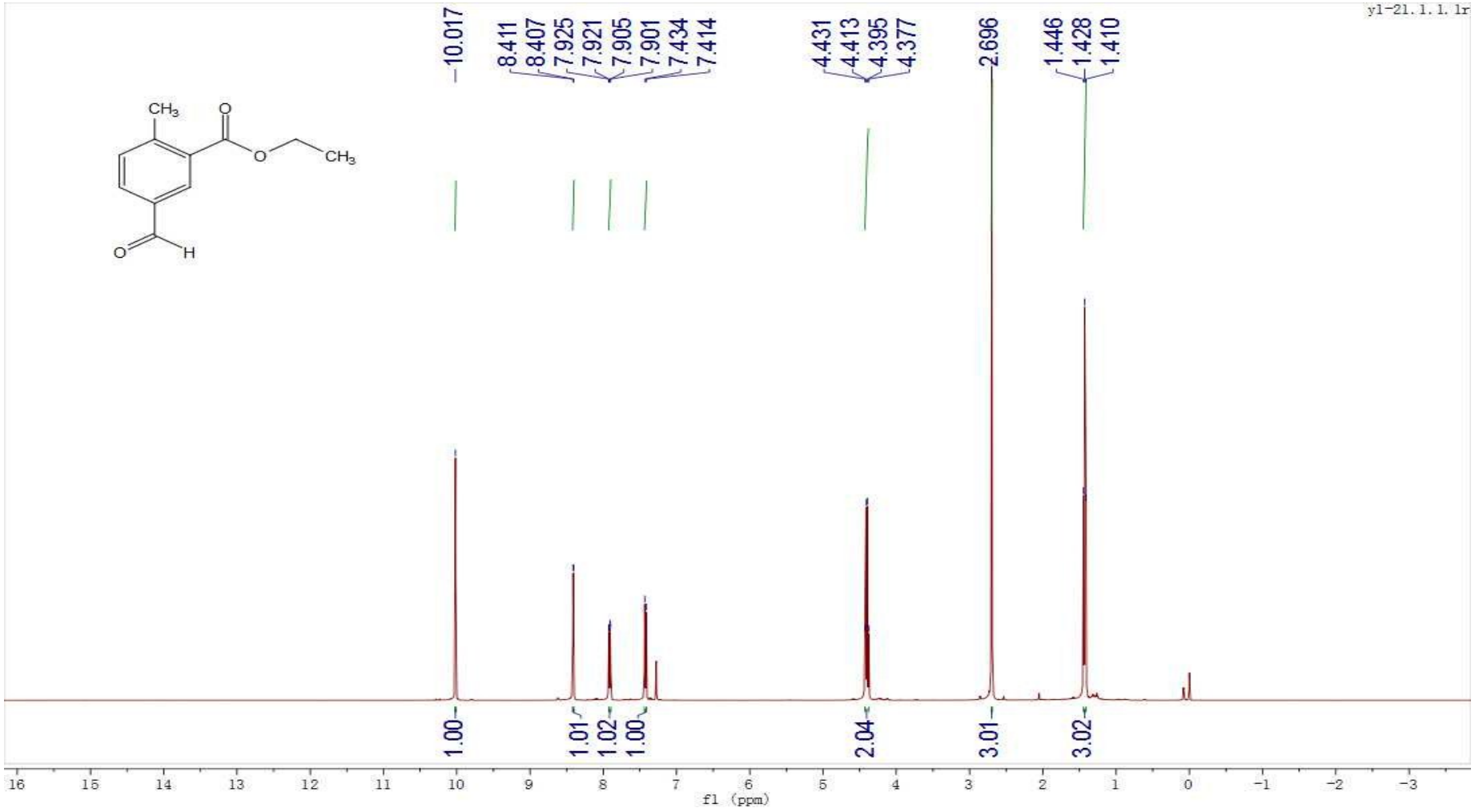
^{1}H NMR spectrum of **5a**



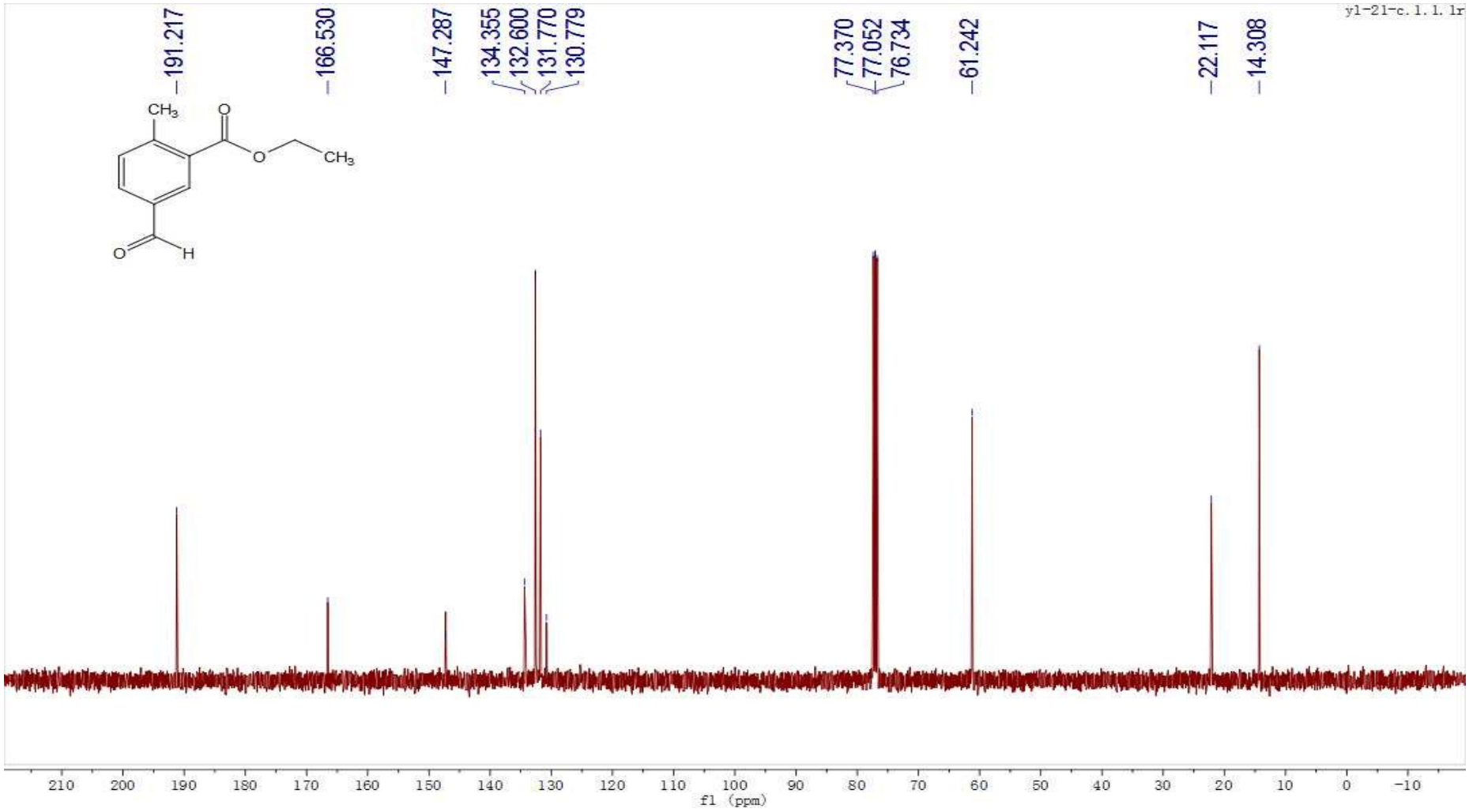
^{13}C NMR spectrum of **5a**



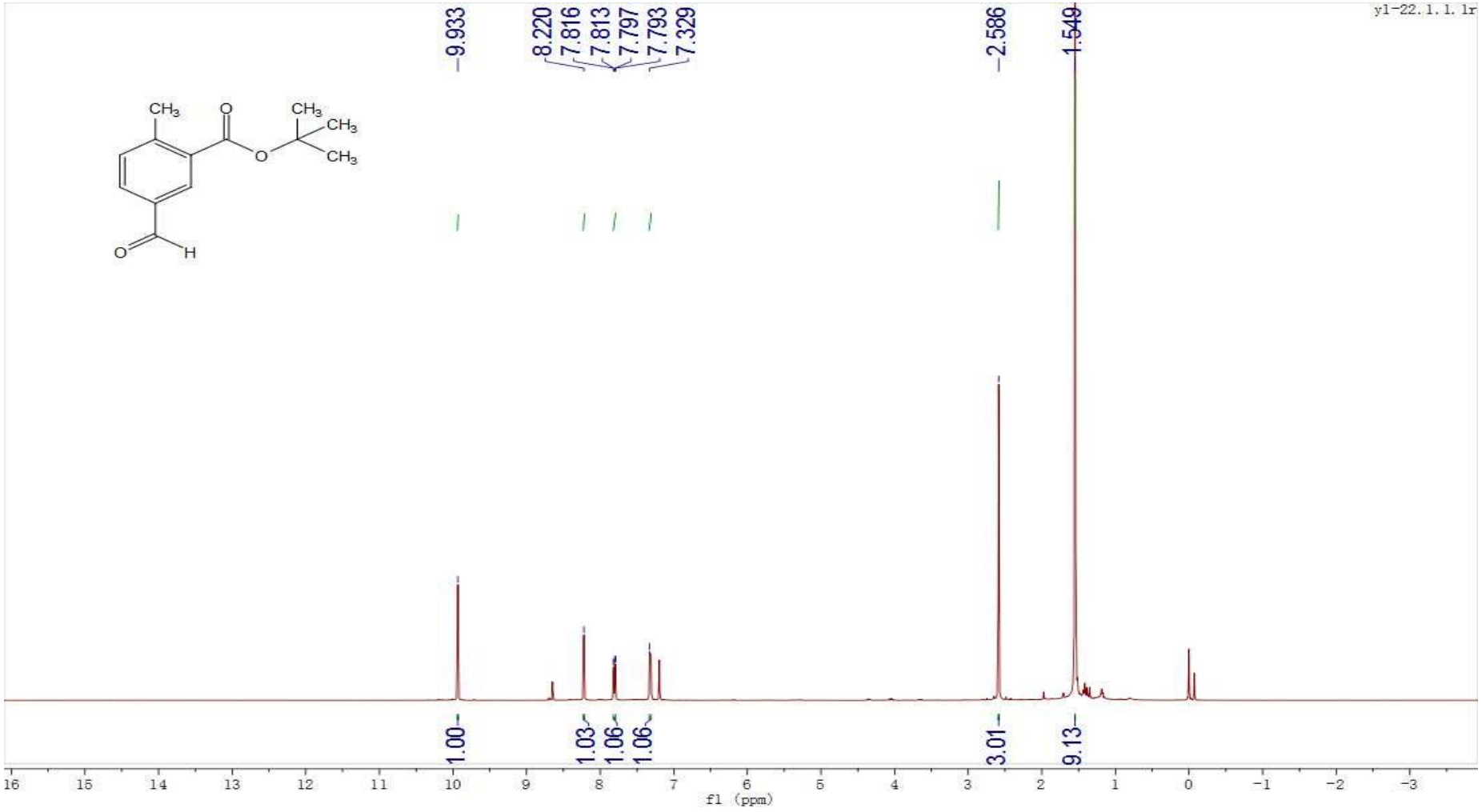
^{1}H NMR spectrum of **5b**



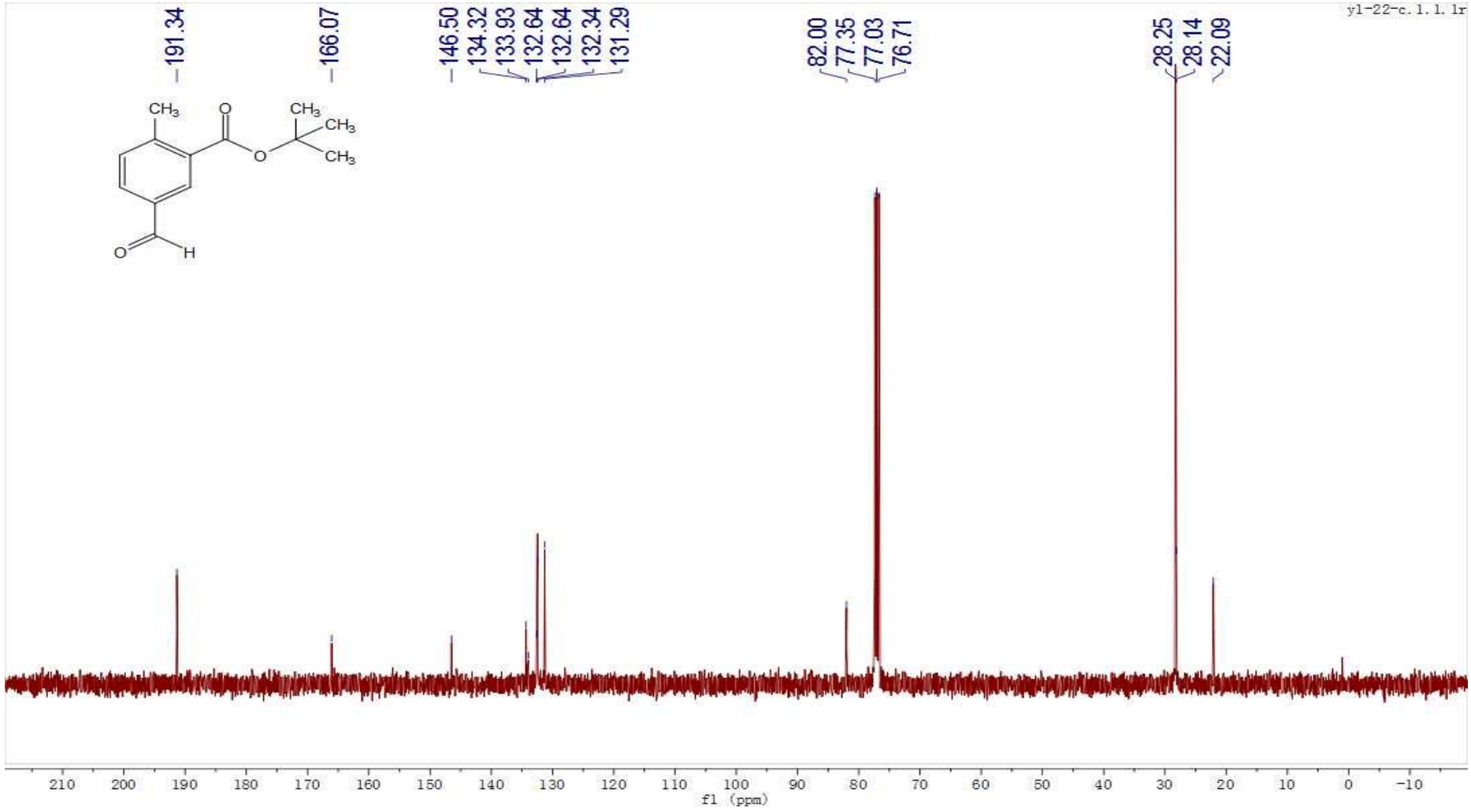
^{13}C NMR spectrum of **5b**



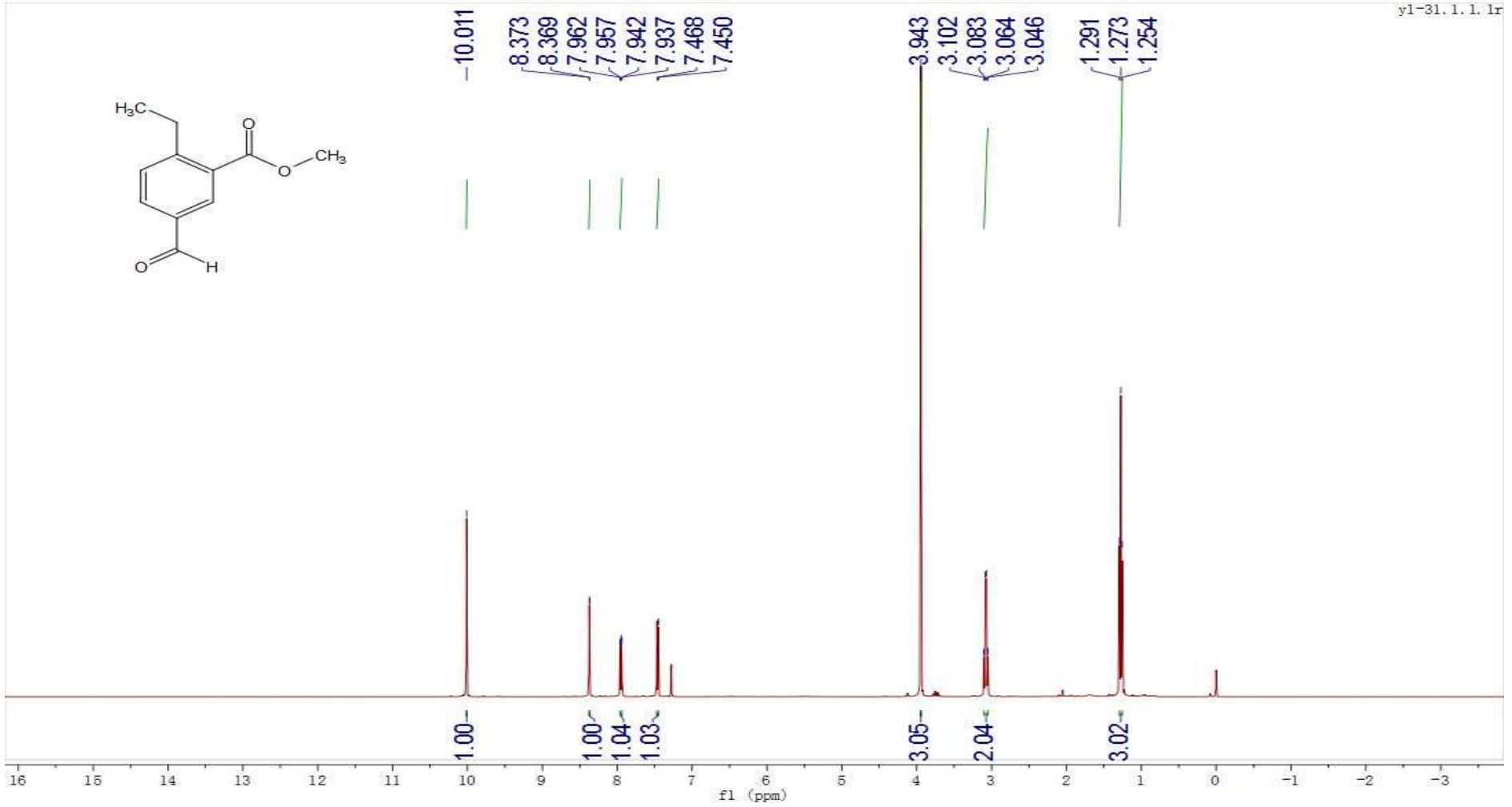
^{1}H NMR spectrum of **5c**



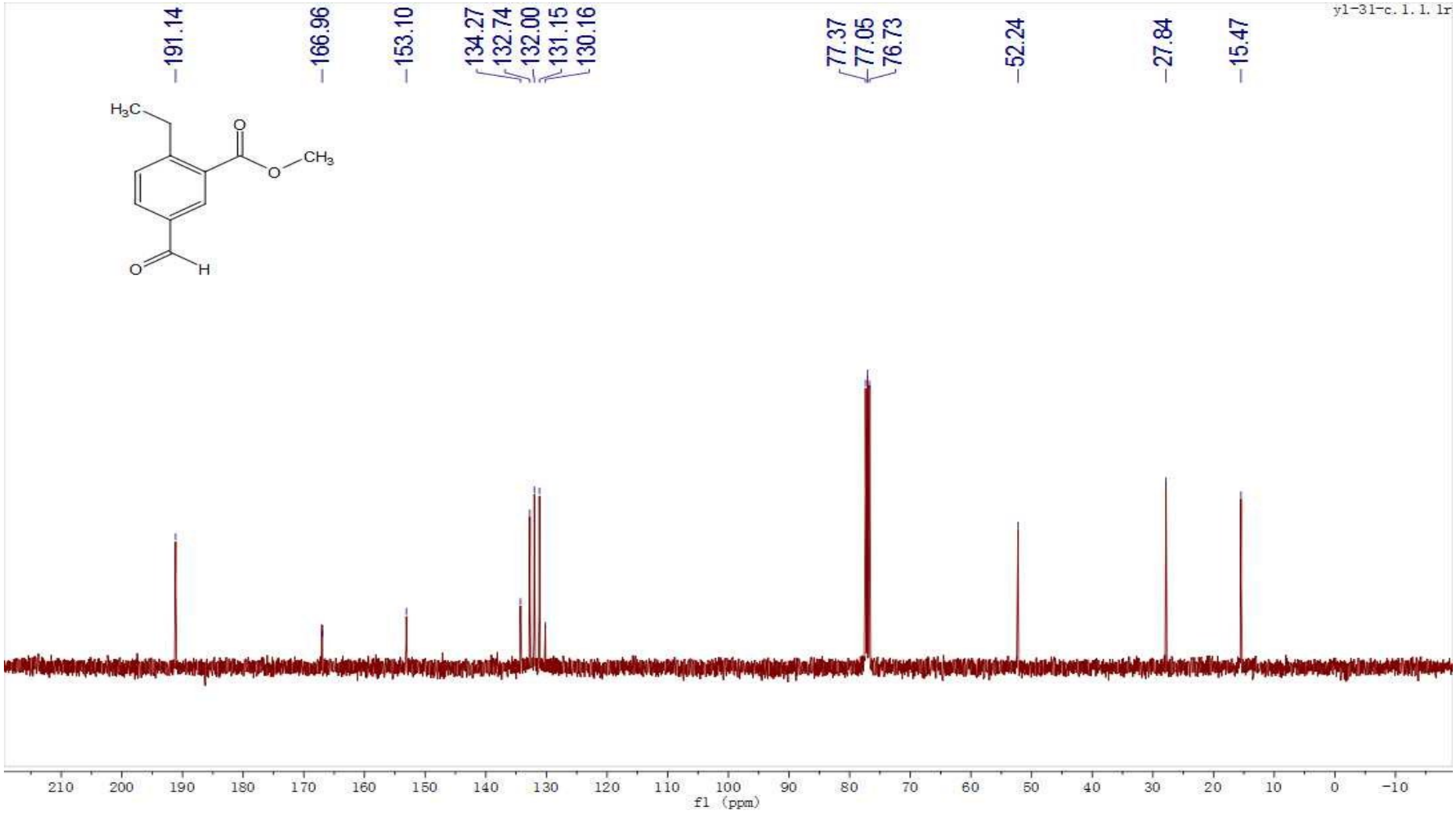
^{13}C NMR spectrum of **5c**



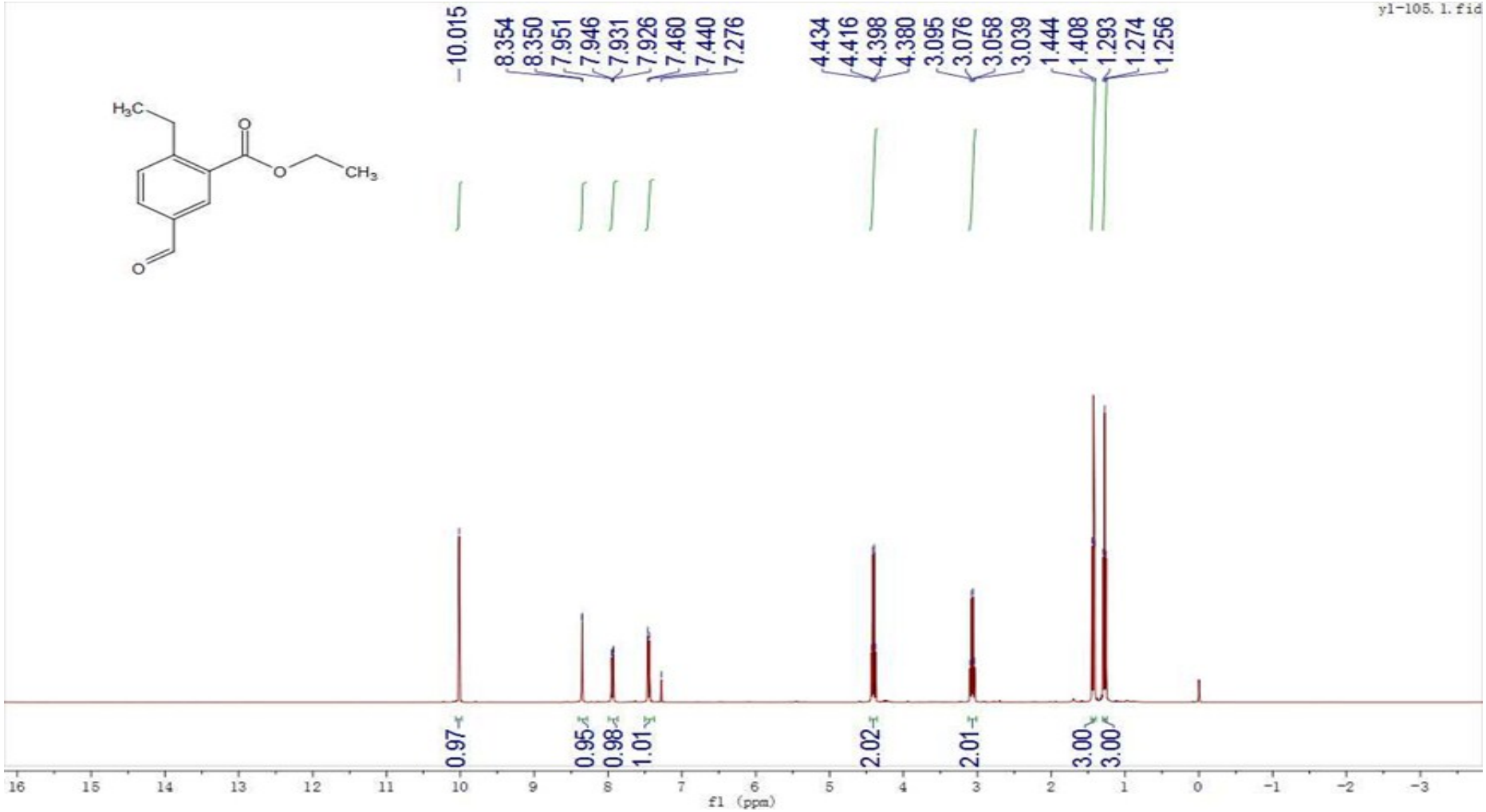
^{1}H NMR spectrum of **5d**



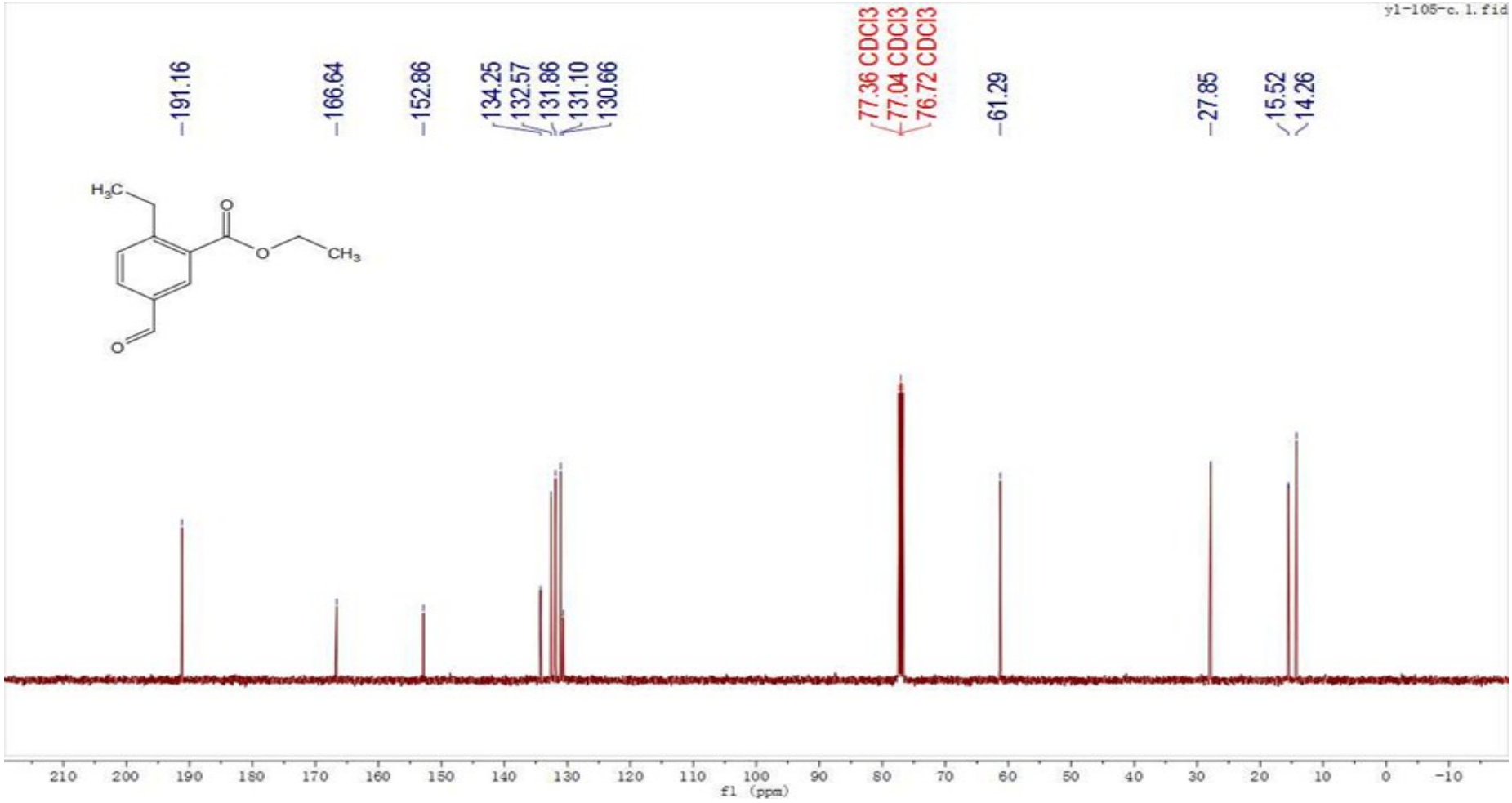
^{13}C NMR spectrum of **5d**



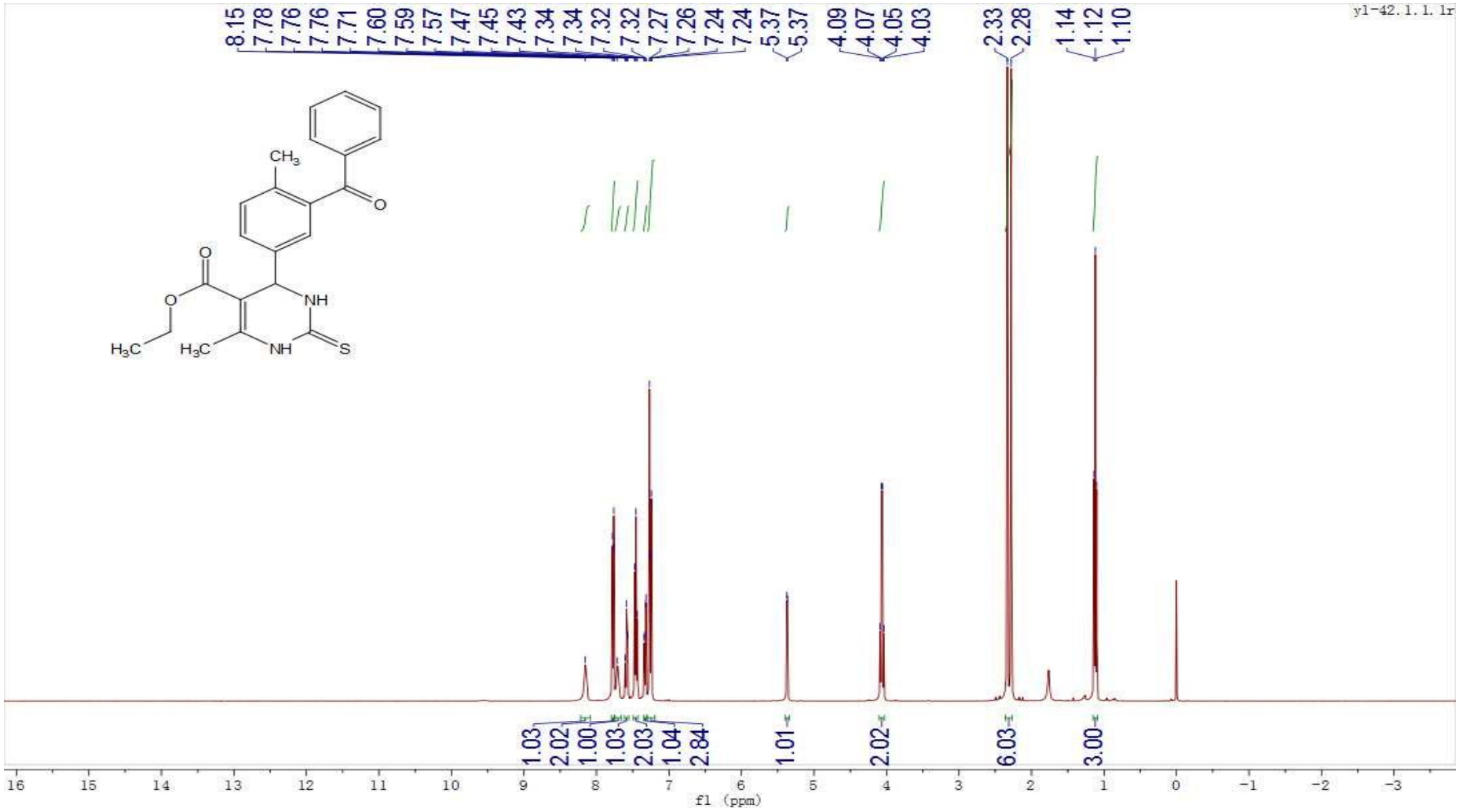
^{1}H NMR spectrum of **5e**



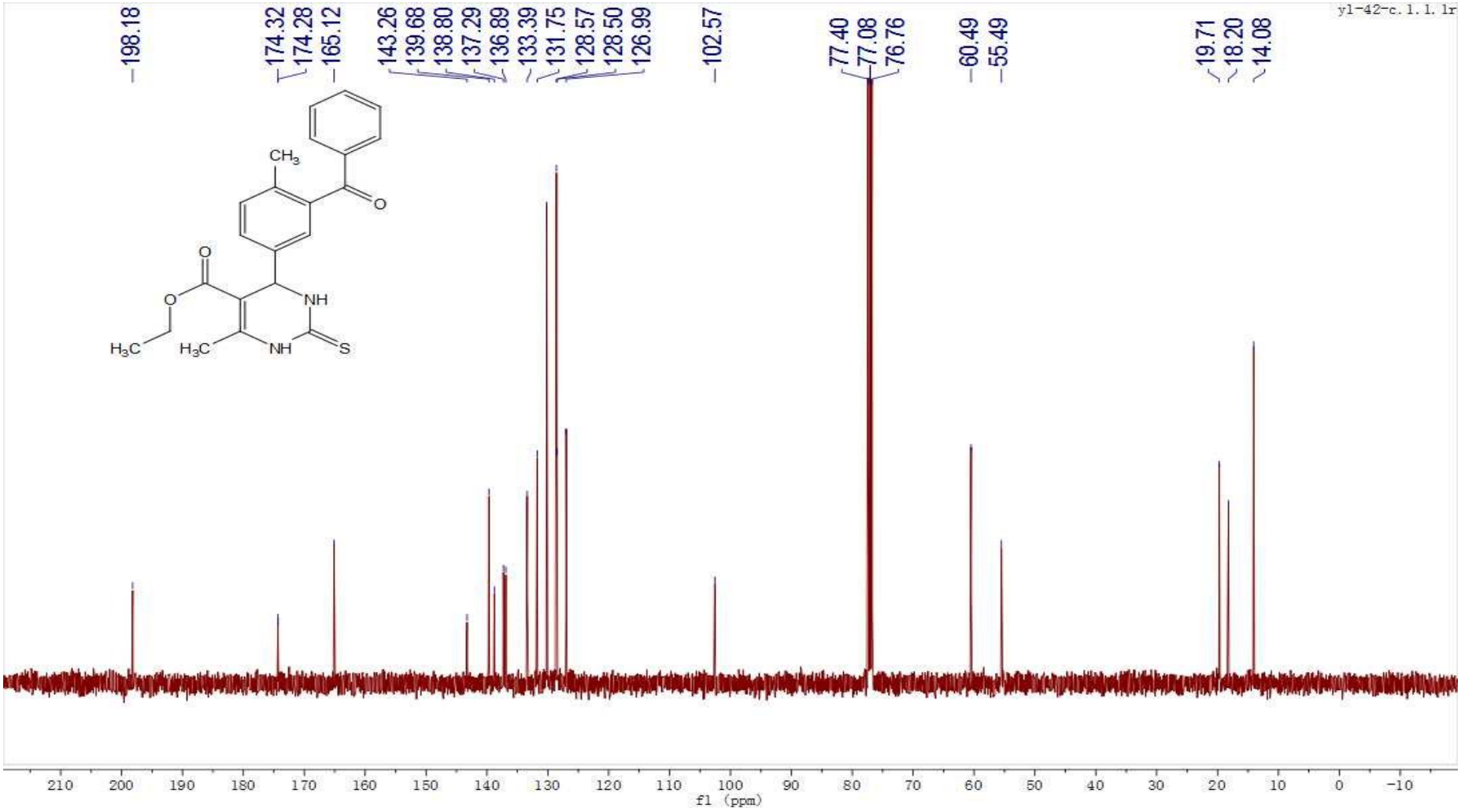
^{13}C NMR spectrum of **5e**



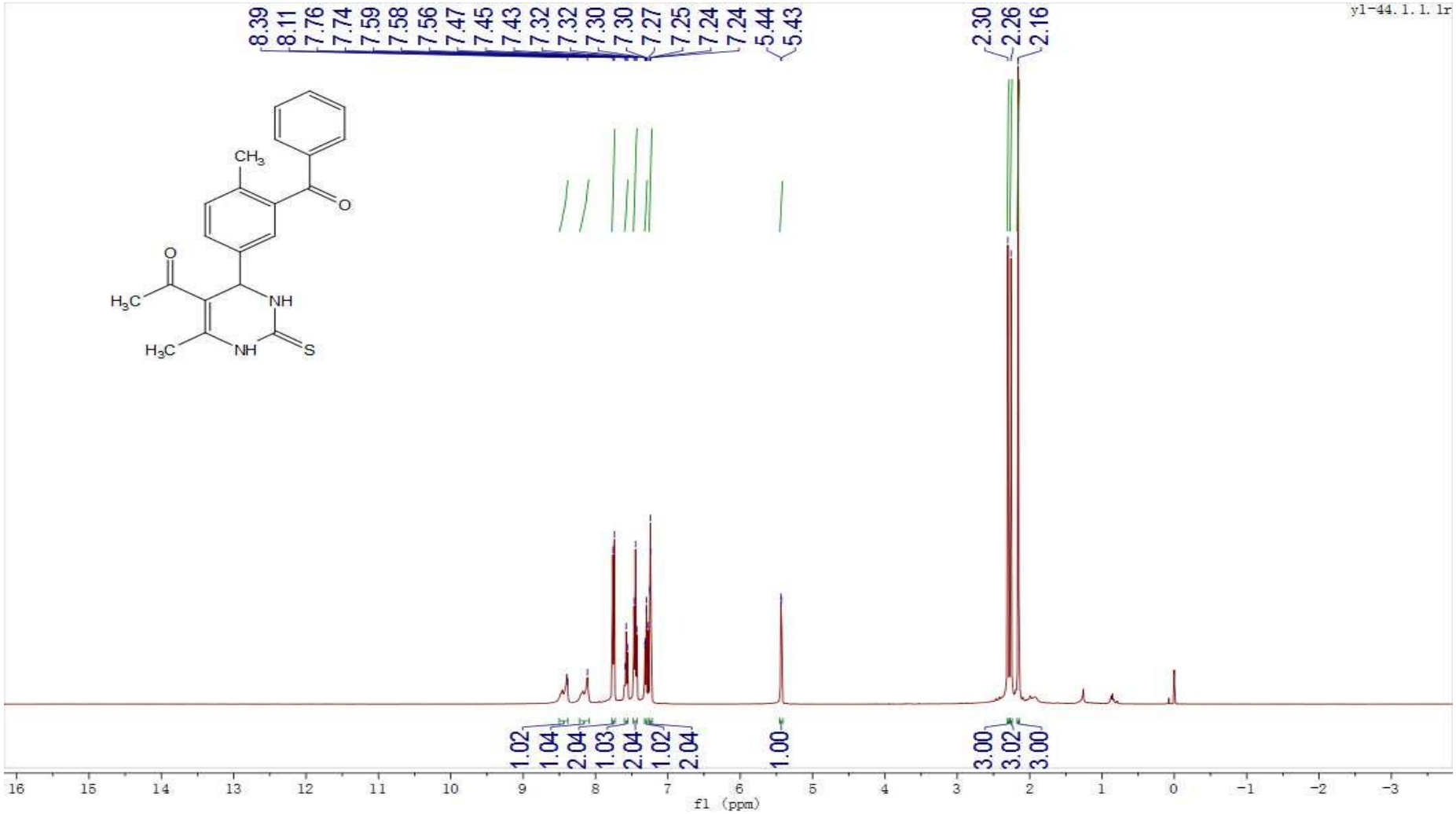
^{1}H NMR spectrum of **9a**



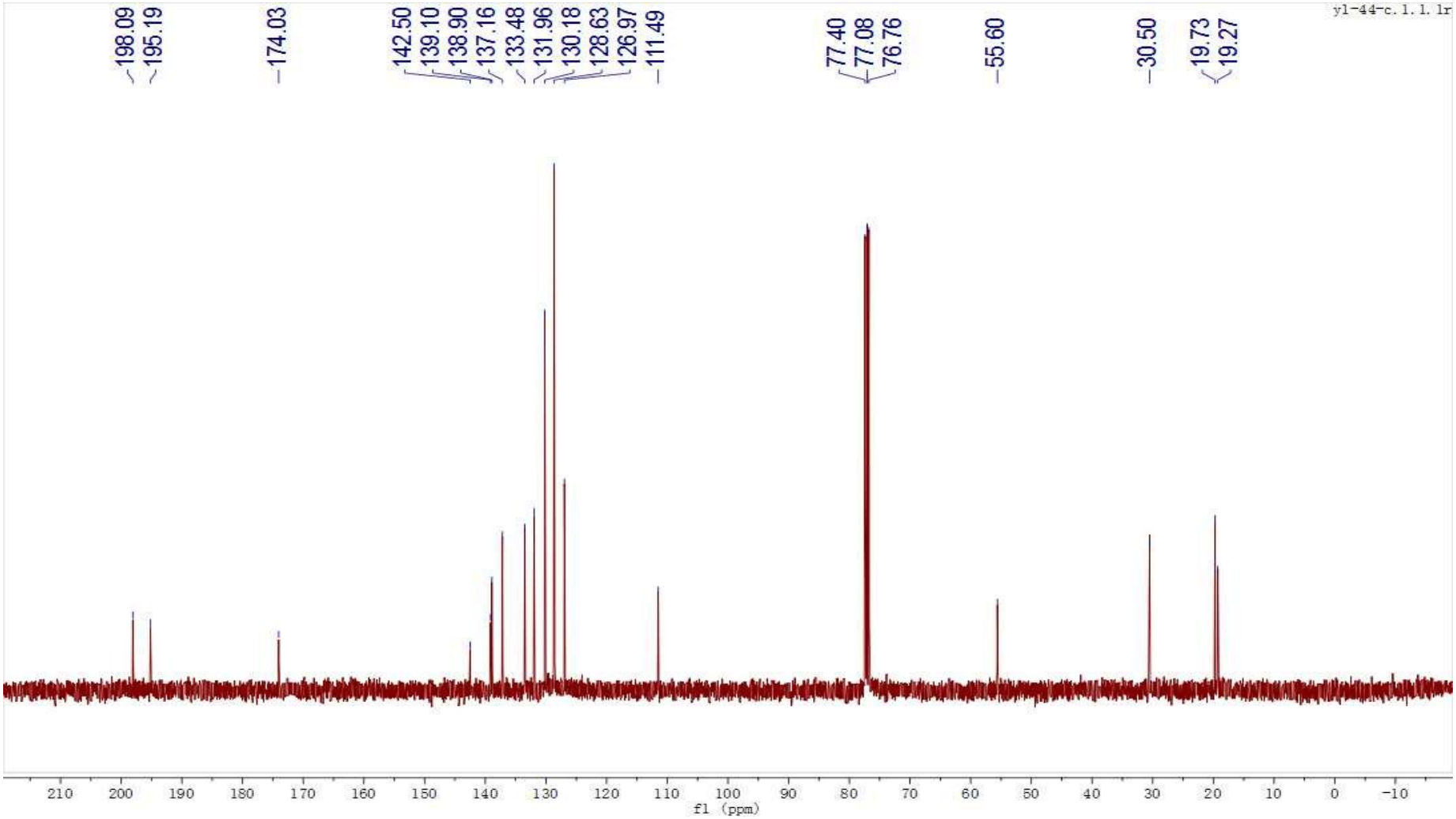
^{13}C NMR spectrum of **9a**



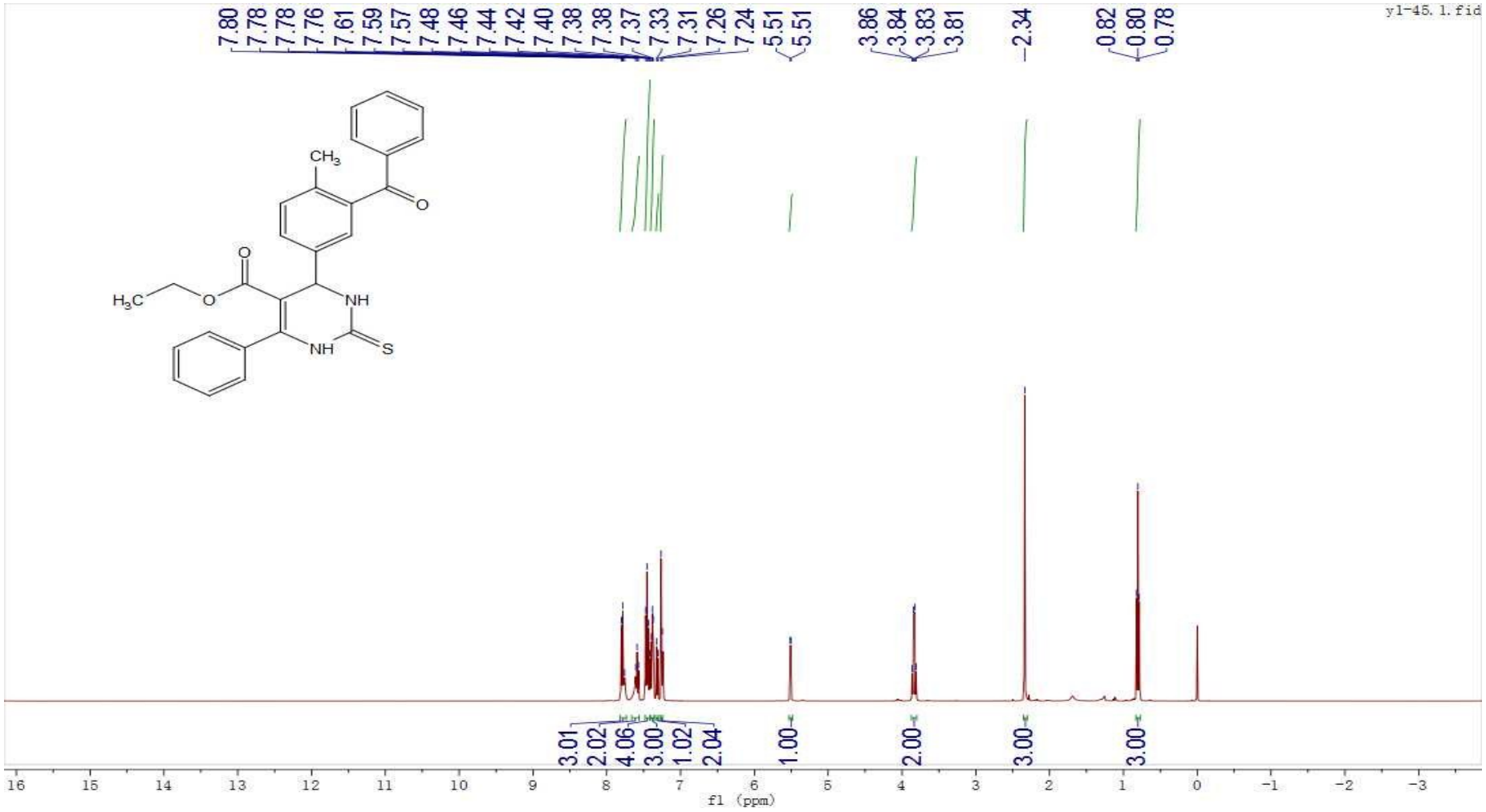
^{1}H NMR spectrum of **9b**



^{13}C NMR spectrum of **9b**



^{1}H NMR spectrum of **9c**



^{13}C NMR spectrum of **9c**